The Synthesis of Oxazole-containing Natural Products

by

Thomas H. Graham

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FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Thomas H. Graham

It was defended on

January 5, 2006

and approved by

Professor Paul E. Floreancig, Department of Chemistry

Professor Kazunori Koide, Department of Chemistry

Professor John S. Lazo, Department of Pharmacology

Professor Peter Wipf, Department of Chemistry
Dissertation Director

ABSTRACT

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Thomas H. Graham, PhD

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The first section describes the synthesis of the $C_{1'}$ to $C_{11'}$ side chain of leucascandrolide A. The key step of the synthesis is a modified Robinson-Gabriel synthesis of the oxazole. The $C_{1'}$ to $C_{11'}$ side chain was constructed in 9 steps and 7% overall yield.

The second section describes the synthesis of 2-alkynyl oxazoles and subsequent transformations into a variety of useful motifs. The conjugate addition of nucleophiles to 2-alkynyl oxazoles under basic conditions affords vinyl ethers, vinyl thioethers and enamines. The addition of ethanedithiol affords dithiolanes that can be transformed into ethyl thioesters and ketones. Nucleophilic additions of thiols to 2-alkynyl oxazolines affords oxazoline thioethers. Additions of halides under acidic conditions stereoselectively affords vinyl halides that can be further transformed by Sonogashira cross-coupling reactions.

The third section describes the synthesis of (-)-disorazole C_1 and analogs. The macrocycle was constructed with minimal protecting group manipulations, using mild esterification and Sonogashira cross-coupling reactions. The convergent synthesis of disorazole C_1 allowed for the synthesis of additional analogs. These analogs include the C_{14}-*t*-butyl and $C_{17\text{-}18}$-cyclopropane derivatives. Results from preliminary biological evaluations of synthetic intermediates, analogs and derivatives are also discussed.

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Finally, I thank my mother and father, my brother and my sisters for their continued support and encouragement.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINOL	1,1'-bi(2-naphthol)
$BrCCl_3$	bromotrichloromethane
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
18-C-6	18-crown-6 ether
CBS	Corey-Bakshi-Shibata (oxazaborolidine)
Chloramine T	*N*-chloro-*para*-toluenesulfonamide sodium salt
CI	chemical ionization
d	day(s)
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Deoxofluor™	bis(2-methoxyethyl)aminosulfur trifluoride
DiBAl-H	diisobutyl aluminum hydride
DIEA	diisopropylethylamine
DIP-Cl	DIP-chloride™; B-chlorodiisopinocampheylborane
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMS	dimethylsulfide
DPTC	dipyridylthionocarbonate
3,4-DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide
EI	electron-impact ionization
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
h	hour(s)
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectroscopy
HMPA	hexamethylphosphoramide
HOBT	1-hydroxybenzotriazole
IBCF	isobutylchloroformate

imid	imidazole
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
L-Selectride®	lithium tri-*sec*-butylborohydride
M	molar
MCPBA	3-chloroperbenzoic acid
Me	methyl
min	minute(s)
mL	milliliter(s)
mol	mole(s)
Mp	melting point
MS	molecular sieves, mass spectroscopy
m/z	mass/charge ratio
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NRPS	non-ribosomal peptide synthetase
PCWP	peroxotungstophosphate
Ph	phenyl
PIFA	[bis(trifluoroacetoxy)iodo]benzene
Piv	pivaloyl
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
i-Pr	isopropyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate)
PyBrOP	bromotripyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
quant.	quantitative
Red-Al®	sodium bis(2-methoxyethoxy)aluminum dihydride
rt	room temperature
SAR	structure-activity relationship
Select-Fluor™	*N*-chloromethyltriethylenediammonium fluoride
Ser-OMe•HCl	serine methyl ester hydrochloride
SEM	2-(trimethylsilyl)ethoxymethyl
SiO_2	silica gel
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide

TBS	*tert*-butyldimethylsilyl
2,4,6-TCBC	2,4,6-trichlorobenzoyl chloride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine-*N*-oxide
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
TsDPEA	*N*-(*para*-toluenesulfonyl)-1,2-diphenylethylenediamine

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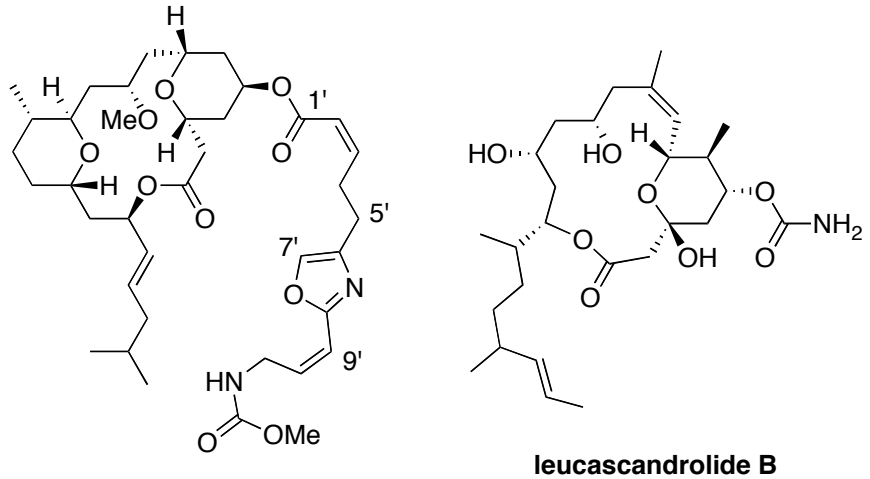
1. Synthesis of the C_1-C_{11} Segment of Leucascandrolide A

1.1. Introduction

1.1.1. The Biology of the Leucascandrolides

Leucascandrolide A and B were isolated by Pietra and coworkers in 1996 from a calcareous sponge *Leucascandra caveolata* collected along the east coast of New Caledonia, Coral Sea (Figure 1).[1,2] The structure of these macrolides were determined by HRMS, MS-MS and 2D NMR, and their absolute configuration was derived from degradation and Mosher ester studies. Significant quantities of leucascandrolide A were isolated (70 mg from 240 g, 0.03% yield) during the original expedition; however, subsequent expeditions failed to isolate additional material. Importantly, the original sponges were necrotic, suggesting that the specimens were extensively colonized by other organisms. The necrotic nature of the sponges, the unique architecture of the leucascandrolides that is uncommon to the calcareous sponges and the inability to isolate additional compound suggest that the leucascandrolides may be microbial in origin.

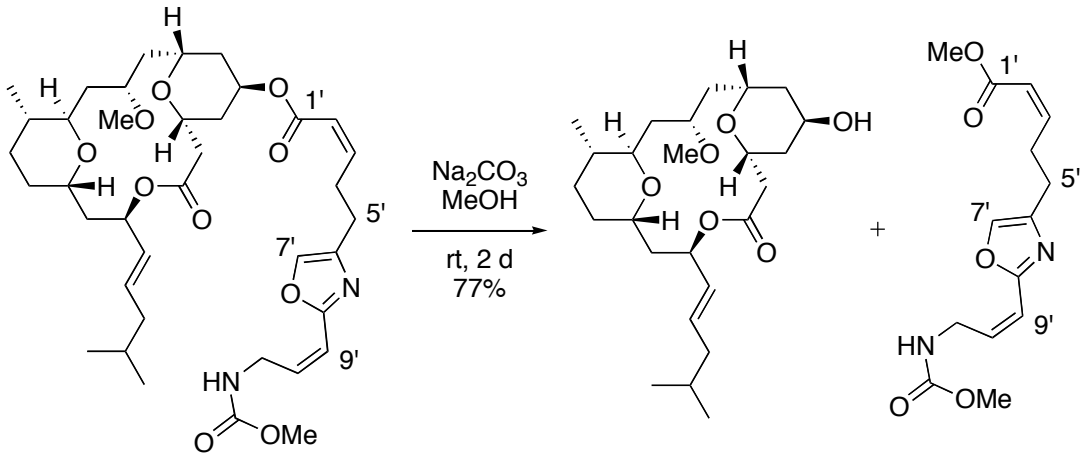
Figure 1. The leucascandrolides.



leucascandrolide A **leucascandrolide B**

Several distinctions between the two leucascandrolides can be noted. Leucascandrolide B is a 16-membered macrolide incorporating one pyran and lacking the oxazole-containing side-chain. Leucascandrolide B demonstrated no significant cytotoxic and antifungal activity. Leucascandrolide A is an 18-membered macrolide which incorporates two pyrans and the oxazole-containing side-chain. In addition, leucascandrolide A demonstrates strong cytotoxic activity *in vitro* in KB and P388 cells (IC_{50}'s of 50 and 250 ng/mL), as well as very strong inhibition of *Candida albicans* (inhibition diameter of 26/40, 23/20, and 20/10 mm/mg per disk). The Pietra group removed the side chain from the macrolide, and determined that the macrolide portion **1** was essential for cytotoxic activity (Scheme 1). The oxazole-containing side-chain **2** was responsible for the anti-fungal activity.[1]

Scheme 1. Separation of leucascandrolide A into two major segments.



leucascandrolide A **1** **2**

The cytotoxic and antifungal activities of leucascandrolide A warrant further investigation of its pharmacological and clinical potential, but the supply is limited by the inability to isolate additional quantities from the natural source.[2] The only method presently available for obtaining a steady supply of leucascandrolide A is synthesis. To date, several total syntheses have been completed by the groups of Leighton,[3] Kozmin,[4] Carreira,[5] Paterson[6] and Panek.[7] Several synthesis of the macrolide segment were also reported.[8,9] As part of a project focused on the synthesis of leucascandrolide A, the $C_{1'}$ to $C_{11'}$ side chain segment was synthesized.[10]

1.1.2. Approaches to the Synthesis of the $C_{1'}$-$C_{11'}$ Segment

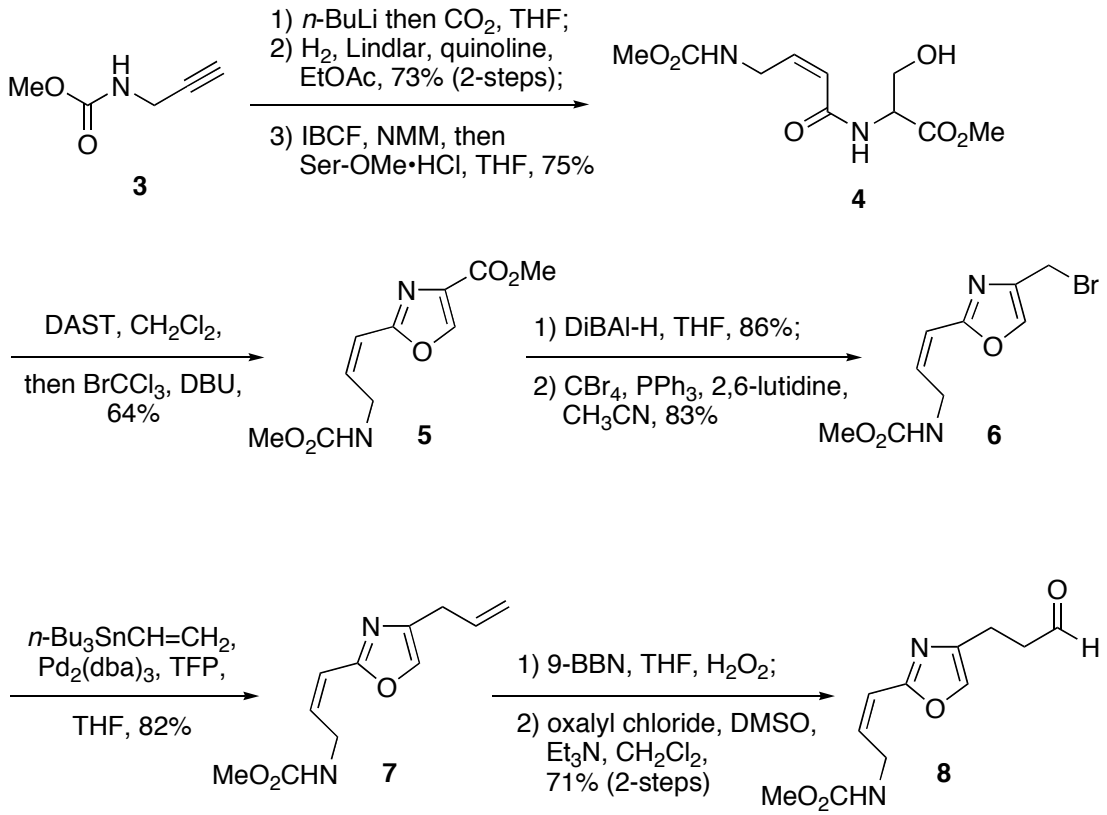
Five syntheses of the leucascandrolide A side chain have been reported and each can be distinguished by the method used to install the oxazole ring.[11] Leighton used the cyclization-oxidation of a hydroxyamide.[3] Kozmin's synthesis used a rhodium

carbenoid mediated cyclization.[4] Both Panek[12] and Paterson[6] used a modified Sonogashira cross-coupling between a 2-trifluoromethylsulfonyl oxazole and a terminal alkyne. The synthesis by Wipf (Section 1.2.2) used an oxidation-cyclization (Robinson-Gabriel) route.[10]

1.1.2.1. Leighton's Synthesis

The Leighton synthesis commenced with the carboxylation of alkyne **3** followed by semi-reduction with hydrogen and Lindlar catalyst to afford the (*Z*)-alkene in 73% yield (Scheme 2). Coupling with serine methyl ester afforded hydroxyamide **4** in 75% yield. The hydroxyamide was then cyclized using DAST and oxidized with $BrCCl_3$/DBU to afford the oxazole **5** in 64% yield.[13] The methyl ester was reduced to the alcohol in 86% yield using diisobutylaluminum hydride and the alcohol was converted to the bromide **6** in 83% yield. Stille cross-coupling afforded **7** which was chemoselectively converted to the alcohol using 9-BBN and hydrogen peroxide. Swern oxidation afforded the aldehyde **8** in 71% yield for the two steps. The aldehyde was then coupled with a phosphonoacetate derivative of the leucascandrolide A macrolide in 55% yield. The side chain segment was prepared in 10 steps and 8% overall yield.

Scheme 2. Leighton's synthesis of the leucascandrolide A side chain.

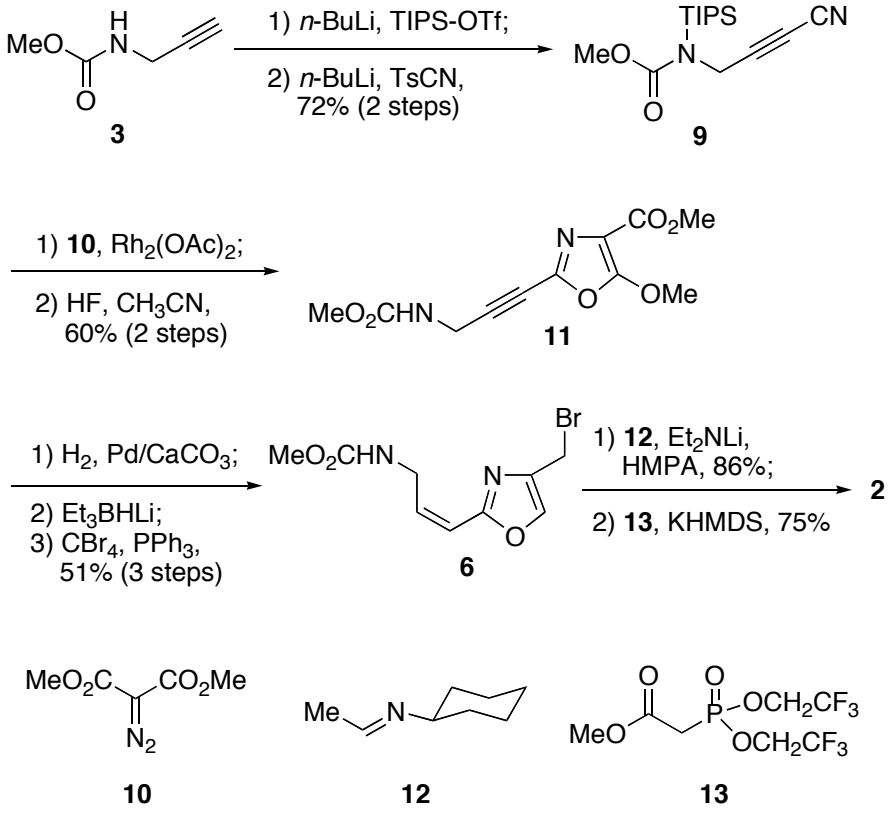


1.1.2.2. Kozmin's Synthesis

Kozmin and coworkers utilized an application of the rhodium carbenoid-mediated cyclization of nitriles and α-diazoketones (Scheme 3).[4] The required nitrile **9** was formed in 72% yield using an optimized, one-pot procedure consisting of TIPS-protection of the amide and cyanation using solid tosyl cyanide.[4b] The key cyclization of **9** and diazodimethylmalonate (**10**) using Helquist's methodology[14] afforded oxazole **11** in 60% yield after TIPS removal. Semi-reduction installed the (*Z*)-alkene and reduction of the methoxyoxazole and the methyl ester afforded the alcohol which was

converted to bromide **6** in 51% yield for the three steps. A two-carbon homologation (86% yield) followed by conversion of the aldehyde to the second (*Z*)-olefin using the Still-Gennari conditions[15] afforded **2** in 75% yield. Leucascandrolide A was completed by saponification of **2** in 89% yield followed by condensation with the C_5-epimer of macrolide **1** using Mitsunobu conditions.[16] The side chain segment **2** was completed in 9 steps and 14% yield.

Scheme 3. Kozmin's synthesis of the leucascandrolide A side chain.



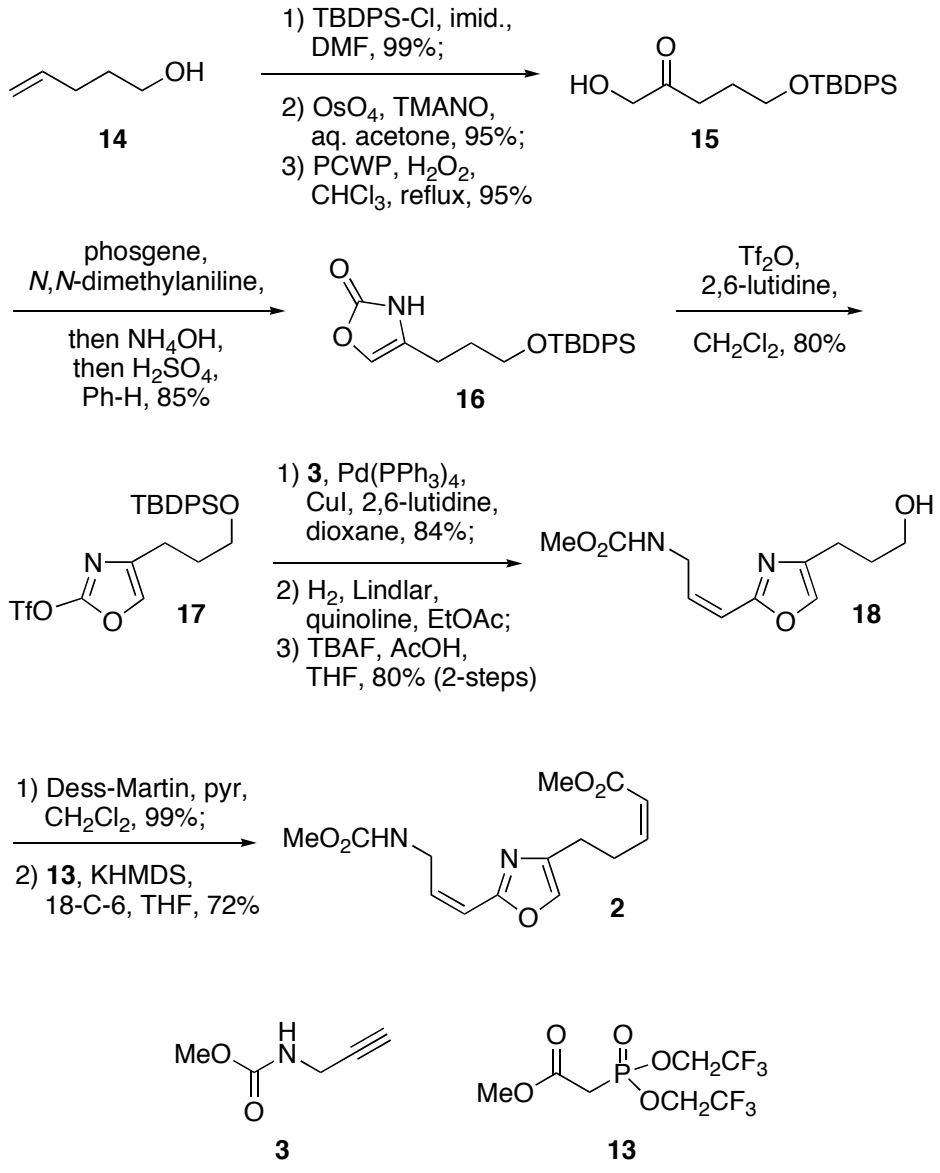
1.1.2.3. Panek's Synthesis and the Paterson Variant

Panek's synthesis began with the nearly quantitative protection of 4-penten-1-ol (**14**) as the TBDPS ether, followed by dihydroxylation of the olefin in 95% yield and selective oxidation of the seconday alcohol to afford the hydroxy ketone **15** in 95% yield. A highly efficient cyclization step using phosgene and ammonium hydroxide afforded **16** in 85% yield. The 2-trifluoromethylsulfonyl oxazole **17** was then formed in 80% yield. Palladium catalyzed cross-coupling of **17** and alkyne **3** occurred in 84% yield. Semi-reduction and removal of the TBDPS group afforded the 3,5-disubstituted oxazole **18** in 80% for the two steps. Finally, Dess-Martin oxidation[17] gave the aldehyde in 99% yield, and subsequent Still-Gennari olefination[15] afforded **2** in 72% yield. The side chain segment was completed in 10 steps and 29% yield. Leucascandrolide A was completed by saponification of **2** and condensation with the macrolide **1** using Mitsunobu conditions.[7]

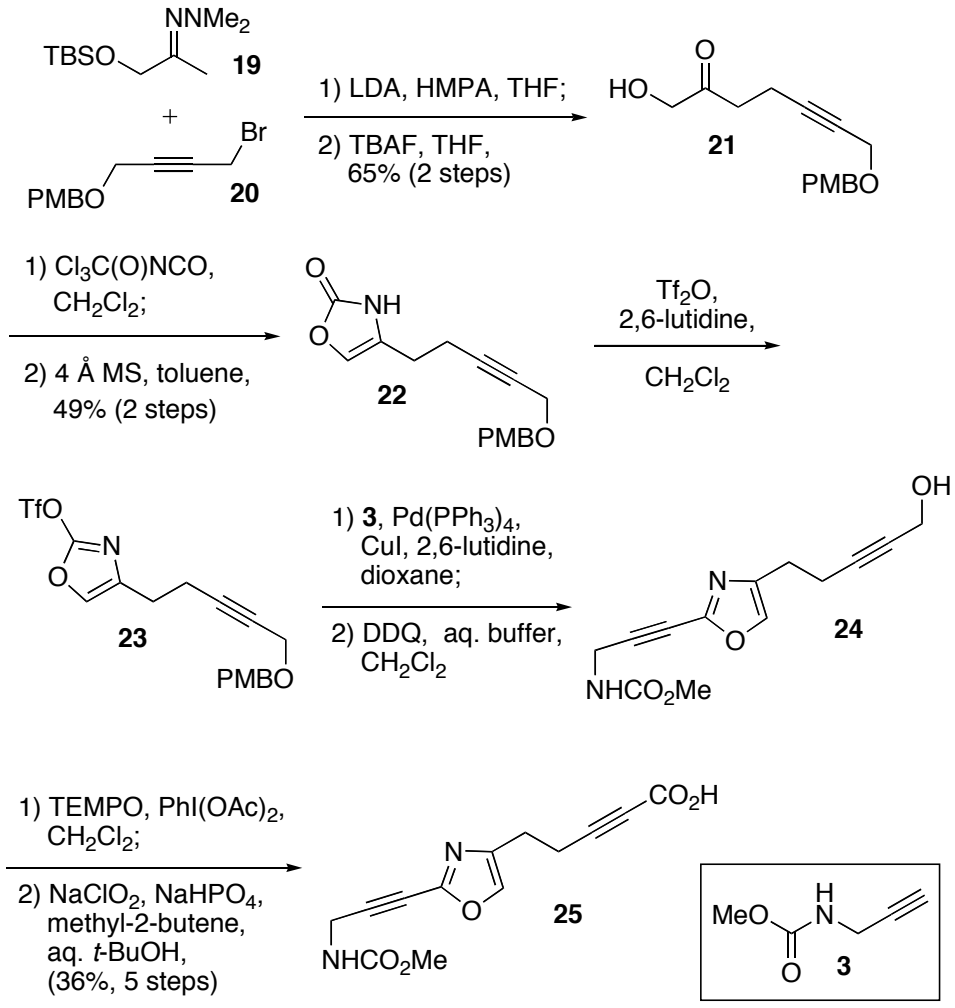
Paterson's route followed a path similar to Panek's. Condensation of the lithium anion of **19** with propargyl bromide **20** afforded **21** in 65% yield. The hydroxy ketone **21** was converted to **22** in 49% yield by trichloroacetylisocyanate treatment followed by heating at reflux with 4 Å molecular sieves. The formation of triflate **23** and palladium-catalyzed cross-coupling with **3** is analagous to the Panek synthesis. Removal of the PMB group with DDQ afforded **24** and oxidation of the alcohol to the acid afforded **25** in 36% yield over the 5 steps (from **22**). The side chain was attached to the macrolide portion via a Mitsunobu esterification[16] and the two alkynes were then

reduced to afford leucascandrolide A. Paterson completed the masked side chain acid **25** in 9 steps and 11% overall yield.

Scheme 4. Panek's synthesis of the leucascandrolide A side chain.



Scheme 5. Paterson's synthesis of the leucascandrolide A side chain.

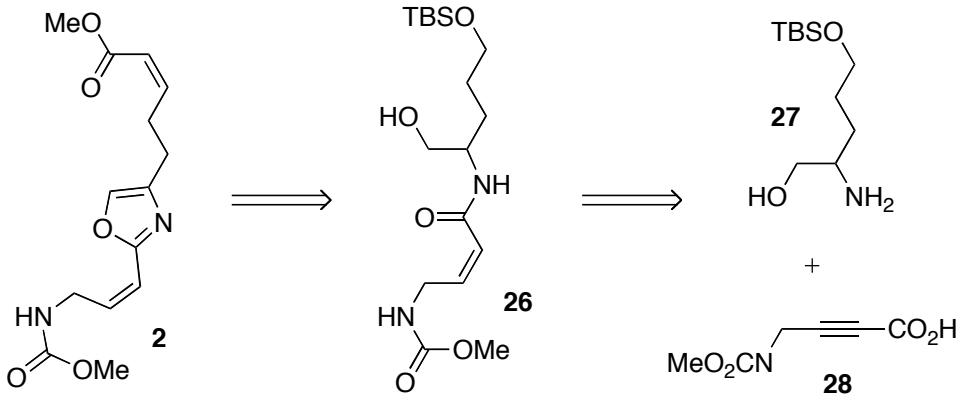


1.2. Synthesis of the $C_{1'}$-$C_{11'}$ Segment of Leucascandrolide A

1.2.1. Retrosynthesis

The oxazole moiety of the leucascandrolide A side chain (**2**) was envisioned to be a key point of disconnection and was derived from hydroxyamide **26** (Figure 2).[10] The hydroxyamide arose from aminoalcohol **27** and alkynoic acid **28**. Fragment **27** was derived from glutamic acid and fragment **28** could be obtained from propargyl amine. The (*Z*)-alkenes would be installed by Lindlar semi-hydrogenation and Still-Gennari olefination.[15]

Figure 2. Retrosynthetic approach to the leucascandrolide A side chain.

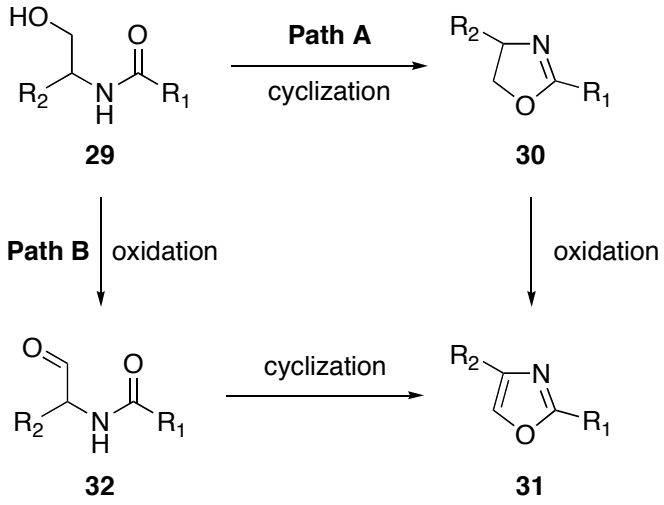


1.2.2. Completion of the C_1–C_{11} Segment

Our approach to the synthesis of the leucascandrolide side chain required the cyclization of a suitably functionalized hydroxyamide.[10] The formation of 2,4-disubstituted oxazoles from hydroxyamides can occur by two general pathways (Figure 3). One route involves a dehydrative cyclization of **29** to the corresponding oxazoline **30** followed by an oxidation to oxazole **31** (Figure 3, path A).[13,18,19] Many methods for the oxazoline oxidation require a C_4-substituent (i.e. R_2) that is electron withdrawing.[18] Most notable is the $BrCCl_3$/DBU system, which takes advantage of an enolizable C_4-proton and is believed to proceed through a C_4-bromooxazole intermediate.[13] The cyclization-oxidation route was used by Leighton and coworkers for the synthesis of the leucascandrolide A side chain (Scheme 2). Several groups reported the synthesis of 2,4-disubstituted oxazoles by the oxidation of oxazolines that lack the C_4-electron withdrawing group and reagents used for this transformation include DDQ,[20,21] and chloranil.[22] Notably, McGarvey and coworkers reported the formation of a variety of 2,4-disubstituted oxazoles in excellent yields (85-95%) by heating a mixture of the oxazoline and DDQ at reflux in benzene for 30-60 min.[20]

An alternate pathway involves modifications of the Robinson-Gabriel synthesis (Figure 3, path B).[23] Oxidation to the formylamide **32** followed by cyclization affords oxazole **31**.[24,25] Importantly, these methods do not rely on the C_4-substituent to be electron withdrawing.

Figure 3. Synthesis of 2,4-disubstituted oxazoles from hydroxyamides.



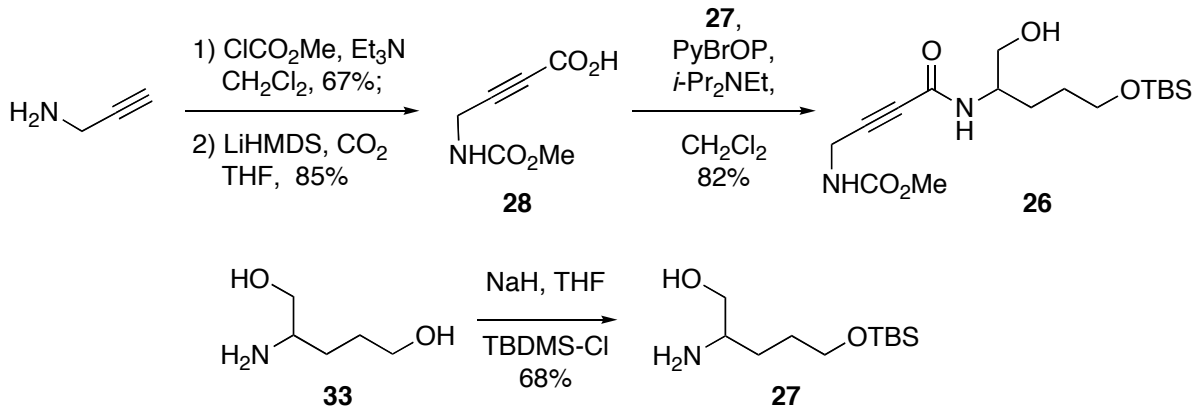
The hydroxyamide **26** for our synthesis of leucascandrolide A is derived from glutamic acid and therefore lacks the electron withdrawing substituent that is utilized for the facile oxidations of the oxazolines to the oxazoles ($BrCCl_3$/DBU and $CuBr_2$/DBU). Based on the available literature, DDQ could reasonably be expected to mediate the oxidation of the oxazoline to the oxazole (Figure 3, path A) while a modified Robinson-Gabriel synthesis was explored for the oxidation-cyclization sequence (Figure 3, path B).

1.2.2.1. Cyclization–Oxidation Approach to the Synthesis of the Oxazole

Hydroxyamide **26** was readily synthesized from fragments **27** and **28** (Scheme 6). *N*-Acylation of propargylamine with methylchloroformate followed by deprotonation with lithium hexamethyldisilazide and carboxylation of the anion with carbon dioxide

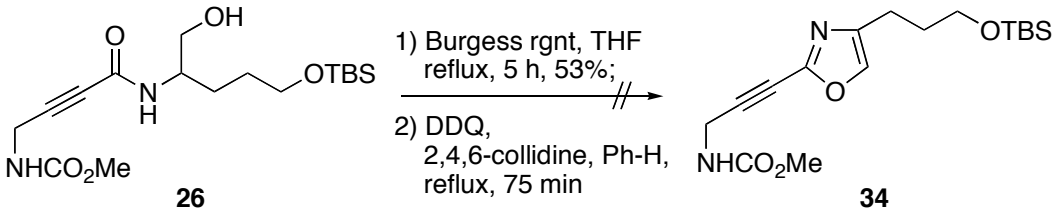
provided alkynoate **28** in 55% overall yield. The aminoalcohol **27** was obtained by selective protection of the known aminodiol **33**.[26] Condensation of acid **28** with amino alcohol **27** using PyBrOP[27] afforded hydroxyamide **26** in 82% yield.

Scheme 6. Synthesis of the hydroxyamide.



Attempts to cyclize **26** using Deoxofluor resulted in low yields of the oxazoline.[28] Cyclization of **26** using Burgess reagent[29,30] afforded the oxazoline in 53% yield. Attempts to oxidize the oxazoline to the oxazole with DDQ resulted in extensive decomposition and only traces of the oxazole **34**.

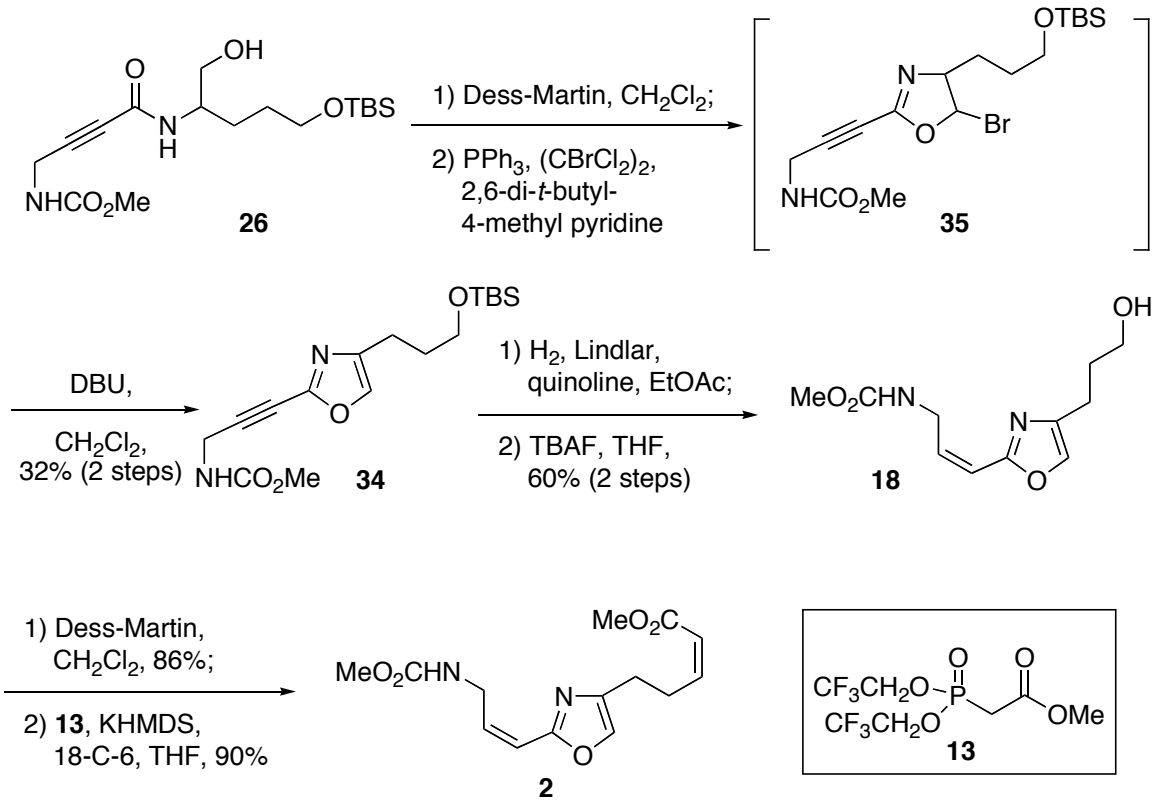
Scheme 7. Attempted synthesis of the oxazole by cyclization-oxidation.



1.2.2.2. Oxidation–Cyclization Approach to the Synthesis of the Oxazole

A second pathway involving the oxidation-cyclization pathway that ultimately proved more rewarding was explored concurrently with the previously discussed studies (Scheme 8). Oxidation of hydroxyamide **26** with Dess-Martin periodinane[17] afforded the formylamide that was subjected to the modified Robinson-Gabriel conditions.[24] Cyclodehydration with triphenylphosphine in the presence of 2,6-di-*t*-butyl-4-methylpyridine provided the intermediate bromooxazoline **35**, which readily eliminated hydrogen bromide upon treatment with DBU to give the oxazole **34** in 32% overall yield. The alkyne was then reduced to the (*Z*)-alkene using Lindlar conditions[31] and the primary alcohol was deprotected with TBAF in THF to afford **18** in 60% yield. The primary alcohol of **18** was oxidized with Dess-Martin periodinane[17] in 86% yield and the resulting aldehyde was condensed with the Still-Gennari reagent[15] to afford the methyl ester **2** in 90% yield. All spectroscopic data, in particular the ^{1}H and ^{13}C NMR resonances of **2**, were in close agreement with the corresponding shifts reported for the natural product.[1] The leucascandrolide A side chain **2** was completed in 9 steps and 7% overall yield.

Scheme 8. Completion of the leucascandrolide A side chain.



1.3. Summary and Conclusions

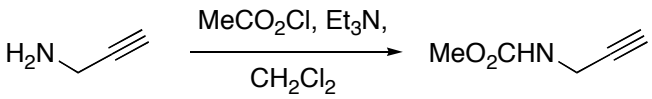
The $C_{1'}$-$C_{11'}$ side chain of leucascandrolide A was completed in 9 steps and 7% overall yield for the longest linear sequence. The key transformation was the preparation of the oxazole moiety by a mild process involving oxidation-cyclodehydration-dehydrohalogenation of the hydroxyamide **26**. The semi-hydrogenation of the alkyne moiety installed the *cis*-alkenyl oxazole derivative and a Still-Gennari olefination was used for the remaining *cis*-alkene.

1.4. Experimental Part

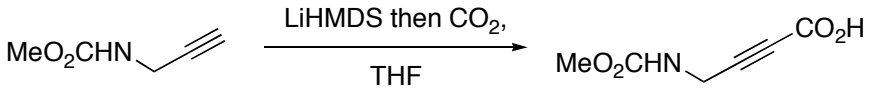
1.4.1. General

All moisture sensitive reactions were performed using syringe-septum techniques under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for more than 4 h prior to use. Reactions at -78 °C employed a solid CO_2-acetone bath. THF and ethyl ether were distilled from sodium/benzophenone ketyl. Methylene choride and toluene were filtered through activated alumina prior to use. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualized using a UV light (254 nm) or by staining with $KMnO_4$ or phosphomolybdic acid. Flash chromatography on SiO_2 was used to purify compounds unless otherwise stated. Concentration refers to removal of the solvent on a rotary evaporator at water aspirator pressure. Melting points are uncorrected. Infrared spectra were acquired using KBr pellets or thin films on NaCl plates (i.e. neat). Chemical shifts were reported in parts per million and the residual solvent peak was used as an internal reference. ^{1}H NMR spectra were acquired in $CDCl_3$ at a frequency of 300 MHz unless stated otherwise and are tabulated as follows: chemical shift (multiplicity, number of protons, coupling constants). ^{13}C NMR were acquired in $CDCl_3$ at a frequency of 75 MHz using a proton decoupled pulse sequence unless otherwise stated.

1.4.2. Experimental Procedures



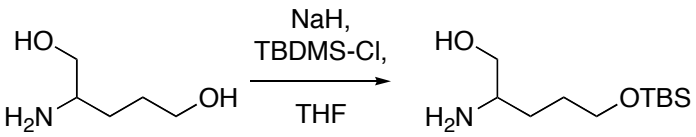
Prop-2-ynylcarbamic acid methyl ester. A solution of propargyl amine (1.0 g, 18 mmol) and triethylamine (3.5 mL, 25 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated dropwise with methyl chloroformate (1.50 mL, 19.5 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, and quenched with 6 N HCl (3 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated onto SiO_2. Purification by chromatography on SiO_2 (30% to 60% ethyl acetate/hexanes) afforded prop-2-ynyl-carbamic acid methyl ester (1.36 g, 67%) as a colorless oil: R_f 0.5 (40% ethyl acetate/hexanes); IR (neat) 3296, 2955, 2123, 1712, 1530, 1256 cm^{-1}; ^1H NMR δ 5.3-5.1 (b, 1 H), 3.92 (bs, 2 H), 3.64 (s, 3 H), 2.21 (s, 1 H); ^{13}C NMR δ 156.8, 80.0, 71.5, 52.5, 30.9; MS (EI) *m/z* (rel intensity) 113 (M^+, 49), 98 (100), 82 (18); HRMS *m/z* calcd for $C_5H_7N_1O_2$ 113.0477, found 113.0479.



28

4-Methoxycarbonylaminobut-2-ynoic acid (28). A solution of lithium hexamethyldisilazide (1.06 M, 11.5 mL, 12.2 mmol) in THF (120 mL) was cooled to –78 °C and treated dropwise with a solution of prop-2-ynyl-carbamic acid methyl ester (649 mg, 5.74 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at –78 °C.

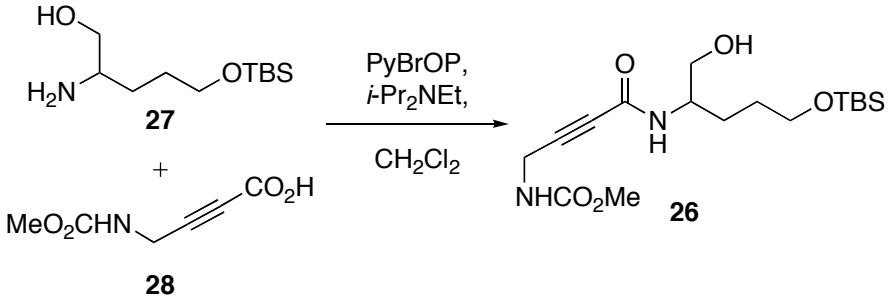
Subsequently, carbon dioxide (from dry ice) was bubbled through the solution for 2 h. The reaction mixture was quenched at –78 °C by aqueous, saturated $NaHCO_3$ (5 mL). After warming to room temperature, the solution was acidified with 6 N HCl and extracted with ethyl acetate. The combined organic layers were concentrated and the residue was dissolved in aqueous $NaHCO_3$ and washed with CH_2Cl_2. The aqueous layer was acidified by slow addition of concentrated HCl and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to yield of **28** (770 mg, 85%) as a slightly yellow oil that crystallized to a white solid upon standing: R_f 0.4 (40% ethyl acetate, 1% TFA/hexanes); Mp 95–96 °C; IR (neat): 3337, 2959, 2244, 1708, 1532, 1255 cm^{-1}; ^1H NMR (CD_3OD) δ 4.04 (s, 2 H), 3.68 (s, 3 H); ^{13}C NMR (CD_3OD) δ 159.3, 156.1, 85.2, 75.8, 53.0, 31.2; MS (EI) *m/z* (rel intensity) 157 (M^+, 54), 139 (38), 113 (7), 98 (100), 82 (15), 81(15), 59 (20); HRMS *m/z* calcd for $C_6H_7N_1O_4$ 157.0375, found 157.0380.



33 **27**

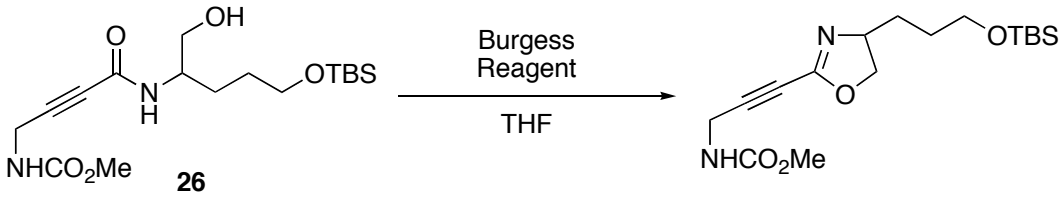
2-Amino-5-(*tert*-butyldimethylsilyloxy)-pentan-1-ol (27). To a suspension of freshly washed (hexanes) sodium hydride (60% dispersion in mineral oil, 41 mg, 1.03 mmol) in THF (40 mL) was added a solution of 2-amino-1,5-pentanediol (122 mg, 1.03 mmol) in hot THF (10 mL). The reaction mixture was stirred for 8 h at room temperature and then treated dropwise with *tert*-butyldimethylsilyl chloride (1 M in THF, 1 mL, 1 mmol). After 20 min, the reaction mixture was evaporated onto SiO_2 and chromatography on SiO_2 (5% to 10% MeOH/CH_2Cl_2 to 10% MeOH, 1%

NH_4OH/CH_2Cl_2) afforded **27** (160 mg, 68%) as a pale yellow oil: R_f 0.3-0.4 (10% $MeOH/CH_2Cl_2$, 3-fold developed); IR (neat) 3345, 2929, 2858, 1635, 1521, 1471, 1388, 1361, 1255, 1098, 836, 776 cm^{-1}; ^1H NMR δ 4.05-3.95 (b, 4 H), 3.69 (t, 1 H, *J* = 9.4 Hz), 3.63 (t, 3 H, *J* = 5.7 Hz), 3.45 (t, 1 H, *J* = 9.4 Hz), 3.07 (bs, 1 H), 1.65-1.49 (m, 4 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 65.0, 63.1, 53.4, 29.3, 26.2, 18.6, -5.1; MS (EI) *m/z* (rel intensity) 202 ($[M-CH_2OH]^+$, 27), 176 (4), 159 (34), 141 (10), 129 (7), 101(12), 84 (47), 75 (84), 70 (100), 56 (20); HRMS *m/z* calcd for $C_{10}H_{24}NOSi$ (M-CH_2OH) 202.1627, found 202.1629.

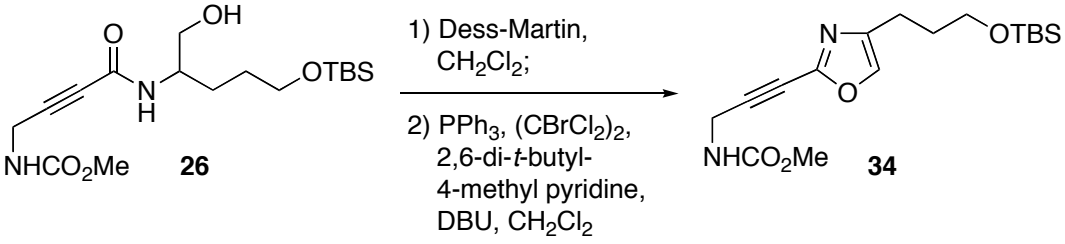


{3-[4-(*tert*-Butyldimethylsilyloxy)-1-hydroxymethylbutylcarbamoyl]-prop-2-ynyl}-carbamic acid methyl ester (26). To a solution of **27** (149 mg, 0.639 mmol) and **28** (84 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) was added diisopropylamine (186 µL, 1.07 mmol). The reaction mixture was cooled to –10 °C, treated with PyBrOP (350 mg, 0.751 mmol) and allowed to warm to room temperature. After 6 h, the reaction was quenched with aqueous $NaHCO_3$. The organic layer was diluted with CH_2Cl_2 (8 mL), sequentially washed with 0.1 N HCl, water and brine, and dried (Na_2SO_4). The solvent was removed under vacuum to yield an orange viscous oil. Purification by chromatography on SiO_2 (ethyl acetate) afforded **26** (163 mg, 82%) as a slightly yellow

oil: R_f 0.5 (ethyl acetate). This compound proved to be unstable and was therefore used immediately after preparation.

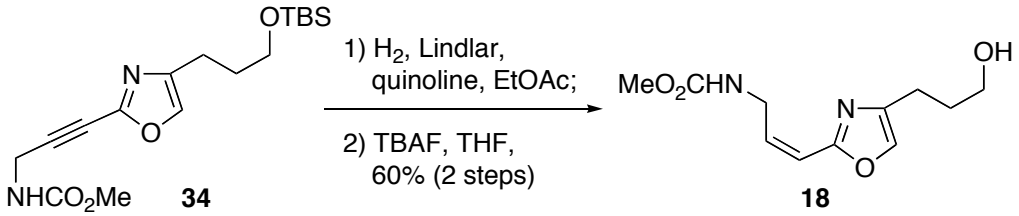


Methyl 3-(4-(3-(*tert*-butyldimethylsilyloxy)propyl)-4,5-dihydrooxazol-2-yl)prop-2-ynylcarbamate. A solution of **26** (56.0 mg, 0.150 mmol, 1.0 equiv) in THF (5 mL) was treated with Burgess reagent (44.0 mg, 0.190 mmol, 1.3 equiv), refluxed for 5 h, cooled to rt and concentrated. Purification of the residue by chromatography on SiO_2 (5% to 10% MeOH/CH_2Cl_2) afforded methyl 3-(4-(3-(*tert*-butyldimethylsilyloxy)propyl)-4,5-dihydrooxazol-2-yl)prop-2-ynylcarbamate (28.0 mg, 53%) as a clear, yellow oil that was used without further purification. ^{1}H NMR δ 4.95 (bs, 1 H), 4.37 (dd, 1 H, J = 9.6, 8.8 Hz), 4.21-4.13 (m, 3 H), 3.90 (app t, 1 H, J = 8.1 Hz), 3.69-3.59 (m, 2 H), 1.69-1.53 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).



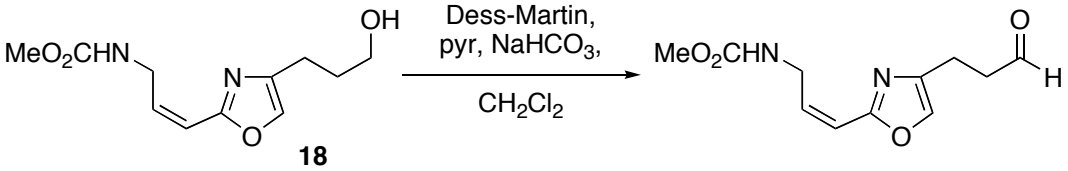
(3-{4-[3-(*tert*-Butyldimethylsilyloxy)-propyl]-oxazol-2-yl}-prop-2-ynyl)-carbamic acid methyl ester (34). To a solution of **26** (75 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (171 mg, 0.404 mmol). The reaction mixture was stirred for 1 h and purified by chromatography on SiO_2 (60% ethyl acetate/hexanes). The resulting clear oil was immediately dissolved in CH_2Cl_2 (10 mL)

and treated with triphenylphosphine (165 mg, 0.629 mmol), 2,6-di-tert-butyl-4-methylpyridine (332 mg, 1.617 mmol) and 1,2-dibromo-1,1,2,2-tetrachloroethane (204 mg, 0.626 mmol). The reaction mixture was stirred for 10 h, treated with DBU (266 µL, 1.78 mmol) and stirred for an additional 6 h. Purification by chromatography on SiO_2 (30% ethyl acetate/hexanes) afforded **34** (23 mg, 32%) as a slightly yellow oil: R_f 0.5 (40% ethyl acetate/hexanes); IR (neat) 2954, 2929, 2857, 2250, 1729, 1587, 1534, 1472, 1255, 1102, 837, 777 cm^{-1}; ^1H NMR δ 7.33 (s, 1 H), 5.11 (bs, 1 H), 4.22 (d, 2 H, *J* = 5.5 Hz), 3.70 (bs, 3 H), 3.62 (t, 2 H, *J* = 6.1 Hz), 2.57 (t, 2 H, *J* = 7.6 Hz), 1.82 (tt, 2 H, *J* = 7.2, 6.6 Hz), 0.87 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR δ 156.7, 145.8, 142.1, 135.4, 87.9, 71.7, 62.2, 52.8, 31.5, 31.3, 26.1, 22.7, 18.5, -5.1; MS (EI) *m/z* (rel intensity) 337 ([M-CH_3]$^+$, 68), 295 (100), 263 (45), 238 (31), 98 (14), 89 (11), 75 (19), 73 (15), 59 (12); HRMS *m/z* calcd for $C_{13}H_{19}N_2O_4Si$ (M-C(CH_3)$_3$) 295.1114, found 295.1116.



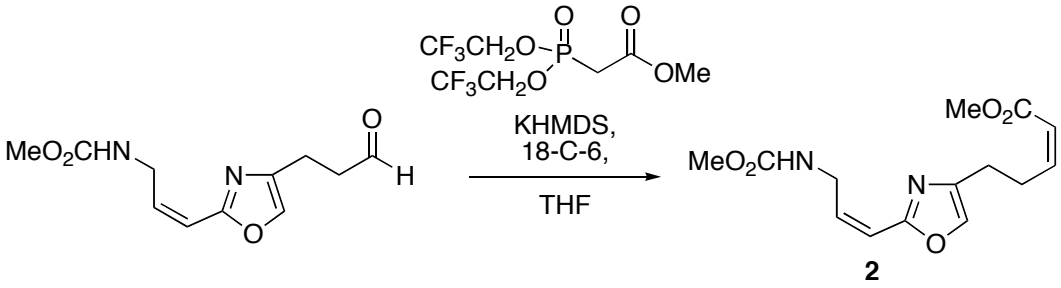
{3-[4-(3-Hydroxypropyl)oxazol-2-yl]-allyl}-carbamic acid methyl ester (18). To a solution of **34** (90 mg, 0.26 mmol) in ethyl acetate (30 mL) was added quinoline (50 µL, 0.42 mmol) and Lindlar catalyst (90 mg). The reaction mixture was stirred for 3 h at room temperature under hydrogen (1 atm) and filtered through Celite and the resulting yellow-orange residue was dissolved in THF (20 mL). Tetra-*n*-butyl-ammonium fluoride (150 mg, 0.57 mmol) was added and the reaction mixture was stirred at room temperature for 14 h. The solvent was removed under vacuum and

purification of the the resulting red, oily residue by chromatography on SiO_2 (ethyl acetate) afforded **18** (36.4 mg, 60%) as a slightly yellow oil: R_f 0.2 (ethyl acetate); ^{1}H NMR δ 7.37 (s, 1 H), 6.29 (d, 1 H, *J* = 11.8 Hz), 6.08 (dt, 1 H, *J* = 11.7, 6.4 Hz), 5.50 (bs, 1 H), 4.35-4.25 (m, 2 H), 3.72 (t, 2 H, *J* = 6.1 Hz), 3.68 (s, 3 H), 2.66 (t, 2 H, *J* = 7.1 Hz), 2.25 (bs, 1 H), 1.90 (tt, 2 H, *J* = 6.8, 6.4 Hz); ^{13}C NMR δ 160.2, 157.4, 141.7, 136.7, 134.0, 116.7, 62.3, 52.4, 39.7, 31.4, 23.0; IR (neat) 3327, 2925, 2851, 1704, 1523, 1264, 1055 cm^{-1}; MS (EI) *m/z* (rel intensity) 240 (M^+, 100), 222 (7), 208 (40), 195 (29), 181 (23), 163 (25), 151 (29), 136 (31), 47 (125), 81 (57), 66 (45), 54 (33); HRMS *m/z* calcd for $C_{11}H_{16}N_2O_4$ 240.1110, found 240.1119.



{3-[4-(3-Oxopropyl)-oxazol-2-yl]-allyl}-carbamic acid methyl ester. To a mixture of **18** (46.3 mg mg, 0.193 mmol, 1.0 equiv), $NaHCO_3$ (50.0 mg, 0.595 mmol, 3.1 equiv) and pyridine (3 drops) in CH_2Cl_2 (2.5 mL) at rt was added Dess-Martin periodinane (246.0 mg, 0.580 mmol, 3.0 equiv). The reaction mixture was stirred for 1.5 h at rt, treated with 10% aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), diluted with CH_2Cl_2 (5 mL), stirred until both phases were clear (ca. 30 min) and then extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid and brine and the combined aqueous washings were backwashed with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to a yellow oil. Purification by chromatography on SiO_2 (80% ethyl acetate/hexanes) afforded {3-[4-(3-oxo-propyl)-oxazol-2-yl]-allyl}-carbamic acid methyl

ester (39.4 mg, 86%) as a clear, colorless oil that was used in the next step without further purification: R_f 0.43, (80% ethyl acetate/hexanes); ^{1}H NMR δ 9.84 (s, 1 H), 7.34 (s, 1 H), 6.27 (d, 1 H, *J* = 11.8 Hz), 6.09 (dt, 1 H, *J* = 12.0, 6.4 Hz), 5.51 (bs, 1 H), 4.30 (t, 2 H, *J* = 6.0 Hz), 3.68 (s, 3 H), 2.90-2.79 (m, 4 H).



5-[2-(3-Methoxycarbonylaminopropenyl)-oxazol-4-yl]-pent-2-enoic acid methyl ester (2). A solution of 18-crown-6 (171.0 mg, 0.647 mmol, 5.7 equiv) and bis-(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphonate (45.0 µL, 0.213 mmol, 1.9 equiv) in THF (1.5 mL) was cooled to –78 °C and treated with a solution of potassium hexamethyldisilazide (28.5 mg, 0.149 mmol, 1.3 equiv) in THF (0.57 mL) over 5 min. The reaction mixture was stirred for an additional 10 min and then a solution of {3-[4-(3-oxopropyl)-oxazol-2-yl]-allyl}-carbamic acid methyl ester (27.0 mg, 0.113 mmol, 1.0 equiv) in THF (2 mL + 2 mL rinse) was added dropwise with stirring. After 5 h at –78 °C, the mixture was quenched with saturated aqueous NH_4Cl (3.0 mL). Upon warming to room temperature, the mixture was diluted with water and extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to a clear, colorless syrup. Purification by chromatography on SiO_2 (20% ethyl acetate/CH_2Cl_2) afforded **2** (30.0 mg, 90%) as a clear, colorless wax: R_f 0.4 (20% ethyl acetate/CH_2Cl_2); IR (neat) 3348, 3136, 2993, 2951, 2923, 2852, 1721, 1521, 1252, 1198,

1003 cm^{-1}; ^1H NMR δ 7.37 (s, 1 H); 6.23-6.31 (m, 2 H), 6.10 (dt, 1 H, *J* = 11.6, 6.4 Hz), 5.82 (dt, 1 H, *J* = 11.5, 1.6 Hz), 5.57 (bs, 1 H), 4.35-4.25 (m, 2 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.01 (ddt, 2 H, *J* = 1.5, 7.3, 7.3 Hz), 2.70 (t, 2 H, *J* = 7.2 Hz); ^1H NMR (C_5D_5N) δ 8.44 (bs, 1 H), 7.61 (s, 1 H); 6.38 (d, 1 H, *J* = 11.9 Hz), 6.32-6.22 (m, 2 H), 5.92 (d, 1 H, *J* = 11.5 Hz), 4.80 (bt, 2 H, *J* = 5.4 Hz), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.14 (dt, 2 H, *J* = 7.3, 7.3 Hz), 2.69 (t, 2 H, *J* = 7.4 Hz); ^{13}C NMR δ 166.9, 160.2, 157.4, 149.1, 141.4, 136.4, 134.1, 120.4, 116.9, 52.4, 51.3, 39.5, 27.7, 25.8; ^{13}C NMR (C_5D_5N) δ 166.6, 160.5, 158.1, 141.7, 138.6, 134.5, 120.4, 115.5, 51.9, 51.0, 40.8, 28.0, 25.9; MS (EI) *m/z* (rel intensity) 294 (M^+, 100), 263 (28), 233 (63), 206 (40), 195 (48), 160 (31), 114 (41), 91 (41); HRMS *m/z* calcd for $C_{14}H_{18}N_2O_5$ 294.1216, found 294.1220.

2. Conjugate Additions to 2-Alkynyl Oxazoles and Oxazolines

2.1. Conjugate Additions Under Basic Conditions

2.1.1. Introduction

Oxazoles and oxazolines that are substituted at the 2- and the 4- positions are a common structural component found in numerous biologically active natural products.[11,32] A subset of the 2,4-oxazole class are those containing a substituent at the 2-position where the β-carbon is at the alcohol or ketone oxidation state (i.e. **36**, Figure 4). Examples include the phorboxazoles,[33] disorazoles[34] and the streptogramin-group A antibiotics (Virginiamycin,[35] Madumycin II[36] and Griseoviridin[37]).

The most developed route to access the motif **36** is the condensation of an aldehyde with a 2-methyl oxazole anion (Figure 5, path A). Numerous metals including lithium diethylamide,[38] zinc,[39] chromium,[40] samarium diiodide[41] and sodium[42] have been employed for this transformation. A less explored disconnection is at the C_β/C_γ bond, which requires the coupling of the C_2-β-aldehyde with a suitable nucleophile (Figure 5, path B). The required aldehyde was envisioned to arise from a 2-ethynyl oxazole (Figure 5, path C). Alternatively, an internal alkyne could be converted to a C_2-β-ketone (Figure 5, path D).

Figure 4. Natural products that contain 2,4-disubstituted oxazoles.

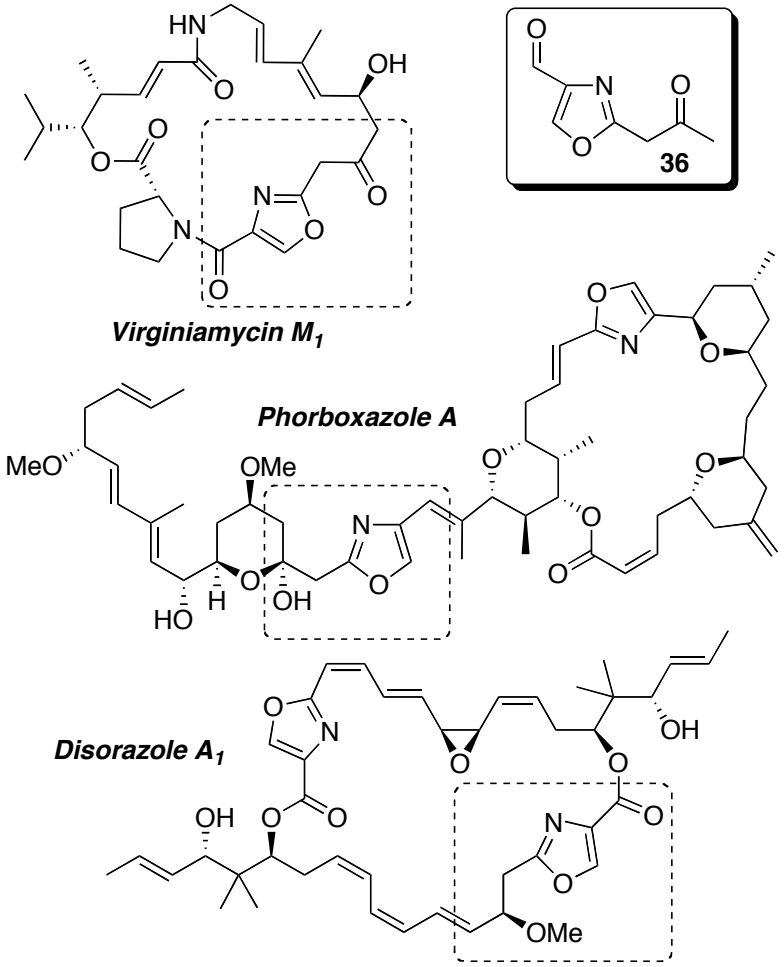
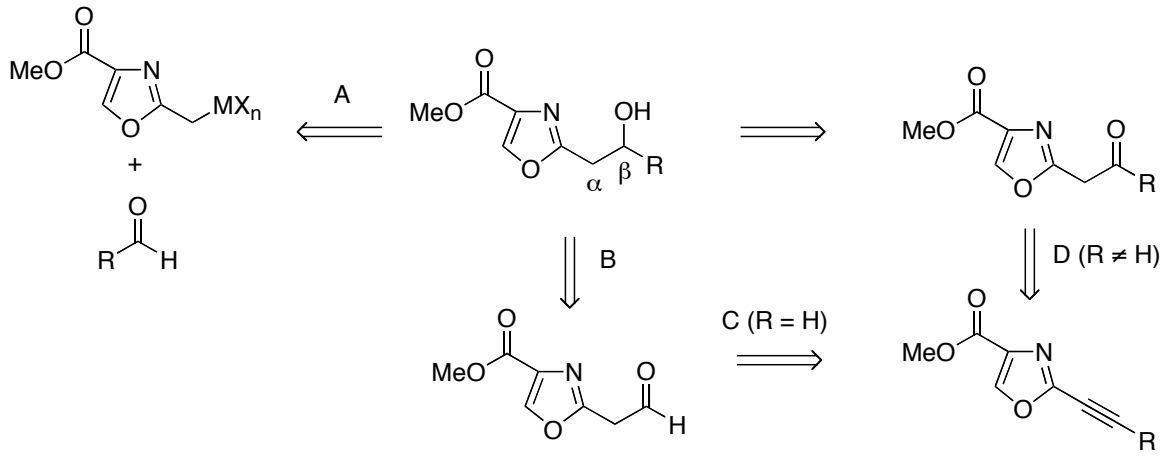


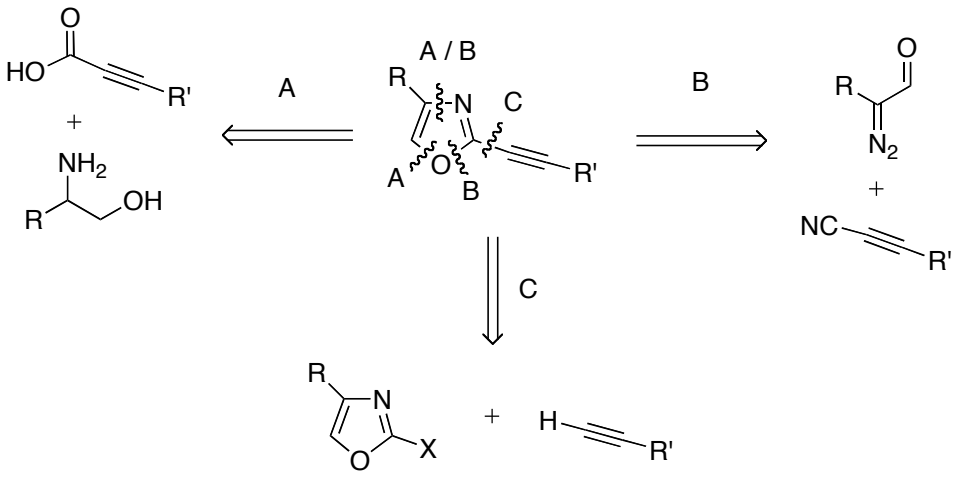
Figure 5. Routes to accessing C_2-β-oxygen substituted oxazoles.



Oxazoles containing a 2-alkynyl substituent are a relatively new structural class that has recently become commonly reported in the chemical literature. Many of the methods for the synthesis of 2-alkynyl oxazoles were developed for the leucascandrolide A side chain (Section 1.1.2). As a result, several synthetic routes to access 2-alkynyl oxazoles are described in the literature (Figure 6). For example, an appropriately functionalized aminoalcohol can be coupled to the alkynoic acid and subsequently cyclized and oxidized to afford the oxazole (Figure 6, path A).[19] Hydroxyamide **26** was oxidized and cyclized using Wipf's modification of the Robinson-Gabriel cyclization (Section 1.2.2.2, Scheme 8).[10] Leighton's route to the leucascandrolide A side chain also utilized a cyclization-oxidation route (Section 1.1.2, Scheme 2).[18] A second method involves the condensation of an α-diazoketone with a nitrile to give the oxazole (Figure 6, path B).[14] Kozmin and coworkers demonstrated the rhodium carbenoid-mediated formation of 2-alkynyl oxazole from alkynyl nitrile and 2-

diazodimethylmalonate in their synthesis of the leucascandrolide A side chain (Section 1.1.2, Scheme 3).[4] In a third method, a 2-trifluoromethylsulfonyl ester substituted oxazole is cross-coupled with a terminal alkyne (Figure 6, path C).[12] Panek and coworkers demonstrated a cross-coupling under Sonogashira conditions to afford 2-alkynyl oxazoles. (Section 1.1.2, Scheme 4).[12]

Figure 6. Common disconnections for the synthesis of 2-alkynyl oxazoles.



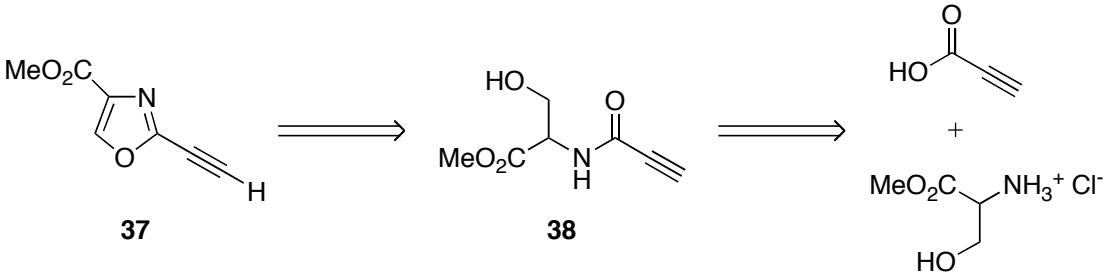
The first method (Figure 6, path A) was chosen to extend the scope of the diethylaminosulfur trifluoride (DAST) mediated cyclization and $BrCCl_3$/DBU oxidation methodology.[13] The advantages of the cyclization-oxidation approach are that the required amino alcohols are commercially available, alkynes can be readily carboxylated to give the alkynoic acids and expensive and potentially toxic transition metal catalysts are not required.

As part of a program directed towards the synthesis of natural products containing oxazoles, the conversion of 2-alkynyl oxazoles into C_2-β-heteroatom-substituted oxazoles was investigated.[43] The conjugate addition of nucleophiles into 2-alkynyl oxazoles serves as a novel strategy for constructing C_2-β-heteroatom substituted oxazoles. Similar conjugate additions can be conducted on oxazolines and some evidence for a metal binding motif is presented.

2.1.2. Synthesis and Conjugate Addition Reactions of a 2-Ethynyl Oxazole.

2-Ethynyloxazole-4-carboxylic acid methyl ester (**37**) was selected for the model studies (Figure 5, path C). The 2-ethynyl oxazole **37** would arise via cyclization and oxidation of hydroxyamide **38**, which in turn would arise from the coupling of propiolic acid and serine methyl ester hydrochloride (Figure 7).

Figure 7. Retrosynthesis of 2-ethynyloxazole-4-carboxylic acid methyl ester.

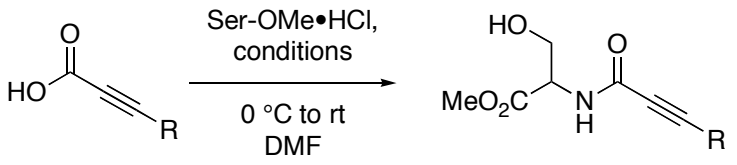


37 **38**

Attempts to couple propiolic acid to serine methyl ester resulted in decomposition.[44] The terminal alkyne was suspected to be the problematic functionality, so several alkyne protecting groups were explored (Table 1).[45]

Condensation of the commercially available 3-trimethysilyl propiolic acid (**39a**) with serine methyl ester hydrochloride using EDCI and HOBT afforded a low yield of the hydroxyamide **40a** (entry 1).[46] Further experimentation with more sterically hindered protecting groups identified PyBOP[47] to be a superior coupling reagent. The TES-protected alkyne **39b** afforded the hydroxyamide **40b** in 70% yield (entry 2).[48] The TBS-protected propiolic acid **39c** afforded the hydroxyamide **40c** in 83% yield (entry 3). Finally, the TIPS-protected propiolic acid **39d** was coupled to serine methyl ester hydrochloride using PyBOP in the presence of diisopropylethylamine and gave the corresponding hydroxyamide **40d** in quantitative yield (entry 4). For large scale preparations, a more cost-effective strategy involved converting **39d** to the triisopropylsilylpropynoyl chloride using oxalyl chloride and catalytic dimethylformamide.[49] The crude acid chloride was then coupled to serine methyl ester hydrochloride in the presence of diisopropylethylamine and afforded the hydroxyamide **40d** in 82% yield on a 22 mmol (5 g) scale (entry 5).

Table 1. Coupling propiolic acid derivatives to serine methyl ester.



39a-d **40a-d**

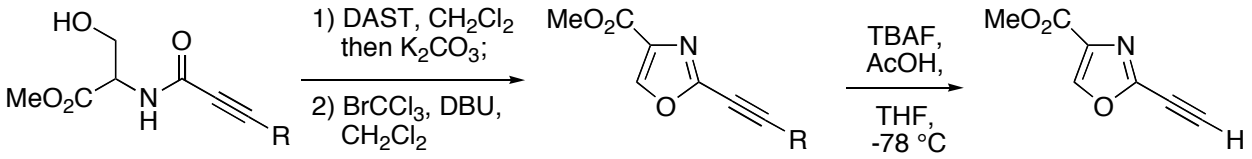
Entry	Acid	R	Conditions	Yield of **40** (%)
1	**39a**	TMS	EDCI, HOBT, DIEA	22
2	**39b**	TES	PyBOP, DIEA	70
3	**39c**	TBS	PyBOP, DIEA	83
4	**39d**	TIPS	PyBOP, DIEA	100
5	**39d**	TIPS	oxalyl chloride, DMF[a]	82

[a] The acid choride was preformed and the crude material was used in the coupling with CH_2Cl_2 as a cosolvent.

The hydroxyamides **40a-d** were then subjected to the cyclization using diethylaminosulfur trifluoride (DAST). Both the TMS- and the TES-protected hydroxyamides **40a** and **40b** afforded low yields (< 60%) of the oxazolines that were mixtures of the trialkylsilyl-protected alkyne and the terminal alkyne. The TBS and TIPS-protected alkynes **40c** and **40d** proved to be more robust, and rapidly cyclized to give the crude oxazolines which were oxidized with $BrCCl_3$ and DBU to furnish the oxazoles **41c** and **41d** in 76% and 74% yield, respectively, for the two steps (Scheme 9). Removal of the triisopropylsilyl group from **41d** with TBAF at ambient temperature gave **37** in low yield. Conducting the reaction at –78 °C afforded **37** in 99% yield.[50] Similarly, the TBS-protected alkyne **41c** afforded **37** in 96% yield. The 2-ethynyl oxazole **37** is a crystalline solid that can be stored for months at ambient temperature

with no special precautions.[51] In general, the TBS-protected alkyne gave similar results to the TIPS protecting group while the only additional advantage of the TBS is that hydroxyamide **40c** and oxazole **41c** proved to be crystalline solids rather than oils.

Scheme 9. Synthesis of the 2-ethynyl oxazole.



40c, R = TBS
40d, R = TIPS

41c, R = TBS, 74% (2 steps)
41d, R = TIPS, 76% (2 steps)

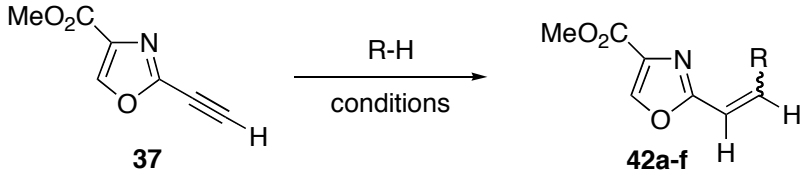
37
R = TBS, 99%
R = TIPS, 96%

The ease of the TBAF deprotection of **41c/d** and the ^{1}H NMR data of **37** which indicated the alkyne proton resonates at 3.29 ppm, suggest that the alkyne is significantly polarized. The alkyne **37** should therefore readily participate in conjugate addition reactions. Indeed, a variety of nucleophiles could be added to the alkyne in a conjugate fashion (Table 2). Both ethanethiol and thiophenol added in moderate to good yield to afford **42a** and **42b**, respectively, and with good (*Z*)-selectivity (Table 2, entries 1-3).[52] 2-Mercaptoethanol afforded only the thioenolether **42c** and did not give the thioxolane even after extended reaction time (Table 2, entry 4). Benzyl alcohol furnished adduct **42d** with good (*Z*)-selectivity, demonstrating access to enol ethers (Table 1, entry 5).[53] Interestingly, secondary amines produced adducts **42e** and **42f** with the (*E*)-configuration in excellent yields (Table 2, entry 6-7).[54] The predominant (*E*)-configuration of the enamine adducts is probably due to the reaction conditions

allowing for equilibration to the thermodynamically more stable product as well as an avoidance of the excessive strain that would exist in the (*Z*)-configuration.

To gain access to the required C_2-β-aldehyde, the deprotection of the derivatives in Table 2 under a variety of standard conditions for the hydrolysis of enol ethers, thioenol ethers and enamines was attempted, but resulted only in decomposition. Removing the conjugation with the oxazole ring was examined (Scheme 10). The addition of ethanedithiol to **37** resulted in bis-addition, giving the 1,3-dithiolane (**43**).[52] Attempts to form the corresponding 1,3-dithiane by using 1,3-propanedithiol under similar conditions resulted in an inseparable mixture of mono- and bis-addition adducts in low yield.

Table 2. Conjugate addition of nucleophiles to a 2-ethynyl oxazole.

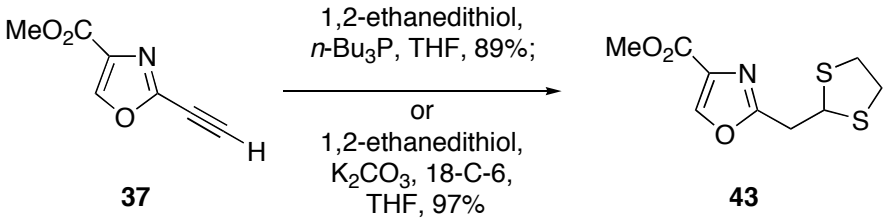


37 **42a-f**

Entry	R-H	Additive	Time (h)[a]	Product	(*Z*/*E*)-ratio	Yield (%)[d]
1	EtSH	*n*-Bu_3P	36	**42a**	10.5/ 1.0	70
2	EtSH	K_2CO_3/18-C-6	1.5	**42a**	16.4/ 1.0	89
3	PhSH	NMM	48	**42b**	1/ 0	97[e]
4	$HOCH_2CH_2SH$	*n*-Bu_3P	25[b]	**42c**	6.4/ 1.0	68[f]
5	$PhCH_2OH$	*n*-Bu_3P	0.5	**42d**	6.4/ 1.0	76
6	Et_2NH	-	20[c]	**42e**	0/ 1	100
7	(*i*-Pr)$_2$NH	-	72	**42f**	0/ 1	100

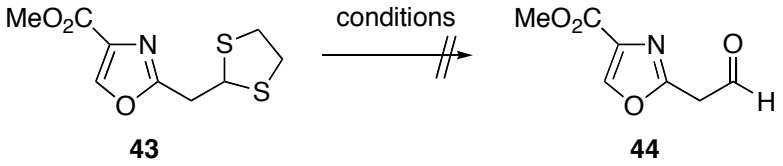
[a] All reactions were conducted at ambient temperture unless noted otherwise. [b] Reaction mixture heated to 66 °C. [c] Reaction mixture heated to 60 °C. [d] Yields were determined after purification on SiO_2 and refer to the major isomer, unless stated otherwise. [e] Purification by recrystallization. [f] Yield is for the (*Z*/*E*)-mixture.

Scheme 10. Conjugate addition of ethanedithiol.



Attempts to deprotect dithiolane **43** using Select-Fluor,[55] PIFA[56] or *N*-bromosuccinimide[57] resulted in decomposition (Table 3). The use of $HgCl_2$/HgO,[58] MeI/$CaCO_3$ [59] or TBHP [60] resulted in recovered dithiolane.

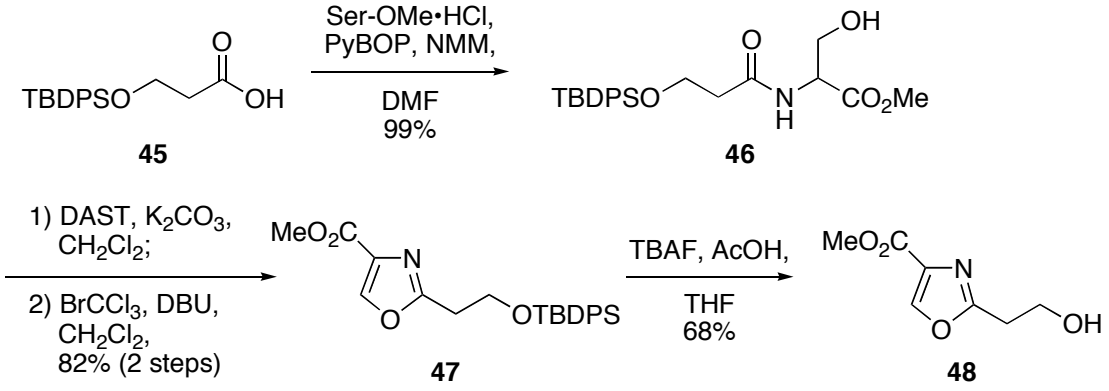
Table 3. Attempted conversion of the dithiolane to the aldehyde.



Entry	Conditions	Result
1	Select-Fluor (2.4 equiv), CH_3CN, rt	decomp.
2	$PhI(OCOCF_3)_2$ (1.5 equiv), 10% aq. MeOH, rt	decomp.
3	*N*-bromosuccinimide, 10% aq. acetone, 0 °C, 10 min	decomp.
4	$HgCl_2$ (2.2 equiv), HgO (2.2 equiv), 10% aq. MeOH, reflux, 6 h	s.m.
5	MeI (2.0 equiv), $CaCO_3$ (5.0 equiv), 10% aq. CH_3CN, 50 °C, 18 h	s.m.
6	70% aq. TBHP (6.0 equiv.), MeOH, reflux, 6 h	s.m.

We speculated that aldehyde **44** was unstable to standard manipulations.[61] To gain insight into the properties of **44**, the corresponding alcohol **48** was synthesized (Scheme 11). The known acid **45**[62] was coupled with serine methyl ester hydrochloride to afford the hydroxyamide **46** in 99% yield. Hydroxyamide **46** was cyclized and oxidized to afford the oxazole **47** in 82% yield for the 2 steps. The TBDPS group was removed with TBAF in THF to afford alcohol **48** in 68% yield.

Scheme 11. Synthesis of the C_2-β-hydroxy substituted oxazole.

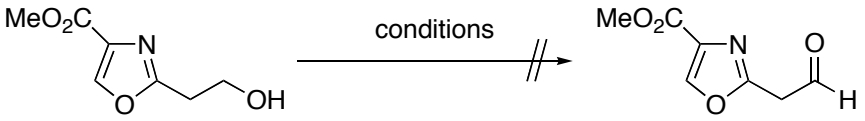


Attempts to oxidize the primary alcohol **48** using Swern (oxalyl chloride, DMSO, Et_3N)[63,64] Dess-Martin periodinane[17] (with and without the $NaHCO_3$ buffer) or TPAP/NMO[65] conditions resulted in decomposition (Table 4). Oxidation with the NaOCl/TEMPO/KBr system[66] did not afford the desired aldehyde, but led to an unidentified product.

The ability of the C_4-methyl ester group to remove electron density from the oxazole ring of **48** was considered as a possible reason for the instability of the

aldehyde product. The reduced electron density in the oxazole could facilitate enolization of the C_2-β-aldehyde, and allow for decomposition to occur. Reduction of the ester to the alcohol would change the electronic nature of the compound and might provide a more stable molecule. Reduction of **47** with diisobutylaluminum hydride and protection of the alcohol as the pivaloate followed by removal of the TBDPS group afforded alcohol **49** in 75% over three steps (Scheme 12). Unfortunately, attempts to oxidize **49** with Dess-Martin periodinane[17] under both buffered ($NaHCO_3$) and non-buffered conditions resulted in decomposition.

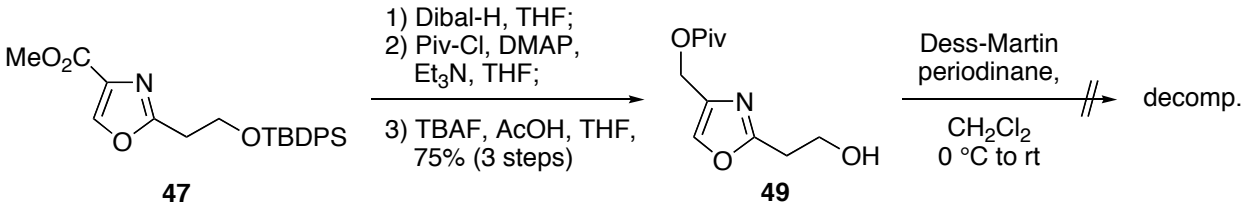
Table 4. Attempts to oxidize the C_2-β-alcohol to the C_2-β-aldehyde.



48 **44**

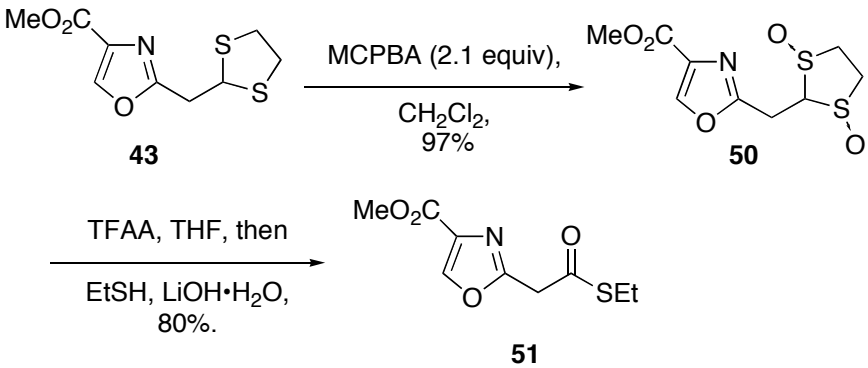
Entry	Conditions	Result
1	Oxalyl chloride, DMSO, CH_2Cl_2, -78 °C, 40 min; then Et_3N, -78 °C, 40 min	decomp.
2	Dess-Martin periodinane, CH_2Cl_2, rt	decomp.
3	Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt	decomp.
4	TPAP/NMO, 4 Å MS, CH_2Cl_2, rt	decomp.
5	NaOCl, TEMPO, KBr, aq. carbonate buffer (pH 8.6), CH_2Cl_2, 0 °C to rt, 2 h	unidentified product

Scheme 12. Reduction of the C_4-methyl ester.



A Fukuyama reduction[67] of the corresponding thioethylester was considered as a mild method to access the aldehyde. A variation of a transformation developed by Aggarwal and coworkers was employed to access the thioester from dithiolane **43**.[68] In this transformation, a 1,3-dithiolanedioxide was rearranged under Pummerer conditions and quenched with ethanethiol to give the thioethylester (Scheme 13).

Scheme 13. Rearrangement of the 1,3-dithiolanedioxide.

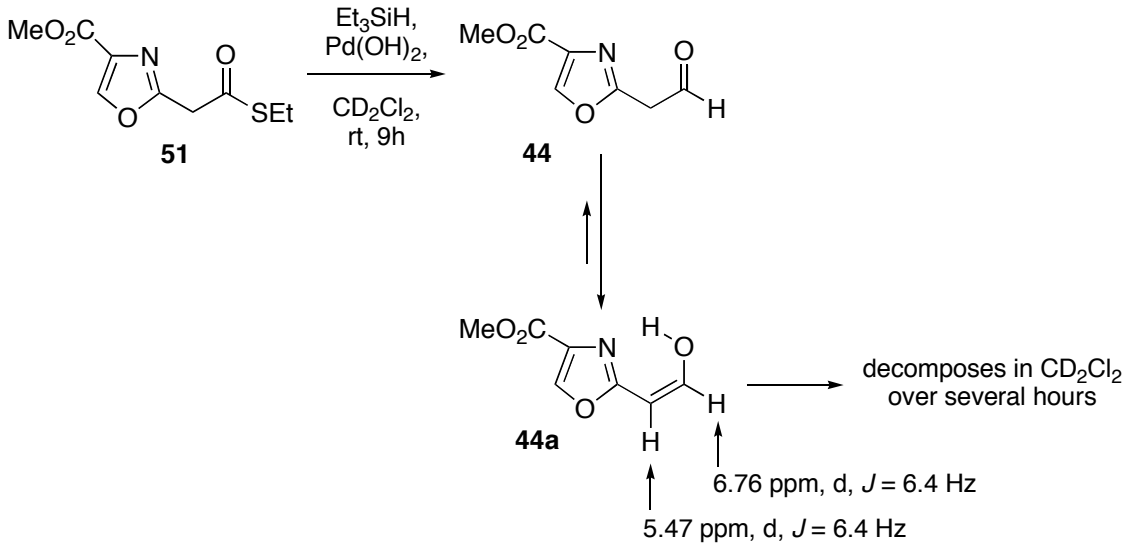


Oxidation of **43** under Trost's conditions[69] gave the 1,3-dithiolane dioxide **50** in 97% yield. The hydrophilic nature of **50** required an anhydrous work-up that involved

evaporating the reaction mixture onto a mixture of Florisil/Celite. The crude product was directly subjected to chromatography on silica gel. The 1,3-dithiolane dioxide **50** was subjected to the Pummerer rearrangement and ethanethiol trapping to give thioethylester **51** in 80% yield.

Reduction of **51** with $Pd(OH)_2$[70] in dichloromethane gave a new compound by TLC analysis, however, all attempts to isolate this compound failed. The experiment was repeated in dichlorodideuteromethane and the crude reaction mixture was filtered and analyzed by ^1H NMR, which revealed no aldehyde signal (Scheme 14). Instead, a pair of doublets was observed at 6.76 and 5.47 ppm with a 6.4 Hz coupling constant. The ^1H NMR data suggest that compound **44** exists exclusively in the tautomeric form **44a**, which may be stabilized by hydrogen bonding to the oxazole nitrogen.[71] The compound decomposed in CD_2Cl_2 at room temperature over several hours into multiple, unidentified compounds. With the experimental evidence suggesting that **44** represented a synthetically challenging intermediate, the focus was shifted to internal alkynes.[72]

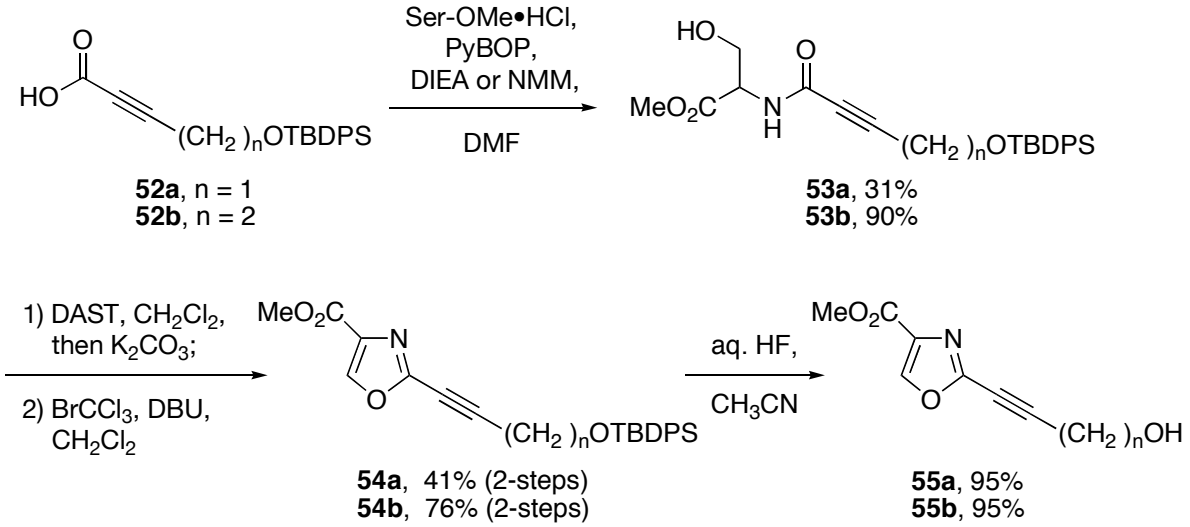
Scheme 14. Fukuyama reduction of the thioester.



2.1.3. Conjugate Additions to Internal Alkynes

Recognizing the limitations of a C_2-β-aldehyde functionality, the potential to access C_2-β-ketones in a similar manner from conjugate additions to internal alkynes was explored. Two systems were chosen as model compounds to give a 4-hydroxy-1-butynyl and a 3-hydroxy-1-propynyl substituted oxazole (Scheme 15). The model systems were selected because of the potential for accessing the 1,3-oxygen substitution of the Streptogramin-Group A antibiotics.[35,36,37]

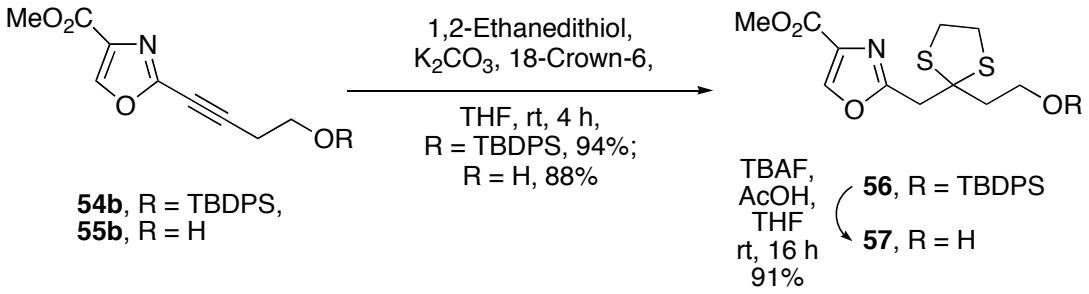
Scheme 15. Synthesis of internal alkynyl oxazoles.



The required 2-alkynyl oxazole was readily accessed starting from the corresponding alkynoic acids **52a** (n = 1)[73] and **52b** (n = 2) (Scheme 15). Coupling the carboxylic acids **52a** and **52b** with serine methyl ester hydrochloride in the presence of PyBOP[47] and an amine base afforded hydroxyamides **53a** and **53b** in 31% and 90% yield, respectively. The hydroxyamides rapidly cyclized in the presence of DAST and oxidation of the crude oxazoline with $BrCCl_3$ and DBU gave oxazoles **54a** and **54b** in 41% and 76% yield, respectively. Removal of the TBDPS group with aqueous HF in CH_3CN afforded the model systems **55a** and **55b** in 95% yield.

The 2-alkynyloxazole **54b** was found to readily accept ethanedithiol at the β-position and gave the 1,3-dithiolane **56** in 94% yield (Scheme 16). The TBDPS ether can then be cleaved from **56** with buffered TBAF in THF to afford the primary alcohol **57**. Alternatively, **55b** also accepts ethanedithiol to directly afford **57**.

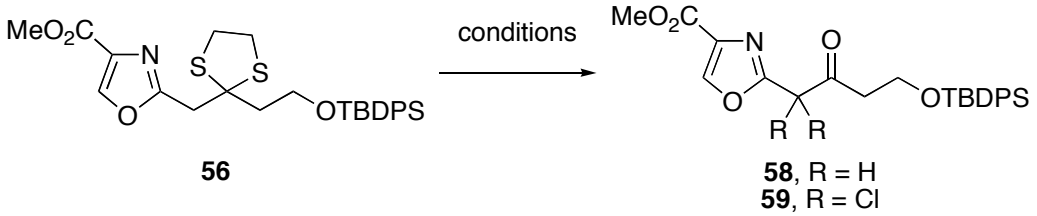
Scheme 16. Addition of ethanedithiol to internal alkynyl oxazoles.



The dithiolane **56** was converted to the ketone **58** in 77% yield using *N*-bromosuccinimide in 10% aqueous acetone (Table 5).[57] Deprotection using a combination of *N*-chlorosuccinimide and silver nitrate[57] gave the corresponding dichloroketone **59**, suggesting that the α-methylene group may enolize under the reaction conditions. The purified ketone **58** is remarkably more stable than the aldehyde, **44**. Other conditions including PIFA,[56] Select-Fluor[55] and Chloramine-T[74] resulted in decomposition of the substrate.

The potential application of the conjugate-addition methodology to natural product synthesis was demonstrated by the racemic synthesis of a protected segment of virginiamycin M_1[35] (Scheme 17). Oxidation of **57** under Swern conditions[41] afforded aldehyde **60** in 81% yield. Addition of 1-lithioproyne and protection of the resulting alcohol as the TBDPS ether afforded **61** in 41% yield over the 2-steps. The conjugate addition methodology affords a 1,3,5-hydroxy-ketone-oxazole motif in a protected form. A potential application for **61** would be as a synthetic intermediate in the synthesis of natural products such as virginiamycin M_1.

Table 5. Unveiling the latent ketone via the dithiolane.

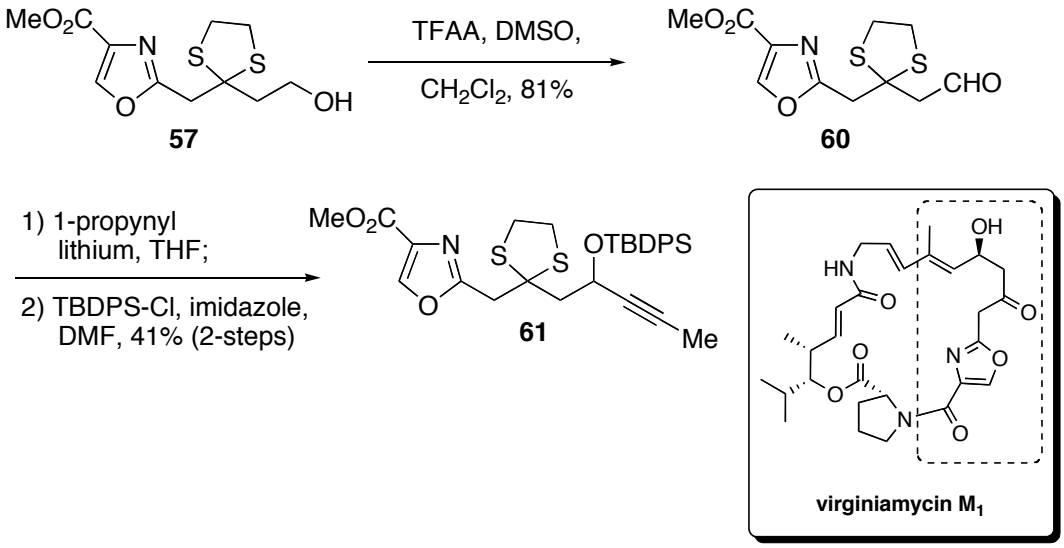


56

58, R = H
59, R = Cl

Entry	Conditions	Result
1	*N*-bromosuccinimide, 10% aq. acetone, 0 °C, 10 min	77% (R = H)
2	*N*-chlorosuccinimide, $AgNO_3$, 20% aq. CH_3CN, 0 °C to rt, 1 h	29% (R = Cl)
3	$PhI(OCOCF_3)_2$ (2.5 equiv), 10% aq. THF, 0 °C to rt, 30 min	decomp.
4	Select-Fluor (2.5 equiv), 5% aq. CH_3CN, 0 °C to rt, 2 h	decomp.
5	Chloramine-T (4.2 equiv), 10% aq. MeOH, 0 °C to rt, 2 h	decomp.

Scheme 17. A potential application of the conjugate-addition methodology to the synthesis of virginiamycin M_1.



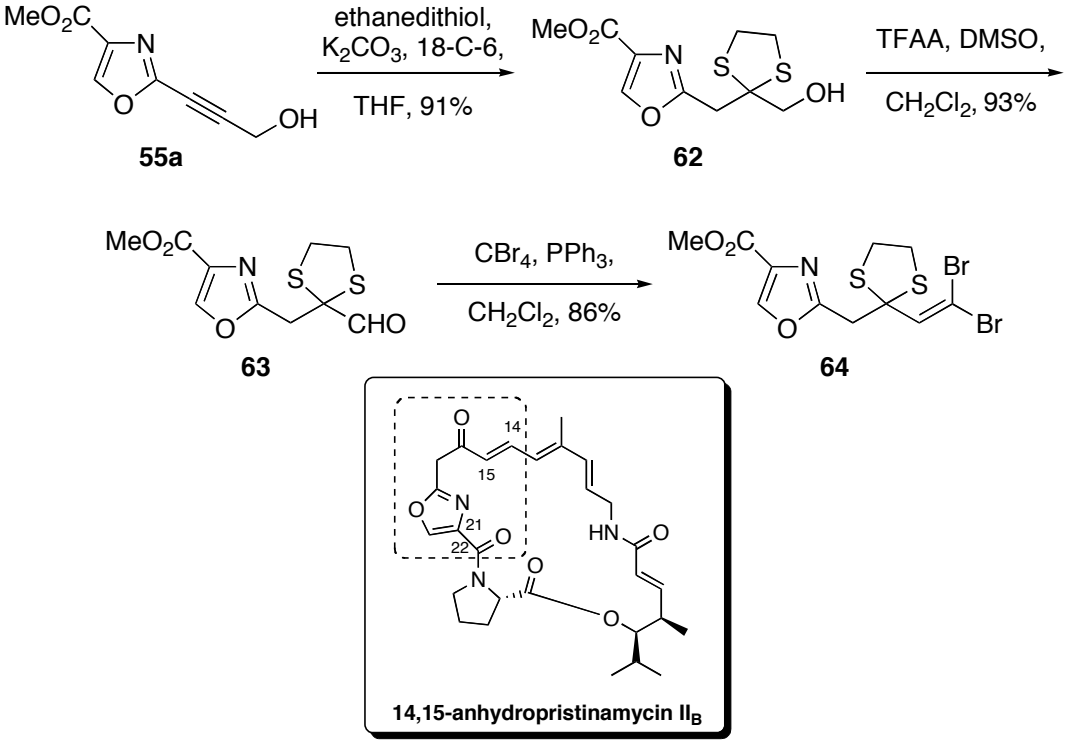
57

60

61

A second example for a potential application for the conjugate-addition methodology to natural product synthesis is 14,15-anhydropristinamycin II_B (Scheme 18).[75,76] Ethanedithiol readily added to alkyne **55a** under the standard conditions to afford dithiolane **62** in 91% yield. The primary alcohol was oxidized under Swern conditions[41] to afford aldehyde **63** in 93% yield. The aldehyde was then homologated with the Corey-Fuchs reagent[77] to afford the dibromoolefin **64** in 86% yield.[78] The product **64** represents the C_{14}-C_{22} segment of 14,15-anhydropristinamycin II_B and is suitably functionalized to serve as an advanced intermediate in convergent natural product synthesis.[79]

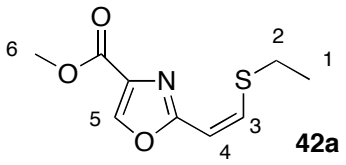
Scheme 18. A potential application of the conjugate-addition methodology to the synthesis of 14,15-anhydropristinamycin II_B.



2.1.4. Preliminary Metal Chelation Studies

Oxazoles with metal chelating substituents represent a privileged class of ligands that are useful in metal mediated catalysis.[80] To further expand the utility and possible applications of the conjugate addition methodology, the potential of the thioenol ether motif of **42a** to bind metals was explored.[81] The hypothesis was tested by stirring a solution of **42a** in $CDCl_3$ with $AgNO_3$ until TLC analysis indicated that **42a** was consumed and only baseline material remained. The mixture was filtered and analyzed by ^1H NMR spectroscopy. A similar experiment was conducted using $Zn(OTf)_2$ and the results are shown in Table 6.

Table 6. Evidence for the chelation of Ag(I) and Zn(II) salts.



42a

Protons	$CDCl_3$ ppm	$CDCl_3$ + $AgNO_3$, ppm (Δ ppm)	$CDCl_3$ + $Zn(OTf)_2$, ppm (Δ ppm)
1	1.38	1.44 (+0.06)	1.41 (+0.03)
2	2.85	3.06 (+0.21)	2.92 (+0.07)
3	6.87	7.03 (+0.16)	7.26 (+0.39)
4	6.34	6.53 (+0.19)	6.93 (+0.59)
5	8.20	8.20 (0)	8.24 (+0.04)
6	3.90	3.92 (+0.02)	3.97 (+0.07)
Recovered (%)	-	98	15[a]

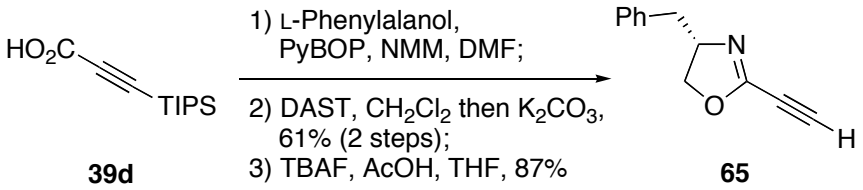
[a] The low recovery is likely due to the voluminous precipitates that were removed by filtration during NMR sample preparation.

For silver (I), the results indicate a significant shift (+0.1-0.2 ppm) in the region of the thioenol ether, as would be expected if the oxazole nitrogen and the sulfur atom were forming a chelate to the metal atom. Aqueous workup and extraction gave a nearly quantitative recovery of **42a**, whose spectral properties returned to the original values listed in Table 6. For Zn(II), a greater shift in the thioenol ether region (+0.4-0.6 ppm) was observed, also suggesting a similar metal chelate is being formed. Again, an aqueous workup returned material whose spectral data were unchanged from the original. Given the initial results and the ease with which the oxazole-thioenol ethers such as **42a** can be prepared, this general motif may be of broad utility in applications where rapid and straightforward access to metal-binding ligands is required.

2.1.5. Conjugate Additions to Oxazolines

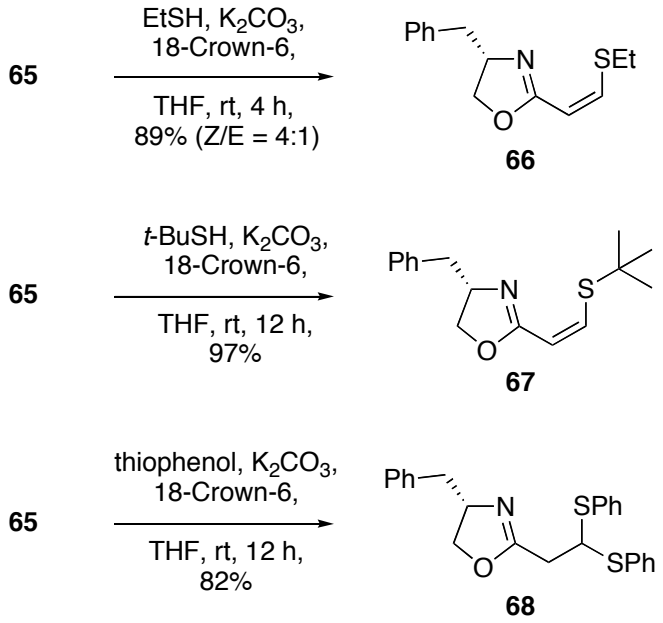
A related motif that has found utility in asymmetric synthesis is the thioether-oxazoline ligand.[81,82] Given the results for the thioether-oxazoles, the possibility of accessing thioether-oxazolines by a similar conjugate addition to the corresponding 2-ethynyl oxazoline was also examined. The known oxazoline **65**[83] was prepared analogously to the oxazoles (Scheme 19). L-Phenylalanol and the TIPS-protected alkynoic acid were condensed using PyBOP,[47] affording the corresponding hydroxyamide which was then cyclized using DAST and K_2CO_3 to provide the oxazoline in 63% yield over the 2 steps. The TIPS group was removed using TBAF buffered with AcOH to afford **65** in 87% yield.

Scheme 19. Synthesis of a 2-ethynyl oxazoline.



The 2-ethynyl oxazoline **65** was found to participate in the conjugate addition reaction with thiols (Scheme 20). Ethanethiol and even the sterically hindered *t*-butyl thiol formed adducts **66** and **67,** respectively, in good to excellent yields and with good (*Z*)-selectivity. Interestingly, similar conditions using thiophenol gave the dithioacetal **68**. The results indicate that the conjugate addition methodology is equally effective for 2-ethynyl oxazolines as it is for the corresponding oxazoles. Along with varying the thiol or the C_4-substituent of the oxazoline, the conjugate addition methodology affords adducts that offer potential for further modifications. The mild conditions, good yields and good (*Z*/*E*)-selectivity offer significant promise as a new method for easily accessing many novel ligands for asymmetric catalysis.

Scheme 20. Conjugate additions to 2-ethynyl oxazolines.



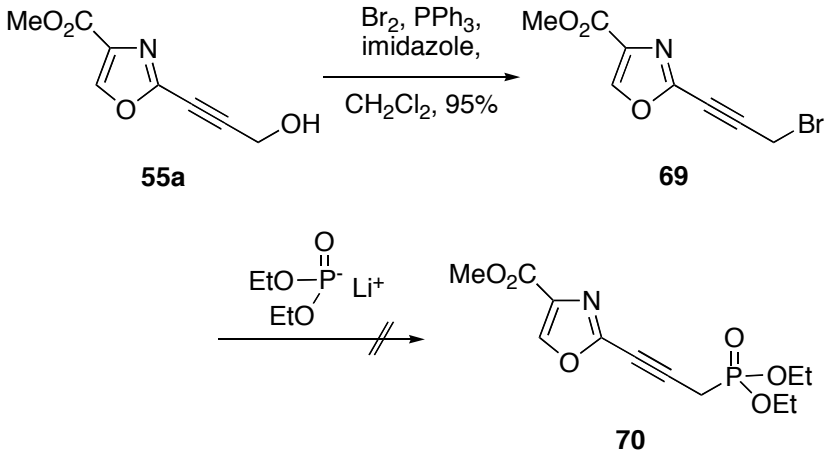
2.1.6. Synthesis of a 2-Allenyl Oxazole

Allenes are important building blocks for organic synthesis.[84] Many methods exist for the synthesis of allenes; however, methods for the metal-free synthesis of allenes are less common and include Mitsunobu[85] and Wittig[86] conditions. A method for the conversion of propargyl bromides into allenes was identified during studies to prepare a phosphonate reagent.

Attempts for obtaining phosphonate **70** were initially met with discouraging results (Scheme 21). Formation of the propargyl bromide **69** from the propargyl alcohol **55a** occurred under standard condtions in 95% yield. Condensation of the propargyl

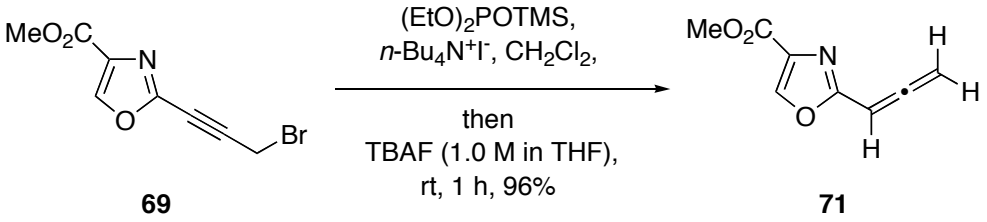
bromide **69** with the lithium anion of diethyl phosphite led to decomposition of the starting material. Milder conditions were explored due to the apparently sensitive nature of the system.

Scheme 21. Attempted synthesis of a phosphonate reagent.



In an effort to identify milder conditions, diethyl trimethylsilyl phosphite with tetra-*n*-butylammonium iodide was stirred with propargyl bromide **69**,[87] however, no reaction was evident by TLC analysis after 30 min at rt. The addition of TBAF unexpectedly afforded the allene **71** in excellent yield (Scheme 22). The use of the less expensive diethylphosphite under these conditions gave similar results, suggesting that the TBAF was simply acting as a base.

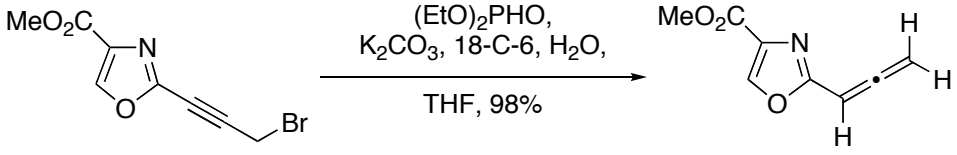
Scheme 22. Initial synthesis of the 2-allenyl oxazole.



69 **71**

When **69** was stirred with diethylphosphite, potassium carbonate and 18-crown-6, allene **71** rapidly formed (< 1 h), however, complete consumption of starting material only occurred when additional water (ca. 5 equiv) was added. The conditions were further refined and allene **71** could be obtained in nearly quantitative yield (Scheme 23). In contrast, subjecting the propargyl alcohol **55a** to the optimized reaction conditions did not afford the allene, even at elevated temperatures (60 °C, 2 h), suggesting that the bromide is essential for the observed reactivity. More control reactions and additional substrates need to be studied to better understand the nature of the allene formation.[88] Expanding the initial studies may lead to a mild method of accessing allenes without the use of metals.[89]

Scheme 23. Optimized synthesis of the 2-allenyl oxazole.



69 **71**

2.2. Conjugate Additions Under Acidic Conditions

2.2.1. Introduction

Oxazoles that are substituted at the 2- and 4-positions are a common structural element found in numerous biologically active natural products.[11] A frequently encountered subset of the 2,4-disubstituted oxazole class are those which contain an unsaturated substituent at the 2-position. Examples include the phorboxazoles,[90] disorazoles[91] and leucascandrolide[1,2] (Figure 8). A general method for the stereospecific installation of either (*E*)- or (*Z*)-alkenyl oxazoles into more complex molecules would be useful. The utility of such a "bidirectional linchpin strategy" would be enhanced if a common, advanced intermediate could give rise to either olefin geometry.[92] Consequently, the use of 2-alkynyl oxazoles as common intermediates in the synthesis of oxazoles with geometrically-defined C_2-unsaturated substituents was explored.[43]

With numerous natural products containing 2-alkenyl substituted oxazoles, significant research has been devoted towards installing this motif. A common disconnection involves the $C_{1'}$ /$C_{2'}$-bond (Figure 9, path A). In the forward direction, the condensation of phosphorous[93] or silicon[94] reagents with an aldehyde furnishes the requisite 2-alkenyl oxazole. The transformation usually gives good selectivity for the formation of the (*E*)-olefin.

Figure 8. Disubstituted oxazoles containing an alkene at the C_2-position.

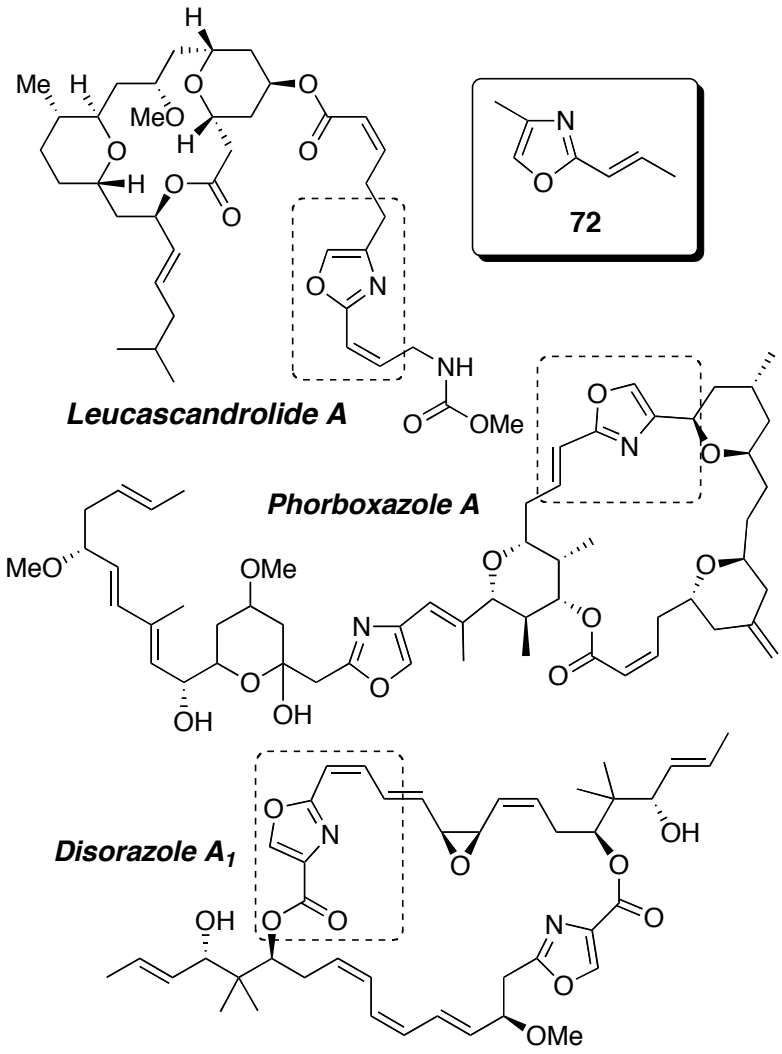
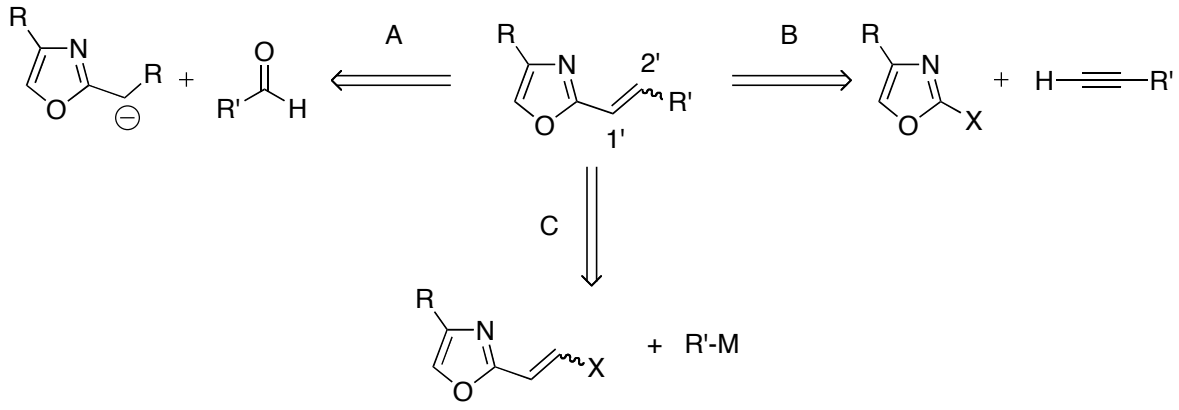


Figure 9. Common retrosynthetic disconnections for 2-alkenyl oxazoles.



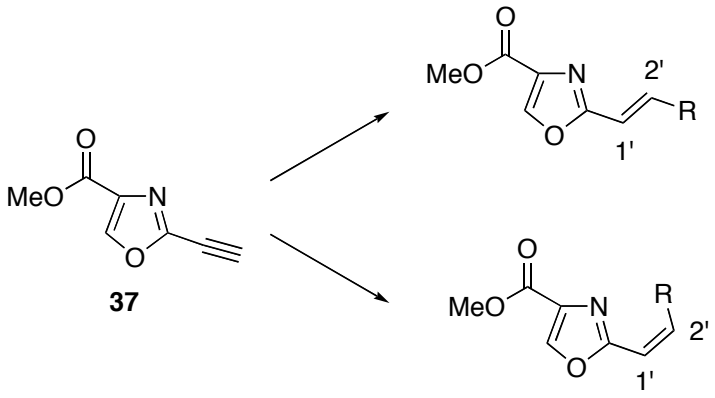
More recently, the disconnection directly at the C_2-carbon of the oxazole was explored by Panek and others (Figure 9, path B).[12,95] Several research groups used this strategy to introduce the (*Z*)-alkene in the leucascandrolide A side chain by Sonogashira coupling of the C_2-triflate with a terminal alkyne followed by semi-reduction with Lindlar catalyst (Section 1.1.2.3).[6,12]

For the present strategy, the less common disconnection at the $C_{2'}/C_{3'}$-carbons was examined (Figure 9, path C). An advantage to this approach is that the geometry of the olefin can be set prior to installation of the oxazole segment and therefore avoids the difficult separation of isomers. In addition, accessing both (*E*)- and (*Z*)-isomers as well as the 2-alkynyl oxazole from a common intermediate would allow for rapid access to analogs for biological structure-activity studies (Figure 10).

Electron deficient alkynes are known to hydrohalogenate when exposed to HI or HBr.[96] Ma and coworkers[97] demonstrated a more convenient approach involving the lithium halide salt in the presence of acetic or trifluoroacetic acid to presumably generate HI or HBr *in situ*.[98] Various electron deficient alkynes hydrohalogenate under

these conditions. Similarly, the alkyne of 2-ethynyl oxazole was suspected to be significantly polarized and would be an ideal candidate for hydrohalogenation.

Figure 10. (*E*)- and (*Z*)-alkenyl oxazoles can be derived from a common intermediate.

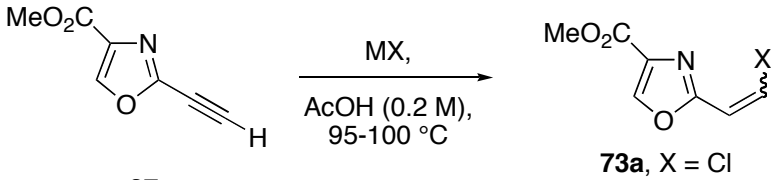


2.2.2. Hydrohalogenation of a 2-Ethynyl Oxazole

The conjugate addition studies under basic conditions suggested that the alkyne of the 2-ethynyl oxazole retained the polarized character of the parent carboxylic acid residue. 2-Alkynoates are known to undergo hydrohalogenation and afford the corresponding vinyl halides.[96,97,98] Gratifyingly, heating **37** in acetic acid in the presence of sodium or lithium halides afforded good to moderate yields of the corresponding vinyl halides (Table 7). The formation of the vinyl bromide **73b** with sodium bromide occurred with a better (*Z*/*E*)-ratio than in the presence of lithium bromide (entries 2 vs 6), and generally there was some unreacted alkyne **37**. For the formation of the vinyl

iodide **73c**, the ratio of (*Z*/*E*)-isomers decreases with increasing quantities of sodium iodide (entries 8, 10, 12) or increasing temperature (entry 10 vs 13).

Table 7. Hydrohalogenation of 2-ethynyloxazole-4-carboxylic acid.



37

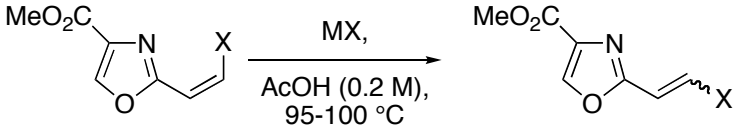
73a, X = Cl
73b, X = Br
73c, X = I

Entry	MX (equiv)	Time (h)	(*Z*/*E*)-ratio[a]	Yield % (*Z*/*E*)[b]
1	NaCl (1.5)	16	1.3 / 1.0	36 (*Z*), 26 (*E*)
2	LiBr (1.5)	16	4.0 / 1.0	71 (*Z*)
3	LiBr (1.0)/LiOAc (3.0)	16	9.1 / 1.0[c]	70 (*Z*)
4	LiBr (1.5)/LiOAc (4.5)	16	20 / 1.0[d]	87 (*Z*)
5	NaBr (1.0)	20	8.0 / 1.0[c]	70 (*Z*)
6	NaBr (1.5)	16	9.0 / 1.0[c]	68 (*Z*)
7	LiI (1.5)	12	5.6 / 1.0	77 (*Z*)
8	NaI (1.0)	12	10.7 / 1.0	90 (*Z*)
9	NaI (1.0)/NaOAc (3.0)	12	>50 / 1.0	92 (*Z*)
10	NaI (1.5)	12	4.2 / 1.0	75 (*Z*)
11	NaI (1.5)/NaOAc (1.5)	12	9.5 / 1.0	84 (*Z*)
12	NaI (3.0)	12	1.1 / 1.0	37 (*Z*), 33 (*E*)
13[e]	NaI (1.5)	12	1.0 / 1.2	22 (*Z*), 28 (*E*)

[a] The (*Z*/*E*)-ratio was determined by ^{1}H NMR analysis of the crude reaction product after aqueous workup. [b] The yield (%) refers to the major isomer and was determined after purification by chromatography on SiO_2. [c] The crude reaction product contained approximately 10% starting material (alkyne). [d] The crude reaction product contained approximately 3% starting material (alkyne). [e] The reaction was conducted in a sealed tube at an oil bath temperature of 150 °C.

To understand the background isomerization that may be occurring during the reaction, the pure (*Z*)-isomers were re-subjected to the identical reaction conditions and the olefin isomerized to afford mainly the (*E*)-isomers (Table 8). The (*Z*/*E*)-ratios in Table 8 (entries 2 and 3) initially appear to be in conflict with the (*Z*/*E*)-ratios in Table 7 (entries 10 and 12), with the only difference being the generation of one equivalent of sodium acetate in the latter transformations. To test the hypothesis that sodium acetate was influencing the outcome of the reaction, the isomerization experiment was conducted with additional sodium acetate and a dramatic decrease in the amount of isomerization was observed (Table 8, entry 4). In addition, sodium acetate inhibited the isomerization of (*E*)-**73c** to (*Z*)-**73c** (Table 9). The beneficial effects of acetate buffer towards improving the (*Z*/*E*)-ratio are evident in the formation of both (*Z*)-**73b** (Table 7, entries 2-4) and (*Z*)-**73c** (Table 7, entries 8 vs 9 and 10 vs 11).

Table 8. Isomerization of (*Z*)-vinyl halides.



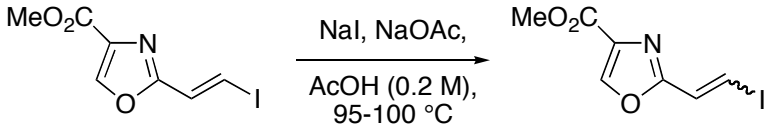
(*Z*)-**73b**, X = Br
(*Z*)-**73c**, X = I

(*E*/*Z*)-**73b**
(*E*/*Z*)-**73c**

Entry	X	MX (equiv)	Time (h)	(*Z*/*E*)-ratio[a]	Yield % (*Z*/*E*)[b]
1	Br	NaBr (1.5)	16	1.0 / 5.9	74 (*E*)
2	I	NaI (1.5)	12	1.0 / 6.7	83 (*E*)
3	I	NaI (3.0)	12	1.0 / 7.8	86 (*E*)
4	I	NaI (1.5) / NaOAc (4.5)	12	6.6 / 1.0	63 (*Z*)

[a] The (*Z*/*E*)-ratio was determined by ^{1}H NMR analysis of the crude reaction product after aqueous workup. [b] The yield (%) refers to the major isomer and was determined after purification by chromatography on SiO_2.

Table 9. Isomerization of the (*E*)-vinyl iodide.



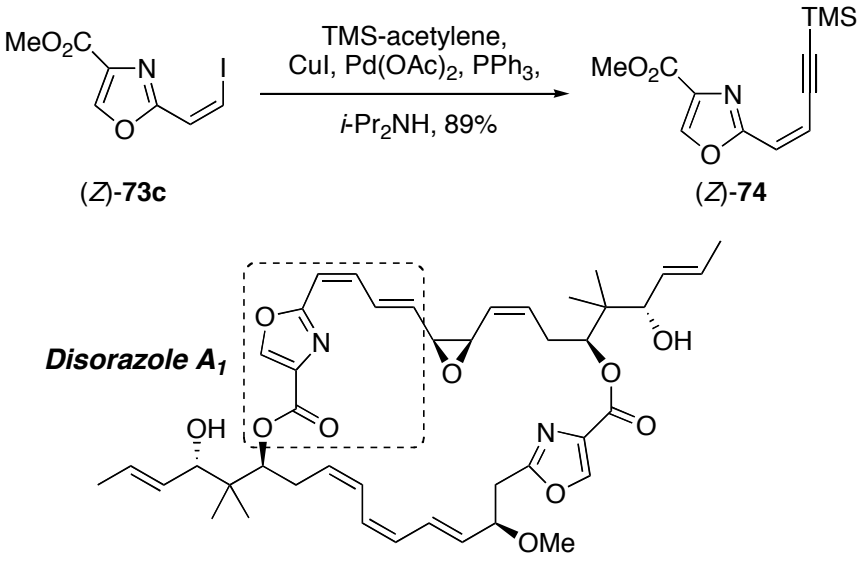
(*E*)-**73c** (*Z/E*)-**73c**

Entry	NaI (equiv)	NaOAc (equiv)	Time (h)	(*Z*/*E*)-ratio[a]	Yield % (*Z*/*E*)[b]
1	1.5	0	12	1.0 / 8.1	84 (*E*)
2	1.5	4.5	12	0 / 1.0	73 (*E*)

[a] The (*Z*/*E*)-ratio was determined by ^{1}H NMR analysis of the crude reaction product after aqueous workup. [b] The yield (%) refers to the major isomer and was determined after purification by chromatography on SiO_2.

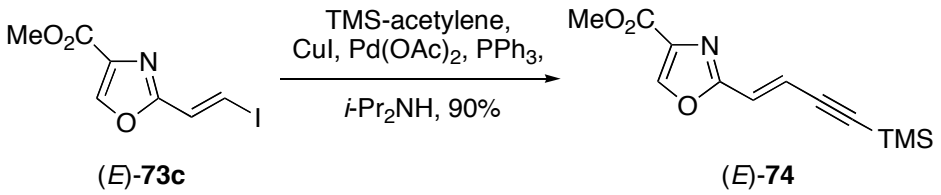
With access to the required (*E*)- and (*Z*)-vinyl halides, the subsequent cross-coupling reactions were studied. (*Z*)-**73c** readily participated in the cross-coupling reaction with trimethylsilyl acetylene under Sonogashira conditions[99] to afford (*Z*)-**73** in 89% yield (Figure 25). It should be noted that (*Z*)-**73** would be difficult to prepare using either of the alternative methods in Figure 9. The Wittig olefination normally favors the (*E*)-isomer[93] and Lindlar reduction of the diyne would require selectivity for one alkyne.

Scheme 24. Sonogashira cross-coupling of the (*Z*)-vinyl iodide.



In a similar manner, (*E*)-**73c** also participated in the Sonogashira cross-coupling[99] reaction with trimethylsilylacetylene to afford (*E*)-**74** in 90% yield (Scheme 25).

Scheme 25. Sonogashira cross-coupling of the (*E*)-vinyl iodide.

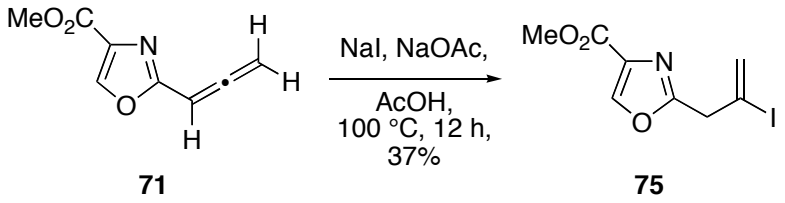


2.2.3. Hydrohalogenation of 2-Allenyl Oxazole

Ma and coworkers also demonstrated that the hydrohalogenation of electron deficient allenes affords the corresponding vinyl halides.[100] In a similar manner, allene

71 afforded vinyl iodide **75** in 37% yield when subjected to the standard hydrohalogenatation conditions (Scheme 26).

Scheme 26. Hydrohalogenation of a 2-allenyl oxazole.



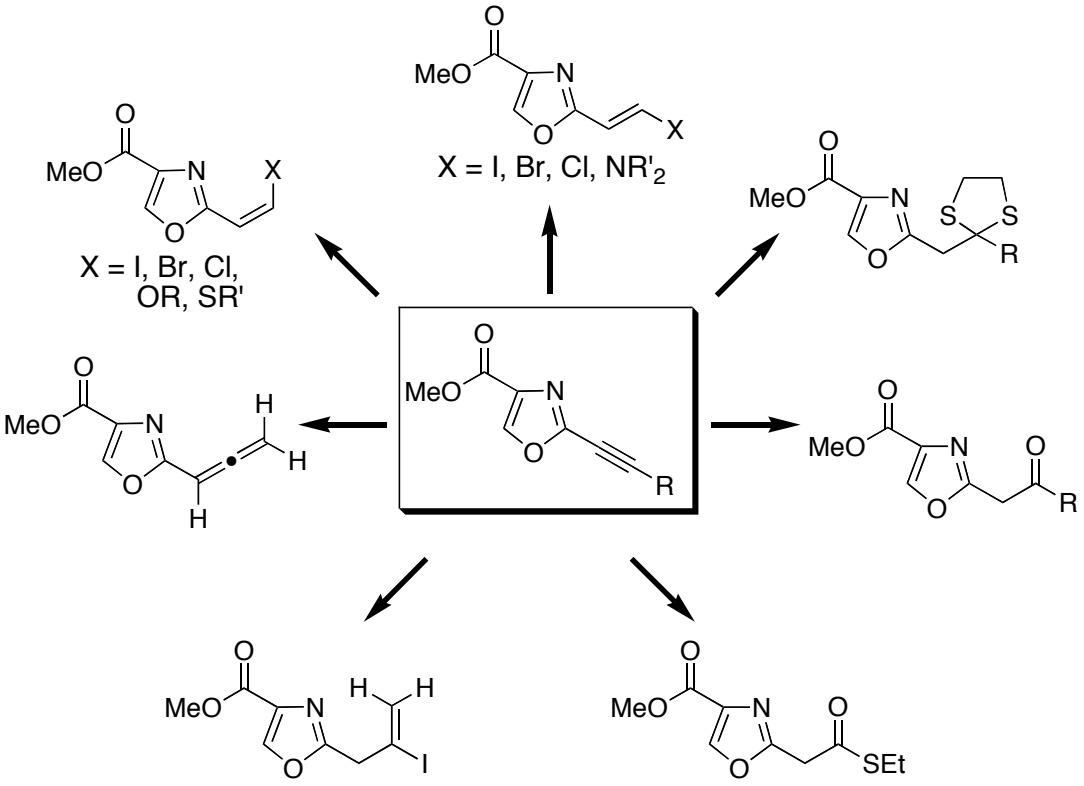
71 **75**

2.3. Summary and Conclusions

Significant structural variations can be obtained from 2-alkynyl oxazoles by using different reaction conditions (Figure 11). 2-Alkynyl oxazoles and oxazolines are easily synthesized from readily available starting materials and participate in conjugate addition reactions. Although the C_2-β-aldehyde **44** could not be accessed, the rearrangement of the 1,3-dithiolane adduct **43** afforded the ethylthioester **51**, which under Fukuyama reduction conditions, affords a glimpse of the unstable enol tautomer **44a**. The 1,3-dithiolane adduct **56** of the internal alkyne can be readily converted to the C_2-β-ketone **58** that is found in numerous biologically active natural products. Internal alkynes can therefore act as a masked form of the C_2-β-ketone that can be unveiled under mild conditions. Evidence that the ethylthioether oxazole adduct **42a** acts as a unique and readily accessible metal-binding motif was presented. The conjugate addition of thiols to the 2-ethynyl oxazoline **65** afforded unique, chiral

thioether-oxazolines that could be used as ligands for asymmetric synthesis. The conjugate addition strategy offers a unique, mild and flexible method for the construction of oxazole motifs found in many biologically active natural products.

Figure 11. Summary of the numerous functionalities that are accessible from 2-alkynyl oxazoles.



The 2-ethynyl oxazole **37** participates in hydrohalogenation reactions to afford predominantly the vinyl bromide and iodide in the (*Z*)-configuration. The addition of an acetate buffer to the reaction mixture improves the (*Z*/*E*)-ratio and the overall yield. The (*E*)-vinyl halide can be obtained by re-subjecting the (*Z*)-isomer to the reaction conditions. Both (*Z*)-**73c** and (*E*)-**73c** readily participate in Pd-catalyzed cross-coupling reactions to afford the corresponding C_2-unsaturated oxazoles (*E*)-**74** and (*Z*)-**74**. The

2-allenyloxazole **71** also hydrohalogenated under similar conditions to afford the vinyl iodide **75**. The conjugate addition and hydrohalogenation methodology uses a common precursor to afford advanced oxazole intermediates that are suitably functionalized for further derivatization. The "linchpin strategy" offers a unique, mild and flexible method for introducing oxazole segments into complex molecules.[92]

2.4. Experimental Part

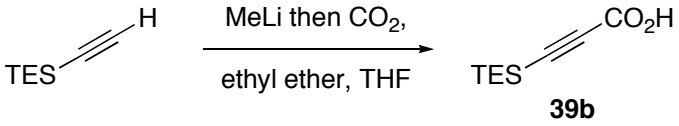
2.4.1. General

All moisture sensitive reactions were performed using syringe-septum techniques under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for more than 4 h prior to use. Reactions at -78 °C employed a solid CO_2-acetone bath. THF and ethyl ether were distilled from sodium/benzophenone ketyl. Methylene choride and toluene were filtered through activated alumina prior to use. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualized using UV light (254 nm) or by staining with $KMnO_4$ or phosphomolybdic acid. Flash chromatography on SiO_2 was used to purify compounds unless otherwise stated. Concentration refers to removal of the solvent on a rotary evaporator at water aspirator pressure. Melting points are uncorrected. Infrared spectra were acquired using KBr pellets or thin films on NaCl plates (i.e. neat). Chemical shifts were reported in parts per million and the residual solvent peak was used as an internal reference. ^1H NMR spectra were acquired in $CDCl_3$ at a frequency

of 300 MHz unless otherwise stated and are tabulated as follows: chemical shift (multiplicity, number of protons, coupling constants). ^{13}C NMR were acquired in $CDCl_3$ at a frequency of 75 MHz using a proton decoupled pulse sequence unless otherwise stated. For acid sensitive samples, $CDCl_3$ was filtered through activated basic alumina (Brockmann I) immediately prior to sample preparation. For optical rotations, concentration (*c*) is reported in g/100 mL.

2.4.2. Experimental Procedures

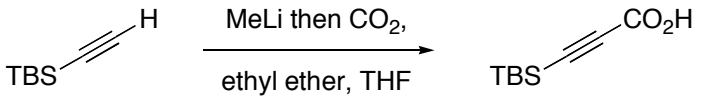
2.4.2.1. Conjugate Additions Under Basic Conditions



39b

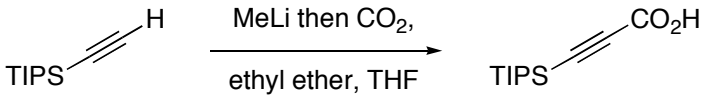
3-(Triethylsilyl)propiolic acid (39b). A solution of triethylsilylacetylene (1.00 mL, 5.602 mmol, 1.0 equiv) in THF (56.0 mL) was cooled under N_2 to 0 °C. A solution of MeLi (1.5 M in ethyl ether, 5.22 mL, 7.83 mmol, 1.4 equiv) was added and the mixture was stirred for 1 h, cooled to –78 °C and CO_2 gas was bubbled into the solution for 1 h. The reaction mixture was quenched by the slow addition of 2.0 M aqueous $NaHSO_4$ (20 mL), warmed to rt and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow syrup that was diluted with toluene (50 mL), poured onto a pad of SiO_2 (40 mm x 40 mm) and eluted with ethyl acetate (5 X 20 mL). The filtrate was concentrated to afford a pale yellow oil. Bulb to bulb distillation (118 °C/ 0.1 mm Hg) afforded **39b** (993.9 mg, 96%) as clear, colorless syrup: ^1H NMR δ 10.18 (bs, 1 H),

1.01 (t, 9 H, *J* = 7.9 Hz), 0.69 (q, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ 157.7, 95.7, 95.3, 7.4, 3.9; IR (neat) 3115, 2858, 2915, 2878, 2628, 2174, 1686 cm^{-1}; MS (EI) *m/z* (rel. intensity) 184 (M^+, 6), 155 ([M-C_2H_5]$^+$, 100), 127 ([M-C_4H_9]$^+$, 34), 111 ([M-C_2H_5-CO_2]$^+$, 17), 103 (69); HRMS (EI) *m/z* calcd for $C_9H_{16}O_2Si$ 184.0920, found 184.0927.



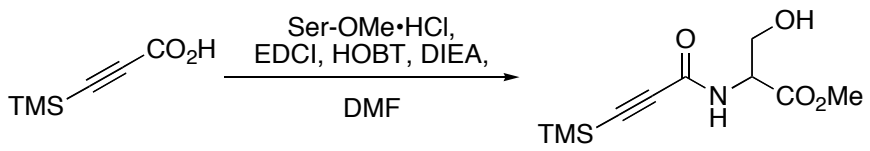
39c

3-(*tert*-Butyldimethylsilyl)propiolic acid (39c). A solution of *tert*-butyldimethylsilylacetylene (1.00 mL, 5.353 mmol, 1.0 equiv) in THF (50.0 mL) was cooled under N_2 to 0 °C. A solution of MeLi (1.5 M in ethyl ether, 5.00 mL, 7.50 mmol, 1.4 equiv) was added and the mixture was stirred for 1 h, cooled to –78 °C and CO_2 gas was bubbled into the solution for 1 h. The reaction mixture was quenched by the slow addition of 2.0 M aqueous $NaHSO_4$ (20 mL), warmed to rt and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow syrup that was diluted with toluene (50 mL), poured onto a pad of SiO_2 (40 mm x 40 mm) and eluted with ethyl acetate (5 X 20 mL). The filtrate was concentrated to afford **39c** (990.1 mg, 100%) as yellow syrup that crystallized to a pale yellow solid under vacuum: Mp 38.4-40.0 °C (ethyl acetate/toluene); ^{1}H NMR δ 10.3 (bs, 1 H), 0.97 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR δ 157.6, 96.3, 94.9, 26.1, 16.7, -5.1; IR (neat) 3104, 2955, 2931, 2889, 2860, 2624, 2175, 1693 cm^{-1}; MS (EI) *m/z* (rel. intensity) 184 (M^+, 22), 169 ([M-CH_3]$^+$, 19), 127 ([M-C_4H_9]$^+$, 45), 75 (100); HRMS (EI) *m/z* calcd for $C_9H_{14}O_2Si$ 184.0920, found 184.0911.



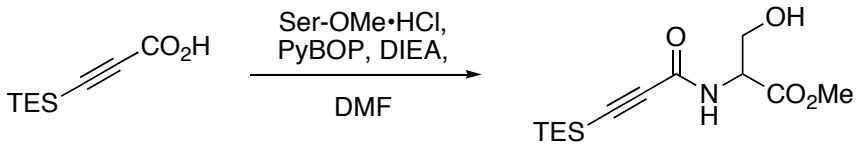
39d

Triisopropylsilylpropiolic acid (39d). A solution of triisopropylsilylacetylene (1.00 mL, 4.46 mmol, 1.0 equiv) in THF (40 mL) was cooled under N_2 to 0 °C. A solution of MeLi (0.9 M in ethyl ether, 7.00 mL, 6.30 mmol, 1.4 equiv) was added and the mixture was stirred for 1 h, cooled to –78 °C and CO_2 gas was bubbled into the solution for 1 h. The reaction mixture was quenched by the slow addition of 2.0 M aqueous $NaHSO_4$ (20 mL), warmed to rt, diluted with water (30 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow syrup that was diluted with toluene (50 mL), poured onto a pad of SiO_2 (40 mm x 40 mm) and eluted with ethyl acetate (5 X 20 mL). The filtrate was concentrated to afford **39d** (1.01 g, 100%) as yellow syrup that crystallized to a pale yellow solid under vacuum: Mp 60.5-62.5 °C (CH_2Cl_2); ^{1}H NMR δ 10.94 (bs, 1 H), 1.21-1.02 (m, 21 H); ^{13}C NMR δ 157.7, 96.1, 95.1, 18.6, 11.1; IR (neat) 3068, 2947, 2892, 2868, 2634, 2503, 2185, 2162, 1683, 1460, 1407, 1266 cm^{-1}; MS (EI) *m/z* (rel. intensity) 226 (M^+, 21), 183 ([M-C_3H_7]$^+$, 100), 155 ([M-C_5H_{11}]$^+$, 79), 139 ([M-C_6H_{15}]$^+$, 79), 127 (100), 111 (80), 85 (78), 83 (87), 75 (84), 69 (70); HRMS (EI) *m/z* calcd for $C_{12}H_{22}O_2Si$ 226.1389, found 226.1388.



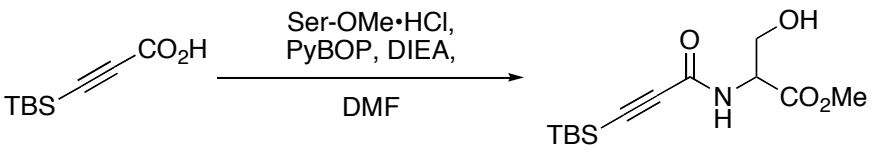
39a **40a**

Methyl 3-hydroxy-2-(3-(trimethylsilyl)propiolamido)propanoate (40a). A suspension of **39a** (513.0 mg, 3.607 mmol, 1.0 equiv), DL-serine methyl ester hydrochloride (617.0 mg, 3.966 mmol, 1.1 equiv) and HOBT (540.0 mg, 3.996, 1.1 equiv) in DMF (3.0 mL) was cooled to 0 °C under argon and treated with EDCI (770.0 mg, 4.016 mmol, 1.1 equiv) and *N*,*N*-diisopropylethylamine (1.40 mL, 8.053 mmol, 2.2 equiv). The cold bath was removed and the mixture was stirred at rt for 8.5 h, treated with saturated aqueous $NaHCO_3$, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M aqueous citric acid, water, and 10% aqueous LiCl, dried (Na_2SO_4), filtered and concentrated to a pale yellow syrup. Purification by chromatography on SiO_2 (60% ethyl acetate/hexanes) afforded **40a** (195.7 mg, 22%) as a clear, colorless syrup: ^{1}H NMR δ 7.08 (s, 1 H), 4.60 (dt, 1 H, J = 7.9, 3.4 Hz), 3.95 (d of AB, 1 H, J = 11.3, 3.6 Hz), 3.83 (d of AB, 1 H, J = 11.3, 3.4 Hz), 3.72 (s, 3 H), 3.58 (bs, 1 H), 0.2 (s, 9 H); ^{13}C NMR δ 170.4, 152.9, 96.9, 93.3, 62.5, 54.8, 52.9, -0.7; IR (neat) 3325, 2958, 2901, 2169, 1745, 1639, 1532 cm^{-1}; MS (EI) *m/z* (rel. intensity) 225 ([M-H_2O]$^+$, 3.1), 213 (37), 184 (46), 125 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{15}NO_3Si$ (M-H_2O) 225.0821, found 225.0825.



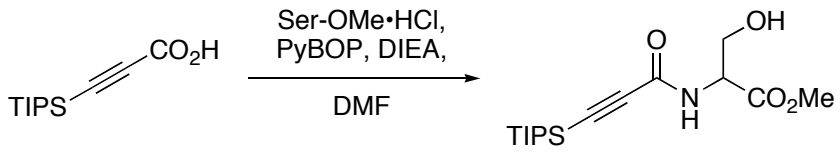
39b **40b**

Methyl 3-hydroxy-2-(3-(triethylsilyl)propiolamido)propanoate (40b). A suspension of **39b** (1.450 g, 7.867 mmol, 1.0 equiv), DL-serine methyl ester hydrochloride (1.840 g, 11.83 mmol, 1.5 equiv) and PyBOP (4.500 g, 8.647 mmol, 1.1 equiv) in DMF (10.0 mL) at 0 °C under argon was treated with diisopropylethylamine (5.00 mL, 28.8 mmol, 3.3 equiv) in one portion. The cold bath was removed and the mixture was stirred at rt for 40 h. Saturated aqueous $NaHCO_3$ was added and the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M aqueous citric acid, water, and 10% aqueous LiCl, dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **40b** (1.574 g, 70%) as a clear, colorless syrup that crystallized to a solid on standing: Mp 76.2-77.2 °C (ethyl acetate/hexanes); ^{1}H NMR δ 6.81 (bd, 1 H, *J* = 7.3 Hz), 4.68 (app dt, 1 H, *J* = 7.6, 3.4 Hz), 4.01 (dd of AB, 1 H, *J* = 11.2, 5.7, 3.6 Hz), 3.93 (dd of AB, 1 H, *J* = 11.3, 5.7, 3.4 Hz), 3.80 (s, 3 H), 2.64 (t, 1 H, *J* = 5.9 Hz), 1.00 (t, 9 H, *J* = 7.9 Hz), 0.66 (q, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ 170.5, 152.9, 98.1, 91.5, 63.1, 55.0, 53.1, 7.5, 4.0; IR (neat) 3414, 3326, 3045, 2957, 2913, 2877, 2166, 1746, 1639, 1529 cm^{-1}; MS (EI) *m/z* (rel. intensity) 267 ([M-H_2O]$^+$, 3.1), 255 (61), 226 (61), 208 (65), 204 (83), 167 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{21}NO_3Si$ (M-H_2O) 267.1291, found 267.1291.



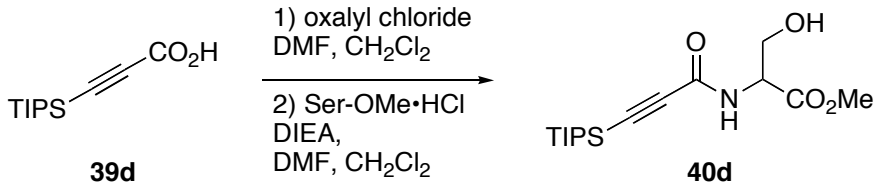
39c **40c**

Methyl 2-(3-(*tert*-butyldimethylsilyl)propiolamido)-3-hydroxypropanoate (40c). A solution of **39c** (2.064 g, 11.12 mmol, 1.0 equiv) and serine methyl ester hydrochloride (2.610 g, 16.78 mmol, 1.5 equiv) in DMF (20 mL) was cooled to 0 °C under argon and treated with PyBOP (6.800 g, 13.07 mmol, 1.2 equiv) and diisopropylethylamine (7.00 mL, 40.3 equiv, 3.6 mmol). The cold bath was removed after 10 min and the mixture was stirred at rt for 18 h, quenched with $NaHCO_3$ (20 mL), stirred for 1 h at rt and extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid (100 mL), water (50 mL), 10% aqueous LiCl (50 mL) and brine (25 mL). The combined aqueous washings were backwashed with one portion of ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **40c** (2.639 g, 83%) as a clear, colorless syrup that crystallized to a white solid on standing: R_f 0.50 (60% ethyl acetate/hexanes); Mp 65.3-66.3 °C (ethyl acetate/hexanes); ^{1}H NMR δ 6.84 (d, 1 H, J = 7.3 Hz), 4.68 (app dt, 1 H, J = 7.2, 3.4 Hz), 4.02 (t of AB, 1 H, J = 11.4, 4.2 Hz), 3.93 (t of AB, 1 H, J = 10.5, 4.1 Hz), 3.80 (s, 3 H), 2.71 (t, 1 H, J = 4.9 Hz), 0.95 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR δ 170.5, 152.9, 97.8, 92.1, 63.0, 55.0, 53.1, 26.2, 16.7, -4.9; IR (neat) 3414, 3325, 3047, 2954, 2931, 2887, 2859, 2168, 1746, 1639, 1530 cm^{-1}; MS (EI) *m/z* (rel. intensity) 285 (M^+, 0.5), 270 ($[M\text{-}CH_3]^+$, 2.5), 267 ($[M\text{-}H_2O]^+$, 2.3), 255 (22), 228 ($[M\text{-}C_4H_9]^+$, 20), 176 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{20}NO_4Si$ (M-CH_3) 270.1162, found 270.1165.



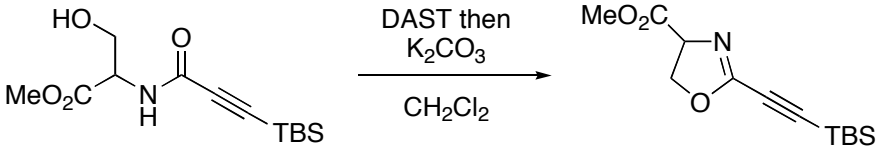
39d **40d**

3-Hydroxy-2-[3-(triisopropylsilyl)propynoylamino]propionic acid methyl ester (40d). To a suspension of **39d** (1.00 g, 4.45 mmol, 1.0 equiv) and DL-serine methyl ester hydrochloride (1.04 g, 6.65 mmol, 1.5 equiv) in DMF (6.0 mL) at 0 °C under argon was added diisopropylethylamine (2.70 mL, 15.5 mmol, 3.5 equiv) and PyBOP (2.54 g, 4.88 mmol, 1.1 equiv) in one portion. The cold bath was removed and the mixture was stirred at rt for 15 h. Saturated, aqueous $NaHCO_3$ (6.0 mL) was added and the mixture was stirred for 1 h at rt, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M aqueous citric acid, water, and 4.0 M aqueous LiCl, dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (40% to 50% ethyl acetate/hexanes) afforded **40d** (1.45 g, 100%) as a clear, colorless syrup: ^{1}H NMR δ 6.81 (d, 1 H, J = 7.3 Hz), 4.68 (app dt, 1 H, J = 7.2, 3.4 Hz), 4.02, 3.94 (d of AB, 2 H, J = 11.3, 3.4 Hz), 3.80 (s, 3 H), 1.07-1.11 (m, 21 H); ^{13}C NMR δ 170.5, 153.0, 99.1, 90.7, 63.1, 55.1, 53.1, 18.7, 11.2; IR (neat) 3421, 3328, 2945, 2892, 2867, 2166, 1747, 1640, 1526, 1463, 1438, 1218 cm^{-1}; MS (EI) *m/z* (rel. intensity) 327 (M^+, 6), 309 ([M-H_2O]$^+$, 10), 297 (16), 284 ([M-C_3H_7]$^+$, 38), 266 ([M-C_3H_7-H_2O]$^+$, 77), 238 (16), 57 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{29}NO_4Si$ 327.1866, found 327.1871.



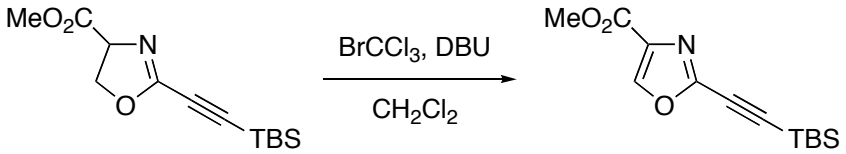
39d **40d**

3-Hydroxy-2-[3-(triisopropylsilyl)propynoylamino]propionic acid methyl ester (40d, scale-up protocol). A solution of **39d** (5.00 g, 22.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled under N_2 to –20 °C and treated with DMF (5 drops). Oxalyl chloride (2.90 mL, 33.24 mmol, 1.5 equiv) was slowly added. The mixture was stirred for 30 min while the bath temperature increased to –10 °C. The cold bath was then removed and the mixture was stirred at rt for 60 min and then concentrated under vacuum, affording an orange-colored oil. The oil was diluted with CH_2Cl_2 (5.0 mL + 5.0 mL rinse) and added via cannula to a stirred mixture of DL-serine methyl ester hydrochloride (5.20 g, 33.4 mmol, 1.5 equiv) and diisopropylethylamine (12.0 mL, 69.0 mmol, 3.1 equiv) in DMF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then at rt for 20 h. Saturated aqueous $NaHCO_3$ (20 mL) was added and after stirring for 1 h at rt, the mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with 1.0 M aqueous citric acid (2 x 100 mL), water (25 mL), and 4.0 M aqueous LiCl (25 mL), dried (Na_2SO_4), filtered and concentrated to an amber syrup. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **40d** (5.90 g, 82%) as a pale yellow syrup. The spectral data were identical to material obtained from the PyBOP coupling.



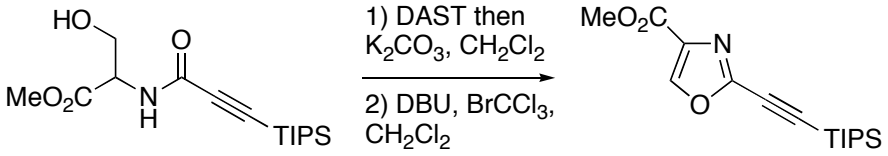
40c

2-((*tert*-Butyldimethylsilyl)ethynyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester. A solution of **40c** (2.630 g, 9.215 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was cooled to –78 °C under argon and treated with DAST (1.280 mL, 9.688 mmol, 1.05 equiv), stirred for 30 min and treated with anhydrous K_2CO_3 (1.910 g, 13.820 mmol, 1.5 equiv), warmed to 0 °C and stirred for 15 min. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was warmed to rt, stirred for 2 h, diluted with H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to an orange-colored oil. Purification by chromatography on SiO_2 (20% to 40% ethyl ether/hexanes) afforded 2-((*tert*-butyldimethylsilyl)ethynyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (2.080 g, 84%) as a pale yellow oil: R_f 0.53 (40% ethyl acetate/hexanes); ^{1}H NMR δ 4.81 (dd, 1 H, *J* = 10.8, 8.2 Hz), 4.54 (app t, 1 H, *J* = 8.5 Hz), 4.44 (dd, 1 H, *J* = 10.8, 8.8 Hz), 3.78 (s, 3 H), 0.94 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR δ 170.8, 151.6, 97.9, 91.9, 69.4, 68.5, 53.0, 26.1, 16.7, -5.0; IR (neat) 2954, 2931, 2888, 2859, 2184, 1747, 1620 cm^{-1}; MS (EI) *m/z* (rel. intensity) 267 (M^+, 13), 252 ([M-CH_3]$^+$, 20), 211 (100), 210 ([M-C_4H_9]$^+$, 35), 208 ([M-CO_2CH_3]$^+$, 56), 180 (16), 168 (46), 108 (70); HRMS (EI) *m/z* calcd for $C_{13}H_{21}NO_3Si$ 267.1291, found 267.1292.



41c

2-((*tert*-Butyldimethylsilyl)ethynyl)oxazole-4-carboxylic acid methyl ester (41c). A solution of 2-((*tert*-butyldimethylsilyl)ethynyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (2.080 g, 7.779 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was cooled to 0 °C under argon and treated with $BrCCl_3$ (0.815 mL, 8.27 mmol, 1.06 equiv) and DBU (1.250 mL, 8.359 mmol, 1.07 equiv). The mixture was stirred at 0 °C for 2 h and then treated with saturated aqueous $NaHCO_3$ (20 mL), stirred at rt for 30 min and extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid (20 mL), water (20 mL) and brine (20 mL). The combined aqueous washings were backwashed with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to a red syrup. Purification by chromatography on SiO_2 (10% to 20% ethyl ether/hexanes) afforded **41c** (1.880 g, 91%) as a clear, colorless syrup that crystallized to a white solid under vacuum: R_f 0.55 (40% ethyl ether/hexanes); Mp 50.5-51.5 °C (ethyl ether/hexanes); ^{1}H NMR δ 8.16 (s, 1 H), 3.91 (s, 3 H), 0.98 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR δ 161.1, 146.8, 144.3, 134.1, 99.8, 90.9, 52.5, 26.1, 16.8, -5.0; IR (neat) 3152, 2954, 2931, 2886, 2859, 2179, 1753, 1731, 1573, 1536 cm^{-1}; MS (EI) *m/z* (rel. intensity) 265 (M^+, 16), 250 ($[M\text{-}CH_3]^+$, 11), 234 ($[M\text{-}OCH_3]^+$, 15), 208 ($[M\text{-}C_4H_9]^+$, 100), 194 (19), 176 (6), 149 (16); HRMS (EI) *m/z* calcd for $C_{13}H_{19}NO_3Si$ 265.1134, found 265.1134.

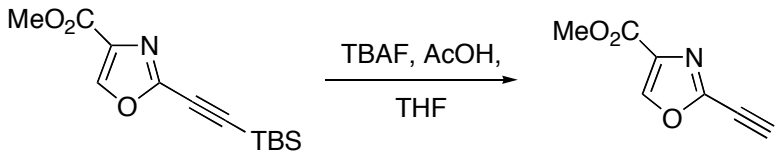


40d **41d**

2-[(Triisopropylsilyl)ethynyl]oxazole-4-carboxylic acid methyl ester (41d). A solution of **40d** (5.90 g, 18.0 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was cooled to –78 °C under argon. Diethylaminosulfurtrifluoride (DAST) (2.80 mL, 21.2 mmol, 1.2 equiv) was added. After 10 min at –78 °C, anhydrous K_2CO_3 (3.74 g, 27.06 mmol, 1.5 equiv) was added and the mixture was stirred at –78 °C for 15 min, then at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ (100 mL) was slowly added (caution: vigorous evolution of gas) and the cold bath was removed. After stirring for 1 h at rt, the mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to an amber oil, which was used without further purification. For analytical purposes, purification by chromatography on SiO_2 (20% to 30% ethyl ether/hexanes) afforded 2-[(triisopropylsilyl)ethynyl]-4,5-dihydrooxazole-4-carboxylic acid methyl ester as a pale yellow syrup: ^{1}H NMR δ 4.84 (dd, 1 H, J = 10.8, 8.4 Hz), 4.57 (app t, 1 H, J = 8.5 Hz), 4.46 (dd, 1 H, J = 10.8, 8.8 Hz), 3.80 (s, 3 H), 1.22-1.09 (m, 21 H); ^{13}C NMR δ 170.8, 151.6, 96.4, 93.1, 69.2, 68.5, 53.0, 18.6, 11.1; IR (neat) 2946, 2893, 2867, 2180, 1747, 1619, 1464, 1437, 1349, 1271, 1221 cm^{-1}; MS (EI) *m/z* (rel. intensity) 309 (M^+, 9), 266 ([M-C_3H_7]$^+$, 100), 250 ([M-CO_2CH_3]$^+$, 11), 238 (34); 224 (13), 196 (15); HRMS (EI) *m/z* calcd for $C_{16}H_{27}NO_3Si$ 309.1760, found 309.1760.

The crude oxazoline was azeotropically dried with toluene (2 x 25 mL) at reduced pressure, diluted with CH_2Cl_2 (100 mL) and cooled to –15 °C under N_2. $BrCCl_3$

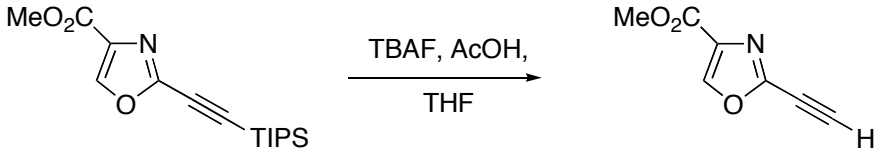
(2.13 mL, 21.61 mmol, 1.2 equiv) was added. DBU (2.96 mL, 19.79 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 1 h while the bath temperature increased to –5 °C. Ethyl ether (100 mL) was added and the mixture was filtered through a pad of SiO_2 (80 mm x 40 mm, prewetted with hexanes). The pad was washed with ethyl ether (150 mL) and the combined filtrate was concentrated to an orange-colored oil. Purification by chromatography on SiO_2 (5% to 20% ethyl ether/hexanes) afforded **41d** (4.09 g, 74%) as a pale yellow syrup: R_f 0.45 (20% ethyl ether/hexanes); ^{1}H NMR δ 8.17 (s, 1 H), 3.91 (s, 3 H), 1.18-1.07 (m, 21 H); ^{13}C NMR δ 161.1, 146.9, 144.2, 134.0, 98.4, 92.1, 52.5, 18.6, 11.2; IR (neat) 3151, 2946, 2892, 2867, 1753, 1732, 1574, 1536, 1465, 1436 cm^{-1}; MS (EI) *m/z* (rel. intensity) 307 (M^+, 19), 292 ($[M-CH_3]^+$, 5), 264 ($[M-C_3H_7]^+$, 100), 236 (34), 222 ($[M-C_6H_{13}]^+$, 8), 208 (32), 194 (16); HRMS (EI) *m/z* calcd for $C_{16}H_{25}NO_3Si$ 307.1604, found 307.1609.



41c **37**

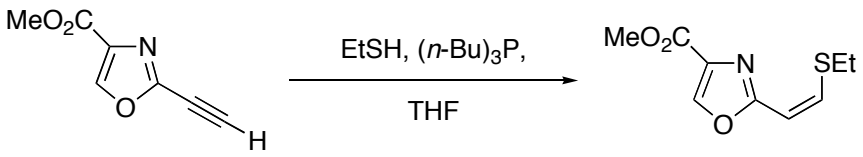
A solution of **41c** (1.880 g, 7.084 mmol, 1.0 equiv) in THF (40 mL) was cooled to –78 °C under argon. A solution of TBAF (1.0 M in THF, 7.80 mL, 7.80 mmol, 1.1 equiv) and glacial AcOH (450 µL, 7.86 mmol, 1.1 equiv) was added dropwise over 5 minutes. The mixture was stirred for 30 min (total) at –78 °C and then treated with saturated aqueous $NaHCO_3$ (25 mL), warmed to rt, diluted with H_2O (25 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to an orange solid that was dissolved in ethyl acetate and filtered through

a pad of SiO_2 (ethyl acetate rinse). The filtrate was concentrated to afford **37** (1.030 g, 96%) as a white, crystalline solid that was analytically identical to the material obtained from the TIPS-protected alkyne.



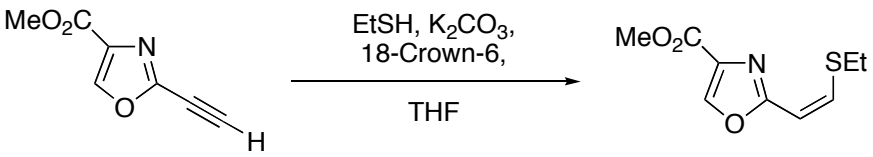
41d **37**

2-Ethynyloxazole-4-carboxylic acid methyl ester (37). A solution of **41d** (76.0 mg, 247 μmol, 1.0 equiv) in THF (2.5 mL) was cooled to –78 °C under argon. A stock solution of TBAF (0.50 mL of a 1.0 M solution on THF) and glacial acetic acid (50 μL) in THF (2.0 mL) was prepared and 1.25 mL was added dropwise over 5 min. After an additional 10 min, saturated, aqueous NH_4Cl was added (3.0 mL) at –78 °C and the mixture was warmed to rt, diluted with water and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford **37** (36.9 mg, 99%) as a white, crystalline solid: Mp 92.0-93.0 °C (CH_2Cl_2); ^{1}H NMR δ 8.20 (s, 1 H), 3.92 (s, 3 H), 3.29 (s, 1 H); ^{13}C NMR δ 160.9, 146.2, 144.7, 134.2, 81.4, 70.5, 52.6; IR (KBr) 3186, 3158, 3116, 2958, 2126, 1729, 1578, 1536, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 151 (M^+, 100), 123 (50), 120 ($[M\text{-}OCH_3]^+$, 77), 100 (99), 93 ($[M\text{-}CO_2CH_3\text{+H}]^+$, 21), 84 (26), 69 (37), 64 (75), 53 (52); HRMS (EI) *m/z* calcd for $C_7H_5NO_3$ 151.0269, found 151.0275.



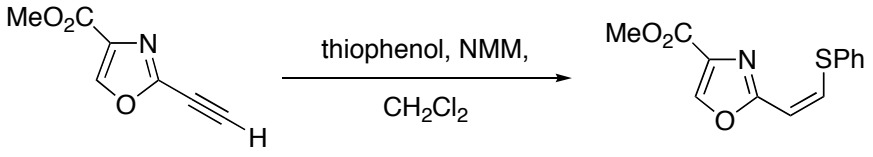
37 **42a**

2-(2-Ethylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (42a). To a solution of **37** (11.0 mg, 73 µmol, 1.0 equiv) in THF (1.0 mL) at rt under N_2, was added ethanethiol (40.0 µl, 540 µmol, 7.4 equiv) and a solution of tri-*n*-butyl phosphine (0.20 mL of a 27 mg/mL solution in THF, 5.4 mg, 26 µmol, 0.4 equiv). After stirring for 36 h at rt under N_2, the mixture was concentrated under vacuum. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*)-ratio of 10.5:1. The residue was purified by chromatography on SiO_2 (30 to 50% ethyl ether/hexanes) to give **42a** (10.9 mg, 70%) as a white solid that contained 7.6% of the (*E*)-isomer. (*Z*)-**42a**: Mp 61.9-63.5 °C (CH_2Cl_2); ^{1}H NMR δ 8.20 (s, 1 H), 6.87 (d, 1 H, *J* = 11.0 Hz), 6.34 (dd, 1 H, *J* = 11.0, 0.7 Hz), 3.90 (s, 3 H), 2.85 (dq, 2 H, *J* = 7.4, 0.7 Hz), 1.38 (dt, 3 H, *J* = 7.4, 0.9 Hz); ^{13}C NMR δ 162.0, 161.9, 143.0, 140.3, 134.5, 109.0, 52.2, 29.8, 15.6; IR (KBr) 3124, 3076, 2979, 2953, 2929, 2870, 2851, 1737, 1611 cm^{-1}; MS (EI) *m/z* (rel. intensity) 213 (M^+, 41), 184 ([M-CH_2CH_3]$^+$, 6), 153 ([M-CH_2CH_3-OCH_3]$^+$, 7), 86 (6), 84 (87), 66 (100); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_3S$ 213.0460, found 213.0459; Characteristic signals for the (*E*)-**42a**: ^{1}H NMR δ 8.10 (s, 1 H), 7.49 (d, 1 H, *J* = 15.6 Hz), 6.32 (d, 1 H, *J* = 15.6 Hz).



37 **42a**

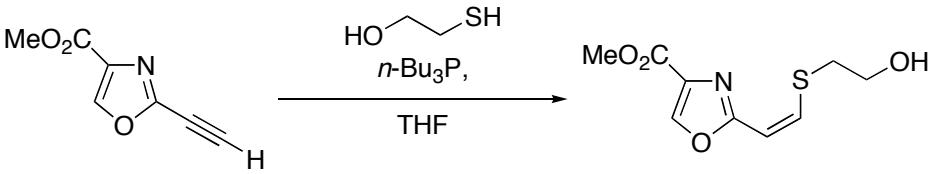
2-(2-Ethylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (42a). To a solution of **37** (20.0 mg, 132 μmol, 1.0 equiv) in THF (1.20 mL) at rt was added thioethanol (75.0 μL, 1.0 mmol, 7.7 equiv) and anhydrous K_2CO_3 (20.0 mg, 145 μmol, 1.1 equiv). 18-Crown-6 was added and the reaction mixture turned pale yellow. After stirring at rt for 1.5 h, the mixture was diluted with ethyl ether (2.0 mL) and filtered through a plug of Florisil/Celite (1:1, v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to a clear, colorless oil. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*)-ratio of 16.4:1.0. The residue was purified by chromatography on SiO_2 (30% to 50% ethyl ether/hexanes) to afford **42a** (25.2 mg, 89%) as a white solid that contained 3.5% of the (*E*)-isomer. The analytical data were identical to material obtained from the tri-*n*-butyl phosphine method.



37 **42b**

2-(2-Phenylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (42b). To a solution of **37** (6.4 mg, 42 μmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at rt under N_2, was added thiophenol (0.100 mL, 0.974 mmol, 23.2 equiv) and *N*-methyl morpholine (10 μL, 0.091 mmol, 2.1 equiv). After stirring for 48 h at rt, the solvent was removed under vacuum to give a pale yellow solid. Recrystallization from ethyl acetate/hexanes afforded **42b**

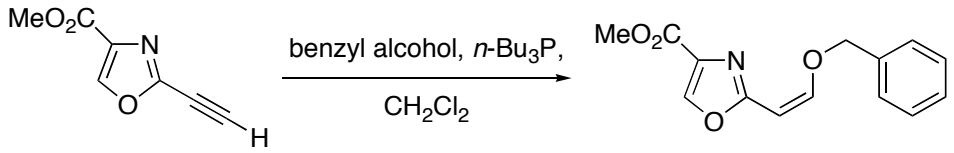
(10.7 mg, 97%) as a white crystalline solid: Mp 119.5-120.5 °C (CH_2Cl_2); ^{1}H NMR δ 8.22 (s, 1 H), 7.49-7.44 (m, 2 H), 7.37-7.28 (m, 3 H), 7.04 (d, 1 H, *J* = 11.0 Hz), 6.38 (d, 1 H, *J* = 11.0 Hz), 3.90 (s, 3 H); ^{13}C NMR δ 161.8, 161.3, 143.1, 140.1, 135.4, 134.5, 131.1, 129.5, 128.3, 109.1, 52.2; IR (KBr) 3124, 3075, 2952, 2848, 1736, 1709, 1614 cm^{-1}; MS (EI) *m/z* (rel. intensity) 261 (M^+, 100), 230 ($[M-OCH_3]^+$, 6), 202 ($[M-OCOCH_3]^+$, 7), 184 ($[M-C_6H_5]^+$, 51), 172 (44), 147 (30), 77 (15); HRMS (EI) *m/z* calcd for $C_{13}H_{11}NO_3S$ 261.0460, found 261.0459.



37 **42c**

2-[2-(2-Hydroxyethylsulfanyl)vinyl]oxazole-4-carboxylic acid methyl ester (42c). To a solution of **37** (50.0 mg, 331 μmol, 1.0 equiv) in THF (3.0 mL) at rt under N_2 was added 2-mercaptoethanol (28.0 μL, 399 μmol, 1.2 equiv). A solution of tri-*n*-butylphosphine (100 mg/mL, 0.330 mL, 33 mg, 0.5 equiv) was added and the mixture was stirred at rt for 1 h then heated to 60 °C for 6 h. The mixture was then heated at reflux for 18 h with no additional change occurring as indicated by TLC analysis. Concentration under vacuum and purification by chromatography on SiO_2 (60% ethyl acetate/hexanes) afforded **42c** (51.6 mg, 68%) in a (*Z*/*E*)-ratio of 6.4:1.0 as an amorphous solid that crystallized on standing: R_f 0.23 (60% ethyl acetate/hexanes); Mp 95.2-97.2 °C (CH_2Cl_2); ^{1}H NMR δ 8.19 (s, 1 H), 6.89 (d, 1 H, *J* = 11.0 Hz), 6.34 (d, 1 H, *J* = 11.0 Hz), 3.90 (s, 3 H), 3.87 (t, 2 H, *J* = 6.0 Hz), 3.02 (t, 2 H, *J* = 6.0 Hz), 2.32 (bs, 1 H); ^{13}C NMR δ 161.9, 161.6, 143.1, 140.3, 134.3, 109.4, 62.1, 52.4, 38.6; IR (KBr)

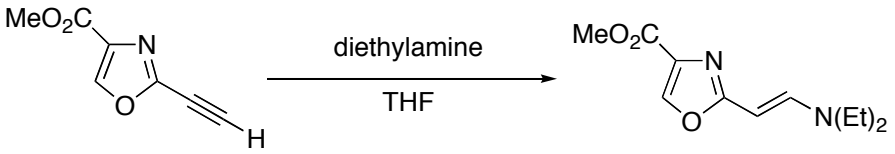
3342, 3176, 3017, 2957, 2929, 1752, 1594, 1441 cm^{-1}; MS (EI) *m/z* (rel. intensity) 229 (M^+, 32), 211 ([M-H_2O]$^+$, 37), 198 ([M-OCH_3]$^+$, 25), 184 ([M-CH_2CH_2OH]$^+$, 100), 151 ([M-$HSCH_2CH_2OH$]$^+$, 52), 139 ([M-CO_2Me-CH_2OH]$^+$, 42), 125 ([M-CO_2CH_3-CH_2CH_2OH]$^+$, 25), 110 (55); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_4S$ 229.0409, found 229.0411. Characteristic signals for the (*E*)-isomer: ^{1}H NMR δ 8.09 (s, 1 H), 7.47 (d, 1 H, *J* = 15.7 Hz), 6.31 (d, 1 H, *J* = 15.7 Hz).



37 **42d**

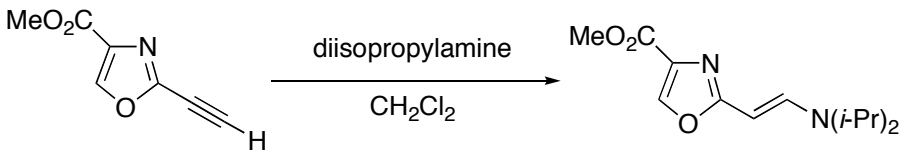
2-(2-Benzyloxyvinyl)oxazole-4-carboxylic acid methyl ester (42d). To a solution of **37** (10.0 mg, 66 μmol, 1.0 equiv)) and benzyl alcohol (20.0 μL, 193 μmol, 2.9 equiv) in CH_2Cl_2 (1.0 mL) was added a solution of tri-*n*-butylphosphine (13.4 mg, 66 μmol, 1.0 equiv) in CH_2Cl_2 (100 μL). The mixture immediately turned yellow then slowly became dark red over 30 min. The mixture was filtered through a plug of SiO_2 (2 cm in a pasteur pipette) and the plug was washed with ethyl ether. The combined filtrate was concentrated under vacuum to a yellow oil. ^{1}H NMR analysis of the oil indicated a (*Z*/*E*)-ratio of 6.4:1.0 Purification by chromatography on SiO_2 (25% ethyl ether/hexanes) afforded **42d** (13.0 mg, 76%) as a white, crystalline solid: R_f 0.31 (60% ethyl ether/hexanes); Mp 79.2-80.5 °C (CH_2Cl_2); ^{1}H NMR δ 8.06 (s, 1 H), 7.64 (d, 1 H, *J* = 12.9 Hz), 7.45-7.31 (m, 5 H), 5.82 (d, 1 H, *J* = 12.9 Hz), 4.95 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR δ 162.0, 156.3, 142.4, 135.5, 133.8, 128.9, 128.8, 127.9, 93.8, 73.0, 52.3; IR (KBr) 3144, 3082, 3027, 2948, 2917, 1719, 1656, 1576, 1452, 1430 cm^{-1}; MS (EI) *m/z* (rel.

intensity) 259 (M^+, 13), 91 (100), 65 (15); HRMS (EI) *m/z* calcd for $C_{14}H_{13}NO_4$ 259.0845, found 259.0855.



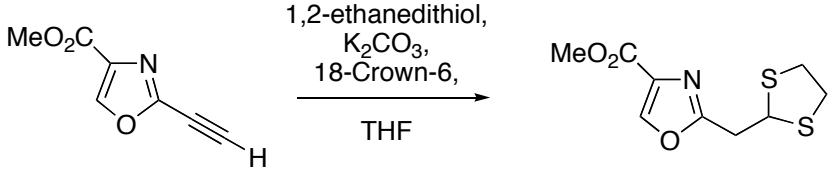
37 **42e**

2-(2-Diethylaminovinyl)oxazole-4-carboxylic acid methyl ester (42e). To a solution of **37** (50.0 mg, 331 µmol, 1.0 equiv) in THF (2.0 mL) at rt under N_2 was added diethylamine (50 µL, 480 µmol, 1.5 equiv). After 4 h at rt, additional diethylamine (50 µL, 480 µmol, 1.5 equiv) was added. After 18 h (total reaction time) at rt, TLC analysis indicated that starting alkyne remained, so additional diethylamine (100 µL, 970 µmol, 3.0 equiv) was added and the mixture was heated to 60 °C for 2 h, then cooled to rt. The volatile components were removed under vacuum and the resulting residue was purified by chromatography on SiO_2 (40% ethyl ether/hexanes) to give **42e** (74.4 mg, 100%) as a clear, colorless oil: R_f 0.23 (60% ethyl ether/hexanes); ^{1}H NMR δ 7.90 (s, 1 H), 7.32 (d, 1 H, *J* = 13.6 Hz), 4.93 (d, 1 H, *J* = 13.6 Hz), 3.83 (s, 3 H), 3.15 (q, 4 H, *J* = 7.1 Hz), 1.11 (t, 6 H, *J* = 7.1 Hz); ^{13}C NMR δ 166.1, 162.6, 145.4, 140.6, 133.3, 80.1, 51.9, 46.1, 13.2; IR (neat) 3161, 3085, 2975, 2945, 2930, 2868, 1738, 1634, 1573, 1553 cm^{-1}; MS (EI) *m/z* (rel. intensity) 224 (M^+, 83), 209 ($[M\text{-}CH_3]^+$, 21), 195 ($[M\text{-}CH_2CH_3]^+$, 44), 164 ($[M\text{-}HOCOCH_3]^+$, 70), 163 (46), 135 (100), 109 (62), 181 (11); HRMS (EI) *m/z* calcd for $C_{11}H_{16}N_2O_3$ 224.1161, found 224.1158.



37 **42f**

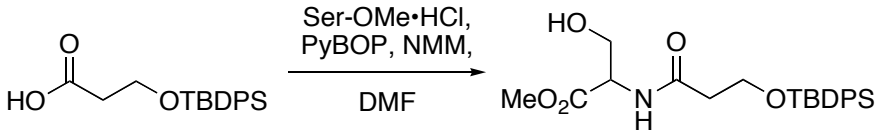
2-(2-Diisopropylaminovinyl)oxazole-4-carboxylic acid methyl ester (42f). To a solution of **37** (10.0 mg, 66 μmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at rt under N_2 was added diisopropylamine (20 μL, 143 μmol, 2.2 equiv). After 24 h at rt, additional diisopropylamine (100 μL, 714 μmol, 10.8 equiv) was added and the mixture was stirred at rt for an additional 48 h (72 h total). Volatile components were removed under vacuum and the resulting residue was purified by chromatography on SiO_2 (40% ethyl ether/hexanes) to afford **42f** (17.0 mg, 100%) as a clear, colorless oil: ^{1}H NMR δ 7.94 (s, 1 H), 7.41 (d, 1 H, *J* = 13.7 Hz), 5.09 (d, 1 H, *J* = 13.7 Hz), 3.87 (s, 3 H), 3.66 (sept, 2 H, *J* = 6.7 Hz), 1.20 (d, 12 H, *J* = 6.7 Hz); ^{13}C NMR δ 166.5, 162.8, 141.4, 140.6, 133.4, 80.6, 52.0, 47.8, 21.7; IR (neat) 3160, 3088, 2975, 2934, 2872, 1743, 1720, 1627, 1571, 1552, 1463, 1435 cm^{-1}; MS (EI) *m/z* (rel. intensity) 252 (M^+, 43), 237 ($[M\text{-}CH_3]^+$, 34), 221 ($[M\text{-}OCH_3]^+$, 8), 209 ($[M\text{-}CH(CH_3)_2]^+$, 100), 195 (36), 192 (16), 177 (38), 163 (62), 149 (31), 135 (27); HRMS (EI) *m/z* calcd for $C_{13}H_{20}N_2O_3$ 252.1474, found 252.1473.



37 **43**

2-[1,3]-Dithiolan-2-ylmethyloxazole-4-carboxylic acid methyl ester (43). To a solution of **37** (342.5 mg, 2.266 mmol, 1.0 equiv) in THF (11.0 mL) at rt was added anhydrous K_2CO_3 (150.0 mg, 1.085 mmol, 0.5 equiv) and 1,2-ethanedithiol (950 μL,

11.3 mmol, 5.0 equiv). 18-Crown-6 was added and the mixture became turbid and pale yellow within 10 min. The solution was stirred for 12 h at rt and then evaporated onto a blend of Florisil/Celite (1:1 v/v). The resulting solid was directly purified by chromatography on SiO_2 (30% to 60% ethyl ether/hexanes) to afford **43** (538.0 mg, 97%) as a white, crystalline solid: Mp 84.0-85.0 °C (ethyl acetate/hexanes); ^{1}H NMR δ 8.15 (s, 1 H), 4.93 (t, 1 H, *J* = 7.4 Hz), 3.87 (s, 3 H), 3.27 (d, 2 H, *J* = 7.4 Hz), 3.23, 3.24 (d of AB, 4 H, *J* = 6.3, 1.3 Hz); ^{13}C NMR δ 162.8, 161.7, 144.1, 133.4, 52.3, 49.9, 39.0, 38.8; IR (KBr) 3165, 3118, 2956, 2919, 1726, 1583, 1437, 1423, 1320, 1159, 1110 cm^{-1}; MS (EI) *m/z* (rel. intensity) 245 (M^+, 25), 217 ($[M-C_2H_4]^+$, 7), 186 ($[M-CO_2CH_3]^+$, 32), 154 ($[M-OCH_3-SCH_2CH_2]^+$, 11), 141 (19), 105 (100), 61 (13), 59 (9); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_3S_2$ 245.0180, found 245.0173.



45 **46**

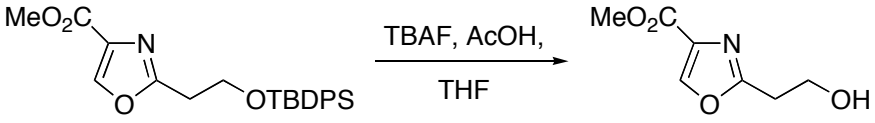
Methyl 2-(3-(*tert*-butyldiphenylsilyloxy)propanamido)-3-hydroxypropanoate (46). A mixture of **45** (4.113 g, 12.52 mmol, 1.0 equiv) and serine methyl ester hydrochloride (2.920 g, 18.77 mmol, 1.5 equiv) in DMF (15.0 mL) was cooled to 0 °C under N_2 and treated with PyBOP (7.170 g, 13.78 mmol, 1.1 equiv) and *N*-methylmorpholine (4.82 mL, 43.8 mmol, 3.5 equiv). The mixture was stirred at 0 °C for 30 min, warmed to rt for 24 h, quenched with saturated aqueous $NaHCO_3$ (50 mL), poured into water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid (2 x 25 mL), water (25 mL) and 4.0 M aqueous LiCl (25 mL). The combined aqueous washings were backwashed with

ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (60% to 100% ethyl acetate/hexanes) afforded **46** (5.314 g, 99%) as a pale yellow syrup that crystallized to a white solid on standing: R_f 0.40 (60% ethyl acetate/hexanes); Mp 77.4-79.4 °C (ethyl acetate/hexanes); ^{1}H NMR (acetone-d6) δ 7.76-7.71 (m, 4 H), 7.56-7.52 (m, 1 H), 7.48-7.34 (m, 6 H), 4.63 (dt, 1 H, *J* = 8.2, 4.2 Hz), 4.26 (bt, 1 H, *J* = 5.3 Hz), 3.99 (t, 2 H, *J* = 6.2 Hz), 3.96-3.91 (m, 1 H), 3.84-3.76 (m, 1 H), 3.67 (s, 3 H), 2.59 (t, 2 H, *J* = 6.2 Hz), 1.04 (s, 9 H); ^{13}C NMR (acetone-d6) δ 171.8, 171.6, 136.3, 134.4, 130.7, 128.7, 63.2, 61.4, 55.6, 52.4, 39.8, 27.2, 19.7; IR (neat) 3365, 3071, 3049, 2955, 2932, 2886, 2858, 1744, 1655, 1537 cm^{-1}; MS (EI) *m/z* (rel. intensity) 414 ([M-CH_3]$^+$, 0.2), 372 ([M-C_4H_9]$^+$, 54), 354 ([M-C_4H_9-H_2O]$^+$, 100), 294 (11), 222 (26), 199 (44); HRMS (EI) *m/z* calcd for $C_{22}H_{28}NO_5Si$ (M-CH_3) 414.1737, found 414.1744.

46 **47**

2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)oxazole-4-carboxylic acid methyl ester (47). A solution of **46** (5.314 g, 12.37 mmol, 1.0 equiv) in CH_2Cl_2 (70.0 mL) was cooled to –78 °C under N_2, treated with DAST (1.80 mL, 13.62 mmol, 1.1 equiv), stirred at –78 °C for 50 min, treated with anhydrous K_2CO_3 (2.56 g, 18.5 mmol, 1.5 equiv), warmed to 0 °C for 15 min and then treated with $NaHCO_3$ (10 mL). The cold bath was removed and the mixture was stirred at rt for 1 h and extracted with CH_2Cl_2. The combined organic layers were concentrated, diluted with a small portion of CH_2Cl_2 and poured

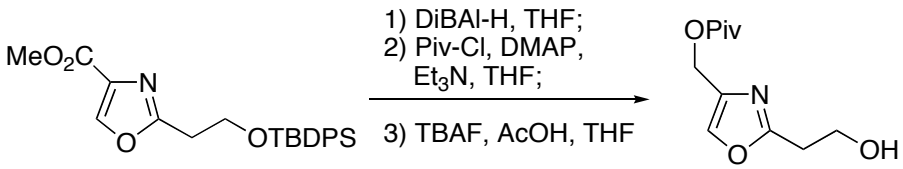
onto a pad of SiO_2 (40 mm x 10 cm). Gradient elution (20% to 40% ethyl ether/CH_2Cl_2) and concentration of the filtrate afforded the crude oxazoline (4.570 g, 90%) as an orange-colored oil that was diluted with CH_2Cl_2 (60 mL), cooled to 0 °C and treated with $BrCCl_3$ (1.220 mL, 12.38 mmol, 1.1 equiv) and DBU (1.820 mL, 12.17 mmol, 1.1 equiv). The cold bath was removed and the mixture was stirred at rt. Additional $BrCCl_3$ (0.150 mL, 1.52 mmol, 0.14 equiv) and DBU (0.180 mL, 1.20 mmol, 0.11 equiv) were added at 2 h and 6 h. After 22 h, the mixture was poured onto a pad of SiO_2 (40 mm x 10 cm) and eluted with 20% ethyl ether/hexanes (200 mL). The filtrate was concentrated to a pale yellow syrup. Purification by chromatography on SiO_2 (20 to 30% ethyl ether/hexanes) afforded **47** (3.726 g, 82%) as a clear, colorless syrup: R_f 0.51 (60% ethyl ether/hexanes); ^{1}H NMR δ 8.13 (s, 1 H), 7.62-7.59 (m, 4 H), 7.44-7.33 (m, 6 H), 4.06 (t, 2 H, *J* = 6.6 Hz), 3.91 (s, 3 H), 3.07 (t, 2 H, *J* = 6.6 Hz), 1.00 (s, 9 H); ^{13}C NMR δ 163.8, 161.9, 144.0, 135.7 (2 C), 133.4, 129.9, 127.9, 61.2, 52.2, 31.9, 26.9, 19.2; IR (neat) 3162, 3131, 3071, 3049, 2954, 2932, 2887, 2857, 1750, 1729, 1587 cm^{-1}; MS (EI) *m/z* (rel. intensity) 394 (M^+, 0.4), 378 ($[M-OCH_3]^+$, 1.8), 352 ($[M-C_4H_9]^+$, 100); HRMS (EI) *m/z* calcd for $C_{19}H_{18}NO_4Si$ (M-C_4H_9) 352.1005, found 352.1009.



47 **48**

2-(2-Hydroxyethyl)oxazole-4-carboxylic acid methyl ester (48). A solution of **47** (87.8 mg, 0.214 mmol, 1.0 equiv) in THF (1.0 mL) at rt was treated with glacial AcOH (15 µL, 0.26 mmol, 1.2 equiv) and TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol, 1.1 equiv), stirred for 24 h, treated with additional TBAF (1.0 M in THF, 0.10 mL, 0.10 mmol, 0.5

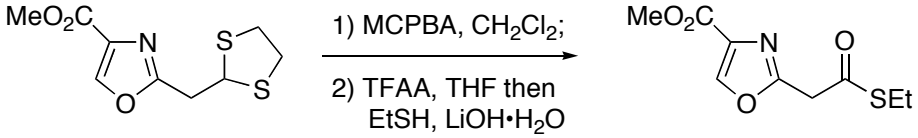
equiv) and stirred at rt for an additional 24 h. The mixture was quenched with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (90% ethyl acetate/hexanes to 100% ethyl acetate) afforded **48** (24.7 mg, 68%) as a clear, colorless syrup: Mp 62.9-63.7 °C (CH_2Cl_2); ^{1}H NMR δ 8.15 (s, 1 H), 4.04 (t, 2 H, *J* = 5.9 Hz), 3.88 (s, 3 H), 3.04 (t, 2 H, *J* = 5.9 Hz), 2.74 (bs, 1 H); ^{13}C NMR δ 164.1, 161.8, 144.1, 133.2, 59.2, 52.3, 31.4; IR (neat) 3394, 2956, 2894, 1736, 1588 cm^{-1}; MS (EI) *m/z* (rel. intensity) 171 (M^+, 0.3), 141 ($[M-OCH_2]^+$, 6), 127 (12); HRMS (EI) *m/z* calcd for $C_6H_7NO_3$ (M-CH_2O) 141.0426, found 141.0426.



47 **49**

(2-(2-Hydroxyethyl)oxazol-4-yl)methyl pivaloate (49). A solution of **47** (418.0 mg, 1.021 mmol, 1.0 equiv) in THF (5.0 mL) was cooled under N_2 to –20 °C, treated with a solution of DiBAl-H (1.0 M in hexanes, 4.00 mL, 4.00 mmol, 3.9 equiv), slowly warmed to 0 °C over 2 h and treated with 1.0 M aqueous L-tartaric acid (4.0 mL) and brine (4.0 mL). The resulting mixture was stirred at rt for 2 h and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow oil that was azeotropically dried with toluene, diluted with THF (5.0 mL), cooled to 0 °C and treated with DMAP (12.0 mg, 0.098 mmol, 0.1 equiv), triethylamine (500 µL, 3.56 mmol, 3.5 equiv) and pivaloyl chloride (250 µL, 2.03 mmol, 2.0 equiv). The mixture was stirred at rt for 12 h, treated with saturated, aqueous

$NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was diluted with THF (5.0 mL), cooled to 0 °C and treated with glacial acetic acid (60.0 µL, 1.05 mmol, 1.0 equiv) and TBAF (1.0 M in THF, 1.50 mL, 1.50 mmol, 1.5 equiv), stirred at rt for 18 h, treated with saturated, aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% ethyl acetate/hexanes) afforded **49** (174.1 mg, 75%, 3 steps) as a clear, colorless syrup: R_f 0.35 (60% ethyl acetate/hexanes); ^{1}H NMR δ 7.52 (s, 1 H,), 4.94 (s, 2 H), 3.96 (bs, 2 H), 3.52 (bs, 1 H), 2.95 (t, 2 H, *J* = 5.9 Hz), 1.15 (s, 9 H); ^{13}C NMR δ 178.4, 163.5, 136.9, 136.1, 59.2, 58.1, 38.9, 31.2, 27.2; IR (neat) 3375, 3142, 2973, 2930, 2875, 1728, 1577 cm^{-1}; MS (EI) *m/z* (rel. intensity) 227 (M^+, 2.8), 197 ([M-C_2H_6]$^+$, 2.0), 142 ([M-$(CH_3)_3CCO$]$^+$, 78), 126 ([M-$(CH_3)_3CCO_2$]$^+$, 32), 57 (C_4H_9, 100); HRMS (EI) *m/z* calcd for $C_{11}H_{17}NO_4$ 227.1158, found 227.1161.

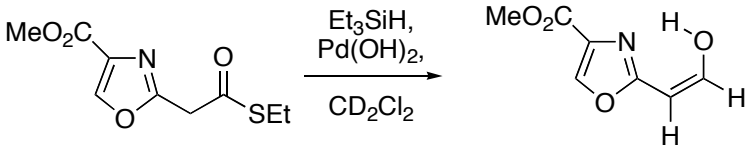


43 **51**

2-Ethylsulfanylcarbonylmethyloxazole-4-carboxylic acid methyl ester (51). A solution of **43** (620 mg, 2.53 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) was cooled under N_2 to –78 °C. A suspension of MCPBA (920 mg, 5.33 mmol, 2.1 eqiv) in CH_2Cl_2 (5.0 mL + 5.0 mL rinse) was added. After 20 min at –78 °C, Florisil/Celite (1:1 v/v) was added and the mixture was warmed to rt and concentrated under vacuum. The resulting mixture was purified by chromatography on SiO_2 (10% methanol/ethyl acetate)

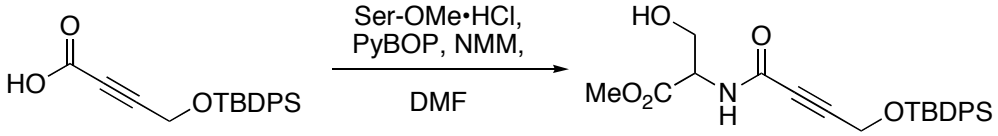
affording the dithiolanedioxide **50** (678 mg, 97%) as a white solid that was used without further purification: R_f 0.25 (10% methanol/ethyl acetate).

A suspension of **50** (62.0 mg, 224 μmol, 1.0 equiv) in THF (3.0 mL) was cooled to 0 °C under N_2 and pyridine (43.0 μL, 530 μmol, 2.4 equiv) was added. TFAA (44.0 μL, 312 μmol, 1.4 equiv) was added dropwise and the mixture was stirred for 30 min at 0 °C. Additional TFAA (10.0 μL, 71 μmol, 0.3 equiv) was added and after an additional 15 min at 0 °C, ethanethiol (166 μL, 2.24 mmol, 10 equiv), water (100 μL, 5.56 mmol, 25 equiv) and $LiOH•H_2O$ (47.0 mg, 1.12 mmol, 5.0 equiv) were sequentially added. After stirring for 1 h at 0 °C, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid, water and brine, dried (Na_2SO_4), filtered and concentrated to a pale yellow oil. Purification by chromatography on SiO_2 (40% ethyl ether/hexanes) afforded **51** (41.0 mg, 80%) as a clear, colorless syrup that contained some impurities as indicated by ^{1}H NMR analysis: R_f 0.20 (40% ethyl ether/hexanes); ^{1}H NMR δ 8.21 (s, 1 H), 4.06 (s, 2 H), 3.88 (s, 3 H), 2.90 (q, 2 H, *J* = 7.4 Hz), 1.23 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 192.0, 161.4, 158.1, 145.0, 133.8, 52.4, 42.9, 24.1, 14.5; IR (neat) 3160, 3124, 2954, 2933, 2868, 2848, 1739, 1688, 1583, 1438, 1323 cm^{-1}; MS (EI) *m/z* (rel. intensity) 229 (M^+, 12), 198 ($[M\text{-}OCH_3]^+$, 9), 168 ($[M\text{-}SCH_2CH_3]^+$, 27), 141 (100), 109 (72), 89 (37), 57 (43); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_4S$ 229.0409, found 229.0399.



51 **44a**

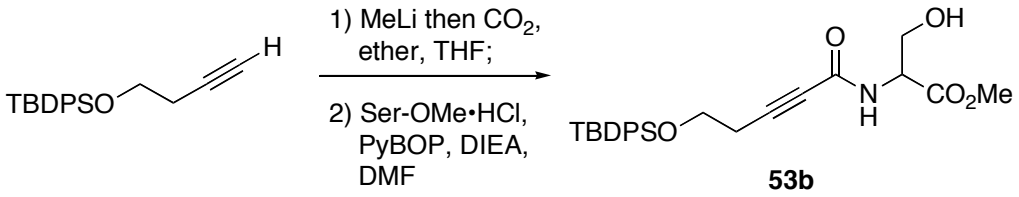
2-(2-Hydroxyvinyl)oxazole-4-carboxylic acid methyl ester (44a). To a solution of **51** (11.0 mg, 48 μmol, 1.0 equiv) in CD_2Cl_2 (1.0 mL) was added $Pd(OH)_2$ (wet Degussa type E101 NE/W, 20% Pd content, 5.5 mg) and the flask was partially evacuated and then flushed with N_2 (2 cycles). Et_3SiH (50 μL, 310 μmol, 6.5 equiv) was added and the mixture was stirred at rt. After 7.5 h, additional Et_3SiH (50 μL, 310 μmol, 6.5 equiv) was added and stirred for 1.5 h (9 h total). The mixture was filtered rapidly through a plug of Florisil/Celite (1:1 v/v) and the filtrate was carefully concentrated under vacuum to approximately 0.5 mL, then transferred to an NMR tube. ^{1}H NMR analysis indicated a **44a**/**51** ratio of 2:1. **44a**: R_f 0.46 (60% ethyl ether/hexanes); ^{1}H NMR (CD_2Cl_2) δ 8.13 (s, 1 H), 6.76 (d, 1 H, *J* = 6.4 Hz), 5.47 (d, 1 H, *J* = 6.4 Hz), 3.85 (s, 3 H).



52a **53a**

Methyl 2-(4-(*tert*-butyldiphenylsilyloxy)but-2-ynamido)-3-hydroxypropanoate (53a). A mixture of **52a** (4.84 g, 14.3 mmol, 1.0 equiv), serine methyl ester hydrochloride (4.00 g, 25.7 mmol, 1.8 equiv) and PyBOP (7.50 g, 14.4 mmol, 1.0 equiv) in DMF (10 mL) was cooled to 0 °C and treated with *N*-methyl morpholine (5.00 mL, 45.3 mmol, 3.2 equiv). The mixture was stirred at rt for 20 h, quenched with saturated,

aqueous $NaHCO_3$, poured into water and extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid, water, 4.0 M aqueous LiCl, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (50% to 70% ethyl acetate/hexanes) afforded **53a** (1.964 g, 31%) as a pale yellow syrup that was used without further purification.

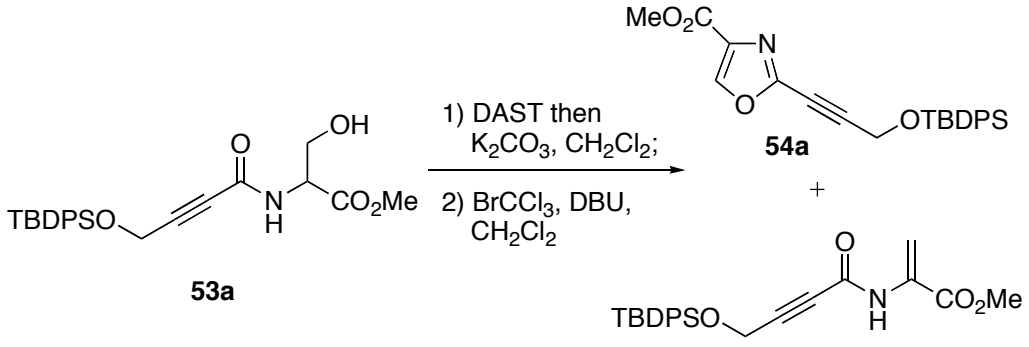


53b

2-[5-(*tert*-Butyldiphenylsilyloxy)pent-2-ynoylamino]-3-hydroxy-propionic acid methyl ester (53b). A solution of 1-(*tert*-butyl)diphenylsiloxybut-3-yne (2.00 g, 6.48 mmol, 1.0 equiv) in THF (40 mL) was cooled to –78 °C under N_2. MeLi (1.5 M in diethyl ether, 6.00 mL, 9.00 mmol, 1.4 equiv) was added and the mixture was stirred at –78 °C for 1 h, warmed to 0 °C for 15 min and then cooled to –78 °C. CO_2 (gas from dry ice, passed over anhydrous $CaSO_4$) was bubbled into the reaction mixture. After 10 min, the mixture was warmed to 0 °C, stirred for 20 min and slowly quenched by the addition of 2.0 M aqueous $NaHSO_4$ (20 mL). The mixture was poured into brine (20 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford 5-(*tert*-butyldiphenylsilyloxy)pent-2-ynoic acid as a pale yellow syrup (2.48 g, quant.) that was used without further purification.

A mixture of the crude 5-(*tert*-butyldiphenylsilyloxy)pent-2-ynoic acid (2.48 g, 7.04 mmol, 1.0 equiv) and DL-serine methyl ester hydrochloride (1.64 g, 10.5 mmol, 1.5 equiv) was dissolved in DMF (10 mL) and cooled to 0 °C under N_2. PyBOP (4.10 g,

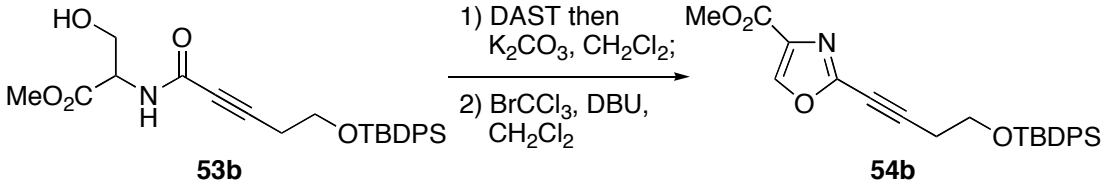
7.88 mmol, 1.1 equiv) and diisopropylethylamine (4.30 mL, 24.7 mmol, 3.5 equiv) were added and the cold bath was removed. After stirring at rt for 36 h, saturated, aqueous $NaHCO_3$ (10 mL) was added and the mixture was stirred for 30 min, then poured into water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid (50 mL), water (50 mL) and 4.0 M aqueous LiCl (50 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (50% ethyl acetate/hexanes) afforded **53b** (2.63 g, 90% for 2 steps) as a clear, colorless syrup: R_f 0.40 (60% ethyl acetate/hexanes); ^{1}H NMR δ 7.68-7.66 (m, 4 H), 7.47-7.37 (m, 6 H), 6.67 (d, 1 H, *J* = 7.4 Hz), 4.67 (ddd, 1 H, *J* = 7.2, 7.2, 3.4 Hz), 3.99 (ddd, 1 H, *J* = 11.2, 5.5, 3.9 Hz), 3.90 (ddd, 1 H, *J* = 11.2, 5.3, 3.5 Hz), 3.81 (t, 2 H, *J* = 6.9 Hz), 3.78 (s, 3 H), 2.57 (t, 2 H, *J* = 6.9 Hz), 2.48 (t, 1 H, *J* = 5.8 Hz), 1.07 (s, 9 H); ^{13}C NMR δ 170.4, 153.4, 135.7, 133.4, 130.0, 128.0, 86.2, 76.0, 63.1, 61.6, 54.9, 53.1, 26.9, 22.9, 19.4; IR (neat) 3412, 3071, 3049, 2955, 2930, 2885, 2858, 2243, 1963, 1894, 1829, 1743, 1644, 1516, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 438 ([M-OH]$^+$, 22), 422 ([M-CH_3OH]$^+$, 47), 396 ([M-C_4H_9]$^+$, 100), 378 ([M-C_4H_9-H_2O]$^+$, 26), 199 (30), 105 (36); HRMS (EI) *m/z* calcd for $C_{21}H_{22}NO_5Si$ (M-C_4H_9) 396.1267, found 396.1279.



2-[4-(*tert*-Butyldiphenylsilyloxy)prop-1-ynyl]oxazole-4-carboxylic acid methyl ester (54a). A solution of **53a** (1.964 g, 4.468 mmol, 1.0 equiv) in CH_2Cl_2 (25.0

mL) was cooled under N_2 to –78 °C, treated with DAST (620 μL, 4.692 mmol, 1.05 equiv), stirred for 15 min and treated with anhydrous K_2CO_3 (1.600 g, 11.58 mmol, 2.6 equiv), warmed to 0 °C and stirred for 1 h. The mixture was treated with saturated, aqueous $NaHCO_3$ (25 mL), stirred at rt for 30 min and then extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was azeotropically dried with toluene (2 mL) at reduced pressure, diluted with CH_2Cl_2 (25.0 mL), cooled to 0 °C and treated with $BrCCl_3$ (530 μL, 5.38 mmol, 1.2 equiv) and DBU (735 μL, 4.92 mmol, 1.1 equiv). After stirring for 40 min at 0 °C, the mixture was diluted with ethyl ether (25.0 mL), poured onto a pad of SiO_2 and the pad was washed with ethyl ether (150 mL). The combined filtrate was concentrated to a yellow syrup. Purification by chromatography on SiO_2 (20% ethyl ether/hexanes) afforded **54a** (770.9 mg, 41%) as a yellow syrup and methyl 2-(4-(*tert*-butyldiphenylsilyloxy)but-2-ynamido)acrylate (505.0 mg, 27%) as a yellow syrup. **54a**: R_f 0.35 (40% ethyl ether/hexanes); ^{1}H NMR δ 8.19 (s, 1 H), 7.71-7.69 (m, 4 H), 7.47-7.37 (m, 6 H), 4.51 (s, 2 H), 3.93 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR δ 161.1, 146.8, 144.5, 135.8, 134.2, 132.6, 130.2, 128.1, 91.7, 72.1, 52.8, 52.5, 26.8, 19.4; IR (neat) 3157, 3072, 3049, 2954, 2932, 2894, 2858, 2254, 1752, 1726, 1573, 1548 cm^{-1}; MS (EI) *m/z* (rel. intensity) 419 (M^+, 10), 388 ([M-OCH_3]$^+$, 9), 362 ([M-C_4H_9]$^+$, 100), 332 ([M-C_4H_9-OCH_3]$^+$, 91); HRMS (EI) *m/z* calcd for $C_{24}H_{25}NO_4Si$ 419.1553, found 419.1563. **Methyl 2-(4-(*tert*-butyldiphenylsilyloxy)but-2-ynamido)acrylate**: R_f 0.49 (40% ethyl ether/hexanes); ^{1}H NMR δ 7.90 (bs, 1 H), 7.72-7.69 (m, 4 H), 7.48-7.39 (m, 6 H), 6.58 (s, 1 H), 5.97 (d, 1 H, *J* = 1.3 Hz), 4.43 (s, 2 H), 3.87 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR δ 164.1, 150.8, 135.8,

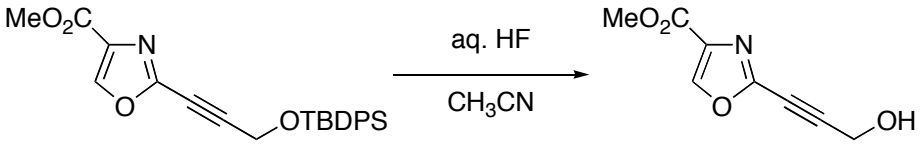
132.6, 130.8, 130.3, 128.1, 110.7, 85.3, 79.1, 53.3, 52.5, 26.9, 19.4; IR (neat) 3389, 3071, 3049, 2956, 2932, 2894, 2858, 2235, 1724, 1676, 1509 cm^{-1}; MS (EI) *m/z* (rel. intensity) 364 ($[M-C_4H_9]^+$, 6), 295 (20), 267 (20), 199 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{18}NO_4Si$ (M-C_4H_9) 364.1005, found 364.0990.



53b **54b**

2-[4-(*tert*-Butyldiphenylsilyloxy)but-1-ynyl]oxazole-4-carboxylic acid methyl ester (54b). A solution of **53b** (2.63 g, 5.81 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was cooled to -78 °C under N_2 and diethylaminosulfurtrifluoride (DAST) (810 µL, 6.13 mmol, 1.1 equiv) was added dropwise over 2 min. The mixture was stirred for 10 min at -78 °C, then anhydrous K_2CO_3 (1.20 g, 8.68 mmol, 1.5 equiv) was added. The -78 °C bath was replaced with a 0 °C bath and, after 10 min, saturated, aqueous $NaHCO_3$ (20 mL) was carefully added (caution: vigorous evolution of gas). The cold bath was removed and the mixture was stirred at rt for 1 h, diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was azeotropically dried at reduced pressure from toluene (10 mL), diluted with CH_2Cl_2 (30 mL) and cooled to 0 °C under N_2. $BrCCl_3$ (630 µL, 6.39 mmol, 1.1 equiv) and DBU (950 µL, 6.35 mmol, 1.1 equiv) were added and the mixture was stirred at 0 °C for 4 h. Hexanes (50 mL) was added and the mixture was poured onto a pad of SiO_2 (40 mm x 40 mm) and eluted with 50% ethyl ether/hexanes. The combined filtrate was concentrated to a yellow syrup which was purified by chromatography on SiO_2 (10% ethyl ether/hexanes) to afford **54b** (1.91 g, 76%) as a

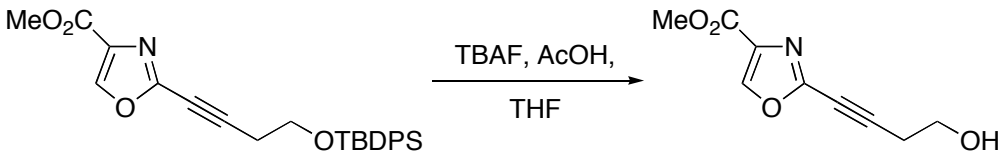
clear colorless, syrup: R_f 0.37 (40% ethyl ether/hexanes); ^{1}H NMR δ 8.15 (s, 1 H), 7.69-7.66 (m, 4 H), 7.47-7.36 (m, 6 H), 3.91 (s, 3 H), 3.86 (t, 2 H, *J* = 6.8 Hz), 2.69 (t, 2 H, *J* = 6.8 Hz), 1.06 (s, 9 H); ^{13}C NMR δ 161.2, 147.3, 144.1, 135.7, 133.9, 133.4, 130.0, 128.0, 92.7, 69.3, 61.6, 52.5, 26.9, 23.5, 19.4; IR (neat) 3158, 3071, 2953, 2932, 2884, 2857, 2249, 1967, 1885, 1829, 1751, 1728, 1574, 1551, 1113 cm^{-1}; MS (EI) *m/z* (rel. intensity) 432 ([M-H]$^+$, 0.3), 418 ([M-CH_3]$^+$, 0.5), 402 ([M-OCH_3]$^+$, 3.3), 376 ([M-C_4H_9]$^+$, 91), 346 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_4Si$ (M-H) 432.1631, found 432.1625.



54a **55a**

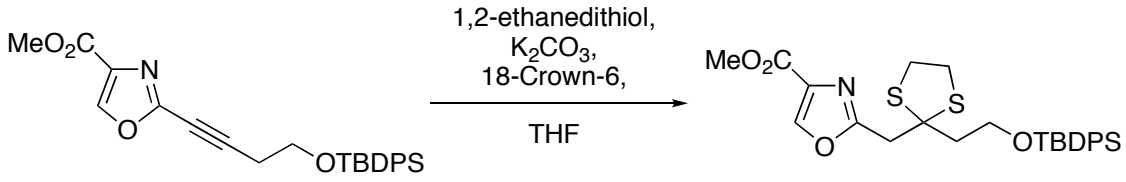
2-(3-Hydroxyprop-1-ynyl)oxazole-4-carboxylic acid methyl ester (55a). A solution of **54a** (275.4 mg, 0.656 mmol, 1.0 equiv) in CH_3CN (10.0 mL) was cooled to 0 °C and treated with 48% aqueous HF (1.0 mL), warmed to rt and stirred for 36 h. The mixture was carefully added to a solution of saturated, aqueous $NaHCO_3$ (75 mL). Ethyl acetate (20 mL) was added and the mixture was stirred at rt for 1 h and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (50% ethyl acetate/hexanes) afforded **55a** (112.4 mg, 95%) as a crystalline, white solid: R_f 0.19 (40% ethyl acetate/hexanes); Mp 100.1-101.1 °C (ethyl acetate/hexanes); ^{1}H NMR δ 8.16 (s, 1 H), 4.50 (s, 2 H), 4.33 (bs, 1 H), 3.85 (s, 3 H); ^{13}C NMR δ 160.9, 146.8, 144.6, 133.6, 92.8, 71.6, 52.5, 50.6; IR (KBr) 3455, 3161, 3113, 3017, 2959, 2921, 2249, 2220, 1736, 1584, 1551 cm^{-1}; MS (EI) *m/z* (rel. intensity) 181 (M$^+$, 79), 152 (100), 150 (M-OCH_3,

54), 120 (43), 100 (64), 83 (81); HRMS (EI) *m/z* calcd for $C_8H_7NO_4$ (M^+) 181.0375, found 181.0379.



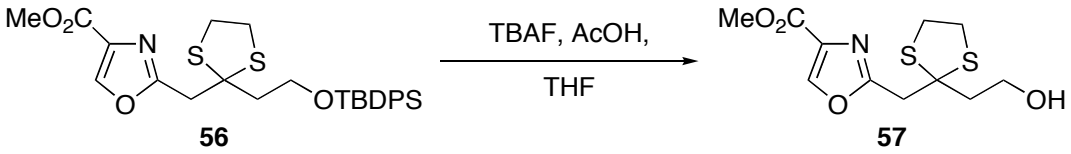
54b **55b**

2-(4-Hydroxybut-1-ynyl)oxazole-4-carboxylic acid methyl ester (55b). A solution of **54b** (640.1 mg, 1.476 mmol, 1.0 equiv) in THF (5.0 mL) at rt was treated with glacial AcOH (125 µL, 2.18 mmol, 1.5 equiv) and a solution of TBAF (1.0 M in THF, 2.20 mL, 2.20 mmol, 1.5 equiv). The mixture was stirred at rt for 18 h, treated with saturated, aqueous NH_4Cl (5 mL), diluted with water (5 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to a pale yellow solid. Purification by chromatography on SiO_2 (60% ethyl acetate/hexanes to 100% ethyl acetate) afforded **55b** (266.3 mg, 92%) as a white solid: R_f 0.18 (60% ethyl acetate/hexanes); Mp 99.5-100.0 °C (ethyl acetate); ^{1}H NMR δ 8.12 (s, 1 H), 3.85 (s, 3 H), 3.83 (t, 2 H, *J* = 6.4 Hz), 3.39 (bs, 1 H), 2.69 (t, 2 H, *J* = 6.4 Hz); ^{13}C NMR δ 161.0, 147.1, 144.1, 133.6, 93.0, 69.2, 60.1, 52.4, 23.6; IR (KBr) 3483, 3160, 3111, 2235, 1724, 1583, 1551 cm^{-1}; MS (EI) *m/z* (rel. intensity) 195 (M^+, 50), 165 (100), 149 ([M-CH_3-CH_2OH]$^+$, 7), 133 ([M-OCH_3-CH_2OH]$^+$, 51); HRMS (EI) *m/z* calcd for $C_9H_9O_4N$ 195.0532, found 195.0541.



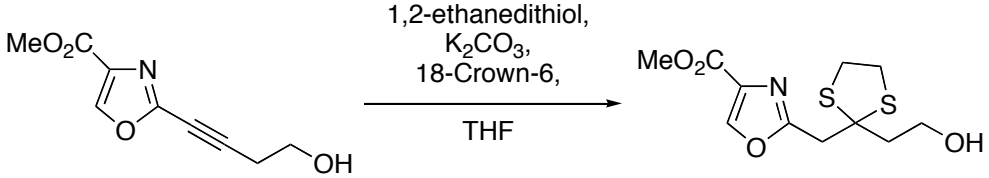
54b **56**

2-{2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-[1,3]dithiolan-2-ylmethyl}oxazole-4-carboxylic acid methyl ester (56). To a solution of **54b** (101.5 mg, 234 μmol, 1.0 equiv) in THF (5.0 mL) at rt was added 1,2-ethanedithiol (100 μL, 1.19 mmol, 5.1 equiv) and anhydrous K_2CO_3 (32.0 mg, 232 μmol, 1.0 equiv). 18-Crown-6 (24.0 mg, 91 μmol, 0.4 equiv) was added and the colorless solution immediately became pale yellow. The mixture was stirred for 4 h at rt, slowly becoming turbid, and was filtered through a plug of Florisil/Celite (1:1 v/v). The filtrate was concentrated and purified by chromatography on SiO_2 (30% ethyl ether/hexanes) to afford **54b** (116.4 mg, 94%) as a clear, colorless oil: R_f 0.29 (40% ethyl ether/hexanes); ^{1}H NMR δ 8.15 (s, 1 H), 7.70-7.66 (m, 4 H), 7.44-7.34 (m, 6 H), 3.96 (t, 2 H, *J* = 6.7 Hz), 3.90 (s, 3 H), 3.53 (s, 2 H), 3.22 (s, 4 H), 2.42 (t, 2 H, *J* = 6.7 Hz), 1.04 (s, 9 H); ^{13}C NMR δ 162.2, 161.8, 144.2, 135.7, 133.6, 133.3, 129.8, 127.8, 66.5, 62.3, 52.2, 44.5, 43.2, 39.9, 26.9, 19.2; IR (neat) 3070, 3048, 2952, 2930, 2890, 2856, 1964, 1897, 1820, 1748, 1729, 1581, 1139 cm^{-1}; MS (EI) *m/z* (rel. intensity) 527 (M^+, 0.04), 513 ($[M-CH_2]^+$, 0.16), 499 ($[M-C_2H_4]^+$, 30), 470 ($[M-C_4H_9]^+$, 51), 199(24), 131(32), 91(100); HRMS (EI) *m/z* calcd for $C_{23}H_{24}NO_4S_2Si$ ($M-C_4H_9$) 470.0916, found 470.0902.



56 **57**

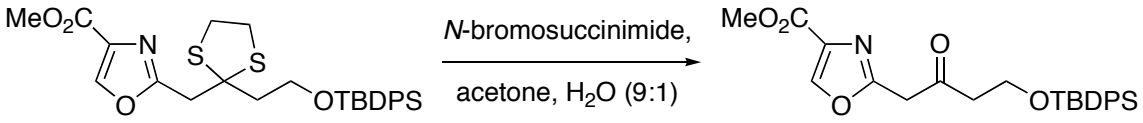
2-((2-(2-Hydroxyethyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (57). A solution of **56** (116.0 mg, 0.220 mmol, 1.0 equiv) in THF (2.0 mL) at rt was treated with glacial AcOH (19.0 µL, 0.332 mmol, 1.5 equiv) and TBAF (1.0 M in THF, 0.330 mL, 0.330 mmol, 1.5 equiv), stirred for 16 h at rt, treated with $NaHCO_3$ (2 mL), diluted with H_2O (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (60% ethyl acetate/hexanes) afforded **57** (57.8 mg, 91%) as a clear, colorless syrup: R_f 0.30 (60% ethyl acetate/hexanes); ^{1}H NMR δ 8.17 (s, 1 H), 3.91 (t, 2 H, *J* = 6.0 Hz), 3.86 (s, 3 H), 3.51 (s, 2 H), 3.37-3.24 (m, 4 H), 2.76 (bs, 1 H), 2.31 (t, 2 H, *J* = 6.0 Hz); ^{13}C NMR δ 162.1, 161.6, 144.2, 133.3, 67.2, 60.8, 52.3, 44.0, 43.6, 40.1 (2 C); IR (neat) 3404, 3160, 2951, 2925, 1736, 1580, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 289 (M^+, 6), 244 ([M-C_2H_4OH]$^+$, 6), 230 ([M-CO_2CH_3]$^+$, 76), 212 (15), 200 (38), 149 (100), 119 (61); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO_4S_2$ 289.0443, found 289.0432.



55b **57**

2-((2-(2-Hydroxyethyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (57). A solution of **55b** (93.5 mg, 0.479 mmol, 1.0 equiv) in THF (5.0 mL) was treated at rt with ethanedithiol (200 µL, 2.384 mmol, 5.0 equiv), anhydrous K_2CO_3

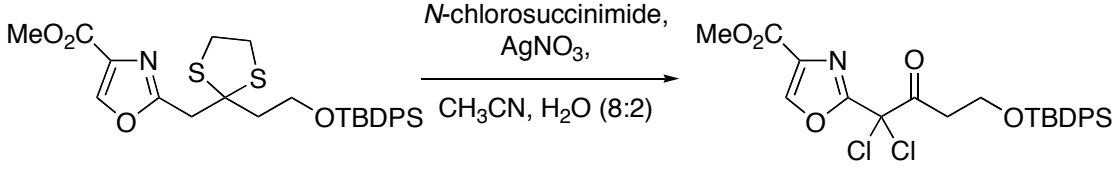
(73.0 mg, 0.528 mmol, 1.1 equiv) and 18-crown-6 (38.0 mg, 0.144 mmol, 0.3 equiv), stirred at rt for 6 h, diluted with ethyl ether (5 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with ethyl ether (5 mL) and the combined filtrate was concentrated. Purification by chromatography on SiO_2 (50% ethyl acetate/hexanes to 100% ethyl acetate) afforded **57** (121.5 mg, 88%) as a clear, colorless syrup. The spectral data were in agreement with the material obtained by TBDPS deprotection.



56 **58**

2-[4-(*tert*-Butyldiphenylsilyloxy)-2-oxobutyl]oxazole-4-carboxylic acid methyl ester (58). A solution of *N*-bromosuccinimide (52.0 mg, 292 μmol, 8.1 equiv) in acetone/water (9:1 v/v; 1.0 mL) was cooled to 0 °C and a solution of **56** (19.0 mg, 36 μmol, 1.0 equiv) in acetone/water (9:1; 1.0 mL) was added dropwise. The mixture became yellow and after 10 min, saturated, aqueous $NaHCO_3$ (1.0 mL) and saturated, aqueous $Na_2S_2O_3$ (1.0 mL) were added. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification of the mixture by chromatography on SiO_2 (20% to 30% ethyl acetate/hexanes) afforded **58** (12.5 mg, 77%) as a clear, colorless wax: R_f 0.43 (40% ethyl acetate/hexanes); ^{1}H NMR δ 8.21 (s, 1 H), 7.66-7.63 (m, 4 H), 7.46-7.36 (m, 6 H), 4.03 (s, 2 H), 3.93 (app q, 2 H, *J* = 6.1 Hz), 3.92 (s, 3 H), 2.73 (app t, 2 H, *J* = 6.1 Hz), 1.03 (s, 9 H); ^{13}C NMR δ 201.7, 161.6, 159.1, 145.0, 135.7, 133.8, 133.3, 130.0, 128.0, 59.5, 52.4, 45.4, 43.3, 27.0, 19.3 ; IR (neat) 3163, 3071, 3049, 2954, 2931, 2888,

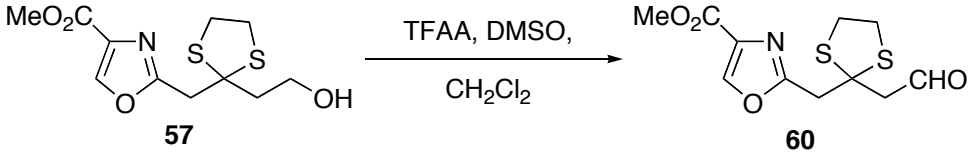
2857, 1964, 1893, 1830, 1729, 1587, 1428, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 420 ($[M\text{-}OCH_3]^+$, 1.3), 394 ($[M\text{-}C(CH_3)_3]^+$, 57), 362 ($[M\text{-}C(CH_3)_3\text{-}OCH_3]^+$, 16), 316 ($[M\text{-}C(CH_3)_3\text{-}C_6H_6]^+$, 29), 199 (100), 105 (44), 77 (32); HRMS (EI) *m/z* calcd for $C_{24}H_{26}NO_4Si$ ($M\text{-}OCH_3$) 420.1631, found 420.1631.



56 **59**

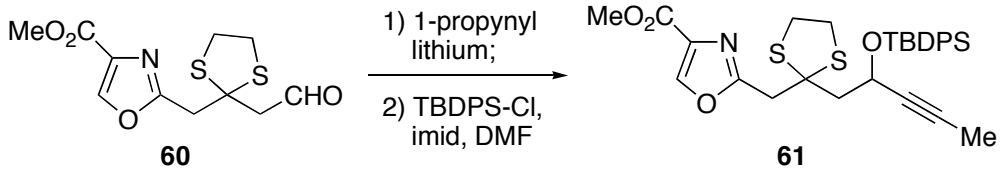
2-[4-(*tert*-Butyldiphenylsilyloxy)-1,1-dichloro-2-oxobutyl]-oxazole-4-carboxylic acid methyl ester (59). A solution of *N*-chlorosuccinimide (46.5 mg, 348 μmol, 4.0 equiv) and $AgNO_3$ (66.5 mg, 391 μmol, 4.5 equiv) in 80% (v/v) aqueous acetonitrile (1.0 mL) was cooled to 0 °C. A solution of **56** (24.2 mg, 87 μmol, 1.0 equiv) in 80% (v/v) aqueous acetonitrile (0.5 mL+ 0.5 mL rinse) was added via syringe. The cold bath was removed and a white precipitate formed. After 30 min, additional *N*-chlorosuccinimide (26.0 mg, 195 μmol, 2.2 equiv) was added in one portion. After an additional 30 min at rt, the mixture was diluted with ethyl ether (5.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The filtrate was diluted with ethyl acetate (10 mL) and washed with saturated, aqueous $Na_2S_2O_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (20% ethyl ether/hexanes) afforded **59** (12.9 mg, 29%) as a clear, colorless oil: R_f 0.43 (40% ethyl ether/hexanes); ^1H NMR δ 8.30 (s, 1 H), 7.67-7.64 (m, 4 H), 7.46-7.37 (m, 6 H), 4.01 (t, 2 H, *J* = 6.1 Hz), 3.93 (s, 3 H), 3.18 (t, 2 H, *J* = 6.1 Hz), 1.02 (s, 9 H); ^{13}C NMR δ 191.6, 160.9, 158.4, 146.3, 135.8, 134.4, 133.3, 130.0, 128.0, 78.8, 59.1, 52.7, 38.7,

26.9, 19.3; IR (neat) 3162, 3071, 3050, 2954, 2931, 2888, 2857, 1959, 1897, 1825, 1752, 1578, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 462 ($[M-C_4H_9]^+$, 11), 426 ($[M-C_2H_5S_2]^+$, 32), 384 (64), 350 (23), 217 (32), 199 (100), 135(32); HRMS (EI) *m/z* calcd for $C_{21}H_{18}NO_5SiCl_2$ (M-C_4H_9) 462.0331, found 462.0312.



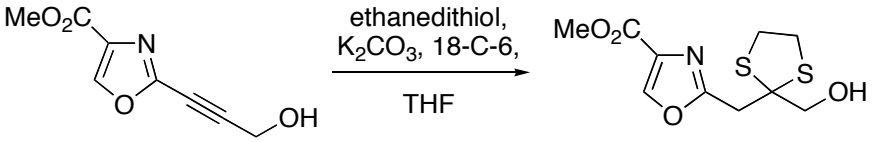
57 **60**

2-((2-(2-Oxoethyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (60). A solution of trifluoroacetic anhydride (30.0 µL, 0.212 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was cooled to –78 °C under N_2, treated with DMSO (30.0 µL, 0.423 mmol, 3.0 equiv), stirred for 30 min and treated via cannula with a solution of **57** (41.4 mg, 0.143 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL + 0.5 mL rinse). The mixture was stirred at –78 °C for 30 min, treated with triethylamine (60.0 µL, 0.428 mmol, 3.0 equiv), stirred for an additional 30 min at –78 °C, treated with saturated, aqueous NH_4Cl (1.0 mL), warmed to rt, diluted with H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 40% ethyl acetate/hexanes) afforded **60** (33.3 mg, 81%) as a clear, colorless syrup: R_f 0.24 (40% ethyl acetate/hexanes); ^1H NMR δ 9.77 (t, 1 H, *J* = 1.5 Hz), 8.18 (s, 1 H), 3.89 (s, 3 H), 3.58 (s, 2 H), 3.36 (s, 4 H), 3.23 (d, 2 H, *J* = 1.5 Hz); ^{13}C NMR δ 199.6, 161.6 (2 C), 144.3, 133.6, 63.0, 53.3, 52.4, 43.8, 40.4 (2 C); IR (neat) 3158, 3117, 2952, 2926, 2844, 2740, 1720, 1581, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 287 (M^+, 12), 244 ($[M-CH_2CHO]^+$, 5), 228 ($[M-CO_2CH_3]^+$, 100), 200 (24), 147 (86), 119 (76); HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO_4S_2$ 287.0286, found 287.0282.



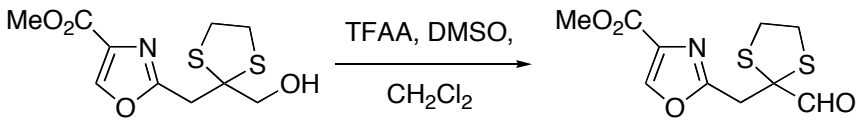
2-((2-(2-(*tert*-Butyldiphenylsilyloxy)pent-3-ynyl)-1,3-dithiolan-2-yl)methyl)-oxazole-4-carboxylic acid methyl ester (61). Propyne (0.5 mL) was condensed into a flask at –78 °C, diluted with THF (1.0 mL) and treated with *n*-BuLi (1.8 M in hexanes, 0.190 mL, 0.342 mmol, 1.1 equiv). The mixture was stirred at –78 °C for 1.5 h, treated via cannula with a solution of the aldehyde (87.3 mg, 0.304 mmol, 1.0 equiv) in THF (1.0 mL + 1.0 mL rinse), stirred at –78 °C for 1.75 h, warmed to 0 °C and quenched with saturated, aqueous NH_4Cl. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% acetone/hexanes) afforded methyl 2-((2-(2-hydroxypent-3-ynyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylate (40.3 mg, 41%) as a clear, colorless oil. This oil (22.3 mg, 0.068 mmol, 1.0 equiv) was diluted in DMF (0.5 mL) and treated with imidazole (14.0 mg, 0.206 mmol, 3.0 equiv), stirred at rt for 3 d, treated with saturated, aqueous $NH_4^+Cl^-$ (3.0 mL), poured into H_2O (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with 4.0 M aqueous LiCl (5.0 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. Purification by chromatography on SiO_2 (20% ethyl acetate/hexanes) afforded **61** (34.4 mg, 89%) as a clear, colorless oil: R_f 0.20 (20% ethyl acetate/hexanes); ^{1}H NMR δ 8.13 (s, 1 H), 7.78-7.71 (m, 4 H), 7.44-7.33 (m, 6 H), 4.72-4.66 (m, 1 H), 3.90 (s, 3 H), 3.61 (s, 2 H), 3.19-3.08 (m, 4 H), 2.65 (d of AB, 1 H, J = 14.5, 6.2 Hz), 2.61 (d of AB, 1 H, J = 14.5, 6.4 Hz), 1.50 (d, 3 H, J = 2.1 Hz), 1.05 (s, 9

H); ^{13}C NMR δ 162.5, 161.9, 144.2, 136.3, 136.1, 134.2, 133.8, 133.4, 129.8, 129.5, 127.7, 127.3, 84.0, 80.5, 66.2, 63.1, 52.3, 51.3, 42.4, 39.8, 39.7, 27.2, 19.4, 3.6; IR (neat) 3071, 3047, 2953, 2930, 2887, 2856, 1749, 1729, 1581 cm^{-1}; MS (EI) *m/z* (rel. intensity) 565 (M^+, 0.1), 508 ([M-C_4H_9]$^+$, 81), 440 (57), 199 (64), 135 (74), 121 (100); HRMS (ESI) *m/z* calcd for $C_{30}H_{35}NO_4SiS_2Na$ (M+Na) 588.1675, found 588.1699.



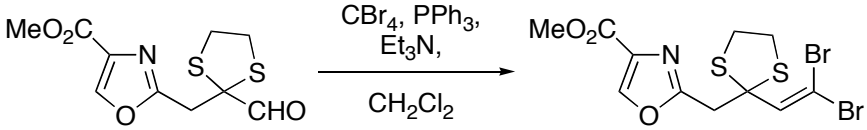
55a **62**

2-((2-(Hydroxymethyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (62). A solution of **55a** (48.0 mg, 0.265 mmol, 1.0 equiv) in THF (2.0 mL) at rt was treated with 1,2-ethanedithiol (110 µL, 1.31 mmol, 4.9 equiv), K_2CO_3 (40.3 mg, 0.292 mmol, 1.1 equiv) and 18-crown-6 (14.0 mg, 0.053 mmol, 0.2 equiv). The resulting yellow, turbid mixture was stirred at rt for 30 min, diluted with ethyl ether (2.0 mL) and filtered through a plug of Florisil/Celite (1:1). The plug was rinsed with ethyl ether (3.0 mL) and the combined filtrate was concentrated. Purification by chromatography on SiO_2 (60% ethyl acetate/hexanes) afforded **62** (66.4 mg, 91%) as a clear, colorless syrup: R_f 0.18 (50% ethyl acetate/hexanes); ^{1}H NMR δ 8.17 (s, 1 H), 3.85 (s, 3 H), 3.75 (d, 2 H, *J* = 6.7 Hz), 3.55 (s, 2 H), 3.30-3.23 (m, 5 H); ^{13}C NMR δ 162.2, 161.6, 144.3, 133.3, 69.8, 69.4, 52.2, 39.6, 38.3; IR (neat) 3419, 3159, 2951, 2926, 2852, 1732, 1582, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 275 (M^+, 1.0), 257 ([M-H_2O]$^+$, 12), 245 (100), 244 (M-OCH_3, 88), 216 ([M-CO_2CH_3]$^+$, 36), 184 (19), 141 (68), 135 (79); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO_4S_2$ 275.0286, found 275.0278.



62 **63**

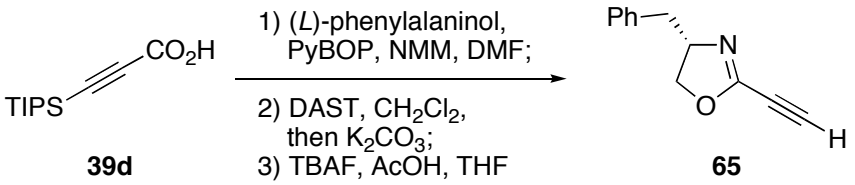
2-((2-Formyl-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (63). A solution of TFAA (50.0 µL, 0.354 mmol, 1.5 equiv) in CH_2Cl_2 (0.5 mL) was cooled to –78 °C under N_2 and treated with a solution of DMSO (50 µL, 0.704mmol, 3.0 equiv) in CH_2Cl_2 (0.5 mL + 0.5 mL rinse). The mixture was stirred for 20 min, treated with a solution of **62** (64.7 mg, 0.235 mmol, 1.0 equiv), stirred for 20 min and treated with triethylamine (100 µL, 0.715 mmol, 3.0 equiv). The mixture was stirred for 90 min at –78 °C, treated with water (1.0 mL), warmed to rt, diluted with water (5.0 mL) and extracted with CH_2Cl_2. The combine organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% ethyl acetate/hexanes) afforded **63** (59.4 mg, 93%) as a clear, colorless syrup: R_f 0.31 (50% ethyl acetate/hexanes); ^{1}H NMR δ 9.12 (s, 1 H), 8.16 (s, 1 H), 3.87 (s, 3 H), 3.62 (s, 2 H), 3.33 (s, 4 H); ^{13}C NMR δ 187.5, 161.7, 161.5, 144.3, 133.5, 69.2, 52.3, 41.1, 34.5; IR (neat) 3158, 2952, 2844, 1712, 1582, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 273 (M^+, 0.1), 244 ([M-CHO]$^+$, 100), 217 (13), 212 (22), 184 (20), 156 (10), 141 (53); HRMS (EI) *m/z* calcd for $C_{10}H_{11}O_4S_2$ 273.0130, found 273.0119.



63 **64**

2-((2-(2,2-Dibromovinyl)-1,3-dithiolan-2-yl)methyl)oxazole-4-carboxylic acid methyl ester (64). A solution of PPh_3 (100.0 mg, 0.381 mmol, 4.1 equiv) in CH_2Cl_2 (1.0

mL) at 0 °C was treated with CBr_4 (62.0 mg, 0.187 mmol, 2.0 equiv), stirred for 20 min, treated with triethylamine (130 µL, 0.927 mmol, 10.0 equiv), stirred for 10 min and treated with a solution of **63** (25.4 mg, 0.093 mmol, 1.0 equiv). The mixture was allowed to warm to rt over 2 h and then was treated with additional PPh_3 (50.0 mg, 0.191 mmol, 2.0 equiv) and CBr_4 (31.0 mg, 0.093 mmol, 1.0 equiv). The mixture was stirred for 22 h (overnight), diluted with ethyl ether (5 mL) and poured onto a pad of SiO_2. The pad was washed with ethyl ether (100 mL) and the combined filtrate was concentrated to a yellow wax. Purification by chromatography on SiO_2 (30% to 40% ethyl acetate/hexanes) afforded **64** (34.2 mg, 86%) as a pale yellow wax: R_f 0.51 (50% ethyl acetate/hexanes); ^{1}H NMR δ 8.21 (s, 1 H), 7.14 (s, 1 H), 3.90 (s, 3 H), 3.80 (s, 2 H), 3.45-3.28 (m, 4 H); ^{13}C NMR δ 161.7, 161.3, 144.5, 141.4, 133.5, 93.5, 66.6, 52.4, 42.4, 40.6 (2 C); IR (neat) 3159, 3021, 2950, 2923, 2846, 1742, 1579 cm^{-1}; MS (EI) *m/z* (rel. intensity) 426 (M^+, 0.1), 398 ($[M-C_2H_4]^+$, 33), 370 (20), 350 (17), 289 (100), 229 (27); HRMS (EI) *m/z* calcd for $C_{11}H_{11}NO_3S_2Br_2$ 426.8547, found 426.8529.



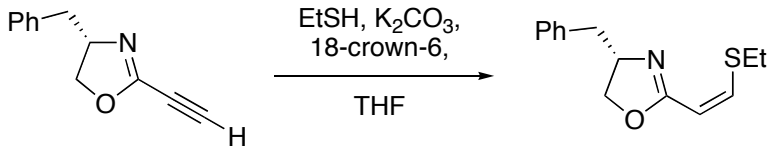
39d **65**

(4*S*)-4-Benzyl-2-ethynyl-4,5-dihydrooxazole (65). A mixture of **39d** (354.0 mg, 1.56 mmol, 1.0 equiv), L-phenylalaninol (354.0 mg, 2.34 mmol, 1.5 equiv) and PyBOP (900.0, 1.73 mmol, 1.1 equiv) in DMF (3.0 mL) was cooled to 0° C and N-methylmorpholine (400 µL, 3.94 mmol, 2.5 equiv) was added. The mixture was allowed to warm to rt, stirred for 20 h, poured into saturated aqueous $NaHCO_3$ (10 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic extracts

were washed with 1.0 M aqueous citric acid (10 mL), water (10 mL) and 4.0 M aqueous LiCl (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 40% ethyl acetate/hexanes) afforded (1*S*)-3-(triisopropylsilyl)propiolic acid (1-benzyl-2-hydroxyethyl)amide (580.9 mg, quant.) as a clear, colorless syrup that was used without further purification: R_f 0.33 (40% ethyl acetate/hexanes), ^{1}H NMR δ 7.34-7.19 (m, 5 H), 6.08 (bd, 1 H, *J* = 7.3 Hz), 4.25-4.08 (m, 1 H), 3.69 (d of AB, 1 H, *J* = 11.1, 3.4 Hz), 3.62 (d of AB, 1 H, *J* = 11.1, 4.4 Hz), 2.37 (bs, 1 H), 1.05-1.08 (m, 21 H), 2.95-2.90 (m, 2 H).

A solution of the hydroxyamide (580.0 mg, 1.61 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) was cooled to –78 °C under N_2. Diethylaminosulfurtrifluoride (DAST) (240 µL, 1.82 mmol, 1.1 equiv) was added and, after 10 min, TLC analysis indicated that the hydroxyamide was consumed. Solid anhydrous K_2CO_3 (340.0 mg, 2.46 mmol, 1.5 equiv) was added and the mixture was stirred at –78 °C for 20 min, then at 0 °C for 20 min. Saturated aqueous $NaHCO_3$ (5 mL) was carefully added (caution: vigorous evolution of gas) and the mixture was stirred for 1 h while warming to rt and then extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% ethyl ether/hexanes) afforded (4*S*)-4-benzyl-2-[(triisopropylsilyl)ethynyl]-4,5-dihydrooxazole (338.3 mg, 63%, 2 steps) as a clear, colorless oil that was used without further purification. ^{1}H NMR δ 7.33-7.19 (m, 5 H), 4.48 (app dq, 1 H, *J* = 5.2, 9.0 Hz), 4.22 (t, 1 H, *J* = 9.0 Hz), 4.00 (t, 1 H, *J* = 8.2 Hz), 3.18 (dd, 1 H, *J* = 13.8, 5.2 Hz), 2.67 (dd, 1 H, *J* = 13.8, 8.9 Hz), 1.10-1.11 (m, 21 H).

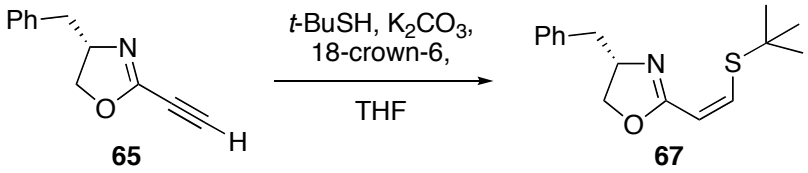
A solution of (4*S*)-4-benzyl-2-[(triisopropylsilyl)ethynyl]-4,5-dihydrooxazole (338.0 mg, 0.990 mmol, 1.0 equiv) in THF (10.0 mL) was cooled under N_2 to –78 °C. Glacial acetic acid (65 µL, 1.1 mmol, 1.1 equiv) and TBAF (1.0 M in THF, 1.10 mL, 1.1 equiv) were added. After 30 min at –78 °C, saturated aqueous $NaHCO_3$ was added and the mixture was warmed to rt, diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 20% ethyl acetate/hexanes) afforded **65** (158.5 mg, 87%) as a clear colorless syrup. The spectral data were in agreement with the literature values: $[\alpha]_D$ -32.8 (*c* 0.85, $CHCl_3$, 22 °C), lit. $[\alpha]_D$ -62.5 (*c* 1.58, $CHCl_3$, 23 °C).[83]



65 **66**

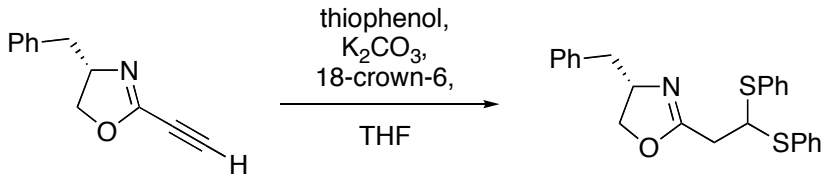
(4*S*)-4-Benzyl-2-(2-ethylsulfanylvinyl)-4,5-dihydro-oxazole (66). To a solution of **65** (12.2 mg, 66 µmol, 1.0 equiv) in THF (0.5 mL) at rt was added ethanethiol (25 µL, 338 µmol, 5.1 equiv) and anhydrous K_2CO_3 (10.2 mg, 74 µmol, 1.1 equiv). 18-Crown-6 (5.0 mg, 19 µmol, 0.3 equiv) was added and the mixture was vigorously stirred for 4 h at rt, diluted with ethyl ether (1.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to a pale yellow oil. Purification by chromatography on SiO_2 (20% ethyl acetate/hexanes) afforded **66** (14.5 mg, 89%) as a clear colorless oil that was a 4:1 (*Z*/*E*) mixture: R_f 0.40 (40% ethyl acetate/hexanes); ^{1}H NMR δ 7.32-7.19 (m, 5 H), 6.82

(d, 1 H, *J* = 10.8 Hz), 5.89 (d, 1 H, *J* = 10.8 Hz), 4.51 (dddd, 1 H, *J* = 9.1, 9.1, 7.3, 5.1 Hz), 4.19 (app t, 1 H, *J* = 8.9 Hz), 4.00 (dd, 1 H, *J* = 8.3, 7.3 Hz), 3.21 (dd, 1 H, *J* = 13.7, 5.0 Hz), 2.79 (q, 2 H, *J* = 7.4 Hz), 2.66 (dd, 1 H, *J* = 13.7, 9.0 Hz), 1.36 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 163.4, 142.7, 138.4, 129.4, 128.7, 126.6, 110.6, 71.4, 68.0, 42.1, 29.8, 15.6; IR (neat) 3060, 3026, 2967, 2925, 1635, 1585, 1493, 1453, 1183 cm^{-1}; MS (EI) *m/z* (rel. intensity) 247 (M^+, 35), 218 ($[M-C_2H_5]^+$, 25), 156 ($[M-C_7H_7]^+$, 100), 128 (58), 91 (57); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NOS$ 247.1031, found 247.1043; Characteristic signals for the (*E*)-isomer: ^{1}H NMR δ 5.94 (d, 1 H, *J* = 15.5 Hz), 4.21 (t, 1 H, *J* = 8.5 Hz), 3.12 (dd, 1 H, *J* = 13.8, 5.4 Hz), 1.35 (t, 3 H, *J* = 7.4 Hz).



(4*S*)-4-Benzyl-2-(2-*tert*-butylsulfanylvinyl)-4,5-dihydrooxazole (67). To a solution of **65** (26.3 mg, 142 μmol, 1.0 equiv) in THF (1.0 mL) at rt was added *t*-butylmercaptane (80 μL, 710 μmol, 5.0 equiv) and anhydrous K_2CO_3 (22.0 mg, 159 μmol, 1.1 equiv). 18-Crown-6 (12.0 mg, 45 μmol, 0.3 equiv) was added and the mixture was stirred for 12 h at rt, diluted with ethyl ether (3.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to give a pale yellow oil. Purification by chromatography on SiO_2 (10% acetone/hexanes) afforded **67** (38.6 mg, 97%) as a clear colorless oil: R_f 0.27 (10% acetone/hexanes, twofold developed); $[\alpha]_D$ +3.6 (*c* 1.34, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.31-7.18 (m, 5 H), 6.98 (d, 1 H, *J* = 11.2 Hz), 5.90 (d, 1 H, *J* = 11.2 Hz), 4.56-4.46 (m, 1 H), 4.17 (app t, 1 H, *J* = 8.8 Hz), 3.99 (app t, 1 H, *J* = 7.8 Hz),

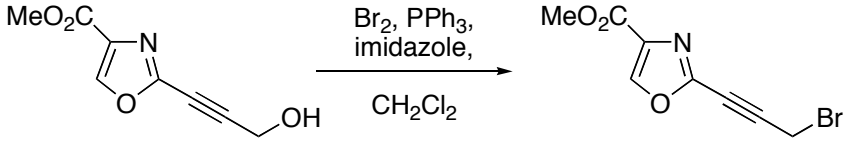
3.22 (dd, 1 H, *J* = 13.6, 4.9 Hz), 2.64 (dd, 1 H, *J* = 13.6, 9.2 Hz), 1.42 (s, 9 H); ^{13}C NMR δ 163.3, 138.7, 138.4, 129.4, 128.6, 126.5, 110.0, 71.4, 68.1, 44.4, 42.1, 30.9; IR (neat) 3083, 3060, 3026, 2961, 2940, 2926, 2898, 2864, 1950, 1875, 1803, 1637, 1582, 1378, 1366, 1184, 1167 cm^{-1}; MS (EI) *m/z* (rel. intensity) 218 ([M-C_4H_9]$^+$, 100), 184 ([M-C_7H_7]$^+$, 22), 128 (81), 117 (53), 100 (22), 91 (53), 57 (37); HRMS (EI) *m/z* calcd for $C_{12}H_{12}NOS$ (M-C_4H_9) 218.0640, found 218.0636.



65 **68**

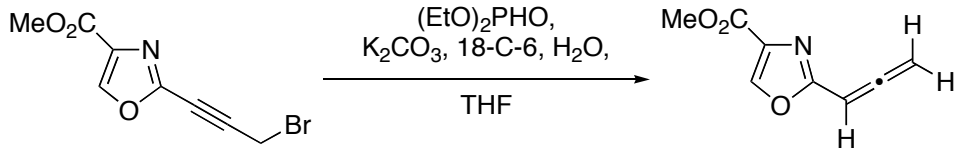
(4*S*)-4-Benzyl-2-(2,2-bisphenylsulfanylethyl)-4,5-dihydrooxazole (68). To a mixture of the oxazoline **65** (29.4 mg, 0.159 mmol, 1.0 equiv) and thiophenol (80 μL, 780 μmol, 4.9 equiv) in THF (1.0 mL) at rt was added anhydrous K_2CO_3 (24.0 mg, 174 μmol, 1.1 equiv) and 18-crown-6 (12.0 mg, 45 μmol, 0.3 equiv). After stirring for 12 h at rt, the mixture was diluted with ethyl ether (3.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated. Purification of the residue by chromatography on SiO_2 (10% acetone/hexanes) afforded **68** (53.1 mg, 82%) as a clear colorless oil: R_f 0.27 (10% acetone/hexanes, twofold developed); $[\alpha]_D$ –14.7 (*c* 1.31, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.54-7.50 (m, 4 H), 7.37-7.19 (m, 11 H), 4.80 (t, 1 H, *J* = 7.5 Hz), 4.43-4.33 (m, 1 H), 4.13 (app t, 1 H, *J* = 8.9 Hz), 3.94 (dd, 1 H, *J* = 8.4, 7.2 Hz), 3.11 (dd, 1 H, *J* = 13.7, 5.6 Hz), 2.81 (dd, 2 H, *J* = 7.6, 0.8 Hz), 2.65 (dd, 1 H, *J* = 13.7, 8.5 Hz); ^{13}C NMR δ 164.4, 138.1, 133.6, 133.4, 133.2, 129.4, 129.1, 128.7, 128.3, 128.2, 126.6, 72.0, 67.6,

54.3, 41.9, 35.3; IR (neat) 3058, 3026, 3002, 2960, 2919, 2898, 1951, 1882, 1807, 1669, 1603, 1582 cm^{-1}; MS (EI) *m/z* (rel. intensity) 405 (M^+, 8), 296 ([M-C_6H_5S]$^+$, 67), 204 ([M-C_7H_7-C_6H_5SH]$^+$, 100), 190 (22), 105 (66), 91 (54), 77 (36), 65 (21); HRMS (EI) *m/z* calcd for $C_{24}H_{23}NOS_2$ 405.1221, found 405.1221.



55a **69**

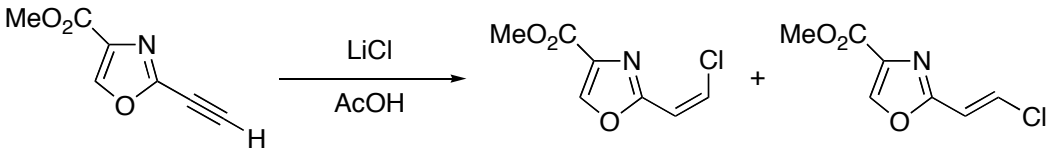
2-(3-Bromoprop-1-ynyl)oxazole-4-carboxylic acid methyl ester (69). A solution of PPh_3 (51.0 mg, 0.194 mmol, 1.4 equiv) in CH_2Cl_2 (0.5 mL) at rt was treated with Br_2 (10.0 µL, 0.195 mmol, 1.4 equiv). A precipitate formed, and after 20 min the mixture was treated with imidazole (12.0 mg, 0.176 mmol, 1.3 equiv). The precipitate dissolved to afford a clear, yellow solution, which was cooled to 0 °C and treated with a solution **55a** (25.0 mg, 0.138 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL + 0.5 mL rinse). The mixture was stirred at 0 °C for 20 min, diluted with hexanes, warmed to rt, stirred for 5 min and then filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with ethyl ether (5.0 mL) and the combined filtrate was concentrated to a clear, colorless oil that solidified to a white solid under vacuum. Purification by chromatography on SiO_2 (20% ethyl acetate/hexanes) afforded **69** (32.1 mg, 95%) as a white, crystalline solid: R_f 0.50 (40% ethyl acetate/hexanes); Mp 82.0-83.0 °C (CH_2Cl_2); ^{1}H NMR δ 8.21 (s, 1 H), 4.08 (s, 2 H), 3.92 (s, 3 H); ^{13}C NMR δ 160.9, 146.2, 144.8, 134.4, 88.1, 73.0, 52.6, 12.3; IR (KBr) 3157, 3093, 3003, 2952, 2240, 1744, 1553 cm^{-1}; MS (EI) *m/z* (rel. intensity) 242 (M^+, 9), 212 (4), 164 ([M-Br]$^+$, 100); HRMS (EI) *m/z* calcd for $C_8H_6NO_3Br$ 242.9531, found 242.9524.



69 **71**

2-(Propa-1,2-dienyl)oxazole-4-carboxylic acid methyl ester (71). A mixture of **69** (50.0 mg, 0.205 mmol, 1.0 equiv), K_2CO_3 (31.0 mg, 0.224 mmol, 1.1 equiv) and 18-crown-6 (5.4 mg, 0.02 mmol, 0.1 equiv) was suspended in THF (1.0 mL) at rt and treated with diethyl phosphate (50.0 µL, 0.388 mmol, 1.9 equiv) and water (18.0 µL, 1.00 mmol, 4.9 equiv). The mixture was vigorously stirred at rt for 2 h and then diluted with ethyl ether (2.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with ethyl ether (5.0 mL) and the combined filtrate was concentrated to an oily, white solid. Purification by chromatography on SiO_2 (20% to 40% ethyl acetate/hexanes) afforded **71** (33.2 mg, 98%) as a white, crystalline solid: R_f 0.39 (40% ethyl acetate/hexanes); Mp 114.1-115.4 °C (toluene); ^{1}H NMR δ 8.16 (s, 1 H), 6.25 (t, 1 H, J = 6.8 Hz), 5.36 (d, 2 H, J = 6.8 Hz), 3.91 (s, 3 H); ^{13}C NMR δ 213.2, 161.7, 158.9, 144.0, 134.5, 83.3, 81.1, 52.4; IR (KBr) 3409, 3140, 3077, 3022, 2993, 1963, 1929, 1713, 1578 cm^{-1}; MS (EI) *m/z* (rel. intensity) 165 (M^+, 47), 134 ([M-OCH_3]$^+$, 32), 133 ([M-$HOCH_3$]$^+$, 100); HRMS (EI) *m/z* calcd for $C_8H_7NO_3$ 165.0426, found 165.0423.

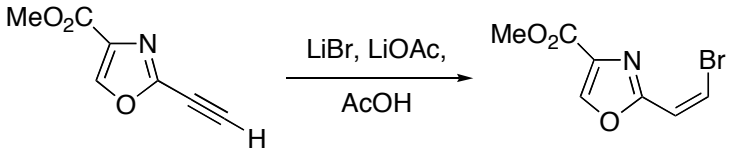
2.4.2.2. Conjugate Additions Under Acidic Conditions



37 (*Z*)-**73a** (*E*)-**73a**

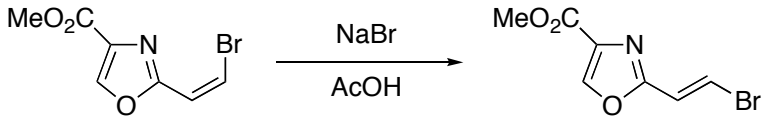
(*Z*)-2-(2-Chlorovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-73a] and 2-(*E*)-(2-chlorovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-73a]. A mixture of **37** (25.0 mg, 165 μmol, 1.0 equiv) and lithium chloride (10.5 mg, 248 μmol, 1.5 equiv) in glacial acetic acid (0.75 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with water. The mixture was extracted with ethyl ether and the combined organic layers were washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with brine, dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*)-ratio of 1.3:1.0. The residue was purified by chromatography on SiO_2 (5 to 10% acetone/hexanes) to afford (*Z*)-**73a** (11.2 mg, 36%) and (*E*)-**73a** (8.0 mg, 26%) as white solids. (*Z*)-**73a**: R_f 0.40 (20% acetone/hexanes, twofold developed); Mp 86.3-87.0 °C (CH_2Cl_2); ^{1}H NMR δ 8.27 (s, 1 H), 6.72, 6.67 (AB, 2 H, *J* = 8.4 Hz), 3.93 (s, 3 H); ^{13}C NMR δ 161.6, 159.0, 143.9, 134.3, 127.0, 116.5, 52.5; IR (KBr) 3165, 3105, 3088, 3038, 2956, 2853, 1744, 1658, 1626, 1564, 1513, 1445 cm^{-1}; MS (EI) *m/z* (rel. intensity) 187 (M^+, 60), 156 ([M-OCH_3]$^+$, 33), 100 (100), 89 (34), 69 (39); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Cl$ 187.0036, found 187.0036; (*E*)-**73a**: R_f 0.50 (20% acetone/hexanes, twofold developed); Mp 87.5-88.3 °C (CH_2Cl_2); ^{1}H NMR δ 8.17 (s, 1 H), 7.28 (d, 1 H, *J* = 13.7 Hz), 6.74 (d, 1 H, *J* = 13.7 Hz), 3.92 (s, 3 H); ^{13}C NMR δ 161.5,

159.2, 143.8, 134.5, 130.4, 119.4, 52.5; IR (KBr) 3152, 3113, 3086, 2961, 1731, 1716, 1619, 1573, 1556 cm^{-1}; MS (EI) *m/z* (rel. intensity) 187 (M^+, 63), 156 ([M-OCH_3]$^+$, 36), 100 (100); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Cl$ 187.0036, found 187.0023.



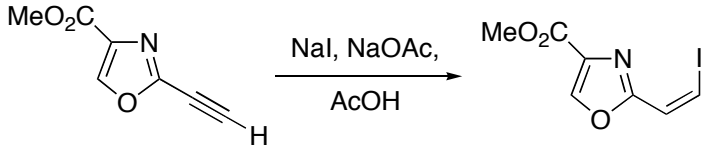
37 (*Z*)-**73b**

(*Z*)-2-(2-Bromovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-73b]. A mixture of **37** (15.0 mg, 99 μmol, 1.0 equiv), lithium bromide (13.0 mg, 150 μmol, 1.5 equiv) and lithium acetate (29.5 mg, 447 mmol, 4.5 equiv) in glacial acetic acid (0.45 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with ethyl acetate (10 mL). The mixture was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and brine (5 mL) and then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*/starting material)-ratio of 32:1.6:1.0. The residue was purified by chromatography on SiO_2 (5 to 10% acetone/hexanes) to afford (*Z*)-**73b** (19.9 mg, 87%) as a white solid: R_f 0.25 (10% acetone/hexanes, twofold developed); Mp 90.1-91.1 °C (CH_2Cl_2); ^{1}H NMR δ 8.27 (s, 1 H), 7.14 (d, 1 H, *J* = 8.7 Hz), 6.89 (d, 1 H, *J* = 8.7 Hz), 3.90 (s, 3 H); ^{13}C NMR δ 161.5, 159.5, 143.7, 134.3, 119.7, 115.4, 52.5; IR (KBr) 3157, 3100, 3083, 3026, 2939, 1744, 1648 cm^{-1}; MS (EI) *m/z* (rel. intensity) 233 (M^+, 54), 231 (M^+, 53), 202 ([M-OCH_3]$^+$, 20), 200 ([M-OCH_3]$^+$, 19), 174 ([M-$OCOCH_3$]$^+$, 7), 172 ([M-$OCOCH_3$]$^+$, 6), 146 (13), 144 (14), 135 (21), 133 (26), 100 (100), 69 (45), 64 (21), 59 (11); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Br$ 230.9531, found 230.9513.



(*Z*)-**73b** (*E*)-**73b**

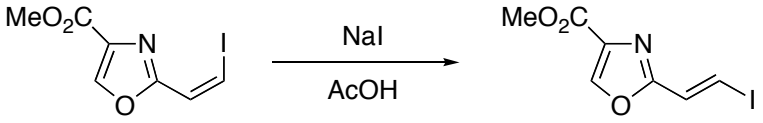
2-(*E*)-(2-Bromovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-73b]. A mixture of (*Z*)-**73b** (20.0 mg, 86 μmol, 1.0 equiv) and sodium bromide (13.3 mg, 129 μmol, 1.5 equiv) in glacial acetic acid (0.37 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with ethyl acetate (10 mL). The mixture was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and brine (5 mL) and then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*)-ratio of 1.0:5.9. The residue was purified by chromatography on SiO_2 (5% acetone/hexanes) affording (*E*)-**73b** (14.8 mg, 74%) as a white solid: R_f 0.34 (10% acetone/hexanes, twofold developed); Mp 118.2-119.2 °C (CH_2Cl_2); ^{1}H NMR δ 8.18 (s, 1 H), 7.48 (d, 1 H, *J* = 14.2 Hz), 7.02 (d, 1 H, *J* = 14.2 Hz), 3.93 (s, 3 H); ^{13}C NMR δ 161.5, 159.9, 143.8, 134.5, 123.1, 118.8, 52.6; IR (KBr) 3152, 3113, 3084, 3012, 2960, 1728, 1710, 1608, 1572, 1556 cm^{-1}; MS (EI) *m/z* (rel. intensity) 233 (M^+, 8), 231 (M^+, 8), 202 ([M-OCH_3]$^+$, 10), 168 (100), 137 ([M-CH_3-Br]$^+$, 34), 110 (84), 109 (37), 67 (57); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Br$ 230.9531, found 230.9531.



37 (*Z*)-**73c**

(*Z*)-2-(2-Iodovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-73c]. A mixture of **37** (25.0 mg, 165 μmol, 1.0 equiv), sodium iodide (24.7 mg, 165 μmol, 1.0 equiv) and sodium acetate (40.7 mg, 496 μmol, 3.0 equiv) in glacial acetic acid (0.75

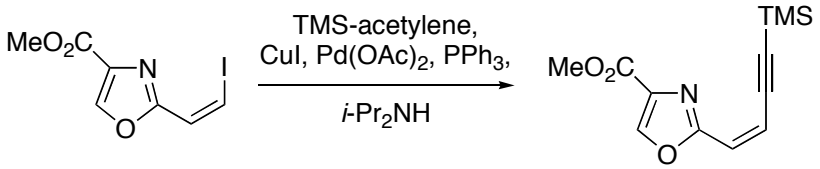
mL) was heated under N_2 to 100 °C for 12 h, then cooled to rt and diluted with ethyl acetate (10 mL). The organic layer was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated $Na_2S_2O_3$ (5.0 mL) and brine (5.0 mL). The combined aqueous washings were backwashed with ethyl acetate (3.0 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a (*Z*/*E*)-ratio of >50:1. Purification by chromatography on SiO_2 (5% to 10% acetone/hexanes) afforded (*Z*)-**73c** (42.2 mg, 92%) as a white solid: R_f 0.23 (10% acetone/hexanes, twofold developed); Mp 88.2-89.2 °C (CH_2Cl_2); ^{1}H NMR δ 8.30 (s, 1 H), 7.54 (d, 1 H, *J* = 9.5 Hz), 7.24 (d, 1 H, *J* = 9.5 Hz), 3.93 (s, 3 H); ^{13}C NMR δ 161.2, 160.2, 143.5, 134.3, 125.9, 87.1, 52.5; IR (KBr) 3161, 3121, 3061, 3008, 2956, 2911, 2845, 1741, 1719, 1629, 1575 cm^{-1}; MS (EI) *m/z* (rel. intensity) 279 (M^+, 100), 248 ([M-OCH_3]$^+$, 14), 220 ([M-$OCOCH_3$]$^+$, 4), 192 (10), 181 (24), 100 (37); HRMS (EI) *m/z* calcd for $C_7H_6NO_3I$ 278.9392, found 278.9392.



(*Z*)-**73c** (*E*)-**73c**

2-(2-(*E*)-Iodovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-73c]. A mixture of (*Z*)-**73c** (41.2 mg, 148 μmol, 1.0 equiv) and sodium iodide (66.6 mg, 444 μmol, 3.0 equiv) in glacial acetic acid (0.75 mL) was heated under N_2 to 100 °C for 12 h, then cooled to rt and diluted with ethyl acetate (10 mL). The organic layer was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated $Na_2S_2O_3$ (5.0 mL) and brine (5.0 mL). The combined aqueous washings were backwashed with ethyl acetate (3.0 mL) and the combined organic extracts were dried

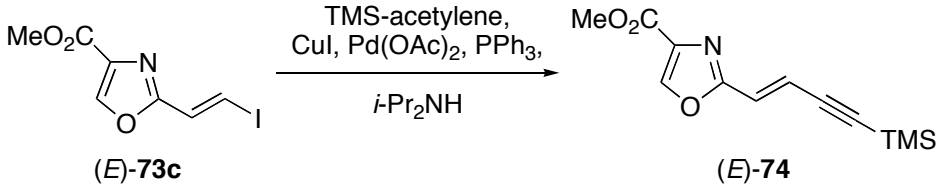
(Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated an (*E*/*Z*)-ratio of 7.8:1.0. Purification by chromatography on SiO_2 (5% acetone/hexanes) afforded (*Z*)-**73c** (2.6 mg, 6%) and (*E*)-**73c** (35.3 mg, 86%) as white solids. (*E*)-**73c**: R_f 0.30 (10% acetone/hexanes, twofold developed); Mp 141.1-142.1 °C (CH_2Cl_2); ^{1}H NMR δ 8.18 (s, 1 H), 7.68 (d, 1 H, *J* = 15.2 Hz), 7.33 (d, 1 H, *J* = 15.2 Hz), 3.92 (s, 3 H); ^{13}C NMR δ 161.5, 160.9, 143.9, 134.3, 130.3, 89.9, 52.5; IR (KBr) 3149, 3108, 3069, 3007, 2955, 1724, 1705, 1570, 1552 cm^{-1}; MS (EI) *m/z* (rel. intensity) 279 (M^+, 100), 248 ([M-OCH_3]$^+$, 20), 220 ([M-$OCOCH_3$]$^+$, 6), 207 (21), 181 (24), 137 ([M-CH_3I]$^+$, 48), 136 (66), 135 (74), 121 ([M-OCH_3-I]$^+$, 22); HRMS (EI) *m/z* calcd for $C_7H_6NO_3I$ 278.9392, found 278.9393.



(*Z*)-**73c** (*Z*)-**74**

(*Z*)-2-[4-(Trimethylsilyl)but-1-en-3-ynyl]oxazole-4-carboxylic acid methyl ester [(*Z*)-74]. A mixture of (*Z*)-**73c** (20.0 mg, 72 μmol, 1.0 equiv), CuI (4.0 mg, 22 μmol, 0.3 equiv), $Pd(OAc)_2$ (2.0 mg, 8 μmol, 0.1 equiv) and PPh_3 (8.0 mg, 30 μmol, 0.4 equiv) was dissolved in *i*-Pr_2NH (0.5 mL) and cooled to 0 °C under N_2. Trimethylsilylacetylene (16.0 μL, 0.11 mmol, 1.6 equiv) was added. The reaction mixture was allowed to warm to room temperature and after 30 min, ethyl ether (2.0 mL) and water (2.0 mL) were added. The mixture was poured into water (5.0 mL) and extracted with ethyl ether. The combined organic layers were washed with 1.0 M aqueous citric acid (5.0 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and

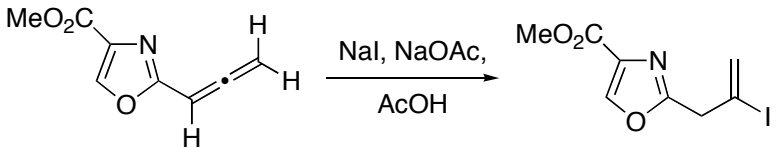
concentrated. Purification of the residue by chromatography on SiO_2 (10% acetone/hexanes) afforded (*Z*)-**74** (19.1 mg, 89%) as a white crystalline solid: R_f 0.21 (20% ethyl ether/hexanes); Mp 51.2-51.9 °C (CH_2Cl_2); ^1H NMR δ 8.23 (s, 1 H), 6.63, 6.06 (AB, 2 H, *J* = 12.0 Hz), 3.93 (s, 3 H), 9.08 (s, 9 H); ^{13}C NMR δ 161.7, 160.8, 143.6, 134.5, 124.0, 116.2, 106.9, 101.4, 52.5, -0.2; IR (KBr) 3178, 3040, 2959, 2900, 2142, 1721, 1616, 1577 cm^{-1}; MS (EI) *m/z* (rel. intensity) 249 (M^+, 27), 234 ($[M-CH_3]^+$, 56), 204 ($[M-C_3H_9]^+$, 67), 190 ($[M-O_2CCH_3]^+$, 100); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO_3Si$ 249.0821, found 249.0812.



(*E*)-**73c** (*E*)-**74**

(*E*)-2-[4-(Trimethylsilyl)but-1-en-3-ynyl]oxazole-4-carboxylic acid methyl ester [(*E*)-74]. A mixture of (*E*)-**73c** (10.0 mg, 36 μmol, 1.0 equiv), CuI (2.0 mg, 11 μmol, 0.3 equiv), $Pd(OAc)_2$ (1.0 mg, 4 μmol, 0.1 equiv) and PPh_3 (4.0 mg, 15 μmol, 0.4 equiv) was dissolved in *i*-Pr_2NH (0.5 mL) and cooled to 0 °C under N_2. Trimethylsilylacetylene (10.0 μL, 70 μmol, 2.0 equiv) was added. The mixture was allowed to warm to rt and after 30 min, ethyl ether (2.0 mL) and water (2.0 mL) were added. The mixture was poured into water (5.0 mL) and extracted with ethyl ether. The combined organic layers were washed with 1.0 M aqueous citric acid (5.0 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by chromatography on SiO_2 (10% to 20% ethyl ether/hexanes) afforded (*E*)-**74** (8.1 mg, 90%) as a white crystalline solid: R_f 0.25 (20% ethyl ether/hexanes); Mp

109.1-109.9 °C (CH_2Cl_2); ^{1}H NMR δ 8.17 (s, 1 H), 6.75, 6.66 (AB, 2 H, *J* = 16.3 Hz), 3.92 (s, 3 H), 0.22 (s, 9 H); ^{13}C NMR δ 161.6, 161.0, 144.0, 134.9, 125.8, 118.4, 104.0, 102.0, 52.5, -0.1; IR (KBr) 3156, 3110, 3055, 2957, 2177, 2127, 1713, 1567 cm^{-1}; MS (EI) *m/z* (rel. intensity) 249 (M^+, 50), 234 ([M-CH_3]$^+$, 100), 218 ([M-CH_3O]$^+$, 17), 190 ([M-O_2CCH_3]$^+$, 27), 204 ([M-C_3H_9]$^+$, 20); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO_3Si$ 249.0821, found 249.0822.



71 **75**

2-(2-Iodoallyl)oxazole-4-carboxylic acid methyl ester (75). A mixture of **71** (14.2 mg, 0.086 mmol, 1.0 equiv), sodium iodide (13.0 mg, 0.087 mmol, 1.0 equiv) and sodium acetate (23.0 mg, 0.280 mmol, 3.3 equiv) was dissolved in glacial AcOH (0.45 mL) and heated under N_2 to 100 °C (oil bath temp) for 12 h, cooled to rt and diluted with ethyl acetate (10 mL). The mixture was washed with 2.0 N NaOH until the washings were pH>9, and then with saturated aqueous $Na_2S_2O_3$. The combined organic layers were backwashed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to an orange-colored oil. Purification by chromatography on SiO_2 (10% to 40% ethyl acetate/hexanes) afforded **75** (9.4 mg, 37%) as a clear, colorless oil: R_f 0.40 (40% ethyl acetate/hexanes); ^{1}H NMR δ 8.22 (s, 1 H), 6.23 (d, 1 H, *J* = 1.7 Hz), 5.93 (d, 1 H, *J* = 1.8 Hz), 4.05 (s, 2 H), 3.92 (s, 3 H); ^{13}C NMR δ 161.7, 144.7, 133.8, 130.1, 98.9, 77.4, 52.5, 44.5; IR (neat) 3159, 3001, 2952, 2848, 1747, 1622, 1583 cm^{-1}; MS (EI) *m/z* (rel. intensity) 293 (M^+, 62), 262 ([M-OCH_3]$^+$,

14), 182 (34), 166 ([M-I]$^+$, 79), 134 (100); HRMS (EI) *m/z* calcd for $C_8H_8NO_3I$ 292.9549, found 292.9543.

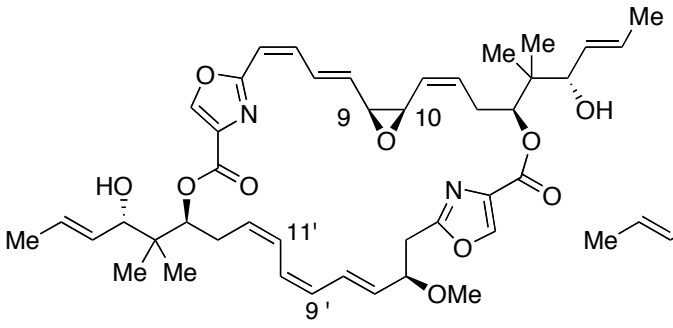
3. Synthesis of Disorazoles C_1 and Analogs

3.1. Introduction

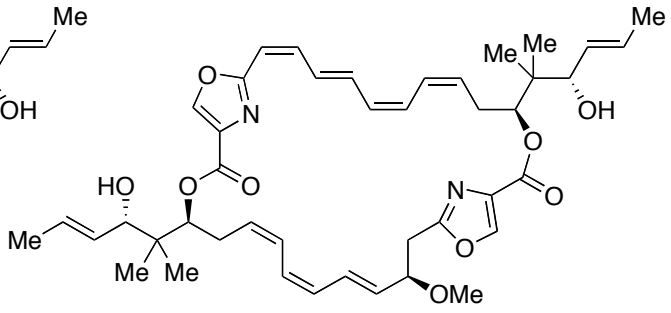
3.1.1. The Biology of the Disorazoles

The disorazoles are a group of 29 related macrodiolides isolated in 1994 by Jansen and coworkers from the fermentation broth of the gliding bacterium *Sorangium cellulosum* (strain So Ce 12).[34] Common to all disorazoles is the dimeric or pseudo-dimeric structure contained within a 30-membered macrodiolide, conjugated polyenes that may be interrupted by oxiranes or diols, and a 1-hydroxy-2-butenyl side chain that is linked through a *gem*-dimethyl unit (Figure 12). The initial report only detailed the connectivity of the atoms as determined by spectroscopic analysis.[34] The relative and absolute stereochemistry of disorazole A_1 was assigned after degradation and fragment synthesis studies.[101] Figure 12 shows the structures of the eight most abundant disorazoles and their abundance (%) relative to all disorazoles. The eight most common disorazoles comprise 92% by weight of all known disorazoles. Notably, disorazole A_1 comprises 71% by weight of all disorazoles and was isolated in multigram quantities from the fermentation broth. The remaining 21 disorazoles were isolated in less than 1% each.

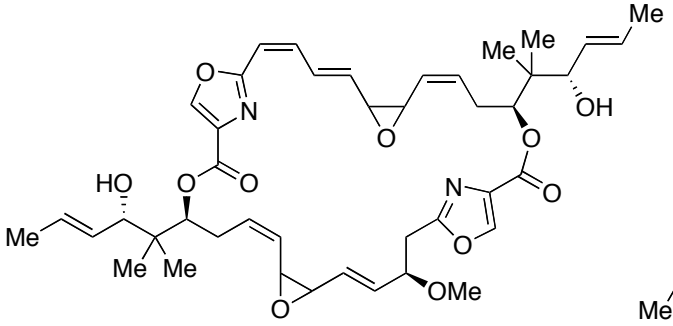
Figure 12. The structures of the eight most abundant disorazoles.



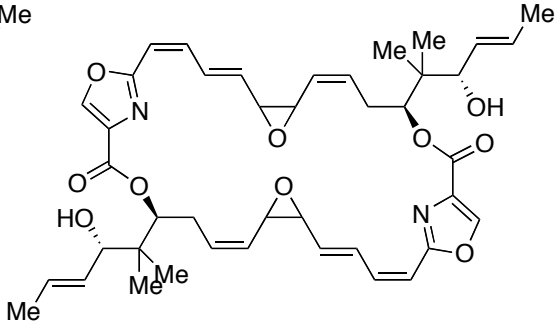
disorazole A_1, 71% (> 2 g)
disorazole A_4 (11' E), 2.2 %
disorazole A_7 (trans-epoxide), 1.6%
disorazole A_5 (9', 11' E), 1.2%
disorazole D_1 (9,10 diol), 1.5%



disorazole F_1
3%



disorazole E_1
9%

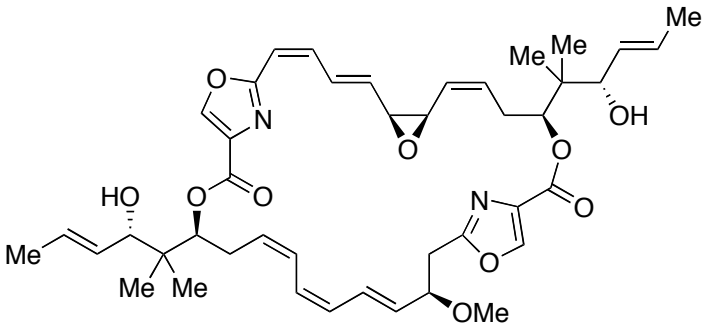


disorazole B_1
3%

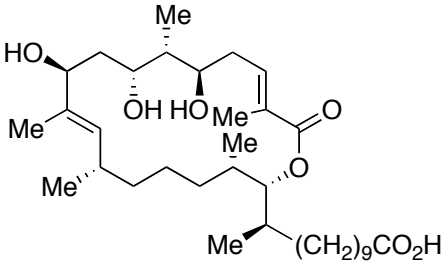
Along with the disorazoles, several other compounds were isolated from *Sorangium cellulosum* strain So Ce 12, including chivosazoles (anti-fungal),[102] sorangiolid (bacteriacidal)[103] and sorangicins (eubacterial RNA polymerase inhibitors)[104] (Figure 13).[105] The varied structures and biological activity demonstrate the diversity of the secondary metabolites that the myxobacteria are capable of producing; in this case, within just one strain of *Sorangium cellulosum*. Notable are the disorazoles and chivosazoles which incorporate serine residues in the form of oxazoles suggesting a

combined biosynthesis by polyketide synthase (PKS) and non-ribosomal peptide synthetases (NRPS).[106] Additionally, the chivosazoles incorporate an appended sugar moiety. Sorangicin and sorangiolide are of purely polyketide origin.

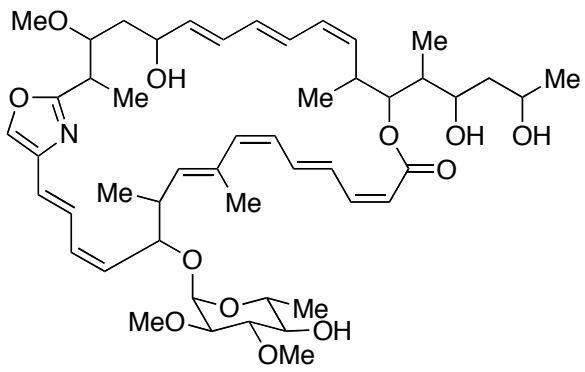
Figure 13. Compound classes isolated from *Sorangium cellulosum* Strain So ce 12.



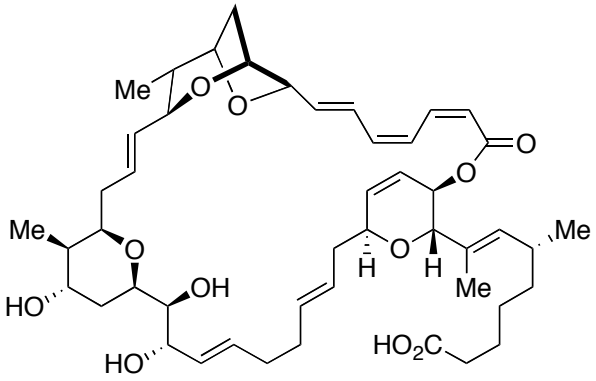
disorazole A_1



sorangiolid



chivosazol

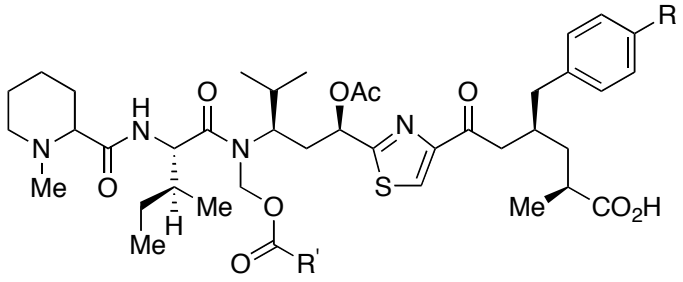


sorangicin A

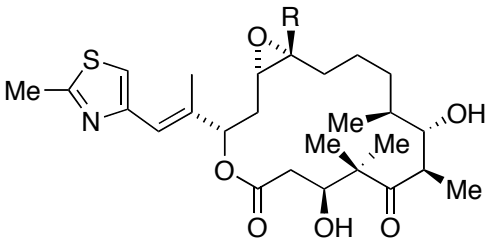
Sorangium cellulosum is a member of the myxobacteria. The myxobacteria are prolific producers of secondary metabolites that have a wide range of biological acitvity.[107] A small subset of these secondary metabolites, including the epothilones,[108] tubulysins[109] and disorazoles,[34] are highly cytotoxic and are known to perturb

microtubules (Figure 14). Epothilones stabilize microtubules in a manner similar to taxol and will displace taxol from the binding site on microtubules.[110] In contrast, tubulysins and disorazoles inhibit tubulin polymerization and therefore have a chemical phenotype more closely related to the vinca alkaloids.[111,112] Both tubulysins and disorazoles are more potent inhibitors of cell proliferation than the epothilones, taxol and vinblastin.[109,111]

Figure 14. Myxobacterium metabolites that affect tubulin polymerization.



tubulysin A, R = OH, R' = $CH_2CH(CH_3)_2$
tubulysin B, R = OH, R' = $CH_2CH_2CH_3$
tubulysin C, R = OH, R' = CH_2CH_3
tubulysin D, R = H, R' = $CH_2CH(CH_3)_2$
tubulysin E, R = H, R' = $CH_2CH_2CH_3$
tubulysin F, R = H, R' = CH_2CH_3
tubulysin G, R =OH, R' = $CH=C(CH_3)_2$
tubulysin H, R = H, R' = CH_3
tubulysin I, R = OH, R' = CH_3



epothilone A, R = H
epothilone B, R = CH_3

Initial studies indicated that disorazole A_1 demonstrates potent cell growth inhibition with an IC_{50} value of 3 pg/mL in L-929 mouse fibroblasts.[34b] Additional studies suggest that disorazole A_1 initiates the decay of microtubules, causes G2/M cell cycle arrest and competes *in vitro* with vinblastin for the tubulin binding site.[113] The extreme potency of the disorazoles has attracted the interest of researchers who are

working to understand how the disorazoles disrupt cellular networks. No synthetic route to the disorazoles existed until 2004,[114] so the biological studies focused on the major metabolite, disorazole A_1, which is available in multigram quantities by fermentation.[34]

Recently, Sasse and coworkers reported the results of their biological studies with disorazole A_1.[111] The antiproliferative effects of disorazole across a variety of animal and human cell lines ranged from 2 to 42 pM. This antiproliferative activity corresponds to 10 to 1000 times greater potency than epothilone B or vinblastin. Disorazole A_1 caused G_2/M-phase cell cycle arrest and induced nuclei enlargement as well as multinucleation and increased the population of hyperploid cells. Interestingly, while signs of apoptosis where evident, many cells maintained full metabolic activity for extended periods of time. Importantly, disorazole A_1 was also found to be a poor substrate for multi-drug resistant cells expressing high levels of P-glycoprotein (PGP). MDR1 PGP is responsible for pumping toxins out of cells and leads to decreased efficacy of anti-cancer pharmaceuticals.[115] There was a discrepancy between the *in vitro* tubulin polymerization experiments, where disorazole A_1 was comparable to vinblastin and whole-cell assays, where disorazole A_1 demonstrated three orders of magnitude higher efficacy. In addition, even short treatments (5 h) led to irreversible effects. The discrepancy between the *in vitro* and whole-cell assays may suggest that disorazole A_1 is being accumulated and strongly bound within the cell, a result that has important therapeutic consequences.[111]

Two groups have focused on understanding the genetic control of disorazole biosynthesis.[116,117] Both groups presented a similar model for the biosynthesis of the

disorazoles and the hypothesis of Müller and coworkers[116] will be discussed with some additional information from the work of Julien and coworkers.[117] Transposon libraries were used to identify the gene clusters that govern the biosynthesis of the disorazoles (Figure 15). Four genes, Dis A through Dis D, were found. Three of the genes, Dis A, Dis B and Dis C, are responsible for ten polyketide synthase (PKS) modules and one non-ribosomal peptide synthetase (NRPS) module. Modules 1 through 7 and the NRPS module assemble the seven acetate and one serine residues that constitute the disorazole monomer.[118] Module 1 is responsible for the loading and construction of the 2-butenoyl ACP_1 thioester. A loading domain for Dis A could not be identified, so some details of module 1 are still unknown.[116] Julien and coworkers suggested that the module 1 KS could be directly loaded by acetyl-CoA, module 1 could be loaded by a process termed “backloading” or module 1 could be loaded by an ACP that is outside of the 10 kb areas on each side of the PKS genes that were sequenced.[117] Module 2 contains the keto-reductase that is responsible for the C_{16}-stereocenter and the *S*-adenosylmethionine (SAM)-dependent methyl transferase (MT_3) that introduces the *gem*-dimethyl substitution at C_{15} of the disorazole monomer. The presence of two MT domains in module 2 indicates that the *gem*-dimethyl groups are introduced under a different mechanism from the *gem*-dimethyls in the epothilones.[117,119] In addition, ACP_{2b} is likely to be inactive due to an absence of a critical serine residue.[117] Module 3 is a standard acetate extension module and is the final complete PKS module encoded by the Dis A gene. Module 4 is split between Dis A and Dis B and constructs a second unit of unsaturation in the disorazole monomer. Modules 5 through 7 are similar to module 4 and result in the completed tetraene bound to ACP_7. Müller and coworkers

suggest that the incorporation of the unusual (*Z*)-olefins in the tetraene results from the elimination of an L-configured alcohol.[116] Conserved domains found in KR_2, KR_4, KR_5 and KR_7 are believed to be responsible for the incorporation of L-configured alcohols during biosynthesis. The product of module 7 is then transferred via module 8 to the NRPS, a process that is governed by the Dis C gene. The HC_{1a} and HC_{1b} domains of the NRPS module are responsible for the introduction and cyclization of a serine residue. Oxidation of the oxazoline to the oxazole is performed by the Ox_1 domain of the NRPS module and affords the completed disorazole monomer bound to PCP_1. Dis C also encodes modules 9 and 10, both of which Müller and coworkers suggest are inactive.[116] Dis D encodes the only acyl transferase (AT) domain as well as an oxidoreductase (Or) domain. The exact function of Dis D in the synthesis of the disorazoles is not known.

Julien and coworkers speculated on the functions of modules 8, 9 and 10.[117,120] The non-extending modules may transfer the polyketide chains between proteins or function in other protein-protein interactions. An alternative explanation for the non-extending modules is to mediate the polyketide transfer between the NRPS and a PKS module and may be related to the incorporation of the serine residue. The steps that lead to the macrocyclic structure of the disorazoles could not be identified from the analysis of the regions bordering the Dis A to Dis D.[116,117] Julien and coworkers suggest that vicinal thioesterase (TE) and carrier protein (CP) domains in the non-extending modules cooperate to afford the completed dimer (Figure 16).[117] The hypothesis encompasses the formation of the "ring-expanded" disorazoles (G_1, G_2, G_3)[34] by acylation of the C_{16}/$C_{16'}$ hydroxyls instead of the C_{14}/$C_{14'}$ positions.[117]

An interesting proposal concerning the formation of pseudodimers such as disorazole A_1 was put forth by Julien and coworkers (Figure 16).[117] The β-hydroxydehydratase (DH) domain of module 7 may function with 50% efficiency, leading to monomer units containing a C_6-hydroxyl substituent rather than the (*Z*)-alkene. Subsequent $C_{14}/C_{14'}$ acylation reactions afford the pseudodimer. Alternatively, the synthesis of a common dimer that is modified by unknown processes to afford the pseudo-dimers could not be ruled out. Subsequent methylation of the C_6-hydroxyl affords the southern segment of disorazole A_1.

The steps that lead to the 29 disorazole derivatives could not be accounted for by Müller's or Julien's genetic analyses. The introduction of oxirane, hydroxyl and methoxy substituents found in many of the disorazoles is believed to occur after the PKS/NRPS assembly, but any genes responsible for these transformations were not identified by either group. Further refinement in the genetic analysis will be required to attain a complete understanding of the biosynthetic pathways that are responsible for the formation of the disorazoles.

Figure 15. Müller's model for the biosynthesis of the disorazoles.[116]

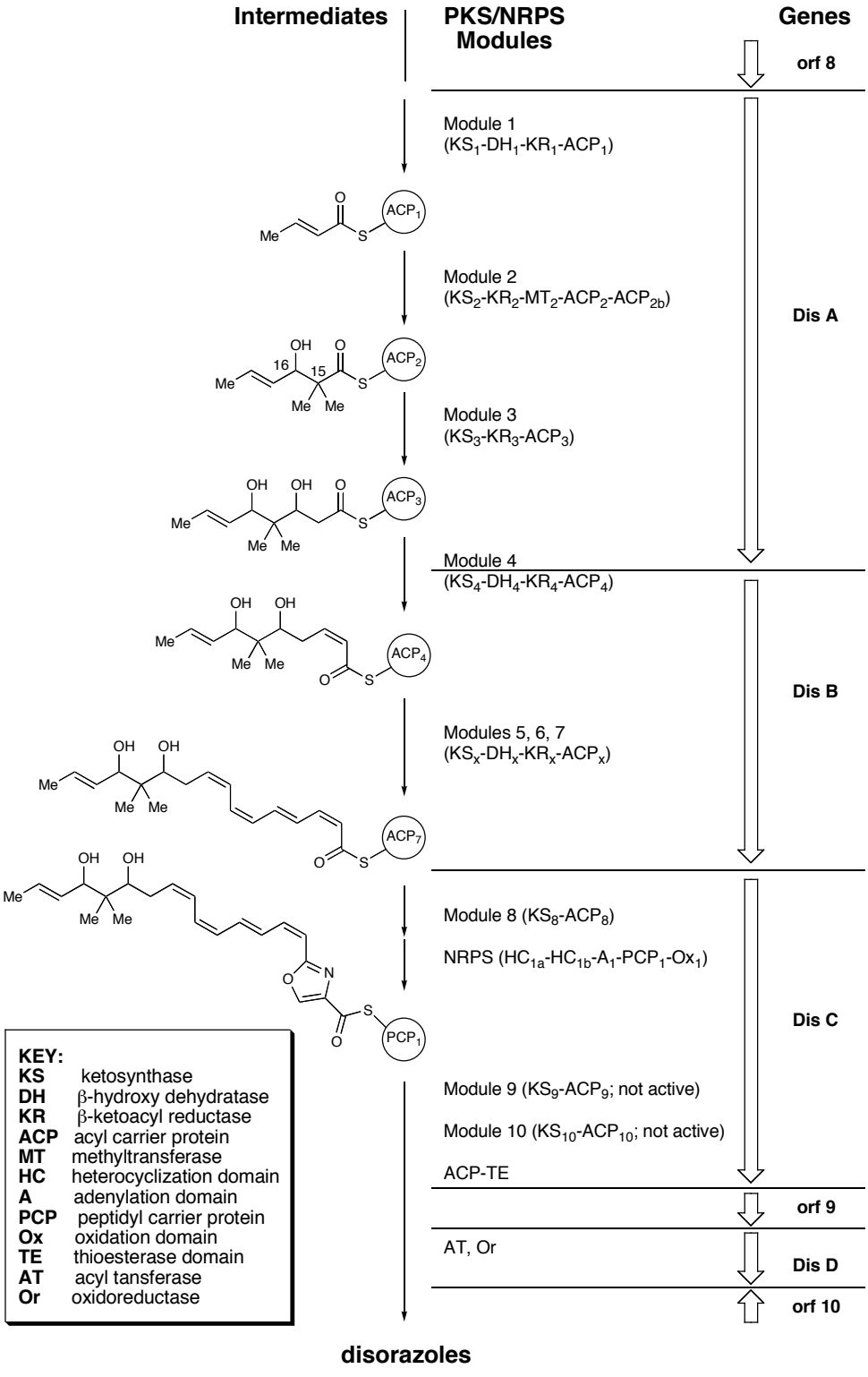
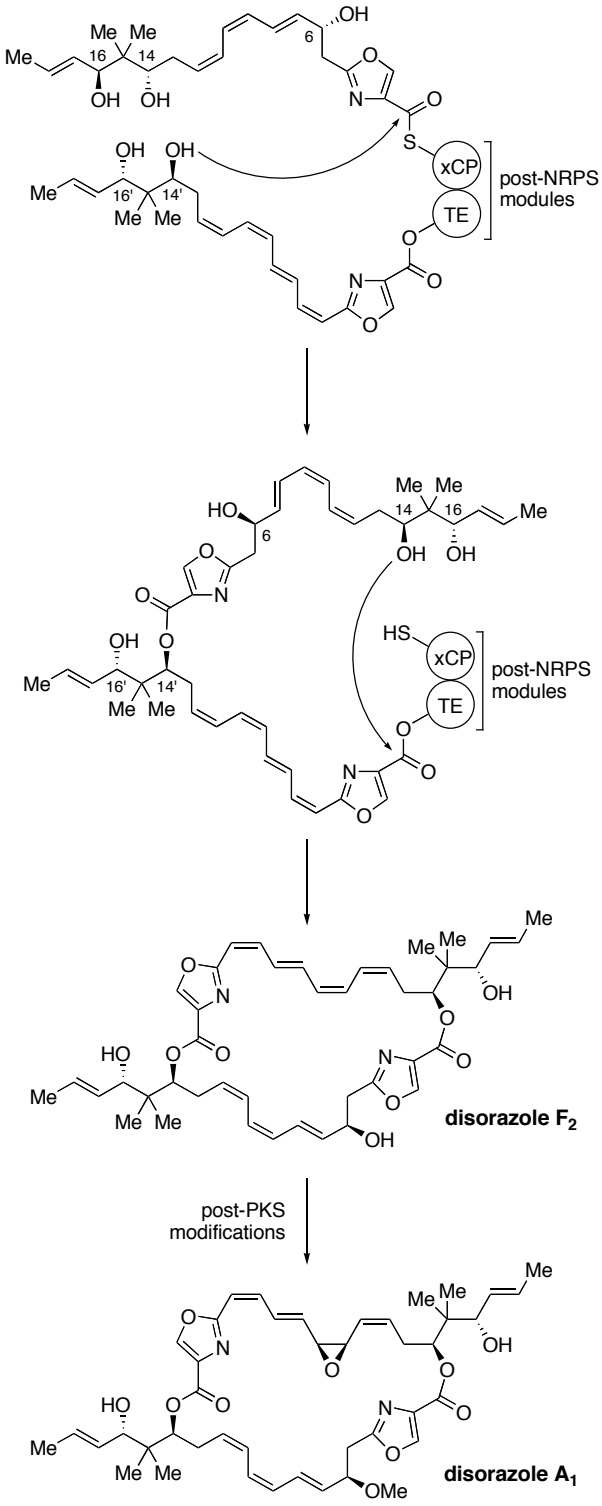


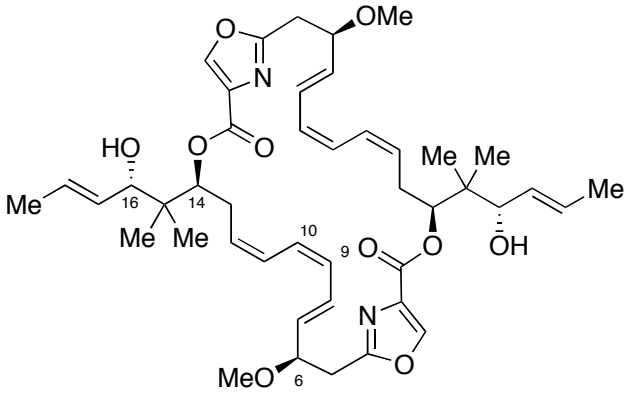
Figure 16. Julien's hypothesis for the dimerization of the disorazole monomers.[117]



3.1.2. Disorazole C_1: An Important Minor Metabolite

Disorazole C_1 (**76**) is a minor metabolite but it is interesting from a synthetic stand point because it is a dimer, and thus the synthesis of a monomer leads to a convergent synthesis of the final compound (Figure 17). In addition, the monomer unit of disorazole C_1 is found in 17 of the 29 disorazoles, so a successful synthesis of disorazole C_1 can be extended to the synthesis of other disorazoles. Disorazole C_1 lacks the potentially labile divinyl oxiranes and tetraenes that are common in the more abundant members of the family, allowing for a more facile synthesis and improving its potential for therapeutic uses. It could be suggested, however, that the extreme potency of the disorazoles is dependent on the divinyl oxiranes found in the more abundant members of the family (Figure 12). A hypothesis linking the activity to the divinyl oxiranes can be tested by making a disorazole that lacks the oxirane and evaluating its biological activity.[121]

Figure 17. The structure of the minor metabolite, disorazole C_1.



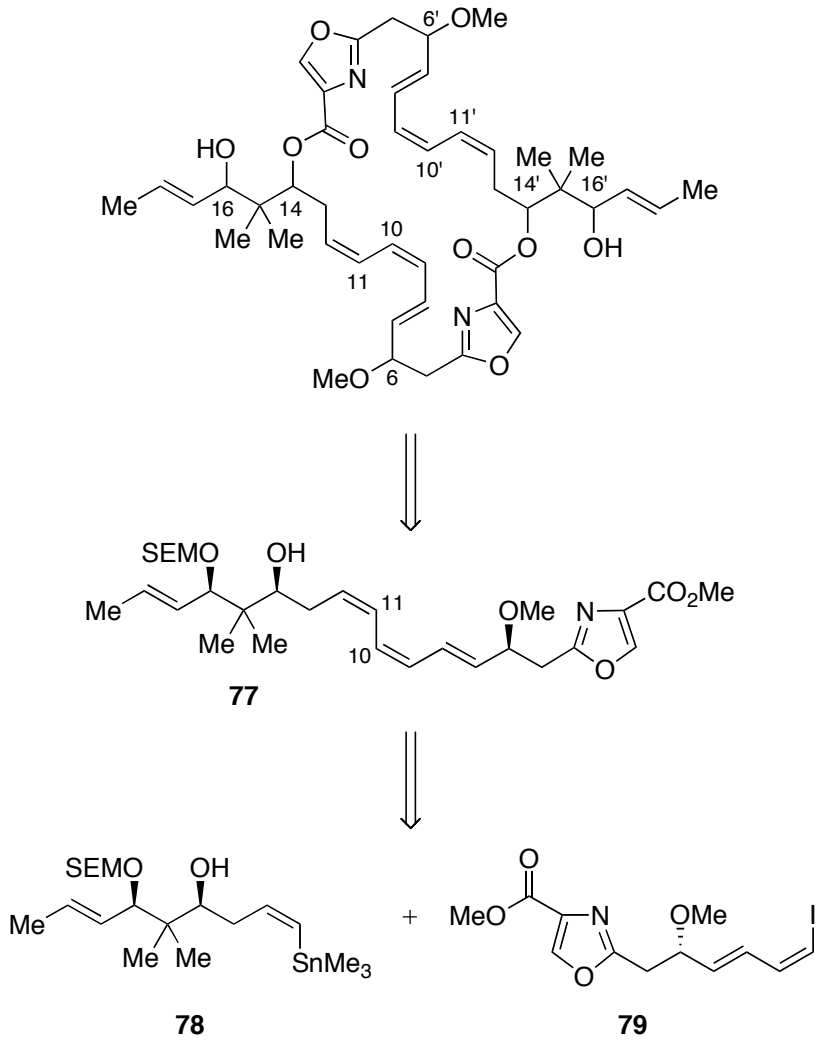
(-)-disorazole C_1
(**76**)

3.1.3. Prior Synthetic Efforts

3.1.3.1. Meyers' Approach to Disorazole C_1

The Meyers group was first to attempt a synthesis of any member of the disorazole class.[122] Disorazole C_1 was chosen as a target because it lacks the potentially labile divinyl oxirane and tetraene moities and has a monomer unit that is common in 17 of the 29 disorazole (Figure 18). Only the gross structure of the disorazoles was known when the Meyers group began their studies, so a successful total synthesis would also define the relative and absolute stereochemistry. The configurations at the $C_6/C_{6'}$, $C_{14}/C_{14'}$ and $C_{16}/C_{16'}$ stereogenic centers were arbitrarily chosen at the outset. Retrosynthetically, Meyers and coworkers took advantage of the dimeric structure of disorazole C_1, separating at the oxazole esters to afford the monomer methyl ester **77**. Disconnection between the C_{10}-C_{11} bond afforded fragments **78** and **79**. A Stille reaction between **78** and **79** was envisioned to afford the potentially labile triene in a highly convergent strategy.

Figure 18. Meyers' original retrosynthetic analysis of disorazole C_1.



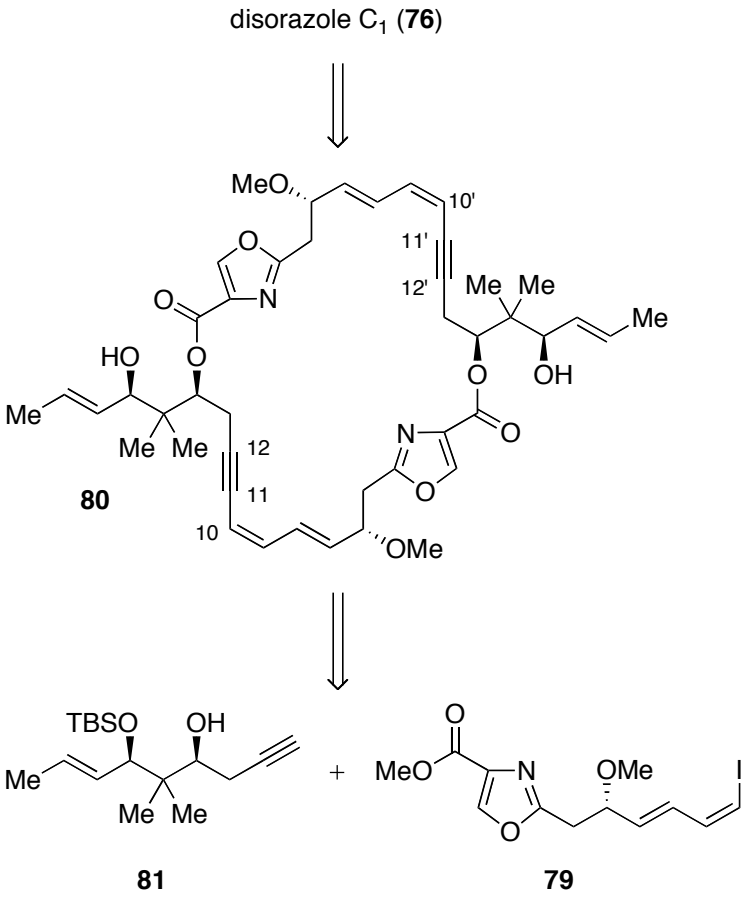
Meyers and coworkers proceeded to synthesize **78** and **79** (*vide infra*).[122] Subsequent Stille cross-coupling using catalytic $Pd(CH_3CN)_2Cl_2$ in DMF afforded 76% yield of a material which ^1H NMR analysis revealed to be similar to the natural product **76**, however, the triene tended to isomerize even during storage at –20 °C. Attempts to form the dimer by double lactonization were unsuccessful. The sensitivity of the triene

unit towards isomerization required the development of a revised strategy involving a masked triene unit.

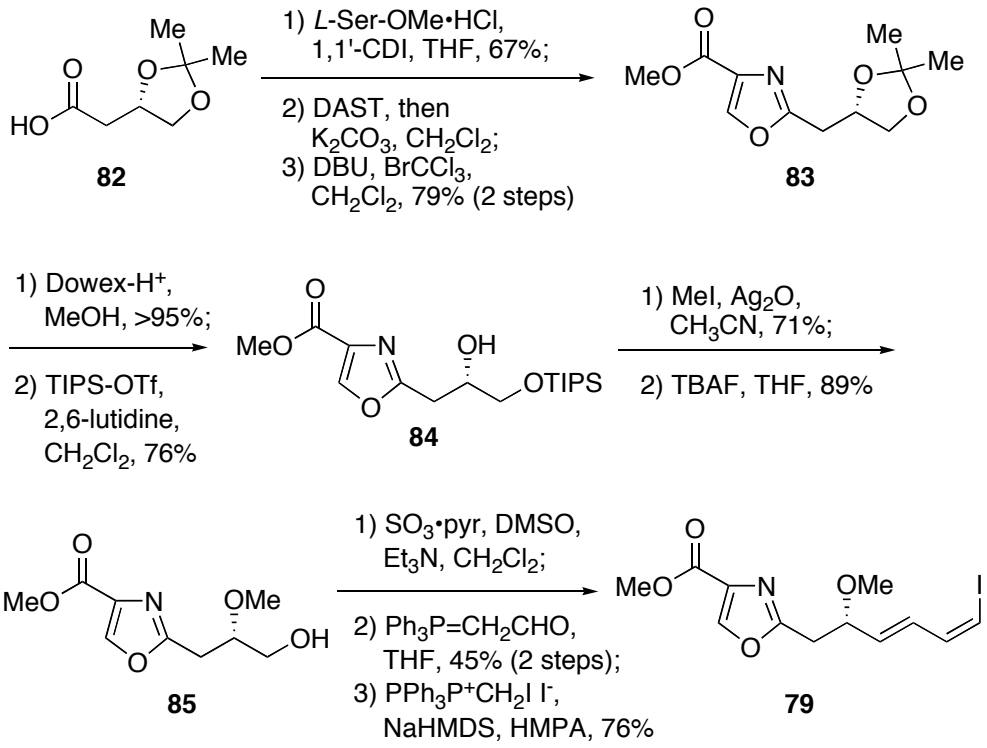
The revised strategy for the synthesis of disorazole C_1 incorporated an alkyne to mask the C_{11}-C_{12} (*Z*)-alkene (Figure 19).[123] Late stage reduction of the alkyne to the alkene would afford the sensitive triene. The incorporation of the alkyne allows for a disconnection at the C_{10}-C_{12} bond, affording oxazole fragment **79** and alkyne fragment **81**. A Sonogashira cross-coupling[99] reaction between **79** and **81** was envisioned to afford the masked triene in a highly convergent strategy.

The synthesis of the oxazole fragment **79** began with the L-malic acid derivative **82** (Scheme 27). The condensation of **82** and L-serine methyl ester using carbodiimidazole afforded the hydroxyamide in 67% yield. The hydroxyamide was cyclized with DAST and oxidized to afford oxazole **83** in 79% yield for the 2 steps. Protecting group manipulations were then required to selectively install the methyl ether. Consequently, removal of the acetal from **83** under acidic conditions afforded the diol in greater than 95% yield. Selective protection of the primary hydroxyl as the TIPS ether afforded **84** in 76% yield and the secondary hydroxyl was transformed to the methyl ether in 71% yield using MeI and silver(I) oxide. Removal of the TIPS group afforded **85** in 89% yield. The primary hydroxyl of **85** was then transformed in 45% yield into the dienal by oxidation to the aldehyde and Wittig homologation. A second homologation under the Stork-Zhao conditions[124] afforded the dienyliodide **79** in 76% yield. The oxazole segment **79** was completed in 10 steps and 8% overall yield.

Figure 19. Meyers' revised retrosynthetic analysis of disorazole C_1.



Scheme 27. Meyers' synthesis of the oxazole segment.

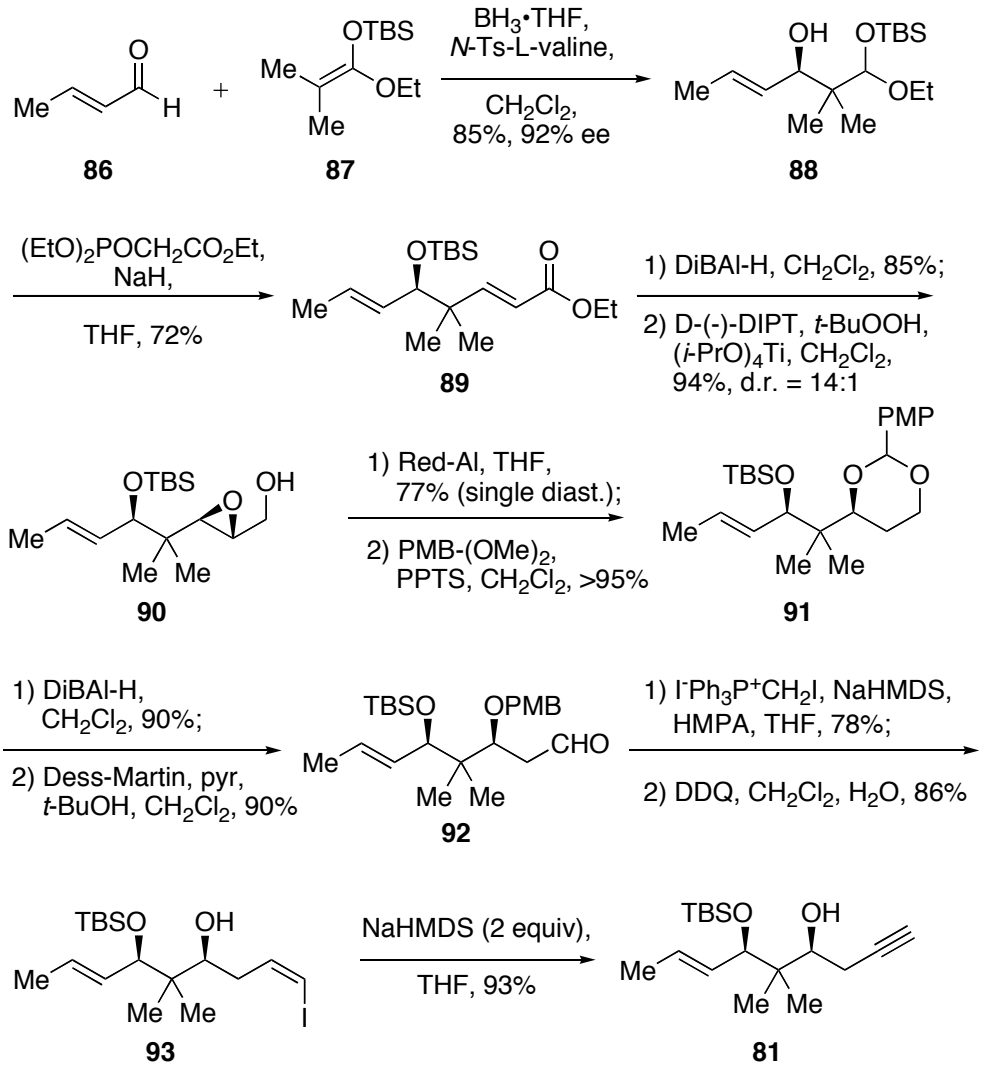


Attention was then turned towards the alkyne **81**, beginning with Kiyooka's modification of the Mukaiyama aldol reaction (Scheme 28).[125] Condensation of methacrolein (**86**) and silylenol ether **87** under the influence of the catalyst generated *in situ* from *N*-tosyl-L-valine and borane•THF complex afforded the aldol product **88** in 85% yield and 92% ee. Subjecting the mixed acetal **88** to Horner-Wadsworth-Emmons conditions triggered the silyl migration that unveiled the latent aldehyde which subsequently condensed with the diethyl phosphonoacetate ethyl ester to afford **89** in 72% yield. Meyers and Hillier found in a separate study that unsaturated aldehydes

and the *gem*-dimethyl substitution are required for this interesting tandem reaction to proceed.[126]

Diisobutylaluminum hydride reduction of the α,β-unsaturated ester **89** afforded the allylic alcohol in 85% yield. The second required stereocenter (C_{14}) was set in 94% yield and a diastereomeric ratio of 14:1 by Sharpless asymmetric epoxidation of the allylic alcohol to afford **90**. The oxirane was reduced with Red-Al in 77% yield to afford the 1,3-diol as a single diastereomer, which was subsequently protected as the *p*-methoxyphenyl acetal **91** in greater than 95% yield. Selective opening to the acetal using diisobutylaluminum hydride afforded the primary alcohol in 90% yield and oxidation to aldehyde **92** with Dess-Martin periodinane[17] occurred in 90% yield. One carbon homologation using the Stork-Zhao conditions[124] and DDQ removal of the PMB ether afforded in 78% and 86% yield, respectively, the vinyl iodide **93**.[127] Elimination of the vinyl iodide using NaHMDS afforded the homopropargylic alcohol **81** in 93% yield. Interestingly, the elimination only occurred in the presence of the hydroxyl group and did not occur with the PMB-protected precursor. The alkyne **81** was constructed in 11 steps and 18% overall yield.

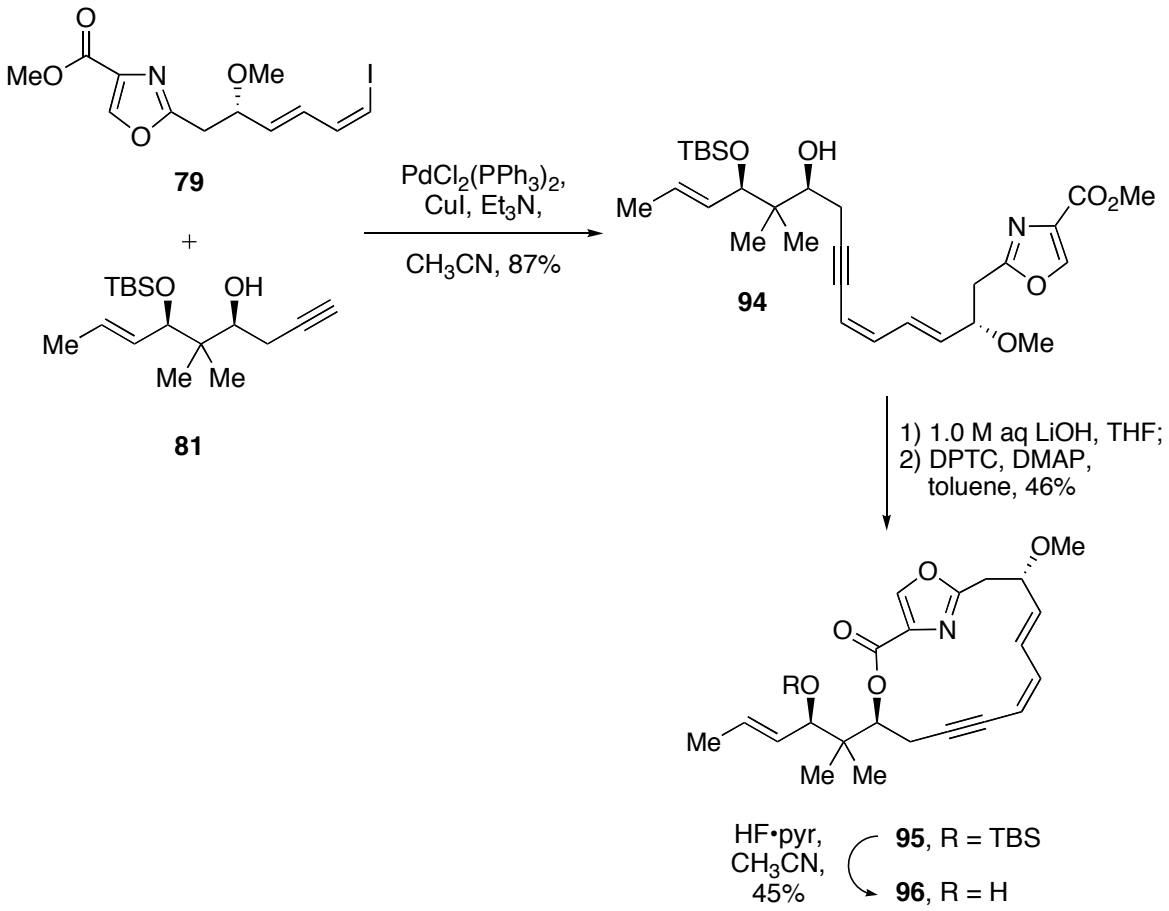
Scheme 28. Meyers' synthesis of the diol segment.



Meyers and coworkers attempted to form the macrocycle using a potentially efficient dimerization of two monomer units constructed from the oxazole fragment **79** and the alkyne fragment **81** (Scheme 29). Sonogashira cross-coupling[99] of **79** and **81** afforded the masked monomer unit **94** in 87% yield. Saponification with LiOH and subsequent cyclization of the hydroxyacid with dipyridylthionocarbonate (DPTC) and

catalytic DMAP afforded the cyclomonomer **95** in 46% with no amounts of the dimer being isolated. Deprotection of **95** with HF•pyr afforded a 3:1 mixture of **96** and the acyl transfer (ring expanded) product from which the major product **96** was crystallized in 45% yield.

Scheme 29. Attempted dimerization of the monomer.

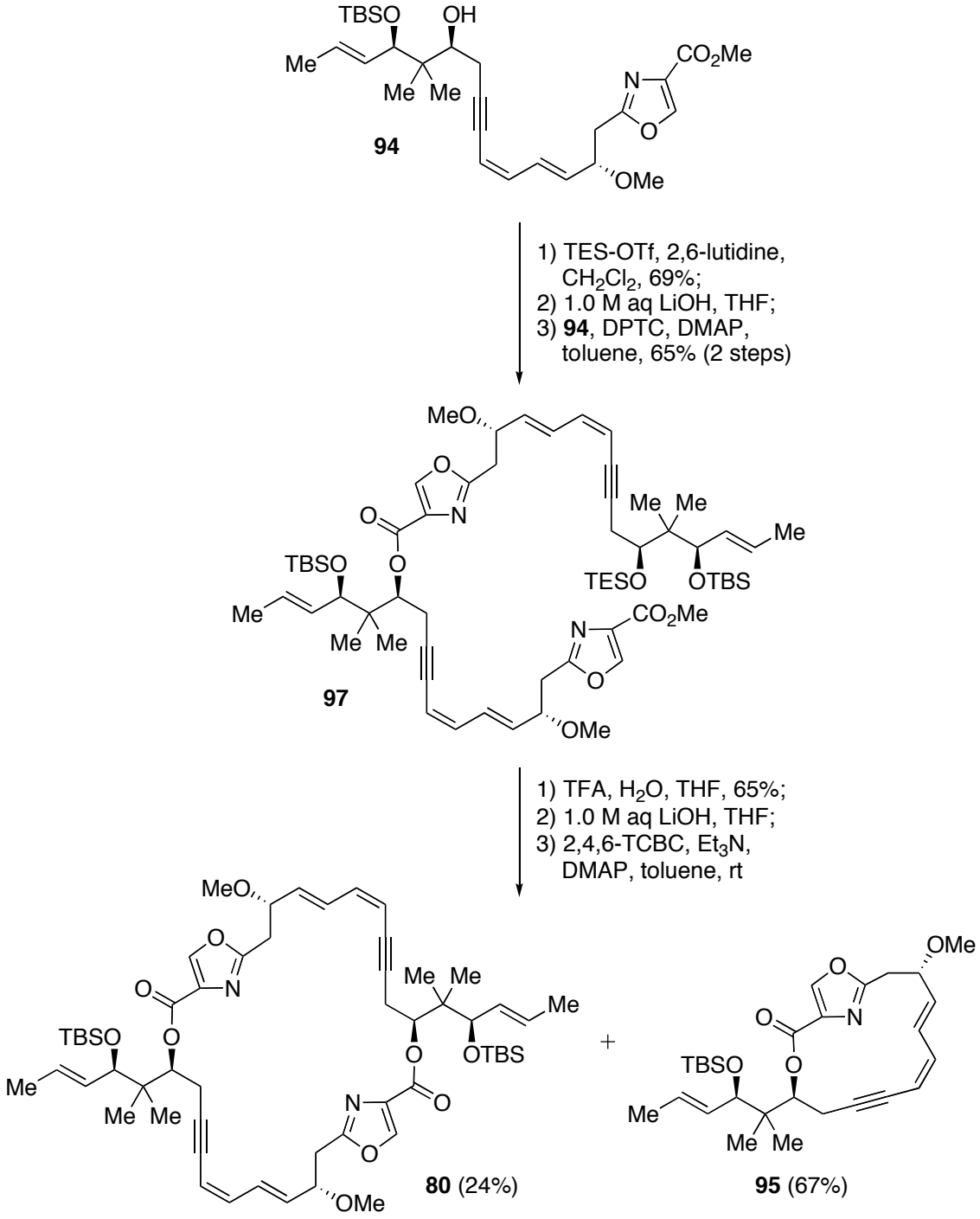


The attempt to efficiently form the dimer from the monomer hydroxyacid was unsuccessful, so an alternative strategy involving a stepwise construction of the macrocycle was pursued (Scheme 30). Protection of the C_{14}-hydroxyl as the TES-ether

occurred in 69% yield. Saponification and condensation with **94** using DPTC and DMAP afforded the protected *seco*-acid methyl ester **97** in 65% yield for the two steps. Removal of the TES group under acidic conditions and saponification of the methyl ester afforded the *seco*-acid which was cyclized under Yamaguchi conditions[128] to afford the macrocyclic dimer **80** in 24% yield. The formation of **80** was accompanied by significant transesterification as indicated by the isolation of the cyclomonomer **95** in 76% yield. Attempts to install the triene unit by reduction of the triple bonds in **80** to afford the trienes were unsuccessful.

Meyers and coworkers pioneered the synthesis of disorazole C_1, and although they were unsuccessful in completing the task, significant knowledge concerning the idiosyncrasies of the disorazoles was gained and documented. Several points are noteworthy. First, the triene unit of the monomer was found to be unstable and placing the alkyne at the $C_{11\text{-}12}$-position of the monomer prevented isomerization of the remaining diene. Second, cyclomonomer formation was a significant side reaction. Third, late stage intermediates appeared to be unstable towards strongly acidic or basic conditions. Fourth, silyl and acyl transfers between the C_{14}- and C_{16}-oxygens occurred with various intermediates. All of these findings were considered when the synthesis of disorazole C_1 was devised (Section 3.2.1).

Scheme 30. Stepwise synthesis of the dimer.



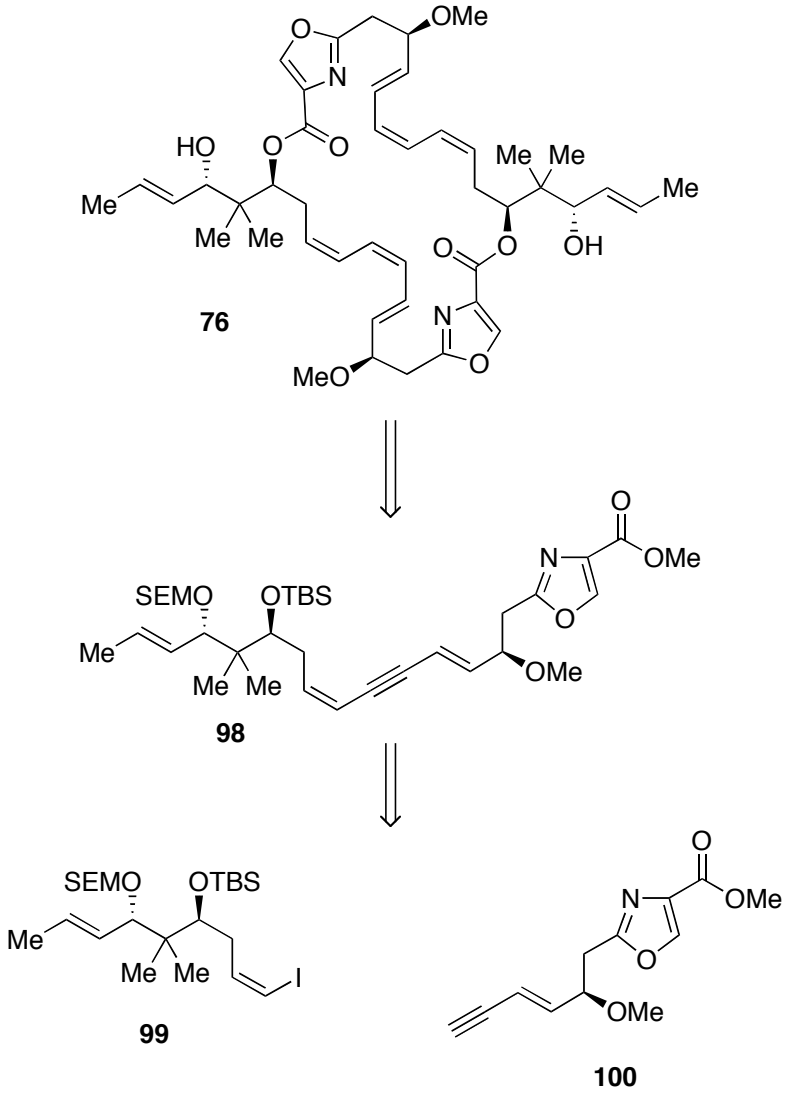
3.1.3.2. Hoffmann's Approach to Disorazole C_1

Hoffmann and coworkers, incorporating the findings of Meyers and coworkers, also utilized an alkyne to mask one of the (*Z*)-alkenes of the triene unit (Figure 20).[129] Preliminary computational estimates suggested that masking the $C_{9\text{-}10}$-alkene would inhibit the formation of the cyclomonomer that was observed by Meyers. Hoffmann also disconnected at the oxazole esters to afford monomer **98**. The monomer was further disconnected at the alkene and alkyne to afford fragments **99** and **100**. Hoffmann and coworkers had the additional advantage of knowing the relative and absolute stereochemical configurations of the disorazoles, based on degradation studies performed by Höfle.[101]

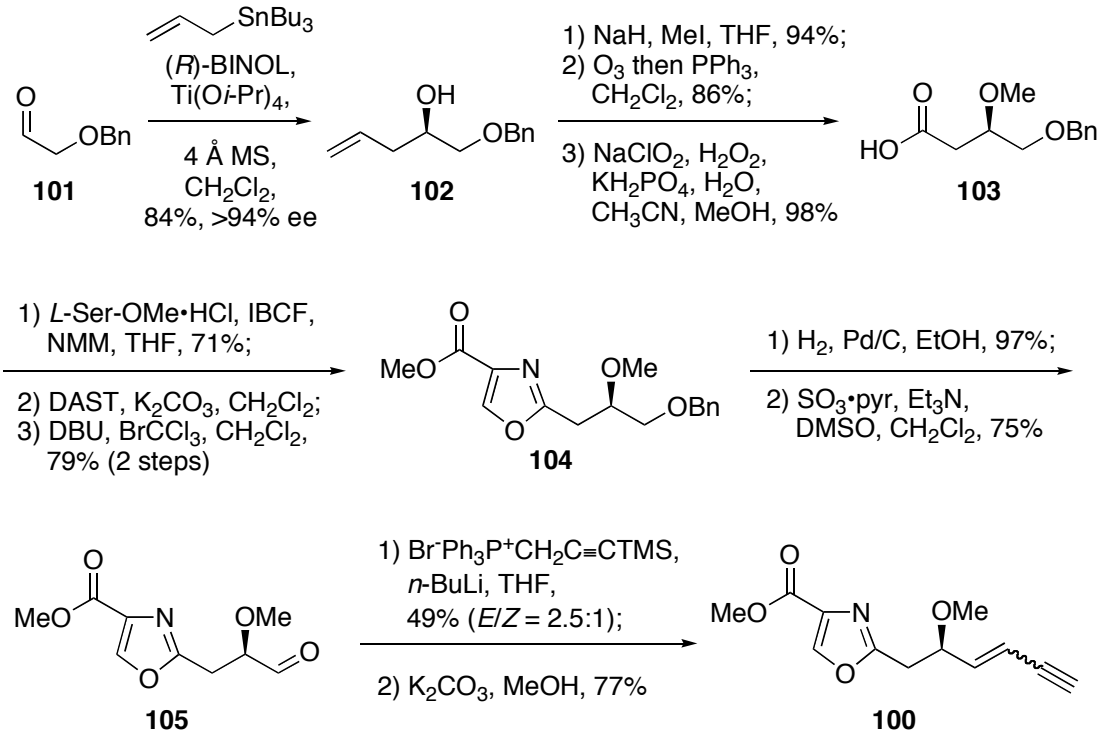
Synthesis of the oxazole fragment **99** began with the Keck allylation[130] of aldehyde **101** to afford homoallylic alcohol **102** in 84% yield and greater than 94% ee. The hydroxyl was converted to the methyl ether in 94% yield. Ozonolysis of the alkene and subsequent oxidation to the carboxylic acid **103** occurred in 86% and 98% yield, respectively. Acid **103** was then coupled to serine methyl ester using the mixed anhydride method to afford the hydroxy amide in 71% yield. Cyclization of the hydroxyamide using DAST and oxidation to the oxazole using $BrCCl_3$ and DBU occurred in 79% yield for the two steps.[13] The benzyl ether was cleaved by hydrogenation in 97% yield and the resulting primary alcohol was oxidized to the aldehyde **105** in 75% yields. The enyne was installed by Wittig olefination in 49% yield and modest (*E*/*Z*)-selectivity. Finally, removal of the trimethylsilyl group with basic methanol afforded the terminal alkyne **100** as an inseparable mixture of (*E*/*Z*)-isomers.

The oxazole segment was completed in 11 steps and 10% yield and was used as a mixture of (*E*/*Z*)-isomers.

Figure 20. Hoffmann's retrosynthetic analysis of the masked monomer unit.



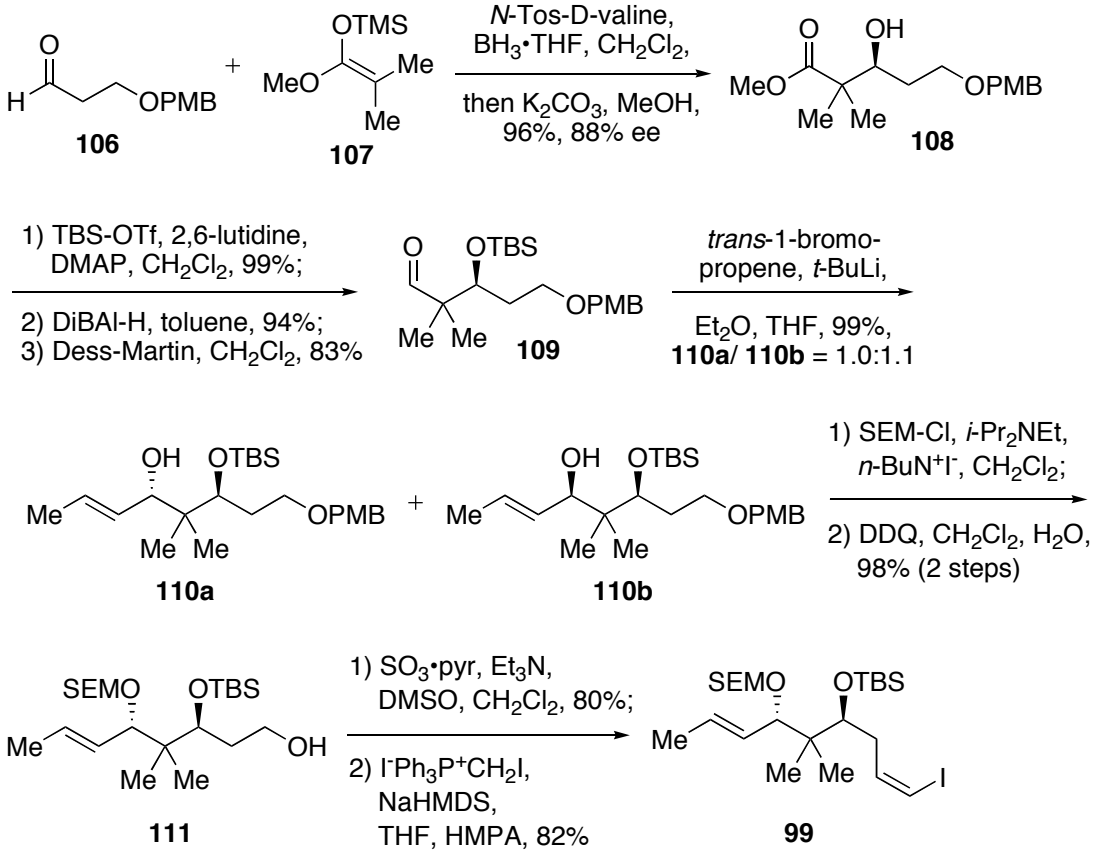
Scheme 31. Hoffmann's synthesis of the oxazole segment.



The synthesis of the diol segment was initiated in a similar manner to Meyers' synthesis, relying on Kiyooka's Mukaiyama aldol methodology[125] to convert aldehyde **106** to **108** in 96% yield and 88% ee. TBS-protection of **108** was nearly quantitative. Reduction of the ester to the alcohol with DiBAl-H and oxidation using Dess-Martin periodinane[17] afforded the aldehyde **109**. Addition of *trans*-propenyl lithium to **109** afforded a nearly quantitative yield of **110a** and **110b** in nearly equivalent amounts. The 1,3-*anti*-diastereomer **110a** was then protected as the SEM ether and the PMB group was removed with DDQ to afford **111** in 98% yield for the two steps. Finally, Parikh-Doering oxidation[131] and homologation using the Stork-Zhao conditions[124]

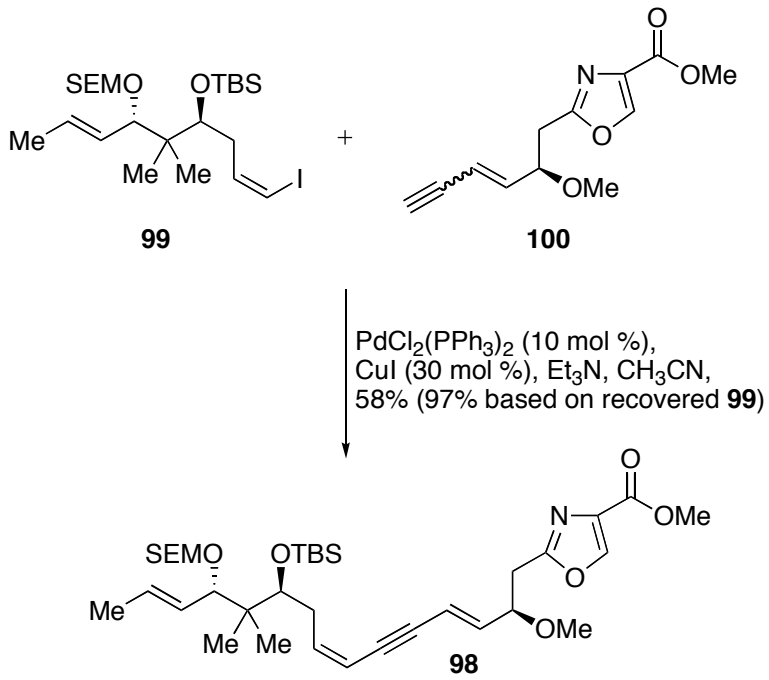
afforded the completed diol segment **99**. This segment was completed in a total of 9 steps and 22% overall yield.

Scheme 32. Hoffmann's synthesis of the diol segment.



Construction of monomer **98** was accomplished using Sonogashira conditions[99] to couple **99** and **100** in 58% yield (Scheme 33). A significant amount of the vinyl iodide **99** was recovered. Efforts concerning the further conversion of **98** to the dimer have not been reported.

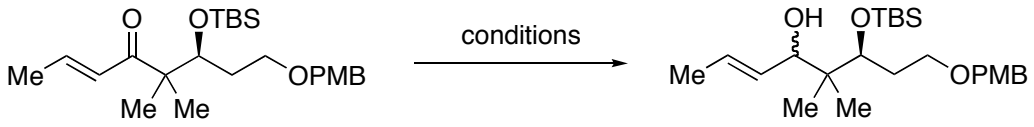
Scheme 33. Completion of the masked monomer unit.



In a later publication, Hoffmann and coworkers detailed their efforts towards setting the C_{16}-stereocenter[132] of **110** by reduction of the corresponding ketone **112** (Table 10).[133] Luche conditions using $LiBH_4$ and $CeCl_3 \bullet 7\ H_2O$ afforded a 58% yield of a mixture of the allylic alcohols, favoring the undesired *syn*-diastereomer (entry 1). The product of a 1,4-reduction was also isolated in 24% yield. The application of the chiral (*R*)-methyl-CBS-oxazaborolidine[134] reagent afforded the allylic alcohols in 78% yield and favored the undesired *syn*-diastereomer by greater than 10:1 (entry 2). The product of 1,4-reduction was isolated in 17% yield. Interestingly, the (*S*)-methyl-CBS-oxazaborolidine reagent[134] afforded only 1,4-reduction product. Reduction using the Terashima reagent[135] afforded only the product of 1,4-reduction in 84% yield. Other

reagents including L-Selectride, lithium aluminum hydride, lithium triethyl borohydride and zinc borohydride/$CeCl_3$•7 H_2O afforded 1,4-reduction products.

Table 10. Diastereoselective reduction of the (*S*)-enantiomer.



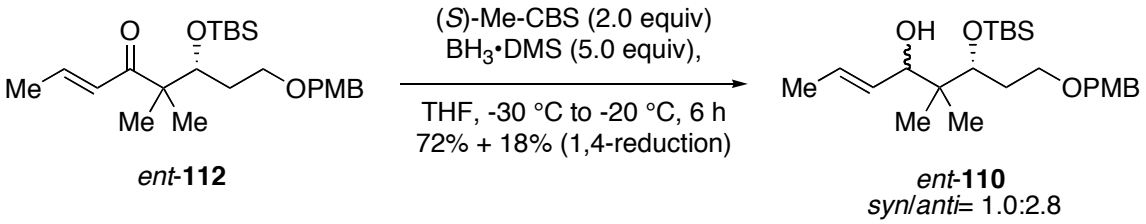
112 **110**

Entry	Reducing Conditions[a]	*syn/anti*	Yield (%)	Comment
1	$LiBH_4$, $CeCl_3$•7 H_2O, MeOH	1.6 / 1.0	58%	24%, 1,4-reduction
2	(*S*)-Me-CBS (2.1 equiv), BH_3•DMS (5.0 equiv)	10.8 / 1.0	78%	17%, 1,4-reduction
3	Terashima reagent	-	-	84%, 1,4-reduction

[a] L-Selectride, $LiAlH_4$, $LiHBEt_3$, $Zn(BH_4)_2/CeCl_3$•7 H_2O and (*R*)-Me-CBS afforded the 1,4-reduction product.

The odd behavior of the CBS-oxazaborolidine was further explored using the opposite enantiomer *ent*-**112** (Scheme 34). Reduction of *ent*-**112** using (*S*)-methyl-CBS-oxazaborolidine[134] afforded 72% of the allylic alcohol *ent*-**110** favoring the 1,3-*anti*-isomer. The 1,4-reduction product was isolated in 18% yield. The results suggest that significant match-mismatch pairing may be occurring in the transitions state leading to the allylic alcohols.

Scheme 34. Diastereoselective reduction of the (*R*)-enantiomer.

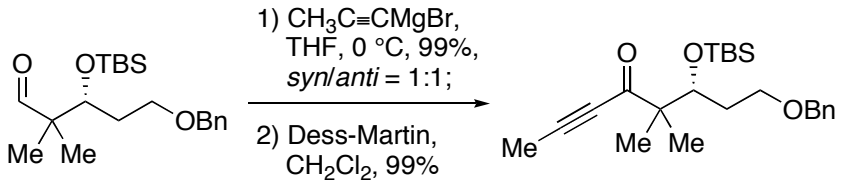


ent-**112**

ent-**110**
syn/*anti*= 1.0:2.8

Reduction of the propargyl ketone **114** was explored as an alternative to the reductions outlined above. The addition of propynyl magnesium bromide to aldehyde **113** afforded the propargylic alcohol in 99% yield with no *syn*/*anti*-selectivity (Scheme 35). Oxidation of the mixture afforded the ketone **114** in 99% yield.

Scheme 35. Propynyl magnesium bromide addition to the C_{16}-aldehyde.



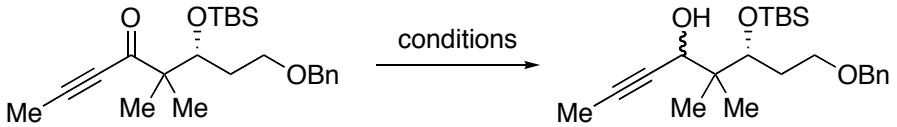
113

114

A variety of conditions were screened for the diastereoselective reduction of the propargylic ketone **114** (Table 11). Luche reduction afforded the propargylic alcohol **115** in 94% yield, but the selectivity was poor (entry 1). Reduction with (*S*)-Me-CBS-oxazaborolidine[134] and borane-dimethylsulfide complex afforded a moderate yield of **115**, favoring the undesired 1,3-*syn*-relationship and a significant amount of **114** was

recovered (entry 2). Similar conditions using catecholborane as the stoichiometric reductant again favored the undesired *syn*-diastereomer to a lesser extent with slightly increased yield and significant amounts of recovered **114** (entry 3). Likewise, the Terashima reagent[135] afforded the undesired *syn*-diastereomer in 82% yield.

Table 11. Diastereoselective reductions of the propargylic ketone.



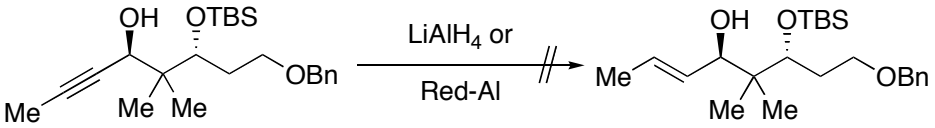
114 **115**

Entry	Reducing Conditions	Yield (%)	*syn/anti*[a]
1	$LiBH_4$, $CeCl_3$•7 H_2O[b]	94	1.0 / 1.5
2	(*S*)-Me-CBS (0.5 equiv), BH_3•DMS (1.0 equiv)	58[b]	5.3 / 1.0
3	(*S*)-Me-CBS (1.0 equiv), catechol borane (2.0 equiv)	66[c]	1.7 / 1.0
4	Terashima reagent (2.1 equiv)	82	2.0 / 1.0

[a] Determined by ^1H NMR analysis. [b] Starting material recovered (35%). [c] Starting material recovered (28%).

Unfortunately, attempts to reduce the propargyl alcohol *anti*-**115** to the allylic alcohol **116** using lithium aluminum hydride or Red-Al were unsuccessful (Scheme 36).

Scheme 36. Attempted alkyne reduction.



115 **116**

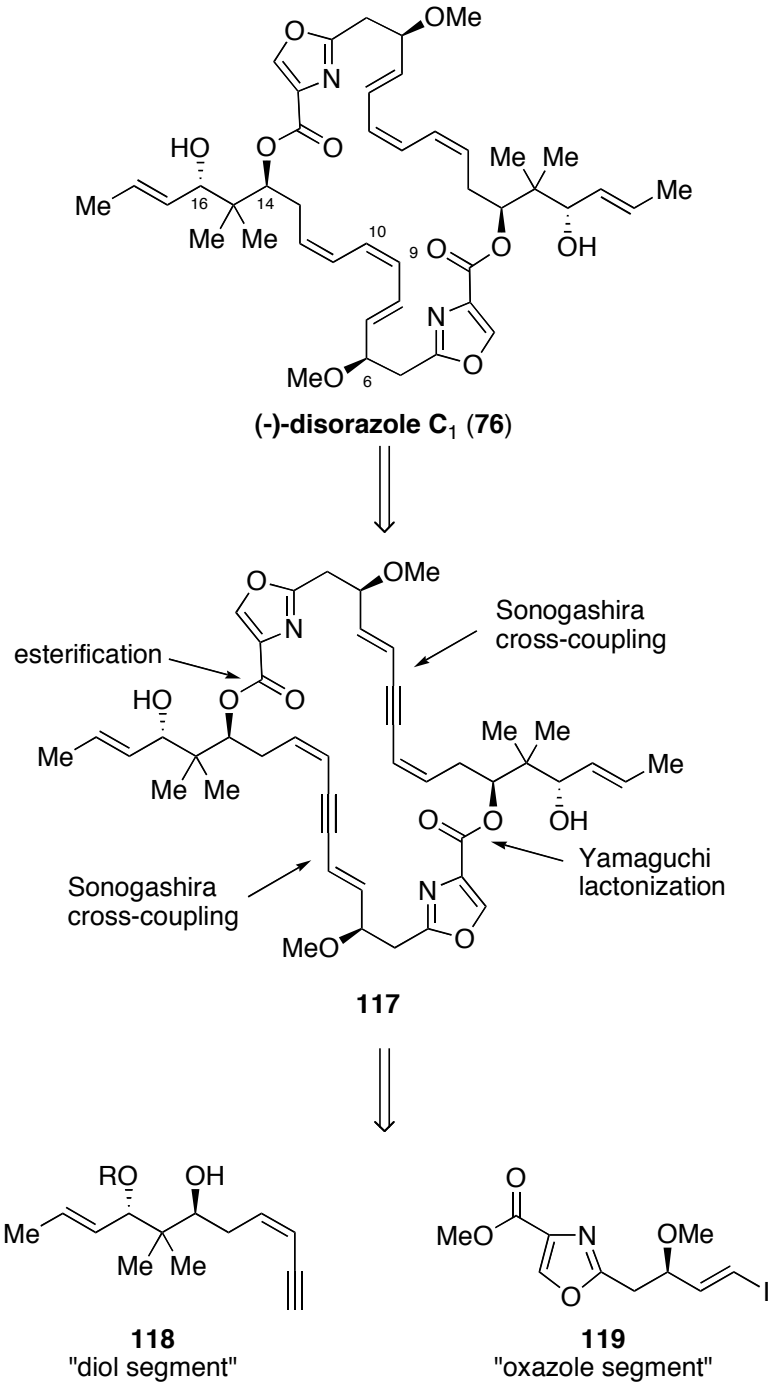
Following on the findings of Meyers and coworkers, Hoffmann and coworkers demonstrated an alternative strategy for the synthesis of a masked monomer unit of disorazole C_1. Importantly, masking of the $C_{9\text{-}10}$-(*Z*)-alkene as an alkyne was demonstrated to be a viable route to the monomer unit although the potential of the alkyne to inhibit cyclomonomer formation was not demonstrated. Additionally, the challenges of stereoselectively installing the propenyl side-chain were demonstrated. In common with the Meyers route, Hoffmann used the masked triene unit as an important disconnection point, allowing for a convergent synthesis.

3.2. Synthesis of Disorazole C_1

3.2.1. Retrosynthetic Analysis

Disorazole C_1 (**76**) was chosen as a target for the reasons mentioned earlier (Section 3.1.2). In addition, the pioneering work of Meyers and Hoffmann offered insight into the challenges that exist in executing a synthesis of this complex molecule. A highly convergent route to disorazole C_1 was developed with special consideration given to the known sensitivity of the late stage intermediates (Figure 20).[114] Retrosynthetically, the dimer was separated into four segments that could be assembled under mild reaction conditions with minimal protecting group manipulations. An obvious disconnection is at the oxazole esters and in the synthetic direction would allow the macrocycle to be formed via a Yamaguchi macrolactonization.[128] Given the known sensitivity of the triene unit of the monomer towards isomerization, one of the (*Z*)-alkenes of the triene unit was masked as an alkyne (**117**) and the complete triene would only be revealed once the dimer was formed. The required dienyne (**117**) offered an opportunity to disconnect between the alkene and the alkyne, leading to the advanced intermediates **118** and **119**, which in the synthetic direction would be connected with a mild Sonogashira cross-coupling.[99]

Figure 21. Retrosynthetic analysis of disorazole C_1.

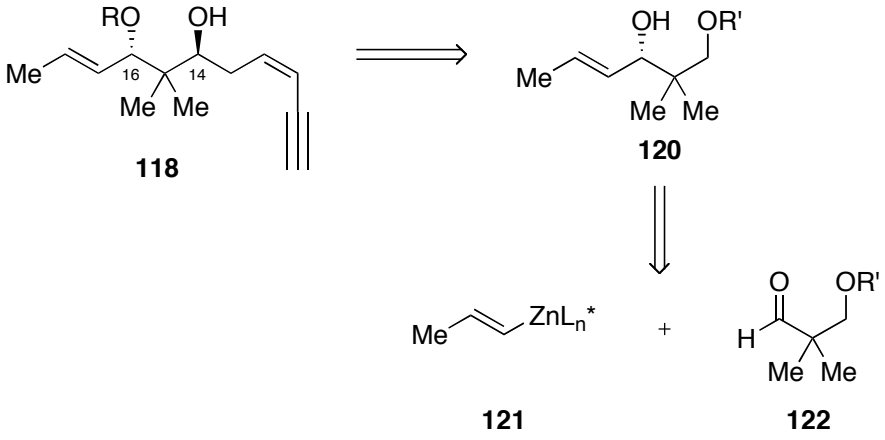


3.2.2. Synthesis of the Diol Segment

3.2.2.1. Preliminary Attempts at Setting the C_{16}-Stereocenter

While the successful synthesis of disorazole C_1 involved an entry into the enantiomeric series by setting the C_{14}-stereocenter[132] with an asymmetric allylation, preliminary synthetic studies explored setting the C_{16}-stereocenter by using an asymmetric vinyl zinc addition (Figure 22).[136] Retrosynthetically, the diol fragment **118** is derived from allylic alcohol **120** which is derived from vinyl zinc **121** and aldehyde **122**.

Figure 22. Initial retrosynthesis of the diol segment.



Model systems were constructed to evaluate the efficiency of the vinyl zinc additions (Scheme 37). Synthesis of the known aldehydes **122a**[137] and **122b**[138] commenced with the monoprotection of 2,2-dimethylpropane-1,3-diol to afford the

known protected diols **124a**[137] and **124b**[138] in 81% and 78% yield, respectively. Oxidation with NaOCl and catalytic TEMPO[66] afforded the corresponding aldehydes **122a** in 88% yield and **122b** in 71% yield.

Scheme 37. Synthesis of the model systems for the vinyl zinc additions.

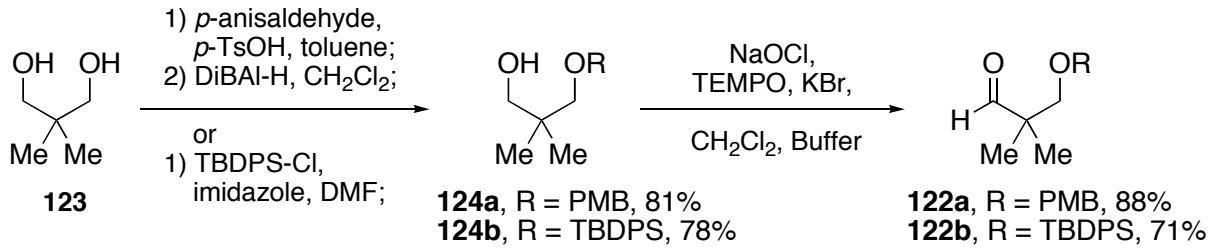
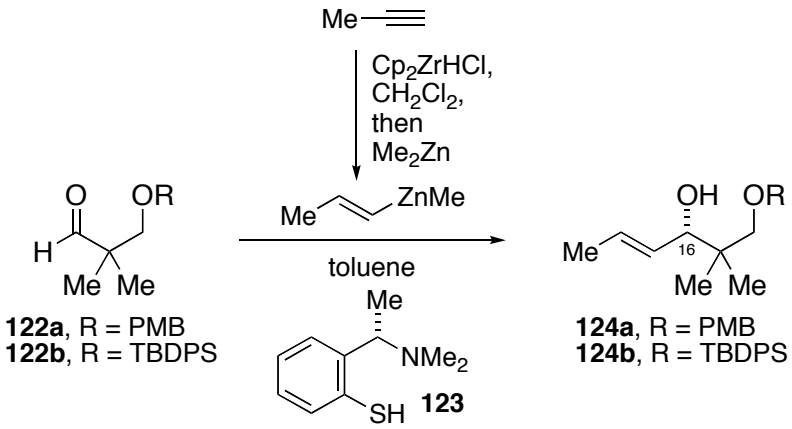


Table 12. Model study for setting the C_{16}-stereocenter.



Entry	Aldehyde	Ligand **123** (equiv)	Temp/ Time	Yield **124** (%)	ee (%)
1	**122a**	-	0 °C, 1 h; rt, 3 h	76	0
2	**122a**	0.25	-14 °C, 18 h	19[a]	24
3	**122b**	0.20	0 °C, 6.5 h	87	33
4	**122b**	0.20	-14 °C, 18 h	75	32

[a] Aldehyde recovered in 49% yield.

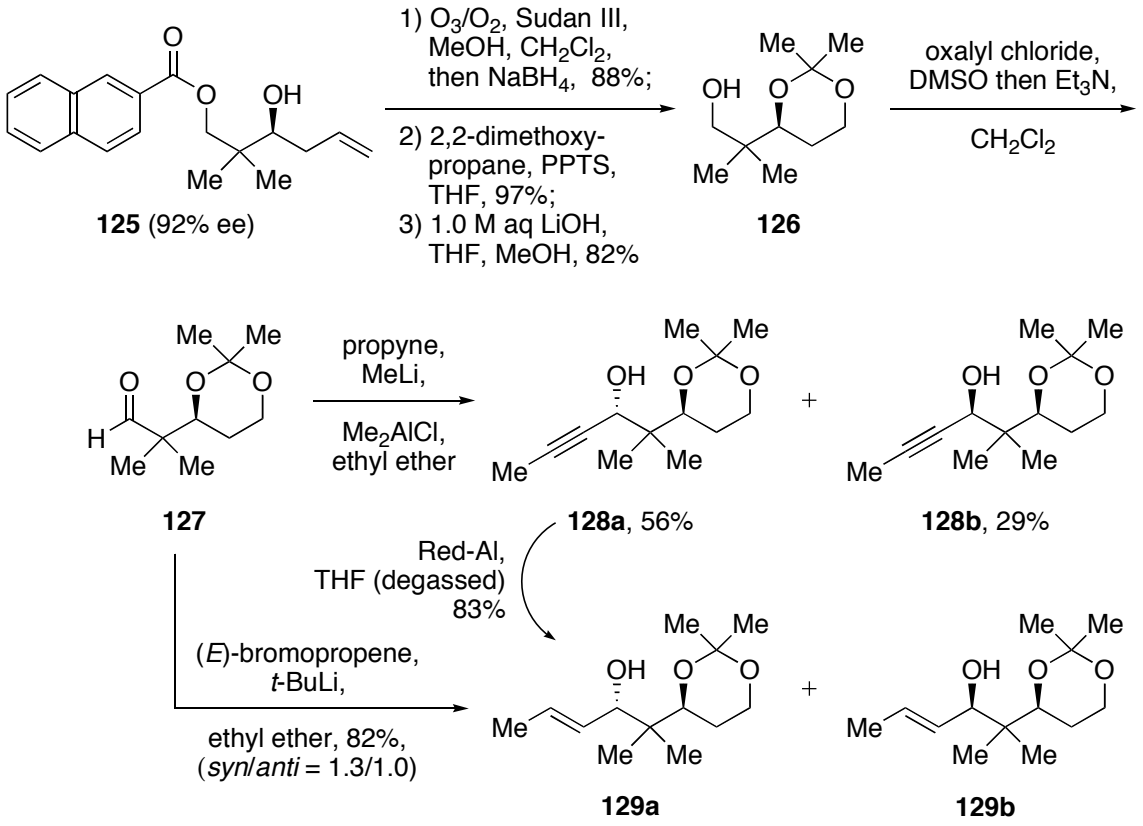
Initial studies focused on the model system containing the *p*-methoxy-benzylether (**122a**) (Table 12). Hydrozirconation of a solution of propyne gas in CH_2Cl_2 followed by a solvent exchange to toluene and addition of the aldehyde afforded the corresponding racemic allylic alcohol **124a** in 76% yield. The standard asymmetric conditions employing ligand **123** afforded the allylic alcohol **124a** in 19% yield and 24% ee with 49% of the aldehyde recovered. Performing the asymmetric reaction at higher temperatures could improve the conversion; however, the enantioselectivity was not expected to improve. The PMB protecting group was suspected to be problematic due to the ability of this group to form chelates. The model system containing the TBDPS ether (**122b**) afforded the corresponding allylic alcohol **124b** in 87% yield with a marginal improvement in the enantioselectivity (Table 4, entry 3). Performing the reaction at lower temperatures afforded **124b** in decreased yield and similar enantioselectivity. Based on the model studies, the asymmetric vinyl zinc addition proved to be inadequate for the present application, so the focus was shifted towards the introduction of the C_{14}-stereocenter.

3.2.2.2. Successful Synthesis of the Diol Segment

The focus of gaining access to the required enantiomeric series shifted to the possibility of setting the C_{14}-stereocenter, thus rendering the bond forming event at the C_{16}-stereocenter diastereoselective (Scheme 38). The homoallylic alcohol **125** was obtained in 91% yield and 92% ee using Carreira's methodology[139] for the addition of allyltrimethylsilane to the corresponding aldehyde under the influence of the catalyst formed *in situ* from TiF_4 and (*S*)-BINOL. The terminal olefin of **125** was then converted

to the alcohol in 88% yield by cleavage with ozone using Sudan III[140] as an indicator, followed by *in situ* reduction with $NaBH_4$.[141] The resulting 1,3-diol was converted to the acetonide in 97% yield by exposure to 2,2-dimethoxypropane and PPTS in THF. The naphthoyl group was removed with aqueous LiOH to afford the protected triol **126** in 82% yield. Oxidation of **126** under Swern conditions[63] afforded the known aldehyde **127**,[142] which was treated with 1-lithiopropyne and dimethylaluminum chloride to afford a mixture of diastereomers **128a** and **128b** in 56% and 29% yield, respectively, after separation by chromatography on triethylamine-deactivated silica gel. Reduction of **128a** using Red-Al in THF initially gave the corresponding allylic alcohol **129a** in 68% yield. The yield of the alkyne reduction was improved to 83% by rigorously degassing the THF, prior to the introduction of Red-Al.[143] Alternatively, propenyl lithium can be added to aldehyde **127** to directly afford a mixture of **129a** and **129b**. The propenyl lithium addition directly affords the desired allylic alcohol, however, the separation of the diastereomers was more difficult due to the poorer resolution during silica gel chromatography. Further efforts towards improving the diastereoselectivity of the addition to aldehyde **127** will be discussed in Section 3.2.2.4.

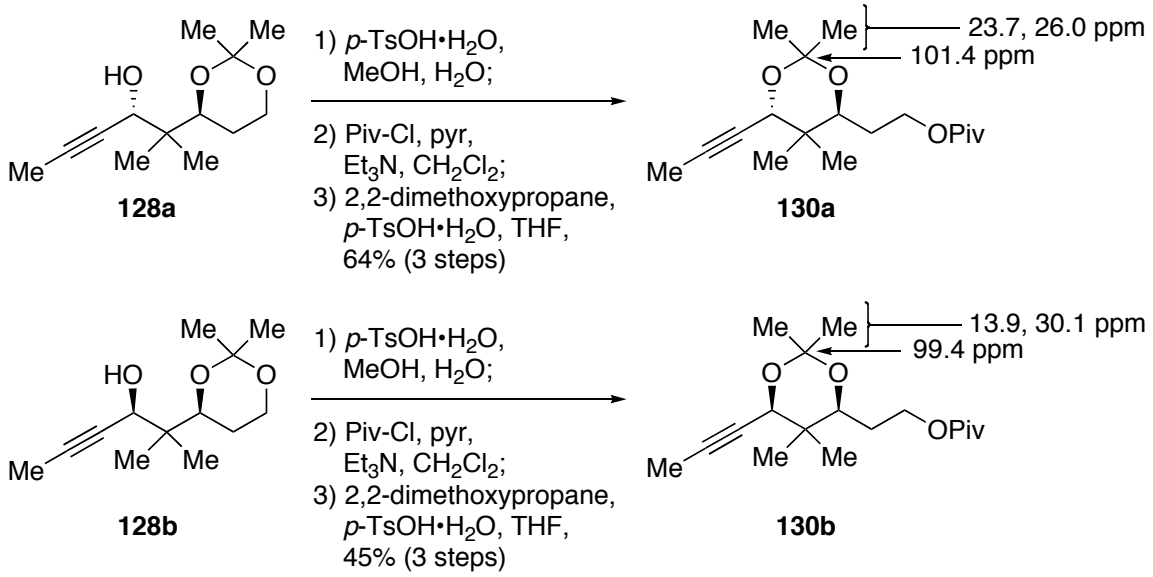
Scheme 38. Synthesis of the diol segment.



The relative stereochemistry of **128a** and **128b** was determined by ^{13}C NMR analysis of the frame-shifted acetonides (Scheme 39).[144] Acetonides **128a** and **128b** were converted to the corresponding triols under acidic conditions. The resulting triols were selectively acylated on the primary alcohol and converted to **130a** and **130b** in 64% and 45% yield, respectively, over three steps. The relative stereochemistry of each 1,3-dioxolane was subsequently determined by ^{13}C NMR analysis to give the assignments shown in Scheme 39.[144] The acetonide **130a** has both C_2-methyl substituents (acetonide numbering) resonating near 25 ppm and a C_2-quaternary

carbon resonating at greater than 100 ppm. According to the studies of Rychnovsky and Evans,[144] these characteristics correspond to the acetonide of a 1,3-*anti*-diol. Acetonide **130b** has one C_2-methyl substituent resonating at less than 20 ppm and the other C_2-methyl substituent resonating near 30 ppm. In addition, the C_2-quaternary carbon resonates at less than 100 ppm. According to the studies of Rychnovsky and Evans,[144] these characteristics correspond to the acetonide of a 1,3-*syn*-diol. Both stereocenters of the diol fragment were installed and assigned. The remaining steps were directed towards installing the enyne.

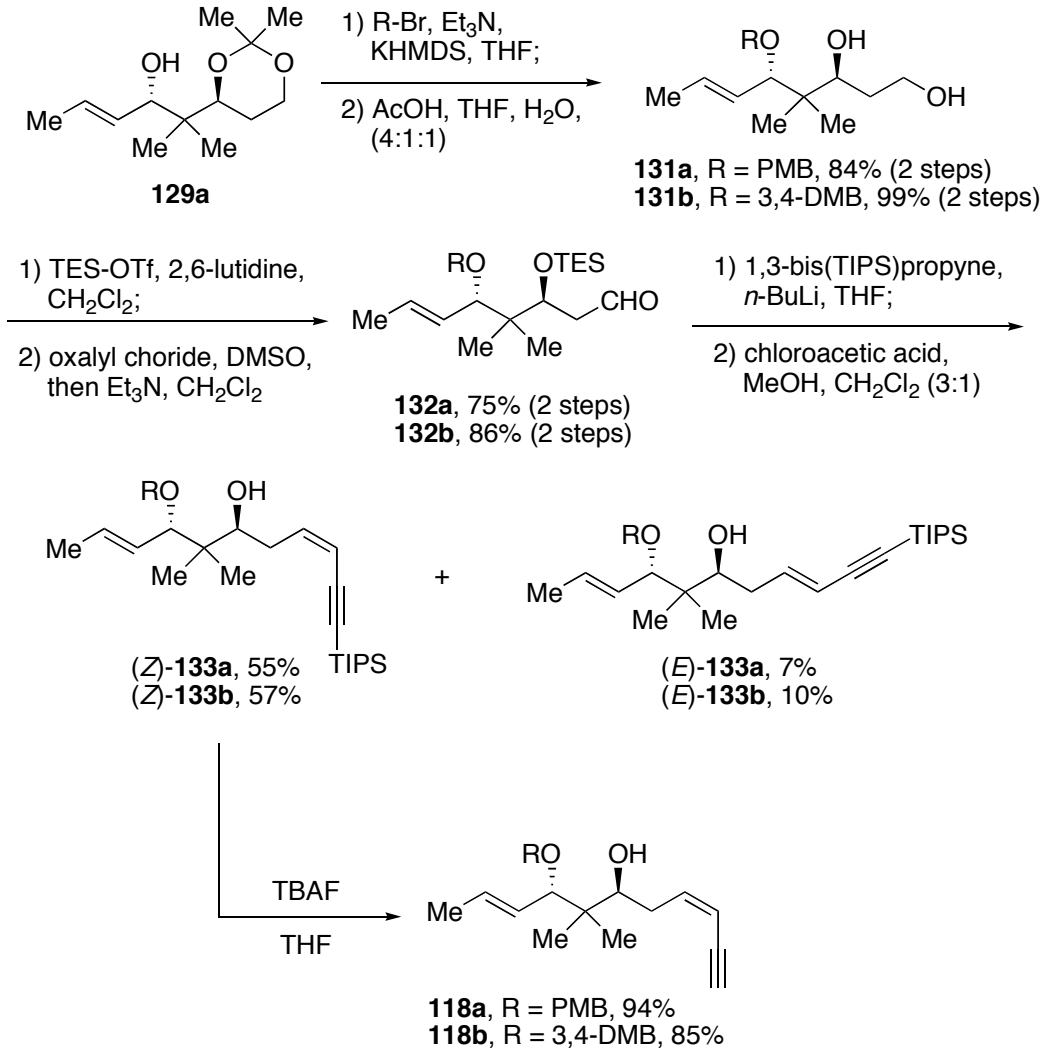
Scheme 39. Determination of the relative stereochemistry of the diol segment.



With the stereocenters installed, standard manipulations afforded the completed diol segment. The allylic alcohol **129a** was converted to the diol **131a** by first protecting the allylic hydroxyl as the *p*-methoxybenzyl ether using freshly distilled *p*-

methoxybenzyl bromide[145] with triethylamine and KHMDS in THF,[146] followed by removal of the acetonide with aqueous acetic acid in THF to afford **131a** in 84% yield for the two steps. Similarly, the 3,4-dimethoxybenzyl ether derivative **131b** was obtained in 99% yield under analogous conditions using freshly prepared 3,4-dimethoxybenzyl bromide,[147] followed by removal of the acetonide. Diols **131a** and **131b** are considered to be key intermediates, because the primary hydroxyl group allows for a variety of transformations to be considered for the installation of the $C_{11\text{-}12}$-(*Z*)-alkene. For the present synthesis, a Peterson olefination using Corey's 1,3-bis-(triisopropylsilyl)propyne[148] was utilized. The (*Z*)-enyne functionality was appended using a four step sequence involving protection of both hydroxyl groups as triethylsilyl ethers followed by selective oxidation under Swern conditions[149] to afford the aldehyde **132a** in 75% yield and aldehyde **132b** in 86% yield for the two steps. The resulting aldehydes were converted to the enynes by exposure to lithiated 1,3-bis-(triisopropyl)propyne[148] followed by removal of the triethylsilyl ether with chloroacetic acid in methanol.[150] The (*E*/*Z*)-isomers were readily separated by column chromatography on silica gel, affording (*Z*)-**133a** in 55% yield and (*E*)-**133a** in 7% yield.[151] The 3,4-dimethoxybenzyl derivative **132b** afforded (*Z*)-**133b** and (*E*)-**133b** in 57% and 10% yield respectively. Deprotection of (*Z*)-**133a** and (*Z*)-**133b** using TBAF in THF afforded the completed diol fragments **118a** and **118b** in 94% and 85% yield, respectively.

Scheme 40. Completion of the diol segment.

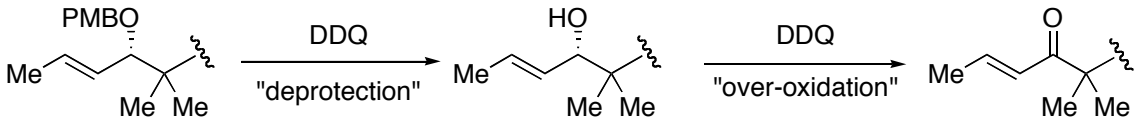


3.2.2.3. A Comment on the C_{16}-Hydroxyl Protecting Group

The choice of a PMB/DMB protecting group for the C_{16}-hydroxyl at first seems risky because of the propensity of allylic alcohol systems to undergo over-oxidation during deprotection (Figure 23).[152] In addition, the behavior of the conjugated dienyne

and the C_6-allylic methoxy during the removal of a methoxybenzyl ether could not be predicted.

Figure 23. Deprotection of allylic PMB ethers can lead to over-oxidation.



Despite these potential complications, several additional considerations factored into the choice of methoxybenzyl ethers as suitable protecting groups for the C_{16}-hydroxyl. First, Meyers and coworkers suggested that late stage intermediates are potentially labile under acidic or basic conditions.[123] The C_{16}-hydroxyl would be deprotected late in the synthesis, so the required protecting group would need to be removed under nearly neutral conditions. The buffered (pH ≈ 7) conditions used during DDQ mediated methoxybenzyl ether cleavage were appealing. Second, the sterically hindered environment of the alcohol must be considered for the deprotection. During model studies, the environment around the C_{14}-C_{16} diol system was found to be sterically encumbered. The aromatic system of the methoxybenzylether would be expected to extend away from the system and therefore, the methoxybenzylether would not suffer from an attenuation of reactivity induced by steric congestion. Third, Meyers and coworkers took advantage of the propensity for silyl groups to transfer within the C_{14}-C_{16} diol system during their studies (Scheme 28).[123,126] The propensity for the oxygen to oxygen migration to occur unexpectedly during a synthetic sequence

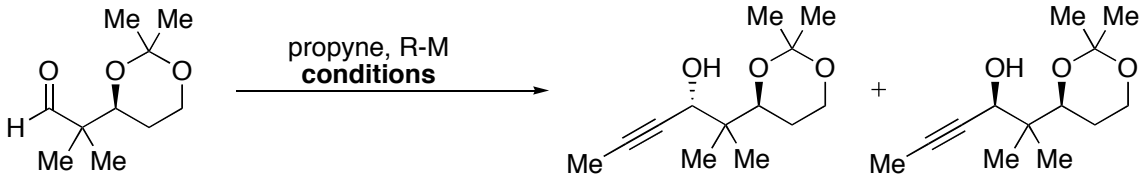
could not be predicted, so silyl groups were avoided. Likewise, there is the potential for acyl transfer to occur in the C_{14}-C_{16} diol system. Several "macrocycle expanded" disorazoles are known, so the energetics of such a reaction may be favorable under the correct conditions. The complication of acyl transfer would most likely occur under any strongly basic or acidic conditions used to deprotect the C_{16}-hydroxyl.[153] Again, DDQ under buffered conditions offered a mild and therefore attractive method for deprotecting the C_{16}-hydroxyl group.

3.2.2.4. Diastereoselective Additions to the C_{16}-Aldehyde

Efforts towards improving the diastereoselectivity of the propynyl lithium addition to the C_{16}-aldehyde focused initially on additives (Table 13). The addition of trimethylaluminum[154] to the lithium acetylide followed by introduction of aldehyde **126** led to a slight increase in the undesired diastereomer **128b** relative to the desired diastereomer **128a** (entry 2) when performed with THF as a solvent. Switching the solvent to toluene afforded only the product of methyl addition (entry 3) while the addition in toluene without any additive favored the formation of **128b** (entry 4). The addition of $ZnCl_2$ in THF resulted in decomposition (entry 5) and TMEDA favored the formation of **128b** (entry 6). The organocerium reagent also favored **128b** and the conversion and yield were also poor (entry 7). The use of diethylaluminum chloride and dimethylaluminum chloride in ethyl ether afforded the only examples that were selective for the diastereomer **128a** (entries 9-14). The dialkylaluminum chloride reactions appeared to stall at –78 °C and warming to 0 °C or rt was required to consume the aldehyde. Extended reaction time (22h) at –55 °C using

dimethylaluminum chloride gave a similar (**128a**/**128b**)-ratio and failed to completely consume the aldehyde. The reaction with dimethylaluminum chloride was quenched after 6 h and ^{1}H NMR analysis of the crude reaction product indicated 70% conversion with a (**128a**/**128b**)-ratio of 2.3/1.0 (entry 15). The results from entries 14 and 15 suggest that the reaction slows and becomes less selective over time, but further experiments are required to elucidate the factors that influence rate and selectivity. Diisobutylaluminum chloride afforded no selectivity (entry 16).

Table 13. Diastereoselective propynyl lithium additions to the C_{16}-aldehyde.



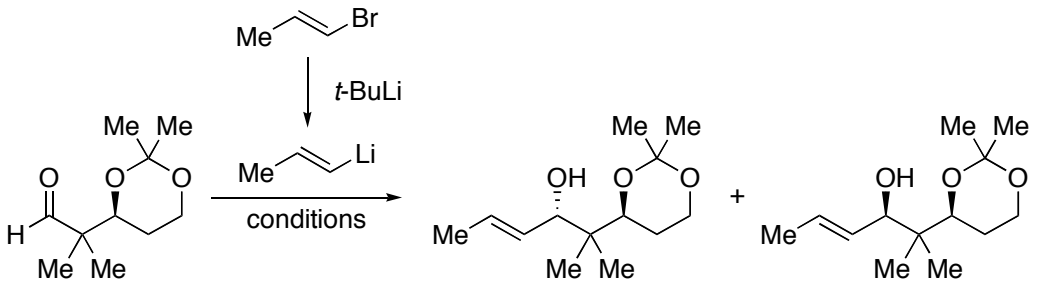
127 **128a** **128b**

Entry	R-M	Solvent	Additive	Temp, Time	Ratio[a] **128a**/ **b**	Yield (%)[b] **128a, b**
1	*n*-BuLi	THF	-	-78 to 0 °C, 1.5 h	1.0/ 1.1	41, 44
2	MeLi	THF	Me_3Al	-78 to 0 °C, 3 h	1.0/ 1.5	34, 52
3	*n*-BuLi	toluene	Me_3Al	-78 °C to rt, 1.5 h	-	-[c]
4	*n*-BuLi	toluene	-	-78 to 0 °C, 1.5 h	1.0/ 1.4	35, 51
5	*n*-BuLi	THF	$ZnCl_2$	-78 °C to rt, 12 h	-	-[d]
6	*n*-BuLi	THF	TMEDA	-78 to 0 °C, 1 h	1.0/1.2	30, 45
7	*n*-BuLi	THF	$CeCl_3$	-78 °C to rt, 12 h	1.0/ 1.4[e]	13, 15
8	MeLi	ether	-	-78 to 0 °C, 3 h	1.0/ 1.3	38, 46
9[f]	MeLi	ether	Et_2AlCl[g]	-78 to 0 °C, 3.5 h	1.3/ 1.0[h]	50, 30
10[i]	MeLi	ether	Et_2AlCl[g]	-78 to 0 °C, 3 h	1.4/ 1.0	52, 36
11[i]	MeLi	THF	Et_2AlCl[g]	-78 °C to rt, 3.5 h	1.0/ 1.0	41, 37
12[i]	MeLi	ether	$EtAlCl_2$[j]	-78 to 0 °C, 3 h	1.3/ 1.0	22, 14
13[i]	MeLi	ether	Me_2AlCl[k]	-78 to 0 °C, 1.5 h	1.8/ 1.0	56, 29
14[i]	MeLi	ether	Me_2AlCl[k]	-55 °C, 22 h	1.6/ 1.0[l]	49, 26
15[i]	MeLi	ether	Me_2AlCl[k]	-55 °C, 6 h	2.3/ 1.0[m]	38, 16
16[i]	MeLi	ether	$(i\text{-Bu})_2AlCl$	-78 to 0 °C, 2.5 h	1.0/ 1.0	25, 26

[a] Product ratio determined by ^1H NMR (C_6D_6) analysis of the crude reaction product. [b] Isolated yields determined after purification by chromatography on SiO_2 (4% acetone, 1% Et_3N/hexanes). [c] Methyl adduct was the predominant product. [d] Decomposition. [e] Aldehyde (16%) present in the crude reaction product. [f] Ratio of aldehyde/Et_2AlCl/propynyl lithium = 1:2.5:5. [g] Et_2AlCl was a commercially available solution (1.8 M) in toluene. [h] Aldehyde (7%) present in the crude reaction product. [i] Ratio of aldehyde/R_2AlCl/propynyl lithium = 1:5:5. [j] $EtAlCl_2$ was a commercially available solution (1.0 M) in hexanes. [k] Me_2AlCl was a commercially available solution (1.0 M) in hexanes. [l] Trace of the aldehyde present in the crude reaction product. [m] Aldehyde (30%) present in the crude reaction product.

The initial studies focused on the addition of propyne to aldehyde **126** because the diastereomers could be readily separated by chromatography on SiO_2. Later, the chromatography conditions were refined so that diastereomers resulting from the propenyl additions to the aldehyde could also be separated, although with poorer resolution. As a result, the diastereoselectivity of the propenyl metal additions was explored with the knowledge that material obtained in these studies could be carried forward in the synthesis (Table 14). Propenyl lithium was generated from isomerically pure propenyl bromide via a metal-halogen exchange using *t*-butyl lithium. The addition in THF favored allylic alcohol **129b** (entry 1). Conducting the reaction in ethyl ether reduced the preference for **129b** relative to **129a** and increased the yield (entry 2). The addition of $CeCl_3$ prior to addition of the aldehyde afforded equal amounts of each diastereomer; however, the yield was poor and the conversion was not complete. Performing the reaction in ethyl ether with $MgBr_2$ gave a (**129a**/**129b**)-ratio similar to the absence of $MgBr_2$; however the yield was improved (entry 4). A variety of copper salts were also explored. The complex formed *in situ* from CuI and tri-*n*-butylphosphine[155] as well as the commercially available Li_2CuCl_4 complex[156] favored the undesired diastereomer **129b** with similar overall yields (entries 5 and 6). The use of the sterically-hindered complex formed *in situ* from CuI and tricyclohexylphosphine as well as the CuBr-dimethylsulfide complex afforded no addition product (entries 7 and 8).[157]

Table 14. Diastereoselective propenyl lithium additions to the C_{16}-aldehyde.



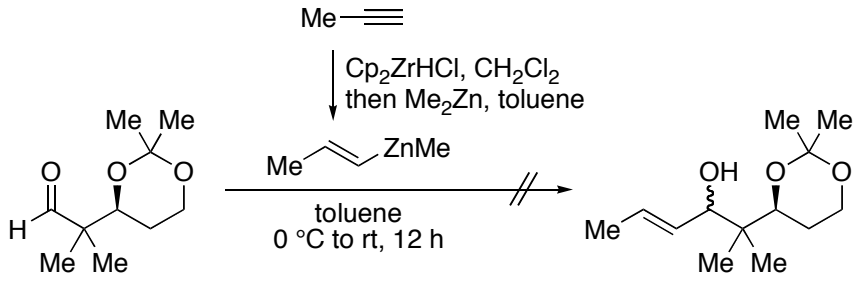
127 **129a** **129b**

Entry	Solvent	Additive	Temp, Time	Ratio[a] **129a/ b**	Combined Yield (%)[b]
1	THF	-	-78 °C, 1 h	1.0/ 1.8	72
2	ethyl ether	-	-78 °C, 1 h	1.0/ 1.3	82
3	THF	$CeCl_3$	-78 °C, 30 min; 0 °C, 30 min	1.0/ 1.0	36 + (7% s.m.)
4	ethyl ether	$MgBr_2$	-78 °C to 0 °C, 30 min	1.0/ 1.2	97
5	THF	CuI•PBu_3	-78 °C, 1 h; 0 °C, 1 h	1.0/ 1.4	82
6	THF	Li_2CuCl_4	-78 °C, 30 min	1.0/ 1.8	83
7	THF	CuI•$P(C_6H_{11})_3$	-78 °C, 1 h; 0 °C, 30 min	-[c]	-
8	THF	CuBr•DMS	-78 °C, 1 h; 0 °C, 30 min	-[c]	-

[a] Product ratio determined by ^{1}H NMR (acetone-d6) analysis of the crude reaction product. [b] Combined yield for both diastereomers after purification by chromatography on SiO_2. [c] No reaction at –78 °C (TLC analysis) and the Cu species likely decomposed upon warming to 0 °C as indicated by a color change from yellow to black.

An attempt to add a propenyl zinc to aldehyde **127** failed to afford the allylic alcohol adducts **129a/b**.[158] The propenyl zinc was formed by hydrozirconation of propyne, followed by transmetallation to zinc. Only starting aldehyde and some traces of olefinic material were present in the ^{1}H NMR spectrum of the crude mixture.

Scheme 41. Attempted addition of a propenyl zinc.



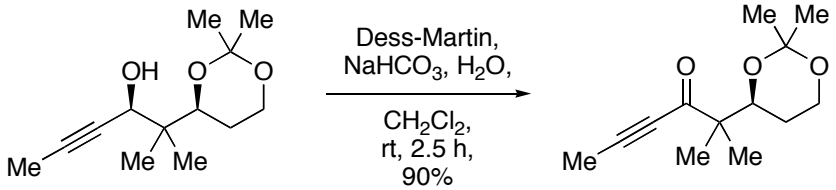
127 **129a/b**

Similar to the results for the propynyl additions, the propenyl additions also indicate a slight preference for the 1,3-*syn*-diastereomer **129b**. The failure to significantly influence the diastereoselectivity of the propynyl or propenyl lithium additions to the C_{16}-aldehyde led to the exploration of alternate routes involving oxidation-reduction sequences.

3.2.2.5. Oxidation and Diastereoselective Reduction Sequence

The most extensive studies on the oxidation-reduction sequence involve the reduction of ketone **134** which was prepared by oxidizing the undesired diastereomer **128b** with Dess-Martin periodinane[17] (Scheme 42).

Scheme 42. Oxidation of the propargyl alcohol to the ketone.



128b **134**

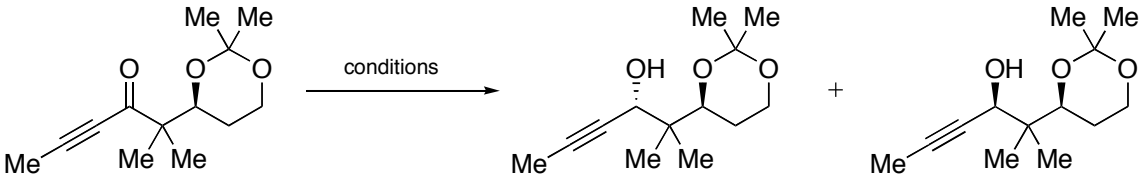
Conditions for the diastereoselective reduction of ketone **134** were screened (Table 15). Luche conditions afforded equal amounts of diastereomers **128a** and **128b** in a 97% combined yield (entry 1). Borane reductions catalyzed by (*R*)-CBS-oxazaborolidine[134] afforded only **128a** in moderate yield, however the product was contaminated by inseparable impurities (entries 2 and 3). Reduction with L-Selectride afforded the product of 1,4-reduction (entry 4). Aluminum-based reagents were explored next. Diisobutylaluminum hydride afforded the desired diastereomer **128a** and the solvent was also found to be important (entries 5-8). Dichloromethane was superior to THF or toluene and afforded a greater than a 3:1 ratio favoring **128a** in 89% combined yield (entry 7). Interestingly, lithium aluminum hydride, $LiAlH_4$/LiI[159] and Red-Al favored the undesired diastereomer **128b** (entries 9-11). Very sterically hindered reagents such as triisobutylaluminum,[160] DiBAl-H/BHT complex[161] and DIP-Cl[162] as well as the Noyori transfer-hydrogenation catalyst[163] afforded none of the desired reduction product. The results from Table 15 suggest that influencing the diastereomeric ratio during the reduction of ketone **134** is challenging. The results also indicate that a sterically encumbered reagent such as diisobutylaluminum hydride will favor the desired diastereomer **128a**, while non-sterically encumbered reagents such as $LiAlH_4$

favor the undesired diastereomer **128b**. Very sterically encumbered reagents will not give the reduction product. Presently, diisobutylaluminum hydride in dichloromethane at low temperature (entry 7) is used to reduce the ketone and allows for the recycling of the undesired C_{16}-epimer, **128b**.

Recycling of the undesired allylic alcohol diastereomer **129b** was also briefly explored. Oxidation of the allylic alcohol **129b** with Dess-Martin periodinane[17] or Swern conditions afforded ketone **135** in 84% and 80% yield, respectively. The use of MnO_2 in dichloromethane afforded **135** in only 36% yield.

Reduction of ketone **135** using the best conditions for the propargylic ketone (Table 15, entry 7) afforded a 2:1 ratio favoring the desired diastereomer **129a** and a combined yield of 56% (Table 17, entry 1). Luche conditions afforded a 1:1 mixture of **129a** and **129b** in 78% combined yield (entry 2).

Table 15. Diastereoselective reductions at the C_{16}-ketone.

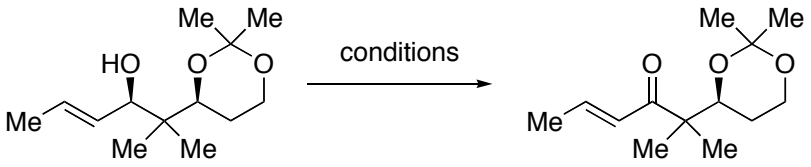


134 **128a** **128b**

Entry	Reagent	Temp, Time	Ratio[a]	Yield (%)[b]
			128a/ b	**128a**, **128b**
1	$NaBH_4$, $CeCl_3$•7 H_2O	0 °C, 2 h	1.0/ 1.0	48, 49
2	(*R*)-CBS, BH_3•DMS, THF	-10 °C to rt, 3 h	1/ 0	73, 0 [d]
3	(*R*)-CBS, BH_3•DMS, toluene	0 °C to +10 °C, 1 h	1/ 0	54, 0 [d]
4	L-Selectride, THF	-78 °C, 2 h	-	-[e]
5	DiBAl-H, THF	-78 °C, 3.5 h	1.1/ 1.0	n. d.[f]
6	DiBAl-H, toluene	-78 °C, 45 min	2.2/ 1.0	64, 28
7	DiBAl-H, CH_2Cl_2	-78 °C, 75 min	3.3/ 1.0	76, 23
8	DiBAl-H, CH_2Cl_2	-95 to -78 °C, 1.5 h	3.5/ 1.0	63, 14
9	$LiAlH_4$, ethyl ether	-78 °C, 1 h	1.0/ 2.3	25, 71
10	$LiAlH_4$, LiI, ethyl ether	-78 °C, 75 min	1.0/ 1.6	27, 49
11	Red-Al	-78 °C, 1.5 h	1.0/ 1.4	n.d.[f]
12	(*i*-Bu)$_3$Al	-78 °C, 75 min	-	- [c]
13	(*i*-Bu)$_3$Al	-78 °C to 0 °C, 30 min	-	- [g]
14	DiBAl-H, BHT, toluene	-78 °C, 1 h	-	- [h]
15	(+)-DIP-Cl, ethyl ether	rt, 22 h	-	(76%) [c]
16	(-)-DIP-Cl, ethyl ether	rt, 48 h	-	(75%) [c]
17	$RuCl_2$(η^6-cymene), (R,R-TsDPEA), KOH	rt, 2 h; 65°, 18 h	-	(99%) [c]

[a] Product ratio determined by ^{1}H NMR (C_6D_6) analysis of the crude reaction product. [b] Isolated yields determined after purification by chromatography on SiO_2 (4% acetone, 1% Et_3N/hexanes). [c] Ketone recovered (%). [d] Isolated material contains inseparable impurities. [e] Isolated material was the product of 1,4-reduction. [f] The yield was not determined. [g] Decomposed on warming to 0 °C. [h] TLC indicated ketone, no reduction occurred.

Table 16. Oxidation of the undesired allylic alcohol to the ketone.

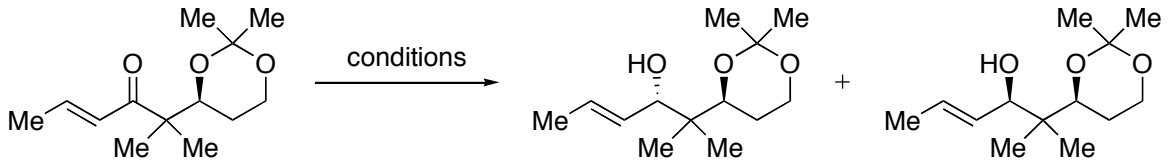


129b **135**

Entry	Reagent	Solvent	Temp, Time	Yield (%)[a]
1	Dess-Martin periodinane, $NaHCO_3$	CH_2Cl_2	0 °C to rt, 1 h	84
2	oxalyl-chloride, DMSO; Et_3N	CH_2Cl_2	-78 °C to rt, 25 min	80
3	MnO_2, CH_2Cl_2	CH_2Cl_2	rt, 20 h	36

[a] Combined yield determined after purification by chromatography on SiO_2.

Table 17. Reduction of the α,β-unsaturated ketone to the allylic alcohol.



135 **129a** **129b**

Entry	Reagent	Solvent	Temp, Time	Ratio[a] **129a/ b**	Combined Yield (%)[b]
1	DiBAl-H	CH_2Cl_2	-78 °C, 1 h	2.0/ 1.0	56
2	$CeCl_3 \bullet 7\ H_2O$	MeOH	0 °C to rt, 2 h	1.0/ 1.0	78

[a] Product ratio determined by ^1H NMR (acetone-d6) analysis of the crude reaction product. [b] Combined yield for the mixture of diastereomers determined after purification by chromatography on SiO_2

3.2.2.6. A Comment on the Diastereoselectivity at the C_{16}-Stereocenter

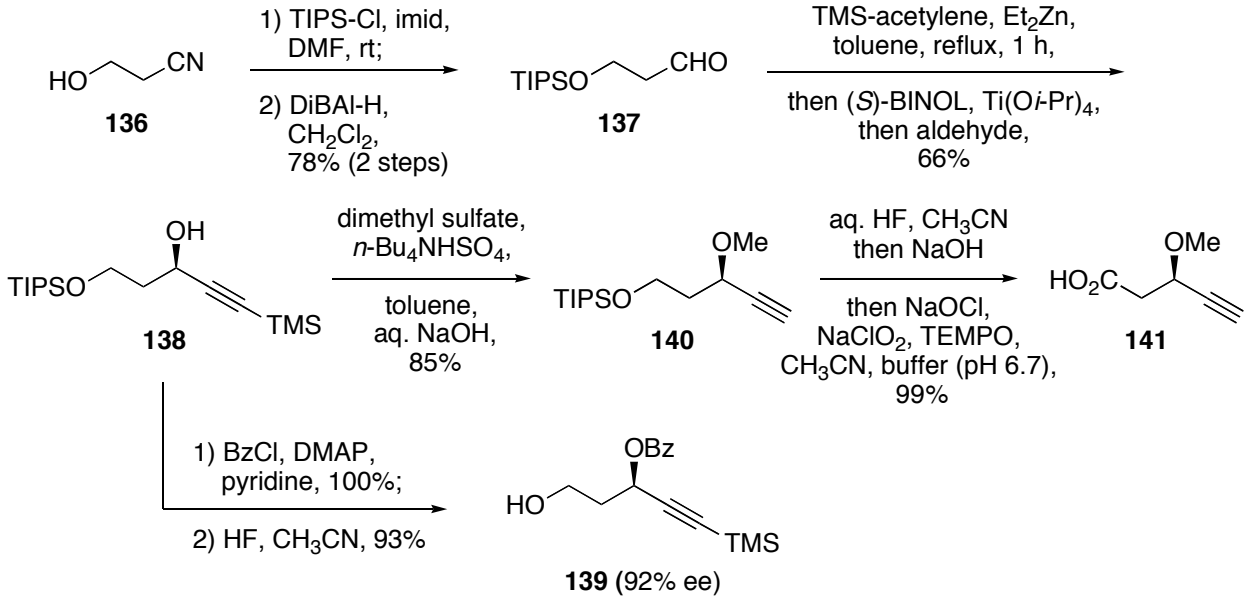
Diastereoselective additions to the C_{16}-aldehyde or reductions of the C_{16}-ketone remain as one of the challenges of the current synthetic sequence. Some general comments can be made about the data given in Table 13, Table 14 and Table 15. Aluminum-based propynyl and hydride reagents demonstrated a unique ability to influence the diastereoselectivity at the C_{16}-stereocenter. Additions of organometallics (propynyl and propenyl) to the aldehyde **127** slightly favor the undesired 1,3-*syn*-epimer but dimethylaluminum chloride afforded the desired 1,3-*anti*-epimer for addition of the propynyl group. Second, reduction of the C_{16}-ketone with diisobutylaluminum hydride is 1,3-*anti*-selective while reduction with $LiAlH_4$ is slightly 1,3-*syn*-selective. The results do suggest that the diastereoselectivity can be influenced by different conditions but the selectivity is only modest. Further investigation into conditions that affect the facial selectivity of organometallic and hydride additions at the C_{16}-aldehyde and ketones is required.

3.2.3. Synthesis of the Oxazole Segment

Synthesis of the oxazole fragment commenced with the protection of commercially available 3-hydroxypropionitrile (**136**) as the triisopropylsilyl ether under standard conditions followed by reduction of the nitrile with diisobutylaluminum hydride to afford the known aldehyde **137**[164] in 78% yield for the two steps (Scheme 43). The transformation of **137** to the propargylic alcohol **138** utilized the methodology of Pu and coworkers.[165] According to this protocol, the alkynyl zinc formed from

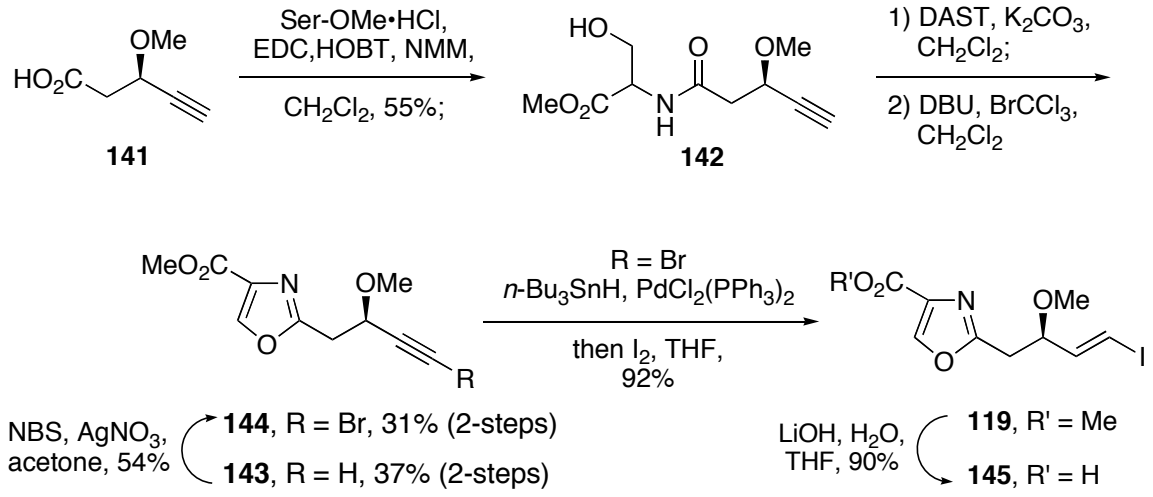
trimethylsilylacetylene and diethylzinc was added to **137** under the influence of the catalyst formed *in situ* from Ti(*i*-OPr)$_4$ and (*S*)-BINOL and afforded **138**[166] in 66% yield. For the determination of the enantioselectivity of the transformation, **138** was converted to benzoate **139** by acylating with benzoyl chloride in pyridine followed by HF-promoted silyl ether cleavage in 93% yield. Chiral HPLC analysis of **139** indicated the enantiomeric excess to be 92%.[167] Dimethylsulfate under phase-transfer conditions was used to convert **138** to the methyl ether **140** in 95% yield with concomitant loss of the trimethylsilyl group. The silyl ether of **140** was converted to the known carboxylic acid **141**[168] in a highly efficient manner by removal of the triisopropylsilyl group with aqueous HF in acetonitrile, neutralization with aqueous NaOH and oxidation of the resulting mixture using the Merck protocol.[169]

Scheme 43. Synthesis of the carboxylic acid for the oxazole segment.



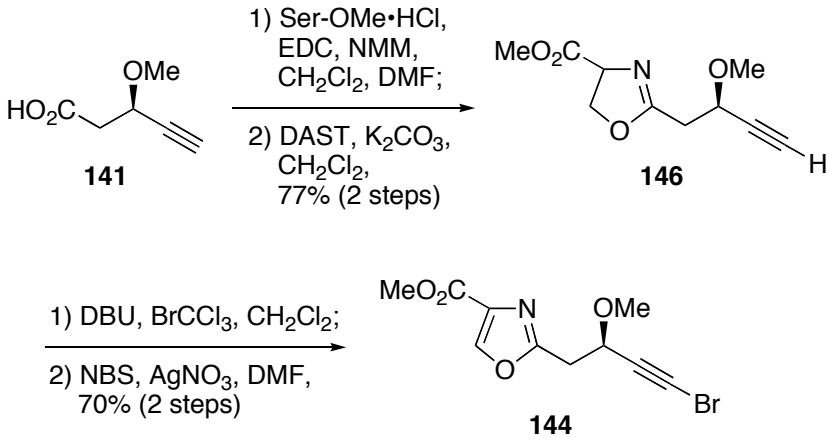
Conversion of **141** to the oxazole was accomplished in three steps by first coupling with DL-serine methyl ester hydrochloride, using EDC and HOBT with *N*-methylmorpholine to afford the hydroxyamide **142** in 55% yield (Scheme 44). Cyclodehydration of the **142** was accomplished using diethylaminosulfurtriflouride (DAST) and K_2CO_3 and the crude oxazoline was oxidized with $BrCCl_3$ and DBU[13] to afford the oxazoles **143** and **144** in 37% and 31% yield, respectively, after tedious separation by chromatography on silica gel. The incorporation of bromine in **144** was an unexpected outcome, but allowed for an efficient conversion to the required vinyl iodide by using palladium-catalyzed hydrostannylation and iodination to afford **119** in 92% yield.[170] The remaining alkynyl oxazole **143** was converted to **144** in moderate yield, using silver nitrate and *N*-bromosuccinimide. Finally, **119** was converted to the carboxylic acid **145** in 90% yield by saponification with aqueous LiOH in THF.

Scheme 44. Completion of the oxazole segment.



The sequence for the oxazole synthesis as shown in Scheme 44 afforded the bromoalkynyl oxazole **144** in 28% yield (4 steps) after conversion of the terminal alkyne **143** to **144**. Improvements to the sequence were made based on two considerations. First, hydroxyamide **142** has limited solubility in dichloromethane, chloroform and ethyl acetate/hexanes mixtures. DMF was added to the coupling reaction to improve the homogeneity of the reaction mixture. In addition, a screening of solvent systems identified acetone as a more suitable solvent and thus acetone or mixtures of acetone/hexanes were used for chromatographic purifications and other pertinent manipulations throughout the sequence. The yield of oxazoline **146** was improved to 77% over the two steps (Scheme 45). Second, the separation of the bromoalkyne and the terminal alkyne was tedious and not amenable to large scale synthesis. The solution to the problem was to directly subject the mixture of **143** and **144** to the bromination conditions using DMF as a solvent to afford the bromoalkyne **144** in 70% yield for the two steps. The improved sequence afforded **144** in 54% yield over the 4-step sequence.

Scheme 45. Improved synthesis of the oxazole segment.



3.2.4. Completion of Disorazole C_1

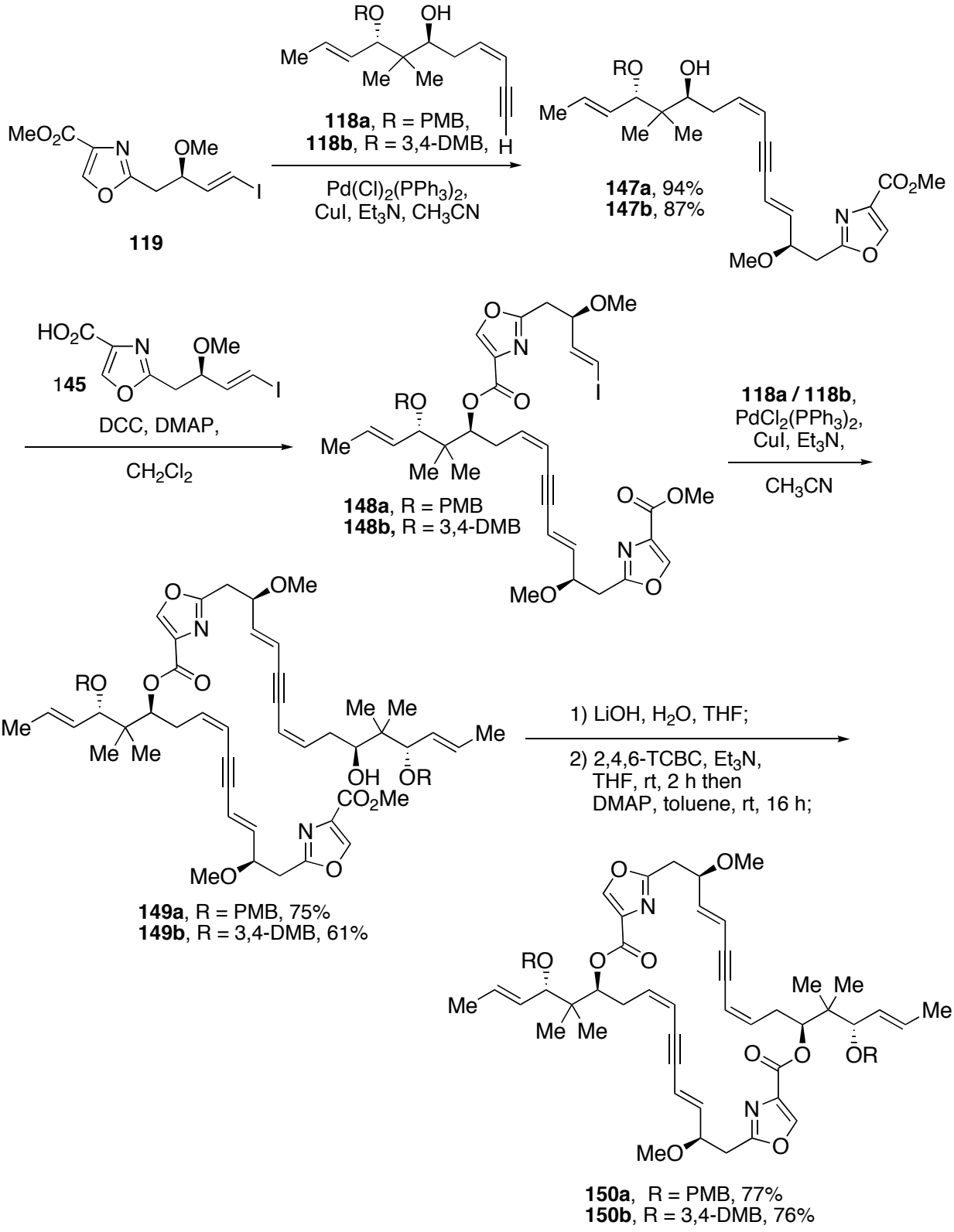
With access to **118a/b**, **119** and **145** the convergent construction of the macrocycle was initiated (Scheme 46). Sonogashira cross-coupling[99] of **118a/b** and **119** afforded the protected monomers **147a** and **147b** in 94% and 87% yield, respectively. Acylation of **147a/b** using DCC and DMAP with an excess of **145**, afforded **148a** and **148b**. A second Sonogashira cross-coupling[99] between **148a/b** and **118a/b** afforded the *seco*-acid methyl esters **149a** and **149b** in 75% and 61% yield, respectively. Selective saponification of the methyl esters with aqueous lithium hydroxide in THF afforded the crude *seco*-acids which were subjected to Yamaguchi lactonization conditions[128] affording the macrocycles **150a** and **150b** in 77% and 76% yield, respectively.

The macrocyclic dimer **150a** was also formed by a direct dimerization of the monomer hydroxy acid (Scheme 47). Saponification of methyl ester **147a** with aqueous LiOH and subsequent dimerization under Yamaguchi conditions[128] afforded the macrocyclic dimer **150a** in 59% yield.

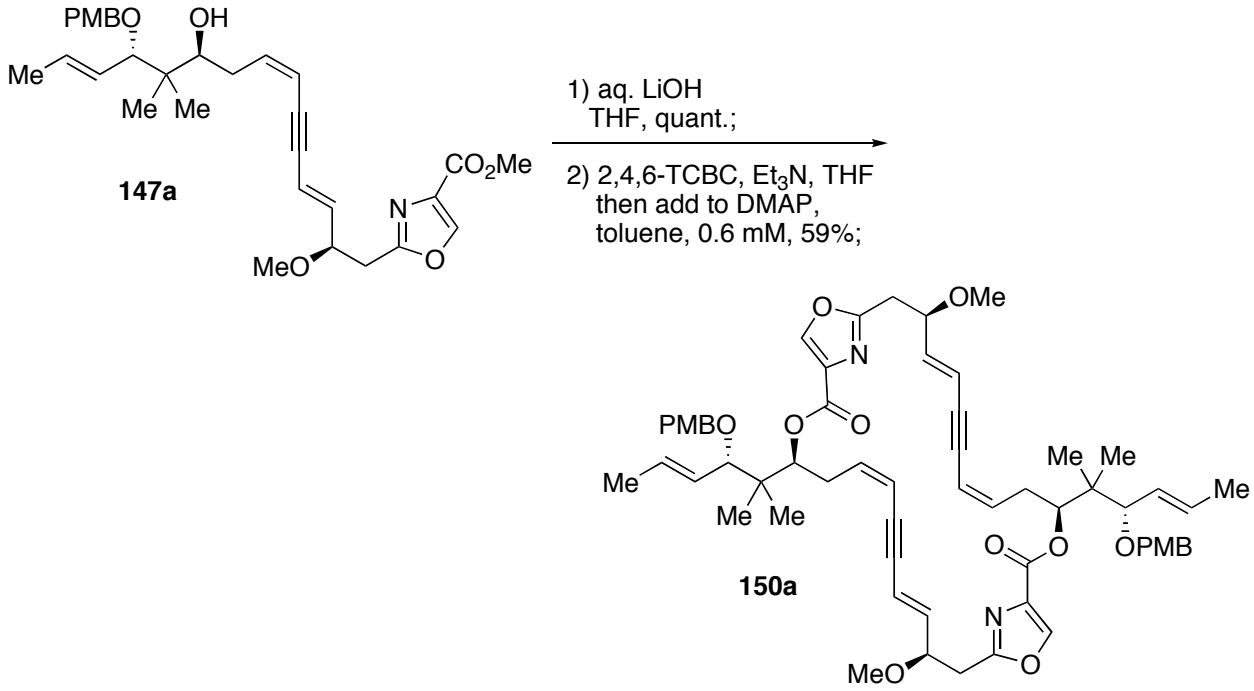
The synthesis of the diol segment afforded material with the C_{16}-hydroxyl masked as a 4-methoxybenzyl or a 3,4-dimethoxybenzyl ether (Scheme 48). The initial studies used the PMB group for the C_{16}-hydroxyl protection. Deprotection of **150a** using DDQ afforded **151** in 61% yield. However, TLC analysis suggested that over-oxidation was occurring, as indicated by the formation of less-polar material. The 3,4-dimethoxybenzyl ethers, which are more reactive to DDQ due to the increased electron density of the aromatic ring, allowed the reaction to be more easily controlled and

improved the yield of **151** to 77%. In addition, no over-oxidation was observed by TLC analysis during the deprotection of the 3,4-dimethoxybenzyl ethers. Finally, **151** was reduced using Lindlar catalyst in the presence of excess quinoline to afford the crude **76** which was purified by HPLC to afford **76** in 57% yield.

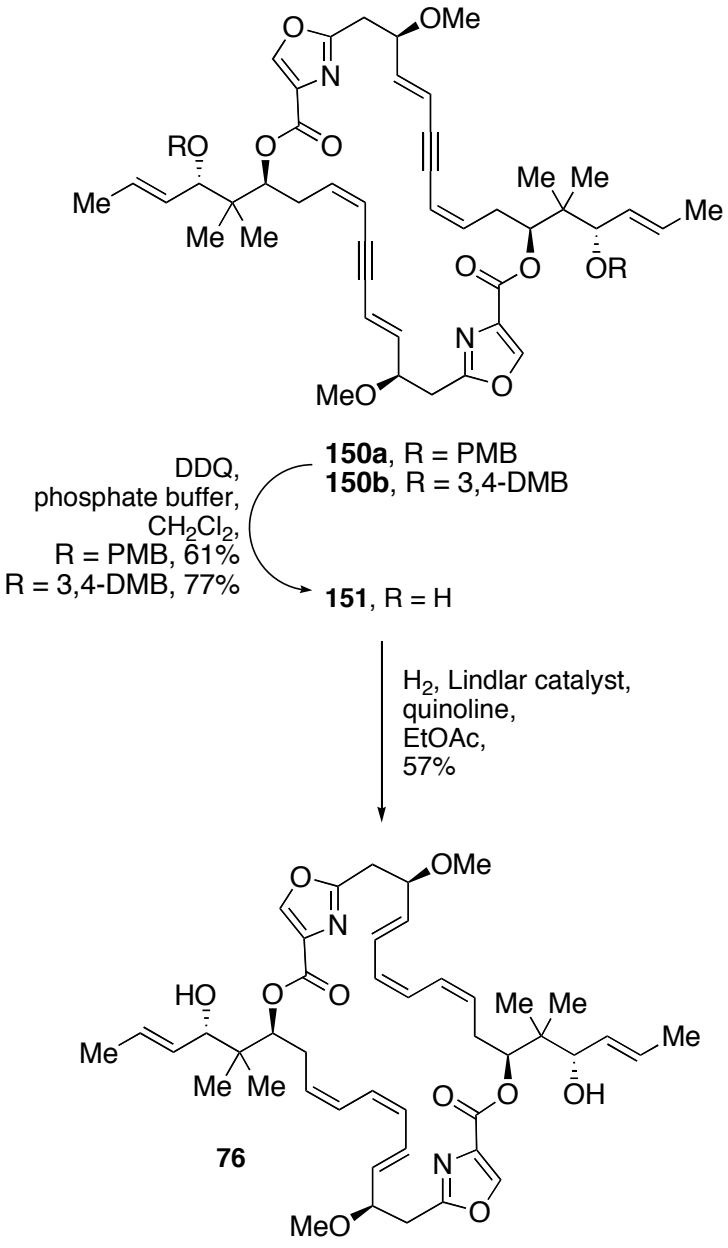
Scheme 46. Stepwise synthesis of the macrocycle.



Scheme 47. Synthesis of the macrocycle by direct dimerization.



Scheme 48. Completion of (-)-disorazole C_1.



3.2.5. Biological Activities for Disorazole C_1 and the Synthetic Intermediates*

The ultimate reason for the synthesis of disorazole C_1 was to obtain material for biological testing. Specifically, the hypothesis that the significant biological activity of disorazole A_1 results from the presence of the divinyl oxirane could now be tested. In addition, testing the synthetic intermediates allows for the evaluation of structure-activity relationships.[171] Disorazole C_1 and seven synthetic intermediates were tested in cellular anti-mitotic assays (Figure 24).[172] Only the synthetic disorazole C_1 (**76**) and the direct alkyne precursor (**151**) had significant biological activity (Table 18).[173] All other synthetic intermediates were inactive at concentrations less than 5 μM. The data suggest that disorazole C_1 (**76**) may have a mechanism of action that is closely related to the vinca alkaloids and distinct from paclitaxel. The results suggest that the macrocyclic structures of **76** and **151** are important for biological activity because all other compounds were inactive. In addition, the difference in activity between the alkyne precursor and synthetic disorazole C_1 suggests that the conformation of the macrocycle is important for the biological activity.

* Biological evaluations were performed by Dr. Alexander P. Ducruet and Rachel P. Sikorski under the supervision of Dr. John S. Lazo and Dr. Andreas Vogt.

Figure 24. Biological evaluation of synthetic (-)-disorazole C_1 and intermediates.

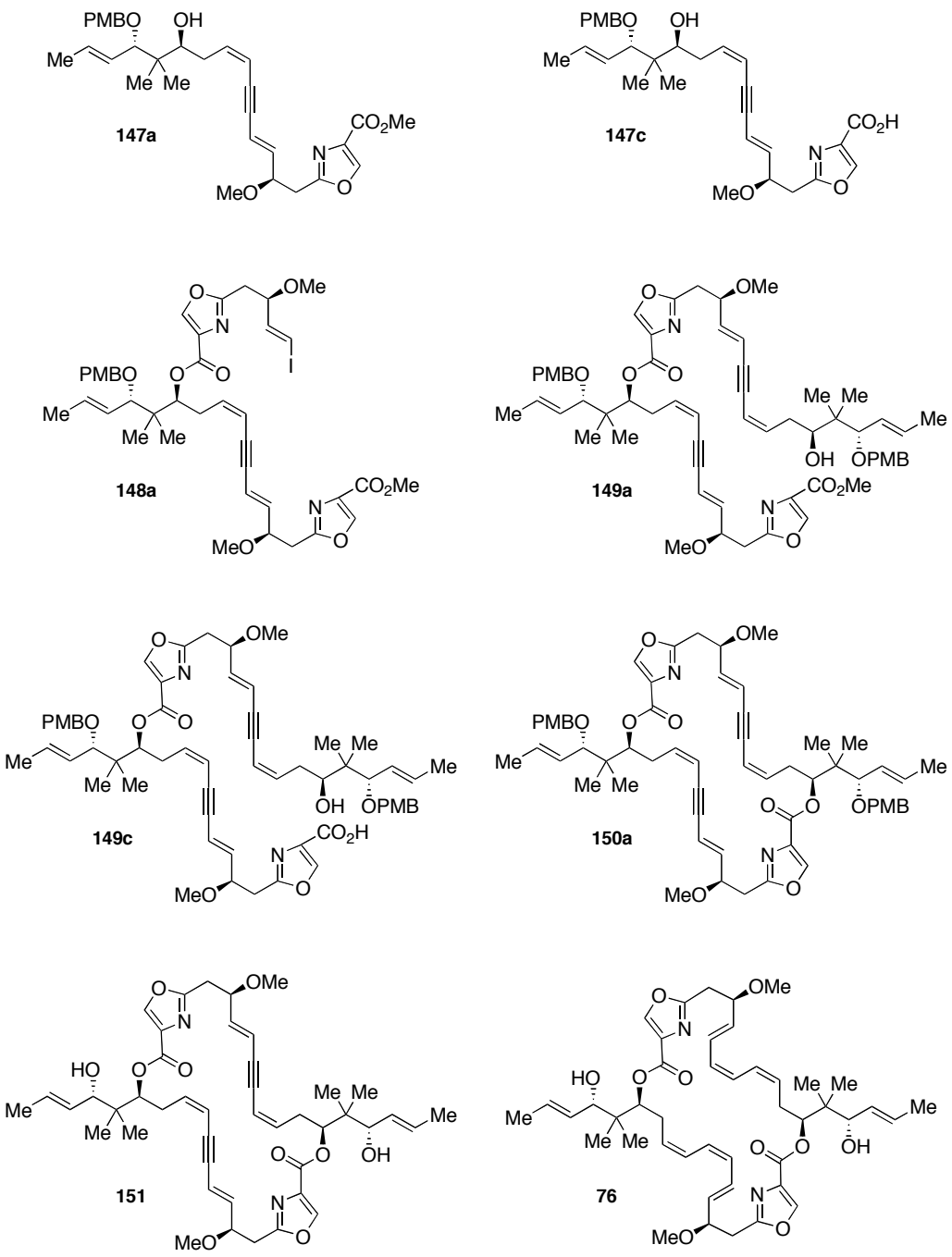


Table 18. High-content analysis of mitotic arrest in HeLa cells treated with antimitotic agents.*

Sample	Cell Density	Nuclear Condensation	Mitotic Index[b]	Tubulin Mass	G2/M Arrest
		EC_{50} (nM)		MEC[c] (nM)	
vincristine	6.9 ± 1.7 (3)	18.0 ± 9.8 (3)	9.8 ± 6.4 (3)	4.1 ± 1.9 (3)	7.3 ± 5.0 (3)
76	14.6 ± 3.8 (3)	19.7 ± 6.6 (3)	5.8 ± 2.4 (3)	7.6 ± 3.6 (3)	9.1 ± 6.0 (3)
151	3912 ± 1143 (3)	>5000 (3)	4401 ± 848 (3)	3733 ± 1186 (3)	5000 ± 0 (3)
vinblastine	0.3 ± 0.2 (3)	1.0 ± 0.9 (3)	0.6 ± 0.3 (3)	0.2 ± 0.1 (3)	0.8 ± 0.7 (3)
colchicine	23.9 ± 0.6 (3)	22.2 ± 3.3 (3)	12.2 ± 0.6 (3)	11.9 ± 1.4 (3)	17.7 ± 6.5 (3)
paclitaxel	6.7 ± 4.7 (2)	14.2 ± 16.2 (2)	4.3 ± 1.8 (2)	3.7 ± 1.9 (2)	1.4 ± 0.2 (2)

[a] average of (n) independent experiments ± SD; [b] percentage of phospho-H3 positive cells; [c] Minimal Effective Concentration

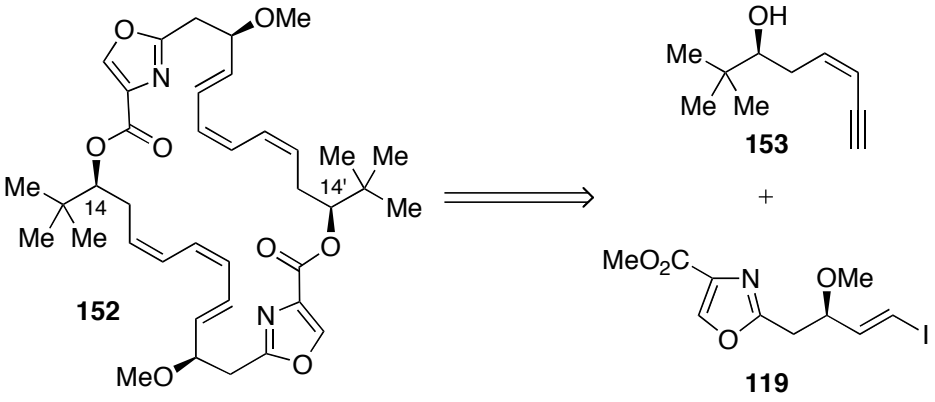
* Biological evaluations were performed by Dr. Alexander P. Ducruet and Rachel P. Sikorski under the supervision of Dr. John S. Lazo and Dr. Andreas Vogt.

3.3. Synthesis of Disorazole C_1 Analogs

3.3.1. Synthesis of the C_{14}-*tert*-Butyl Analog

The initial goal for the synthesis of analogs focused on simplifying the structure while still maintaining the biological activity. The current synthesis of disorazole C_1 requires significant synthetic steps to install the but-2-en-1-ol side chain. Replacing the side chain with a methyl group would give the simpler C_{14}-*tert*-butyl analog **152** which retains the C_{14}-stereocenter and some of the steric properties found in the parent molecule (Figure 25). The *t*-butyl analog has the additional advantage of a significantly shorter synthesis and obviates the tedious chromatographic separations of the C_{16}-diastereomers (Sections 3.2.2.4 and 3.2.2.5).

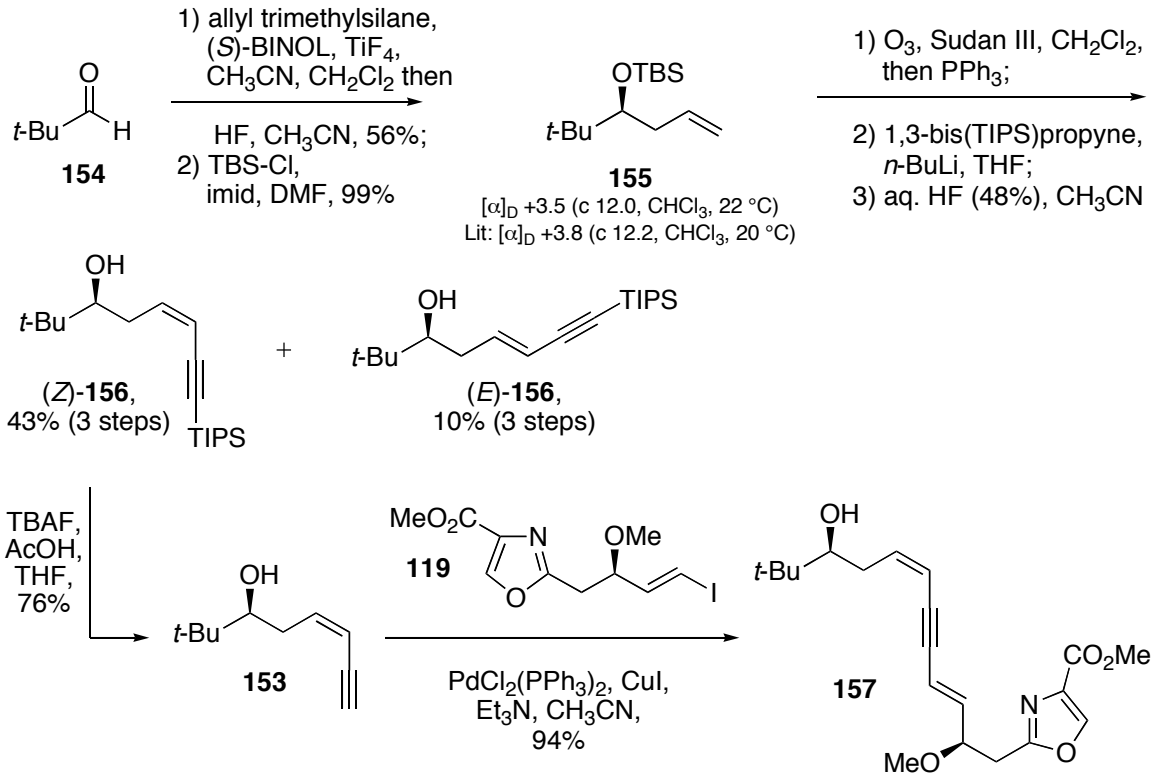
Figure 25. The C_{14}-*t*-butyl analog of (-)-disorazole C_1.



Synthesis of the *t*-butyl analog **152** required the synthesis of fragment **153** and followed a similar route as the synthesis of the disorazole C_1 diol fragment (Scheme

49). Pivaldehyde (**154**) was subjected to the allylation conditions as reported by Carreira to afford the crude homoallylic alcohol in 56% yield.[174,175] The crude alcohol was then treated with TBS-Cl and imidazole in DMF at elevated temperature to afford the known homoallylic silyl ether **155** in nearly quantitative yield.[176] A comparison with literature $[\alpha]_D$ values indicated that the enantiopurity of **155** was 91% ee.[176] A three-step sequence involving ozonolysis and reductive workup gave the aldehyde which was condensed with 1,3-bis(triisopropylsilyl)propynyl lithium to afford the enyne. Cleavage of the TBS ether with aqueous HF in acetonitrile afforded (*Z*)-**156** and (*E*)-**156** in 43% and 10% yield, respectively. As before, enynes (*Z*)-**156** and (*E*)-**156** were readily separable by column chromatography on silica gel. The triisopropylsilyl group of (*Z*)-**156** was removed using TBAF buffered with acetic acid to afford enyne **153** in 76% yield. Cross-coupling **153** with vinyl iodide **119** under Sonagashira conditions[99] afforded the *t*-butyl monomer methyl ester **157** in 94% yield.

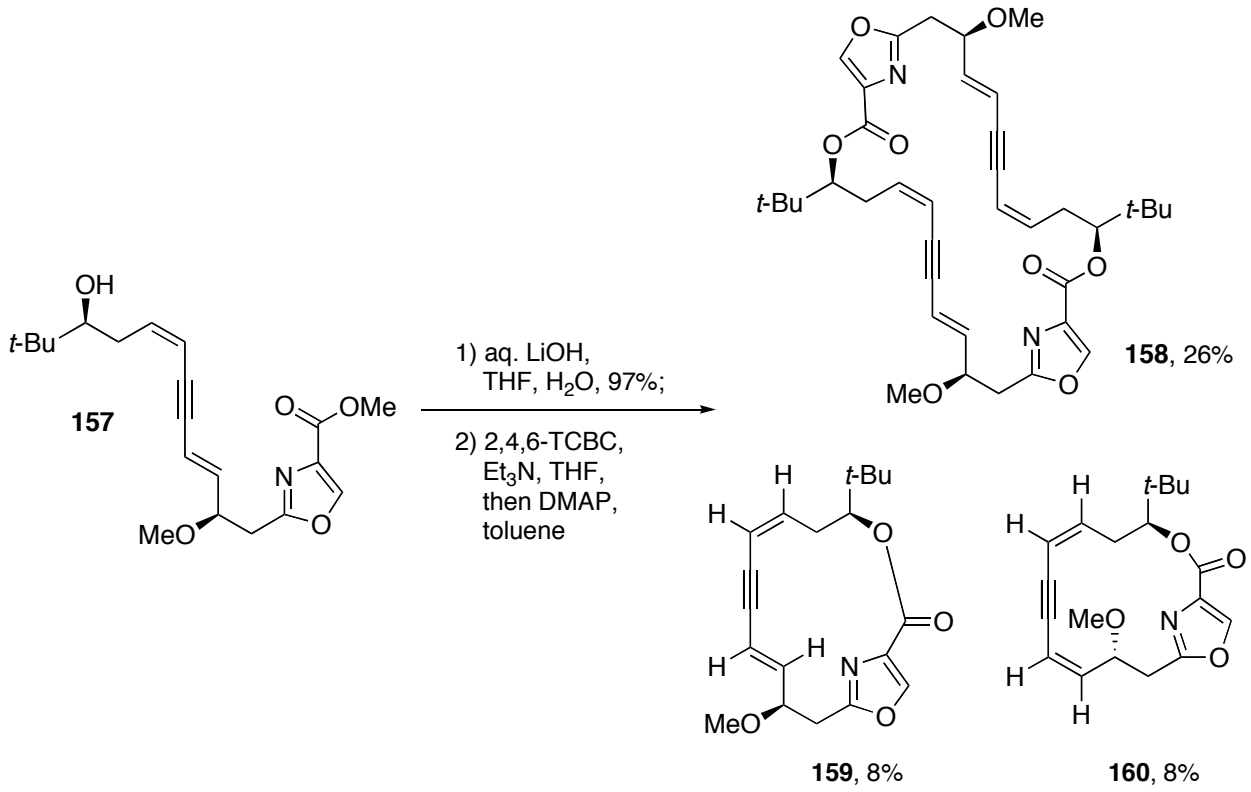
Scheme 49. Synthesis of the C_{14}-*t*-butyl analog monomer unit.



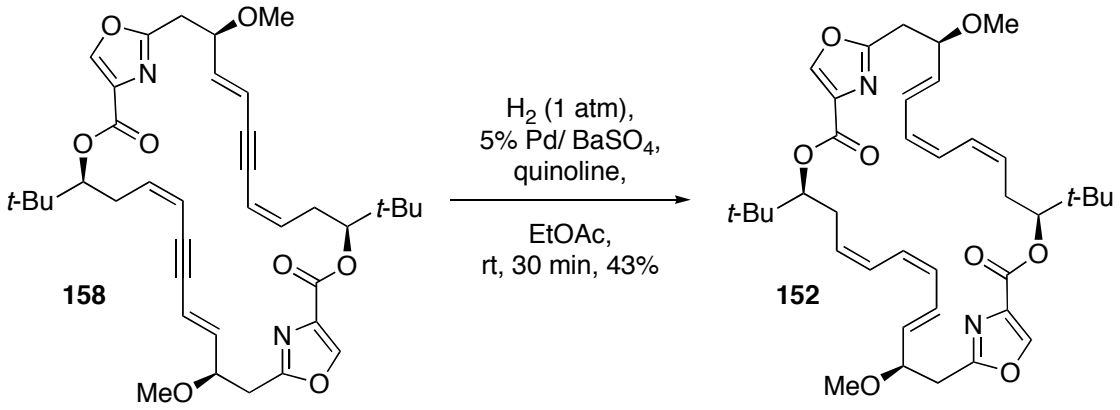
The dimer **158** was constructed from the monomer hydroxyacid under Yamaguchi conditions[128] (Scheme 50). Saponification of methyl ester **157** afforded the crude monomer hydroxyacid in 97% yield. The hydroxyacid was subjected to the Yamaguchi conditions[128] to afford the dimer **158** in 26% yield. The cyclomonomers **159** and **160** were each isolated in 8% yield after separation by HPLC.

The *t*-butyl analog **152** was completed by reduction of **158** using Pd/$BaSO_4$ poisoned with quinoline in 43% yield after purification by HPLC (Scheme 51).

Scheme 50. Synthesis of the C_{14}-*t*-butyl analog macrocycle.



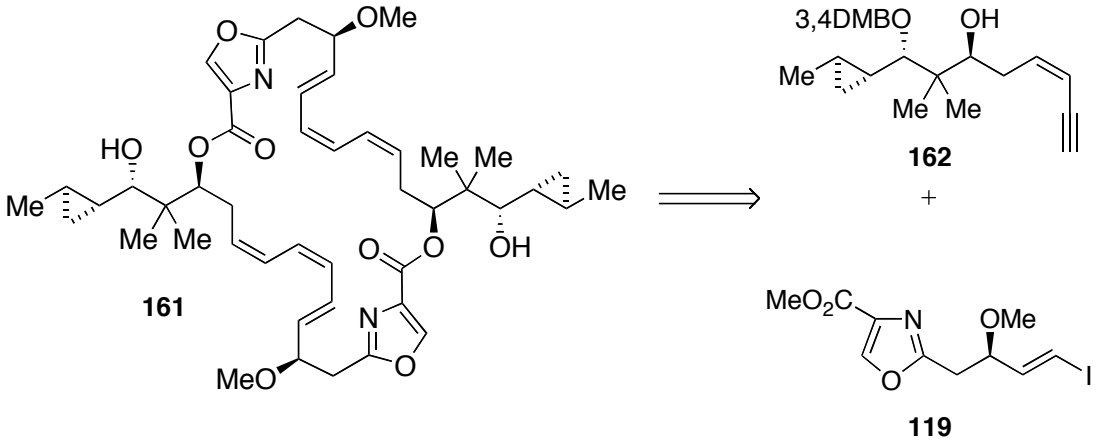
Scheme 51. Alkyne reduction to afford the *t*-butyl analog.



3.3.2. Synthesis of the $C_{17\text{-}18}$-Cyclopropyl Analog

The next analog that was chosen as a synthetic target was the $C_{17\text{-}18}$-cyclopropyl analog **161** (Figure 26). Cyclopropanes are often used as alkene isosteres[177] or to modify biologically active compounds.[178] The *t*-butyl analog proved to be biologically inactive (Section 3.3.5), so the cyclopropyl analog was chosen to better understand how the alkene contributes to the activity of disorazole C_1. An advantage of the cyclopropyl analog is that it is expected to maintain similar geometrical properties of the alkene. Access to the cyclopropyl target required the modified diol segment **162** (Figure 26).

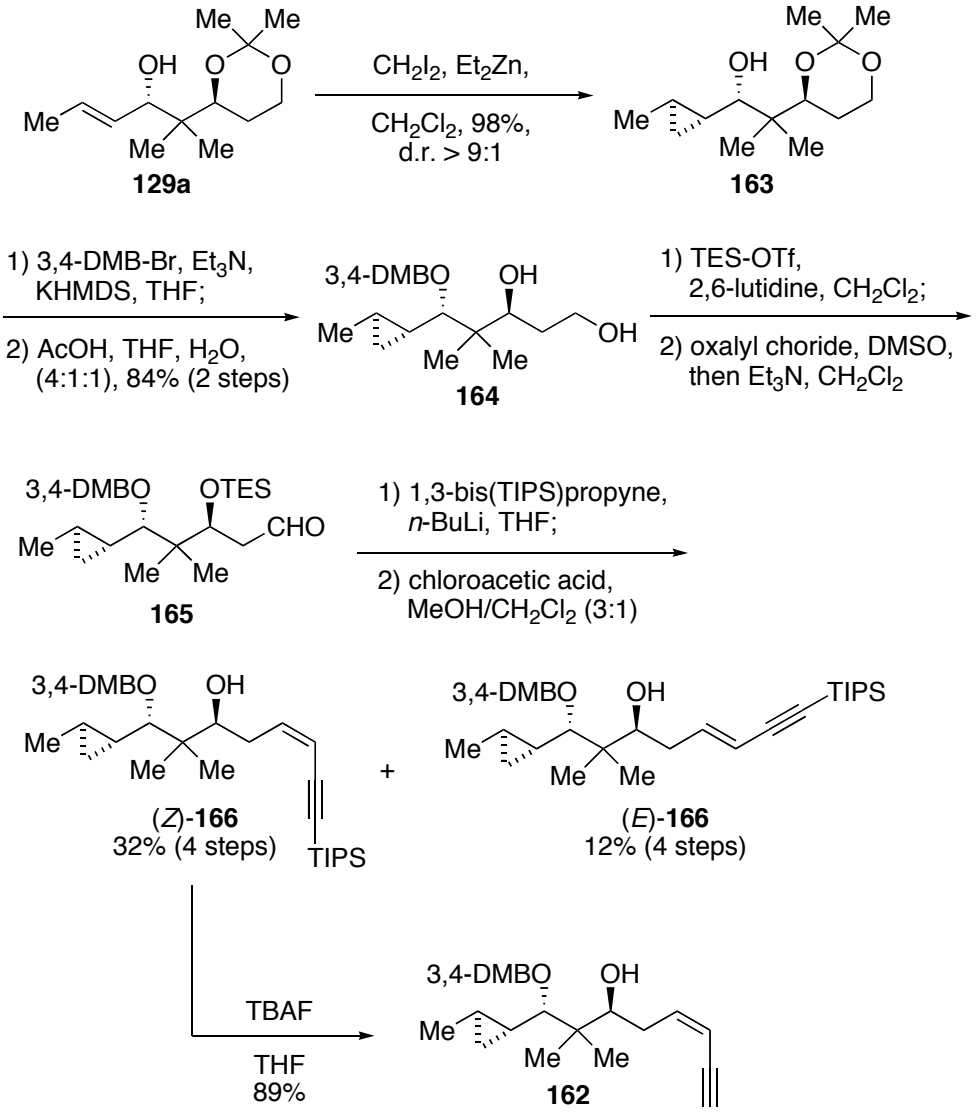
Figure 26. The $C_{17\text{-}18}$-cyclopropyl analog of (-)-disorazole C_1.



The synthesis of the cyclopropane modified diol segment began with the allylic alcohol **129a** which was subjected to a Furukawa-modified Simmons-Smith cyclopropanation[179] to afford the cyclopropane adduct **163** in 98% yield and excellent diastereoselectivity. Crystals suitable for x-ray diffractions were prepared by low-

temperature crystallization from hexanes and confirmed the relative stereochemistry of **163** (Appendix Section 4.2). The alcohol was protected as the 3,4-dimethoxybenzyl ether and the acetonide was removed to afford diol **164** in 84% yield for the two steps. Protection of the diol as the bis-triethylsilylether and selective oxidation under Swern conditions afforded aldehyde **165**. Condensation of **165** with 1,3-bis(triisopropylsilyl)-propynyl lithium and removal of the remaining triethylsilylether under mildly acidic conditions afforded (*Z*)-**166** and (*E*)-**166** in 32% and 12% yield after separation by chromatography on silica gel. The triisopropylsilyl group was removed from (*Z*)-**166** with TBAF in THF to afford the completed cyclopropane diol segment **162** in 89% yield.

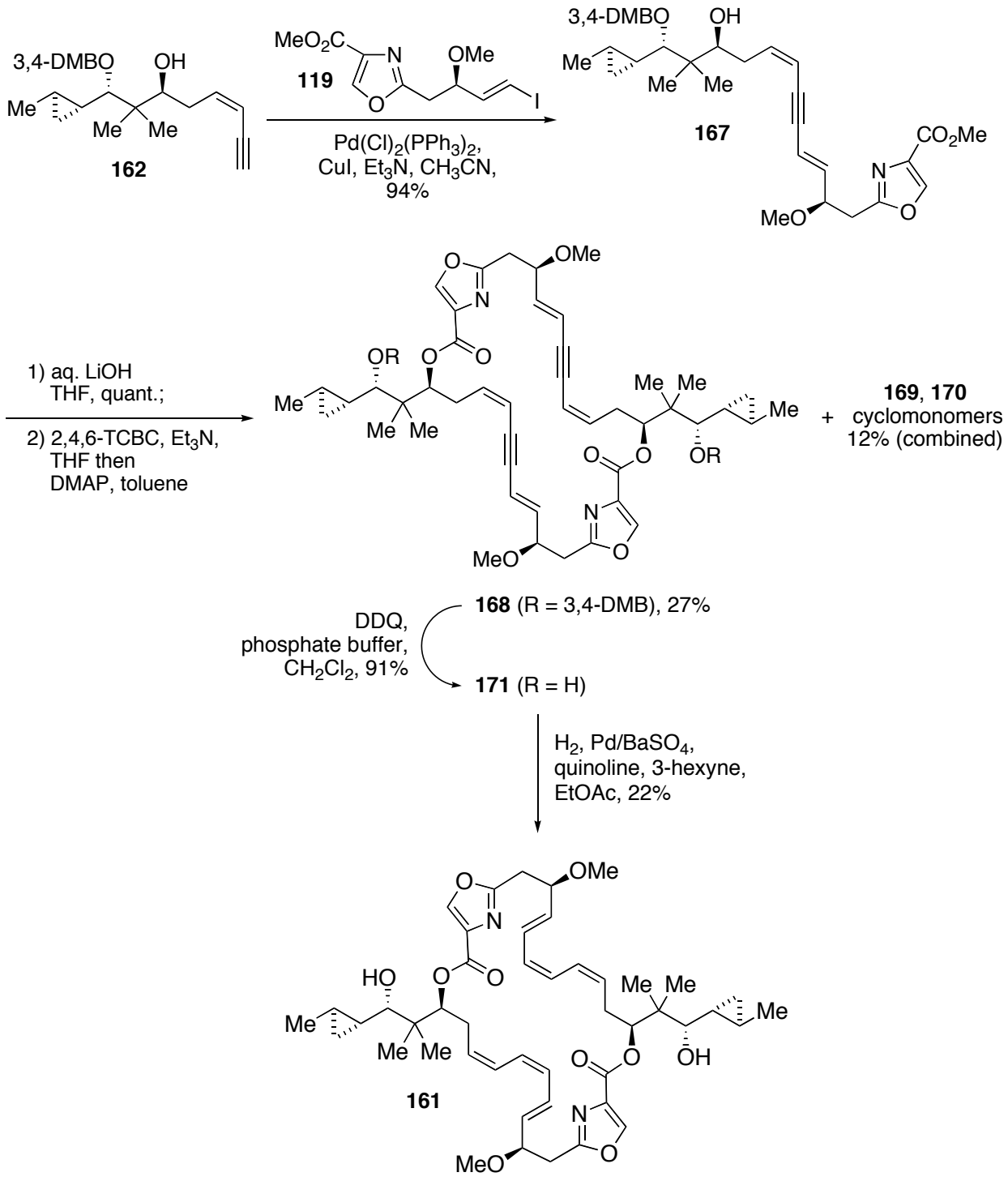
Scheme 52. Synthesis of the $C_{17\text{-}18}$-cyclopropane enyne.



The cyclopropyl analog was completed using a similar route to that used for disorazole C_1 (Scheme 53). Cross-coupling the enyne **162** and vinyl iodide **119** under Sonogashira conditions[99] afforded the monomer methyl ester **167** in 94% yield. Saponification of the methyl ester afforded the crude hydroxyacid that was

immediatedly subjected to the Yamaguchi conditions[128] to afford the dimer **168** in 27% yield after purification by HPLC. A mixture of cyclomonomers **169** and **170** was also isolated in 12% yield. The 3,4-dimethoxybenzyl protecting groups were then removed with DDQ under buffered conditions to afford the diol in 91% yield. The yield for the alcohol deprotection is higher than for the deprotection of the parent allylic alcohol system of disorazole C_1. In addition, no overoxidation to the ketone was observed, and this represents a synthetic advantage to replacing the (*E*)-alkene with the cyclopropane. Finally, reduction of the alkynes using hydrogen and quinoline-poisoned Pd on $BaSO_4$ afforded the completed $C_{17\text{-}18}$-cyclopropyl analog of (-)-disorazole C_1 (**161**) in 22% yield after purification by HPLC.

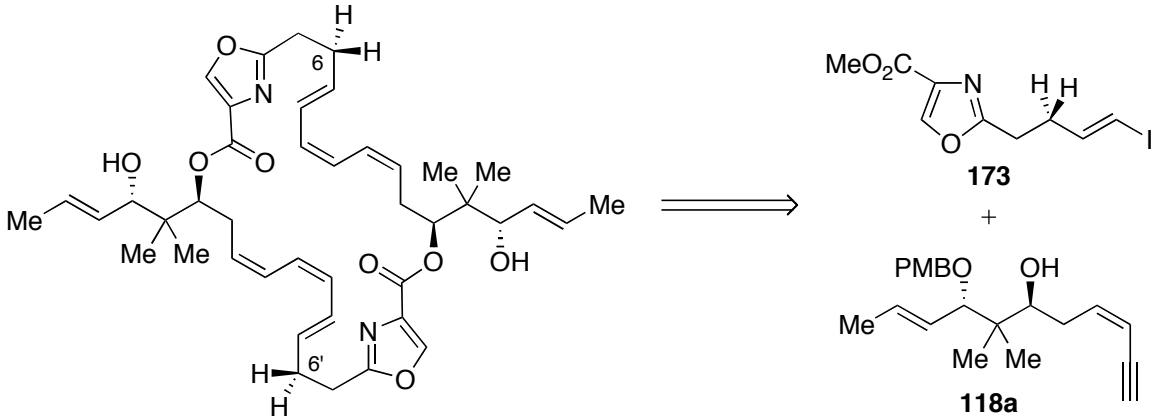
Scheme 53. Completion of the $C_{17\text{-}18}$-cyclopropane analog



3.3.3. Attempted Synthesis of the C_6-Desmethoxy Analog

Concurrent with the goals of simplifying the structure of disorazole C_1 while maintaining the biological activity, a third analog was selected which lacks the C_6-methoxy substituents, **172** (Figure 27). The advantage of the desmethoxy compound is the shortened synthetic sequence. Additionally, the potential for using the methoxy substituent as an anchor point for affinity labels if it proves to the inconsequential to the biological activity could also be evaluated. The disadvantage of removing the allylic methoxy substituent is the potential disruption of the macrocycle conformation or the destabilization of the sensitive triene unit.

Figure 27. The C_6-desmethoxy analog of (-)-disorazole C_1.

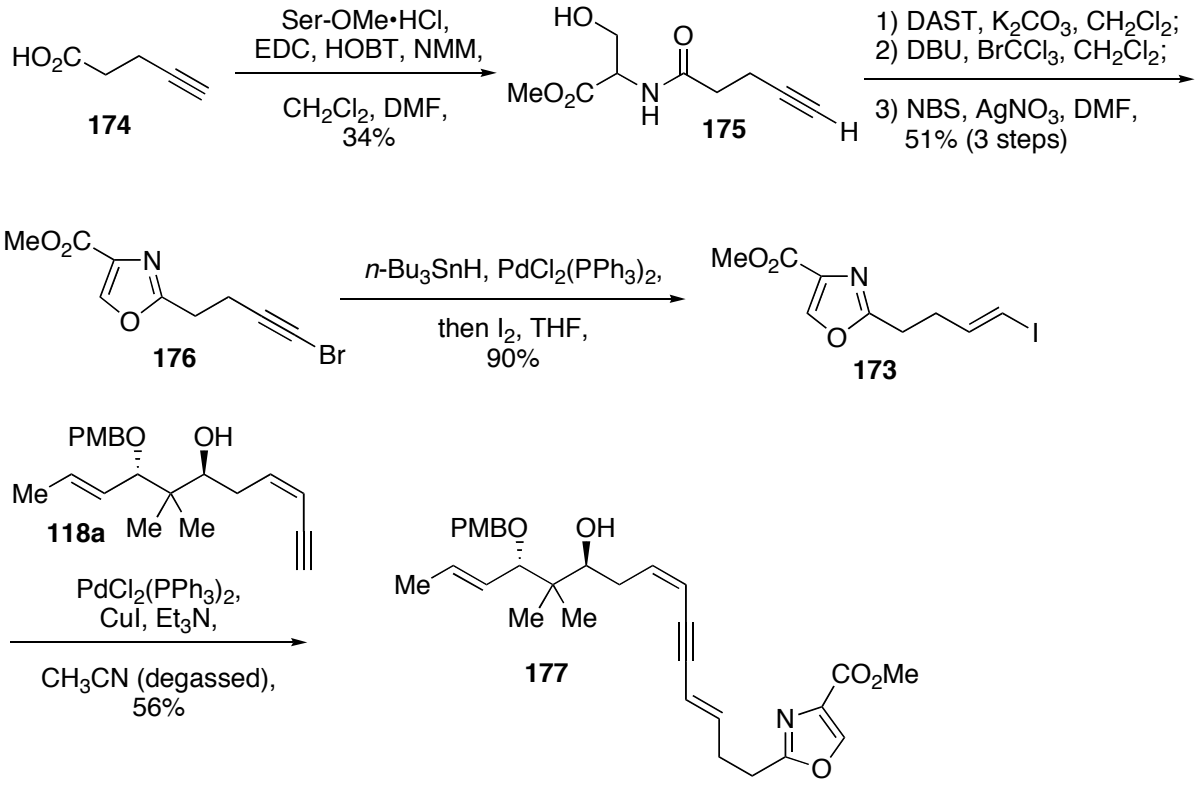


172

The synthesis of the desmethoxy analog **172** involved a modification of the oxazole segment and began with the coupling of commercially available 4-pentynoic acid (**174**) to serine methyl ester in 34% yield (Scheme 54). Cyclization of

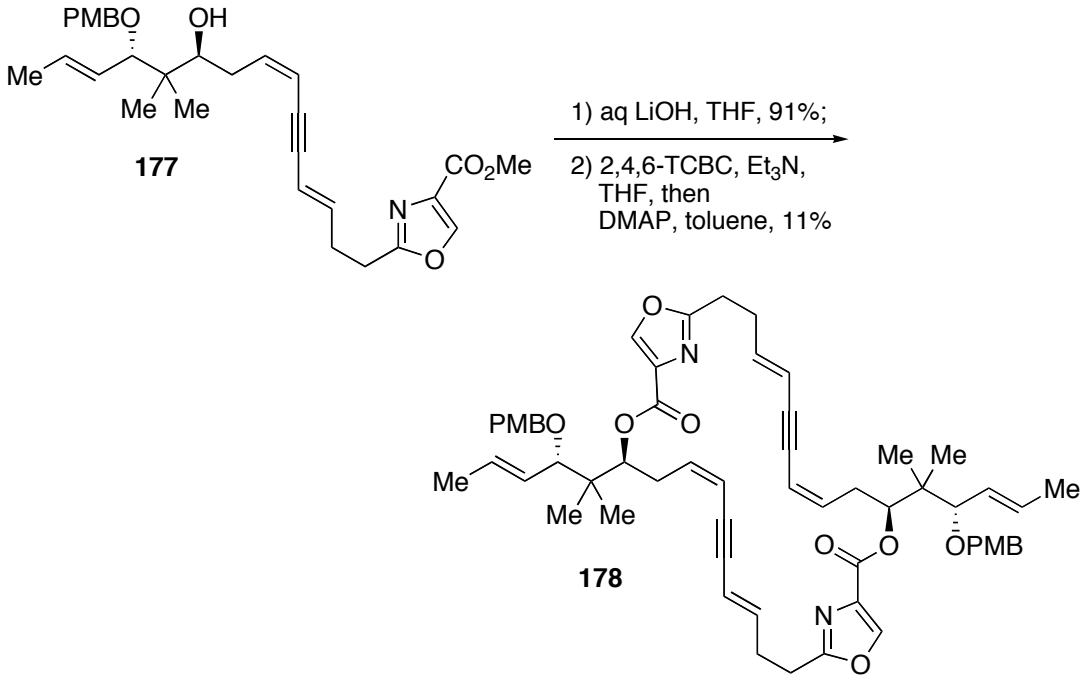
hydroxyamide **175** with DAST and oxidation of the resulting oxazoline to the oxazole using $BrCCl_3$ and DBU[13] afforded a mixture of the terminal alkyne and the bromoalkyne. The mixture was treated with *N*-bromosuccinimide and silver nitrate in DMF to afford the bromoalkyne **176** in 51% yield over the three steps. The bromoalkyne **176** was converted to the vinyl iodide **173** in 90% yield by the efficient one-pot palladium-catalyzed hydrostannylation-iodination sequence. Sonogashira cross-coupling[99] of **173** with enyne **118a** afforded the C_6-desmethoxymonomer methyl ester **177** in 56% yield.

Scheme 54. Synthesis of the desmethoxy monomer.



Direct formation of the C_6-desmethoxy dimer by saponification of the monomer **177** and dimerization under Yamaguchi conditions[128] afforded a low yield of the dimer **178** (Scheme 55). The reason for the low yield of **178** was unknown, so a longer, step-wise approach towards the dimer was explored next.

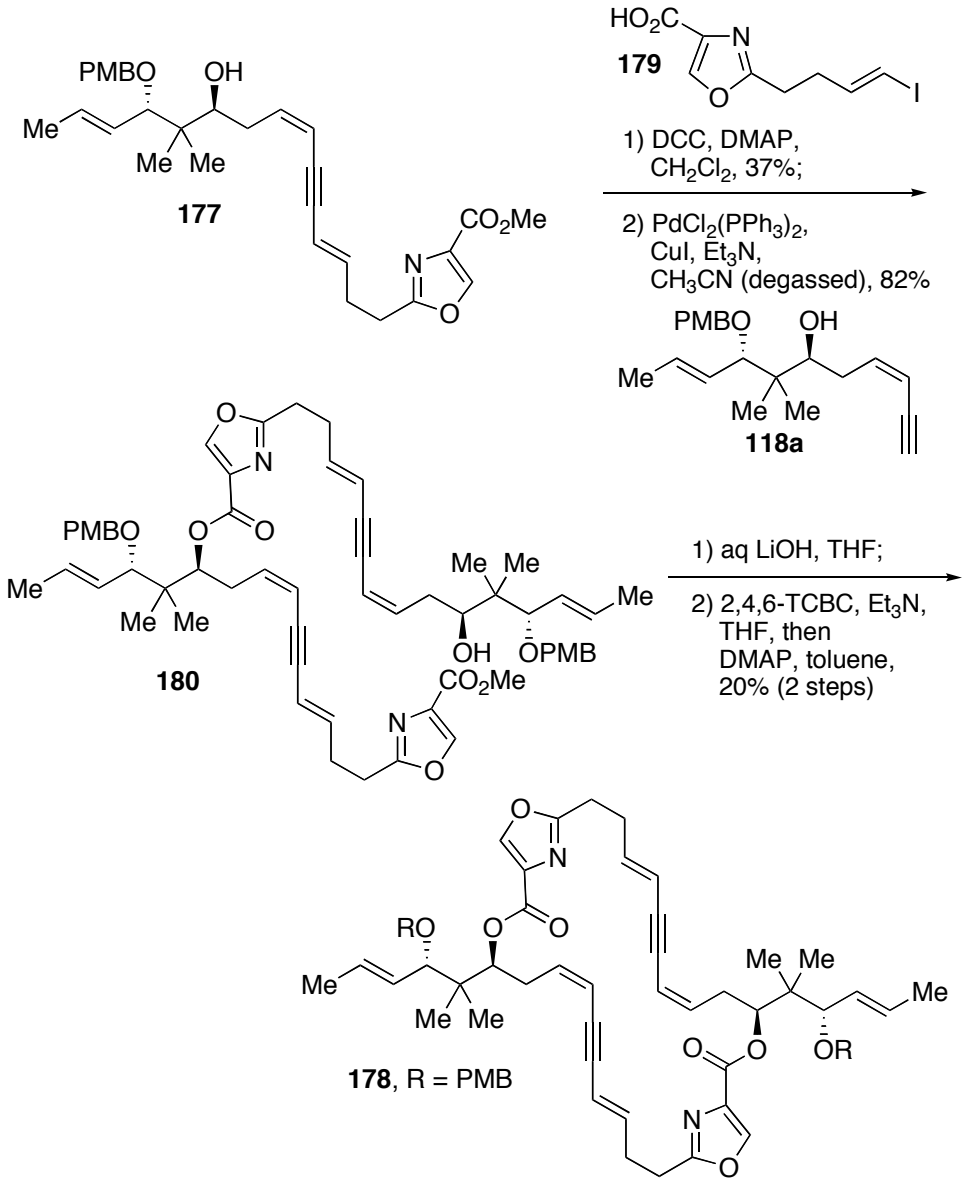
Scheme 55. Direct synthesis of the desmethoxy dimer.



The step-wise approach to the synthesis of the desmethoxy analog was analogous to the synthesis of disorazole C_1 and began with the acylation of monomer **177** with the oxazole acid **179** using DCC and DMAP to afford the ester in 37% yield. Cross-coupling with enyne **118a** afforded the *seco*-acid methyl ester **180** in 82% yield. Selective saponification and cyclization of the crude hydroxyacid afforded the dimer **178** in 20% yield.[180] The low yields for the sequence were accompanied by the inability

to obtain material that was pure by ^{1}H NMR. For these reasons, further attempts to complete the C_6-desmethoxy analog of disorazole C_1 (**172**) were abandoned.[181]

Scheme 56. Stepwise synthesis of the desmethoxy dimer.

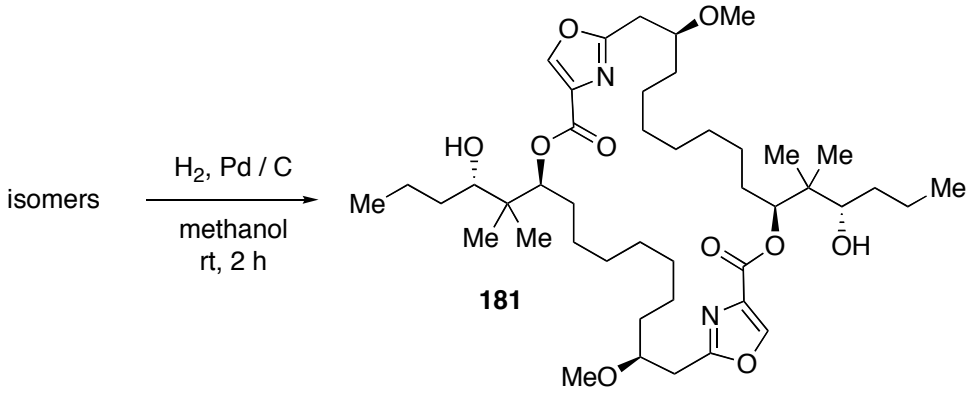


3.3.4. Additional Analogs

3.3.4.1. Hydrogenated Disorazole C_1

The semi-hydrogenation of bis-alkyne **151** to afford disorazole C_1 (**76**) (Scheme 48) was accompanied by a variety of byproducts that had a similar structure and may result from olefin isomerization or olefin saturation. The byproducts converged to **181** upon exposure to hydrogen and palladium on carbon (Scheme 57). The saturated analog **181** was submitted for biological testing (Section 3.3.5).

Scheme 57. Saturation of the disorazole C_1 olefins.

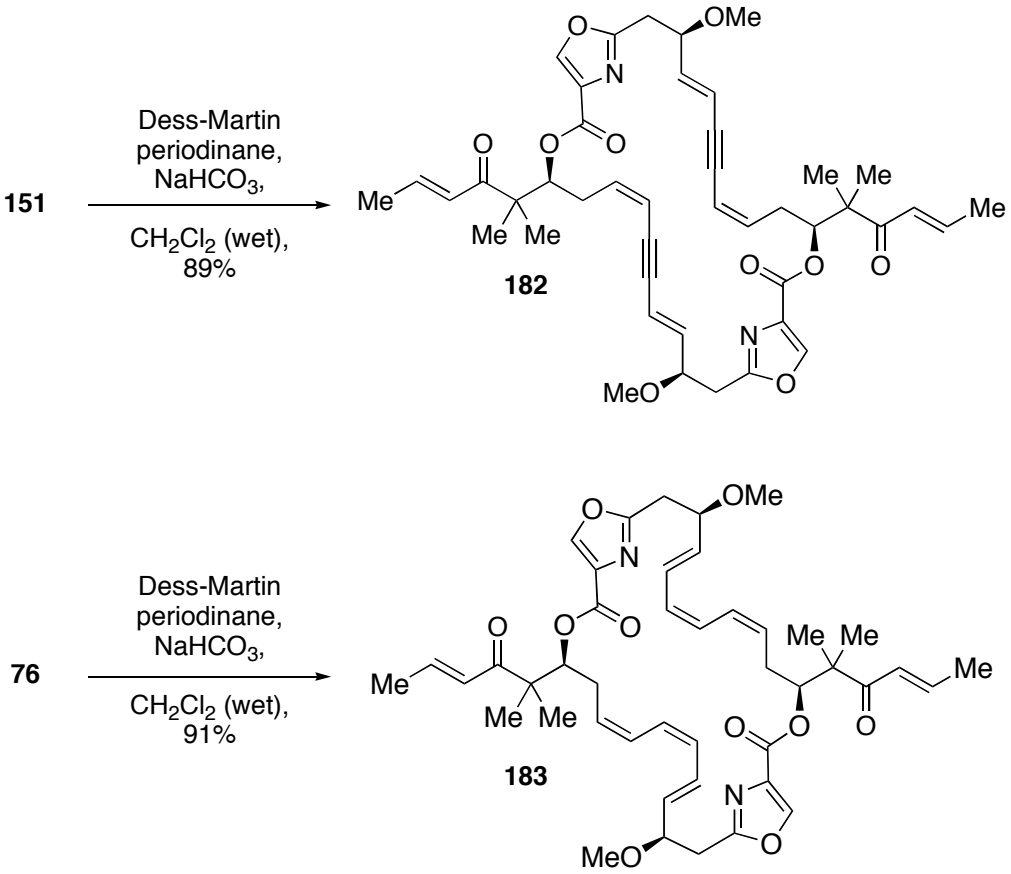


3.3.4.2. Synthesis of C_{16}-Didehydrodisorazole C_1

A hypothesis concerning the activity of disorazole C_1 is that the allylic alcohol side chains of disorazole C_1 undergo oxidations *in vivo*, affording an α,β-unsaturated ketone. The oxidized disorazole C_1 could then cause a disruption in the cellular network by irreversibly binding to a protein via the conjugate addition of an amino acid residue to the α,β-unsaturated ketone. This hypothesis was tested by oxidizing the

bis-alkyne **151** and disorazole C_1 (**76**) to the corresponding α,β-unsaturated ketones **182** and **183** in 89% and 91% yields, respectively, using buffered Dess-Martin periodinane.[17] The resulting ketone analogs **182** and **183** were subjected to biological testing (Section 3.3.5).

Scheme 58. α,β-Unsaturated ketone analogs of disorazole C_1 and the alkyne precursor.



3.3.5. Biological Activities for the Disorazole C_1 Analogs

The analogs of disorazole C_1 that were submitted for biological evaluation are summarized in Figure 28. The initial biological evaluation of disorazole C_1 and the synthetic intermediates indicated that only disorazole C_1 (**76**) and the alkyne precursor **151** had biological activity (Section 3.2.5). The *t*-butyl analogs **152** and **158** and the cyclomonomers **159** and **160** were not active at concentrations less than 5 μM. Likewise, the saturated analog **181** was also not active. The hypothesis concerning an *in vivo* oxidation of the allylic alcohol to an α,β-unsaturated ketone that could act as an alkylating reagent can also be discounted because enones **182** and **183** were not active. Finally, the cyclopropyl analogs **171** and **161** were also not active.

The results from the biological evaluation of the disorazole C_1 analogs indicate that the 2-butene-1-ol side chain is essential for activity. The energy minimized conformations of the analogs were evaluated to understand how this group influences the conformations of the macrocycle.[182] The mimimized structures are shown in Appendix Section 4.3. The conformation of disorazole C_1 (**76**) indicates a twisted structure that places the side chains in close proximity (Figure 30). The bis-alkyne (**151**) adopts a less-twisted conformation that places one of the methoxy groups on the concave face of the macrocycle (Figure 31).[173] The *t*-butyl analog **152** indicates a flattened structure with the *t*-butyl groups on opposite sides of the molecule and suggests that the side chains can have a significant impact on the overall conformation of the molecule (Figure 32). The cyclopropyl analog **161** adopts a similar conformation

to disorazole C_1 (**76**) (Figure 33). The diketone analog **182** is flattened relative to disorazole C_1 (**76**) (Figure 34). Finally, disorazole A_1 adopts a conformation similar to disorazole C_1 (**76**) (Figure 35). These results suggest that subtle changes in structure can lead to a significant change in the conformation of the macrocycle. The possibility that the natural product is binding in a different conformation still exists and a more definite SAR model can only be developed by testing additional analogs.[183]

Figure 28. Analogs of disorazole C_1 that were submitted for biological evaluation.

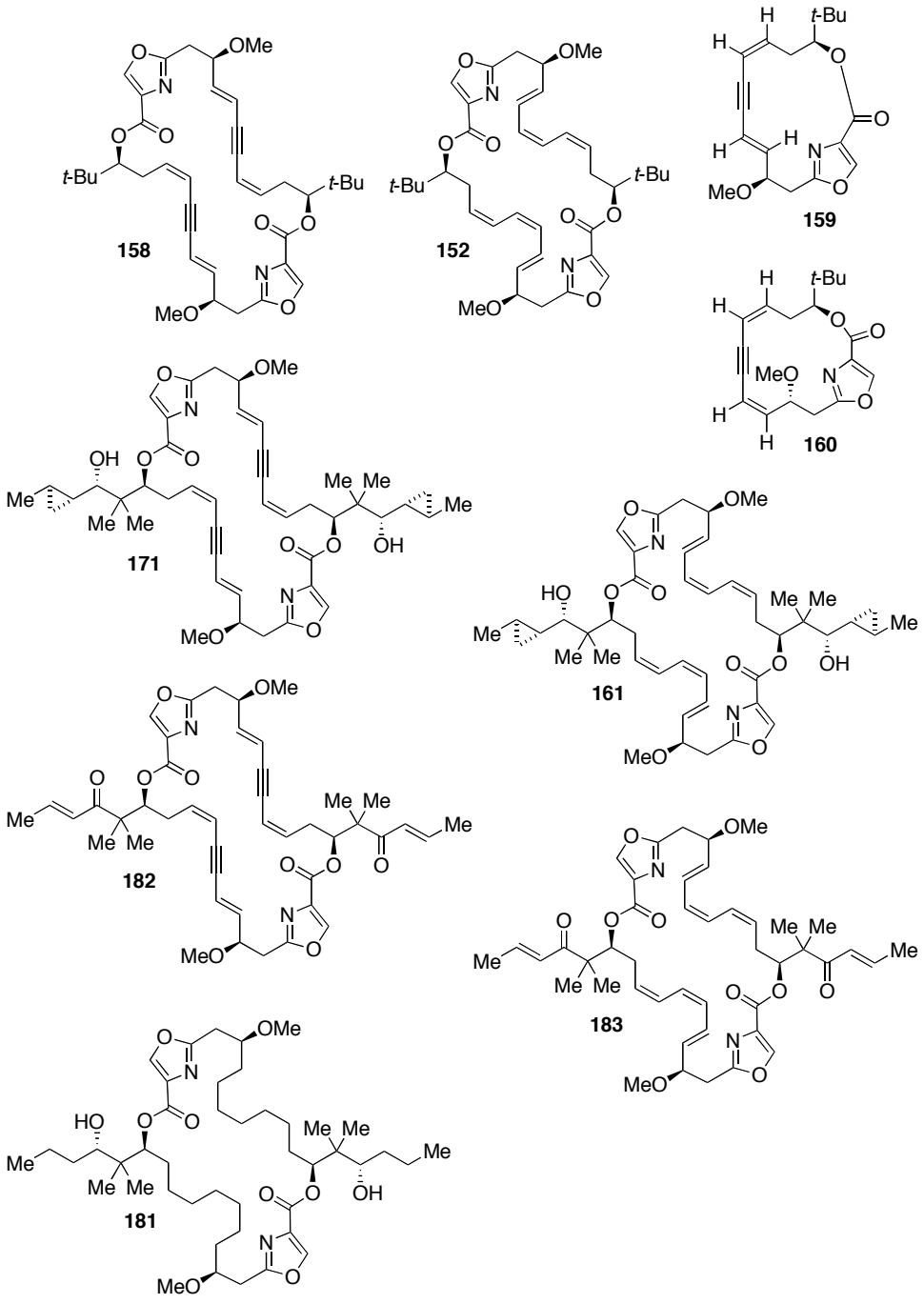


Table 19. Summary of the high-content analysis of mitotic arrest in HeLa cells treated with disorazole C_1 and analogs.*

Sample	Cell Density	Nuclear Condensation	Mitotic Index[b]	Tubulin Mass	G2/M Arrest
	EC_{50} (nM)			MEC[c] (nM)	
76	14.6 ± 3.8	19.7 ± 6.6	5.8 ± 2.4	7.6 ± 3.6	9.1 ± 6.0
151	3912 ± 1143	>5000	4401 ± 848	3733 ± 1186	5000 ± 0
147a	>5000	>5000	>5000	>5000	>5000
147c	>5000	>5000	>5000	>5000	>5000
148a	>5000	>5000	>5000	>5000	>5000
149a	>5000	>5000	>5000	>5000	>5000
149c	>5000	>5000	>5000	>5000	>5000
150a	>5000	>5000	>5000	>5000	>5000
152	>5000	>5000	>5000	>5000	>5000
158	>5000	>5000	>5000	>5000	>5000
159	>5000	>5000	>5000	>5000	>5000
160	>5000	>5000	>5000	>5000	>5000
161	>5000	>5000	>5000	>5000	>5000
171	>5000	>5000	>5000	>5000	>5000
181	>5000	>5000	>5000	>5000	>5000
182	>5000	>5000	>5000	>5000	>5000
183	>5000	>5000	>5000	>5000	>5000

[a] average of (n = 3) independent experiments ± SD; [b] percentage of phospho-H3 positive cells; [c] Minimal Effective Concentration. For positive controls, refer to Table 18.

* Biological evaluations were performed by Dr. Alexander P. Ducruet and Rachel P. Sikorski under the supervision of Dr. John S. Lazo and Dr. Andreas Vogt.

3.4. Summary and Conclusions

A highly convergent and stereoselective synthesis of disorazole C_1 (**76**) was completed. Notable features include the installation of the absolute configurations of each fragment by titanium (IV)/BINOL mediated additions of allyl trimethylsilane[139] or zinc acetylides[165] to aldehydes. The oxazole was installed using the DAST mediated cyclodehydration and the $BrCCl_3$/DBU oxidation methodology[13] to afford bromoalkyne **144** which was transformed to the vinyl iodide using a highly efficient hydro-stannylation/iodination sequence.[170] The macrocycle was constructed with minimal protecting group manipulations, using mild esterification and Sonogashira cross-coupling reactions. Finally, the C_{16}-hydroxyl protecting group was removed under mild conditions and reduction of the alkyne afforded disorazole C_1 (**76**).

The convergent synthesis of disorazole C_1 allowed for the synthesis of additional analogs. These analogs include the C_{14}-*t*-butyl analog **152** and the $C_{17\text{-}18}$-cyclopropyl analog **161**. Attempts to prepare the C_6-desmethoxy analog failed due to low yields. Additional derivatives include the diketones **181** and **182** and the fully reduced derivative **181**. Only synthetic disorazole C_1 (**76**) and the alkyne precursor **151** demonstrated anti-proliferative activity in cellular assays. All other analogs and derivatives proved to be inactive at less than 5 μM in biological assays.[172,183]

We initially embarked on the synthesis of (-)-disorazole C_1 with the idea that a convergent synthesis would allow other members of the disorazole family to be prepared. The biological profile of disorazole C_1 or any of the other minor metabolites

in the disorazole family had not been reported. Gratifyingly, our synthesis and biological evaluation proved that the synthetically challenging divinyl oxirane and tetraene segments found in the more abundant disorazoles were not required for potent biological activity.[121] Our initial SAR studies also proved that the activity is strongly dependant on the structure of the natural product. Even minor changes, such as cyclopropanation of the $C_{17\text{-}18}$-olefin or oxidation of the C_{16}-alcohol, led to significantly lower activities in biological assays.[183] In addition, we currently believe that the C_6-methoxy is important for the stability of the natural product because our attempts to prepare the C_6-desmethoxy analog failed. The preparation of more analogs will be required to further probe the correlation between the structural features of the molecule and the biological activity and molecular stability profiles. The preparation of other members of the disorazole family would allow for a direct comparison of activities in biological assays and lead to an improved understanding of the SAR.

The potent antiproliferative activity and extraordinary SAR profile suggest that disorazole C_1 participates in a very specific interaction within the cellular network and is therefore a promising candidate for anti-cancer therapies. The apparent irreversibility of the cellular response to the disorazoles is another interesting property of the disorazoles.[111,183] The exact cellular target of the disorazoles remains to be unequivocally elucidated and will require the synthesis of labeled natural product. The current synthetic route to disorazole C_1 is convergent and allows for numerous opportunties to prepare labeled material. Finally, the current synthetic route has the potential to afford significant quantities of disorazole C_1 and analogs for *in vivo* testing.

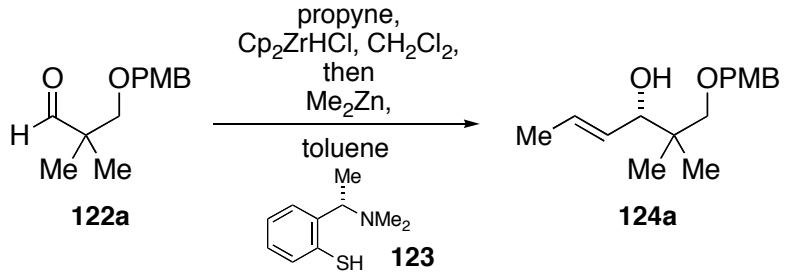
3.5. Experimental Part

3.5.1. General

All moisture sensitive reactions were performed using syringe-septum techniques under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for more than 4 h prior to use. Reactions at -78 °C employed a solid CO_2-acetone bath. THF and ethyl ether were distilled from sodium/benzophenone ketyl. Methylene choride and toluene were filtered through activated alumina prior to use. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualized using UV light (254 nm) or by staining with $KMnO_4$ or phosphomolybdic acid. Flash chromatography on SiO_2 was used to purify compounds unless otherwise stated. Concentration refers to removal of the solvent on a rotary evaporator at water aspirator pressure. Melting points are uncorrected. Infrared spectra were acquired using KBr pellets or thin films on NaCl plates (i.e. neat). Chemical shifts were reported in parts per million and the residual solvent peak was used as an internal reference. ^{1}H NMR spectra were acquired in $CDCl_3$ at a frequency of 300 MHz unless stated otherwise and are tabulated as follows: chemical shift (multiplicity, number of protons, coupling constants). ^{13}C NMR were acquired in $CDCl_3$ at a frequency of 75 MHz using a proton decoupled pulse sequence unless stated otherwise. For acid sensitive samples, $CDCl_3$ was filtered through activated basic alumina (Brockmann I) immediately prior to sample preparation. For optical rotations, concentration (*c*) is reported in g/100 mL. Semi-preparative HPLC was performed using a 10 mm x 25 mm SiO_2 column.

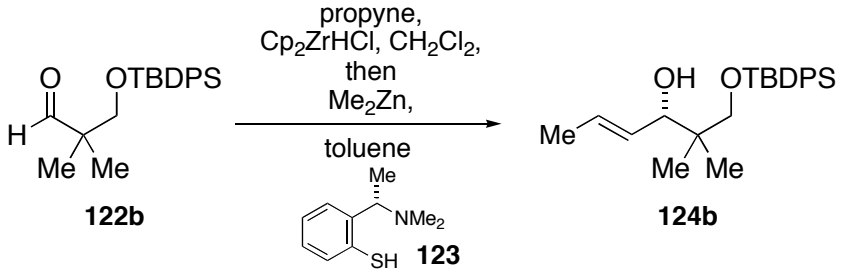
3.5.2. Experimental Procedures

3.5.2.1. Synthesis of Disorazole C_1



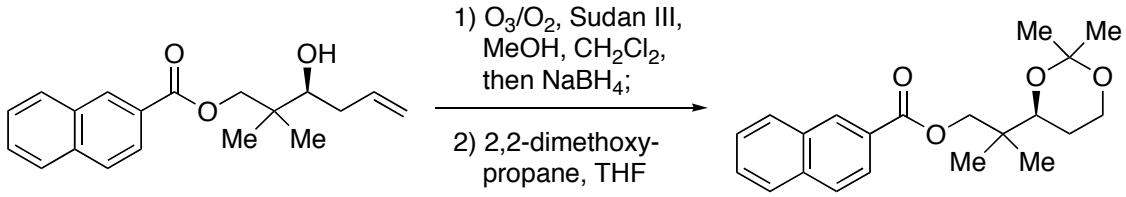
(*S*,*E*)-1-(4-Methoxybenzyloxy)-2,2-dimethylhex-4-en-3-ol (124a). A suspension of Cp_2ZrHCl (70.0 mg, 0.271 mmol, 1.2 equiv) in CH_2Cl_2 (4.0 mL) was stirred at rt while gaseous propyne was bubbled into the solution for 30 min. The solvent was removed *in vacuo* and toluene (2.0 mL) was added. The mixture was cooled to –78 °C and treated with Me_2Zn (2.0 M in toluene, 0.112 mL, 0.225 mmol, 1.0 equiv) and ligand **123** (10.0 mg, 0.055 mmol, 0.25 equiv), warmed to –15 °C for 1 h, treated with a solution of **122a** (50.0 mg, 0.225 mmol, 1.0 equiv) in toluene (2.0 mL) and stirred under argon for 20 h at –15 °C. A small amount of saturated aqueous $NaHCO_3$ was added and the mixture was filtered through a pad of Florisil/Celite (1:1). The filtrate was washed with brine, dried (Na_2SO_4), filtered and concentrated to a pale yellow oil. Purification by chromatography on SiO_2 (10% to 20% ethyl ether/hexanes) afforded recovered aldehyde **122a** (29.3 mg, 49%) and **124a** (11.0 mg, 19%) as a clear, colorless oil. Analysis by analytical HPLC (Chiralcel-OD, 0.46 cm x 25 cm, 1% isopropanol/hexanes, 1.0 mL/min, 254 nm) indicated 24% ee [R_t(major)= 14.09 min, R_t(minor)= 16.17 min)]: ^{1}H NMR δ 7.24 (dt, 2 H, J = 8.6, 1.8 Hz), 6.88 (dt, 2 H, J = 8.6,

1.9 Hz), 5.65 (q of AB, 1 H, *J* = 15.2, 6.4 Hz), 5.47 (dq of AB, 1 H, *J* = 15.2, 7.3, 1.4 Hz), 4.43 (s, 2 H), 3.86 (dd, 1 H, *J* = 7.1, 4.2 Hz), 3.80 (s, 3 H), 3.36 (d, 1 H, *J* = 4.3 Hz), 3.36, 3.24 (AB, 2 H, *J* = 8.8 Hz), 1.69 (d, 3 H, *J* = 6.4 Hz), 0.89 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR δ 159.4, 130.6, 130.1, 129.4, 128.2, 113.9, 80.2, 79.2, 73.4, 55.4, 38.4, 23.0, 20.1, 18.0; IR (neat) 3476, 2960, 2935, 2910, 2856, 1612, 1586, 1514 cm^{-1}; MS (EI) *m/z* (rel. intensity) 264 (M^+, 3.8), 191 ([M-$CH_3(CH_2)_2CHOH]^+$, 3.7), 138 (54), 121 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1723.



(*S*,*E*)-1-(*tert*-Butyldiphenylsilyloxy)-2,2-dimethylhex-4-en-3-ol (122b). A suspension of Cp_2ZrHCl (150.0 mg, 0.582 mmol, 1.9 equiv) in CH_2Cl_2 (4.0 mL) was stirred at rt while gaseous propyne was bubbled into the solution for 10 min. The solvent was removed *in vacuo* and toluene (1.0 mL) was added. The mixture was cooled to –78 °C and treated with Me_2Zn (2.0 M in toluene, 0.270 mL, 0.540 mmol, 1.8 equiv) and ligand **123** (11.0 mg, 0.061 mmol, 0.2 equiv), warmed to 0 °C for 30 min, treated with a solution of **122b** (101.7 mg, 0.297 mmol, 1.0 equiv) in toluene (0.4 mL + 0.4 mL rinse) and stirred under argon for 6.5 h at 0 °C. The mixture was treated with a small amount of water (0.2 mL), followed by anhydrous Na_2SO_4, stirred for 10 min and filtered through a pad of Florisil/Celite (1:1). The filtrate was concentrated to a clear, colorless syrup. Purification by chromatography on SiO_2 (5% ethyl ether/hexanes)

afforded **124b** (98.8 mg, 87%) as a clear, colorless oil. Analysis by analytical HPLC (Chiralcel-OD, 0.46 cm x 25 cm, 2% isopropanol/hexanes, 0.5 mL/min, 254 nm) indicated 33% ee [R_t(major)= 9.00 min, R_t(minor)= 9.98 min)]: ^{1}H NMR δ 7.73-7.69 (m, 4 H), 7.49-7.39 (m, 6 H), 5.75 (q of AB, 1 H, *J* = 15.2, 6.4 Hz), 5.58 (dq of AB, 1 H, *J* = 15.2, 7.2, 1.4 Hz), 4.04 (dd, 1 H, *J* = 6.8, 3.5 Hz), 3.57, 3.48 (AB, 2 H, *J* = 9.8 Hz), 3.39 (d, 1 H, *J* = 3.9 Hz), 1.74 (dd, 3 H, *J* = 6.3, 0.7 Hz), 1.10 (s, 9 H), 0.92 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR δ 135.9, 133.0, 130.7, 130.0, 128.3, 127.9, 80.0, 73.0, 39.1, 27.0, 22.4, 19.7, 19.4, 18.1; IR (neat) 3480, 3071, 3049, 2960, 2931, 2858, 1959, 1890, 1824, 1670, 1590, 1472, 1428 cm^{-1}; MS (EI) *m/z* (rel. intensity) 325 ([M-C_4H_9]$^+$, 15), 307 ([M-C_4H_9-H_2O]$^+$, 18), 269 (10), 229 (35), 199 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{25}O_2Si$ (M-C_4H_9) 325.1624, found 325.1618.

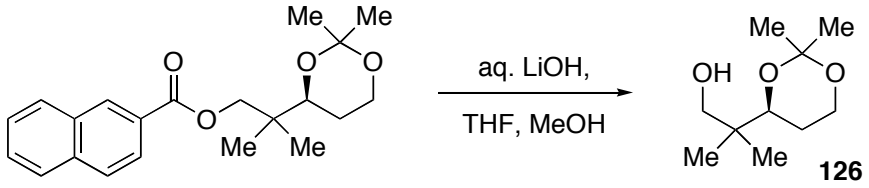


125

Naphthalene-2-carboxylic acid 2-[(4*S*)-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methylpropyl ester. A solution of **125** (9.46 g, 31.7 mmol, 1.0 equiv) in methanol (100 mL) and CH_2Cl_2 (50 mL) containing Sudan III (1.0 mg) was cooled to –78 °C. O_3/O_2 was bubbled through the mixture for approximately 40 min until the color changed to a pale yellow. $NaBH_4$ (1.80 g, 47.6 mmol, 1.5 equiv) was added in one portion and the reaction mixture was stirred at –78 °C for 10 min and then warmed to 0 °C for 1 h. Additional $NaBH_4$ (1.80 g, 47.6 mmol, 1.5 equiv) was added and the cold bath was removed. After stirring for 1 h at rt, 1.0 M aqueous citric acid (100 mL) and brine (100

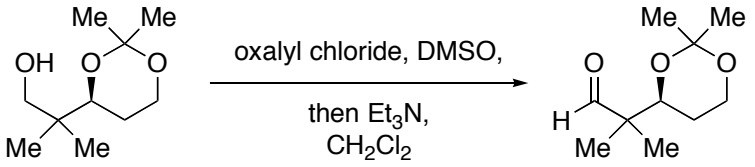
mL) were added and the mixture was stirred for 10 min and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (30% to 80% ethyl acetate/hexanes) afforded (3*S*)-naphthalene-2-carboxylic acid 3,5-dihydroxy-2,2-dimethylpentyl ester (8.420 g, 88%) as a pale yellow glass that was used without further purification: R_f = 0.38 (60% ethyl acetate/hexanes). A solution of this ester (8.35 g, 27.6 mmol, 1.0 equiv) in THF (100 mL) was cooled to 0 °C, and PPTS (500 mg, 2.00 mmol, 0.1 equiv) and then 2,2-dimethoxypropane (20.0 mL, 163 mmol, 5.9 equiv) was added. The cold bath was removed and the mixture was stirred at rt for 48 h, quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (3% ethyl acetate, 1% triethylamine/hexanes, then 100% ethyl acetate) afforded the acetonide and a small amount of starting diol which was re-subjected and purified as above. The two batches were combined to afford naphthalene-2-carboxylic acid 2-[(4*S*)-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methylpropyl ester (9.140 g, 97%) as a clear, colorless syrup: $[\alpha]_D$ +27.4 (*c* 1.40, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.60 (s, 1 H), 8.06 (dd, 1 H, *J* = 8.6, 1.0 Hz), 7.97 (d, 1 H, *J* = 7.5 Hz), 7.89 (d, 2 H, *J* = 8.7 Hz), 7.62-7.52 (m, 2 H), 4.31, 4.16 (AB, 2 H, *J* = 10.7 Hz), 3.99 (dd, 1 H, *J* = 11.7, 2.8 Hz), 3.95-3.86 (m, 2 H), 1.78 (app dq, 1 H, *J* = 12.1, 5.6 Hz), 1.44-1.40 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.04 (s, 6 H); ^{13}C NMR δ 166.8, 135.7, 132.7, 131.1, 129.5, 128.4, 128.0, 126.9, 125.3, 98.6, 72.5, 70.5, 60.4, 37.8, 30.0, 25.4, 21.5, 19.5, 19.3; IR (neat) 3060, 2991, 2966, 2940, 2874, 1717, 1631, 1603 cm^{-1}; MS (EI) *m/z* (rel. intensity) 342 (M^+, 24), 327 ($[M-CH_3]^+$, 35), 284 ($[M-C_4H_{10}]^+$,

15), 211 (6), 172 (42), 155 (100), 115 (66); HRMS (EI) *m/z* calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1835.



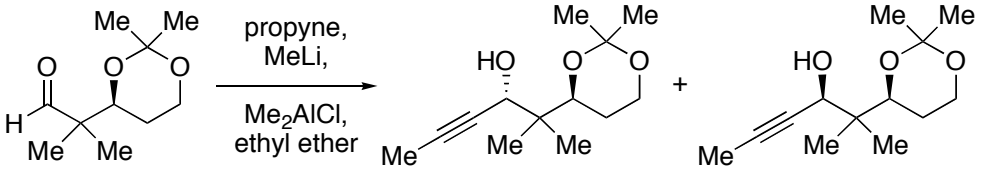
126

2-{(4*S*)-2,2-Dimethyl-[1,3]dioxan-4-yl}-2-methyl-propan-1-ol (126). A solution of naphthalene-2-carboxylic acid 2-[(4*S*)-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methylpropyl ester (1.59 g, 4.64 mmol, 1.0 equiv) in THF (20 mL) and MeOH (5 mL) was cooled to 0 °C and treated with 1.0 M aqueous LiOH (5.00 mL, 5.00 mmol, 1.1 equiv). The reaction mixture was allowed to warm to rt and after 20 h, diluted with ethyl ether (20 mL) and washed with water (20 mL) and brine (20 mL). The combined aqueous layers were backwashed with ethyl ether (5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% ethyl ether/hexanes) afforded **126** (720.0 mg, 82%) as a pale yellow oil: R_f 0.20 (40% ethyl ether/hexanes); $[\alpha]_D$ +13.3 (*c* 1.50, $CHCl_3$, 22 °C); ^{1}H NMR δ 3.94 (app dt, 1 H, *J* = 11.8, 2.8 Hz), 3.86 (ddd, 1 H, *J* = 11.7, 5.7, 1.8 Hz), 3.78 (dd, 1 H, *J* = 11.9, 2.5 Hz), 3.53 (dd, 1 H, *J* = 10.9, 5.9 Hz), 3.35 (dd, 1 H, *J* = 10.9, 5.3 Hz), 3.00 (app t, 1 H, *J* = 5.7 Hz), 1.75 (app dq, 1 H, *J* = 12.4, 5.7 Hz), 1.44 (s, 3 H), 1.38-1.31 (m, 1 H), 1.36 (s, 3 H), 0.88 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 98.7, 77.4, 71.7, 60.3, 37.8, 30.1, 25.7, 22.2, 19.4, 19.2; IR (neat) 3441, 2991, 2963, 2873, 1475, 1460 cm^{-1}; MS (EI) *m/z* (rel. intensity) 173 ([M-CH_3]$^+$, 48), 115 (12), 88 (21), 73 (76), 61 (100); HRMS (EI) *m/z* calcd for $C_9H_{17}O_3$ (M-CH_3) 173.1178, found 173.1180.



126 **127**

(*S*)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-methylpropanal (127).[142] A solution of oxalyl chloride (3.30 mL, 37.8 mmol, 1.5 equiv) in CH_2Cl_2 (250 mL) was cooled under N_2 to –78 °C and treated via cannula with a solution of CH_2Cl_2 (5.0 mL+5.0 mL rinse). The reaction mixture was stirred for 20 min, treated via cannula with a solution of **126** (4.70 g, 25.0 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL+5.0 mL rinse), stirred at –78 °C for an additional 30 min, and treated with triethylamine (15.00 mL, 106.9 mmol, 4.3 equiv). The solution was stirred at –78 °C for 2 h, treated with water (50 mL), warmed to rt, poured into water (50 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was diluted with anhydrous ethyl ether and filtered through a plug of SiO_2. The plug was rinsed with ethyl ether and the filtrate was concentrated to give **127** as a yellow oil that was used in the following transformation without further purification: R_f 0.50 (40% ethyl ether/hexanes).

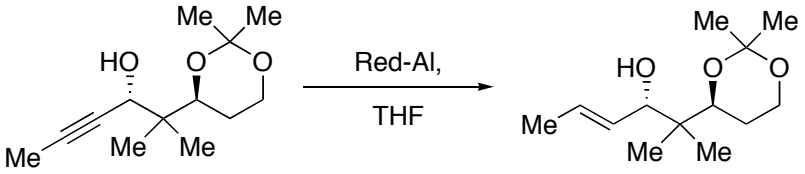


127 **128a** **128b**

(3*S*)-2-{(4*S*)-2,2-Dimethyl-[1,3]-dioxan-4-yl}-2-methylhex-4-yn-3-ol (128a) and (3*R*)-2-{(4*S*)-2,2-dimethyl-[1,3]-dioxan-4-yl}-2-methylhex-4-yn-3-ol (128b).

Propyne (ca. 1 mL) was condensed into a flask at –78 °C, diluted with ethyl ether (5.0 mL) and treated with MeLi (1.5 M in ethyl ether, 2.80 mL, 4.20 mmol, 5.1 equiv). Additional ethyl ether (5.0 mL) was added and the reaction mixture was warmed to 0 °C for 30 min, cooled to –78 °C and treated with Me_2AlCl (1.0 M in hexanes, 4.20 mL, 4.20 mmol, 5.1 equiv) and a solution of the aldehyde (153.4 mg, 0.824 mmol, 1.0 equiv) in ethyl ether (1.0 mL + 1.0 mL rinse). After 1 h at –78 °C and then 30 min at 0 °C, the mixture was treated with 1.0 M aqueous sodium tartrate (10 mL) and brine (10 mL), stirred until the organic phase was clear (ca. 1 h) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (4% acetone, 1% triethylamine/hexanes) afforded **128a** (103.9 mg, 56%) and **128b** (53.5 mg, 29%) as clear, colorless syrups. **128a**: R_f 0.34 (10% acetone/hexanes, twofold developed); $[\alpha]_D$ +39.5 (*c* 1.11, $CHCl_3$, 22 °C); ^{1}H NMR δ 4.29 (dd, 1 H, *J* = 11.9, 2.4 Hz), 4.07 (dq, 1 H, *J* = 9.4, 2.1 Hz), 3.99 (dd, 1 H, *J* = 11.9, 2.8 Hz), 3.89 (ddd, 1 H, *J* = 11.7, 5.4, 1.8 Hz), 3.83 (d, 1 H, *J* = 8.8 Hz), 1.87 (d, 3 H, *J* = 2.2 Hz), 1.78 (app dq, 1 H, *J* = 12.4, 5.4 Hz), 1.52 (s, 3 H), 1.38 (s, 3 H), 1.32 (app dq, 1 H, *J* = 12.9, 2.3 Hz), 1.04 (s, 3 H), 0.88 (s, 3 H); ^{1}H NMR (C_6D_6) δ 4.32 (dq, 1 H, *J* = 8.2, 2.2 Hz), 4.13 (dd, 1 H, *J* = 11.9, 2.4 Hz), 3.62-3.52 (m, 2 H), 3.33 (d, 1 H, *J* = 8.2 Hz), 1.54 (d, 3 H, *J* = 2.2 Hz), 1.52-1.46 (m, 1 H), 1.33 (s, 6 H), 1.08 (s, 3 H), 0.82 (s, 3 H), 0.77 (ddd, 1 H, *J* = 12.7, 4.8, 2.5 Hz); ^{13}C NMR δ 98.8, 81.8, 78.9, 75.1, 72.2, 60.5, 40.6, 30.0, 25.5, 21.8, 19.3, 19.0, 3.8; IR (neat) 3458, 2991, 2969, 2938, 2876, 2224, 1468, 1427 cm^{-1}; MS (EI) *m/z* (rel. intensity) 211 ($[M\text{-}CH_3]^+$, 16), 187 ($[M\text{-}C_3H_3]^+$, 7), 161 (49), 115 (86), 69 (73), 59 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_3$ (M-CH_3) 211.1334, found

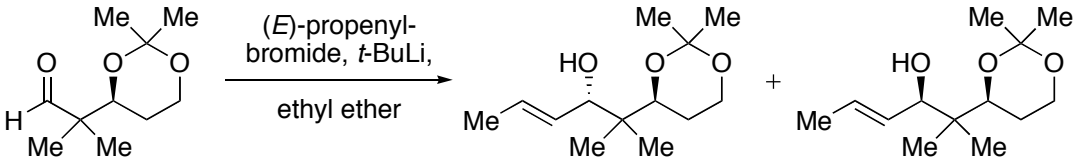
211.1330; **128b**: R_f 0.26 (10% acetone/hexanes, twofold developed); $[\alpha]_D$ +31.1 (*c* 1.36, $CHCl_3$, 22 °C); ^{1}H NMR δ 4.31 (s, 1 H), 3.96 (app dt, 1 H, *J* = 11.8, 2.8 Hz), 3.93-3.83 (m, 2 H), 3.19 (bs, 1 H), 1.86 (d, 3 H, *J* = 2.2 Hz), 1.82-1.72 (m, 1 H), 1.46 (s, 3 H), 1.41-1.34 (m, 1 H), 1.36 (s, 3 H), 1.02 (s, 3 H), 0.87 (s, 3 H); ^{1}H NMR (C_6D_6) δ 4.42 (d, 1 H, *J* = 2.0 Hz), 3.81 (dd, 1 H, *J* = 11.8, 2.5 Hz), 3.62 (td, 1 H, *J* = 5.8, 2.1 Hz), 3.59 (td, 1 H, *J* = 11.5, 2.8 Hz), 2.20 (bs, 1 H), 1.66-1.52 (m, 1 H), 1.51 (d, 3 H, *J* = 2.2 Hz), 1.40 (s, 3 H), 1.29 (s, 3 H), 1.18 (s, 3 H), 0.91 (s, 3 H), 0.95-0.88 (m, 1 H); ^{13}C NMR δ 98.7, 81.7, 78.5, 76.3, 71.1, 60.4, 41.4, 30.0, 25.8, 20.4, 19.4, 15.9, 3.8; IR (neat) 3441, 2969, 2935, 2877, 2243, 1468, 1381 cm^{-1}; MS (EI) *m/z* (rel. intensity) 211 ([M-CH_3]$^+$, 22), 197 (6), 171 (6), 151 (29), 129 (80), 115 (100), 83 (96), 59 (77); HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_3$ 211.1334, found 211.1340.



128a **129a**

2-[(4*S*)-2,2-Dimethyl-[1,3]dioxan-4-yl]-2-methyl-hex-4-en-3-ol (129a). A solution of **128a** (2.315 g, 10.23 mmol, 1.0 equiv) in THF (50 mL) was degassed (freeze-pump-thaw, 3 cycles), flushed with argon and slowly treated with Red-Al (65% w/w in toluene, 9.00 mL, 30.0 mmol, 2.9 equiv). After the evolution of gas ceased (ca. 15 min), the reaction mixture was heated to 70-75 °C (oil bath temperature) under argon for 25 h, cooled to 0 °C and treated with *i*-PrOH (5 mL). When the evolution of gas ceased, Na_2SO_4•10 H_2O (11.00 g) was added and the mixture was vigorously stirred at 0 °C for 1 h and filtered through a pad of Florisil/Celite (1:1 v/v). The pad was rinsed with ethyl

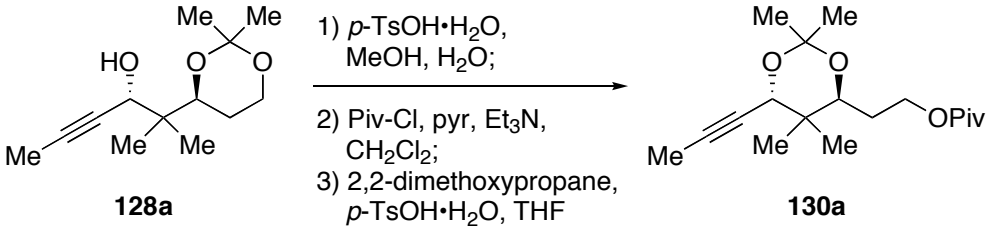
ether and the combined filtrates were concentrated to give a yellow oil. Purification by chromatography on SiO_2 (1% triethylamine/hexanes to 5% acetone, 1% triethylamine/hexanes) afforded **129a** (1.940 g, 83%) as a yellow syrup. A white crystalline solid resulted upon storage at –35 °C for >1 month: R_f 0.50 (10% acetone/hexanes, three-fold developed); Mp 34.9-36.9 °C (acetone, hexanes, triethylamine); $[\alpha]_D$ -0.26 (*c* 1.56, $CHCl_3$, 22 °C); ^{1}H NMR δ 5.67 (dq, 1 H, *J* = 15.0, 6.3 Hz), 5.51 (ddd, 1 H, *J* = 15.2, 6.8, 1.2 Hz), 3.94 (app dt, 1 H, *J* = 11.8, 2.7 Hz), 3.89-3.84 (m, 3 H), 3.71 (d, 1 H, *J* = 6.0 Hz), 1.80 (app dq, 1 H, *J* = 12.1, 5.6 Hz), 1.71 (d, 3 H, *J* = 6.3 Hz), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.31 (app dq, 1 H, *J* = 15.3, 2.1 Hz), 0.91 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR δ 130.5, 127.9, 98.7, 79.8, 76.2, 60.5, 39.9, 30.1, 25.4, 21.1, 20.7, 19.2, 18.1; IR (neat) 3485, 2987, 2967, 2938, 2875, 1671, 1470, 1412 cm^{-1}.



127 **129a** **129b**

(*S*,*E*)-2-((*S*)-2,2-Dimethyl-1,3-dioxan-4-yl)-2-methylhex-4-en-3-ol (129a) and (*R*,*E*)-2-((*S*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylhex-4-en-3-ol (129b). A solution of (*E*)-bromopropene (50.0 μL, 0.582 mmol, 2.5 equiv) in ethyl ether (0.5 mL) at – 78 °C was treated with a solution of *t*-BuLi (1.7 M in pentane, 0.685 mL, 1.165 mmol, 5.0 equiv), warmed to 0 °C for 10 min, cooled to –78 °C and treated with a solution of **127** (43.4 mg, 0.233 mmol, 1.0 equiv) in ethyl ether (0.5 mL + 0.5 mL rinse) via cannula. The mixture was stirred for 1 h at –78 °C, treated with saturated aqueous NH_4Cl (1.0 mL) and water (1.0 mL), warmed to rt, diluted with water (10 mL) and extracted with

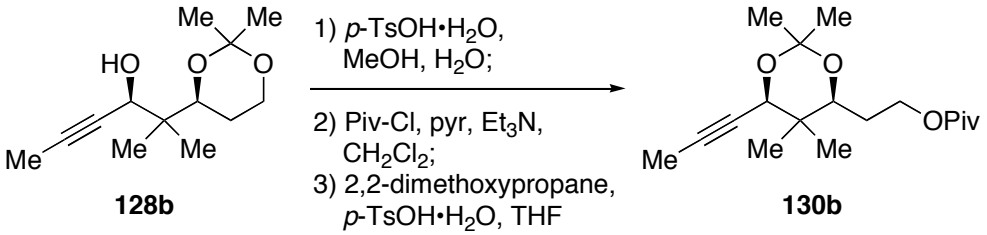
ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR indicated a diastereomeric ratio of 1.0:1.3 (**129a**/**129b**). Purification by chromatography on SiO_2 (4% acetone, 1% triethylamine/hexanes) afforded the diastereomeric mixture of **129a** and **129b** (43.5 mg, 82%) as a clear, colorless oil. The diastereomers can be separated by chromatography on SiO_2 using the same solvent system, however, this usually required several columns (2-3) and was therefore only performed on larger quantities of material. **129b:** R_f 0.42 (10% acetone/hexanes, three-fold developed); $[\alpha]_D$ +41.7 (*c* 1.46, $CHCl_3$, 22 °C); ^{1}H NMR δ 5.61 (q of AB, 1 H, *J* = 15.2, 6.3 Hz), 5.47 (dd of AB, 1 H, *J* = 15.2, 7.6, 1.4 Hz), 3.91 (d, 1 H, *J* = 8.3 Hz), 3.98-3.78 (m, 3 H), 3.39 (s, 1 H),1.72 (app dq, 1 H, *J* = 12.6, 5.6 Hz), 1.68 (d, 3 H, *J* = 6.3 Hz), 1.44 (s, 3 H), 1.35 (s, 3 H), 1.37-1.31 (m, 1 H), 0.90 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR δ 130.4, 128.7, 98.6, 80.8, 77.2, 60.4, 40.4, 30.0, 25.6, 20.7, 19.5, 18.0, 15.2; IR (neat) 3465, 2990, 2965, 2937, 2876, 1672 cm^{-1}.



128a **130a**

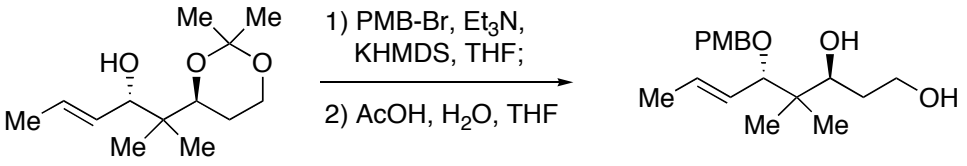
2,2-Dimethylpropionic acid 2-[(4*S*,6*S*)-(2,2,5,5-tetramethyl-6-prop-1-ynyl[1,3]dioxan-4-yl)]ethyl ester (130a). A solution of **128a** (39.0 mg, 172 µmol, 1.0 equiv) was treated at rt with water (50 µL) and *p*-TsOH•H_2O (10.0 mg, 53.0 µmol, 0.3 equiv). After 12 h at rt, triethylamine (0.1 mL) was added and the mixture was concentrated. Purification of the residue by chromatography on SiO_2 (3% to 5% MeOH/CH_2Cl_2) afforded a white solid [R_f 0.34 (5% MeOH/CH_2Cl_2)] that was dissolved in

CH_2Cl_2 (1.0 mL) and treated with triethylamine (100 μL), pyridine (10 μL) and pivaloyl chloride (75 μL). After 12 h at rt, the reaction mixture was poured into 1.0 M aqueous citric acid and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was dried azeotropically with toluene, diluted with THF (1.0 mL) and treated with *p*-TsOH•H_2O (10 mg) and 2,2-dimethoxypropane (1.0 mL). After 4 h at rt, triethylamine (0.1 mL) was added and the mixture was concentrated onto Florisil/Celite (1:1, v/v) and purified by chromatography on SiO_2 (5% ethyl ether/hexanes) to afford **130a** (34.2 mg, 64%, 3 steps) as a clear, colorless syrup: R_f 0.30 (10% ethyl ether/hexanes); $[\alpha]_D$ –35.0 (*c* 1.59, $CHCl_3$, 22 °C); ^{1}H NMR δ 4.22-4.15 (m, 1 H), 4.17 (dd, 1 H, *J* = 4.5, 2.2 Hz), 4.07 (app dt, 1 H, *J* = 9.8, 5.0 Hz), 3.67 (dd, 1 H, *J* = 10.9, 1.9 Hz), 1.85 (d, 3 H, *J* = 2.3 Hz), 1.82-1.69 (m, 1 H), 1.65-1.51 (m, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.18 (s, 9 H), 0.92 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 178.6, 101.4, 83.7, 76.0, 71.4, 70.1, 61.3, 38.9, 38.8, 28.6, 27.4, 26.0, 23.7, 21.6, 19.5, 3.9; IR (neat) 2969, 2937, 2873, 2240, 1730, 1481, 1464 cm^{-1}; MS (EI) *m/z* (rel. intensity) 295 ([M-CH_3]$^+$, 24), 184 (7), 159 (14), 151 (12), 133 (19), 94 (42), 82 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{27}O_4$ (M-CH_3) 295.1909, found 295.1901.



2,2-Dimethylpropionic acid 2-[(4*S*,6*R*)-(2,2,5,5-tetramethyl-6-prop-1-ynyl[1,3]dioxan-4-yl)]ethyl ester (130b). Using the same procedure as for **130a**, **128b** (50.0 mg, 221 μmol) afforded **130b** (31.0 mg, 45%) as a clear, colorless syrup: R_f 0.23

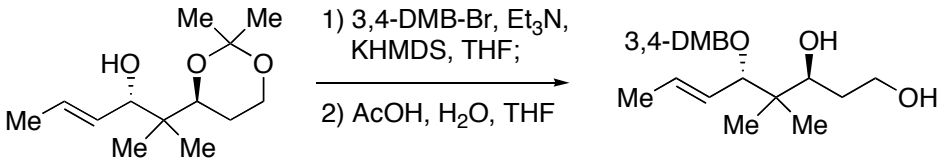
(10% ethyl ether/hexanes); $[\alpha]_D$ –26.1 (*c* 1.53, $CHCl_3$, 22 °C); ^1H NMR δ 4.32 (d, 1 H, *J* = 2.1 Hz), 4.18-4.03 (m, 2 H), 3.58 (dd, 1 H, *J* = 10.4, 1.5 Hz), 1.86 (d, 3 H, *J* = 2.1 Hz), 1.84-1.75 (m, 1 H), 1.64-1.54 (m, 1 H), 1.41 (s, 6 H), 1.18 (s, 9 H), 1.03 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR δ 178.6, 99.4, 82.4, 75.7, 74.0, 71.4, 61.4, 38.9, 36.6, 30.1, 29.0, 27.4, 21.3, 19.1, 13.9, 3.9; IR (neat) 2971, 2937, 2874, 2239, 1729, 1481, 1465 cm^{-1}; MS (EI) *m/z* (rel. intensity) 295 ($[M-CH_3]^+$, 96), 271 (6), 201 (14), 187 (39), 159 (72), 151 (50), 133 (100), 73 (128); HRMS (EI) *m/z* calcd for $C_{17}H_{27}O_4$ (M-CH_3) 295.1909, found 295.1907.



129a **131a**

(3*S*,5*S*)-5-(4-Methoxybenzyloxy)-4,4-dimethyl-oct-6-ene-1,3-diol (131a). To a solution of freshly distilled *p*-methoxybenzylbromide[184] (5.20 mL, 31.0 mmol, 3.6 equiv) in THF (40 mL) at rt was added triethylamine (7.20 mL, 51.3 mmol, 6.0 equiv) under N_2. The mixture became turbid and **129a** (1.94 g, 8.50 mmol, 1.0 equiv) in THF (5 mL + 5 mL rinse) was added via cannula. The mixture was cooled to –78 °C and KHMDS was added as a solid in one portion, followed by THF (10 mL). The reaction mixture was stirred at –78 °C for 1 h, then at rt for 2 h, treated with saturated aqueous NH_4Cl (20 mL) and H_2O (20 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give a yellow oil that was diluted with a mixture of glacial acetic acid (26 mL), THF (7 mL) and water (7 mL), heated at 60 °C for 12 h, poured into water (40 mL) and extracted with ethyl acetate. The combined organic layers were washed with 2.0 N NaOH until the

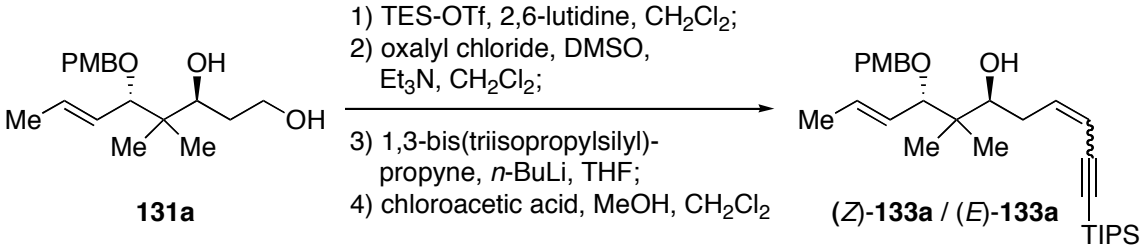
washings had a pH > 9, extracted with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% to 80% ethyl acetate/hexanes) afforded **131a** (2.20 g, 84%) as a pale yellow syrup: R_f 0.24 (60% ethyl acetate/hexanes); $[\alpha]_D$ +22.9 (*c* 1.33, $CHCl_3$, 22 °C); ^1H NMR δ 7.21 (dt, 2 H, *J* = 8.7, 2.4 Hz), 6.87 (dt, 2 H, *J* = 8.7, 2.4 Hz), 5.68 (dq, 1 H, *J* = 15.4, 6.4 Hz), 5.48 (ddq, 1 H, *J* = 15.4, 8.5, 1.5 Hz), 4.51 (d, 1 H, *J* = 11.2 Hz), 4.19 (d, 1 H, *J* = 11.2 Hz), 3.88-3.77 (m, 2 H), 3.80 (s, 3 H), 3.75 (dd, 1 H, *J* = 9.2, 3.8 Hz), 3.62 (d, 1 H, *J* = 8.5 Hz), 3.53 (bs, 2 H), 1.80 (dd, 3 H, *J* = 6.3, 1.4 Hz), 1.68-1.53 (m, 2 H), 0.88 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR δ 159.5, 131.9, 130.0, 129.8, 127.5, 114.1, 88.1, 79.0, 70.1, 63.0, 55.5, 40.8, 33.0, 21.9, 21.3, 18.1; IR (neat) 3423, 2964, 2934, 2876, 1612, 1586, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{28}O_4Na$ (M+Na) 331.1885, found 331.1884.



129a **131b**

(3*S*,5*S*,6*E*)-5-(3,4-Dimethoxybenzyloxy)-4,4-dimethyloct-6-ene-1,3-diol (131b). A solution of 3,4-dimethoxybenzyl bromide (1.310g, 5.669 mmol, 3.0 equiv) in THF (10.0 mL) at rt under N_2 was treated with triethylamine (1.60 mL, 11.4 mmol, 6.1 equiv). After 2 min, a white precipitate formed and **129a** (429.6 mg, 1.881 mmol, 1.0 equiv) in THF (2.5 mL + 2.5 mL rinse) was added via cannula. The mixture was cooled to –78 °C and treated with a solution of KHMDS (1.20 g, 5.72 mmol, 3.0 equiv) in THF (5.0 mL). The white precipitate dissolved and the mixture became bright yellow in color. After stirring for 10 min at –78 °C, the mixture was warmed to 0 °C for 10 min

and the yellow color dissipated and a white precipitate formed. The resulting turbid mixture was stirred at rt for 30 min, treated with saturated aqueous NH_4Cl (10 mL), poured into water (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to a yellow syrup that was diluted with a mixture of THF (4.0 mL), glacial acetic acid (4.0 mL) and water (4.0 mL), stirred at rt for 18 h, diluted with ethyl acetate (100 mL) and washed with 2.0 aqueous N NaOH until the washings were pH>9. The aqueous washings were backwashed with ethyl acetate (3x) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (70% ethyl acetate/hexanes to 100% ethyl acetate) afforded **131b** (632.4 mg, 99%) as a clear, pale yellow syrup: R_f 0.24 (80% ethyl acetate/hexanes); $[\alpha]_D$ +28.2 (*c* 1.24, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.81-6.80 (m, 3 H), 5.65 (dq, 1 H, *J* = 15.2, 6.3 Hz), 5.47 (ddd, 1 H, *J* = 15.3, 8.6, 1.4 Hz), 4.50, 4.18 (AB, 2 H, *J* = 11.4 Hz), 4.20-4.16 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.86-3.72 (m, 3 H), 3.61 (d, 1 H, *J* = 8.6 Hz), 3.34 (bs, 1 H), 1.78 (dd, 3 H, *J* = 6.3, 1.3 Hz), 1.67-1.52 (m, 2 H), 0.86 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR δ 149.3, 148.9, 131.9, 130.5, 127.5, 120.8, 111.6, 111.3, 87.9, 78.7, 70.3, 62.8, 56.1, 56.0, 40.8, 33.1, 21.7, 21.2, 18.0; IR (neat) 3448, 2963, 2939, 2876, 1667, 1607, 1593, 1517 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{30}O_5Na$ (M+Na) 361.1991, found 361.1988.



(3*Z*,6*S*,8*S*,9*E*)-8-(4-Methoxybenzyloxy)-7,7-dimethyl-1-(triisopropylsilyl)-undeca-3,9-dien-1-yn-6-ol [(*Z*)-133a] and (3*E*,6*S*,8*S*,9*E*)-8-(4-methoxybenzyloxy)-7,7-dimethyl-1-(triisopropyl-silyl)-undeca-3,9-dien-1-yn-6-ol [(*E*)-133a]. A solution of **131a** (149.4 mg, 484.0 μmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and treated with 2,6-lutidine (330 μL, 2.83 mmol, 5.9 equiv) and triethylsilyl triflate (320 μL, 1.42 mmol, 2.9 equiv). The reaction mixture was stirred at 0 °C for 30 min, treated with saturated aqueous $NaHCO_3$, poured into water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (1% triethylamine/hexanes) afforded a clear, colorless oil (343.8 mg) that was used without further purification: R_f 0.27 (2.5% ethyl ether/hexanes). Characteristic signals: ^{1}H NMR δ 7.23 (d, 2 H, *J* = 8.7 Hz), 6.85 (app dt, 2 H, *J* = 8.7, 2.5 Hz), 5.61 (dq, 1 H, *J* = 15.3, 6.3 Hz), 5.39 (ddq, 1 H, *J* = 15.3, 8.7, 1.5 Hz), 4.48 (d, 1 H, *J* = 11.5 Hz), 4.16 (d, 1 H, *J* = 11.5 Hz), 3.80 (s, 3 H), 3.70 (dt, 1 H, *J* = 9.4, 5.0 Hz), 3.63 (d, 1 H, *J* = 8.7 Hz), 3.60-3.52 (m, 1 H), 1.75 (dd, 3 H, *J* = 6.3, 1.5 Hz), 0.85 (s, 3 H), 0.79 (s, 3 H).

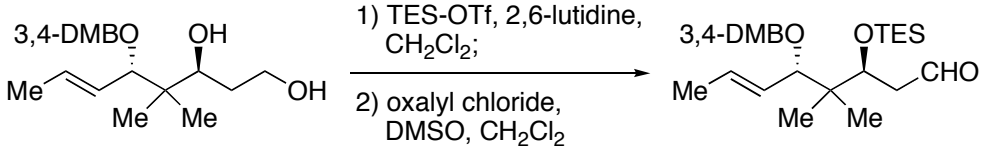
A solution of oxalyl chloride (225 μL, 2.58 mmol, 4.0 equiv) in CH_2Cl_2 (4.0 mL) was cooled to –78 °C and treated with a solution of dimethylsulfoxide (362 μL, 5.10 mmol, 8.0 equiv) in CH_2Cl_2 (1.0 mL). After 15 min, a solution of the bis(triethylsilyl)ether (343.0 mg, 639.0 μmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL + 1.5 mL rinse) was added via

cannula. The reaction mixture was stirred at –78 °C for 20 min and at -40 °C for 20 min, then cooled to –78 °C and treated with triethylamine (1.34 mL, 9.55 mmol, 14.9 equiv). After 15 min, the solution was warmed to rt, poured into water (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (5% ethyl ether/hexanes) afforded **132a** (152.0 mg, 75% for 2 steps) as a clear colorless oil that was used without further purification. Characteristic signals: ^{1}H NMR δ 9.77 (dd, 1 H, *J* = 2.9, 1.5 Hz), 7.22 (d, 2 H, *J* = 8.5 Hz), 6.86 (d, 2 H, *J* = 8.6 Hz), 5.61 (dq, 1 H, *J* = 15.4, 6.4 Hz), 5.44 (ddd, 1 H, *J* = 15.3, 8.9, 1.5 Hz), 4.48 (d, 1 H, *J* = 11.4 Hz), 4.35 (dd, 1 H, *J* = 6.5, 4.4 Hz), 4.12 (d, 1 H, *J* = 11.4 Hz), 3.80 (s, 3 H), 3.60 (d, 1 H, *J* = 8.9 Hz), 2.64 (dd of AB, 1 H, *J* = 16.7, 4.4, 1.5 Hz), 2.48 (dd of AB, 1 H, *J* = 16.7, 6.5, 2.9 Hz), 1.76 (dd, 3 H, *J* = 6.3, 1.4 Hz), 0.93 (t, 9 H, *J* = 7.8 Hz), 0.85 (s, 3 H), 0.80 (s, 3 H), 0.58 (q, 6 H, *J* = 7.8 Hz).

1,3-Bis(triisopropylsilyl)propyne (255.0 mg, 723.0 μmol, 2.0 equiv) was azeotropically dried with hexanes (2 x 1 mL) at reduced pressure, diluted with THF (1.0 mL) and cooled to 0 °C under N_2. A solution of *n*-BuLi (1.5 M in hexanes, 480 μL, 720 μmol, 2.0 equiv) was added and the mixture was stirred for 1 h, affording a pale yellow solution that was cooled to –78 °C and treated via cannula with a solution of **132a** (152.0 mg, 361.0 μmol, 1.0 equiv) in THF (1.0 + 1.0 mL rinse). After 30 min at –78 °C, saturated aqueous NH_4Cl solution (3.0 mL) was added and the reaction mixture was warmed to rt, poured into water (5.0 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil. Polar impurities were removed by chromatography on SiO_2 (2%

ethyl ether/hexanes), affording a pale yellow oil [R_f 0.30 (2.5% ethyl ether/hexanes)] that was diluted with MeOH (7.5 mL) and CH_2Cl_2 (2.5 mL), treated with chloroacetic acid (100.0 mg, 106.0 μmol, 2.9 equiv), stirred for 14 h at rt and concentrated. The residue was purified by chromatography on SiO_2 (10% ethyl ether/hexanes) to afford (*Z*)-**133a** (96.8 mg, 55%) and (*E*)-**133a** (13.0 mg, 7%). (*Z*)-**133a**: R_f 0.16 (10% ethyl ether/hexanes); $[\alpha]_D$ –28.2 (*c* 1.12, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.20, 6.85 (app t of AB, 4 H, *J* = 8.7, 2.8 Hz), 6.20 (ddd, 1 H, *J* = 10.9, 8.1, 6.0 Hz), 5.67 (dq, 1 H, *J* = 15.3, 6.3 Hz), 5.59 (app dt, 1 H, *J* = 10.9, 1.5 Hz), 5.48 (ddq, 1 H, *J* = 15.3, 8.5, 1.5 Hz), 4.51, 4.18 (AB, 2 H, *J* =11.3 Hz), 3.80 (s, 3 H), 3.62 (d, 1 H, *J* = 8.7 Hz), 3.63-3.55 (m, 1 H), 2.64 (dddd, 1 H, *J* = 14.6, 8.1, 2.6, 1.4 Hz), 2.25 (dddd, 1 H, *J* = 14.6, 10.2, 6.0, 1.6 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.4 Hz), 1.64-1.05 (m, 21 H), 0.90 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 159.4, 143.5, 131.7, 130.3, 129.6, 127.7, 114.0, 110.4, 104.2, 95.1, 88.2, 77.0, 70.1, 55.5, 41.1, 33.3, 22.0, 20.9, 18.9, 18.1, 11.5; IR (neat) 3492, 2942, 2865, 2145, 1668, 1613, 1586 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{48}O_3SiNa$ (M+Na) 507.3270, found 507.3270; (*E*)-**133a**: R_f 0.29 (10% ethyl ether/hexanes); $[\alpha]_D$ –14.7 (*c* 0.95, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.20 (d, 2 H, *J* = 8.5 Hz), 6.86 (d, 2 H, *J* = 8.5 Hz), 6.33 (app dt, 1 H, *J* = 15.8, 7.2 Hz), 5.67 (dq, 1 H, *J* = 15.3, 6.4 Hz), 5.56 (d, 1 H, *J* = 15.9 Hz), 5.47 (ddd, 1 H, *J* = 15.4, 8.5, 1.4 Hz), 4.51 (d, 1 H, *J* = 11.3 Hz), 4.17 (d, 1 H, *J* = 11.3 Hz), 3.80 (bs, 3 H), 3.79 (s, 1 H), 3.59 (d, 1 H, *J* = 8.5 Hz), 3.58-3.53 (m, 1 H), 2.21 (dd, 1 H, *J* = 14.4, 7.4 Hz), 2.04 (dddd, 1 H, *J* = 14.3, 10.0, 7.0, 1.2 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.2 Hz), 1.08-1.06 (m, 21 H), 0.86 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR δ 159.4, 144.1, 131.8, 130.2, 129.8, 127.6, 114.0, 111.5, 106.1, 89.0, 87.7, 76.9, 70.0, 55.5, 41.0, 35.9, 22.0, 21.0,

18.8, 18.1, 11.5; IR (neat) 3490, 2960, 2942, 2891, 2865, 2171, 2131, 1613, 1586, 1514, 1464 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{48}O_3SiNa$ (M+Na) 507.3270, found 507.3294.

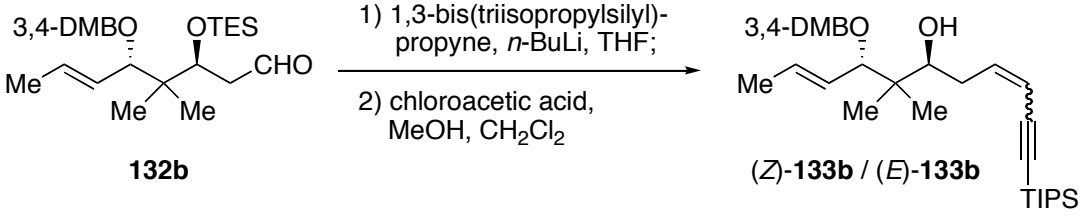


131b **132b**

(3*S*,5*S*,6*E*)-5-(3,4-Dimethoxybenzyloxy)-4,4-dimethyl-3-(triethylsilyloxy)oct-6-enal (132b). A solution of **131b** (632.4 mg, 1.869 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) was cooled under N_2 to 0 °C and treated with 2,6-lutidine (1.40 mL, 12.0 mmol, 6.4 equiv) and triethylsilyltriflate (1.35 mL, 5.97 mmol, 3.2 equiv). The mixture was stirred at 0 °C for 45 min and quenched with saturated aqueous NH_4Cl (20 mL) and water (10 mL), stirred for 30 min at rt and then extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid (50 mL) and brine, dried (Na_2SO_4), filtered and concentrated to a turbid, pale yellow oil which was diluted with ethyl ether and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with ethyl ether and the combined filtrate was concentrated to a clear, pale yellow oil that was used without further purification.

A solution of oxalyl chloride (650 µL, 7.45 mmol, 4.0 equiv) in CH_2Cl_2 (20.0 mL) was cooled under N_2 to –78 °C and treated with a solution of DMSO (1.10 mL, 15.5 mmol, 8.3 equiv) in CH_2Cl_2 (1.0 mL + 1.0 mL rinse). The mixture was aged at –78 °C for 15 min and then treated with a solution of the crude bis(triethysilyl)ether in CH_2Cl_2 (5.0 mL + 5.0 mL rinse). The mixture was stirred for 25 min at –78 °C, 20 min at –40 °C , 15 min at –78 °C, treated with triethylamine (4.00 mL, 28.5 mmol, 15.2 mmol), stirred for

10 min at –78 °C, warmed to rt over 25 min and then treated with water (20 mL). The mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 20% ethyl ether/hexanes) afforded **132b** (720.3 mg, 86%) as a clear, colorless oil: R_f 0.41 (40% ethyl ether/hexanes); $[\alpha]_D$ +0.101 (*c* 1.49, $CHCl_3$, 22 °C); ^1H NMR (C_6D_6) δ 9.54 (app t, 1 H, *J* = 1.0 Hz), 6.94-6.92 (m, 2 H), 6.64 (d, 1 H, *J* = 7.8 Hz), 5.58-5.40 (m, 2 H), 4.60 (d, 1 H, *J* = 11.4 Hz), 4.52 (dd, 1 H, *J* = 6.4, 4.2 Hz), 4.22 (d, 1 H, *J* = 11.4 Hz), 3.69 (d, 1 H, *J* = 8.0 Hz), 3.54 (s, 3 H), 3.41 (s, 3 H), 2.44 (dd of AB, 1 H, *J* = 17.1, 4.2, 1.0 Hz), 2.34 (dd of AB, 1 H, *J* = 17.1, 6.5, 2.3 Hz), 1.58 (d, 3 H, *J* = 5.1 Hz), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.95 (t, 9 H, *J* = 6.4 Hz), 0.68-0.60 (m, 6 H); ^{13}C NMR (C_6D_6) δ 200.6, 150.8, 150.1, 132.7, 131.2, 129.7, 120.5, 112.9 (2 C), 85.0, 72.1, 70.5, 56.2 (2 C), 49.2, 43.4, 20.8, 19.4, 18.1, 7.6, 6.2; IR (neat) 2955, 2912, 2876, 2834, 2723, 1725, 1609, 1593, 1517, 1465 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{42}O_5SiNa$ (M+Na) 473.2699, found 473.2666.

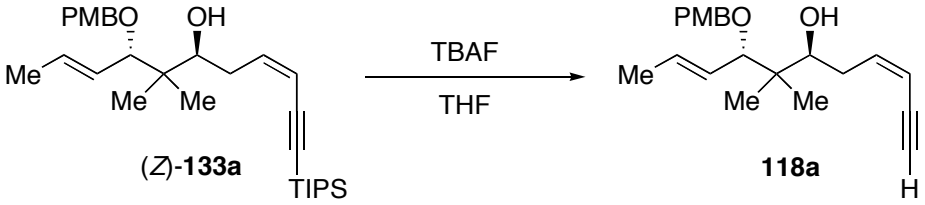


132b (*Z*)-**133b** / (*E*)-**133b**

(3*Z*,6*S*,8*S*,9*E*)-8-(3,4-Dimethoxybenzyloxy)-7,7-dimethyl-1-(triisopropylsilyl)-undeca-3,9-dien-1-yn-6-ol [(*Z*)-133b] and (3*E*,6*S*,8*S*,9*E*)-8-(3,4-dimethoxybenzyl-oxy)-7,7-dimethyl-1-(triisopropyl-silyl)-undeca-3,9-dien-1-yn-6-ol [(*E*)-133b]. A solution of 1,3-bis(triisopropylsilyl)propyne (1.130 g, 3.203 mmol, 2.0 equiv) was azeotropically dried with hexanes at reduced pressure, diluted with THF (10.0 mL),

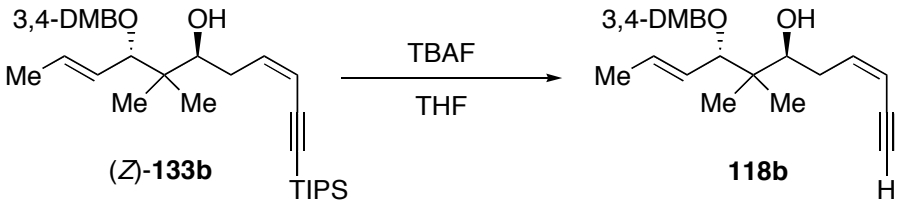
cooled to 0 °C under N_2 and treated with a solution of *n*-BuLi (1.5 M in hexanes, 2.15 mL, 3.23 mmol, 2.0 equiv). The mixture was warmed to rt and stirred for 1.5 h, cooled to –78 °C and treated via cannula with a solution of **132b** (720.0 mg, 1.600 mmol, 1.0 equiv) in THF (1.0 mL + 1.0 mL rinse). The mixture was stirred for 3 h at –78 °C and treated with saturated aqueous NH_4Cl (10 mL), warmed to rt, diluted with H_2O (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated, diluted with CH_2Cl_2 (5.0 mL) and MeOH (15.0 mL) and treated with chloroacetic acid (200.0 mg, 2.116 mmol, 1.3 equiv). The mixture was stirred at rt for 20 h, treated with additional chloroacetic acid (200.0 mg, 2.116 mmol, 1.3 equiv), stirred for an additional 28 h (48 h total), concentrated, diluted with ethyl ether (20 mL) and washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (20% to 40% ethyl ether/hexanes) afforded (*E*)-**133b** (84.6 mg, 10%) and (*Z*)-**133b** (467.6 mg, 57%): (*Z*)-**133b**: R_f 0.26 (40% ethyl ether/hexanes); $[\alpha]_D$ –17.8 (*c* 1.14, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.83 (m, 3 H), 6.19 (ddd, 1 H, *J* = 10.8, 7.9, 6.6 Hz), 5.66 (dq, 1 H, *J* = 15.2, 6.3 Hz), 5.59 (d, 1 H, *J* = 10.9 Hz), 5.48 (dd, 1 H, *J* = 15.3, 8.5 Hz), 4.51 (d, 1 H, *J* = 11.4 Hz), 4.19 (d, 1 H, *J* = 11.4 Hz), 3.87 (s, 3 H), 3.87 (s, 3 H), 3.73 (d, 1 H, *J* = 4.2 Hz), 3.63 (d, 1 H, *J* = 8.6 Hz), 3.64-3.59 (m, 1 H), 2.65 (dd, 1 H, *J* = 13.6, 7.1 Hz), 2.28 (ddd, 1 H, *J* = 15.6, 10.2, 6.1 Hz), 1.79 (d, 3 H, *J* = 6.3 Hz), 1.11-1.07 (m, 21 H), 0.90 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 149.2, 148.8, 143.5, 131.7, 130.7, 127.7, 120.6, 111.4, 111.1, 110.4, 104.2, 95.2, 88.1, 77.0, 70.3, 56.1, 56.0, 41.1, 33.3, 21.9, 20.9, 18.9, 18.1, 11.5; IR (neat) 3493, 2942, 2865, 2144, 1898, 1611, 1593, 1516 cm^{-1}; HRMS (ESI) *m/z* calcd for

$C_{31}H_{50}O_4SiNa$ (M+Na) 537.3376, found 537.3398. (*E*)-**133b**: R_f 0.47 (40% ethyl ether/hexanes); $[\alpha]_D$ -15.1 (*c* 1.64, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.82-6.81 (m, 3 H), 6.33 (app dt, 1 H, *J* = 15.9, 7.0 Hz), 5.67 (dq, 1 H, *J* = 15.3, 6.4 Hz), 5.57 (d, 1 H, *J* = 15.9 Hz), 5.47 (dd, 1 H, *J* = 15.3, 8.6 Hz), 4.51 (d, 1 H, *J* = 11.5 Hz), 4.18 (d, 1 H, *J* = 11.5 Hz), 3.87 (s, 6 H), 3.72 (d, 1 H, *J* = 4.4 Hz), 3.60 (d, 1 H, *J* = 8.5 Hz), 3.65-3.55 (m, 1 H), 2.23 (dd, 1 H, *J* = 14.2, 7.3 Hz), 2.12-2.02 (m, 1 H), 1.79 (d, 3 H, *J* = 6.3 Hz), 1.06-1.04 (m, 21 H), 0.86 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 149.2, 148.9, 144.0, 131.8, 130.6, 127.6, 120.7, 111.6, 111.5, 111.1, 106.1, 89.0, 87.6, 76.9, 70.2, 56.1, 56.0, 41.0, 35.9, 21.9, 21.0, 18.8, 18.1, 11.5; IR (neat) 3491, 2942, 2865, 2170, 2130, 1593, 1516, 1464, 1418 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{50}O_4SiNa$ (M+Na) 537.3376, found 537.3394.



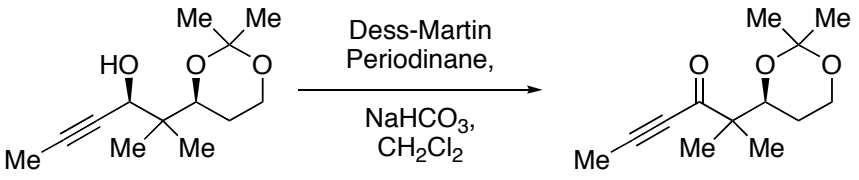
(6*S*,8*S*)-8-(4-Methoxybenzyloxy)-7,7-dimethylundeca-3,9-dien-1-yn-6-ol (118a). A solution of (*Z*)-**133a** (99.7 mg, 206 μmol, 1.0 equiv) in THF (2.0 mL) was cooled to 0 °C and a solution of TBAF (1.0 M in THF, 250 μL, 250 μmol, 1.2 equiv) was added. The reaction mixture was allowed to warm to rt and stirred for 14 h. Saturated aqueous $NaHCO_3$ solution (5.0 mL) was added and the mixture was poured into water and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% ethyl ether/hexanes) afforded **118a** (63.9 mg, 94%) as a clear, colorless syrup: R_f 0.26 (20% ethyl ether/hexanes); $[\alpha]_D$ –9.05 (*c* 1.48, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.21 (app dt, 2 H, *J* =

8.7, 2.8 Hz), 6.86 (app dt , 2 H, *J* = 8.7, 2.8 Hz), 6.24 (app dtd, 1 H, *J* = 10.9, 7.2, 0.7 Hz), 5.69 (dq, 1 H, *J* = 15.3, 6.3 Hz), 5.55-5.44 (m, 2 H), 4.51(d, 1 H, *J* = 11.2 Hz), 4.19 (d, 1 H, *J* = 11.2 Hz), 3.79 (app s, 4 H), 3.65 (d, 1 H, *J* = 8.5 Hz), 3.58 (ddd, 1 H, *J* = 10.0, 4.7, 2.5 Hz), 3.07 (d, 1 H, *J* = 1.6 Hz), 2.55 (bdd, 1 H, *J* = 14.4, 7.7 Hz), 2.28 (dddd, 1 H, *J* = 14.5, 10.1, 6.7, 1.2 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.5 Hz), 0.90 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 159.4, 144.6, 131.7, 130.2, 129.7, 127.6, 114.0, 109.0, 87.9, 81.6, 80.9, 77.3, 70.0, 55.4, 41.0, 33.2, 21.9, 21.2, 18.1; IR (neat) 3482, 3290, 3031, 2965, 2937, 2913, 2874, 2837, 2095, 1613, 1586, 1514 cm^{-1}; MS (EI) *m/z* (rel. intensity) 328 (M^+, 0.3), 258 (1.3), 163 (1.4), 121 (100), 96 (26); HRMS (EI) *m/z* calcd for $C_{21}H_{28}O_3$ 328.2038, found 328.2040.



(3*Z*,6*S*,8*S*,9*E*)-8-(3,4-Dimethoxybenzyloxy)-7,7-dimethylundeca-3,9-dien-1-yn-6-ol (118b). A solution of (*Z*)-**133b** (275.6 mg, 535.3 μmol, 1.0 equiv) in THF (2.0 mL) was treated with a solution of TBAF (1.0 M in THF, 700 μL, 700 μmol, 1.3 equiv) and stirred at rt for 8 h. Saturated aqueous $NaHCO_3$ solution (5.0 mL) was added and the mixture was poured into water (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (20% to 40% ethyl ether/hexanes) afforded **118b** (162.7 mg, 85%) as a clear, colorless syrup: R_f 0.31 (20% acetone/hexanes); $[\alpha]_D$ –1.81 (*c* 0.83, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.84-6.81 (m, 3 H), 6.24 (ddd, 1 H, *J* = 10.8, 7.5, 6.9 Hz),

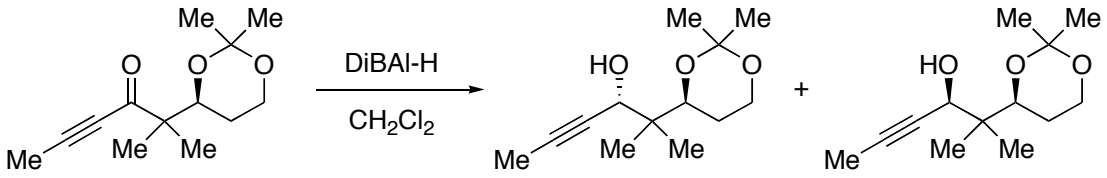
5.68 (dq, 1 H, *J* = 15.3, 6.4 Hz), 5.55-5.44 (m, 2 H), 4.51 (d, 1 H, *J* = 11.4 Hz), 4.20 (d, 1 H, *J* = 11.4 Hz), 3.87 (s, 6 H), 3.77 (d, 1 H, *J* = 5.0 Hz), 3.66 (d, 1 H, *J* = 8.6 Hz), 3.61-3.55 (m, 1 H), 3.07 (d, 1 H, *J* = 2.2 Hz), 2.56 (dd, 1 H, *J* = 14.4, 7.7 Hz), 2.30 (ddd, 1 H, *J* = 15.4, 9.3, 6.9 Hz), 1.80 (dd, 3 H, *J* = 6.3, 1.1 Hz), 0.90 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR δ 149.2, 148.8, 144.6, 131.8, 130.6, 127.6, 120.7, 111.5, 111.1, 109.1, 87.8, 81.7, 80.9, 77.4, 70.2, 56.1, 56.0, 41.1, 33.3, 21.8, 21.3, 18.1; IR (neat) 3482, 3286, 2964, 2937, 2905, 2875, 2833, 2094, 1667, 1608, 1593, 1516 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}O_4Na$ (M+Na) 381.2042, found 381.2055.



128b **134**

(*S*)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-methylhex-4-yn-3-one (134). A solution of **128b** (106.0 mg, 0.468 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) was treated at rt with $NaHCO_3$ (150.0, 1.786 mmol, 3.8 equiv) and Dess-Martin periodinane (485.0 mg, 1.143 mmol, 2.4 equiv) and stirred at rt for 1 h. Analysis by TLC indicated that the reaction was sluggish, so water (1.0 μL, 55 μmol, 0.12 equiv) was added. After 1.5 h, saturated aqueous $NaHCO_3$ (4.5 mL) and saturated aqueous $Na_2S_2O_3$ (4.5 mL) were carefully added. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (4% acetone, 1% triethylamine/hexanes) afforded **134** (95.0 mg, 90%) as a white, crystalline solid: R_f 0.41 (30% acetone/hexanes); Mp 71.6-73.6 °C (hexanes/acetone/triethylamine); $[\alpha]_D$ +31.9 (*c* 1.13, $CHCl_3$, 22 °C); ^{1}H NMR δ 4.29 (dd,

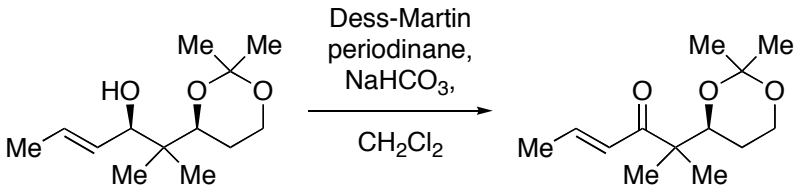
1 H, *J* = 11.7, 2.4 Hz), 3.97 (dt, 1 H, *J* = 11.8, 2.8 Hz), 3.84 (ddd, 1 H, *J* = 11.6, 5.3, 1.6 Hz), 2.01 (s, 3 H), 1.63 (app dq, 1 H, *J* = 5.4, 12.2 Hz), 1.41 (s, 3 H), 1.34 (dd, 1 H, *J* = 4.5, 2.1 Hz), 1.29 (s, 3 H), 1.12 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR δ 192.6, 98.7, 90.9, 78.7, 72.9, 60.1, 51.6, 29.8, 25.4, 20.4, 19.1, 18.1, 4.2; IR (KBr) 3328, 2979, 2948, 2884, 2289, 2217, 1670 cm^{-1}; MS (EI) *m/z* (rel. intensity) 224 (M^+, 1.0), 209 ($[M-CH_3]^+$, 100), 166 (16), 149 (69), 115 (31); HRMS (EI) *m/z* calcd for $C_{12}H_{17}O_3$ (M-CH_3) 209.1178, found 209.1181.



134 **128a** **128b**

(3*S*)-2-{(4*S*)-2,2-Dimethyl-[1,3]-dioxan-4-yl}-2-methylhex-4-yn-3-ol (128a) and **(3*R*)-2-{(4*S*)-2,2-dimethyl-[1,3]-dioxan-4-yl}-2-methylhex-4-yn-3-ol (128b)**. A solution of **134** (1.102 g, 4.915 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) was cooled to –78 °C under N_2, treated with a solution DiBAl-H (1.0 M in hexanes, 5.50 mL, 5.50 mmol, 1.1 equiv) over 5 min, stirred for 45 min at –78 °C, treated with acetone (1.0 mL), stirred for 15 min, treated with 1.0 M aqueous sodium tartrate (10 mL), warmed to rt and vigorously stirred until the layers separated (ca. 2 h). The mixture was extracted with ethyl ether and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to a clear, pale yellow syrup. ^{1}H NMR (benzene-d6) analysis indicated a ratio **128a**/**128b** = 2.9/1.0. Purification by chromatography on SiO_2 (4% acetone, 1% triethylamine/hexanes to 20% acetone, 1% triethylamine/hexanes) afforded **128a**

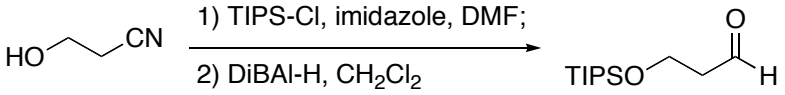
(827.8 mg, 74%) and **128b** (242.9 mg, 22%) and a mixture of diastereomers **128a**/**128b** = 1.0/1.0 (34.0 mg, 3%).



129b **135**

(*S*,*E*)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-methylhex-4-en-3-one (135). A solution of **129b** (27.8 mg, 0.122 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C and treated with $NaHCO_3$ (51.0 mg, 0.607 mmol, 5.0 equiv) and Dess-Martin periodinane (85.0 mg, 0.200 mmol, 1.6 equiv), warmed to rt and stirred for 1 h and treated with saturated aqueous $NaHCO_3$ (2.0 mL) and saturated aqueous $Na_2S_2O_3$ (2.0 mL). The mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL), stirred until both phases were clear (ca. 1 h) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (4% acetone, 1% triethylamine/hexanes) afforded **135** (23.3 mg, 84%) as a clear, colorless oil that crystallized to a white solid on standing: R_f 0.34 (10% acetone/hexanes); Mp 52.2-54.0 °C (CH_2Cl_2); $[\alpha]_D$ -1.76 (*c* 1.70, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.83 (dq, 1 H, *J* = 15.1, 6.9 Hz), 6.51 (dq, 1 H, *J* = 15.1, 1.5 Hz), 4.01 (dd, 1 H, *J* = 11.7, 2.5 Hz), 3.90 (td, 1 H, *J* = 11.9, 2.8 Hz), 3.79 (ddd, 1 H, *J* = 11.7, 5.4, 1.9 Hz), 1.83 (dd, 3 H, *J* = 6.9, 1.6 Hz), 1.56 (app dq, 1 H, *J* = 12.0, 5.5 Hz), 1.37 (s, 3 H), 1.30-1.28 (m, 1 H), 1.28 (s, 3 H), 1.08 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR δ 203.0, 142.1, 127.3, 98.5, 73.4, 60.1, 49.7, 29.8, 25.7, 20.3, 19.8, 19.1, 18.4; IR (KBr) 2999, 2991, 2982, 2970, 2942, 2916, 2901, 2877, 2723, 1690, 1625 cm^{-1}; MS (EI) *m/z* (rel. intensity) 211 ([M-15]$^+$,

1.8), 168 ([M-CO$(CH_3)_2$]$^+$, 3.0), 151 (1.4), 115 (4.2), 59 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_3$ (M-CH_3) 211.1334, found 211.1309.

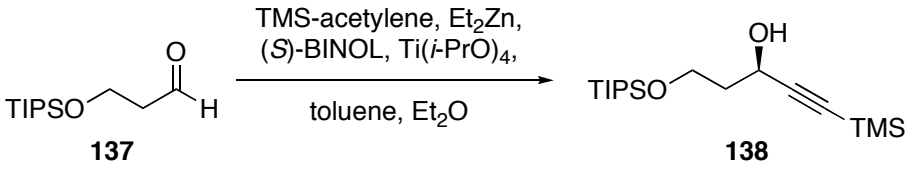


136 **137**

3-(Triisopropylsilyloxy)propionaldehyde (137).[164] A mixture of **136** (2.00 mL, 29.3 mmol, 1.0 equiv) and imidazole (4.00 mL, 58.7 mmol, 2.0 equiv) in DMF (3.0 mL) was treated at rt with TIPS-Cl (6.90 mL, 32.2 mmol, 1.1 equiv). After a brief exothermic period, the mixture was stirred at rt for 16 h, quenched with saturated aqueous NH_4Cl solution, diluted with water and extracted with ethyl ether. The combined organic layers were washed with 4.0 M aqueous LiCl, dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation (88 °C/0.1 mm Hg) afforded 3-triisopropylsilyloxypropionitrile (6.77 g, quant) as a clear colorless oil that was used without further purification: R_f 0.57 (20% acetone/hexanes, twofold developed).

A solution of 3-triisopropylsilyloxypropionitrile (7.21 g, 31.7 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was cooled to -10 °C under N_2. The flask was partially evacuated and flushed with N_2 (2 cycles), DiBAl-H (1.0 M in hexanes, 45.0 mL, 45.0 mmol, 1.4 equiv) was added and the reaction mixture was stirred at -10 °C for 50 min and then added via cannula to a mixture of 1.0 M aqueous L-tartaric acid (100 mL) and brine (100 mL). The solution was vigorously stirred until both phases were clear and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give an orange-colored oil that was poured onto a pad of SiO_2 (wetted with ethyl ether). The pad was washed with ethyl ether (250 mL)

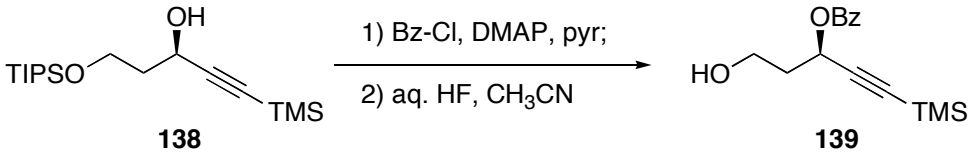
and the combined filtrates were concentrated to a yellow oil. Bulb to bulb distillation (75 °C/0.1 mm Hg) afforded **137** as a clear colorless oil (4.83 g, 66%) that was used without further purification. For analytical purposes, a sample was purified by chromatography on SiO_2 (5% ethyl acetate/hexanes) to afford **137** as a clear, colorless oil: R_f 0.69 (20% acetone/hexanes, twofold developed); ^{1}H NMR δ 9.80 (t, 1 H, *J* = 2.1 Hz), 4.05 (t, 2 H, *J* = 6.0 Hz), 2.58 (dt, 2 H, *J* = 6.0, 2.1 Hz), 1.15-0.99 (m, 21 H); ^{13}C NMR δ 202.1, 58.1, 46.9, 18.1, 12.1; IR (neat) 2944, 2892, 2867, 2726, 1730, 1464, 1389, 1111 cm^{-1}; MS (EI) *m/z* (rel. intensity) 187 ([M-C_3H_7]$^+$, 41), 157 (41), 145 (100), 129 (59), 117 (60), 101 (58), 87 (46); HRMS (EI) *m/z* calcd for $C_9H_{19}O_2Si$ (M-C_3H_7) 187.1154, found 187.1158.



137 **138**

(3*R*)-5-(Triisopropylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-ol (138).[185] A solution of trimethylsilylacetylene (245 μL, 1.73 mmol, 4.0 equiv) and diethylzinc (175 μL, 1.71 mmol, 4.0 equiv) in toluene (2.0 mL) was heated at reflux under N_2 for 1 h. A voluminous precipitate formed, and the reaction mixture was cooled to rt and slowly treated with (*S*)-BINOL (62.0 mg, 220 μmol, 0.5 equiv). After addition of ethyl ether (8.0 mL) and Ti(*i*-OPr)$_4$ (130 μL, 440 μmol, 1.0 equiv), the mixture turned red-orange and was stirred at rt for 1 h before addition of **137** (100.0 mg, 434 μmol, 1.0 equiv). After 20 h at rt, 1.0 M aqueous L-tartaric acid (3 mL) and brine (3 mL) were added and the reaction mixture was vigorously stirred for 1 h and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and

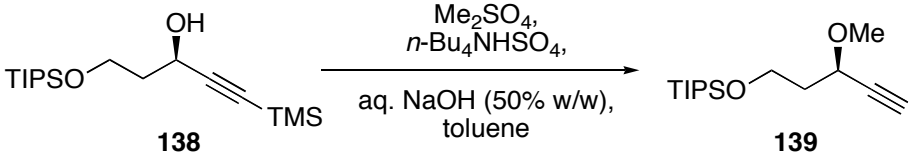
concentrated. Purification by chromatography on SiO_2 (5% to 20% ethyl ether/hexanes) afforded **138** (93.8 mg, 66%) as a clear, colorless oil: R_f 0.18 (5% ethyl ether/hexanes); $[\alpha]_D$ +21.0 (*c* 1.42, $CHCl_3$, 22 °C); 4.63 (dd, 1 H, *J* = 10.0, 5.7 Hz), 4.16 (ddd, 1 H, *J* = 10.0, 8.2, 3.7 Hz), 3.91 (ddd, 1 H, *J* = 10.0, 5.8, 4.2 Hz), 3.66 (d, 1 H, *J* = 5.9 Hz), 2.02 (app ddt, 1 H, *J* = 14.2, 8.2, 4.2 Hz), 1.85 (app dtd, 1 H, *J* = 14.2, 6.1, 3.7 Hz), 1.14-1.03 (m, 21 H), 0.16 (s, 9 H); ^{13}C NMR δ 106.4, 89.4, 62.8, 61.9, 38.5, 18.1, 11.9, 0.1; IR (neat) 3418, 2958, 2944, 2894, 2867, 2172, 1464 cm^{-1}; MS (EI) *m/z* (rel. intensity) 285 ($[M-C_3H_7]^+$, 12), 177 (14), 145 (18), 131 (51), 119 (100), 103 (32), 75 (35); HRMS (EI) *m/z* calcd for $C_{14}H_{29}O_2Si_2$ (M-C_3H_7) 285.1706, found 285.1701.



138 **139**

(3*R*)-3-Benzoyloxy-5-trimethylsilylpent-4-yn-1-ol (139). A solution of **138** (32.0 mg, 97 μmol, 1.0 equiv) in pyridine (1.0 mL) was treated with 4-dimethylaminopyridine (1.0 mg, 8.0 μmol, 0.1 equiv) and benzoyl chloride (50.0 μL, 430 μmol, 4.4 equiv) and stirred at rt for 4 h, treated with saturated aqueous $NaHCO_3$ solution and stirred for an additional 30 min at rt. The mixture was extracted with ethyl ether and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (0% to 2.5% ethyl ether/hexanes) afforded (3*R*)-3-benzoyloxy-1-triisopropylsilyloxy-5-trimethylsilylpent-4-yne (41.8 mg, 100%) as a clear, colorless oil. A portion of this oil (25.0 mg, 58.0 μmol, 1.0 equiv) was dissolved in CH_3CN (2.0 mL), treated with 48% aqueous HF (0.1 mL), stirred for 12 h at rt, poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl ether. The combined

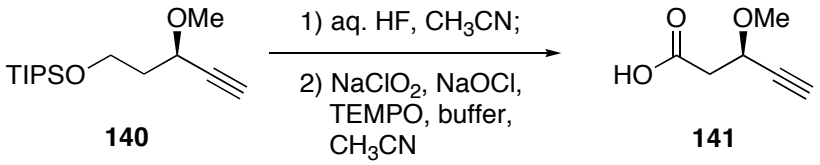
organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 40% ethyl ether/hexanes) afforded **139** (14.9 mg, 93%) as a clear colorless oil: R_f 0.35 (40% ethyl ether/hexanes); $[\alpha]_D$ +22.5 (*c* 0.89, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.09-8.06 (m, 2 H), 7.61-7.56 (m, 1 H), 7.48-7.44 (m, 2 H), 5.85 (t, 1 H, *J* = 6.5 Hz), 3.90-3.74 (m, 2 H), 2.16 (app dt, 2 H, *J* = 6.1, 6.1 Hz), 2.00 (bs, 1 H), 0.18 (s, 9 H); ^{13}C NMR δ 165.9, 133.5, 130.1, 130.0, 128.6, 102.4, 91.7, 62.6, 58.9, 38.3, 0.0; IR (neat) 3434, 3064, 2960, 2929, 2898, 2179, 1725, 1602, 1585, 1452 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_3SiNa$ (M+Na) 299.1079, found 299.1066. The enantiomeric excess was determined to be 92% by analytical HPLC (Chiralcel-OD, 0.46 cm x 25 cm, 4% isopropanol/hexanes, 1 mL/min, UV detection at 254 nm, R_t (major) = 7.85 min, R_t (minor) = 11.08 min.



138 **139**

(3*S*)-1-Triisopropylsilyloxy-3-methoxypent-4-yne (139). A solution of **138** (4.764 g, 14.50 mmol, 1.0 equiv) in toluene (15 mL) was cooled to 0 °C and treated with 50% (w/w) aqueous NaOH (15 mL), *n*-Bu_4NHSO_4 (1.710 g, 5.040 mmol, 0.35 equiv) and dimethylsulfate (6.90 mL, 72.9 mmol, 5.0 equiv). The reaction mixture was vigorously stirred for 1 h at 0 °C, then for an additional 2.5 h at rt, cooled to 0 °C and treated with methanol (3.0 mL, 74 mmol, 5 equiv), stirred for 15 min and warmed to rt. The resulting gel was dissolved with water (30 mL) and ethyl ether (10 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (0% to 5% ethyl

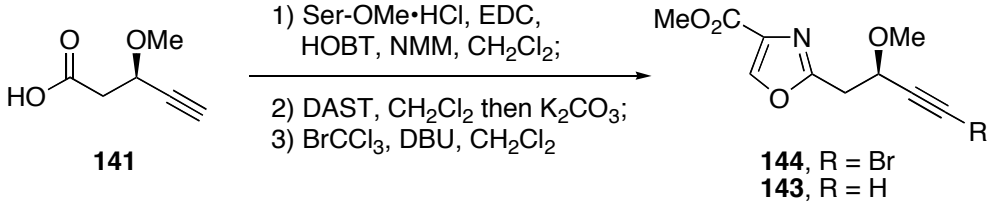
ether/hexanes) afforded **139** (3.730 g, 95%) as a clear, colorless oil: R_f 0.23 (2.5% ethyl ether/hexanes); ^{1}H NMR δ 4.19 (ddd, 1 H, *J* = 7.8, 7.8, 1.9 Hz), 3.91-3.77 (m, 2 H), 3.42 (s, 3 H), 2.43 (d, 1 H, *J* = 2.0 Hz), 2.03-1.84 (m, 2 H), 1.12-1.01 (m, 21 H); ^{13}C NMR δ 83.0, 73.9, 68.0, 59.3, 56.8, 39.1, 18.2, 12.2; IR (neat) 3311, 2943, 2892, 2867, 2823, 2108, 1464, 1111 cm^{-1}; MS (EI) *m/z* (rel. intensity) 227 ([M-C_3H_7]$^+$, 7), 175 (7), 145 (84), 133 (100), 117 (28), 75 (38); HRMS (EI) *m/z* calcd for $C_{12}H_{23}O_2Si$ (M-C_3H_7) 227.1467, found 227.1465.



140 **141**

(3*R*)-3-Methoxypent-4-ynoic acid (141).[168] A solution of **140** in acetonitrile (20 mL) in a polypropylene reaction vessel was treated at 0 °C with 48% aqueous HF (2.00 mL, 55.2 mmol, 4.1 equiv) and stirred at rt for 24 h. The reaction mixture was cooled to 0 °C and treated with a solution of NaOH (2.00 g, 50.0 mmol, 3.7 equiv) in water (5 mL), warmed to rt, poured into 1.3 M phosphate buffer (pH 6.7, 50 mL) and diluted with acetonitrile (30 mL). TEMPO (2.00 g, 1.28 mmol, 0.1 equiv), $NaClO_2$ (3.00 g, 33.3 mmol, 2.5 equiv) and NaOCl solution (0.5 mL) were added. The mixture turned dark purple and was heated to 45 °C (oil bath temperature). After 4 h, additional $NaClO_2$ (3.00 g, 33.3 mmol, 2.5 equiv) was added. After a total of 18 h, methanol (10 mL) was added and the color changed to yellow. The mixture was poured into 2.0 N HCl (100 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil that was treated with 2.0 N aqueous NaOH solution (20 mL) and water (20 mL). The resulting mixture was washed

with ethyl ether (2 x 35 mL), acidified with 2.0 N aqueous $NaHSO_4$ (40 mL) and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford **141** as a pale yellow oil (1.701 g, 99%) that was used without further purification: R_f 0.50 (60% ethyl acetate/hexanes); $[\alpha]_D$ +64.1 (*c* 1.25, $CHCl_3$, 22 °C); ^{1}H NMR δ 9.84 (bs, 1 H), 4.39 (ddd, 1 H, *J* = 7.8, 5.3, 2.0 Hz), 3.42 (s, 3 H), 2.79 (d of AB, 1 H, *J* = 16.1, 8.1 Hz), 2.76 (d of AB, 1 H, *J* = 16.0, 5.3 Hz), 2.50 (d, 1 H, *J* = 2.0 Hz); ^{13}C NMR δ 175.9, 80.8, 74.9, 67.0, 57.0, 40.9; IR (neat) 3452, 3290, 2997, 2830, 2622, 2117, 1717, 1404 cm^{-1}; MS (EI) *m/z* (rel. intensity) 128 (M^+, 0.4), 127 ($[M-H]^+$, 3.7), 113 ($[M-CH_3]^+$, 8), 98 (7), 82 (7), 70 (26), 69 (100); HRMS (EI) *m/z* calcd for $C_6H_7O_3$ (M-H) 127.0395, found 127.0395.



141

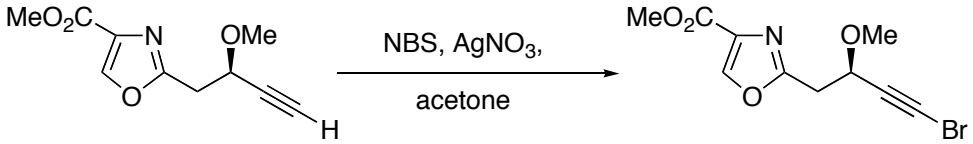
144, R = Br
143, R = H

2-[(2*R*)-4-Bromo-2-methoxybut-3-ynyl]oxazole-4-carboxylic acid methyl ester (144) and 2-[(2*R*)-2-methoxybut-3-ynyl]oxazole-4-carboxylic acid methyl ester (143). A mixture of **141** (384.0 mg, 2.997 mmol, 1.0 equiv), serine methyl ester hydrochloride (700.0 mg, 4.499 mmol, 1.5 equiv) and 1-hydroxybenzotriazole (400.0 mg, 2.960 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (7.5 mL), cooled to 0 °C and treated with EDC (640.0 mg, 3.339 mmol, 1.1 equiv) and *N*-methylmorpholine (830.0 µL, 7.5 mmol, 2.5 equiv). The reaction mixture was stirred at rt for 16 h and then treated with saturated aqueous $NaHCO_3$ (10 mL), stirred for 1 h, diluted with water (10 mL), and extracted with ethyl acetate. The combined organic layers were washed with

1.0 M aqueous citric acid (10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (80 to 100% ethyl acetate/hexanes) afforded **142** (379.5 mg, 55%) as a clear, colorless syrup that was used without further purification: R_f 0.39 (ethyl acetate).

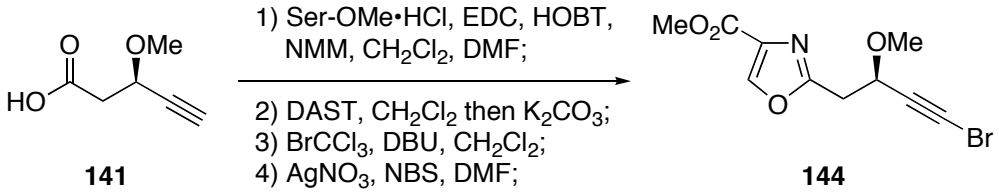
A solution of **142** (379.5 mg, 1.655 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was cooled to –78 °C and treated with diethylaminosulfurtrifluoride (DAST) (250.0 µL, 1.9 mmol, 1.1 equiv), stirred at –78 °C for 1 h and then treated with anhydrous K_2CO_3 (580.0 mg, 4.20 mmol, 2.5 equiv). After 20 min, the reaction mixture was warmed to 0 °C, stirred for 20 min, carefully quenched by addition of $NaHCO_3$ solution (10 mL) and stirred for 1 h while warming to rt. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to give an orange-colored oil that was azeotropically dried at reduced pressure with toluene (3 mL) and diluted with CH_2Cl_2 (10 mL). The solution was cooled to 0 °C and treated with $BrCCl_3$ (340.0 µL, 3.5 mmol, 2.1 equiv) and DBU (450.0 µL, 3.0 mmol, 1.8 equiv), stirred for 20 h at +4 °C and then diluted with ethyl ether (10 mL). The mixture was poured onto a pad of SiO_2 (40 mm x 40 mm, prewetted with ethyl ether) and the pad was washed with ethyl ether (200 mL). The combined filtrates were concentrated and purified by chromatography on SiO_2 (4% to 10% ethyl acetate/CH_2Cl_2) to afford **144** (176.1 mg, 37%) as a white solid and **143** (106.3 mg, 31%) as a clear, colorless oil. **144**: R_f 0.63 (2.5% ethyl acetate/CH_2Cl_2, twofold developed); Mp 80.4-81.4 °C (CH_2Cl_2); $[\alpha]_D$ +21.3 (*c* 1.25, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.17 (s, 1 H), 4.50 (dd, 1 H, *J* = 7.5, 6.1 Hz), 3.90 (s, 3 H), 3.39 (s, 3 H), 3.23 (d of AB, 1 H, *J* = 15.0, 7.8 Hz), 3.21 (d of

AB, 1 H, *J* = 15.0, 6.0 Hz); ^{13}C NMR δ 161.8, 161.7, 144.4, 133.7, 77.3, 69.5, 57.0, 52.4, 47.8, 35.0; IR (neat) 3169, 3119, 2998, 2954, 2885, 2834, 2198, 1724, 1586 cm^{-1}; MS (EI) *m/z* (rel. intensity) 288 (M^+, 10), 272 ($[M-CH_3]^+$, 16), 258 (8), 208 ($[M-Br]^+$, 8), 203 (16), 178 ($[M-Br-OCH_3]^+$, 10), 147 ($[M-C_6H_6O_3N]^+$, 100); HRMS (EI) *m/z* calcd for $C_{10}H_{10}O_4NBr$ 286.9793, found 286.9788; **143**: R_f 0.49 (2.5% ethyl acetate/CH_2Cl_2, twofold developed); $[\alpha]_D$ +23.3 (*c* 1.15, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.16 (s, 1 H), 4.47 (ddd, 1 H, *J* = 8.0, 6.1, 2.0 Hz), 3.89 (s, 3 H), 3.39 (s, 3 H), 3.24 (d of AB, 1 H, *J* = 15.0, 7.7 Hz), 3.21 (d of AB, 1 H, *J* = 15.0, 6.1 Hz), 2.48 (d, 1 H, *J* = 2.0 Hz); ^{13}C NMR δ 161.8, 144.3, 133.6, 80.6, 75.4, 68.5, 56.8, 52.3, 35.0; IR (neat) 3265, 3161, 3121, 2996, 2952, 2850, 2828, 2114, 1743, 1586 cm^{-1}; MS (EI) *m/z* (rel. intensity) 210 ($[M+H]^+$, 11), 194 ($[M-CH_3]^+$, 6), 178 ($[M-OCH_3]^+$, 14), 151 (88), 149 (100); HRMS (EI) *m/z* calcd for $C_9H_8NO_4$ ($M-CH_3$) 194.0453, found 194.0450.



143 **144**

2-[(2*R*)-4-Bromo-2-methoxybut-3-ynyl]oxazole-4-carboxylic acid methyl ester (17). A solution of **143** (25.0 mg, 120 μmol, 1.0 equiv) in acetone (1.0 mL) was treated at rt with $AgNO_3$ (2.0 mg, 12 μmol, 0.1 equiv) and *N*-bromosuccinimide (23.5 mg, 132 μmol, 1.1 equiv). After 1 h, hexanes (3.0 mL) were added, and the mixture was filtered through a plug of Florisil/Celite (1:1, v/v). The plug was rinsed with ethyl ether (3.0 mL) and the combined filtrates were concentrated. Purification by chromatography on SiO_2 (20% to 30% ethyl acetate/hexanes) afforded **144** (18.5 mg, 54%) as a clear, colorless glass that crystallized to a white solid under vaccum.



141 **144**

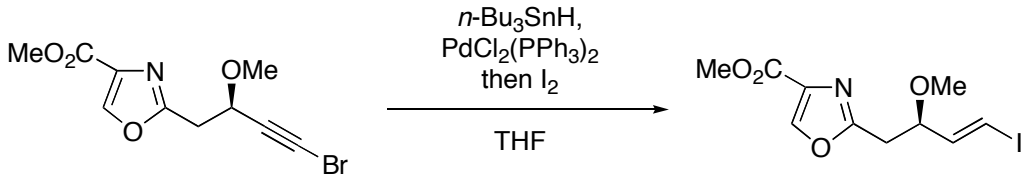
Improved sequence for the synthesis of 144: A suspension of **141** (700.0 mg, 5.464 mmol, 1.0 equiv), serine methyl ester hydrochloride (1.300g, 8.356 mmol, 1.5 equiv) and HOBT (100.0 mg, 0.740 mmol, 0.14 equiv) in CH_2Cl_2 (5.0 mL) and DMF (1.0 mL) was treated with EDC (1.600g, 8.346 mmol, 1.5 equiv) cooled to 0 °C and treated with *N*-methylmorpholine (1.510 mL, 13.69 mmol, 2.5 equiv) and stirred at 0 °C for 30 min, warmed to rt and stirred for 20 h. The mixture was diluted with ethyl acetate (10 mL) and poured into 1.0 M aqueous citric acid (25 mL) and separated. The organic layer was washed with 4.0 M aqueous LiCl (10 mL) and the LiCl wash was added to the aqueous portion. The resulting aqueous mixture was extracted with ethyl acetate (10 x 50 mL) until TLC analysis indicated that no more product remained in the aqueous. All of the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (50% acetone/hexanes to 100% acetone) afforded **142** (2.049 g) as a pale yellow syrup that was contaminated with DMF (^{1}H NMR) and was used without further purification.

The hydroxyamide **142** was suspended in hot CH_2Cl_2 (40 mL), cooled to –78 °C under N_2, treated with DAST (1.550 mL, 11.73 mmol, 2.1 equiv), stirred for 20 min at –78 °C, treated with anhydrous K_2CO_3 (3.00 g, 21.7 mmol, 4.0 equiv), stirred for 20 min at –78 °C, quenched with saturated aqueous $NaHCO_3$ (10 mL) and water (20 mL), warmed to rt, stirred for 45 min and extracted with CH_2Cl_2. The combined organic

were dried (Na_2SO_4), filtered and concentrated to a dark red oil. Purification by chromatography on SiO_2 (30% to 50% acetone/hexanes) afforded the oxazoline (885.8 mg, 77%, 2 steps) as a red-brown oil that was used without further purification. R_f 0.33 (40% acetone/hexanes).

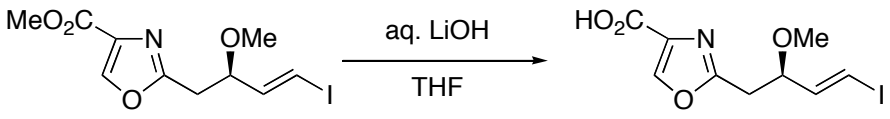
The oxazoline (885.8 mg, 4.191 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with $BrCCl_3$ (1.30 mL, 13.2 mmol, 3.1 equiv) and DBU (1.30 mL, 8.69, 2.1 equiv) and allowed to slowly warm to rt. After 8 h, the mixture was diluted with hexanes (10 mL) and poured onto a pad of SiO_2. The pad was washed with 50% acetone/hexanes and the combined filtrate was concentrated to a red oil. Purification by chromatography on SiO_2 (20% to 40% acetone/hexanes) afforded the mixture of **143** and **144** as a pale yellow oil (839.5 mg) that crystallized on standing and was used without further purification.

A solution of the oxazoles **143** and **144** (839.5 mg, 4.013 mmol, 1.0 equiv) in DMF (10 mL) at 0 °C was treated with *N*-bromosuccinimide (785.0 mg, 4.410 mmol, 1.1 equiv) and $AgNO_3$ (68.0 mg, 0.40 mmol, 0.1 equiv), warmed to rt, stirred for 2 h and diluted with ethyl acetate (50 mL). The mixture was washed with water and brine, dried (Na_2SO_4), filtered and concentrated to a yellow, crystalline solid. Purification by chromatography on SiO_2 (20% to 40% acetone/hexanes) afforded **144** (846.9 mg, 70%, 2 steps) as a white, crystalline solid.



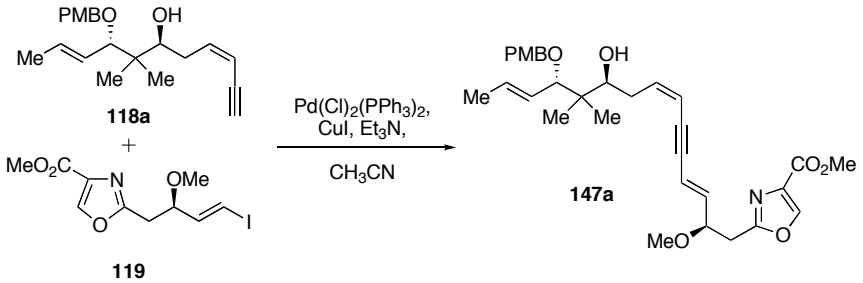
144 **119**

2-[(2*R*)-4-Iodo-2-methoxybut-3-enyl]oxazole-4-carboxylic acid methyl ester (119). A solution of **144** (241.4 mg, 838.0 μmol, 1.0 equiv) and $PdCl_2(PPh_3)_3$ (5.0 mg, 7.0 μmol, 0.01 equiv) in THF (3.0 mL) was cooled under N_2 to –78 °C. The flask was evacuated, flushed with N_2 and *n*-Bu_3SnH (450 μL, 1670 μmol, 2.0 equiv) was added in one portion. The reaction mixture was stirred at –78 °C for 105 min then at 0 °C for 105 min, and treated with a solution of I_2 (250 mg, 985 μmol, 1.2 equiv) over 30 min, such that a dark brown color persisted. The mixture was quenched with saturated aqueous $NaHCO_3$ (3.0 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) solutions. Ethyl acetate (10 mL) was added and the mixture was stirred for 30 min at rt and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% ethyl acetate/hexanes) afforded **119** (259.0 mg, 92%) as a clear, colorless syrup: R_f 0.40 (20% ethyl acetate/hexanes); $[\alpha]_D$ –0.74 (*c* 10.8, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.15 (s, 1 H), 6.44 (dd, 1 H, *J* = 14.5, 5.8 Hz), 6.43 (d, 1 H, *J* = 14.4 Hz), 4.13-4.06 (m, 1 H), 3.90 (s, 3 H), 3.26 (s, 3 H), 3.07 (dd, 1 H, *J* = 15.0, 7.5 Hz), 2.99 (dd, 1 H, *J* = 15.0, 5.8 Hz); ^{13}C NMR δ 162.3, 161.7, 144.6, 144.3, 144.2, 133.6, 81.3, 80.2, 57.1, 52.3, 34.1; IR (neat) 3159, 2989, 2950, 2826, 1743, 1585, 1437 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NO_4INa$ (M+Na) 359.9709, found 359.9702.



119 **145**

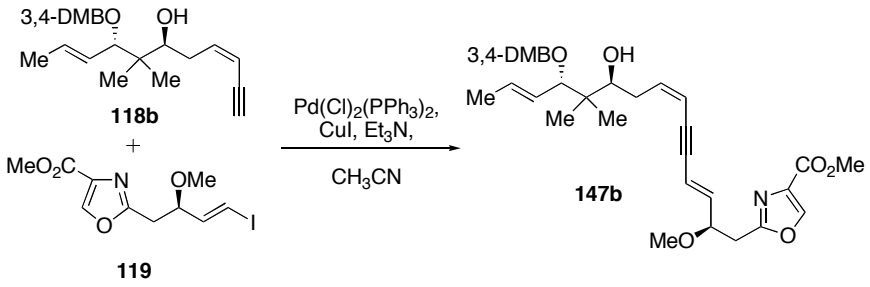
2-[(2*R*)-4-Iodo-2-methoxybut-3-enyl]oxazole-4-carboxylic acid (145). To a solution of **119** (166.0 mg, 492.0 µmol, 1.0 equiv) in THF (5.0 mL) was added at rt 1.0 M LiOH (1.10 mL, 1.10 mmol, 2.2 equiv). After stirring for 12 h at rt, the mixture was poured in water (20 mL) and washed with ethyl acetate (10 mL), and the organic washing was discarded. The aqueous layer was acidified with 2.0 M $NaHSO_4$ and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford **145** (154.4 mg, 97%) as a beige, crystalline solid that was used without further purification: Mp 117.0-119.0 °C (ethyl acetate); $[\alpha]_D$ +5.9 (*c* 1.36, MeOH, 22 °C); ^{1}H NMR (acetone-d6) δ 8.46 (s, 1 H), 6.64 (d, 1 H, *J* = 14.6 Hz), 6.60 (dd, 1 H, *J* = 14.6, 6.8 Hz), 4.17 (app q, 1 H, *J* = 6.8 Hz), 3.25 (s, 3 H), 3.12-3.03 (m, 2 H); ^{13}C NMR (acetone-d6) δ 163.0, 162.2, 146.0, 145.6, 134.4, 81.7, 80.7, 56.9, 34.3; IR (neat) 3142, 3040, 2988, 2927, 2822, 2578, 1678, 1597 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_9H_{10}NO_4INa$ (M+Na) 345.9552, found 345.9555.



2-{(2*R*,10*S*,12*S*)-[10-Hydroxy-2-methoxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl]}-oxazole-4-carboxylic acid methyl ester (147a). A mixture of **119** (11.3 mg, 34.0 µmol, 1.0 equiv) and **118a** (12.0 mg, 37.0

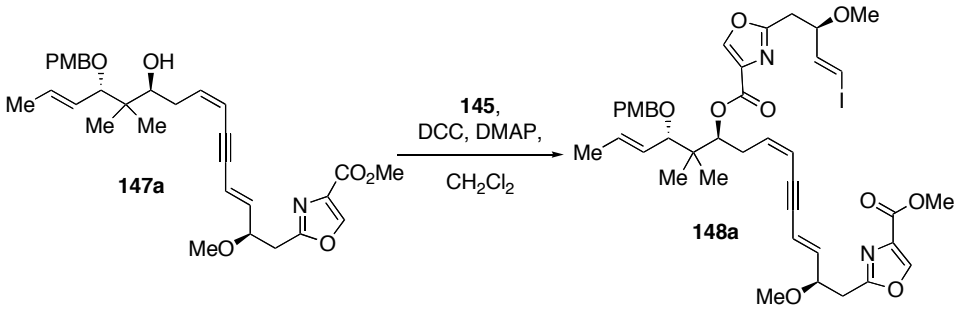
μmol, 1.1 equiv) was azeotropically dried at reduced pressure with toluene (1.0 mL) and then hexanes (1.0 mL), and dissolved in CH_3CN (0.5 mL). The solution was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (1.0 mg, 1.0 μmol, 0.04 equiv) and CuI (2.0 mg, 11 μmol, 0.3 equiv were added and the mixture was degassed by freeze-pump-thaw (1 cycle), placed in a –20 °C bath under N_2, and treated with triethylamine (30 μL, 21 μmol, 6 equiv). The yellow mixture became almost colorless before turning to a dark red-brown color. After 15 min, the cold bath was removed and the reaction mixture was stirred at rt for 60 min, quenched with 0.05 M phosphate buffer (pH 7, 3.0 mL), poured into water (5.0 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (20% to 40% ethyl acetate/hexanes) afforded **147a** (16.8 mg, 94%) as a pale yellow syrup: R_f 0.31 (40% ethyl acetate/hexanes), $[\alpha]_D$ –25.2 (*c* 0.99, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.14 (s, 1 H), 7.21 (d, 2 H, *J* = 8.6 Hz), 6.85 (d, 2 H, *J* = 8.6 Hz), 6.17 (dt, 1 H, *J* = 10.8, 7.2 Hz), 5.92 (dd, 1 H, *J* = 15.9, 7.0 Hz), 5.84 (dd, 1 H, *J* = 15.9, 2.0 Hz), 5.67 (dd, 1 H, *J* = 15.4, 6.3 Hz), 5.64 (dd, 1 H, *J* = 10.6, 1.8 Hz), 5.48 (ddd, 1 H, *J* = 15.3, 8.5, 1.5 Hz), 4.50 (d, 1 H, *J* = 11.2 Hz), 4.18 (d, 1 H, *J* = 11.2 Hz), 4.16 (ddd, 1 H, *J* = 13.1, 7.4, 5.8 Hz), 3.90 (s, 3 H), 3.79 (app s, 4 H), 3.64 (d, 1 H, *J* = 8.5 Hz), 3.61-3.54 (m, 1 H), 3.25 (s, 3 H), 3.08 (dd, 1 H, *J* = 15.0, 7.8 Hz), 2.96 (dd, 1 H, *J* = 15.0, 5.7 Hz), 2.53 (dd, 1 H, *J* = 14.1, 7.6 Hz), 2.26 (dddd, 1 H, *J* = 14.3, 10.0, 6.8, 1.0 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.4 Hz), 0.90 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR δ 162.6, 161.8, 159.4, 144.2, 143.4, 140.3, 133.6, 131.8, 130.2, 129.7, 127.6, 114.0, 109.8, 91.1, 89.0, 88.5, 87.9, 79.4, 77.4, 70.1, 57.0, 55.5, 52.3, 41.1, 34.8, 33.4, 21.9, 21.2, 18.1; IR

(neat) 3477, 3160, 3027, 2937, 2873, 2832, 2182, 1747, 1612, 1585, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{39}NO_7Na$ (M+Na) 560.2624, found 560.2648.



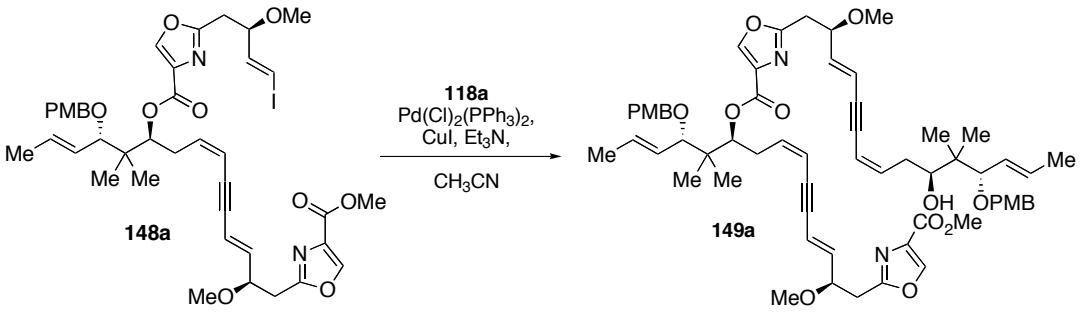
2-{(2*R*,10*S*,12*S*)-[10-Hydroxy-2-methoxy-12-(3,4-dimethoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl]}-oxazole-4-carboxylic acid methyl ester (147b). A mixture of **119** (93.7 mg, 0.278 mmol, 1.0 equiv) and **118b** (110.2 mg, 0.307 mmol, 1.1 equiv) was azeotropically dried at reduced pressure with toluene (1.0 mL) and then hexanes (1.0 mL), and dissolved in CH_3CN (3.0 mL). The solution was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (10.0 mg, 14 μmol, 0.05 equiv) and CuI (11.0 mg, 58 μmol, 0.2 equiv) were added and the mixture was degassed by freeze-pump-thaw (1 cycle), placed in a 0 °C bath under N_2, and treated with triethylamine (235 μL, 1.68 mmol, 6 equiv). The yellow mixture became almost colorless before turning to a dark red-brown color. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt over 10 min, quenched with 0.05 M phosphate buffer (pH 7, 3.0 mL), poured into water (10.0 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **147b** (138.0 mg, 87%) as a pale yellow wax: R_f 0.27 (50% ethyl acetate/hexanes); $[\alpha]_D$ –25.2 (*c* 1.34, $CHCl_3$, 22 °C); ^1H NMR δ 8.14 (s, 1 H), 6.84-6.81 (m, 3 H), 6.18 (app dt, 1 H, *J* =

10.7, 7.2 Hz), 5.93 (dd, 1 H, *J* = 15.9, 7.0 Hz), 5.84 (dd, 1 H, *J* = 15.9, 1.8 Hz), 5.77-5.58 (m, 2 H), 5.48 (ddd, 1 H, *J* = 15.3, 8.5, 1.5 Hz), 4.50 (d, 1 H, *J* = 11.3 Hz), 4.19 (d, 1 H, *J* = 11.3 Hz), 4.15 (app dt, 1 H, *J* = 13.2, 7.3 Hz), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 3.76 (d, 1 H, *J* = 4.8 Hz), 3.65 (d, 1 H, *J* = 8.6 Hz), 3.62-3.56 (m, 1 H), 3.24 (s, 3 H), 3.07 (dd, 1 H, *J* = 15.0, 7.7 Hz), 2.95 (dd, 1 H, *J* = 15.0, 5.7 Hz), 2.54 (dd, 1 H, *J* = 14.1, 7.5 Hz), 2.28 (ddd, 1 H, *J* = 16.0, 9.3, 7.0 Hz), 1.80 (d, 3 H, *J* = 6.3 Hz), 0.91 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 162.6, 161.8, 149.2, 148.8, 144.2, 143.3, 140.3, 133.5, 131.9, 130.6, 127.6, 120.7, 114.0, 111.4, 111.0, 109.8, 91.2, 88.4, 87.8, 79.4, 77.5, 70.3, 57.0, 56.1, 56.0, 52.3, 41.1, 34.7, 33.4, 21.8, 21.2, 18.1; IR (neat) 3480, 3158, 2937, 2871, 2833, 2186, 1747, 1587, 1517 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{41}NO_8Na$ (M+Na) 590.2730, found 590.2724.



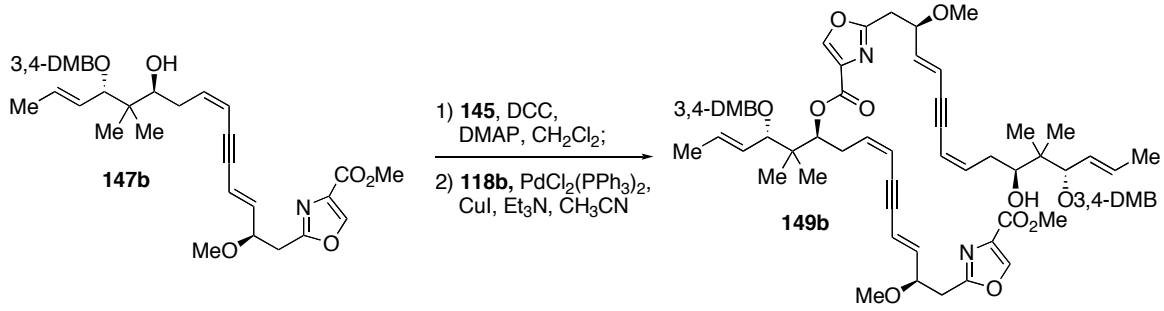
2-[(2*R*,10*S*,12*S*)-10-{2-[(2*R*)-4-Iodo-2-methoxybut-3-enyl]oxazol-4-oyloxy}-2-methoxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl]-oxazole-4-carboxylic acid methyl ester (148a). A solution of **145** (154.4 mg, 478.0 μmol, 1.9 equiv), **147a** (134.8 mg, 251.0 μmol, 1.0 equiv) and DMAP (31.0 mg, 254 μmol, 1.0 equiv) in CH_2Cl_2 (2.25 mL) was cooled to 0 °C under N_2 and dicyclohexylcarbodiimide (260.0 mg, 1260 μmol, 5.0 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 10 min then at rt for 14 h, diluted with

hexanes (5 mL) and filtered through a plug Florisil/Celite (1:1, v/v). The plug was rinsed with ethyl ether (5 mL) and the combined filtrates were concentrated. Purification by chromatography on SiO_2 (30% to 50% ethyl acetate/hexanes) afforded **148a** (169.0 mg, 80%) as a pale yellow syrup that was used without further purification. For analytical purposes, a sample was further purified by chromatography on SiO_2 (30% to 50% ethyl acetate/hexanes) to afford **148a** as a clear, colorless wax: R_f 0.23 (40% ethyl acetate/hexanes); $[\alpha]_D$ +50.5 (*c* 1.26, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.16 (s, 1 H), 7.96 (s, 1 H), 7.24 (d, 2 H, *J* = 8.5 Hz), 6.82 (d, 2 H, *J* = 8.6 Hz), 6.46 (d of AB, 1 H, *J* = 14.5, 6.2 Hz), 6.44 (AB, 1 H, *J* = 14.5 Hz), 5.97 (dd, 2 H, *J* = 15.9, 7.1 Hz), 5.85 (dd, 1 H, *J* = 16.0, 1.8 Hz), 5.65 (dq, 1 H, *J* = 15.1, 6.4 Hz), 5.56 (d, 1 H, *J* = 10.8 Hz), 5.46 (dd, 1 H, *J* = 8.5, 1.3 Hz), 5.40 (dd, 1 H, *J* = 9.2, 3.7 Hz), 4.36 (d, 1 H, *J* = 10.8 Hz), 4.08 (d, 1 H, *J* = 10.8 Hz), 4.20-4.01 (m, 2 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.47 (d, 1 H, *J* = 8.5 Hz), 3.28 (s, 3 H), 3.27 (s, 3 H), 3.14-2.95 (m, 4 H), 2.75-2.57 (m, 2 H), 1.76 (dd, 3 H, *J* = 6.1, 1.0 Hz), 0.97 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR δ 162.6, 162.1, 161.8, 160.8, 159.2, 144.7, 144.2, 143.7, 140.7 (2 C), 133.8, 133.6, 131.2, 129.8, 128.2, 113.8, 111.2, 91.5, 88.2, 84.4, 81.3, 80.1, 79.4, 77.4, 77.1, 70.1, 57.1, 55.4, 52.3, 42.1, 34.8, 34.1, 31.6, 25.2, 19.8, 19.6, 18.0; IR (neat) 3160, 2976, 2936, 2879, 1739, 1611, 1585, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{40}H_{47}N_2O_{10}INa$ (M+Na) 865.2173, found 865.2209.



(2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-14-Methoxy-4-(4-methoxybenzyloxy)-15-(4-(methoxycarbonyl)oxazol-2-yl)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-2-methoxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-carboxylate (149a). A mixture of **148a** (100.5 mg, 119.0 μmol, 1.0 equiv) and **118a** (74.4 mg, 227 μmol, 1.9 equiv) was azeotropically dried at reduced pressure with hexanes (0.5 mL) and dissolved in CH_3CN (2.0 mL). The solution was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (4.0 mg, 6.0 μmol, 0.05 equiv) and CuI (4.0 mg, 21 μmol, 0.2 equiv) were added and the mixture was degassed by freeze-pump-thaw (1 cycle) and placed in a –20 °C bath under N_2. Triethylamine (110 μL, 784 μmol, 7 equiv) was added and the yellow solution became almost colorless before changing to a dark red-brown color. After 25 min, the cold bath was removed and the reaction mixture was stirred at rt for 50 min, quenched with 0.05 M phosphate buffer (pH 7, 5.0 mL) and ethyl acetate (5.0 mL), stirred at rt for 20 min, poured into brine and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **149a** (116.6 mg, 94%) as a yellow wax: R_f 0.18 (40% ethyl acetate/hexanes); $[\alpha]_D$ +29.5 (*c* 1.01, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.16 (s, 1 H), 7.95 (s, 1 H), 7.22 (app t, 4 H, *J* = 9.1 Hz), 6.83

(app t, 4 H, *J* = 8.8 Hz), 6.17 (app dt, 1 H, *J* = 10.7, 7.2 Hz), 6.00-5.82 (m, 5 H), 5.74-5.61 (m, 3 H), 5.56 (d, 1 H, *J* = 10.8 Hz), 5.52-5.37 (m, 3 H), 4.50 (d, 1 H, *J* = 11.2 Hz), 4.36 (d, 1 H, *J* = 10.8 Hz), 4.18 (d, 1 H, *J* = 11.4 Hz), 4.16 (app t, 2 H, *J* = 6.6 Hz), 4.08 (d, 1 H, *J* = 10.8 Hz), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.64 (d, 1 H, *J* = 8.5 Hz), 3.63-3.54 (m, 1 H), 3.47 (d, 1 H, *J* = 8.5 Hz), 3.27 (s, 3 H), 3.25 (s, 3 H), 3.10 (dd, 1 H, *J* = 14.9, 7.6 Hz), 2.94 (dd, 1 H, *J* = 14.9, 5.3 Hz), 3.10-3.00 (m, 2 H), 2.74-2.59 (m, 2 H), 2.53 (dd, 1 H, *J* = 14.1, 7.7 Hz), 2.26 (ddd, 1 H, *J* = 15.8, 9.2, 6.9 Hz), 1.78 (d, 3 H, *J* = 6.4 Hz), 1.76 (d, 3 H, *J* = 6.3 Hz), 1.70 (bs, 1 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR δ 162.6, 162.5, 161.8, 160.8, 159.5, 159.1, 144.2, 143.7, 143.3, 140.7, 140.5, 133.7, 133.6, 131.7, 131.2, 130.3, 129.8, 129.7, 128.1, 127.7, 114.0, 113.9, 113.8, 91.5, 91.2, 88.4, 88.2, 88.0, 84.3, 79.4, 70.1, 70.0, 57.0, 55.5, 52.3, 42.1, 41.2, 34.8, 33.4, 31.6, 21.9, 21.1, 19.7, 19.6, 18.1; IR (neat) 3479, 2968, 2935, 2187, 1740, 1612, 1585, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{61}H_{74}N_2O_{13}Na$ (M+Na) 1065.5089, found 1065.5087.

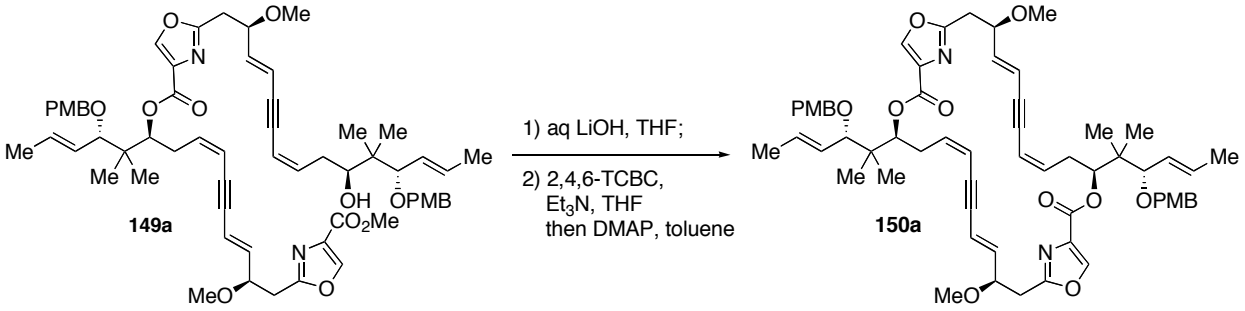


(2*E*,4*S*,6*S*,8*Z*,12*E*,14*R*)-4-(3,4-Dimethoxybenzyloxy)-14-methoxy-15-(4-(methoxycarbonyl)oxazol-2-yl)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*,13*E*)-12-(3,4-dimethoxybenzyloxy)-10-hydroxy-2-methoxy-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-carboxylate (149b). A

mixture of **147b** (85.0 mg, 0.149 mmol, 1.0 equiv), **145** (80.0 mg, 0.248 mmol, 1.7 equiv) and DMAP (20.0 mg, 0.164 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C and treated with DCC (160.0 mg, 0.775 mmol, 5.2 equiv). The mixture was stirred at 0 °C for 15 min then rt overnight (18 h). The mixture was diluted with hexanes (5 mL) and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with ethyl acetate and the combined filtrate was concentrated. Purification by chromatography on SiO_2 (50% ethyl acetate/hexanes) afforded a pale yellow, oily solid that was used without further purification.

A mixture of the oily solid and **118b** (65.9 mg, 0.184 mmol, 1.2 equiv) in CH_3CN (2.0 mL) was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (5.0 mg, 7.0 μmol, 0.05 equiv) and CuI (6.0 mg, 32 μmol, 0.2 equiv) were added and the mixture was degassed by freeze-pump-thaw (1 cycle) and placed in a 0 °C bath under N_2. Triethylamine (125 μL, 891 μmol, 6.0 equiv) was added and the yellow solution became almost colorless before changing to a dark red-brown color. The reaction mixture was stirred at 0 °C for 2 h then warmed to rt for 30 min, quenched with phosphate buffer (0.5 M NaH_2PO_4, 0.5 M Na_2HPO_4, 3.0 mL), poured into water (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (50% to 80% ethyl acetate/hexanes) afforded **149b** (99.7 mg, 61%, 2 steps) as a pale, yellow wax: R_f 0.26 (60% ethyl acetate/hexanes); $[\alpha]_D$ +17.1 (*c* 1.57, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.16 (s, 1 H), 7.98 (s, 1 H), 6.94-6.76 (m, 6 H), 6.18 (app dt, 1 H, *J* = 10.6, 7.4 Hz), 6.00-5.91 (m, 3 H), 5.85 (app dt, 2 H, *J* = 15.9, 2.5 Hz), 5.74-5.40 (m, 8 H), 4.51 (d, 1 H, *J* = 11.3 Hz), 4.35 (d, 1 H, *J* = 10.9 Hz), 4.20 (d, 1 H, *J* = 11.6 Hz), 4.19-4.13 (m, 2 H), 4.08 (d, 1 H, *J* =

10.8 Hz), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 2 H), 3.76 (d, 1 H, *J* = 4.8 Hz), 3.65 (d, 1 H, *J* = 8.5 Hz), 3.61-3.57 (m, 1 H), 3.49 (d, 1 H, *J* = 8.6 Hz), 3.26 (s, 3 H), 3.24 (s, 3 H), 3.08 (app dt, 2 H, *J* = 15.0, 7.7 Hz), 2.96 (app dt, 2 H, *J* = 14.9, 5.5 Hz), 2.70-2.63 (m, 2 H), 2.54 (dd, 1 H, *J* = 14.1, 7.0 Hz), 2.28 (ddd, 1 H, *J* = 15.4, 9.6, 7.0 Hz), 1.79 (d, 3 H, *J* = 10.0 Hz), 1.78 (d, 3 H, *J* = 9.7 Hz), 0.98 (s, 3 H), 0.95 (s, 3 H), 0.91 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 162.5 (2 C), 161.8, 160.8, 149.1, 148.9, 148.9, 148.8, 148.4, 144.4, 144.2, 143.8, 143.3, 141.4, 140.7, 140.5, 133.63, 133.5, 131.8, 131.5, 131.4, 130.6, 128.0, 127.5, 120.6, 120.5, 113.9, 113.7, 111.8, 111.4, 111.2, 111.0, 110.8, 110.5, 109.8, 91.5, 91.2, 88.4, 88.1, 87.8, 84.3, 79.3 (2 C), 77.4, 70.3 (2 C), 57.0, 56.9, 56.1, 56.0 (2 C), 42.0, 41.1, 34.7, 33.3, 31.5, 21.8, 21.2, 19.6, 19.4, 18.1 (2 C), 15.4; IR (neat) 3481, 2969, 2937, 2877, 2834, 2251, 2184, 1739, 1585, 1517 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{63}H_{78}N_2O_{15}Na$ (M+Na) 1125.5300, found 1125.5270.

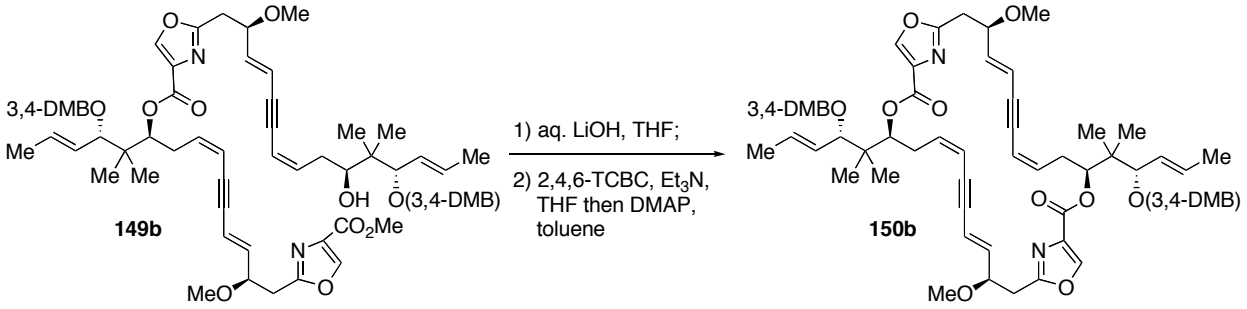


(16,16')-Bis(4-methoxybenzyloxy)-(9,9',10,10')-didehydrodisorazole C$_1$ (150a). A solution of **149a** (33.4 mg, 32.0 μmol, 1.0 equiv) in THF (1.0 mL) was treated at rt with 1.0 M aqueous LiOH solution (65 μL, 65 μmol, 2.0 equiv). After 13.5 h, the reaction mixture was diluted with water (5 mL), poured into 2.0 M aqueous $NaHSO_4$ (5 mL) and extracted with ethyl acetate. The combined organic layers were dried

(Na_2SO_4), filtered and concentrated to afford the *seco*-acid (32.2 mg, 98%) as a yellow wax that was used without further purification. Characteristic signals for the *seco*-acid: ^{1}H NMR δ 8.22 (s, 1 H), 7.96 (s, 1 H), 7.22 (app t, 4 H, *J* = 8.8 Hz), 6.83 (app t, 4 H, *J* = 9.0 Hz), 6.17 (app dt, 1 H, *J* = 10.7, 7.2 Hz), 6.02-5.81 (m, 5 H), 5.75-5.39 (m, 7 H), 4.51 (d, 1 H, *J* = 11.2 Hz), 4.36 (d, 1 H, *J* = 10.8 Hz), 4.19 (d, 1 H, *J* = 11.2 Hz), 4.21-4.13 (m, 2 H), 4.08 (d, 1 H, *J* = 10.9 Hz), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.65 (d, 1 H, *J* = 8.7 Hz), 3.61 (dd, 1 H, *J* = 10.3, 2.6 Hz), 3.48 (d, 1 H, *J* = 8.5 Hz), 3.29 (s, 3 H), 3.26 (s, 3 H), 3.18-2.94 (m, 4 H), 2.75-2.65 (m, 2 H), 2.57-2.50 (m, 1 H), 2.33-2.22 (m, 1 H), 1.79 (d, 3 H, *J* = 6.2 Hz), 1.76 (d, 3 H, *J* = 6.1 Hz), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.91 (s, 3 H), 0.87 (s, 3 H).

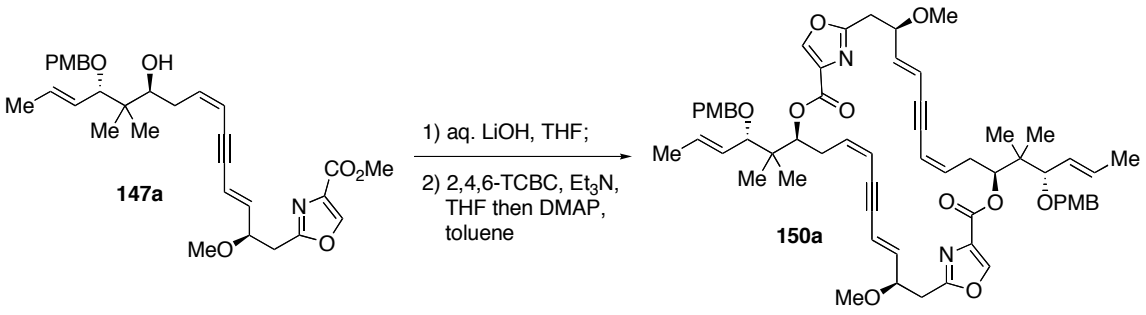
The crude *seco*-acid (32.2 mg, 31.3 μmol, 1.0 equiv) was azeotropically dried at reduced pressure with benzene (1 mL) and then THF (2 x 1 mL), diluted with THF (2.5 mL) and treated at rt with triethylamine (90 μL, 640 μmol, 20 equiv) and 2,4,6-trichlorobenzoyl chloride (50 μL, 320 μmol, 10 equiv). After 2 h, the turbid reaction mixture was diluted with toluene (1.5 mL) and added dropwise via syringe pump (4 mL/h) to a stirred solution of DMAP (154.0 mg, 1260 μmol, 40 equiv) in toluene (45 mL) at rt. After the addition was complete, the syringe was rinsed with toluene (2 x 1.0 mL) and the rinse was added to the reaction mixture. After stirring at rt for an additional 12 h (16 h total), the solution was treated with saturated aqueous NH_4Cl (10 mL) and water (10 mL) and the mixture was stirred for 30 min and then extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 40% ethyl acetate/hexanes) afforded **150a** (25.2 mg,

79%) as a clear, colorless wax: R_f 0.30 (40% ethyl acetate/hexanes); $[\alpha]_D$ +150.5 (*c* 0.82, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.97 (s, 2 H), 7.27 (d, 4 H, *J* = 8.4 Hz), 6.83 (d, 4 H, *J* = 8.5 Hz), 6.00-5.92 (m, 4 H), 5.71-5.58 (m, 4 H), 5.52-5.41 (m, 6 H), 4.37 (d, 2 H, *J* = 10.7 Hz), 4.11 (d, 2 H, *J* = 10.7 Hz), 4.17-4.11 (m, 2 H), 3.79 (s, 6 H), 3.46 (d, 2 H, *J* = 8.4 Hz), 3.36 (s, 6 H), 3.32 (dd, 2 H, *J* = 16.2, 4.0 Hz), 2.99 (dd, 2 H, *J* = 14.2, 9.9 Hz), 2.95 (dt, 2 H, *J* = 13.8, 10.9 Hz), 2.36 (bd, 2 H, *J* = 13.8 Hz), 1.77 (d, 6 H, *J* = 6.1 Hz), 0.98 (s, 12 H); ^{13}C NMR δ 161.8, 160.7, 159.2, 143.5, 141.4, 140.7, 134.0, 131.3, 131.2, 129.9, 128.2, 113.8 (2 C), 112.1, 91.1, 88.0, 84.4, 79.9, 76.4, 70.2, 57.0, 55.5, 41.9, 34.7, 31.7, 19.7, 19.6, 18.0; IR (neat) 2971, 2935, 2877, 2853, 2190, 1737, 1612, 1585, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{60}H_{70}N_2O_{12}Na$ (M+Na) 1033.4826, found 1033.4838.



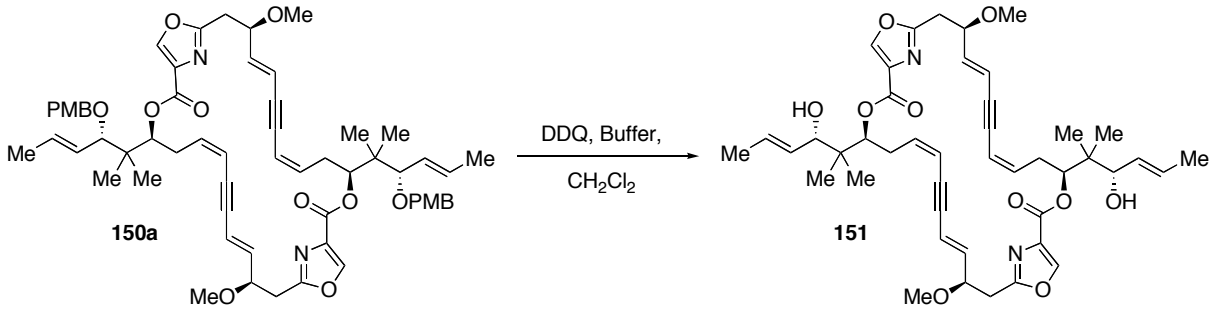
(16,16')-Bis(3,4-dimethoxybenzyloxy)-(9,9',10,10')-didehydrodisorazole C_1 (150b). A solution of **149b** (68.0 mg, 61.6 μmol, 1.0 equiv) in THF (2.0 mL) and water (0.1 mL) was treated at rt with 1.0 M aqueous LiOH solution (137 μL, 137 μmol, 2.2 equiv). After 12 h, the reaction mixture was poured into 2.0 M aqueous $NaHSO_4$ (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford the *seco*-acid as yellow syrup that was azeotropically dried with toluene at reduced pressure, diluted with THF (2.0 mL) and treated with triethylamine (175.0 μL, 1.247 mmol, 20 equiv) and 2,4,6-trichlorobenzoyl

chloride (96.0 μL, 0.614 mmol, 10 equiv). The mixture was stirred at rt for 2.5 h and diluted with toluene to give a solution (10 mL) that was added via syringe pump (2.4 mL/h) to a solution of DMAP (380 mg, 3.11 mmol, 50 equiv) in toluene (100 mL) at rt. The mixture was stirred at rt for 12 h, treated with 1.0 M aqueous citric acid (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% to 50% ethyl acetate/hexanes) afforded **150b** (49.8 mg, 76%) as a clear, colorless syrup: R_f 0.26 (50% ethyl acetate/hexanes); $[\alpha]_D$ +120.4 (*c* 1.08, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.99 (s, 2 H), 6.94 (d, 2 H, *J* = 1.8 Hz), 6.87 (dd, 2 H, *J* = 8.2, 1.8 Hz), 6.79 (d, 2 H, *J* = 8.2 Hz), 5.96 (dd, 2 H, *J* = 15.9, 7.6 Hz), 6.00-5.92 (m, 2 H), 5.62 (dd, 2 H, *J* = 15.8, 1.7 Hz), 5.71-5.59 (m, 2 H), 5.54-5.42 (m, 8 H), 4.36 (d, 2 H, *J* = 10.7 Hz), 4.13-4.09 (m, 2 H), 4.11 (d, 2 H, *J* = 10.7 Hz), 3.89 (s, 6 H), 3.86 (s, 6 H), 3.47 (d, 2 H, *J* = 8.5 Hz), 3.36-3.28 (m, 2 H), 3.35 (s, 6 H), 2.98 (dd, 2 H, *J* = 14.0, 10.0 Hz), 2.36 (bd, 2 H, *J* = 14.0 Hz), 1.77 (dd, 6 H, *J* = 6.2, 1.0 Hz), 0.99 (s, 6 H), 0.99 (s, 6 H); ^{13}C NMR δ 161.8, 160.7, 148.9, 148.4, 143.5, 141.3, 140.6, 133.8, 131.6, 131.4, 128.0, 120.6, 113.8, 112.1, 111.9, 110.9, 91.0, 88.0, 84.3, 79.8, 76.2, 70.4, 57.0, 56.0 (2 C), 41.8, 34.5, 31.5, 19.6, 19.4, 18.1; IR (neat) 2971, 2937, 2878, 2833, 1738, 1585, 1517 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{62}H_{74}N_2O_4Na$ (M+Na) 1093.5038, found 1093.4962.



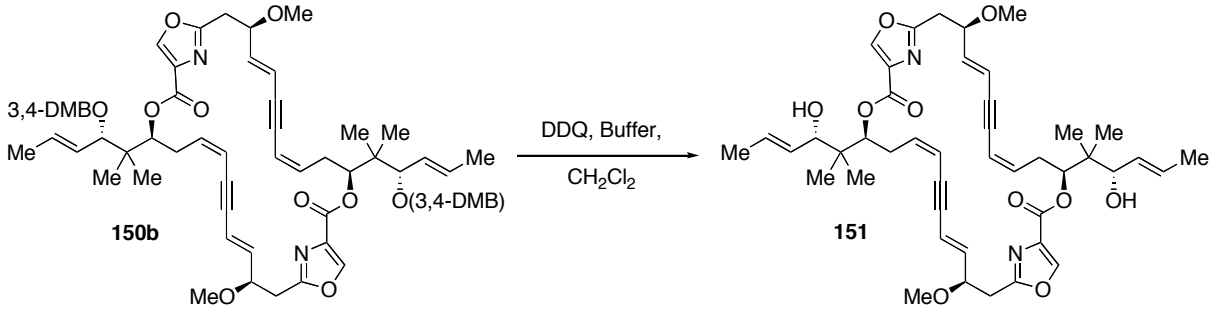
(16,16')-Bis(4-methoxybenzyloxy)-(9,9',10,10')-didehydrodisorazole C_1 (150a). A solution of **147a** (16.1 mg, 30 μmol, 1.0 equiv) in THF (1.0 mL) was treated with 1.0 M aqueous LiOH (65 μL, 65 μmol, 2.2 equiv), stirred at rt for 18 h, poured in 2.0 M aqueous $NaHSO_4$ (5.0 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to a pale yellow wax (17.6 mg, quant.) that was used without further purification. Characteristic signals: ^{1}H NMR δ 8.22 (s, 1 H), 7.21 (d, 2 H, *J* = 8.7 Hz), 6.85 (d, 2 H, *J* = 8.6 Hz), 6.18 (app td, 1 H, *J* = 10.7, 7.3 Hz), 5.94 (d of AB, 1 H, *J* = 15.8, 6.9 Hz), 5.87 (d of AB, 1 H, *J* = 15.9, 1.7 Hz), 5.75-5.63 (m, 2 H), 5.49 (ddd, 1 H, *J* = 15.4, 8.5, 1.4 Hz), 4.51 (d, 1 H, *J* = 11.2 Hz), 4.21-4.13 (m, 1 H), 4.19 (d, 1 H, *J* = 11.2 Hz), 3.79 (s, 3 H), 3.65 (d, 1 H, *J* = 8.6 Hz), 3.61 (dd, 1 H, *J* = 10.1, 2.6 Hz), 3.26 (s, 3 H), 3.09 (d of AB, 1 H, *J* =15.1, 7.7 Hz), 3.01 (d of AB, 1 H, *J* = 15.1, 5.6 Hz), 2.54 (dd, 1 H, *J* = 13.5, 7.7 Hz), 2.27 (ddd, 1 H, *J* = 16.7, 9.9, 6.7 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.3 Hz), 0.91 (s, 3 H), 0.86 (s, 3 H). The crude hydroxyacid (17.6 mg) was azeotropically dried with toluene (1.0 mL) at reduced pressure, dissolved in THF (1.0 mL) and treated with triethylamine (85.0 μL, 0.606 mmol, 20.2 equiv) and 2,4,6-trichlorobenzoylchloride (47.0 μL, 0.301 mmol, 10.0 equiv) at rt. After stirring for 2 h at rt, the turbid mixture was diluted with toluene to give a 4.0 mL solution that was added via syringe pump (1.0 mL/h) to a stirred solution of DMAP

(150 mg, 1.31 mmol, 44 equiv) in toluene (50 mL). After stirring for 12 h, the syringe was rinsed with toluene (0.5 mL x 3) and the rinse was added to the reaction mixture which was stirred for an additional 6 h, treated with saturated aqueous NH_4Cl (10 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were sequentially washed with 1.0 M aqueous citric acid (10 mL) , water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was diluted with ethyl acetate (1 mL) and filtered through a plug of Florisil/Celite (1:1 v/v), the plug was rinsed with ethyl acetate (5 mL) and the filtrate was concentrated. Purification by chromatography on SiO_2 (30% to 50% ethyl acetate/hexanes) afforded **150a** (8.9 mg, 59%, 2 steps) as a clear, colorless wax.



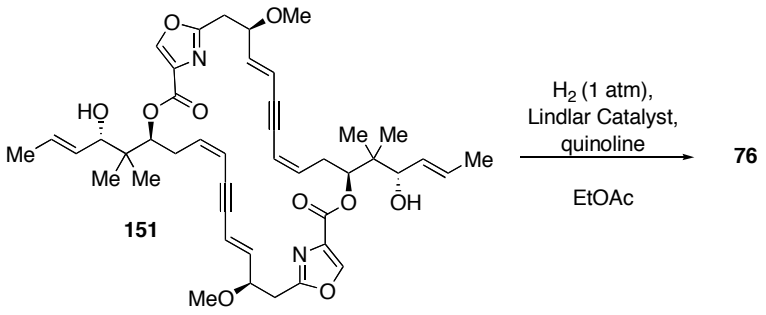
(9,9',10,10')-Didehydrodisorazole C_1 (151). A biphasic mixture of **150a** (10.5 mg, 10.0 μmol, 1.0 equiv), CH_2Cl_2 (1.0 mL) and aqueous phosphate buffer (0.5 M in Na_2HPO_4 and 0.5 M in NaH_2PO_4, 1.0 mL) was treated at rt with DDQ (20.0 mg, 88.0 μmol, 8.8 equiv). After 15 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was diluted in ethyl acetate, filtered through a plug of SiO_2, and the plug was rinsed with ethyl acetate. The combined filtrates were

concentrated to a pale, yellow wax. Purification by preparative HPLC on SiO_2 (10 mm x 25 mm, 0.5% to 1.5% MeOH/CH_2Cl_2 over 60 min) afforded **151** (4.7 mg, 61%) as a clear, colorless wax: R_f 0.23 (60% ethyl acetate/hexanes); $[\alpha]_D$ +187.8 (*c* 0.37, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.11 (s, 2 H), 6.03 (dd, 2 H, *J* = 15.9, 7.4 Hz), 5.94 (app dq, 2 H, *J* = 10.7, 5.3 Hz), 5.68 (d, 2 H, *J* = 14.9 Hz), 5.57 (d, 2 H, *J* = 7.4 Hz), 5.71-5.50 (m, 4 H), 5.34 (dd, 2 H, *J* = 10.9, 2.4 Hz), 4.15-4.09 (m, 2 H), 3.85 (d, 2 H, *J* = 7.1 Hz), 3.36 (s, 6 H), 3.37-3.26 (m, 2 H), 3.07-2.95 (m, 4 H), 2.53 (bs, 2 H), 2.45-2.35 (m, 2 H), 1.71 (d, 6 H, *J* = 5.9 Hz), 0.98 (s, 6 H), 0.96 (s, 6 H); ^{13}C NMR δ 162.1, 161.6, 144.1, 141.6, 140.0, 133.4, 129.5, 113.5, 112.7, 91.2, 87.9, 79.7, 57.1, 41.9, 34.6, 31.1, 19.3, 18.7, 18.1; IR (neat) 3477, 3165, 2969, 2929, 2884, 2854, 2187, 1736, 1629, 1583, 1466, 1451 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{44}H_{54}N_2O_{10}Na$ (M+Na) 793.3676, found 793.3702.



(9,9',10,10')-Didehydrodisorazole C_1 (151). A biphasic mixture of **150b** (49.8 mg, 46.5 µmol, 1.0 equiv), CH_2Cl_2 (1.0 mL) and aqueous phosphate buffer (0.5 M in Na_2HPO_4 and 0.5 M in NaH_2PO_4, 1.0 mL) was treated at 0 °C with DDQ (42.0 mg, 185 µmol, 4.0 equiv). After 15 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Purification by

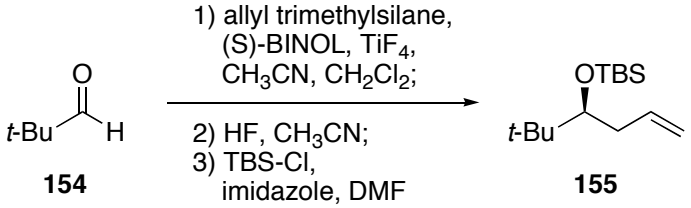
chromatography on SiO_2 (50% to 90% ethyl acetate/hexanes) afforded **151** (27.4 mg, 77%) as a clear, colorless wax.



(-)-Disorazole C_1 (1). A flask containing a mixture of (9,9',10,10')-didehydro-disorazole C_1 (2.1 mg, 2.7 μmol, 1.0 equiv), quinoline (10.0 μL, 85.0 μmol, 31 equiv) and Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with Pb, 1.2 mg) in ethyl acetate (0.5 mL) was evacuated and flushed with H_2 (3 cycles). The reaction mixture was stirred at rt under H_2 (1 atm) for 1 h and then filtered through a plug of Florisil/Celite (1:1). The plug was rinsed with ethyl acetate (5 mL) and the combined filtrates were concentrated. Purification by preparative HPLC on SiO_2 (10 mm x 25 mm, 34% ethyl acetate/hexanes, 7 mL/min, UV detection at 254 nm) and collection of the fractions with R_t = 34 to 40 min afforded a clear colorless wax that was further purified by preparative HPLC on SiO_2 (10 mm x 25 mm, 0.5% to 2% MeOH/CH_2Cl_2 over 60 min, 7 mL/min, UV detection at 254 nm). Collection of the fractions with R_t = 37 to 40 min afforded 1 (1.2 mg, 57%) as a clear, colorless wax: R_f 0.50 (5% MeOH/CH_2Cl_2, twofold developed); $[\alpha]_D$ -136 (*c* 0.05, MeOH, 22 °C); lit. $[\alpha]_D$ –124.8 (*c* 0.6, MeOH, 22 °C); UV-vis (0.22 mM, MeOH, 22 °C) λ_{max} (log ε) 272 nm (3.98); ^{1}H NMR (600 MHz, CD_3OD) δ 8.23 (s, 2 H), 6.50 (dd, 2 H, *J* = 15.2, 11.5 Hz), 6.40 (app t, 2 H, *J* = 11.2 Hz), 6.28 (dd, 2 H, *J* = 11.4, 11.1 Hz), 5.91 (dd, 2 H, *J* = 11.2, 10.9 Hz), 5.66 (dq, 2 H, *J* = 15.2, 6.6 Hz),

5.57 (ddd, 2 H, *J* = 15.2, 7.8, 1.4 Hz), 5.54 (dd, 2 H, *J* = 15.0, 8.3 Hz), 5.48 (app dt, 2 H, *J* = 10.0, 6.7 Hz), 5.25 (dd, 2 H, *J* = 11.3, 2.2 Hz), 4.13 (ddd, 2 H, *J* = 7.8, 7.2, 5.5 Hz), 3.84 (d, 2 H, *J* = 7.8 Hz), 3.21 (s, 6 H), 2.99 (dd, 2 H, *J* = 15.5, 7.4 Hz), 2.76 (dd, 2 H, *J* = 15.5, 5.4 Hz), 2.69 (ddd, 2 H, *J* = 13.8, 10.9, 10.2 Hz), 2.38 (dd, 2 H, *J* = 13.8, 6.1 Hz), 1.69 (dd, 6 H, *J* = 6.4, 1.3 Hz), 1.00 (s, 6 H), 0.95 (s, 6 H); ^{13}C NMR (151 MHz, CD_3OD) δ 164.12, 162.26, 145.83, 134.15, 134.09, 131.68, 130.88, 129.96, 129.63, 129.30, 127.36, 126.79, 80.57, 78.75, 77.84, 56.83, 42.70, 35.97, 29.24, 19.41, 19.32, 18.03; HRMS (ESI) *m/z* calcd for $C_{44}H_{58}N_2O_{10}Na$ (M+Na) 797.3989, found 797.3997.

3.5.2.2. Synthesis of the C_{14}-*t*-Butyl Analog

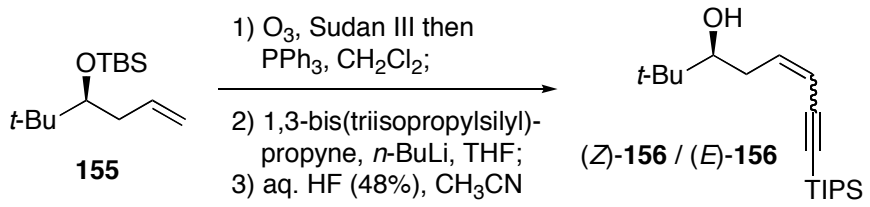


154 **155**

(*S*)-3-(*t*-Butyldimethylsilyloxy)-2,2-dimethylhex-5-ene (155). A solution of TiF_4 (223.0 mg, 1.800 mmol, 0.1 equiv) in CH_3CN (2.5 mL) was treated with (*S*)-BINOL (1.030 g, 3.597 mmol, 0.2 equiv) at rt. The resulting red-brown mixture was stirred at rt for 15 min, concentrated in vacuo and held under high vacuum for 30 min. CH_2Cl_2 (10 mL) was added and the mixture was cooled to 0 °C and treated with allyl trimethylsilane (10.0 mL, 62.9 mmol, 3.5 equiv). After stirring for 1.5 h at 0 °C, pivaldehyde (2.00 mL, 18.0 mmol, 1.0 equiv) was added and the mixture was stirred for 5 h at 0 °C, poured into 50% ethyl ether/hexanes (75 mL) and filtered through a pad of SiO_2. The pad was washed with 50% ethyl ether/hexanes (100 mL) and the combined

filtrates were concentrated, diluted with CH_3CN (20 mL), and treated with 48% aqueous HF (1.0 mL). The mixture was stirred for 30 min at rt then treated with saturated aqueous $NaHCO_3$ (50 mL) and ethyl ether (25 mL) and stirred at rt for 12 h. The mixture was extracted with ethyl ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (5% acetone/hexanes) afforded the known homoallylic alcohol[174] as a clear, colorless oil (1.288 g, 56%) that was used without further purification.

A solution of (*S*)-2,2-dimethylhex-5-en-3-ol (1.20 g, 9.36 mmol, 1.0 equiv) in DMF (2.0 mL) was treated with imidazole (1.60 g, 23.5 mmol, 2.5 equiv) and *t*-butyldimethylsilyl chloride (2.12 g, 14.1 mmol, 1.5 equiv) and stirred at 60 °C (oil bath temp). After 18 h, additional imidazole (0.650 g, 9.55 mmol, 1.0 equiv) and *t*-butyldimethylsilyl chloride (0.70 g, 4.64 mmol, 0.5 equiv) was added. The mixture was stirred for an additional 18 h, cooled to rt and treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl ether. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to a yellow oil. Purification by chromatography on SiO_2 (hexanes) afforded **155** as a clear colorless oil (2.249 g, 99%). $[\alpha]_D$ +3.5 (*c* 12.0, $CHCl_3$, 22 °C); Lit: $[\alpha]_D$ +3.8 (*c* 12.2, $CHCl_3$, 20 °C).[176]

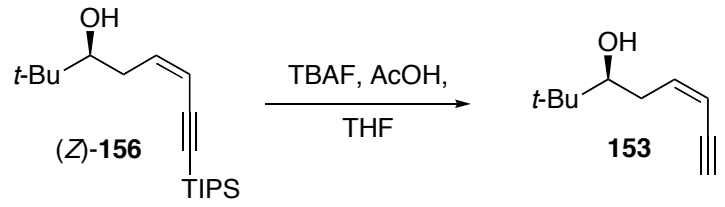


(*S*,*Z*)-2,2-Dimethyl-8-(triisopropylsilyl)oct-5-en-7-yn-3-ol [(*Z*)-156] and **(*S*,*E*)-2,2-dimethyl-8-(triisopropylsilyl)oct-5-en-7-yn-3-ol [(*E*)-156]**. A solution of **155** (1.04 g, 4.27 mmol, 1.0 equiv) and Sudan III (1.0 mg) in CH_2Cl_2 (20.0 mL) was cooled to –78 °C and treated with a stream of O_3/O_2 until the red color dissipated. PPh_3 (1.23 g, 4.69 mmol, 1.1 equiv) was added and the mixture was warmed to rt, stirred for 2 h, diluted with hexanes (25 mL) and poured onto a pad of SiO_2. The pad was rinsed (50% CH_2Cl_2/hexanes, 100 mL) and the combined filtrate was concentrated to a clear, colorless syrup that was contaminated with PPh_3 and used without further purification.

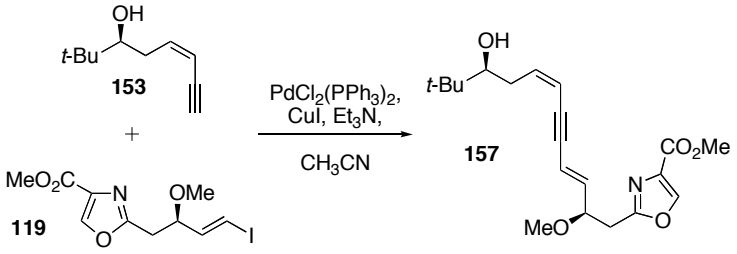
A solution of 1,3-bis(triispropylsilyl)propyne (2.15 g, 6.10 mmol, 1.4 equiv) in THF (20 mL) was cooled to 0 °C and treated with *n*-BuLi (1.5 M in hexanes, 3.70 mL, 5.55 mmol, 1.3 equiv), warmed to rt, stirred for 1 h and cooled to –78 °C. A solution of the aldehyde in THF (5.0 mL + 5.0 mL rinse) was added via cannula. The mixture was stirred at –78 °C for 1.5 h, warmed to 0 °C for 25 min and treated with saturated aqueous NH_4Cl (10 mL) and water (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (100% hexanes) to remove the polar impurities afforded a pale yellow oil that was used without further purification.

A biphasic mixture of the TBS ether in CH_3CN (20 mL) in a glass reaction vessel was treated with 48% aqueous HF (2.0 mL), stirred at rt for 36 h and then added

portionwise to saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with ethyl ether and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (100% hexanes to 10% ethyl ether/hexanes) afforded (*Z*)-**156** (572.1 mg, 43%, 3-steps) and (*E*)-**156** (136.0 mg, 10%, 3 steps). (*Z*)-**156:** R_f 0.32 (20% ethyl ether/hexanes); $[\alpha]_D$ –0.50 (*c* 1.40, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.10 (ddd, 1 H, *J* = 10.8, 7.7, 7.1 Hz), 5.66 (app dt, 1 H, *J* = 10.8, 1.2 Hz), 3.32 (bd, 1 H, *J* = 10.4 Hz), 2.58 (dddd, 1 H, *J* = 14.5, 6.9, 2.5, 1.5 Hz), 2.42 (dddd, 1 H, *J* = 14.5, 10.3, 7.8, 1.1 Hz), 1.51 (bs, 1 H), 1.08 (s, 21 H), 0.93 (s, 9 H); ^{13}C NMR δ 142.6, 111.9, 103.7, 95.8, 79.3, 35.2, 33.4, 25.9, 18.9, 11.5; IR (neat) 3416, 2958, 2944, 2893, 2866, 2145, 1464 cm^{-1}; MS (EI) *m/z* (rel. intensity) 265 (M^+, 14), 247 ($[M-H_2O]^+$, 46), 222 ($[M-C_3H_7]^+$, 87), 179 ($[M-C_6H_{14}]^+$, 30), 157 (100), 131 (87), 103 (96), 75 (89); HRMS (EI) *m/z* calcd for $C_{16}H_{29}OSi$ ($M-C_3H_7$) 265.1988, found 265.1978; (*E*)-**156:** R_f 0.54 (20% ethyl ether/hexanes); $[\alpha]_D$ –33.8 (*c* 2.88, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.26 (ddd, 1 H, *J* = 15.7, 8.0, 6.7 Hz), 5.62 (d, 1 H, *J* = 15.8 Hz), 3.28 (bd, 1 H, *J* = 10.2 Hz), 2.37 (ddt, 1 H, *J* = 14.3, 6.5, 1.7 Hz), 2.05 (app dt, 1 H, *J* = 14.3, 10.1 Hz), 1.58 (bs, 1 H), 1.07 (s, 21 H), 0.91 (s, 9 H); ^{13}C NMR δ 143.3, 112.8, 105.7, 89.7, 78.7, 35.9, 35.0, 25.9, 18.8, 11.5; IR (neat) 3456, 2958, 2944, 2889, 2866, 2172, 2131, 1464 cm^{-1}; MS (EI) *m/z* (rel. intensity) 308 (M^+, 3), 293 ($[M-CH_3]^+$, 4), 265 ($[M-C_3H_7]^+$, 100), 222 ($[M-C_6H_{14}]^+$, 53), 180 (22), 157 (42); HRMS (EI) *m/z* calcd for $C_{16}H_{29}OSi$ ($M-C_3H_7$) 265.1988, found 265.1985.

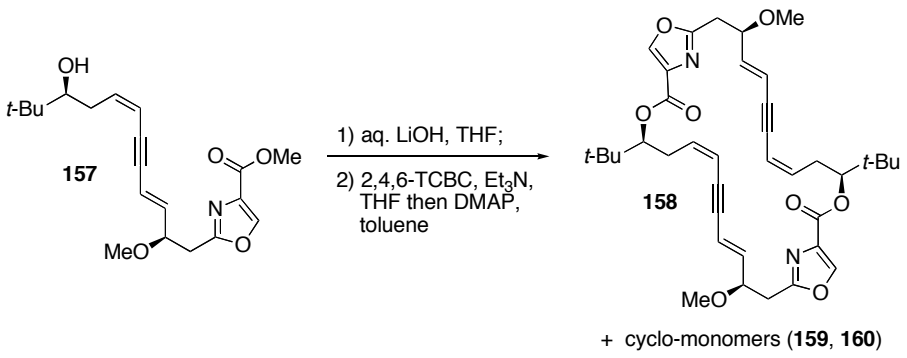


(3*S*,5*Z*)-2,2-Dimethyloct-5-en-7-yn-3-ol (153). A solution of (*Z*)-**156** (572.0 mg, 1.854 mmol, 1.0 equiv) in THF (10.0 mL) was treated with glacial AcOH (110 μL, 1.91 mmol, 1.0 equiv) and TBAF (1.0 M in THF, 2.10 mL, 2.10 mmol, 1.1 equiv) and stirred for 12 h at rt. The mixture was treated with saturated aqueous $NaHCO_3$ (5 mL), poured into H_2O (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (100% hexanes to 20% ethyl ether/hexanes) afforded **153** (215.0 mg, 76%) as a clear, colorless oil: R_f 0.41 (40% ethyl ether/hexanes); $[\alpha]_D$ –38.4 (*c* 2.81, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.17 (dtd, 1 H, *J* = 10.8, 7.1, 0.8 Hz), 5.57 (d, 1 H, *J* = 10.8 Hz), 3.31 (bd, 1 H, *J* = 10.1 Hz), 3.10 (d, 1 H, *J* = 1.9 Hz), 2.57 (app ddt, 1 H, *J* = 14.4, 7.1, 1.8 Hz), 2.34 (dddd, 1 H, *J* = 14.4, 10.2, 7.9, 1.1 Hz), 1.59 (bs, 1 H), 0.93 (s, 9 H); ^{13}C NMR δ 143.9, 110.2, 82.1, 80.5, 79.4, 35.2, 33.1, 25.8; IR (neat) 3424, 3311, 3032, 2959, 2907, 2870, 2097, 1614, 1479 cm^{-1}.



2-((2*R*,3*E*,7*Z*,10*S*)-10-Hydroxy-2-methoxy-11,11-dimethyldodeca-3,7-dien-5-ynyl)oxazole-4-carboxylic acid methyl ester (157). A mixture of **153** (121.0 mg,

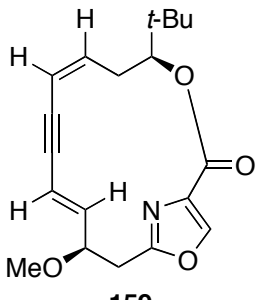
0.795 mmol, 1.2 equiv) and **119** (227.0 mg, 0.673 mmol, 1.0 equiv) was dissolved in CH_3CN (4.0 mL). The solution was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (29.0 mg, 41.3 μmol, 0.06 equiv) and CuI (34.0 mg, 0.178 mmol, 0.3 equiv) were added and the mixture was degassed by freeze-pump-thaw (1 cycle), placed in a 0 °C bath under N_2, and treated with triethylamine (660 μL, 4.71 μmol, 7.0 equiv). The yellow mixture became almost colorless before turning to a dark red-brown color. The reaction mixture was stirred at 0 °C for 2 h, quenched with aqueous phosphate buffer (0.5 M Na_2HSO_4, 0.5 M NaH_2SO_4, 4.0 mL), poured into water (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 50% ethyl acetate/hexanes) afforded **157** (227.8 mg, 94%) as a pale yellow syrup: R_f 0.36 (50% ethyl acetate/hexanes); $[\alpha]_D$ –24.1 (*c* 1.34, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.16 (s, 1 H), 6.10 (app dt, 1 H, *J* = 10.7, 7.4 Hz), 5.97 (d of AB, 1 H, *J* = 15.9, 7.1 Hz), 5.86 (d of AB, 1 H, *J* = 15.9, 2.0 Hz), 5.69 (d, 1 H, *J* = 8.9 Hz), 4.17 (app dt, 1 H, *J* = 7.3, 6.0 Hz), 3.90 (s, 3 H), 3.34-3.25 (m, 2 H), 3.27 (s, 3 H), 3.10 (d of AB, 1 H, *J* = 15.0, 7.7 Hz), 2.99 (d of AB, 1 H, *J* = 15.0, 5.8 Hz), 2.55 (ddd of AB, 1 H, *J* = 14.5, 7.0, 2.4, 1.5 Hz), 2.32 (ddd of AB, 1 H, *J* = 14.5, 10.3, 7.8, 1.0 Hz), 0.93 (s, 9 H); ^{13}C NMR δ 162.4, 161.7, 144.1, 142.4, 140.5, 133.4, 113.7, 110.8, 91.4, 87.9, 79.3, 79.2, 56.9, 52.2, 35.2, 34.6, 33.1, 25.7; IR (neat) 3467, 3162, 2954, 2909, 2870, 2827, 2185, 1743, 1586 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NO_5Na$ (M+Na) 384.1787, found 384.1793.



2-((2*R*,3*E*,7*Z*,10*S*)-10-Hydroxy-2-methoxy-11,11-dimethyldodeca-3,7-dien-5-ynyl)oxazole-4-carboxylic ester cyclodimer (158), (4*S*,6*Z*,10*E*,12*R*)-4-*tert*-butyl-12-methoxy-3,15-dioxa-17-azabicyclo[12.2.1]heptadeca-1(16),6,10,14(17)-tetraen-8-yn-2-one (159) and (4*S*,6*Z*,10*Z*,12*R*)-4-*tert*-butyl-12-methoxy-3,15-dioxa-17-azabicyclo[12.2.1]heptadeca-1(16),6,10,14(17)-tetraen-8-yn-2-one (160). A solution of **157** (44.9 mg, 0.124 mmol, 1.0 equiv) in THF (2.0 mL) and water (0.2 mL) was treated at rt with 1.0 M aqueous LiOH solution (270 µL, 0.270 mmol, 2.2 equiv). After 20 h, the reaction mixture was poured into 2.0 M aqueous $NaHSO_4$ (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford a yellow wax (45.0 mg, 104%) that was diluted with anhydrous ethyl ether, filtered through a plug of cotton and concentrated to a yellow wax (42.0 mg, 97%) that was used without further purification.

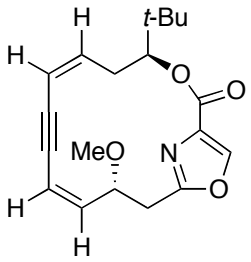
A solution of the crude hydroxyacid (18.6 mg, 0.535 mmol, 1.0 equiv) in THF (2.0 mL) was treated with triethylamine (40.0 µL, 0.285 mmol, 5.3 equiv) and 2,4,6-trichlorobenzoyl chloride (30.0 µL, 0.192 mmol, 3.6 equiv). The mixture was stirred at rt for 2 h, diluted with toluene to give 3.0 mL solution, which was added to a solution of DMAP (65.0 mg, 0.532 mmol, 9.9 equiv) in toluene (2.0 mL) via syringe pump (4.1

mL/h). After the addition was complete, the mixture was stirred at rt for an additional 2 h, treated with 1.0 M aqueous citric acid (5.0 mL), poured into H_2O (5.0 mL) and extracted with ethyl acetate. The combined organic layer was sequentially washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 50% ethyl acetate/hexanes) afforded a mixture of cyclomonomers **159**/**160** (3.1 mg) and dimer **158** (6.0 mg). The dimer was further purified by semi-prep HPLC (SiO_2, 20% ethyl acetate/hexanes, 8 mL/min, 254 nm) to afford **158** (4.6 mg, 26%) as a clear, colorless wax. The cyclomonomers **159**/**160** were separated by semi-prep HPLC (SiO_2, 10% ethyl acetate/hexanes, 8 mL/min, 254 nm) to afford **159** (1.4 mg, 8%) and **160** (1.4 mg, 8%) as clear, colorless waxes. **158:** R_f 0.27 (40% ethyl acetate/hexanes); $[\alpha]_D$ +183.6 (*c* 0.76, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.06 (s, 2 H), 6.00 (dd, 2 H, *J* = 15.9, 7.6 Hz), 5.95 (dt, 2 H, *J* = 10.6, 5.1 Hz), 5.65 (dd, 2 H, *J* = 15.9, 1.8 Hz), 5.54 (d, 2 H, *J* = 10.7 Hz), 5.08 (dd, 2 H, *J* = 11.1, 2.5 Hz), 4.16-4.09 (m, 2 H), 3.37 (s, 6 H), 3.31 (dd, 2 H, *J* = 14.1, 3.7 Hz), 3.03 (dd, 2 H, *J* = 14.1, 9.6 Hz), 2.96-2.88 (m, 2 H), 2.39-2.33 (m, 2 H), 1.01 (s, 18 H); ^{13}C NMR δ 161.9, 161.0, 143.6, 141.5, 140.3, 133.7, 113.7, 112.5, 91.0, 88.0, 79.9, 79.8, 57.1, 34.9, 34.6, 31.3, 26.2; IR (neat) 3164, 3027, 2964, 2931, 2872, 2828, 2191, 1739, 1583 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{38}H_{46}N_2O_8Na$ (M+Na) 681.3152, found 681.3152.



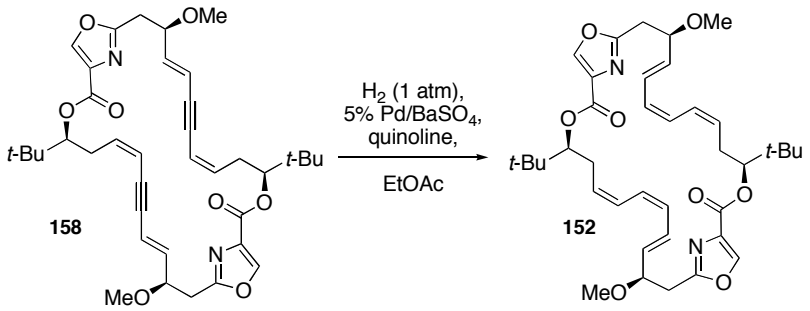
159: R_f 0.23 (20% ethyl acetate, hexanes); $[\alpha]_D$ +98.0 (*c* 0.41, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.11 (s, 1 H), 5.96 (dt, 1 H, *J* = 10.6, 7.2 Hz), 5.92 (dd, 1 H, *J* = 16.0, 8.7 Hz), 5.59 (dd, 1 H, *J* =

10.9, 2.4 Hz), 5.22 (dd, 1 H, *J* = 16.0, 2.5 Hz), 4.82 (dd, 1 H, *J* = 6.5, 1.9 Hz), 3.96 (dt, 1 H, *J* = 8.7, 6.5 Hz), 3.10 (dd, 1 H, *J* = 13.4, 8.7 Hz), 3.32 (s, 3 H), 3.36 (dd, 1 H, *J* = 13.4, 6.5 Hz), 2.71 (ddd, 1 H, *J* = 14.3, 10.4, 6.5 Hz), 2.42 (dd, 1 H, *J* = 13.2, 7.2 Hz), 1.03 (s, 9 H); ^{13}C NMR δ 161.7, 161.6, 144.3, 141.6, 140.2, 134.6, 112.1, 111.6, 91.5, 88.2, 81.6, 80.5, 57.3, 35.5, 35.1, 32.3, 26.0; IR (neat) 3161, 3119, 3020, 2961, 2932, 2872, 2825, 2182, 1721, 1578 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_4Na$ (M+Na) 352.1525, found 352.1494



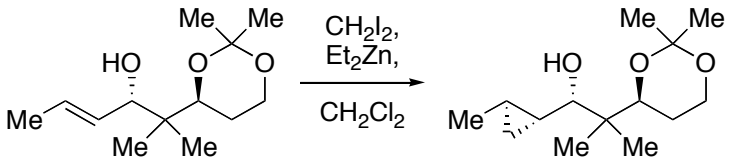
160

160: R_f 0.24 (20% ethyl acetate/hexanes); $[\alpha]_D$ +6.94 (*c* 0.49, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.11 (s, 1 H), 5.99 (dd, 1 H, *J* = 11.3, 1.8 Hz), 5.84 (dd, 1 H, *J* = 11.3, 7.4 Hz), 5.84 (dt, 1 H, *J* = 11.0, 5.5 Hz), 5.47 (d, 1 H, *J* = 10.8 Hz), 4.89 (dd, 1 H, *J* = 11.0, 1.3 Hz), 4.17 (t, 1 H, *J* = 9.3 Hz), 3.33 (s, 3 H), 3.20 (dd, 1 H, *J* = 14.3, 2.0 Hz), 3.01 (dd, 1 H, *J* = 14.3, 10.6 Hz), 2.80 (dt, 1 H, *J* = 13.0, 11.0 Hz), 2.24 (dd, 1 H, *J* = 13.0, 5.6 Hz), 1.04 (s, 9 H); ^{13}C NMR δ 162.3, 161.0, 144.1, 141.0, 139.1, 135.2, 114.0, 113.0, 92.7, 90.2, 81.5, 77.7, 56.8, 34.7, 33.6, 31.6, 26.3; IR (neat) 3162, 3118, 3022, 2962, 2928, 2872, 1719, 1577 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_4Na$ (M+Na) 352.1525, found 352.1509.



2-((2*R*,3*E*,5*Z*,7*Z*,10*S*)-10-Hydroxy-2-methoxy-11,11-dimethyldodeca-3,5,7-trienyl)oxazole-4-carboxylic ester cyclodimer (152). A solution of **158** (7.5 mg, 11.4 μmol, 1.0 equiv), quinoline (13.0 μL, 110 μmol, 9.7 equiv) and 5% $Pd/BaSO_4$ was suspended in ethyl acetate (1.0 mL) and the flask was flushed with H_2 (evacuate/flush, 3 cycles). The mixture was stirred at rt for 30 min and TLC (30% acetone/hexanes, threefold developed) indicated that the starting material was consumed. The mixture was filtered through a plug of Florisil/Celite (1:1). The plug was rinsed with ethyl acetate and the combined filtrates were concentrated. Purification by semi-prep HPLC (SiO_2, 20% ethyl acetate/hexanes, 8 mL/min, 254 nm) afforded **152** (3.2 mg, 43%) as a clear, colorless wax: R_f 0.47 (50% ethyl acetate/hexanes); $[\alpha]_D$ –27.8 (*c* 0.46, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.91 (s, 2 H), 6.44 (dd, 2 H, *J* = 15.0, 11.3 Hz), 6.35 (app t, 2 H, *J* = 11.8 Hz), 6.20 (app t, 2 H, *J* = 11.2 Hz), 5.93 (app t, 2 H, *J* = 10.9 Hz), 5.60-5.49 (m, 2 H), 5.56 (app dt, 2 H, *J* = 15.0, 8.6 Hz), 5.07 (dd, 2 H, *J* = 10.9, 2.0 Hz), 4.13 (dd, 2 H, *J* = 13.9, 7.8 Hz), 3.27 (s, 6 H), 3.14 (dd, 2 H, *J* = 14.8, 5.7 Hz), 2.82 (dd, 2 H, *J* = 14.8, 7.6 Hz), 2.55 (app t of AB, 2 H, *J* = 14.3, 10.0 Hz), 2.39 (app t of AB, 2 H, *J* = 14.8, 5.9 Hz), 0.97 (s, 18 H); ^{13}C NMR δ 162.5, 161.1, 143.4, 133.5, 133.4, 130.1, 129.1, 128.3, 125.9, 125.6, 80.6, 80.1, 56.8, 35.2, 35.0, 28.3, 26.2; IR (neat) 3166, 2964, 2929, 2871, 1740, 1584 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{38}H_{50}N_2O_8Na$ (M+Na) 685.3465, found 685.3479.

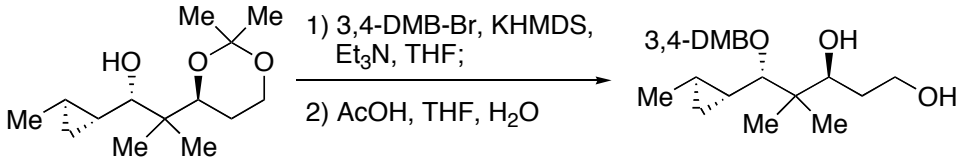
3.5.2.3. **Synthesis of the $C_{17\text{-}18}$-Cyclopropyl Analog**



129a **163**

(*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxan-4-yl)-2-methyl-1-((1*R*,2*R*)-2-methylcyclopropyl)propan-1-ol (163). A solution of **129a** (309.9 mg, 1.357 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) at 0 °C was treated with CH_2I_2 (1.10 mL, 13.7 mmol, 10.1 equiv) and a solution of Et_2Zn (1.0 M in hexanes, 6.80 mL, 6.90 mmol, 5.0 equiv). The resulting opaque, white mixture was stirred at 0 °C for 1 h and then treated with a mixture of 1.0 M aqueous sodium tartrate (5.0 mL) and brine (5.0 mL). The mixture was warmed to rt, poured into water (10 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis indicated a d.r. > 9:1 (α/β). Purification by chromatography on SiO_2 (2.5% ethyl ether, 1% triethylamine/hexanes to 20% ethyl ether, 1% triethylamine/hexanes) afforded **163** (321.4 mg, 98%) as a white, crystalline solid. Recrystallization from hexanes at –40 °C (freezer) afforded colorless needles: R_f 0.27 (40% ethyl ether/hexanes); Mp 81.4-82.2 °C (hexanes); $[\alpha]_D$ –36.4 (*c* 1.82, $CHCl_3$, 22 °C); ^{1}H NMR δ 3.99-3.83 (m, 3 H), 3.59 (bs, 1 H), 2.87 (d, 1 H, *J* = 5.8 Hz), 1.77 (qd, 1 H, *J* = 12.0, 5.6 Hz), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.36-1.31 (m, 1 H), 1.02 (d, 3 H, *J* = 5.5 Hz), 0.96 (s, 3 H), 0.92 (s, 3 H), 0.65-0.48 (m, 3 H), 0.29-0.24 (m, 1 H); ^{13}C NMR δ 98.8, 81.0, 76.8, 60.4, 40.9, 30.0, 25.4, 22.2, 21.2, 20.7, 19.1, 18.4, 12.4, 10.5; IR (KBr) 3511, 3072, 2999, 2960, 2946, 2889 cm^{-1}; MS (EI) *m/z* (rel. intensity) 227 ([M-CH_3]$^+$, 0.7), 167

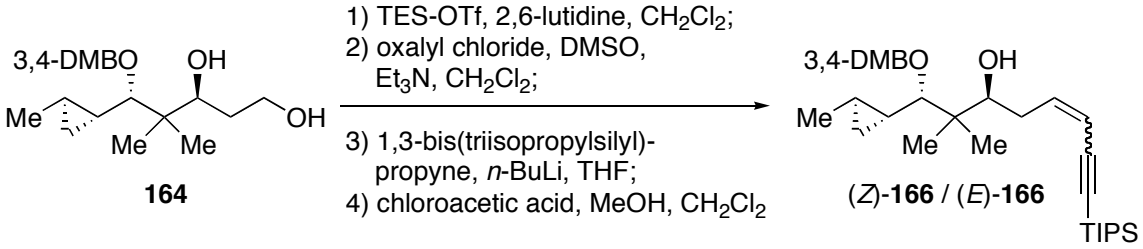
([M-$C_3H_7O_2$]$^+$, 0.8), 143 (11), 74 (54), 59 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{23}O_3$ (M-CH_3) 227.1647, found 227.1679.



163 **164**

(3*S*,5*S*)-5-(3,4-Dimethoxybenzyloxy)-4,4-dimethyl-5-((1*R*,2*R*)-2-methylcyclopropyl)pentane-1,3-diol (164). A solution of freshly prepared 3,4-dimethoxybenzylbromide (776.0, 3.358 mmol, 3.0 equiv) in THF (5.0 mL) was treated with triethylamine (950 µL, 6.77 mmol, 6.0 equiv). A precipitate formed and a solution of **163** (271.3, 1.120 mmol, 1.0 equiv) in THF (2.5 mL + 2.5 mL rinse) was added via cannula. The mixture was cooled to –78 °C and a solution of KHMDS (95% purity, 700 mg, 3.34 mmol, 3.0 equiv) in THF (2.0 mL) was added via cannula. The resulting bright yellow mixture was stirred for 10 min at – 78 °C and then warmed to 0 °C for 20 min. The yellow color faded and a precipitate formed. The resulting milky-white mixture was warmed to rt for 30 min, treated with saturated aqueous NH_4Cl (5.0 mL) and water (15 mL) and extracted with ethyl ether. The combined organic layers were concentrated and the residue was diluted with THF (2.0 mL), treated with water (2.0 mL) and glacial acetic acid (8.0 mL), stirred at rt for 48 h, diluted with ethyl acetate (20 mL) and washed with 2.0 M aqueous NaOH until the washings were pH>9. The combined aqueous washings were backwashed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (50% to 80% ethyl acetate/hexanes) afforded **164** (331.2 mg,

84%, 2 steps) as a clear, colorless wax: R_f 0.33 (60% ethyl acetate/hexanes); $[\alpha]_D$ –18.3 (*c* 1.53, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.87-6.80 (m, 3 H), 4.81 (d, 1 H, *J* = 10.8 Hz), 4.41 (d, 1 H, *J* = 4.5 Hz), 4.35 (d, 1 H, *J* = 10.8 Hz), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.88-3.81 (m, 2 H), 3.37 (bs, 1 H), 2.78 (d, 3 H, *J* = 8.9 Hz), 1.75-1.59 (m, 3 H), 1.08 (d, 3 H, *J* = 5.2 Hz), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.71-0.48 (m, 4 H); ^{13}C NMR δ 149.1, 148.8, 130.8, 120.5, 111.2, 111.1, 91.5, 79.7, 72.3, 63.1, 56.1, 56.0, 42.5, 33.1, 22.4, 22.3, 19.4, 18.3, 12.9, 10.5; IR (neat) 3424, 3064, 2951, 2873, 2837, 1609, 1594, 1517 cm^{-1}; MS (EI) *m/z* (rel. intensity) 352 (M^+, 0.4), 199 (6), 168 (18), 151 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2261.



(1*S*,3*S*,*Z*)-1-(3,4-Dimethoxybenzyloxy)-2,2-dimethyl-1-((1*R*,2*R*)-2-methylcyclopropyl)-8-(triisopropylsilyl)oct-5-en-7-yn-3-ol [(*Z*)-166] and (1*S*,3*S*,*E*)-1-(3,4-dimethoxybenzyloxy)-2,2-dimethyl-1-((1*R*,2*R*)-2-methylcyclopropyl)-8-(triisopropylsilyl)oct-5-en-7-yn-3-ol [(*E*)-166]. A solution of **164** (331.2 mg, 0.940 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with 2,6-lutidine (880 µL, 7.55 mmol, 8.0 equiv) and triethysilyl triflate (880 µL, 3.891 mmol, 4.1 equiv), stirred for 35 min at 0 °C and treated with saturated aqueous NH_4Cl (5.0 mL) and water (5.0 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid (25 mL), water (25 mL) and brine (25 mL). The combined aqueous washings were backwashed with CH_2Cl_2 and the combined organic layers

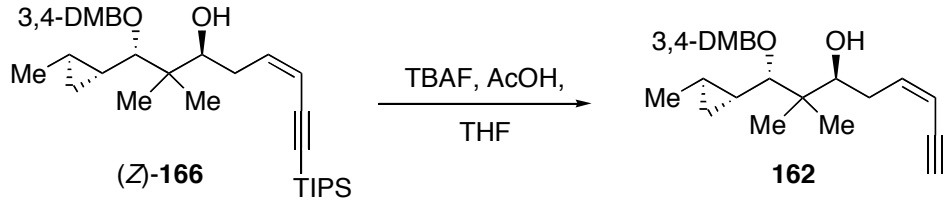
were dried (Na_2SO_4), filtered and concentrated. The residue was diluted with anhydrous ethyl ether (5.0 mL) and filtered through a plug of Florisil/Celite (1:1 v/v) to afford the bis(triethylsilyl)ether as a clear, pale yellow syrup (827.9 mg) that was used without further purification.

A solution of oxalyl chloride (330 μL, 3.78 mmol, 4.0 equiv) in CH_2Cl_2 (10 mL) was cooled to –78 °C and a solution of DMSO (535 μL, 7.54, 8.0 equiv) in CH_2Cl_2 (1.0 mL + 1.0 mL rinse) was added. The mixture was stirred for 20 min at –78 °C and a solution of the bis(triethylsilyl)ether in CH_2Cl_2 (2.5 mL + 2.5 mL rinse) was added via cannula. The mixture was stirred at –78 °C for 5 min, warmed to –40 °C for 20 min, cooled to –78 °C for 20 min, treated with triethylamine (2.00 mL, 14.3 mmol, 15.2 equiv), warmed to rt over 30 min and treated with water (20 mL). The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was diluted with anhydrous ethyl ether (2.0 mL), filtered through a plug of Florisil/Celite (1:1 v/v) and the filtrate was concentrated to a yellow oil that was used without further purification.

A solution of 1,3-bis(triisopropylsilyl)propyne (686.0 mg, 1.944 mmol, 2.0 equiv) was azeotropically dried at reduced pressure with hexanes (3 mL), diluted with THF (5.0 mL), cooled to 0 °C and treated with a solution of *n*-BuLi (1.5 M in hexanes, 1.00 mL, 1.50 mmol, 1.6 equiv). The mixture was warmed to rt for 1 h, cooled to –78 °C and treated with a solution of the aldehyde in THF (2.5 mL + 2.5 mL rinse). The mixture was stirred for 4 h at –78 °C, warmed to 0 °C for 15 min, treated with saturated aqueous NH_4Cl (5.0 mL) and water (5.0 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification

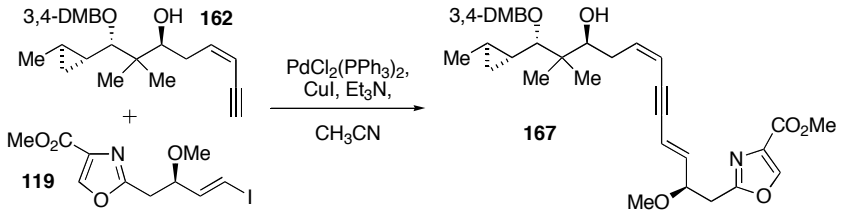
of the residue by chromatography on SiO_2 (10% ethyl ether/hexanes) removed the polar impurities, giving a pale yellow syrup that was diluted with CH_2Cl_2 (5.0 mL) and MeOH (15 mL), treated with chloroacetic acid (200 mg, 2.116 mmol, 2.25 equiv), stirred at rt for 36 h, quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10 to 30% ethyl ether/hexanes) afforded (*E*)-**166** (62.1 mg, 12%, 4 steps) and (*Z*)-**166** (160.0 mg, 32%, 4 steps). (*E*)-**166**: R_f 0.47 (40% ethyl ether/hexanes); $[\alpha]_D$ –30.1 (*c* 1.83, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.86-6.79 (m, 3 H), 6.35 (app dt, 1 H, *J* = 15.9, 7.1 Hz), 5.60 (d, 1 H, *J* = 15.9 Hz), 4.79 (d, 1 H, *J* = 10.9 Hz), 4.35 (d, 1 H, *J* = 10.9 Hz), 3.89-3.86 (m, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.68 (ddd, 1 H, *J* = 9.8, 4.3, 2.4 Hz), 2.76 (d, 1 H, *J* = 9.0 Hz), 2.28 (dd, 1 H, *J* = 14.3, 7.2 Hz), 2.20-2.10 (m, 1 H), 1.11-1.05 (m, 24 H), 0.99 (s, 3 H), 0.98 (s, 3 H), 0.70-0.47 (m, 4 H); ^{13}C NMR δ 149.2, 148.8, 144.0, 131.1, 120.4, 111.6, 111.2, 111.1, 106.0, 91.0, 89.1, 72.3, 56.1, 56.0, 42.8, 36.1, 22.5, 21.8, 19.5, 18.8, 18.7, 18.3, 12.9, 11.7, 11.5, 10.5; IR (neat) 3482, 2943, 2889, 2865, 2131, 1610, 1593 cm^{-1}; MS (EI) *m/z* (rel. intensity) 528 (M^+, 1.9), 485 ([M-C_3H_7]$^+$, 2.3), 151 (100); HRMS (EI) *m/z* calcd for $C_{32}H_{52}O_4Si$ 528.3635, found 528.3625. (*Z*)-**166**: R_f 0.32 (40% ethyl ether/hexanes); $[\alpha]_D$ –29.4 (*c* 2.84, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.84-6.76 (m, 3 H), 6.19 (ddd, 1 H, *J* = 10.9, 7.7, 6.3 Hz), 5.58 (d, 1 H, *J* = 10.9 Hz), 4.78 (d, 1 H, *J* = 10.8 Hz), 4.33 (d, 1 H, *J* = 10.8 Hz), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.69-3.65 (m, 1 H), 2.77 (d, 1 H, *J* = 8.8 Hz), 2.66 (dd, 1 H, *J* = 14.3, 7.8 Hz), 2.39-2.29 (m, 1 H), 1.06 (s, 21 H), 1.15-1.03 (m, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.69-0.45 (m, 4 H); ^{13}C NMR δ 149.3, 148.8, 143.4, 131.3, 120.2, 111.4 (2 C), 110.3, 104.2, 95.1,

91.0, 77.3, 72.4, 56.1, 56.0, 42.9, 33.6, 22.3, 21.7, 19.6, 18.8, 18.2, 12.7, 11.5, 10.5; IR (neat) 3479, 2943, 2865, 2144, 1609, 1594, 1518 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{52}O_4SiNa$ 551.3533, found 551.3500.



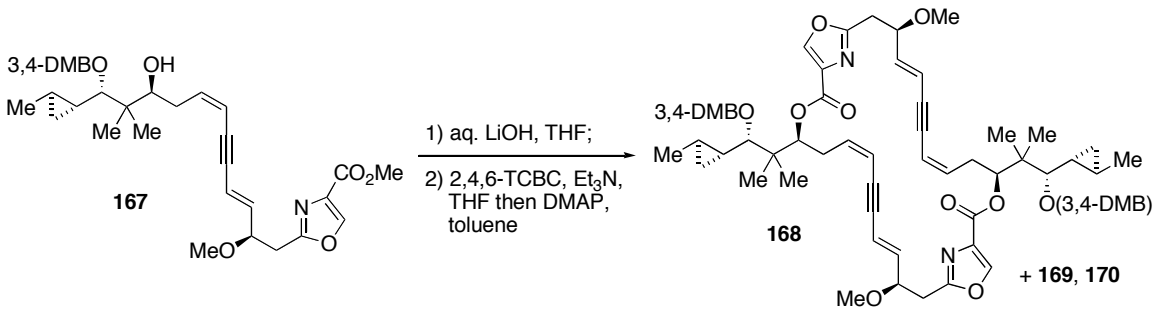
(1*S*,3*S*,*Z*)-1-(3,4-Dimethoxybenzyloxy)-2,2-dimethyl-1-((1*R*,2*R*)-2-methylcyclopropyl)oct-5-en-7-yn-3-ol (162). A solution of (*Z*)-**166** (160.0 mg, 0.303 mmol, 1.0 equiv) in THF (3.0 mL) at rt was treated with glacial acetic acid (35.0 µL, 0.606 mmol, 2.0 equiv) and a solution of TBAF (1.0 M in THF, 0.600 mL, 0.600 mmol, 2.0 equiv), stirred at rt for 36 h, poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 50% ethyl ether/hexanes) afforded **162** (100.1 mg, 89%) as a clear, colorless syrup: R_f 0.26 (40% ethyl ether/hexanes); $[\alpha]_D$ –30.0 (*c* 1.07, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.85-6.78 (m, 3 H), 6.24 (app dt, 1 H, *J* = 10.9, 7.2 Hz), 5.53 (dd, 1 H, *J* = 10.8, 2.1 Hz), 4.80 (d, 1 H, *J* = 10.8 Hz), 4.35 (d, 1 H, *J* = 10.8 Hz), 3.90-3.85 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.66 (ddd, 1 H, *J* = 9.9, 4.4, 2.4 Hz), 3.07 (d, 1 H, *J* = 1.6 Hz), 2.80 (d, 1 H, *J* = 8.2 Hz), 2.59 (ddt, 1 H, *J* = 14.0, 7.4, 1.5 Hz), 2.35 (dddd, 1 H, *J* = 14.4, 10.0, 6.9, 1.0 Hz), 1.07 (d, 3 H, *J* = 5.5 Hz), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.70-0.46 (m, 4 H); ^{13}C NMR δ 149.1, 148.7, 144.6, 131.1, 120.3, 111.2, 111.1, 109.0, 90.9, 81.7, 80.9, 77.9, 72.2, 56.0 (2 C), 42.8, 33.4, 22.4, 22.1, 19.5, 18.3, 12.9, 10.4; IR (neat) 3472, 3288, 3063, 2949, 2868, 2836,

2094, 1608, 1593, 1516 cm^{-1}; MS (EI) *m/z* (rel. intensity) 372 (M^+, 1.4), 288 (1.3), 151 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_4$ 372.2301, found 372.2292.



Methyl 2-((2*R*,3*E*,7*Z*,10*S*,12*S*)-12-(3,4-dimethoxybenzyloxy)-10-hydroxy-2-methoxy-11,11-dimethyl-12-((1*R*,2*R*)-2-methylcyclopropyl)dodeca-3,7-dien-5-ynyl)oxazole-4-carboxylate (167). A solution of **162** (52.5, 0.141 mmol, 1.1 equiv) and **119** (43.0 mg, 0.128 mmol, 1.0 equiv) in CH_3CN (1.0 mL) was degassed (freeze-pump-thaw, 2 cycles), treated with $PdCl_2(PPh_3)_2$ (5.0 mg, 7.1 μmol, 0.05 equiv) and CuI (5.0 mg, 0.026 mmol, 0.2 equiv), degassed (1 cycle), placed in a 0 °C bath and treated with triethylamine (120 μL, 0.855 mmol, 6.7 equiv). The mixture became almost colorless then rust-brown and was stirred at 0 °C for 1 h, warmed to rt for 30 min and treated with phosphate buffer (0.5 M Na_2HPO_4, 0.5 M NaH_2PO_4, 1.0 mL). After stirring at rt for 30 min, the mixture was diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) afforded **167** (70.0 mg, 94%) as a clear, colorless wax: R_f 0.35 (50% ethyl acetate/hexanes); $[\alpha]_D$ –34.0 (*c* 1.69, $CHCl_3$, 22 °C); ^1H NMR δ 8.14 (s, 1 H), 6.86-6.78 (m, 3 H), 6.19 (dt, 1 H, *J* = 10.7, 7.2 Hz), 5.92 (d of AB, 1 H, *J* = 15.9, 7.0 Hz), 5.86 (d of AB, 1 H, *J* = 15.9, 1.8 Hz), 5.66 (d, 1 H, *J* = 10.7 Hz), 4.81 (d, 1 H, *J* = 10.8 Hz), 4.35 (d, 1 H, *J* = 10.8 Hz), 4.14 (app q, 1 H, *J* = 7.2 Hz), 3.93-3.89 (m, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.86 (s, 3

H), 3.69-3.64 (m, 1 H), 3.24 (s, 3 H), 3.05 (d of AB, 1 H, *J* = 15.0, 7.8 Hz), 2.96 (d of AB, 1 H, *J* = 15.0, 5.6 Hz), 2.81 (d, 1 H, *J* = 8.9 Hz), 2.56 (d of AB, 1 H, *J* = 14.2, 7.2 Hz), 2.37 (app t of AB, 1 H, *J* = 14.3, 8.1 Hz), 1.09 (d, 3 H, *J* = 5.4 Hz), 1.04 (s, 3 H), 1.03 (s, 3 H), 0.71-0.48 (m, 4 H); ^{13}C NMR δ 162.5, 161.7, 149.1, 148.7, 144.1, 143.3, 140.3, 133.4, 131.0, 120.3, 113.9, 111.2, 111.0, 109.8, 91.1, 90.9, 88.4, 79.3, 78.0, 72.2, 56.9, 56.0 (2 C), 52.2, 42.8, 34.6, 33.5, 22.3, 22.2, 19.5, 18.2, 12.9, 10.4; IR (neat) 3468, 2950, 2870, 2835, 2251, 2184, 1745, 1586, 1517 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{43}NO_8Na$ (M+Na) 604.2886, found 604.2841.



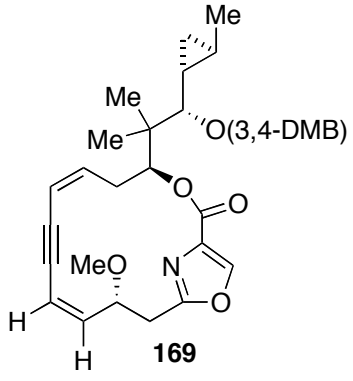
2-((2*R*,3*E*,7*Z*,10*S*,12*S*)-12-(3,4-Dimethoxybenzyloxy)-10-hydroxy-2-methoxy-11,11-dimethyl-12-((1*R*,2*R*)-2-methylcyclopropyl)dodeca-3,7-dien-5-ynyl)oxazole-4-carboxylic acid ester cyclodimer (168), (4*S*,6*Z*,10*Z*,12*R*)-4-((*S*)-1-(3,4-dimethoxybenzyloxy)-2-methyl-1-((1*R*,2*R*)-2-methylcyclopropyl)propan-2-yl)-12-methoxy-3,15-dioxa-17-azabicyclo[12.2.1]heptadeca-1(16),6,10,14(17)-tetraen-8-yn-2-one (169) and (4*S*,6*Z*,10*E*,12*R*)-4-((*S*)-1-(3,4-dimethoxybenzyloxy)-2-methyl-1-((1*R*,2*R*)-2-methylcyclopropyl)propan-2-yl)-12-methoxy-3,15-dioxa-17-azabicyclo-[12.2.1]heptadeca-1(16),6,10,14(17)-tetraen-8-yn-2-one (170). A solution of **167** (36.2 mg, 0.062 mmol, 1.0 equiv) in THF (1.0 mL) and water (0.1 mL) was treated with 1.0 M aqueous LiOH (140 μL, 0.140 mmol, 2.2 equiv), stirred at rt for 12 h, poured into

2.0 M aqueous $NaHSO_4$ (10 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford the crude hydroxyacid that was used within several hours of preparation: ^{1}H NMR δ 8.21 (s, 1 H), 6.87-6.78 (m, 3 H), 6.19 (dt, 1 H, *J* = 10.6, 7.2 Hz), 5.92 (d of AB, 1 H, *J* = 15.9, 6.9 Hz), 5.87 (AB, 1 H, *J* = 15.9 Hz), 5.66 (d, 1 H, *J* = 10.5 Hz), 4.81 (d, 1 H, *J* = 10.7 Hz), 4.36 (d, 1 H, *J* = 10.7 Hz), 4.15 (app q, 1 H, *J* = 6.7 Hz), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.82-3.89 (m, 1 H), 3.69 (dd, 1 H, *J* = 10.0, 2.3 Hz), 3.24 (s, 3 H), 3.07 (d of AB, 1 H, *J* = 14.9, 7.7 Hz), 2.98 (d of AB, 1 H, *J* = 15.1, 5.5 Hz), 2.82 (d, 1 H, *J* = 8.9 Hz), 2.58 (dd, 1 H, *J* = 14.1, 7.4 Hz), 2.42-2.32 (m, 1 H), 1.08 (d, 3 H, *J* = 5.3 Hz), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.69-0.49 (m, 4 H).

A solution of the dry hydroxyacid in THF (2.0 mL) at rt was treated with triethylamine (85.0 μL, 0.606 mmol, 9.7 equiv) and 2,4,6-trichlorobenzoylchloride (50.0 μL, 0.320 mmol, 5.1 equiv), stirred at rt for 1 h, diluted with toluene (8.0 mL) and added to a solution of DMAP (153 mg, 1.25 mmol, 20 equiv) in toluene (20.0 mL) via syringe pump (3.9 mL/h). After the addition was complete, the syringe was rinsed with toluene (1.0 mL) and this solution was added to the reaction mixture. After stirring for an additional 4 h at rt, the mixture was treated with 1.0 M aqueous citric acid (10 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were sequentially washed with water, saturated aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 60% ethyl acetate/hexanes) afforded **168** (14.7 mg) and a mixture of **169** and **170** (4.1 mg). Purification of **168** by semi-prep HPLC (35% ethyl acetate/hexanes,

8 mL/min, 254 nm, $R_t \approx$ 20 min) on SiO_2 afforded **168** (9.3 mg, 27%) as a clear, colorless wax: R_f 0.34 (50% ethyl acetate/hexanes); $[\alpha]_D$ +144.6 (*c* 1.29, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.98 (s, 2 H), 7.05 (d, 2 H, *J* = 1.8 Hz), 6.93 (dd, 2 H, *J* = 8.1, 1.7 Hz), 6.80 (d, 2 H, *J* = 8.2 Hz), 5.99-5.90 (m, 2 H), 5.96 (dd, 2 H, *J* = 15.9, 7.5 Hz), 5.66 (dd, 2 H, *J* = 11.0, 2.3 Hz), 5.64 (dd, 2 H, *J* = 15.7, 1.9 Hz), 5.51 (d, 2 H, *J* = 9.6 Hz), 4.71 (d, 2 H, *J* = 10.4 Hz), 4.25 (d, 2 H, *J* = 10.3 Hz), 4.16-4.09 (m, 2 H), 3.90 (s, 6 H), 3.86 (s, 6 H), 3.36 (s, 6 H), 3.30 (dd, 2 H, *J* = 14.1, 3.8 Hz), 3.05-2.94 (m, 4 H), 2.55 (d, 2 H, *J* = 8.5 Hz), 2.33 (bd, 2 H, *J* = 11.2 Hz), 1.12 (s, 6 H), 1.09 (d, 6 H, *J* = 5.4 Hz), 1.05 (s, 6 H), 0.63-0.61 (m, 4 H), 0.50-0.44 (m, 4 H); ^{13}C NMR δ 161.8, 160.9, 149.1, 148.6, 143.6, 141.3, 140.6, 133.9, 132.4, 120.4, 113.7, 112.2, 111.9, 111.2, 91.1, 88.0 87.1, 79.9, 76.6, 72.7, 57.1, 56.2, 56.1, 43.8, 34.6, 31.7, 20.2, 20.0, 19.9, 18.3, 12.7, 10.6; IR (neat) 2943, 2866, 2834, 1737, 1584, 1516 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{64}H_{78}N_2O_{14}Na$ (M+Na) 1121.5351, found 1121.5295

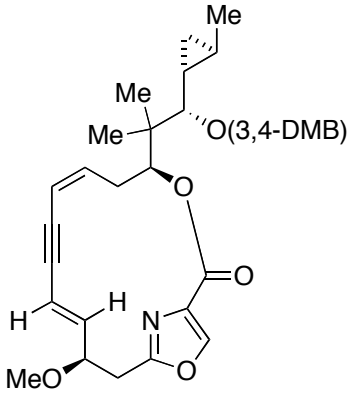
Purification by semi-prep HPLC (20% ethyl acetate/hexanes, 8 mL/min, 254 nm) on SiO_2 of the combined mixture of cyclomonomers from several reactions (8.8 mg) afforded **169** ($R_t \approx$ 14 min, 4.8 mg, 55% of the mixture) and **170** ($R_t \approx$ 17 min, 2.5 mg, 28% of the mixture).



169

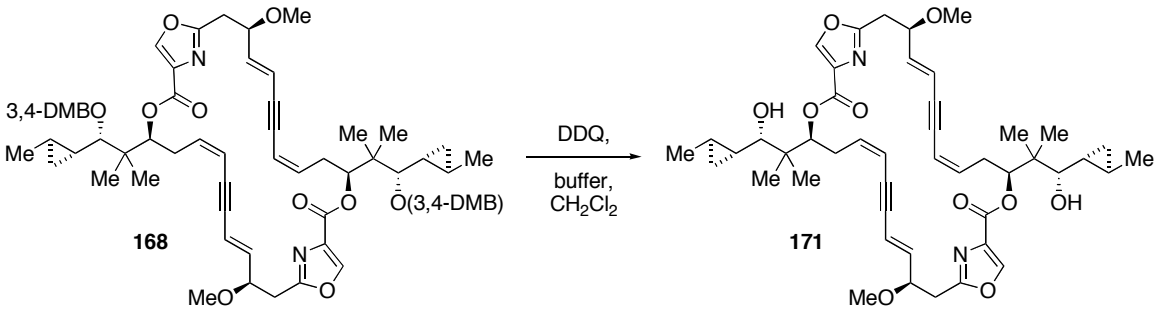
169: R_f 0.41 (40% ethyl acetate/hexanes); $[\alpha]_D$ +23.6 (*c* 0.36, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.09 (s, 1 H), 7.05 (d, 1 H, *J* = 1.7 Hz), 6.95 (dd, 1 H, *J* = 8.1, 1.6 Hz), 6.82 (d, 1 H, *J* = 8.1 Hz), 5.96 (dd, 1 H, *J* = 11.4, 1.7 Hz), 5.85 (d, 1 H, *J* = 8.0 Hz), 5.87-5.78 (m, 1 H), 5.51 (d, 1 H, *J* = 10.8 Hz), 5.45 (d, 1

H, *J* = 10.8 Hz), 4.73 (d, 1 H, *J* = 10.6 Hz), 4.32 (d, 1 H, *J* = 10.6 Hz), 4.16 (app t, 1 H, *J* = 9.0 Hz), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.33 (s, 3 H), 3.20 (dd, 1 H, *J* = 14.0, 1.9 Hz), 3.00 (dd, 1 H, *J* = 14.0, 10.6 Hz), 3.00 (dd, 1 H, *J* = 10.6 Hz), 2.84 (app q, 1 H, *J* = 11.7 Hz), 2.66 (d, 1 H, *J* = 8.8 Hz), 2.22 (dd, 1 H, *J* = 13.1, 5.4 Hz), 1.14 (s, 3 H), 1.10 (d, 3 H, *J* = 5.9 Hz), 1.09 (s, 3 H), 0.68-0.51 (m, 3 H), 0.46-0.41 (m, 1 H); ^{13}C NMR δ 162.2, 161.0, 149.0, 148.4, 144.3, 141.1, 139.4, 135.5, 132.4, 120.2, 113.8, 112.8, 111.6, 110.9, 92.6, 90.1, 86.9, 78.3, 77.9, 77.4, 72.6, 56.8, 56.1, 43.5, 33.7, 32.0, 31.1, 20.0, 19.9, 18.3, 12.6, 10.7; IR (neat) 2929, 2866, 2847, 1716, 1590, 1577 cm^{-1}; MS analysis pending.

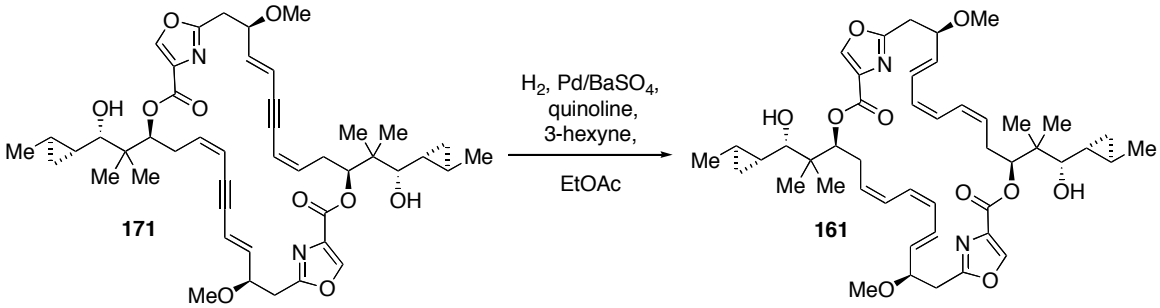


170

170: R_f 0.33 (40% ethyl acetate/hexanes); $[\alpha]_D$ +77.2 (*c* 0.25, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.07 (s, 1 H), 7.06 (d, 1 H, *J* = 1.6 Hz), 6.92 (dd, 1 H, *J* = 8.1, 1.6 Hz), 6.81 (d, 1 H, *J* = 8.2 Hz), 5.96 (dd, 1 H, *J* = 10.7, 7.1 Hz), 5.90 (dd, 1 H, *J* = 16.0, 8.6 Hz), 5.58 (dd, 1 H, *J* = 11.0, 2.3 Hz), 5.42 (dd, 1 H, *J* = 6.5, 1.5 Hz), 5.23 (dd, 1 H, *J* = 16.0, 2.4 Hz), 4.72 (d, 1 H, *J* = 10.5 Hz), 4.29 (d, 1 H, *J* = 10.5 Hz), 4.01-3.87 (m, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.37 (dd, 1 H, *J* = 13.5, 6.6 Hz), 3.32 (s, 3 H), 3.09 (dd, 1 H, *J* = 13.5, 8.4 Hz), 2.71 (ddd, 1 H, *J* = 14.6, 10.5, 6.8 Hz), 2.63 (d, 1 H, *J* = 8.6 Hz), 2.47 (dd, 1 H, *J* = 14.5, 6.8 Hz), 1.11 (s, 6 H), 1.10 (d, 3 H, *J* = 6.5 Hz), 0.64-0.44 (m, 4 H); ^{13}C NMR δ (characteristic signals) 161.7, 161.2, 149.0, 148.4, 144.3, 134.7, 132.4, 120.2, 112.0, 111.6, 110.9, 91.5, 88.4, 86.9, 72.6, 57.3, 56.1, 44.1, 20.0, 19.5, 18.3, 12.7; IR (neat) 2962, 2927, 2853, 1721 cm^{-1}; MS analysis pending.



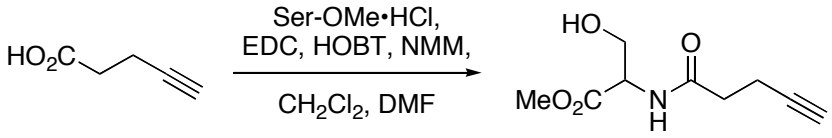
(17*R*,17'*R*,18*R*,18'*R*)-($C_{17\text{-}18}C_{17'\text{-}18'}$)-Bis(cyclopropyl)-(9,9',10,10')-didehydro-disorazole C_1 (171). A solution of **168** (11.3 mg, 10.3 μmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) and phosphate buffer (0.5 M $NaHPO_4$, 0.5 M NaH_2PO_4, 1.0 mL) was cooled to 0 °C, treated with DDQ (10.0 mg, 44.1 mmol, 4.3 equiv) and stirred for 30 min, while slowly warming to rt. Saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL) was added and the mixture was diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (20% to 80% ethyl acetate/hexanes) afforded **171** (7.5 mg, 91%) as a clear, colorless wax: R_f 0.27 (60% ethyl acetate/hexanes); $[\alpha]_D$ +189.9 (*c* 0.85, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.08 (s, 2 H), 6.02 (dd, 2 H, *J* = 15.9, 7.5 Hz), 5.94 (app dt, 2 H, *J* = 5.0, 10.6 Hz), 5.66 (dd, 2 H, *J* = 15.9, 1.8 Hz), 5.56 (bd, 2 H, *J* = 10.6 Hz), 5.38 (dd, 2 H, *J* = 11.1, 2.2 Hz), 4.14-4.07 (m, 2 H), 3.37 (s, 6 H), 3.30 (dd, 2 H, *J* = 14.2, 4.2 Hz), 3.08-2.96 (m, 4 H), 2.72 (d, 2 H, *J* = 8.6 Hz), 2.44-2.34 (m, 4 H), 1.07-1.04 (m, 18 H), 0.71-0.57 (m, 4 H), 0.45 (app dt, 2 H, *J* = 8.6, 4.6 Hz), 0.29 (app dt, 2 H, *J* = 8.1, 4.8 Hz); ^{13}C NMR δ 162.1, 161.5, 144.0, 141.7, 140.1, 133.5, 113.5, 112.6, 91.2, 88.0, 79.8, 78.9, 78.9, 78.0, 57.1, 42.8, 34.6, 31.2, 22.1, 19.7, 18.9, 18.3, 13.4, 10.7; IR (neat) 3515, 2970, 2930, 2188, 1734, 1583 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{46}H_{58}N_2O_{10}Na$ (M+Na) 821.3989, found 821.4019.



(17*R*,18*R*)-$C_{17\text{-}18}C_{17'\text{-}18'}$-Bis(cyclopropyl) disorazole C_1 (161). A mixture of **171** (4.0 mg, 5.0 μmol, 1.0 equiv), $Pd/BaSO_4$ (4.0 mg), quinoline (8.0 μL, 68 μmol, 14 equiv), and 3-hexyne (7.0 μL, 62 μmol, 12 equiv) was suspended in ethyl acetate (0.5 mL, degassed under vacuum at rt), stirred under H_2 (1 atm) for 1.5 h and filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with additional ethyl acetate and the combined filtrate was concentrated. Purification by SiO_2 semi-preparative HPLC (45% ethyl acetate/hexanes, 8 mL/min, 254 nm, $R_t \approx 16.0$ min) afforded semi-pure **161** (1.1 mg, 28%). The material (3.3 mg) from 3 reductions and purifications was pooled and further purified by SiO_2 semi-preparative HPLC (1% to 2% $MeOH/CH_2Cl_2$ over 30 min, 8 mL/min, 254 nm, R_t = 23.4-25.3 min) to afford **161** (2.6 mg, 79%, 22% overall yield) as a clear, colorless wax: R_f 0.39 (80% ethyl acetate/hexanes); $[\alpha]_D$ –57.3 (*c* 0.26, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.90 (s, 2 H), 6.44 (dd, 2 H, *J* = 15.1, 11.3 Hz), 6.37 (app t, 2 H, *J* = 11.0 Hz), 6.26 (app t, 2 H, *J* = 11.1 Hz), 5.96 (app t, 2 H, *J* = 10.9 Hz), 5.59 (dd, 2 H, *J* = 15.2, 8.4 Hz), 5.52 (bt, 2 H, *J* = 9.9 Hz), 5.34 (d, 2 H, *J* = 10.0 Hz), 4.12 (app q, 2 H, *J* = 6.4 Hz), 3.26 (s, 6 H), 3.05 (d of AB, 2 H, *J* = 15.2, 6.0 Hz), 2.84 (d of AB, 2 H, *J* = 15.2, 6.5 Hz), 2.75-2.63 (m, 4 H), 2.41-2.34 (m, 4 H), 1.06-1.02 (m, 18 H), 0.69-0.54 (m, 4 H), 0.44 (app dt, 2 H, *J* = 8.6, 4.4 Hz), 0.28 (app dt, 2 H, *J* = 8.5, 4.7 Hz); ^{13}C NMR δ 162.5, 161.6, 144.0, 133.6, 133.1, 129.9, 128.9, 128.5, 126.3, 125.6, 79.7, 78.9, 78.5,

56.9, 42.8, 35.3, 28.2, 22.0, 19.5, 18.8, 18.3, 13.4, 10.7; IR (neat) 3467, 2954, 2925, 2854, 1732, 1583 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{46}H_{62}N_2O_{10}Na$ (M+Na) 825.4302, found 825.4315.

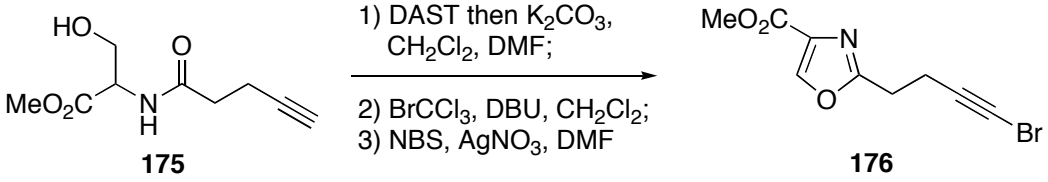
3.5.2.4. Attempted Synthesis of the C_6-Desmethoxy Analog



174 **175**

Methyl 3-hydroxy-2-pent-4-ynamidopropanoate (175). A mixture of 4-pentynoic acid (**174**) (1.00g, 10.2 mmol, 1.0 equiv), serine methyl ester hydrochloride (2.380 g, 15.30 mmol, 1.5 equiv), and HOBT (275 mg, 2.04 mmol, 0.2 equiv) was dissolved in DMF (2.0 mL), diluted with CH_2Cl_2 (10 mL) and treated with EDC (2.630 g, 13.72 mmol, 1.3 equiv). The mixture was cooled to 0 °C, treated with NMM (3.00 mL, 27.2 mmol, 2.7 equiv) and allowed to warm to rt. After 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), stirred for 30 min at rt and separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 1.0 M aqueous citric acid (75 mL), water, brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (80% ethyl acetate/hexanes to 100% ethyl acetate) afforded **175** (682.8 mg, 34%) as a clear, colorless syrup: R_f 0.39 (ethyl acetate); ^1H NMR δ 7.03 (d, 1 H, *J* = 7.8 Hz), 4.60 (dt, 1 H, *J* = 7.8, 3.5 Hz), 3.92 (d of AB, 1 H, *J* = 11.3, 3.8 Hz), 3.80 (d of AB, 1 H, *J* = 11.3, 3.4 Hz), 3.72 (s, 3 H), 2.46 (app s, 4 H), 2.00 (s, 1 H); ^{13}C NMR δ 171.9, 171.2, 82.8,

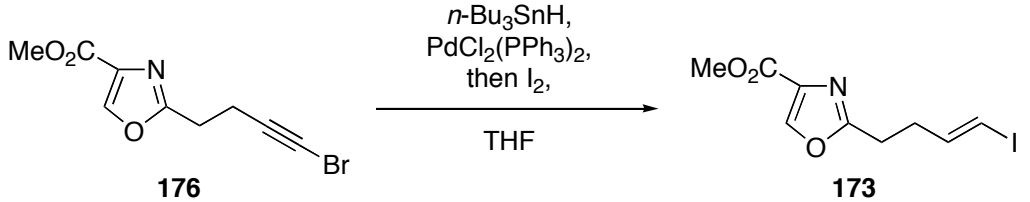
69.6, 62.9, 54.7, 52.8, 34.9, 14.8; IR (neat) 3366, 3291, 3079, 2955, 2888, 2118, 1743, 1651, 1538 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_9H_{13}NO_4Na$ (M+Na) 222.0742, found 222.0733.



175 **176**

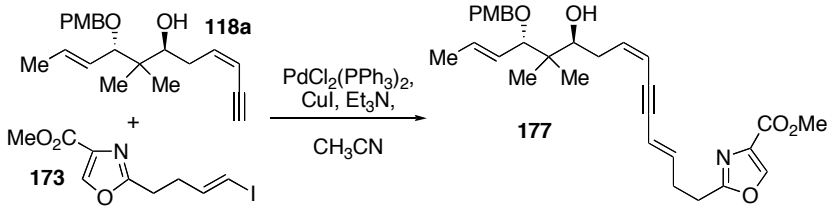
Methyl 2-(4-bromobut-3-ynyl)oxazole-4-carboxylate (176). A solution of **175** (680.0 mg, 3.414 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) and DMF (0.1 mL) was cooled to –78 °C, treated with DAST (500 µL, 3.78 mmol, 1.1 equiv), stirred for 30 min and treated with anhydrous K_2CO_3 (1.420 g, 10.27 mmol, 3.0 equiv). The mixture was stirred for 5 min, warmed to 0 °C for 10 min, quenched with saturated aqueous $NaHCO_3$ (20 mL) and stirred at rt for 2 h. The mixture was extracted with ethyl acetate and the combined organic layers were washed with 4.0 M aqueous LiCl (10 mL), dried (Na_2SO_4), filtered and concentrated to a red oil. The red oil was azeotropically dried at reduced pressure with toluene (10 mL) and diluted with CH_2Cl_2 (20.0 mL). The resulting solution was cooled to 0 °C and treated with $BrCCl_3$ (1.01 mL, 10.2 mmol, 3.0 equiv) and DBU (1.53 mL, 10.2 mmol, 3.0 equiv). The mixture was allowed to warm to rt over 3 h, diluted with ethyl ether (20 mL) and filtered through a pad of SiO_2 (40 mm x 40 mm). The pad was rinsed with ethyl ether (200 mL) and the combined filtrate was concentrated to an orange oil. Purification by chromatography on SiO_2 (20% to 40% ethyl acetate/hexanes) afforded a yellow syrup that crystallized to a yellow solid under vacuum. The yellow solid was dissolved in DMF (5.0 mL) and treated with *N*-bromosuccinimide (530 mg, 2.99 mmol, 1.1 equiv) and silver nitrate (45.0 mg, 0.265

mmol, 0.7 equiv) and stirred at rt for 4 h. The mixture was diluted with ethyl ether (20 mL), washed with water (2x) and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 20% acetone/hexanes) afforded **176** (453.0 mg, 51%, 3 steps) as a white crystalline solid: R_f 0.23 (20% acetone/hexanes); Mp 91.4-92.3 °C (acetone/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1 H), 3.88 (s, 3 H), 3.02 (t, 2 H, *J* = 7.4 Hz), 2.69 (t, 2 H, *J* = 7.4 Hz); ^{1}H NMR (acetone-d6) δ 8.47 (s, 1 H), 3.81 (s, 3 H), 3.03 (t, 2 H, *J* = 7.3 Hz), 2.73 (t, 2 H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 163.7, 161.7, 144.2, 133.4, 77.7, 52.3, 40.3, 27.4, 17.8; ^{13}C NMR (acetone-d6) δ 164.4, 162.0, 145.5, 134.0, 79.2, 51.9, 40.4, 27.6, 17.7; IR (KBr) 3154, 3120, 2954, 2854, 2221, 2206, 1723, 1587, 1574 cm^{-1}; MS (EI) *m/z* (rel. intensity) 257 (M^+, 3), 242 ($[M\text{-}CH_3]^+$, 17), 227 ($[M\text{-}CH_3O]^+$, 34), 199 ($[M\text{-}CO_2CH_3]^+$, 82), 178 ($[M\text{-}Br]^+$, 37); HRMS (EI) *m/z* calcd for $C_8H_5NO_3Br$ (M-CH_3) 241.9453, found 241.9449.



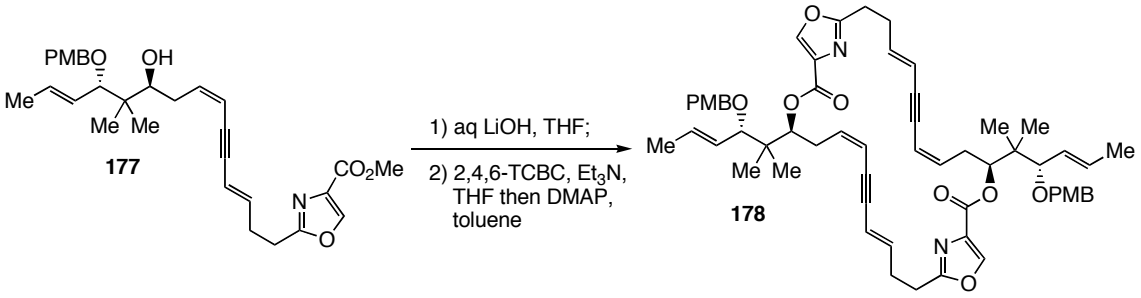
(*E*)-Methyl 2-(4-iodobut-3-enyl)oxazole-4-carboxylate (173). A solution of **176** (450.0 mg, 1.744 mmol, 1.0 equiv) in THF (10.0 mL) was cooled to –78 °C and treated with $PdCl_2(PPh_3)_2$ (11.5 mg, 16.4 μmol, 0.01 equiv) and *n*-Bu_3SnH (960 μL, 3.57 mmol, 2.05 equiv). The mixture was stirred at –78 °C for 1 h, warmed to 0 °C for 2 h and treated with a solution of I_2 (530 mg, 2.09 mmol, 1.2 equiv) in THF (2.0 mL). The resulting brown solution was stirred at 0 °C for 25 min, treated with saturated aqueous $Na_2S_2O_3$ (15 mL), saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous KF (2.0

mL), stirred for 30 min at rt and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% acetone/hexanes) afforded **173** (434.9 mg, 81%) as a white crystalline solid: R_f 0.39 (30% acetone/hexanes); Mp 56.0-57.5 °C (acetone/hexanes); ^{1}H NMR δ 8.15 (s, 1 H), 6.53 (app dt, 1 H, *J* = 14.3, 7.1 Hz), 6.14 (d, 1 H, *J* = 14.4 Hz), 3.90 (s, 3 H), 2.91 (app t, 2 H, *J* = 7.4 Hz), 2.55 (app q, 2 H, *J* = 7.1 Hz); ^{13}C NMR δ 164.1, 161.4, 143.8, 143.3, 133.1, 76.9, 52.0, 32.8, 26.8; IR (KBr) 3153, 3113, 3057, 2959, 2927, 2852, 1724, 1585, 1438, 1316 cm^{-1}; MS (EI) *m/z* (rel. intensity) 307 (M^+, 0.8), 276 ([M-OCH_3]$^+$, 2.8), 180 ([M-I]$^+$,100); HRMS (EI) *m/z* calcd for $C_8H_7NO_2I$ 275.9522 (M-OCH_3) 275.9522, found 275.9522.



2-((3*E*,7*Z*,10*S*,12*S*,13*E*)-10-Hydroxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-methyl carboxylate (177). A solution of **173** (104.0 mg, 0.339 mmol, 1.0 equiv) and **188a** (122.0 mg, 0.371 mmol, 1.1 equiv) in CH_3CN (2.0 mL) was degassed by freeze-pump-thaw (2 cycles). $PdCl_2(PPh_3)_2$ (12.0 mg, 17.1 μmol, 0.05 equiv) and CuI (12.0 mg, 63.0 μmol, 0.2 equiv) were added and the mixture was degassed by freeze-pump-thaw (1 cycle), placed in a 0 °C bath under N_2, and treated with triethylamine (300 μL, 2.14 mmol, 6.3 equiv). The yellow mixture became almost colorless before turning to a dark red-brown color. After 1.5 h at 0 °C, the reaction mixture was quenched with phosphate buffer (0.5 M

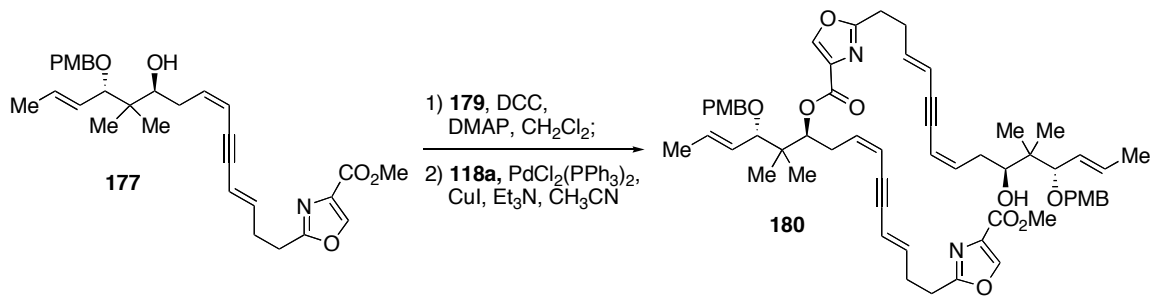
NaH_2PO_4, 0.5 M Na_2HPO_4, 3.0 mL), poured into water (10.0 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (2 columns, 10% to 30% acetone/hexanes, then 20% to 50% ethyl acetate/hexanes) afforded **177** (96.4 mg, 56%) as a clear, colorless syrup: R_f 0.32 (40% ethyl acetate/hexanes); $[\alpha]_D$ –9.7 (*c* 1.50, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.13 (s, 1 H), 7.20 (d, 2 H, *J* = 8.7 Hz), 6.84 (d, 2 H, *J* = 8.7 Hz), 6.16-6.08 (m, 1 H), 6.06 (dt, 1 H, *J* = 15.4, 7.0 Hz), 5.73-5.61 (m, 3 H), 5.47 (ddq, 1 H, *J* = 15.4, 8.6, 1.5 Hz), 4.49 (d, 1 H, *J* = 11.2 Hz), 4.18 (d, 1 H, *J* = 11.2 Hz), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.64 (d, 1 H, *J* = 8.5 Hz), 3.57 (dd, 1 H, *J* = 10.0, 2.4 Hz), 2.90 (d, 1 H, *J* = 8.6 Hz), 2.88 (d, 1 H, *J* = 8.0 Hz), 2.64-2.47 (m, 3 H), 2.24 (dddd, 1 H, *J* = 15.7, 10.0, 6.7, 1.2 Hz), 1.79 (dd, 3 H, *J* = 6.3, 1.4 Hz), 0.89 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR δ 164.8, 161.9, 159.4, 144.0, 142.4, 140.6, 133.4, 131.7, 130.2, 129.7, 127.7, 114.0, 112.1, 110.0, 92.0, 87.9, 86.4, 77.4, 70.0, 55.5, 52.3, 41.1, 33.3, 30.3, 27.7, 21.9, 21.2, 18.1; IR (neat) 3478, 3163, 2964, 2916, 2875, 2215, 2180, 1747, 1612, 1586 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{37}NO_6Na$ (M+Na) 530.2519, found 530.2499.



2-((3*E*,7*Z*,10*S*,12*S*,13*E*)-10-Hydroxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-carboxylic ester cyclodimer (178). A solution of **177** (22.0 mg, 43.3 μmol, 1.0 equiv) in THF (1.0 mL) and water (0.1

mL) at rt was treated with 1.0 M aqueous LiOH (100 μL, 100 μmol, 2.3 equiv), stirred for 12 h, poured in 2.0 M aqueous $NaHSO_4$ (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to an orange colored wax, which was diluted with anhydrous ethyl ether and filtered through a plug of cotton. The cotton plug was rinsed with ethyl ether and the combined filtrate was concentrated to a red-colored wax (19.4 mg, 91%) that was used without further purification.

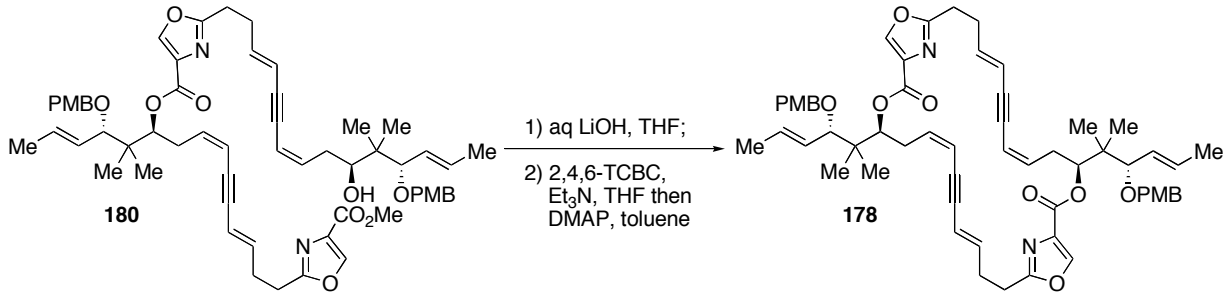
A solution of the monomer acid (19.4 mg, 39.3 μmol, 1.0 equiv) in THF (2.5 mL) at rt was treated with triethylamine (110 μL, 0.784 mmol, 20.0 eqiv) and 2,4,6-trichlorobenzoyl chloride (60.0 μL, 0.384 mmol, 10.0 equiv). The mixture was stirred at rt for 1.5 h and diluted with toluene to give a solution (10 mL) that was added via syringe pump (2.6 mL/h) to a solution of DMAP (224.0 mg, 1.834 mmol, 46.7 equiv) in toluene (9.0 mL) at rt. After the addition was complete, the mixture was stirred for an additional 12 h, quenched with 1.0 M citric acid (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10 to 40% ethyl acetate/hexanes) afforded **178** (2.0 mg, 11%) as a pale yellow wax. See below for spectroscopic data.



(2*E*,4*S*,6*S*,8*Z*,12*E*)-4-(4-Methoxybenzyloxy)-15-(4-(methoxycarbonyl)oxazol-2-yl)-5,5-dimethylpentadeca-2,8,12-trien-10-yn-6-yl 2-((3*E*,7*Z*,10*S*,12*S*,13*E*)-10-hydroxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-carboxylate (180). A solution of **177** (74.4 mg, 0.147 mmol, 1.0 equiv) and **179** (85.0 mg, 0.290 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) was treated at 0 °C with DMAP (18.0 mg, 0.146 mmol, 1.0 equiv) and DCC (151.0 mg, 0.732 mmol, 5.0 equiv). The cold bath was removed and the mixture was stirred at rt for 18 h, diluted with hexanes (5.0 mL) and poured onto a pad of SiO_2. The pad was rinsed with 50% ethyl acetate/hexanes (200 mL) and the filtrate was concentrated to an orange oily residue. Purification by chromatography on SiO_2 (40% to 50% ethyl acetate/hexanes) afforded the vinyl iodide (42.4 mg, 37%) that was used without further purification.

A solution of the vinyl iodide (40.0 mg, 51.1 μmol, 1.0 equiv) and **118a** (33.6 mg, 102 μmol, 2.0 equiv) in CH_3CN (1.0 mL) was degassed (freeze-pump-thaw, 2 cycles) and treated with CuI (2.0 mg, 11 μmol, 0.2 equiv) and $PdCl_2(PPh_3)_2$ (3.5 mg, 5.0 μmol, 0.1 equiv). The mixture was degassed (1 cycle), cooled to 0 °C, treated with triethylamine (43.0 μL, 0.307 mmol, 6.0 equiv), stirred for 2 h at 0 °C and then treated with pH 7 aqueous phosphate buffer (1.0 mL). The mixture was warmed to rt, poured into water (10 mL) and extracted with ethyl acetate. The combined organic layers were

washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (30% to 50% ethyl acetate/hexanes) afforded **180** (41.0 mg, 82%) as a yellow wax that was used without further purification.

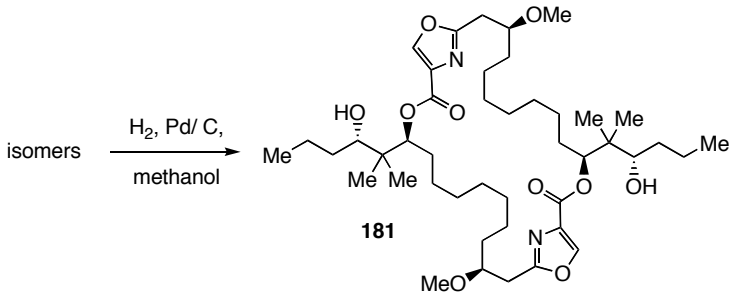


2-((3*E*,7*Z*,10*S*,12*S*,13*E*)-10-Hydroxy-12-(4-methoxybenzyloxy)-11,11-dimethylpentadeca-3,7,13-trien-5-ynyl)oxazole-4-carboxylic ester cyclodimer (178). A solution of **180** (26.0 mg, 26.4 μmol, 1.0 equiv) in THF (1.0 mL) was treated at rt with 1.0 M aqueous LiOH (60.0 μL, 60.0 μmol, 2.3 equiv), stirred for 24 h, poured into 2.0 M $NaHSO_4$ (10 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to a reddish-orange wax that was dissolved in anhydrous ethyl ether and filtered through a cotton plug to remove the reddish-orange solids. The cotton plug was rinsed with anhydrous ethyl ether and the combined filtrate was concentrated to afford the *seco*-acid (18.9 mg, 73%) as a yellow wax that was used without further purification.

A solution of the *seco*-acid (18.9 mg, 19.5 μmol, 1.0 equiv) in THF (2.0 mL) was treated at rt with triethylamine (27.0 μL, 0.193 mmol, 9.9 equiv) and 2,4,6-trichlorobenzoyl chloride (15.0 μL, 96.0 μmol, 4.9 equiv), stirred for 2 h and diluted with toluene to give a solution (6.0 mL) that was added via syringe pump (1.5 mL/h) to a solution of DMAP (50.0 mg, 0.409 mmol, 21.0 equiv) in toluene (5.0 mL). After 18 h

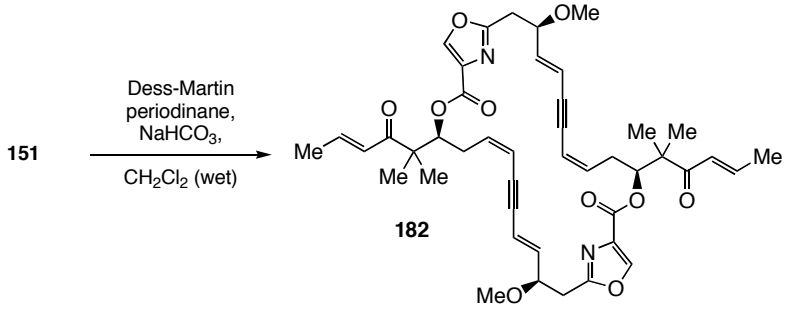
(total reaction time), the mixture was poured into 1.0 M aqueous citric acid (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (40% ethyl acetate/hexanes) afforded a clear colorless wax that was further purified by semi-preparative HPLC (SiO_2, 20% ethyl acetate/hexanes, 8.0 mL/min, 254 nm) to afford **178** (4.9 mg, 26%) as a clear, colorless wax that consisted of one major and two minor compounds. Major compound: ^{1}H NMR δ 7.96 (s, 1 H), 7.28-7.22 (m, 2 H), 6.82 (app dt, 2 H, *J* = 8.7, 2.6 Hz), 6.07 (dt, 1 H, *J* = 15.7, 7.2 Hz), 5.89 (dq, 1 H, *J* = 10.4, 5.2 Hz), 5.70-5.58 (m, 3 H), 5.52 (d, 1 H, *J* = 10.4 Hz), 5.47-5.44 (m, 1 H), 5.40 (dd, 1 H, *J* = 10.6, 2.6 Hz), 4.37 (d, 1 H, *J* = 10.9 Hz), 4.11 (d, 1 H, *J* = 10.9 Hz), 3.78 (s, 3 H), 3.46 (d, 1 H, *J* = 8.5 Hz), 3.02-2.81 (m, 3 H), 2.65-2.60 (m, 1 H), 2.42-2.32 (m, 1 H), 1.75 (d, 3 H, *J* = 6.2 Hz), 0.96 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR δ 164.7, 160.9, 159.1, 143.6, 141.2, 139.7, 133.8, 131.2, 129.8, 128.1, 113.7, 112.2, 92.1, 86.3, 84.2, 77.4, 76.7 (2 C), 69.7, 55.4, 41.9, 31.6, 30.7, 27.9, 19.7, 19.5, 18.1.

3.5.2.5. Additional Analogs



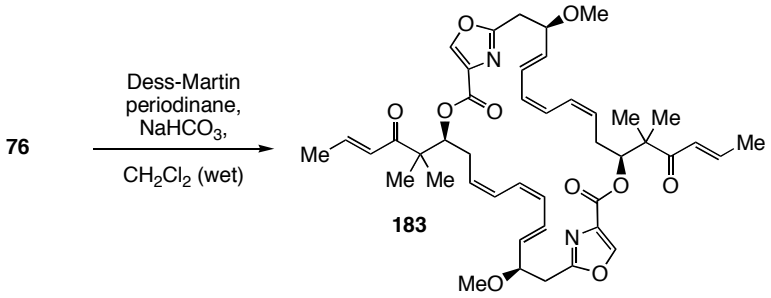
(7,7',8,8',9,9',10,10',11,11',12,12',17,17',18,18')-Octahydrodisorazole C_1 (182). A solution of the byproducts from the semi-reduction of **151** (4.0 mg, 5.2 mmol, 1.0

equiv) in MeOH (2.0 mL) was treated with 3% Pd on carbon. The flask was evacuated, flushed with H_2 and stirred at rt for 2 h. The mixture was filtered through a plug of Florisil/Celite (1:1 v/v). The plug was rinsed with acetone and the combined filtrate was concentrated. Purification by chromatography on SiO_2 (2 columns: 10% to 20% acetone/hexanes, then 10% to 80% ethyl acetate/hexanes) afforded **181** (2.5 mg, 61%) as a clear, colorless wax: R_f 0.47 (40% acetone/hexanes); $[\alpha]_D$ -0.40 (*c* 0.20, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.14 (s, 2 H), 5.21 (d, 2 H, *J* = 8.8 Hz), 3.63 (app tt, 2 H, *J* = 6.0, 6.0 Hz), 3.38 (s, 6 H), 3.25 (bs, 2 H), 3.14-3.07 (m, 2 H), 3.05 (d of AB, 2 H, *J* = 15.1, 4.7 Hz), 2.96 (d of AB, 2 H, *J* = 15.1, 7.0 Hz), 1.64-1.13 (m, 36 H), 0.88 (s, 6 H), 0.86 (s, 6 H), 0.95-0.78 (m, 6 H); ^{13}C NMR δ 163.6, 162.6, 144.1, 133.3, 80.3, 79.0, 74.8, 74.4, 57.2, 42.0, 33.9, 33.0, 32.4, 29.6, 29.4, 29.3, 26.5, 25.3, 20.6, 19.2, 18.1, 14.4; IR (neat) 3518, 3153, 3104, 2929, 2857, 1719, 1583, 1465 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{44}H_{75}N_2O_{10}$ (M+H) 791.5422, found 791.5464; *m/z* calcd for $C_{44}H_{74}N_2O_{10}Na$ (M+Na) 813.5241, found 813.5278.



(9,9',10,10',16,16')-Tetradehydrodisorazole C_1 (182). A solution of **151** (2.8 mg, 3.6 μmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL, wetted by shaking with brine in a separatory funnel) was treated at 0 °C with $NaHCO_3$ (5.5 mg, 65 μmol, 18 equiv) and Dess-Martin periodinane (7.5 mg, 18 μmol, 4.9 equiv). The cold bath was removed and

the resulting milky-white reaction mixture was stirred for 1 h at rt, and treated with a mixture of saturated aqueous $NaHCO_3$ (2.0 mL) and saturated aqueous $Na_2S_2O_3$ (2.0 mL). After stirring for 10 min at rt, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 60% ethyl acetate/hexanes) afforded **182** (2.5 mg, 89%) as a clear, colorless wax: R_f 0.52 (60% ethyl acetate/hexanes); $[\alpha]_D$ +153.1 (*c* 0.42, $CHCl_3$, 22 °C); ^{1}H NMR δ 8.04 (s, 2 H), 6.98 (dq, 2 H, *J* = 13.8, 6.8 Hz), 6.58 (dd, 2 H, *J* = 15.1, 1.2 Hz), 5.98 (dd, 2 H, *J* = 16.0, 7.4 Hz), 5.91 (dd, 2 H, *J* = 10.4, 5.3 Hz), 5.65 (dd, 2 H, *J* = 16.1, 1.9 Hz), 5.60 (dd, 2 H, *J* = 10.9, 2.6 Hz), 5.54 (d, 2 H, *J* = 10.6 Hz), 4.13 (app dt, 2 H, *J* = 9.2, 3.9 Hz), 3.36 (s, 6 H), 3.33-3.26 (m, 2 H), 3.03 (dd, 2 H, *J* = 14.3, 9.5 Hz), 2.91 (dt, 2 H, *J* = 13.7, 10.7 Hz), 2.26 (bd, 2 H, *J* = 13.6 Hz), 1.90 (d, 6 H, *J* = 6.4 Hz), 1.26 (s, 6 H), 1.23 (s, 6 H); ^{13}C NMR δ 200.8, 162.0, 160.6, 144.6, 143.9, 141.5, 139.2, 133.4, 126.2, 113.6, 112.9, 91.3, 87.7, 79.6, 76.1, 57.1, 50.3, 34.6, 31.9, 21.7, 19.9, 18.6; IR (neat) 2966, 2927, 2854, 2192, 1741, 1688, 1624, 1584 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{44}H_{50}N_2O_{10}Na$ (M+Na) 789.3363, found 789.3417.

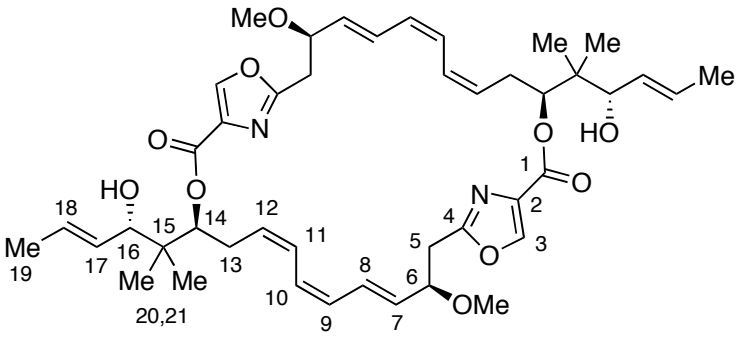


(16,16')-Didehydrodisorazole C_1 (183). A solution of **76** (1.0 mg, 1.3 μmol, 1.0 equiv) in wet CH_2Cl_2 (0.5 mL) was cooled to 0 °C and treated with $NaHCO_3$ (5.0 mg, 60 μmol, 46 equiv) and Dess-Martin periodinane (7.0 mg, 17 μmol, 12 equiv). The cold

bath was removed and the mixture was stirred at rt for 30 min. A mixture of saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL) was added and the mixture was stirred at rt for 30 min and then extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 60% ethyl acetate/hexanes) afforded **183** (0.9 mg, 91%) as a slightly impure clear, colorless wax. Due to the small amount of sample, only partial characterization was possible: R_f 0.44 (60% ethyl acetate/hexanes); R_f 0.44 (60% ethyl acetate/hexanes); $[\alpha]_D$ –27.1 (*c* 0.14, $CHCl_3$, 22 °C); ^{1}H NMR δ 7.90 (s, 2 H), 6.98 (app dq, 2 H, *J* = 14.0, 7.0 Hz), 6.57 (dd, 2 H, *J* = 15.1, 1.5 Hz), 6.41 (dd, 2 H, *J* = 15.1, 11.2 Hz), 6.34 (app t, 2 H, *J* = 11.1 Hz), 6.14 (app t, 2 H, *J* = 11.2 Hz), 5.91 (app t, 2 H, *J* = 10.9 Hz), 5.59-5.45 (m, 6 H), 4.13 (app q, 2 H, *J* = 7.7 Hz), 3.27 (s, 6 H), 3.14 (dd, 2 H, *J* = 14.8, 5.6 Hz), 2.83 (dd, 2 H, *J* = 14.7, 7.8 Hz), 2.52 (app dt, 2 H, *J* = 14.3, 10.4 Hz), 2.28 (dd, 2 H, *J* = 15.1, 6.3 Hz), 1.90 (dd, 6 H, *J* = 6.9, 1.2 Hz), 1.22 (s, 6 H), 1.18 (s, 6 H); IR (neat) 2962, 2924, 2853, 1740, 1688, 1625 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{44}H_{54}N_2O_{10}Na$ (M+Na) 793.3676, found 793.3655.

4. APPENDIX

4.1. Disorazole C_1



(-)-disorazole C_1 (76)

Comparison of ^{1}H NMR Data:

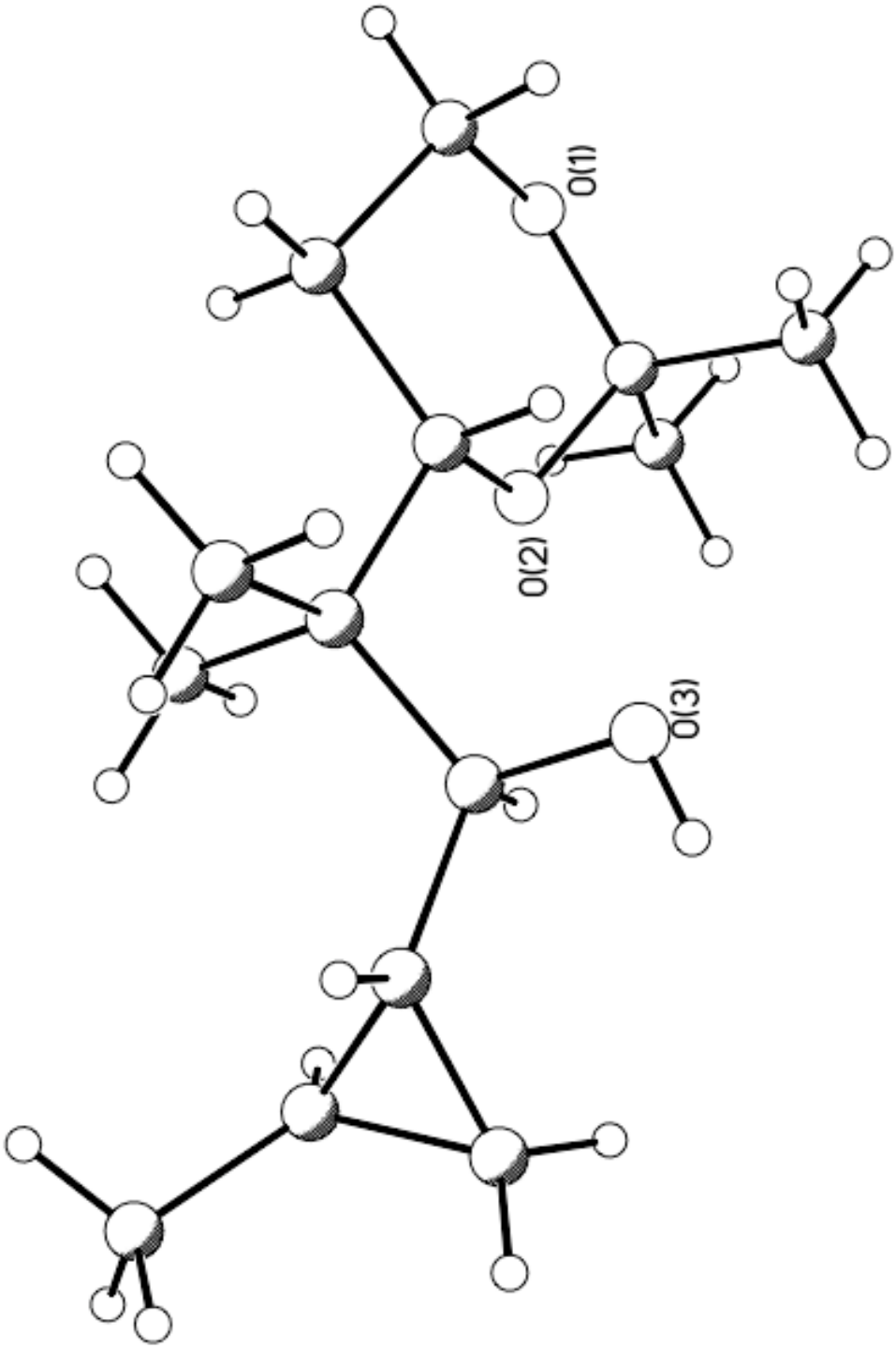
	literature[34]			experimental		
Proton #	d [ppm]	mult	J [Hz]	d [ppm]	mult	J [Hz]
3-H	8.28	s	-	8.23	s	-
5-Ha	3.04	dd	7.4, 15.5	2.99	dd	7.4, 15.5
5-Hb	2.81	dd	5.4, 15.5	2.76	dd	5.4, 15.5
6-H	4.17	ddd	5.4, 7.4, 8.5	4.13	ddd	5.5, 7.2, 7.8
7-H	5.58	dd	8.5, 15.1	5.54	dd	8.3, 15.0
8-H	6.54	dd	11.4, 15.1	6.50	dd	11.5, 15.2
9-H	5.96	dd	11, 11.4	5.91	dd	11.2, 10.9
10-H	6.32	dd	11, 11.4	6.28	dd	11.1, 11.4
11-H	6.44	dd	11.1, 11.4	6.40	app t app	11.2
12-H	5.53	ddd	6.3, 11, 11	5.48	dt	10.0, 6.7
13-Ha	2.72	ddd	10.9, 11.3, 13.6	2.69	ddd	10.2, 10.9, 13.8
13-Hb	2.43	dd	6.3, 13.6	2.38	dd	6.1, 13.8
14-H	5.30	dd	2.2, 11.3	5.25	dd	2.2, 11.3
16-H	3.88	d	7.8	3.84	d	7.8
17-H	5.61	ddq	7.8, 15.2, 1.2	5.57	ddd	7.8, 15.2, 1.4
18-H	5.71	dq	15.2, 6.3	5.66	dq	15.2, 6.6
19-H3	1.74	dd	1.2, 6.3	1.69	dd	1.3, 6.4
20-H3	1.05	s	-	1.00	s	-
21-H3	0.99	s	-	0.95	s	-
6-OCH_3	3.25	s	-	3.21	s	-
16-OH	-	-	-	-	-	-
16-OH	-	-	-	-	-	-

Comparison of ^{13}C NMR Data:

	Literature[34]	Experimental	Lit. - Exp.
Carbon #	d [ppm]	d [ppm]	Δd [ppm]
1	162.27	162.26	0.01
2	134.12	134.09	0.03
3	145.81	145.83	-0.02
4	164.13	164.12	0.01
5	35.97	35.97	0.00
6	80.59	80.57	0.02
7	134.17	134.15	0.02
8	129.94	129.96	-0.02
9	129.31	129.30	0.01
10	126.79	126.79	0.00
11	127.35	127.36	-0.01
12	130.88	130.88	0.00
13	29.27	29.24	0.03
14	78.81	78.75	0.06
15	42.73	42.70	0.03
16	77.85	77.84	0.01
17	131.70	131.68	0.02
18	129.62	129.63	-0.01
19	18.02	18.03	-0.01
20	19.45	19.41	0.04
21	19.34	19.32	0.02
6-OCH_3	56.84	56.83	0.01

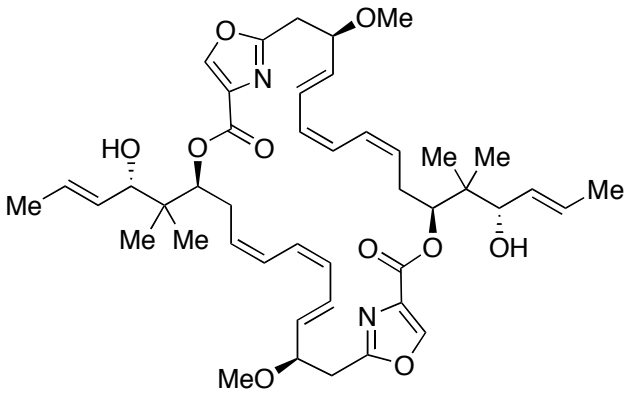
4.2. Crystal Structure of the Cyclopropane Adduct

Figure 29. Crystal structure of cyclopropane adduct **163**.



4.3. Minimized Conformations for Disorazole C_1 and Analogs

Figure 30. Minimized conformation of (-)-disorazole C_1 (**76**).



(-)-Disorazole C_1

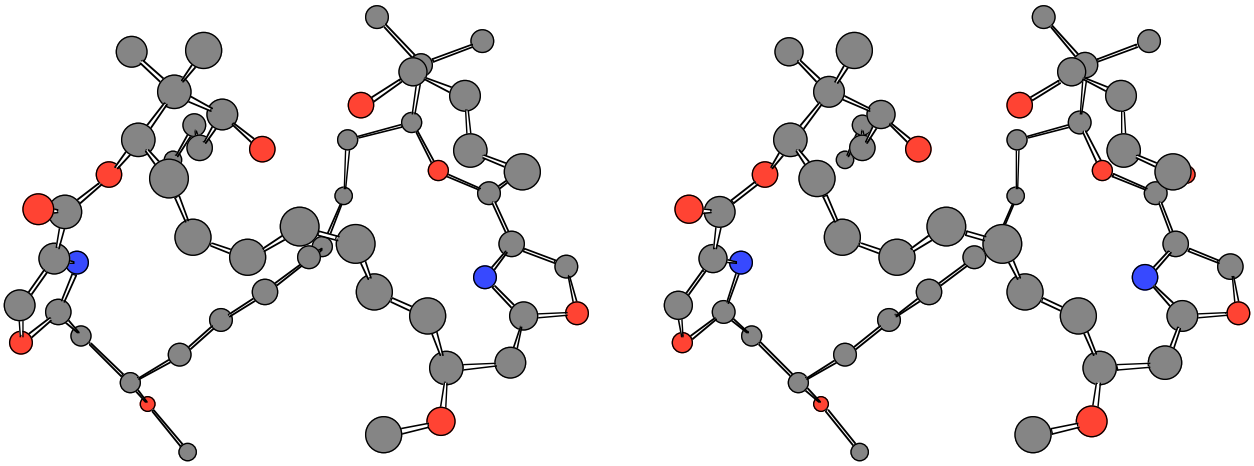


Figure 31. Minimized conformation alkyne precursor **151**.

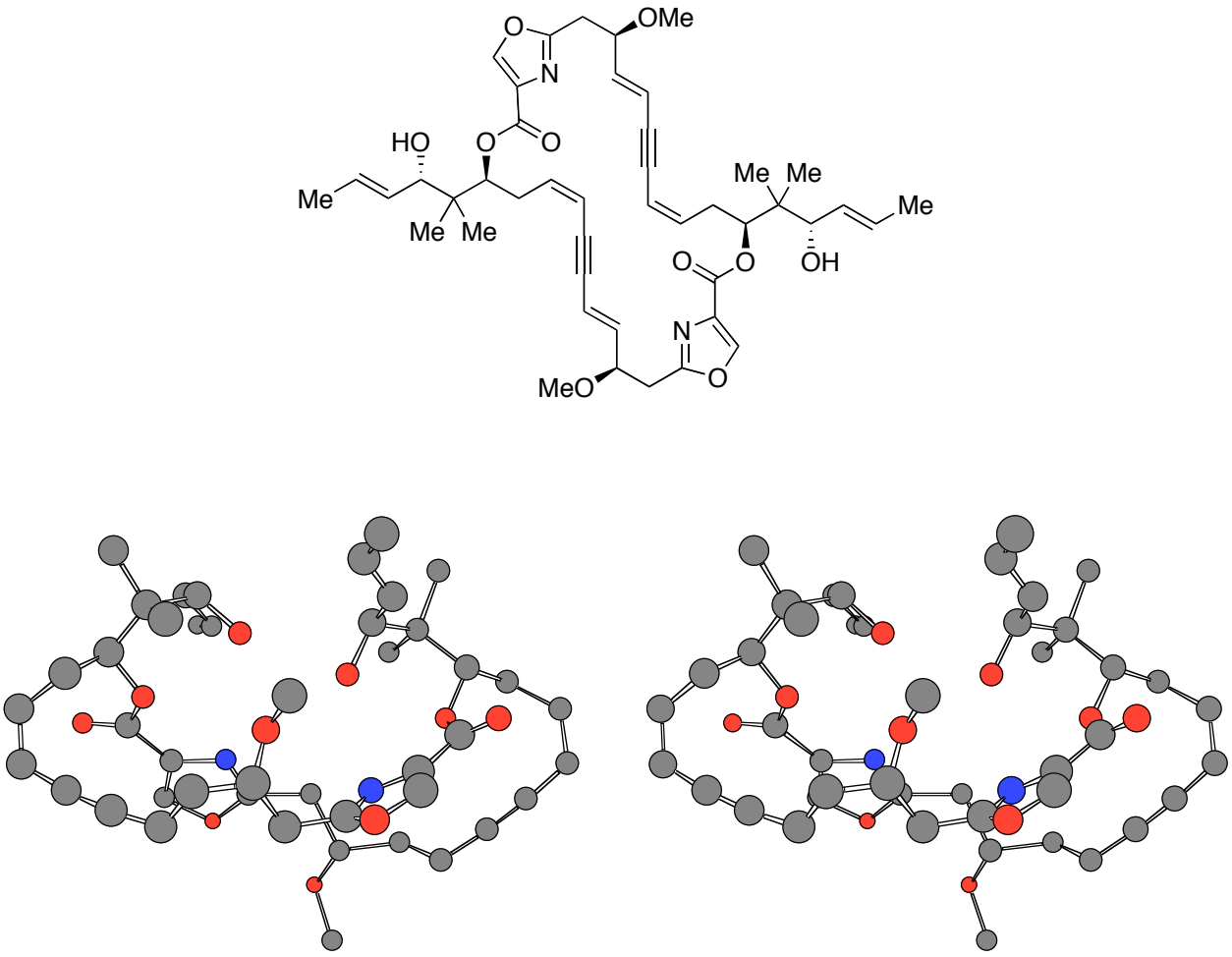
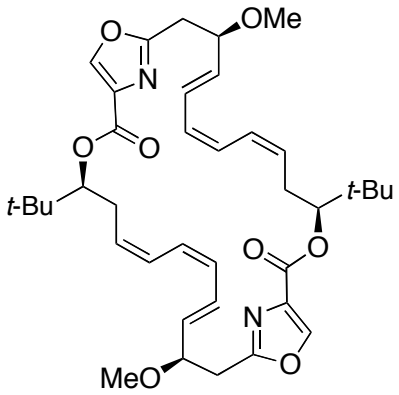
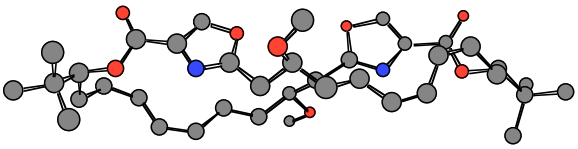


Figure 32. Minimized conformation of the *t*-butyl analog **152**.





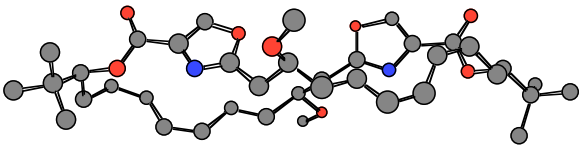


Figure 33. Minimized conformation of cyclopropyl analog **161**.

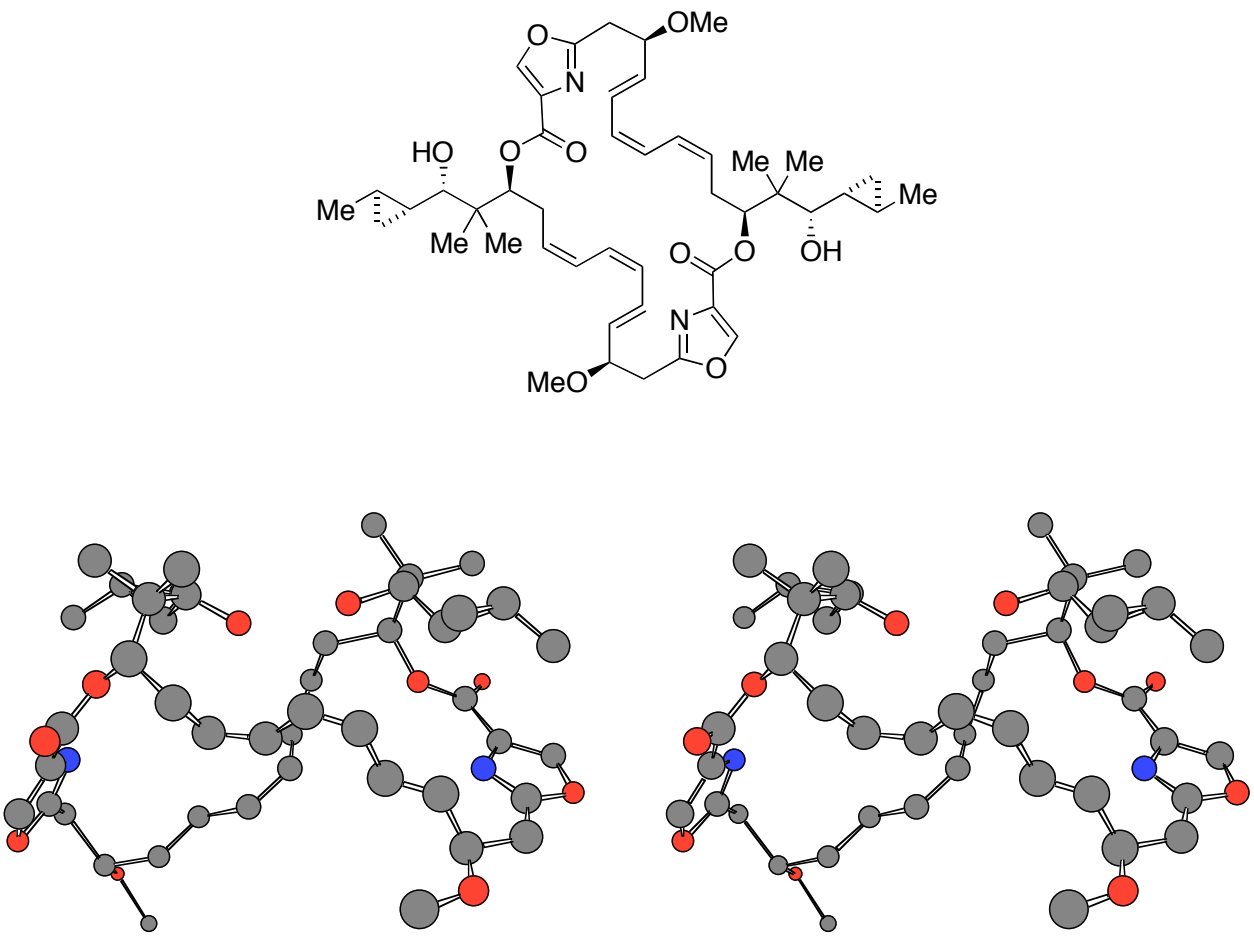


Figure 34. Minimized conformation of the enone analog **183**.

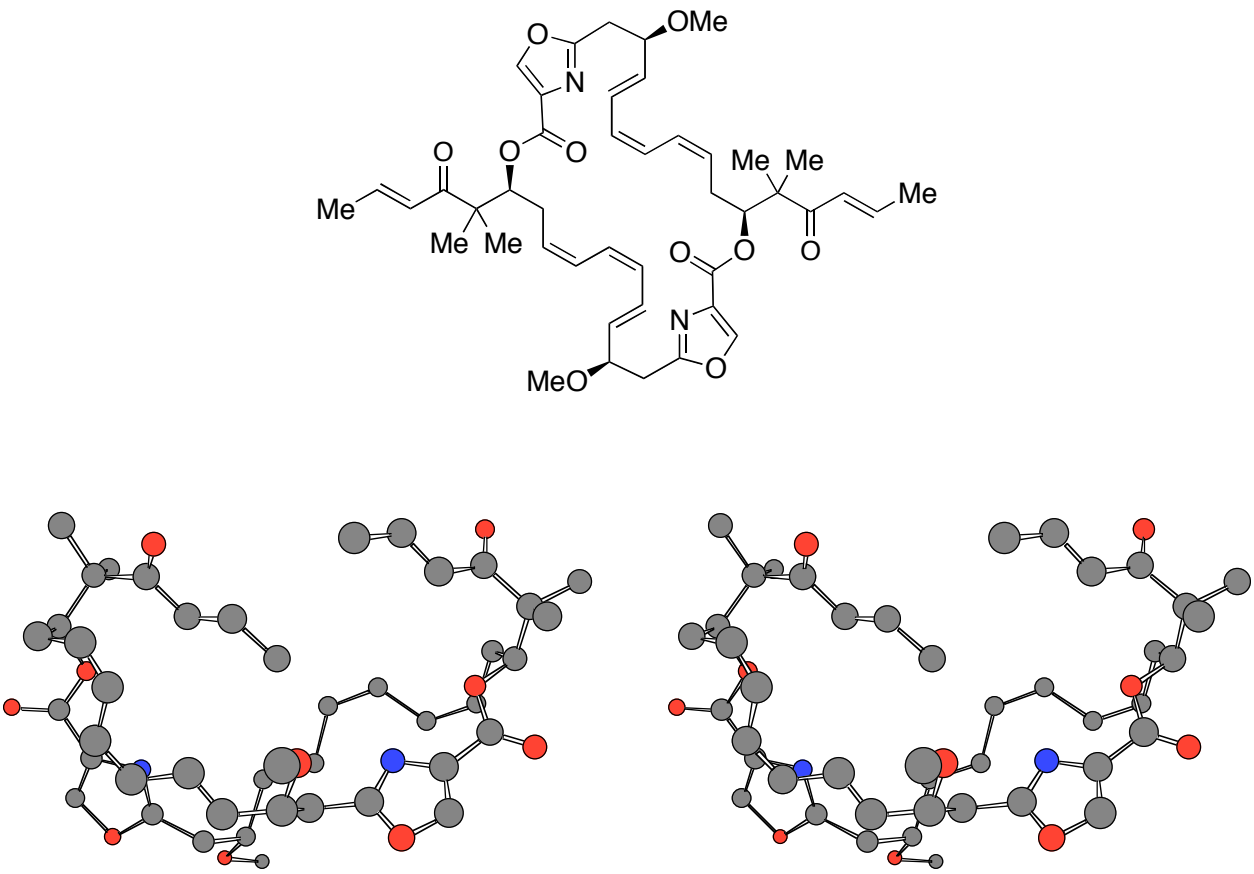
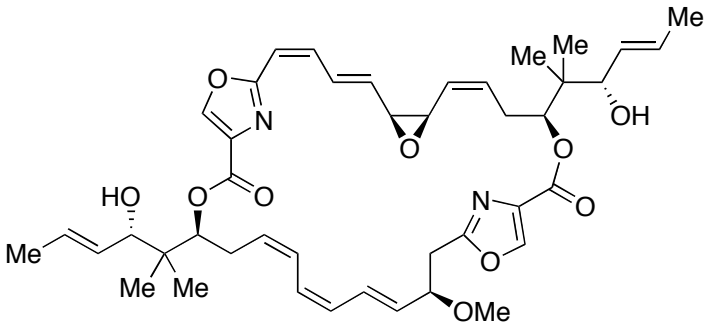
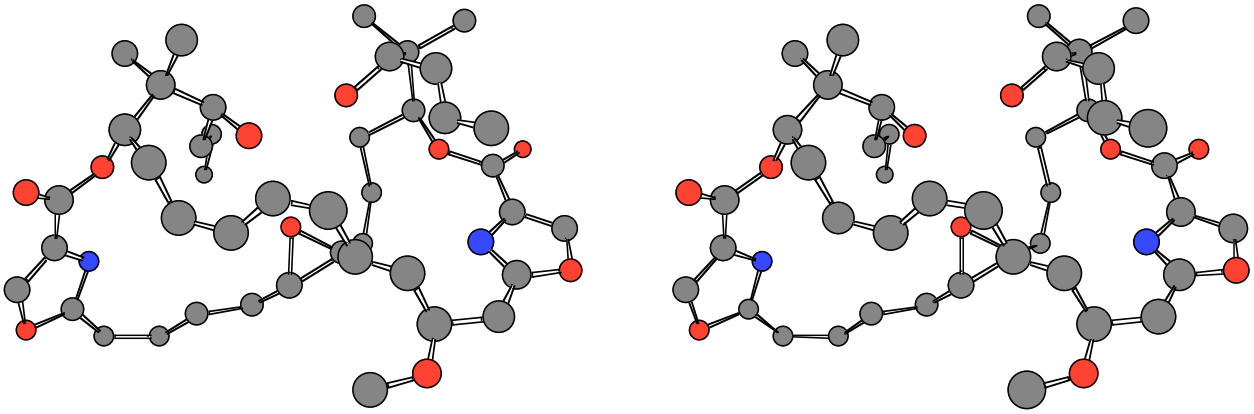


Figure 35. Minimized conformation of disorazole A_1.



Disorazole A_1



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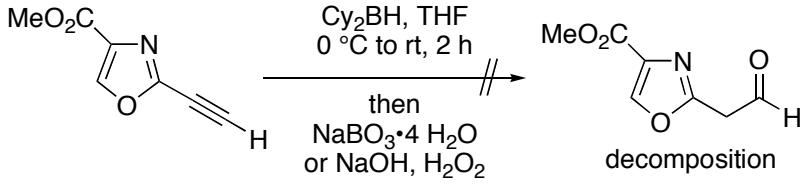

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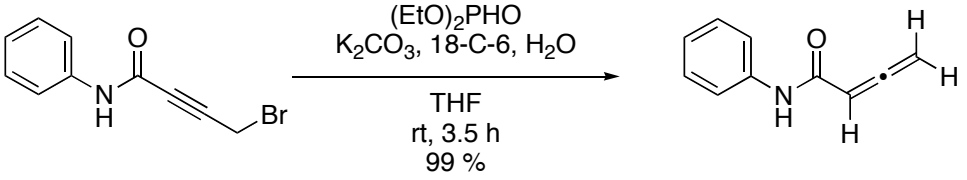

***N*-Phenylbuta-2,3-dienamide.** A solution of 4-bromo-*N*-phenylbut-2-ynamide (21.2 mg, 0.089 mmol, 1.0 equiv) in THF (1.0 mL) and water (8.0 µL, 0.44 mmol, 5.0 equiv) was treated with diethylphosphite (23.0 µL, 0.179 mmol, 2.0 equiv), K_2CO_3 (13.0 mg, 0.094 mmol, 1.1 equiv) and 18-crown-6 (2.5 mg, 9.5 µmol, 0.1 equiv), stirred at rt for 3.5 h, diluted with ethyl ether (2.0 mL) and filtered through plug of SiO_2. The SiO_2 plug was rinsed with ethyl ether (15 mL) and the combined filtrate was concentrated. Purification by chromatography on SiO_2 (40% ethyl ether/hexanes afforded *N*-phenylbuta-2,3-dienamide (14.1 mg, 99%) as a white, crystalline solid: R_f 0.29 (60% ethyl ether/hexanes); Mp 111.0-112.5 °C (ethyl ether/hexanes); ^{1}H NMR δ 7.62 (bs, 1 H), 7.52 (d, 2 H, *J* = 7.8 Hz), 7.32 (t, 2 H, *J* = 7.9 Hz), 7.11 (t, 1 H, *J* = 7.4 Hz), 5.77 (app t, 1 H, *J* = 6.7 Hz), 5.35 (d, 2 H, *J* = 6.7 Hz); ^{13}C NMR δ 212.0, 162.6, 137.9, 129.2, 124.5, 119.8, 92.1, 81.5; IR (neat) 3445, 3272, 3239, 3186, 3133, 3078, 3062, 1969, 1944, 1649, 1600 cm^{-1}; MS (EI) *m/z* (rel. intensity) 159 (M^+, 43), 131 ($[M-C_2H_4]^+$, 12), 93 (100); HRMS (EI) *m/z* calcd for $C_{10}H_9NO$ 159.0684, found 159.0678.

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[180] Purification by HPLC afforded an inseparable mixture of at least 3 compounds, the major being the intended product and the minor compounds being closely related (^{1}H NMR).

[181] Observations during the attempts to prepare the C_6-desmethoxy analog suggest that the intermediate compounds are not as stable as those containing the methoxy substituent. The compounds in the C_6-desmethoxy series may be prone to polymerization as evidenced by the insoluble materials that were often filtered away from samples.

[182] Minimizations were performed with Macromodel (MM2*). Chloroform was used as a solvent.

[183] The results of the SAR-studies will be disclosed in full detail at a later date.

[184] The density of PMB-Br was assumed to be 1.2 g/mL. For a procedure to prepare PMB-Br, refer to ref. 145.

[185] *Ent*-**138** has previously been prepared by (-)-pinanyl-9-BBN reduction of the ketone: $[\alpha]_D$ –20.1 (*c* 1.7, $CHCl_3$, 23 °C) in 97% ee as determined by conversion to the Mosher ester. Refer to ref. 164b.