Synthetic Studies on (*E*)-Alkene Peptide Isosteres and Thiophene-containing Furanosteroids.

by

Bryan Hall Wakefield

B.S. West Virginia University, 2002

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Bryan Hall Wakefield

It was defended on

July 1, 2008

and approved by

Professor Paul Floreancig, Department of Chemistry

Professor Scott Nelson, Department of Chemistry

Professor John Lazo, Department of Pharmacology

Dissertation Advisor: Professor Peter Wipf, Department of Chemistry

Synthetic Studies on (*E*)-Alkene Peptide isosteres and Thiophene-containing Furanosteroids.

Bryan Hall Wakefield, PhD

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Peptide isosteres are important tools for the understanding of peptide function and for the development of drugs. (*E*)-Alkene peptide isosteres are particularly useful due to their close geometric match of the amide bond structure. We developed a method for the generation of a small library of (*E*)-alkene peptide isosteres on solid support via cuprate mediated S_N2' ring opening of allylic BUS-aziridines. We also studied the selectivity for the opening of these aziridines in the solution phase.

Halenaquinone is a marine natural product that was first isolated in 1983 from the Pacific sponge *Xestosongia exigua*. We realized the synthesis of a thiophene-containing analog, *thio*-halenaquinone. The key steps include an alkynyl ketone-benzocylcobutane Diels-Alder reaction to construct the naphthalene subunit, a Heck cyclization to form the quaternary carbon, and a ring closing metathesis to install the final ring. This compound showed an IC_{90} ~5 μM against Pfnek-1 and an analog that had an IC_{90} ~3 μM. Based on these results we designed and synthesized a simplified analog that showed an IC_{90} ~4 μM. This compound was selected to move on to animal testing and the synthesis was optimized for the preparation of and 200 mg of the lead structure.

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LIST OF ABBREVIATIONS

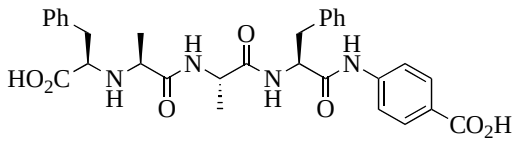
Ac	acetyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
BUS	*t*-butylsulfonyl
CAN	ceric ammonium nitrate
Cbz	carbobenzoxy
DBU	1,8-diazabicyclo[4.3.0]non-5-ene
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DiBAL	diisobutylaluminum hydride
DIPEA	diisopropylethyl amine
DMA	dimethylacetamide
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
e.e.	enantiomeric excess
EI	electron impact
ES	electrospray ionization
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	3-chloroperoxybenzoic acid
MOM	methoxylmethyl
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
Ns	2-nitrotoluenesulfonate
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFFH	fluoro-N, N, N, N’-tetramethylformamidinium hexafluorophosphate

THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tr	triphenylmethyl
Ts	4-toluenesulfonyl
μwave	microwave

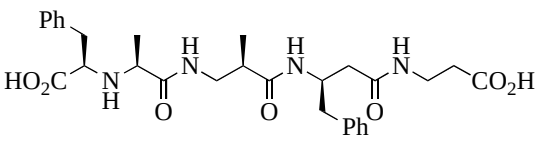
1.0 SYNTHESIS OF (*E*)-ALKENE PEPTIDE ISOSTERES VIA AZIRIDINE RING OPENING

1.1 INTRODUCTION

Peptides are important intermediates of biochemical pathways and have a vast array of biological activities. They act as hormones, neurotransmitters, growth factors and enzyme substrates.[1] Though peptides are at the heart of many biological processes, they are rarely utilized as therapeutic agents due to their poor pharmacokinetic profile, poor bioavailability, low absorption, short life time, and their immunogenic effects.[2] Attempts to address these shortcomings have led to the development of peptidomimetics. Designing peptidomimetics involves the selection of a lead peptide, followed by modifications to the backbone and/or side chains in an attempt to improve the affinity and potency for the target of interest while also improving the pharmacokinetic profile.[3-7] For example the Perlmutter group has illustrated this point through the incorporation of a β-amino acid residue into a known EP24.15 inhibitor (Figure 1).[8] The inhibitor maintained activity while eliminating degradation by EP24.11.



1
IC_{50} 0.2 μM
Degrdn by EP24.11 100%



2
IC_{50} 2.8 μM
Degrdn by EP24.11 0%

Figure 1. An example of peptidomimetics improving stablity.

Peptidomimetics were originally defined by Farmer[9,10] as potentially novel scaffolds designed to replace the entire peptide backbone while retaining the istosteric topography of the enzyme-bound peptide conformation. As work in this area has increased, the term peptidomimetic is used frequently to describe numerous structural types.[11] This has expanded the definition to any molecule designed to perform the function of a peptide.[12] Peptidomimetics are now being grouped into three structural classifications.[11] Type-I mimetics contain isosteric backbone modifications, but otherwise map onto the lead structure atom for atom. Type-II mimetics are non-peptide small molecules that bind to peptide receptors. Type-III mimetics are seemingly unrelated to the original peptide, but possess the proper functionality on a novel scaffold displayed correctly in space to serve as a topographical mimic. HIV-protease inhibitors **3**[13,14] and **4**[15] are examples of type-I peptidomimetics, which contain isosteric amide bond replacements such as epoxide, ketomethyl, and hydroxy-ethylene units (Figure 2). Another example of this class of mimetics is **5**[16,17] which inhibits the formation of catalytically active heterodimeric (R1/R2) enzyme in herpes simplex virus (Figure 2).

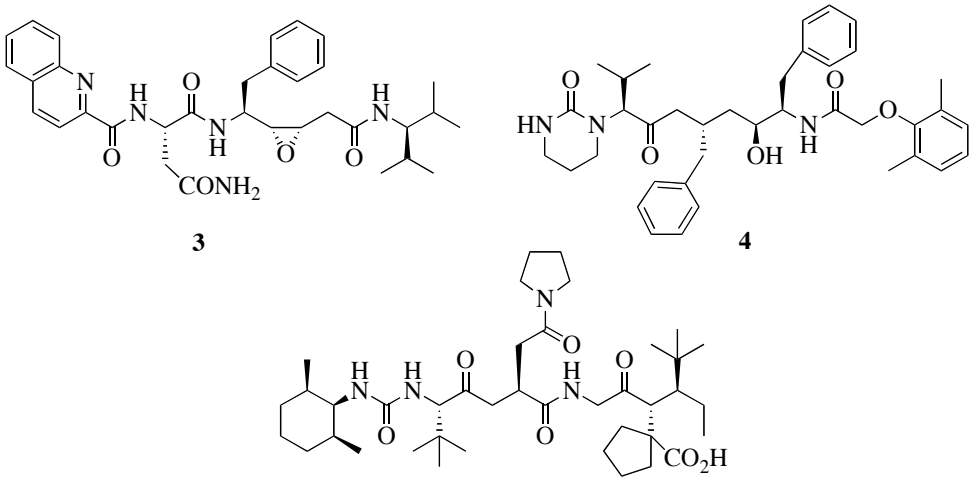


Figure 2. Examples of Type I peptidomimetics.

The HIV-1 protease inhibitor **6**,[18] angiotensin II antagonist **7**[19] and farnesyltransferase inhibitor **8**,[20,21] are examples of type-III mimetics. While none of these compounds contain peptide-like structures, their functionality allows for interaction with target enzymes (Figure 3). Peptides containing conformationally restricted amino acid units, some heterocycles and natural products are also deemed peptidomimetics because they act at the same site or receptor as a peptide.[22] Though the term peptidomimetic is very broad, mimetics regardless of structure have been important in the development and understanding of peptide function and drug discovery.

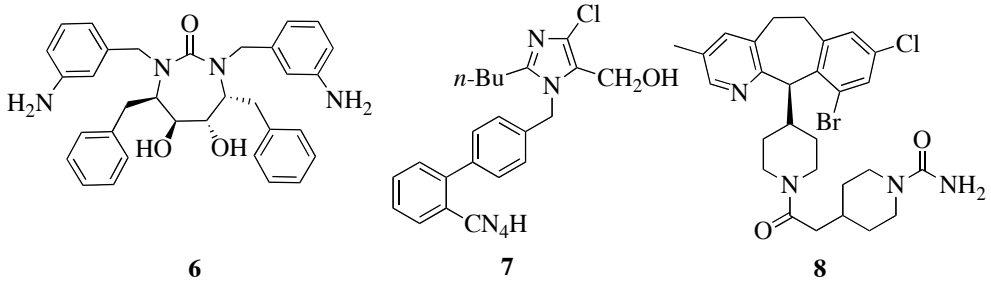


Figure 3. Examples of Type III peptidomimetics.

1.1.1 Amide Bond Replacement

Amides are rigid, polar, normally planar, and usually the nitrogen hydrogen and carbonyl group are positioned in a nearly *trans*-orientation.[23] The conformation of a peptide is defined by the dihedral angles of the backbone, ϕ and ψ (Figure 4). The angle ϕ refers to the torsion angle between the amino group and the α-carbon, while ψ refers to the torsion angle between the α-carbon and the carbonyl group.[24] While these angles are free to change by the rotation of a single bond, the steric interactions between the substituents on the α-carbon and N-atoms limit the rotational freedom. As a consequence, the conformations available to a peptide, based on the rotation of these angles, are decreased as the steric bulk at the α-carbon increases.[25]

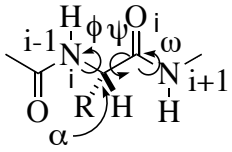


Figure 4. Bond angle designations in linear peptides.

The amide bond is the most common linkage in the peptide backbone and thus has become one of the most frequent sites of modification when developing peptidomimetics. Since peptides are prevalent in many biological pathways, nature has developed a myriad of enzymes that effectively cleave peptides into their amino acid building blocks. Enzymes have evolved to catalyze the proteolytic cleavage of peptide bonds between natural and some unnatural amino acid sequences. Since the amide bond is a major site of peptide degradation, replacement of this bond should improve the stability toward proteolytic cleavage.[26]

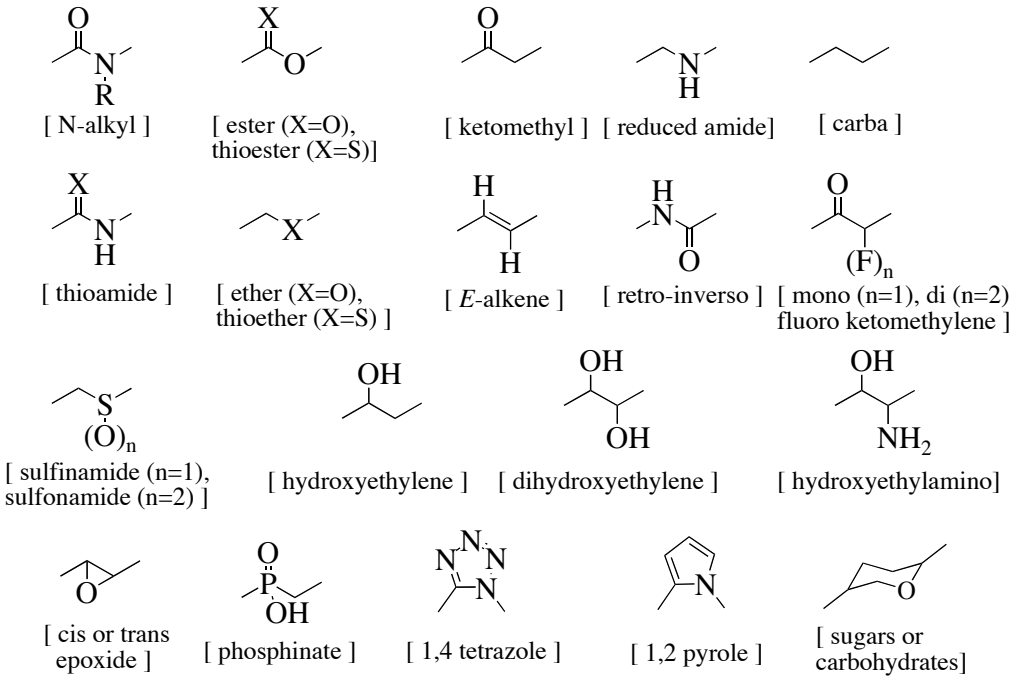
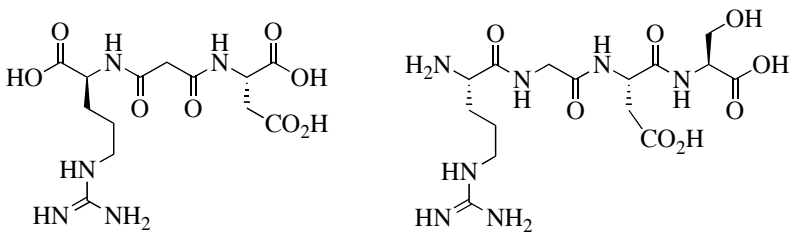


Figure 5. Examples of amide bond replacements.

Pseudopeptides have been developed with numerous replacements for the amide bond (Figure 5).[23] The development of effective mimetics requires consideration of the mimetic's ability to simulate the steric, electronic, conformational and solvation properties of the amide bond. While no isosteric replacement maintains all of the properties of the original amide bond, each group has unique properties that allow for its use as a mimetic.

Retro-inverso (Ψ [NHCO]) isosteres maintain the amide bond structure, but invert the position of nitrogen and carbonyl carbon. This allows for the conservation of the side chain topology, but protects against enzymatic cleavage.[27,28] The partial retro-inverso amide **9** shows both increased inhibition of tumor metastasis as well as greater metabolic stability and selectivity when compared to the Arg-Gly-Asp-Ser sequence **10** found in many metastasis inhibitors.[29,30]



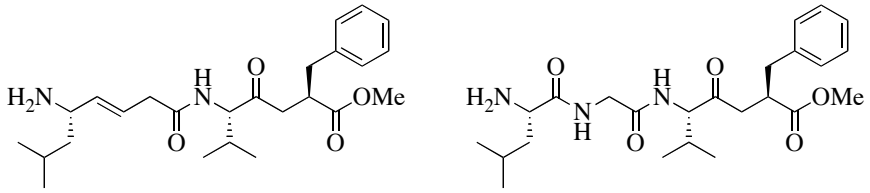
9 **10**

Figure 6. Example of retro-inverso isostere and parent structure.

The reduced amide and ketomethylene groups remove one of the atoms of the amide bond. A reduced amide ($\Psi[CH_2NH]$) allows for rotation of the ω angle and imparts greater stability toward enzymatic degradation because the amine becomes protonated at physiological pH. The ketomethylene isostere ($\Psi[COCH_2]$) retains the ability to accept a hydrogen bond, but lacks the rigidity of the parent amide.[31] This group is resistant to proteolytic cleavage since a carbon-carbon bond must be cleaved instead of a carbon-nitrogen bond. The ketomethylene isostere has shown biological activity and has been used in the development of thrombin inhibitors.[32]

Hydroxyethylene and (*E*)-alkene isosteres change multiple aspects of the amide bond, yet are still effective mimetics. Hydroxyethylene ($\Psi[CH(OH)CH_2]$) isosteres, such as **4** (Figure 2), were developed from the statin segment of pepstatin-A, a naturally occurring aspartyl protease inhibitor discovered by Umezawa.[23,33] This isosteric replacement is mainly used as a transition state mimetic for the tetrahedral intermediate formed in the proteolytic cleavage. The (*E*)-alkene ($\Psi[(E)$-CH=CH]) is the best isosteric mimetic to approximate the rigidity, bond angle and bond length of the amide bond.[34-39] This isosteric replacement has been used in the development of various peptide analogues that show biological activity such as enkephalin mimics, inhibitors of ACE, HIV-1

protease, protein kinase,[40-42] and reactive oxygen generation.[43-45] Additionally these compounds have been introduced into polypeptide sequences to examine their effect on protein structure and function.[46,47] The (*E*)-alkene isostere Leu Ψ[*E*-CH=CH]Gly-Val-Phe-OCH_3 **11** was shown to be a competitive inhibitor of human amniotic renin and more potent than the analogous renin substrate **12** without the isosteric replacment.[48]



11 **12**

Figure 7. Example of (*E*)-alkene isostere (**11**) and parent structure (**12**).

1.1.2 (*E*)-Alkene Peptide Isosteres

Molecules containing (*E*)-alkene isosteres can display potent biological activity.[36,43-45,49,50] These findings suggest that this isostere is well suited to mimic the amide bond. The (*E*)-alkene isosteric replacement not only removes the hydrolyzable amide bond, but effectively mimics its rigidity, bond length ($C_i(\alpha)$-$C_{i-1}(\alpha)$) and bond angles (Figure 8).[26] Additional, methyl- and CF_3-substituted alkenes have been shown to promote β-turn formation.[51] The CF_3-substituted olefins have also been shown to more closely reproduce the dipole moment of the amide when compared to other olefinic amide bond replacements.[51] The promise of (*E*)-alkene isosteres has led to the development of synthetic methodology which focuses on rearrangements, metathesis and S_N2' additions.

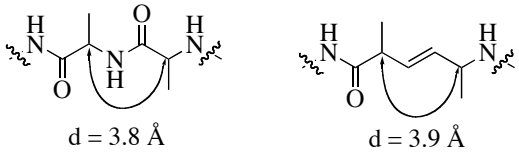
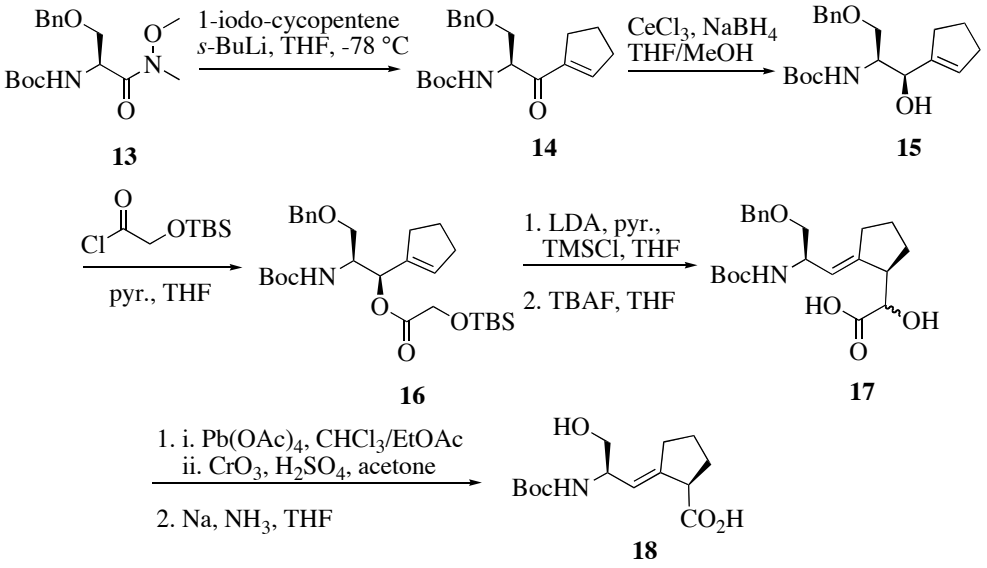


Figure 8. Distances between the α-carbon of residue i and the carbonyl group of residue i+1 in peptides and (*E*)-alkene isosteres.

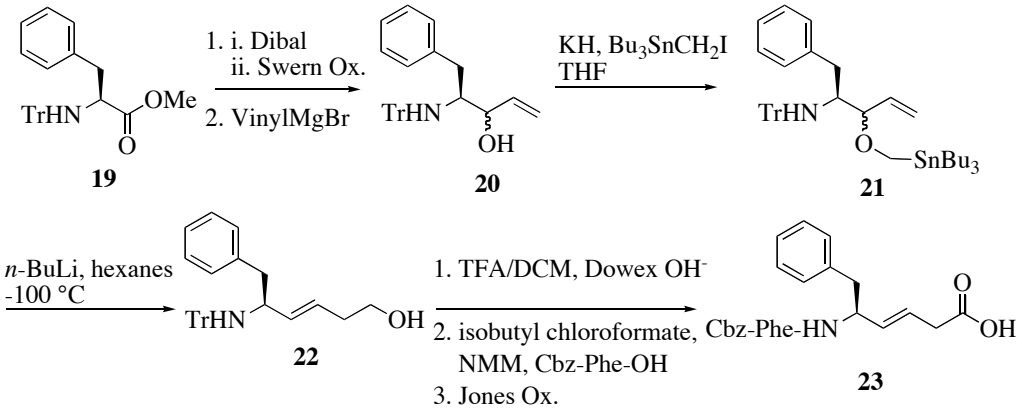
Etzkorn *et al.* were able to access Ser-*trans*-Pro mimetics through an Ireland-Claisen rearrangement (Scheme 1).[52] Addition of the lithiate of 1-iodo-cyclopentene to the easily prepared Weinreb amide of *N*-Boc-*O*-benzyl-L-serine afforded compound **14**. Luche reduction of the ketone gave the alcohol **15** in a 4:1 mixture a diastereomers. The desired (*S,R*)-isomer was acetylated to yield **16** the Ireland-Claisen precursor. Upon treatment with LDA, TMSCl and pyridine, **16** underwent the rearrangement to yield **17** as the major diastereomer. Cleavage and oxidation of the hydroxy acid followed by removal of the benzyl group yielded the Boc-Ser-Pro-OH isostere **18**.



13 **14** **15** **16** **17** **18**

Scheme 1. Etzkorn's synthesis of a Ser-*trans*-Pro mimetic.

Liskamp and Bol were able to construct Phe Ψ[(*E*)-CH_2=CH_2)Gly mimetics by employing a [2.3] Still-Wittig approach (Scheme 2).[53] Reduction of Tr-Phe-OMe **19** to the corresponding aldehyde followed by vinyl addition yielded the allylic alcohol **20**. Alkylation with tributyltinmethyl iodine gave the Still-Wittig precursor **21**. Upon treatment with *n*-BuLi, the rearrangement took place to afford **22**. Trityl deprotection followed by coupling to *N*-Cbz-Phe-OH and oxidation yielded Cbz-Phe-PheΨ[(E)-CH_2=CH_2)Gly-OH **23**.

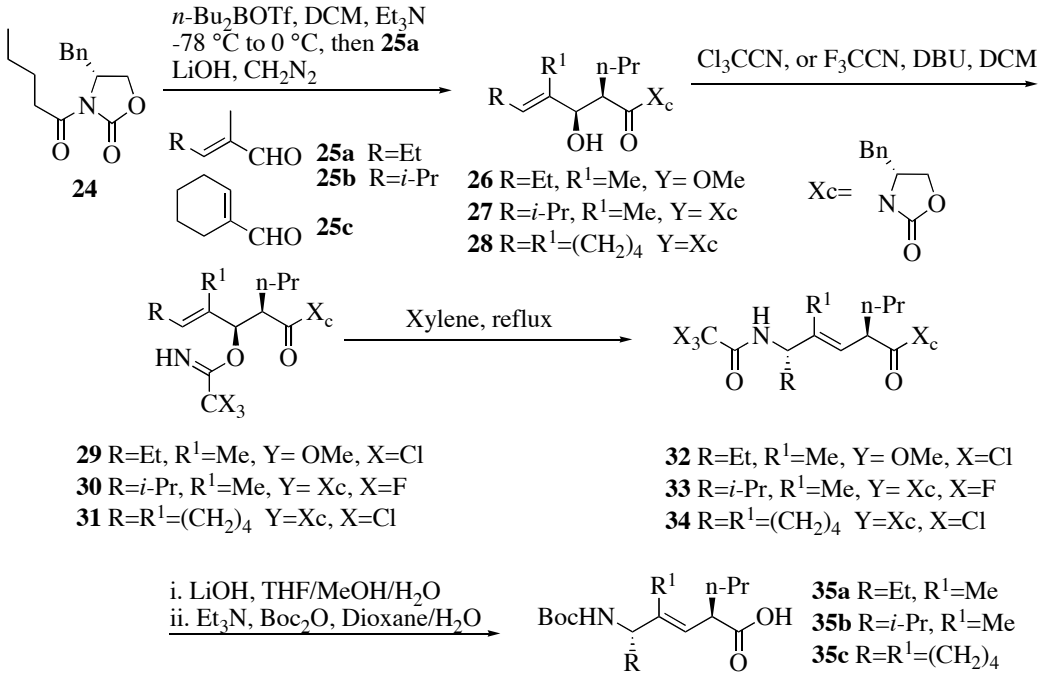


Scheme 2. Liskamp and Bol's synthesis of Phe Ψ[(*E*)-CH_2=CH_2)Gly mimetics.

Wai *et al.* utilized an Overman rearrangement to install trisubstituted (*E*)-alkene isosteres (Scheme 3).[54] An Evans aldol reaction between oxazolidinone **24** and aldehydes **25a-c** followed by acetimidate formation led to compounds **29-31**. Heating in xylenes afforded the rearrangement products **32-34**. Treatment with LiOH and Boc_2O gave the unnatural Ψ[(*E*)-C(CH_3)=CH) pseudopeptides **35a-c**.

Olefin metathesis has been employed by Miller *et al.* to synthesize various dipeptide isosteres (Table 1).[55] The treatment of allylic amines **36a-c** with 3-methyl

butenoate and Grubbs catalyst yielded peptide isosteres **37a-c** in moderate yield. Though the amines were racemic in these examples, the use of the enantiomerically pure amine **36d** derived from *N*-Boc-Pro yielded **37d** in 85% and 80% ee. Though this method uses readily available starting materials, the need to use the amines in excess is a major limitation.

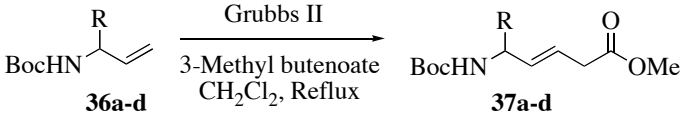


Scheme 3. Wai's synthesis of (*E*)-alkene isosteres.

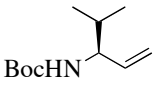
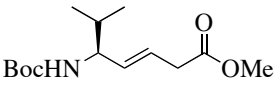
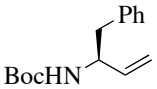
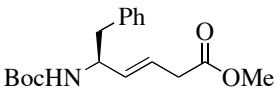
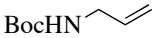
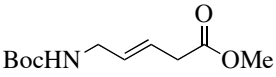
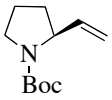
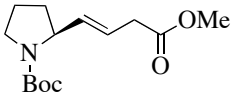
A popular way to construct (*E*)-alkene isosteres is via S_N2'-additions to displace aziridines, activated alcohols, and carbamates. The initial work on S_N2'-aziridine ring opening was carried out independently by Wipf and Fritch[26] and Ibuka *et al.* (Scheme 4).[26,56] Starting from either *N*-Boc-threonine methyl ester **38** or the free anime **42**, aziridines **40** and **44** were accessible. Activation of alcohol **38** followed by reduction of the ester and treatment with base afforded aziridine **39**. Aziridine **43** was constructed by

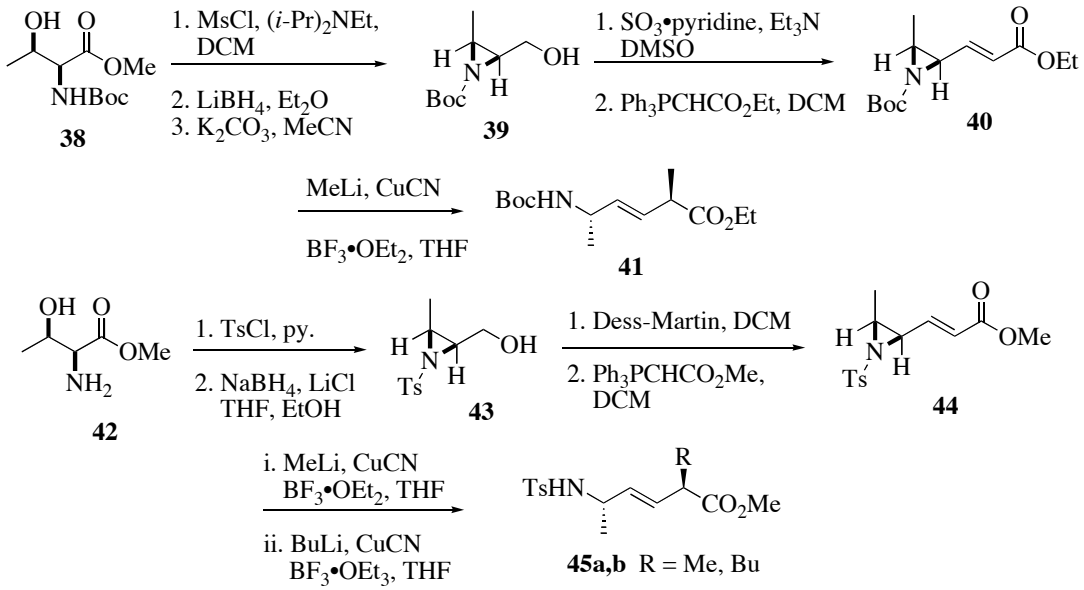
treatment with tosyl chloride followed by reduction of the ester and treatment with base. Upon oxidation of alcohol and olefination, alkenylaziridines **40** and **44** were reacted with various cuprates. Treatment of **40** with MeLi, CuCN and BF_3•OEt_2 led to the (*E*)-alkene **41** in 68% yield. Aziridine **44** was subjected to MeLi or BuLi, CuCN and BF_3•OEt_2 conditions and yielded the corresponding isosteres **45a-b** in 74% and 86%, respectively.

Table 1. Olefin metathesis to form (*E*)-alkene peptide isosteres.



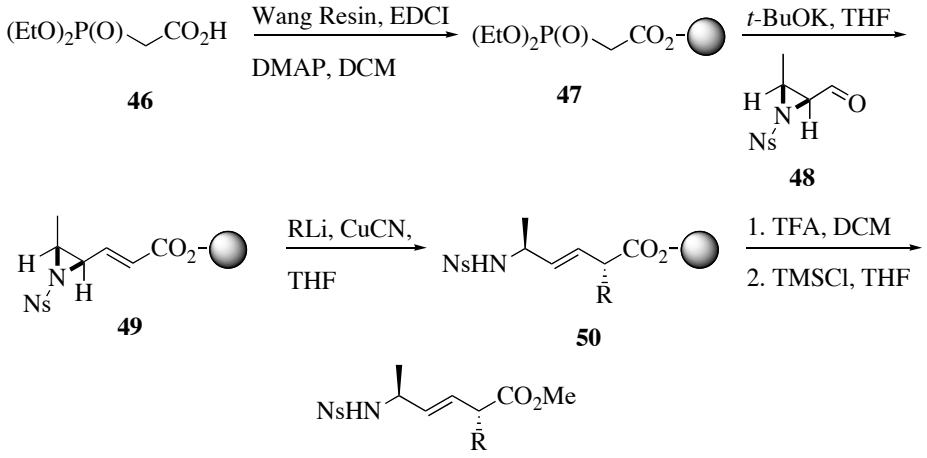
36a-d **37a-d**

Entry	Amine	Amine Equiv.	Product	Yield [%]	E/Z ratio
1	 **36a**	3	 **37a**	60	>10:1
2	 **36b**	3	 **37b**	67	>10:1
3	 **36c**	2	 **37c**	31	>10:1
4	 **36d**	5	 **37d**	83	



Scheme 4. Wipf's method for synthesizing (*E*)-aalkene peptide isosteres.

The Wipf group continued to be active in this area of research in 1997, Wipf and Henninger reported the first synthesis of (*E*)-alkene peptide isosteres via S_N2'-aziridine opening on solid support (Scheme 5).[57] The initial step was the synthesis of a novel resin-bound Horner Wadsworth-Emmons reagent **47,** which was accessed by EDCI coupling of acid **46** with Wang Resin. Treatment of the resin with KO*t*-Bu followed by addition of **48** yielded the resin-bound aziridine **49**. Upon exposure to a variety of cuprates, **49** underwent ring opening, which led to **50a-e**. Acidic cleavage, followed by esterification with TMS-Cl, MeOH yielded **51a-e** in 74-55% yield. This methodology could be applied to iterative solid phase peptide synthesis or to the development of combinatorial libraries.

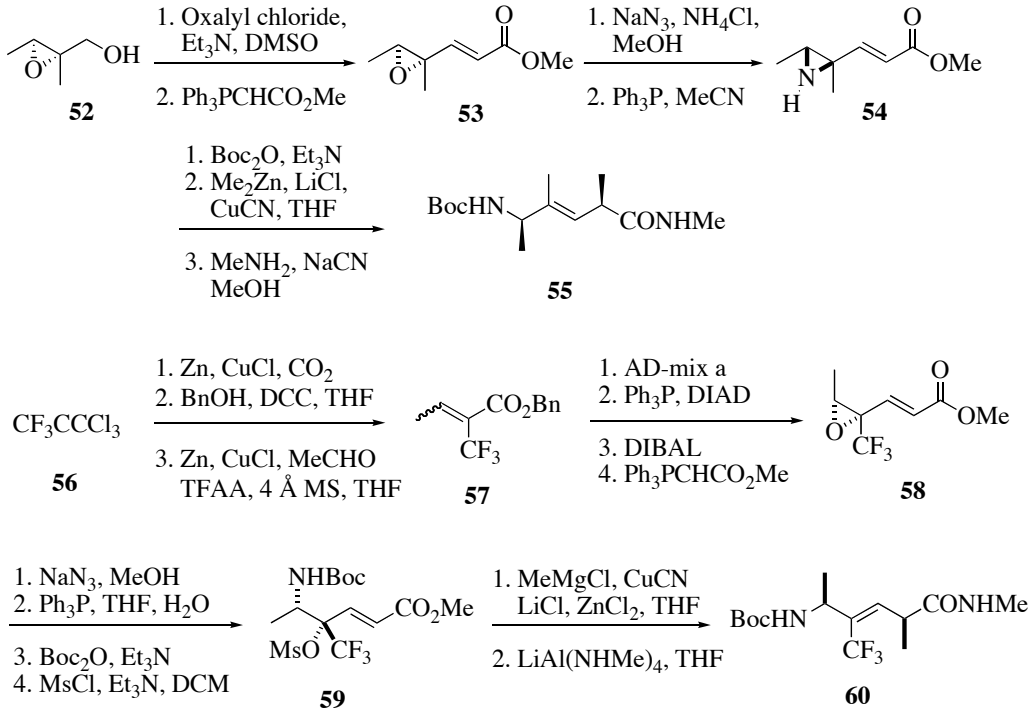


Scheme 5. S_N2'-Opening of allylic aziridines with cuprates on solid support**.**

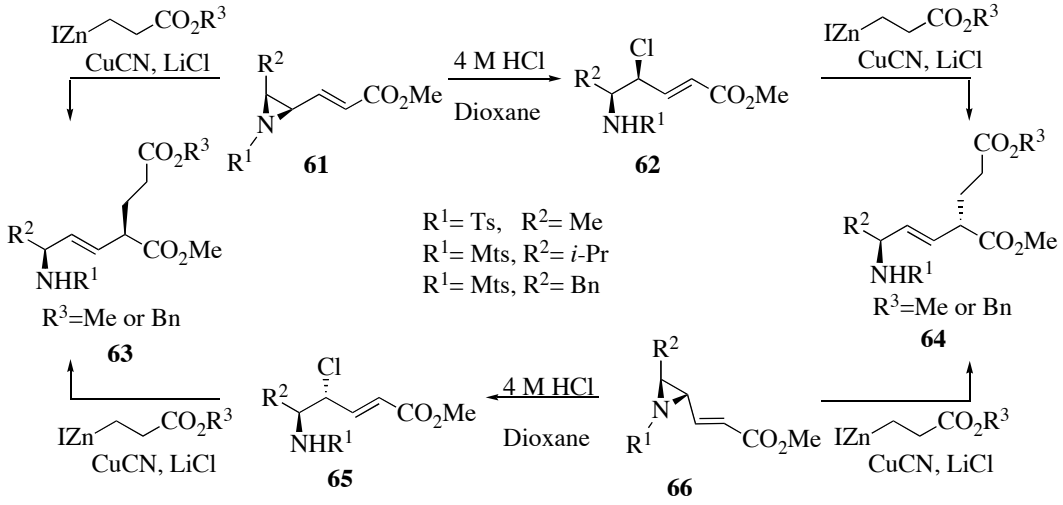
In 1998, Wipf *et. al.* were able to synthesize both methyl- and CF_3-substituted alkene isosteres and show that they promote β-turn formation (Scheme 6).[51] Starting from the epoxyalcohol **52**, epoxide **53** was accessed via Swern oxidation, followed by Wittig olefination. The epoxide was treated with NaN_3, then the resulting azide was reduced with Ph_3P and cyclized to form **54** in 13% yield. The aziridine was subsequently Boc-protected, and exposed to Me_2Zn, CuCN and LiCl. The resulting (*E*)-alkene isostere was treated with $MeNH_2$, which yielded the amide **55** in 33% yield. A similar synthetic route was initially purposed for the synthesis of the CF_3-analogue, **56** was converted to **57** via a carbonylation, DCC coupling of the acid and Reformatsky addition-elimination. The desired (*Z*)-olefin isomer was isolated, subjected to Sharpless dihydroxylation, followed by Ph_3P-promoted epoxide formation. Reduction of the benzyl ester followed by Wittig olefination yielded **58**. Treatment with NaN_3 and Ph_3P afforded the amino alcohol, but the desired ring closure did not occur. Boc-protection of the amine and subsequent mesylation of the alcohol gave **59**. Treatment with MeMgBr, CuCN, LiCl and $ZnCl_2$

facilitated an *anti*-S_N2'-displacement of the mesylate, and treatment with $LiAl(NHMe)_4$ gave **60** in 65% yield.

The Fujii group has developed S_N2'-addition chemistry to yield a wide array of alkene peptidomimetics. Early work in the group focused on the ability to access both (*L*,*L*) and (*L*,*D*) dipeptide mimetics from the same starting material (Scheme 7).[58-60] Treatment of aziridine **61** with $IZn(CH_2)_2CO_2R^3$, CuCN and LiCl afforded the (*L*,*L*) dipeptide isostere **63**. Exposure of **66** to the same reagents gave the (*L*,*D*)-diastereomer **64**. Treatment of **59** with HCl afforded the opened aziridine **62**, which upon treatment with cuprate underwent an *anti*-S_N2'-displacement of the chloride to yield **64**. The same procedure can be used to access **63** from **66**. This allows a single aziridine to yield either diastereomer of the isostere selectively.



Scheme 6. Synthesis of trisubstituted (*E*)-alkene peptide isosteres.

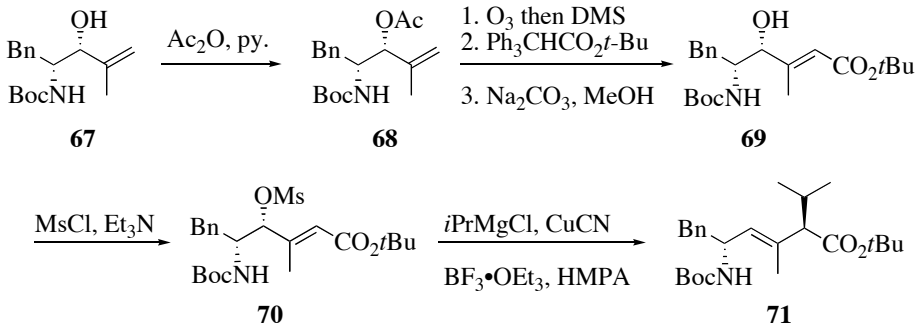


Scheme 7. Fujii's (*E*)-alkene synthesis.

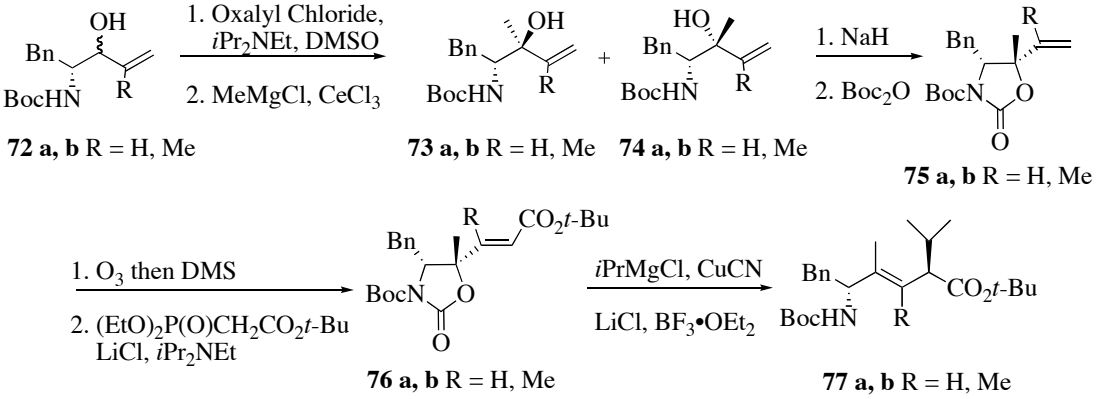
Fujii and co-workers were also able to access systems similar to **62** and **65** without using an aziridine as an intermediate (Scheme 8).[61-63] Alcohol **67** was obtained in a few steps from *N*-Boc-Phe-OMe, and subsequent protection of the alcohol with Ac_2O yielded **68**. Conversion of the olefin to the ketone via ozonolysis, followed by Wittig olefination and removal of the acetate group yielded **69**. Mesylation of the alcohol followed by treatment with *i*PrMgCl, CuCN, BF_3•OEt_2 afforded the trisubstituted olefin **71**.

In 2002, the Fujii group investigated the S_N2'-openings of oxazolidinones (Scheme 9).[61,64] Alcohols **72a-b** were oxidized to the corresponding ketone, followed by treatment with MeMgCl to yield a mixture of **73** and **74**. Treating the desired isomer **73** with NaH and Boc_2O afforded oxazolidinone **75**. Ozonolysis followed by olefination yielded the allylic oxazolidinone **76**. The dipeptide isosteres **77** were produced upon

exposure of **76** to *i*PrMgCl, CuCN and LiCl. This method afforded access to both tri- and tetrasubstituted alkenes of biological interest.



Scheme 8. Fujii's S_N2'-displacement of allylic mesylate to form (*E*)-alkene.

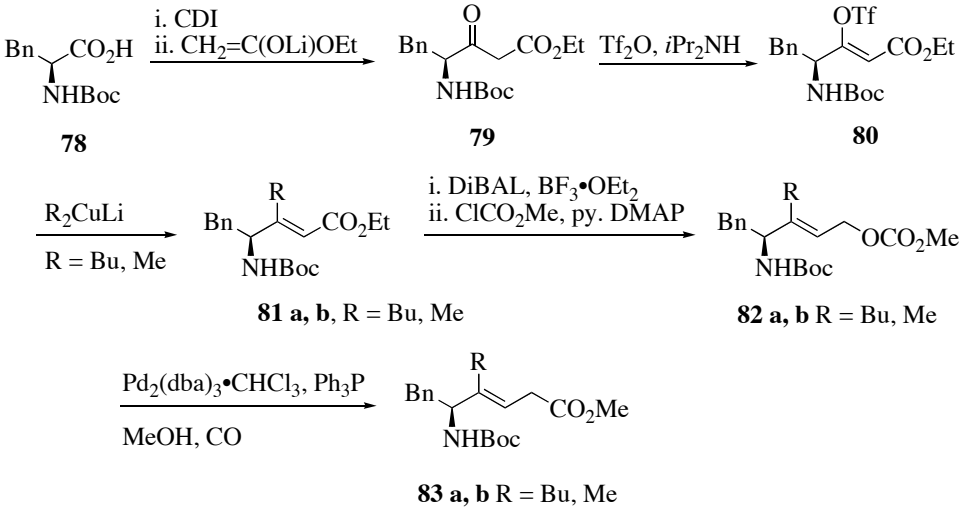


Scheme 9. S_N2'-Opening of an oxazolidinone to form an (*E*)-alkene peptide isostere.

The Fujii group has published an interesting route to trisubstitued (*E*)-alkene peptide isosteres via a palladium-catalyzed carbonylation (Scheme 10).[65] Treatment of phenylalanine with CDI followed by the lithium enolate of ethyl acetate gave **79**. Exposure to base and trapping with Tf_2O afforded enol trifalte **80**. This compound was converted to the **81** via treatment of alkylcuprates. Reduction with DiBAL and treatment

with methyl chloroformate yielded allylic carbonate **82**. Upon exposure to catalytic palladium in MeOH under and atmosphere of CO, **82** underwent convertion to the desired dipeptide isostere **83**.

Wipf and co-workers were able to access (*E*)-alkene peptide utilizing the hydrozirconation-imine addition methodology developed in their group.[38] Treatment of alkyne **84** with Cp_2ZrHCl, followed by transmetaltion to Me_2Zn and addition to *N*-Boc-isovaleraldimine afford **85** as a mixture of diastereomers. Upon silyl removal and protection of the resulting alcohol as the acetate, the diastereomers were separated. Deprotection of the alcohol and subsequent oxidation to the acid gave **87**. This building block was used in the synthesis of (*E*)-alkene peptide isostere containing analogs of the cyclic peptide Gramicidin S.



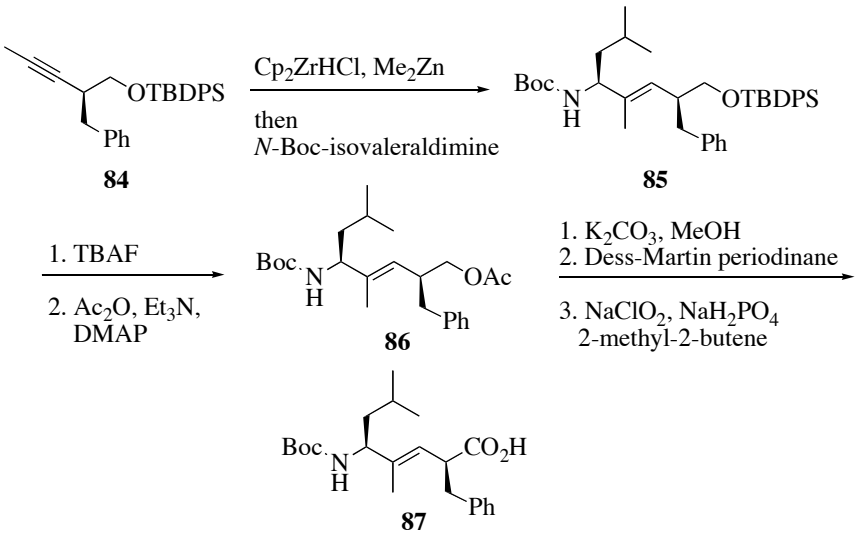
78 **79** **80**

81 a, b, R = Bu, Me

82 a, b R = Bu, Me

83 a, b R = Bu, Me

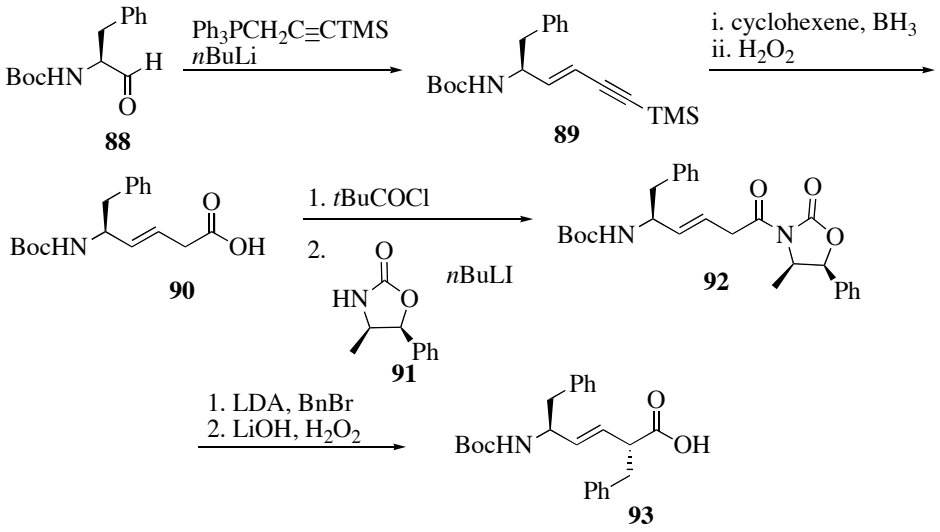
Scheme 10. Palladium-catalyzed carbonylation approach to (*E*)-alkene peptide isosteres.



Scheme 11. Imine addition route to (*E*)-alkene peptide isosteres.

The Kelly group has developed a route to (*E*)-alkene peptide isosteres that allows for the generation of gram quantities of material for the incorporation into polypeptides (Scheme 12).[46] Wittig olefination of aminoaldehyde **88** afforded the eneyne in good yield and high enantiomeric excess. Hydroboration of the alkyne followed by oxidation gave **90,** which was converted to imide **92**. Alkylation followed by cleavage of the auxillary gave dipeptide isostere **93**.

These methods offer a variety of routes for the synthesis of (*E*)-alkene peptidomimetics. As such, a large variety of mimetics incorporating both natural and unnatural side chains can be developed. This allows for an increase in our understanding of peptide interaction with enzymes or receptors and may be used in the development of pharmaceuticals.



Scheme 12. Kelly method for the synthesis of (*E*)-alkene peptide isosteres.

1.1.3 The mechanism of copper-mediated S_N2' reactions

The S_N2' reaction is formally defined as a bimolecular nucleophilic substitution with allylic rearrangement. This reaction has been known since the 1920's, but until the last 25 years it has seen little synthetic use due to the formation of mixtures of regio- and stereoisomers. Useful chemistry[66,67] was developed once it was found that allylic acetates underwent more selective S_N2' reaction in the presence of organocuprates.[68,69]

S_N2' reactions of allylic halides and organometalic reagents, in the absence of copper, typically favor addition when the approaching nucleophile is *syn* to the leaving halide.[70] In the presence of a copper source, the addition follows exclusively an *anti*-pathway, where the nucleophile and leaving group are on opposite sides of the olefin. Corey proposed a possible explanation for this change in selectiviy in which the copper coordinates with the olefin and the departing halide (Figure 9).[71] The filled d^{10} orbital of copper was able to simultaneously interact with the π^* orbital of the carbon-carbon

double bond and the σ^* orbital of the C-X bond (Figure 9, eq 1). This interaction not only serves to activate both the olefin for attack and the halide for displacement, but also delivers the nucleophile to the side opposite the leaving group, yielding high *anti*-selectivity. A similar mechanism has been proposed by Marshall for the *anti*-S_N2' opening of vinylepoxides (Figure 9, eq 2).[72] As in the previous example, the copper interacts with the antibonding orbitals of the olefin and the epoxide allowing the nucleophile to add in an *anti*-fashion.

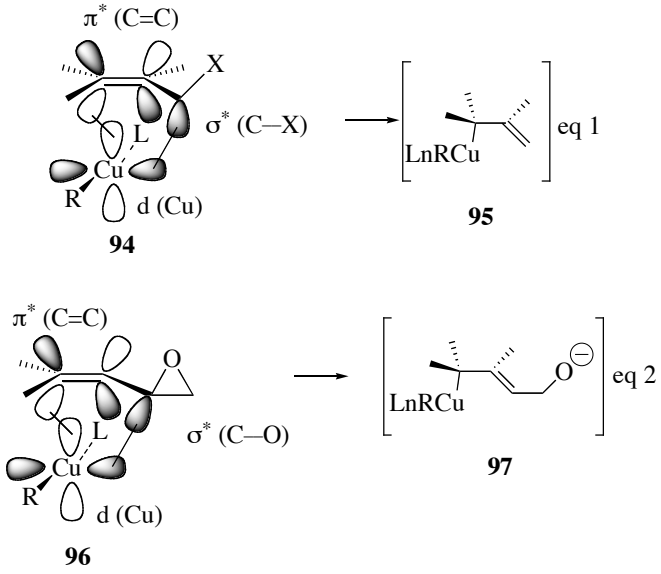


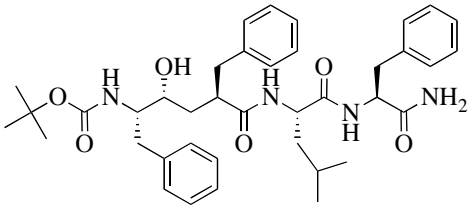
Figure 9. Interaction of Cu d^{10}-orbitals with the anti-bonding orbitals of an allylic halide or epoxide.

1.2 SYNTHESIS OF (*E*)-ALKENE PEPTIDE ISOSTERES IN SOLUTION AND ON SOLID SUPPORT VIA CUPRATE MEDIATED S_N2' REACTIONS

1.2.1 L-685,458: Lead Compound for Library Synthesis

γ-Secretase is responsible for the cleavage of the amyloid β-protein precursor (APP) affording the carboxyl terminal amyloid β-protein (Aβ), the major constituent of the protein plaques associated with Alzheimer's Disease (AD).[73] These plaques are formed, in part, due to the highly lipophilic character of the Aβ protein and activate an inflammatory process that initiates the clinical onset and progression of AD.[74-78] While considered essential to the understanding of the etiology of AD, the γ-secretase protease is yet to be well characterized and much of its function is still not clear. New insight to elucidate the γ-secretase behavior was gained by the development of inhibitors.[79-82]

L-685,458 (Figure 10) is a specific γ-secretase inhibitor possessing a hydroxyethylene dipeptide isostere, suggesting that it serves as a transition state analog within the catalytic site of an aspargyl protease.[83] Due to the potency and selectivity L-685,458 exhibits over other protease inhibitors, it seems to be a good model for the synthesis of peptidomimetics of the type of **98** (Figure 11). We envisioned the replacement of the central amide bond with either a di- or trisubstituted (*E*)-alkene peptidomimetic, installed via the S_N2'-aziridine ring opening. By replacing this bond, we hoped to construct a molecule that had improved stability toward proteolytic cleavage, but retained the biological activity of the lead structure.

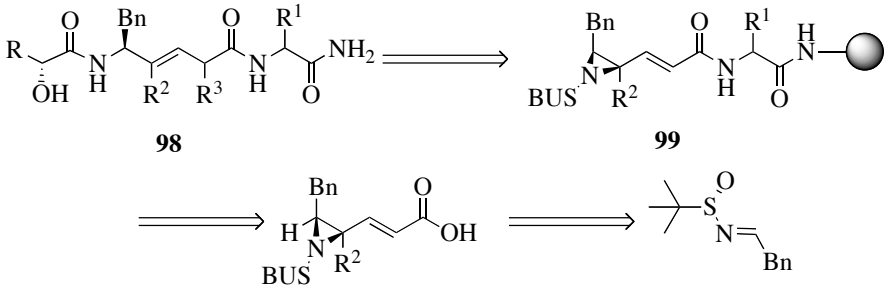


L-685,458

Figure 10. Structure of L-685,458.

1.2.2 Retrosynthetic analysis for a library based on L-685,458

Retrosynthetically, the removal of the nitrogen protecting group and coupling with α-hydroxy carboxylic acids would yield mimetics **98**. The resin-bound aziridine **99** would arise from the coupling of aziridines of type **100** with polystyrene resins loaded with various amino acids. The required aziridines would be synthesized using an aza-Darzens approach starting from imine **101**.

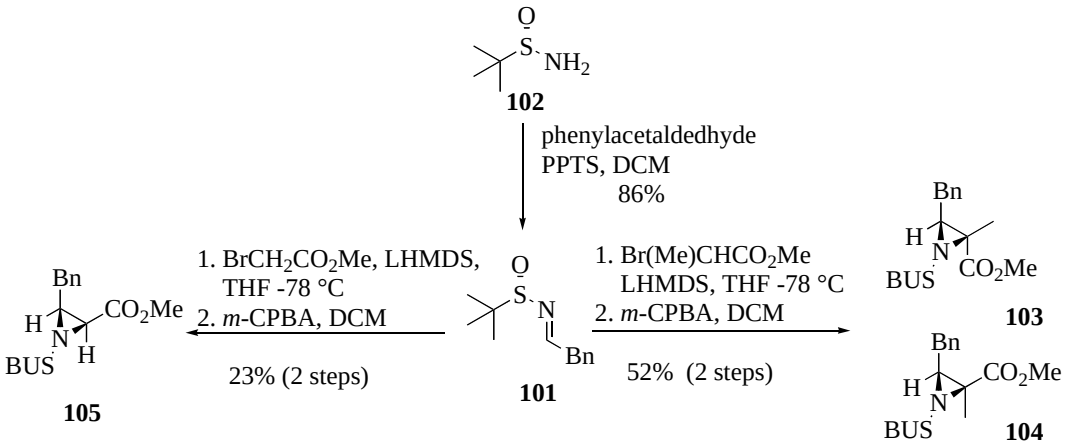


98 **99** **100** **101**

Figure 11. Retrosynthetic analysis of the isostere library.

1.2.3 Synthesis of allylic aziridines

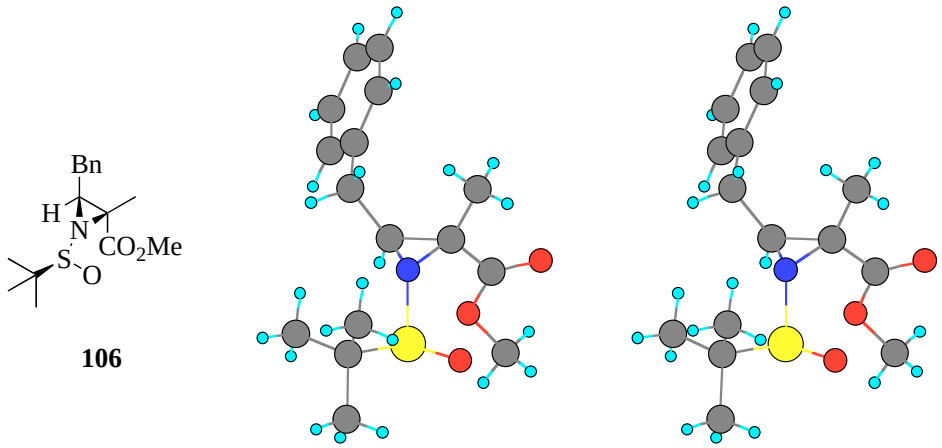
The synthesis of the required allylic aziridines began with the condensation of *t*-butylsulfinamide[84-86] with phenylacetaldehyde in the presence of PPTS and $MgSO_4$ to give imine **101** in 89% yield (Scheme 13). Treatment of methyl-2-bromopropionate with LHMDS at –78 °C followed by the addition of **101** afforded an *N*-sulfinyl aziridine which upon exposure to *m*-CPBA yielded **103** and **104** in 52% combined yield.[87] Using the same procedure with methyl-bromoacetate yielded **105** in 23% yield. A crystal structure of the aziridine intermediate **106**, before *m*-CPBA oxidation, confirmed the relative and absolute configuration of the azirdination step (Figure 12).[87]



Scheme 13. Synthesis of di- and trisubstituted aziridines

The BUS-group is not a typical nitrogen protecting group[88] and furthermore it has not been demonstrated to be an activating group for allylic aziridines for S_N2'-displacement. A tosyl group would be better suited to both the addition chemistry and subsequent removal, but formation of the imine is difficult due to isomerization during

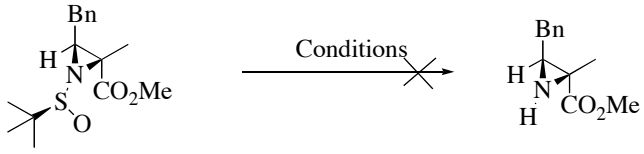
the reaction.[87,89] Cleavage of the sulfoxide followed by protection of the free nitrogen as a tosyl amide would offer an alternative method for introduction of the tosyl function. The deprotection of the aziridine **106** with acid or under nucleophilic conditions did not afford the desired material (Table 2).



106

Figure 12. X-ray crystal structure of aziridine **106**.

Table 2. Attempted deprotection of aziridine **106**.

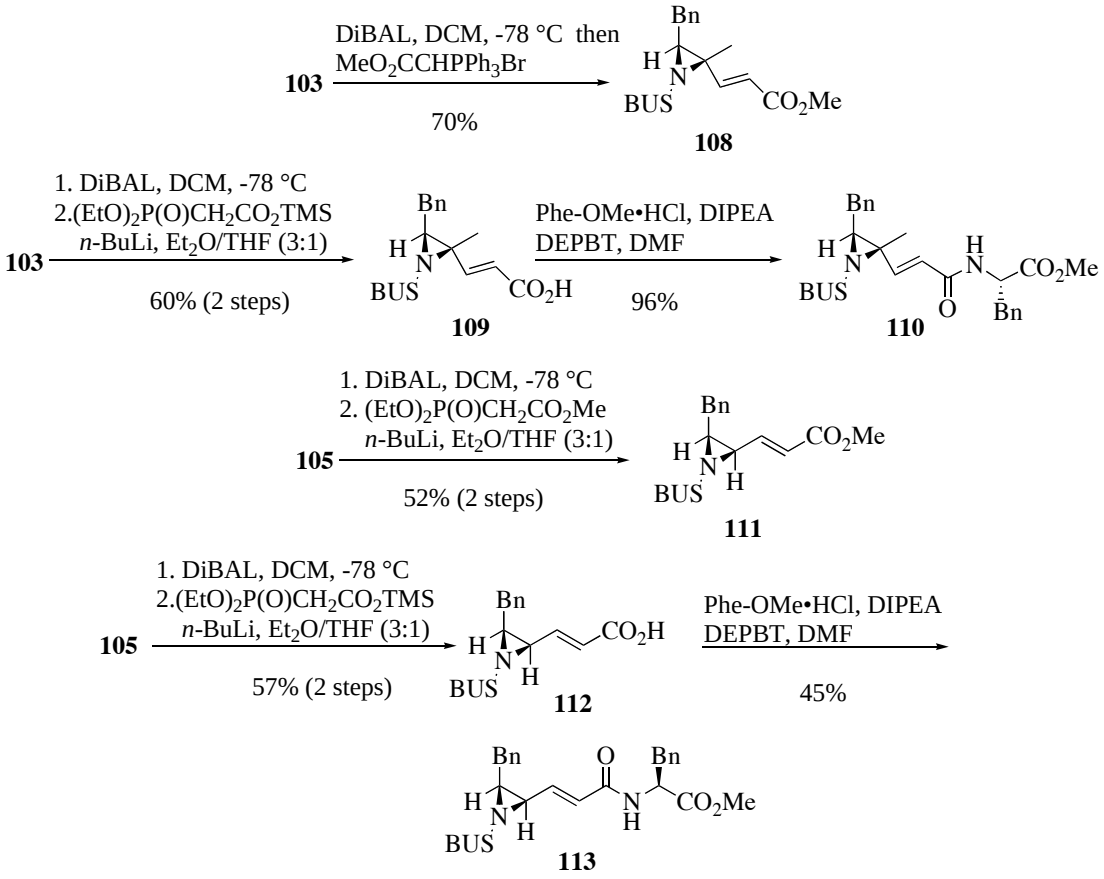


106 **107**

Entry	Conditions	Temp	Time (h)	Result
1	HCl, MeOH	r.t.	0.5	dec.
2	5 equiv TFA, 1:1 Acetone/H_2O	r.t.	1	dec.
3	MeMgBr, THF	-78 °C	3	dec. + ester addition

To study the reactivity of BUS-activated allylic aziridines, several model systems were constructed (Scheme 14). Treatment of **103** with DiBAL at –78 °C followed by Wittig olefination conditions yielded the α,β-unsaturated methyl ester **108** in 70% yield.

Treatment of the same aldehyde intermediate with trimethylsilyl diethylphosphonoacetate yielded the α,β-unsaturated acid **109** in 60% yield. This acid was then coupled to L-Phe-OMe with DEPBT to afford in 96% the α,β-unsaturated amide **110**. Similarly, aziridine **105** was treated with DiBAL at –78 °C, followed by treatment with either methyl diethylphosphonoacetate or trimethylsilyl diethylphosphonoacetate to yield the α,β-unsaturated methyl ester **111** or acid **112** in 57% and 52%, respectively. When acid **112** was coupled to L-Phe-OMe, **113** was isolated in 45% yield.

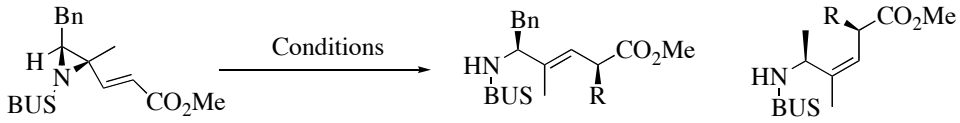


Scheme 14. Synthesis of allylic aziridines from **103** and **105**.

1.2.4 S_N2'-Opening of allylic Bus-protected aziridines in solution phase

With these compounds in hand, it was possible to test the ability of the BUS group to activate aziridines for S_N2'-reactions. Treatment of **108** with Me_2Zn, CuCN and LiCl led to formation of **114a/115b** as an inseparable 12:1 mixture of isomers in 77% combined yield (Table 3, Entry 1). Treatment of this mixture with DiBAL at 0 °C led to alcohol **116** in 68%. Treatment with *i*-PrMgCl, *i*-BuMgCl, or phenethylMgCl and CuCN gave product ratios ranging from 3:1 to 9:1 by NMR and isolated yields from 55-73% (Table 3, Entries 2-4). The relative configuration of these products was confirmed by x-ray analysis of ester **114c** (Figure 12) and alcohol **116** (Figure 14), both showing the (*L*,*D*)-dipeptide isostere as the major isomer.

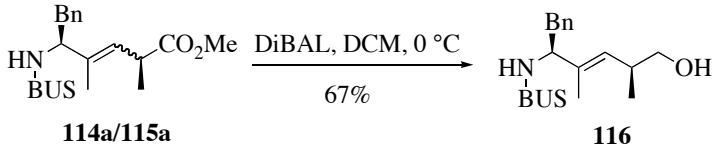
Table 3. S_N2'-Ring opening of **108** with various cuprate reagents



108 **114a-d** **115a-d**

Entry	Conditions[a]	R	Ratio[b] (**114**/**115**)	Yield[c,d]
1	Me_2Zn, CuCN, 2 equiv LiCl	Me	12:1	77%
2	*i*-PrMgCl, CuCN	*i*-Pr	9:1	55%
3	*i*-BuMgCl, CuCN	*i*-Bu	4.9:1	73%
4	PhenethylMgCl, CuCN	Phenethyl	3:1	61%

[a]3 equiv reagents, -20 °C, THF, 3 h. [b]Determined by NMR. [c]Mixture of isomers. [d]Isolated yield.



114a/115a **116**

Scheme 15. Reduction of ester mixture **114a/115a**.

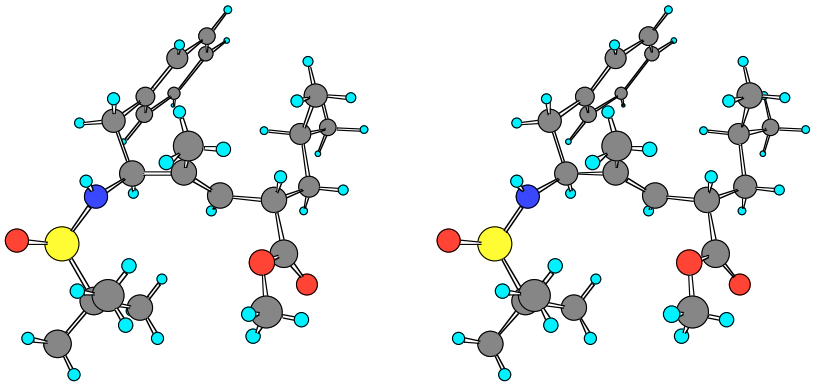


Figure 13. X-ray crystal structure of **114c**.

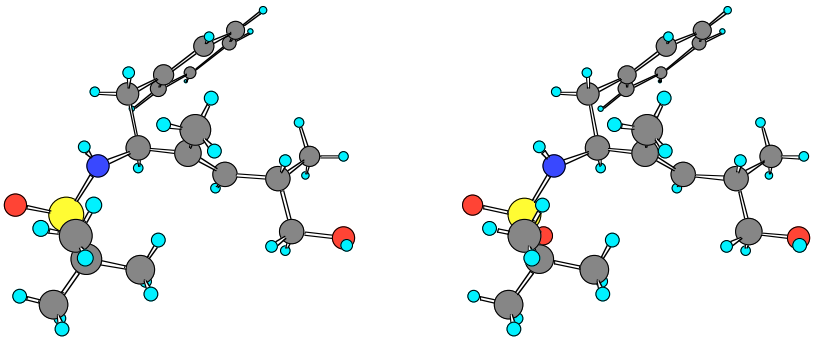


Figure 14. X-ray crystal structure of **116**.

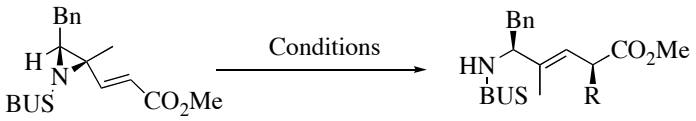
The addition of a benzyl group to these substrates proved to be more difficult than the addition of alkyl groups (Table 4). Attempts to achieve high yielding reactions with short reaction times met with limited success. The treatment of **108** with Bn_2Zn, CuCN and LiCl or BnMgCl and CuBr•DMS at –78 °C for 3 or 8 h, respectively, gave no reaction

(Table 4, Entry 1 and 9). Treatment with BnMgCl and CuCN at –78 ºC to –20 º C led to only the formation of the reduced compound **114f** (Table 4, Entry 2). The addition of LiCl to this reaction afforded a mixture of **114f** and the desired compound **114e** in 55% and 34% yield respectively (Table 4, Entry 3). When $ZnCl_2$ was added to the above mixture, the reaction became more sluggish and required 18 h and warming from either 0 ºC or –20 ºC to room temperature to go to completion, but the desired product was isolated in 80% yield as a single isomer (Table 4, Entry 4 and 5). Once conditions were found that afforded the product in good yield, attempts were made to shorten the reaction time to allow a more straightforward application of this procedure to solid phase synthesis. Allowing the reaction to warm up more quickly did not afford shorter reaction times (Table 4, Entry 6-8).

The key transformation for the library synthesis was the S_N2'-opening of aziridines coupled to amino acids. No compounds similar to **110** have been extensively studied in this type of reaction. Treating **110** to the standard S_N2'-addition conditions led to the formation of **117a, b** and **d** in good yields in isomer ratios of 9:1 to 3:1 (Table 5, Entries 1, 2 and 4). Since these results were similar to those obtained for the reaction of **108** under identical conditions, the additional steric bulk and stereocenter did not greatly affect the selectivity of the reaction in most cases. Unexpectedly, the treatment of **110** with *i*-BuMgCl and CuCN gave a reversal of selectivity affording **118c** as the major isomer in a 3:1 ratio in 66% yield. The structure of the major compounds was assigned by comparision to the spectra of compounds **114a-d** and **115c**. Though these reactions provide a moderate to high yield, they were slow and did not go to completion after 3 h. This could be due to the steric bulk of the amino acid side chain, deprotonation of the

amide and electronic repulsion of the nucleophile, or complexation of the rate-accelerating Lewis acid to the backbone amides.

Table 4. Addition of a benzyl substituent to **108** via S_N2'-ring opening.



108

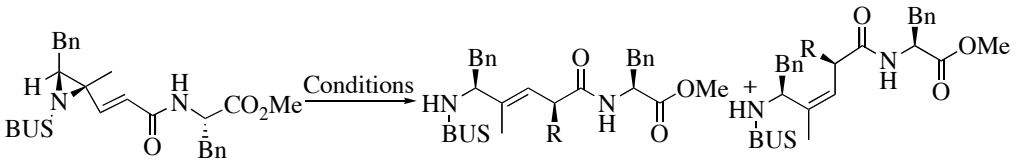
114e R= Bn
114f R= H

Entry[a]	BnMgCl (eq)	CuX (eq)	LiCl (eq)	$ZnCl_2$ (eq)	Temp	Time (h)	Product
1	Bn_2Zn (3)	CuCN (3)	6	-	-78 °C	3	**108**
2	BnMgCl (3)	CuCN (3)	-	-	-78 °C to -20 °C	3	**114f**
3	BnMgCl (10)	CuCN (10)	20	-	0 °C to r.t.	18	**114f** (55%)[b], **114e** (34%)[b]
4	BnMgCl (10)	CuCN (10)	20	10	-20 °C to r.t.	18	**114e** (80%)[b]
5	BnMgCl (10)	CuCN (10)	20	10	0 °C to r.t.	18	**114e** (80%)[b]
6	BnMgCl (10)	CuCN (10)	20	10	0 °C to r.t.	1	**108**:**114e** (10:1)[c]
7	BnMgCl (10)	CuCN (10)	20	10	0 °C to r.t.	3	**108**:**114e** (10:1)[c]
8	BnMgCl (10)	CuCN (10)	20	10	0 °C to r.t.	6	**108**:**114e** (3.4:1)[c]
9	BnMgCl (10)	CuBr•DMS (10)	20	-	-78 °C	8	**108**

[a] All reaction run on 0.028 mmol scale. [b] Isolated yield. [c] Ratio determined by NMR.

After extensive investigation of the *2*,3-*trans*-aziridine, focus shifted to the reaction of the *2*,3-*cis*-aziridines. Ring opening of **111** afforded compounds **119a-d** as single isomers in high yields of 100-72%. Similarly, the S_N2'-reaction of **113** yielded **120** in 61% as a single isomer (Scheme 16). As in the reactions of **110**, the selectivity of the addition was not affected by the incorporation of the phenylalanine residue, but the reaction rate was decreased.

Table 5. S_N2'-Ring opening of **110** with various cuprate reagents.

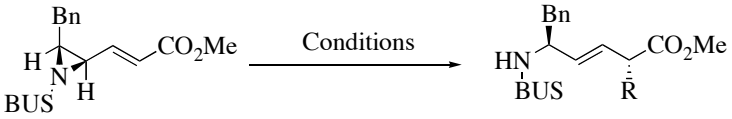


110 **117a-d** **118a-d**

Entry	Conditions	R	Ratio[b] (**117**/**118**)	Yield[c,d]
1	Me_2Zn, CuCN, 2 eq LiCl	Me	9:1	100%
2	*i*-PrMgCl, CuCN	*i*-Pr	3:1	84%
3	*i*-BuMgCl, CuCN	*i*-Bu	1:3	66%
4	PhenethylMgCl, CuCN	Phenethyl	7:1	67%

[a] 3 eq of reagent, -20 °C, THF, 3 h. [b] Determined by NMR. [c] Mixture of isomers. [d] Isolated yiled.

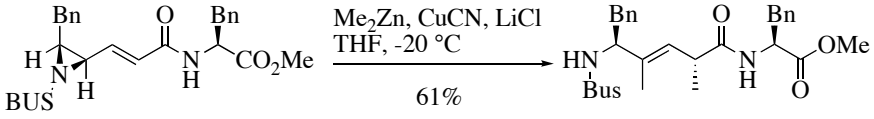
Table 6. S_N2'-Ring opening of **111** with various cuprate reagents.



111 **1119a-d**

Entry	Conditions	R	Yield[c,d]
1	Me_2Zn, CuCN, 2 eq LiCl	Me	100%
2	*i*-PrMgCl, CuCN	*i*-Pr	84%
3	*i*-BuMgCl, CuCN	*i*-Bu	66%
4	PhenethylMgCl, CuCN	Phenethyl	67%

[a] 3 eq of reagent, -20 °C, THF, 3 h. [b] Determined by NMR. [c] Mixture of isomers. [d] Isolated yield.



113 **120**

Scheme 16. S_N2'-Ring opening of **113**.

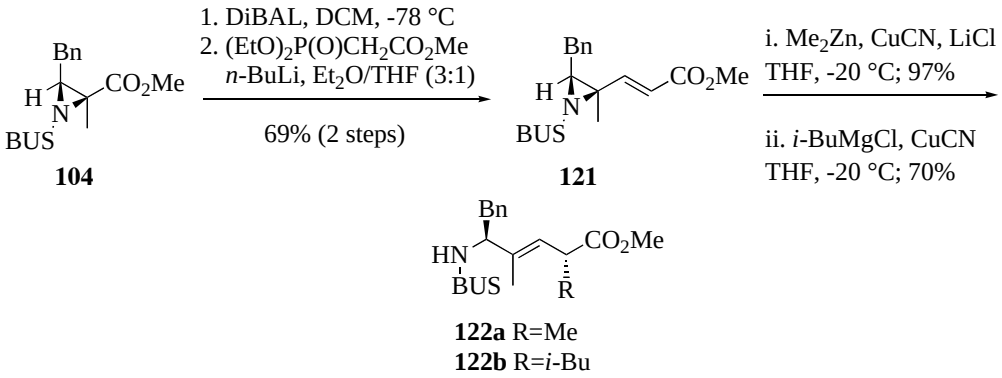
1.2.5 Determination of the minor isomer generated by addition to 2,3-*trans* allylic aziridines

The origin of the minor isomer formed when the *2*,3-*trans*-aziridines **108** and **110** were subjected to S_N2'-ring opening was investigated. Initially, the structure of the minor isomer was not known, but there were two reasonable possible assignments. For example, an epimer at the newly formed stereocenter could arise from a *syn*-S_N2'-reaction. Another possiblily was the generation of a (*Z*)-olefin, which could arise from the reaction of the allylic aziridine in a different conformation.

To examine the possibility of a *syn*-addition pathway, the product of this reaction was independently synthesized (Scheme 17). Treatment of **104** with DiBAL at –78 °C and then exposure to methyl diethylphosphonacetate yielded **121** in 69%. Treatment with Me_2Zn, CuCN, LiCl or *i*-BuMgCl and CuCN provided the (*L*,*L*) dipeptide isostere **122a-b** as single diastereomers in 97% and 70% yield, respectively. Comparison of ^1H NMR of **122a-b** to those of the mixtures of **114a/115a** and **114c/115c** showed that the characteristic signal at 5.57 ppm for the minor isomer was not present. This demonstrated that the minor isomer was not generated from reaction of **108** via *syn*-S_N2'-addition.

The other possibility would be the reaction of the aziridine **108** from two different ground state conformations. The extended conformation **123** (Figure 15), where the enone points away from the aziridine, undergoes *anti*- S_N2'-addition, leading to the major product **114a**. The other conformation could be generated by rotation of a single bond to place the enone beneath the aziridine shown for **124**. *Anti*-S_N2'-addition to this

conformation would yield the (*Z*)-alkene **114a**. The energetic difference between these conformations has been calculated for the simpler *N*-methylsulfonyl-*trans*-2-methyl-3-vinyl aziridine to be 3.4 kcal/mol.[90] This energy difference was not sufficient to totally eliminate the higher energy conformation, so it was possible to generate the (*Z*)-alkene in this manner. Single crystal x-ray analysis of **118c** confirmed the structure of the minor isomer generated in this progress as the (*Z*)-alkene (Figure 16).



Scheme 17. Synthesis of the epimer of **114a** and **114c**.

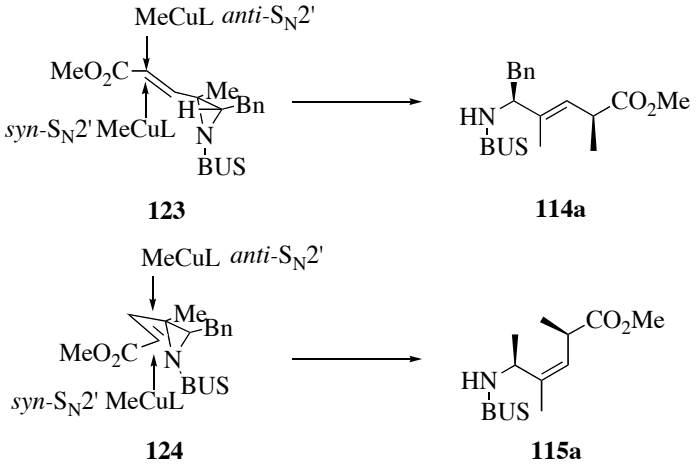


Figure 15. Possible reactive conformations of **108** and the resulting addition products.

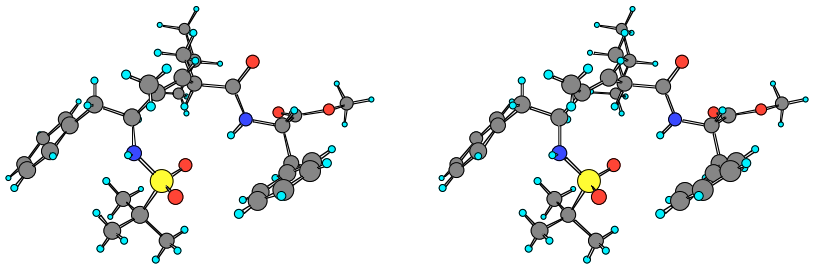
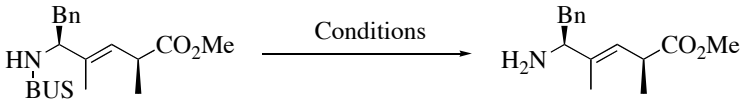


Figure 16. X-ray crystal structure of **118c**.

1.2.6 Attempted deprotection of the BUS amide

The final aspect of BUS-group chemistry to be investigated was its removal from allylic amines, but this transformation proved to be problematic. Treatment of **114a/115a** under the standard BUS-deprotection conditions[91] (TFA/anisole or trific acid/anisole Table 7, Entries 1 and 2) led to decomposition, presumably via cleavage of the carbon-nitrogen bond. Treatment with LAH[92] or Red-Al[93,94], which is known to cleave sulfonamides, led to the isolation of alcohol **116** but no cleavage of the BUS-group. Although the BUS-group could not be removed, it was decided to transfer this procedure to solid phase and investigate the opportunities for library development using these substrates.

Table 7. Attempted deprotection of the BUS-amide



114a/115a **125**

Entry	Conditions	Temp	Time (h)	Result
1	TFA, anisole	r.t.	16	dec.
2	Triflic acid, anisole	r.t.	3	dec.
3	LAH	0 °C to r.t.	48	**116**
4	Red-Al	0 °C to r.t.	48	**116**

1.2.7 The synthesis of a library on solid support

The goal in this phase of the project was the synthesis of a library of analogs based on compound **L-685,458**. We wished to exploit the chemistry developed in the group[47] to effect S_N2'-aziridine opening on solid support. The three points of diversity that could be introduced would arise from the coupling of various amino acids, the addition of different cuprates and from variation of the structure of aziridines **109** and **112** bound to the solid support (Figure 17). The BUS-group on the nitrogen of **126** would help to mimic the Boc-group found on the parent peptide. By replacing the central amide bond, we hoped increase the metabolitic stability of the peptide. To help facilitate

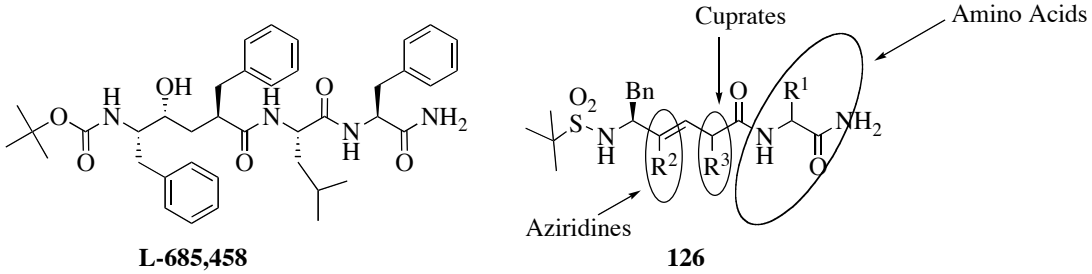


Figure 17. The structures L-685,458 and (*E*)-alkene analog **126**.

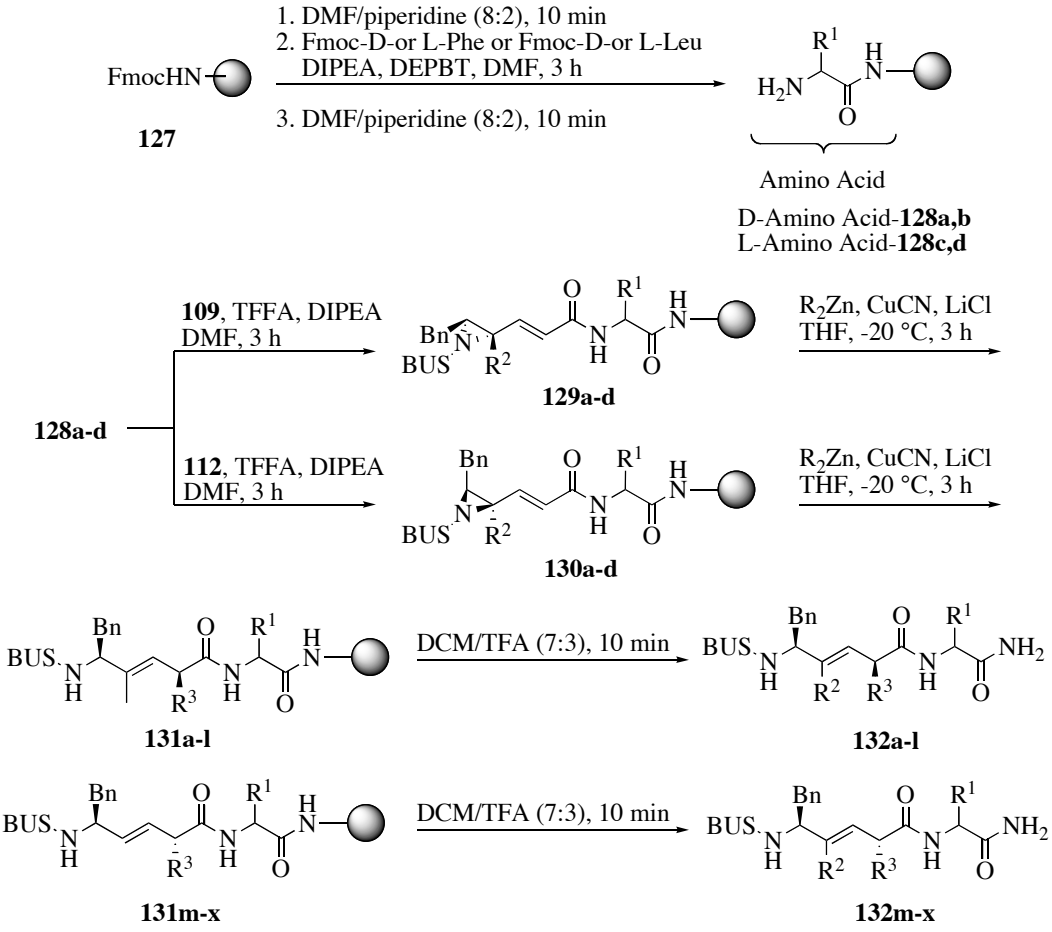
this work, we would carry out all solid-phase reactions using a New Brunswick Scientific Bohdan Mini Block, which was designed to agitate and filter the resins used in parallel reactions. This instrument consisted of three components: a) an orbital shaker; b) a reaction block and c) a fritted reaction tube (Figure 18 a, b, c). Up to 48 fritted test

tubes could be placed in a single block allowing for up to 96 reactions to be conducted when both blocks were used. The top of the reaction block was fitted with a septum that sealed the reaction tubes. This unit was used to support the reaction vessels and filter excess solvent or reagent from the reaction tube. The block has a built in valve that may be closed to ensure none of the reaction mixture escaped from the tube and could be easily opened to empty the vessel at the end of the reaction. Figure 19c shows the 3 mL fritted reaction tube. The resins were placed in the fritted tube, where all the reactions, washings, and drying were performed without transfer to different vessels.

A B C

Figure 18. The three components of the Bohdan Mini Block system.

The library synthesis would begin with the Fmoc deprotection of polystyrene Rink resin **127** to unmask the free amine; this amine would then be coupled to the amino acids and subsequently deprotected to yield **128a-d**. The aziridine would then be coupled to the resin bound amino acid to yield **129a-d** and **130a-d**. At this point, cuprates would be added to open the aziridine, followed by acidic cleavage to yield **132a-x** (Scheme 18).



Scheme 18. Synthesis of tri-peptide isosteres on solid support.

Based on our previous results on solid-supported aziridine opening,[57] coupled with the results from the solution phase studies of **108**, **110**, **111**, and **113**, it was anticipated that this sequence would afford the library members in good yield with high purities. While the solution phase data seemed to suggest that this process would be effective on solid phase, the initial data suggested otherwise. The library was made under the conditions shown in Scheme 18 but the results were disappointing (Table 8). While

the reactions proceeded as expected, the addition of the methyl group gave variable results. The methyl additions worked to form **132a, d, g, j** effectively, but not **132m, p, s, v** (Table 8). Based on solution phase data, these two aziridines react similarly, so this result was problematic. A possible reason for these variable results was the cooling system of the Bohdan blocks. The recirculating chiller used was unable to reach and maintain the desired –20 °C within the reaction block. This not only led to higher than desired temperatures, but uneven cooling within the reaction block. Changing the cooling system from a recirculation chiller to a simple dry ice 1:1 ethylene gycol/water bath allowed for a more uniform temperature throughout the reaction block and could easily be maintained at the desired –20 °C. A resynthesis of half the library that gave poor results before led to improved conversion (Table 8, Trial 2).

As this work progressed, it became necessary to modify the solid support that was used, since the original Argo-Gel resin was no longer available. The switch was made to Nova-Biochem Rink Resin, which was also a polystyrene support, but had a higher loading capacity of 0.62 mmol/g. With this resin in hand, the methyl and ethyl additions to **129a-d** were repeated and afforded similar yields ensuring there was no difference in reactivity (Table 9).

After establishing that this new resin performed well for this application, an attempt was made to synthesize a library with methyl, ethyl, and benzyl substituents (Table 10). The benzyl additions were conducted under conditions similar to Table 4, Entry 4, except that the temperature was kept at –20 °C for 12 h, then increase to 0 °C for 6 h. Though these reactions were conducted under similar conditions as the successful solution phase experiments, no product was observed. The yields from the methyl and

ethyl additions were comparable to those in Table 9. The purity of the material directly after cleavage from the resin was determined for the successful conversions. The purities were found to be low to moderate and work was begun to improve this aspect of the methodology.

Table 8. Summary of yields of (*E*)-alkene peptide library members (Scheme 18).

Entry	Amino Acid	R^2	R^3	Trial 1 yield[a]	Trial 2 yield[a]	Entry	Amino Acid	R^2	R^3	Trial 1 Yield[a]	Trial 2 Yield[a]
132a	L-Phe	Me	Me	40%	17%	**132m**	L-Phe	H	Me	trace[b]	ND[c]
132b	L-Phe	Me	Et	49%[a]	27%	**132n**	L-Phe	H	Et	31%	ND[c]
132c	L-Phe	Me	Ph	trace[b]	ND[c]	**132o**	L-Phe	H	Ph	n.d.	ND[c]
132d	D-Phe	Me	Me	46%	36%	**132p**	D-Phe	H	Me	trace[b]	ND[c]
132e	D-Phe	Me	Et	51%	29%	**132q**	D-Phe	H	Et	42%	ND[c]
132f	D-Phe	Me	Ph	trace[b]	ND[c]	**132r**	D-Phe	H	Ph	n.d.	ND[c]
132g	L-Leu	Me	Me	54%	34%	**132s**	L-Leu	H	Me	trace[b]	ND[c]
132h	L-Leu	Me	Et	44%	28%	**132t**	L-Leu	H	Et	37%	ND[c]
132i	L-Leu	Me	Ph	trace[b]	ND[c]	**132u**	L-Leu	H	Ph	n.d.	ND[c]
132j	D-Leu	Me	Me	13%	28%	**132v**	D-Leu	H	Me	trace[b]	ND[c]
132k	D-Leu	Me	Et	53%	30%	**132w**	D-Leu	H	Et	53%	ND[c]
132l	D-Leu	Me	Ph	trace[b]	ND[c]	**132x**	D-Leu	H	Ph	n.d.	ND[c]

[a]Isolated yield [b]Determined by LCMS, UV detection 210 nm [c]ND = Not determined

Table 9. Test of Nova-Biochem Rink resin using methyl and ethyl additions (Scheme 18).

Entry	Amino Acid	R^2	R^3	Yield[a]
132a	L-Phe	Me	Me	40%
132b	L-Phe	Me	Et	32%
132d	D-Phe	Me	Me	29%
132e	D-Phe	Me	Et	36%
132g	L-Leu	Me	Me	34%
132h	L-Leu	Me	Et	28%
132j	D-Leu	Me	Me	24%
132k	D-Leu	Me	Et	30%

[a] Isolated yield

The reactions that were effective in solution phase did not always translate to the solid phase. The reaction of the Grignard-derived cuprates, *i*-PrMgCl, *i*-BuMgCl or phenethylMgCl and CuCN with **129a** gave unexpectedly poor results. Product formation was observed in low yield when using *i*-PrMgCl and CuCN, but no product was observed with *i*-BuMgCl or phenethylMgCl and CuCN. To insure that the poor reactiviy was not simply due to a poor quality of the reagent, the additions to **108**, **110**, and **129a** were conducted using the same batch of cuprate reagent. The additions to **108** and **110** went as in previous attemps (Table 3, Entries 3 and 4, Table 5, Entries 3 and 4), but no reaction was observed with the resin bound aziridine. The reaction of **110** in the presence of the resin-bound aziridine **129a** went to completion, but again no addition to the resin-bound aziridine was observed. These results would indicate that these reagents are not well suited for use in solid phase reactions using the current reaction block technique.

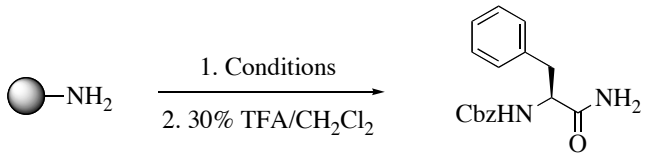
Table 10. Summary of yields and purities of (*E*)-alkene peptide library members (Scheme 18).

Entry	Amino Acid	R^2	R^3	Purity[a]	Yield[b]	Entry	Amino Acid	R^2	R^3	Purity[a]	Yield[b]
132a	L-Phe	Me	Me	ND	40%	**132m**	L-Phe	H	Me	60%	29%
132b	L-Phe	Me	Et	50%	32%	**132n**	L-Phe	H	Et	68%	17%
132y	L-Phe	Me	Bn	-	-	**132cc**	L-Phe	H	Bn	-	-
132d	D-Phe	Me	Me	ND	36%	**132p**	D-Phe	H	Me	66%	26%
132e	D-Phe	Me	Et	55%	29%	**132q**	D-Phe	H	Et	61%	30%
132z	D-Phe	Me	Bn	-	-	**132dd**	D-Phe	H	Bn	-	-
132g	L-Leu	Me	Me	ND	36%	**132s**	L-Leu	H	Me	54%	30%
132h	L-Leu	Me	Et	37%	39%	**132t**	L-Leu	H	Et	55%	36%
132aa	L-Leu	Me	Bn	-	-	**132ee**	L-Leu	H	Bn	-	-
132j	D-Leu	Me	Me	47%	24%	**132v**	D-Leu	H	Me	55%	36%
132k	D-Leu	Me	Et	55%	30%	**132w**	D-Leu	H	Et	60%	26%
132bb	D-Leu	Me	Bn	-	-	**132ff**	D-Leu	H	Bn	-	-

[a]Isolated yield [b]Determined by LCMS, UV detection at 210 nm [c]ND = Not determined

After establishing which reactions were successful on solid phase, the sequence was futher. The easiest and most important step to investigate was the initial coupling, since a poor yield in this step would perpetuate itself through the synthesis. In addition to investigating yield, a second rink resin developed by Polymer Labs was introduced to see if it offered any advantage over the Nova-Biochem resin. *N*-Cbz-Phe was coupled to each resin, under a variety of conditions; the resin was dried over night, and then cleaved. The standard conditions used in the previous library trials, 1.5 equiv of DEPBT and amino acid, led to product in 60% and 34% yield (Table 11, Entries 1 and 4) after cleavage. An increased amount of DEPBT and amino acid proved the yield of isolated product with both resins, but the yields using the Polymer Labs resins were not as high for the Nova-Biochem resin.

Table 11. Optimization studies of the initial coupling reaction using Cbz-Phe-OH.



133 **134**

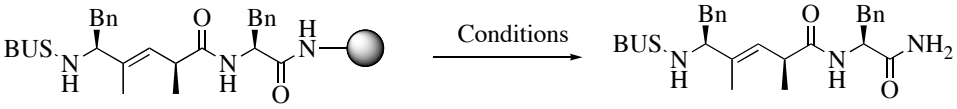
Entry	Resin	Conditions[a]	Yield[b]
1	Nova-BioChem Rink Amide	1.5 equiv DEPBT, Cbz-N-Phe-OH	60%
2	Nova-BioChem Rink Amide	5.0 equiv DEPBT, Cbz-N-Phe-OH	65%
3	Nova-BioChem Rink Amide	10.0 equiv DEPBT, Cbz-N-Phe-OH	73%
4	Polymer Labs Rink	1.5 equiv DEPBT, Cbz-N-Phe-OH	34%
5	Polymer Labs Rink	5.0 equiv DEPBT, Cbz-N-Phe-OH	52%
6	Polymer Labs Rink	10.0 equiv DEPBT, Cbz-N-Phe-OH	56%

[a]An equimolar amount of DIPEA was added to the reagents in a solution of DMF, 3 h, rt. [b]Isolated yield.

After investigating the resin loading, the focus then shifted to the final cleavage step from the resin. The original conditions for this cleavage, 30% TFA in

dichloromethane at room temperature, are rather harsh. The amount of TFA was decreased as well as the temperature in hopes of affording material with increased purity after cleavage from the solid support. While cooling the reaction increased the purity from 50 to 71% (Table 12, Entries 1 and 2), changing the amount of TFA had little effect (Table 12, Entries 2-4). The best purity was obtained when 20% TFA in dichloromethane at 0 °C was used (Table 12).

Table 12. Optimization studies for compound cleavage from the resin.



131a **132a**

Entry	Resin	Conditions	Temp.	Purity[a]
1	Nova-BioChem Rink Amide	7:3 TFA:CH_2Cl_2	r.t.	50%
2	Nova-BioChem Rink Amide	7:3 TFA:CH_2Cl_2	0 °C	71%
3	Nova-BioChem Rink Amide	8:2 TFA:CH_2Cl_2	0 °C	78%
4	Nova-BioChem Rink Amide	9:1 TFA:CH_2Cl_2	0 °C	76%

[a]Before column chromatography determined by HPLC, UV detection at 210 nm.

After investigating the first and last steps on solid phase, different resins and applying some observations from the solution phase reactions, the conditions for the synthesis of the library were modified. The coupling of amino acids to the resin changed from a single reaction with 1.5 equiv of amino acid and DEPBT to the reaction being conducted twice with 5 equiv of the reagents. The reaction time in the coupling of the aziridines **109** and **112** to the solid-supported amino acid was extended to 6 h from 3. Finally, since observations of the solution phase reactions that generated compounds **117a-d** and **120** had shown that 3 h were not sufficient for the reaction to reach completion, the reaction time on solid phase was increased to 6 h. These new conditions

were then applied to the synthesis of the methyl- and ethyl-substituted members of the library. However, the yields were not increased by using these new conditions but were significantly worse. Due to the decreased yield, the purities were not determined, but based on comparison of the crude ^{1}H NMR of these samples with those from Table 10, they were comparable.

The major difference between the optimization experiments and the library synthesis was the number of operations. While it ass trivial to focus on four to six reactions simultaneously, it became increasingly difficult to give the same individual care to 16-24 separate reactions. Although some aspects of the chemistry were operationally simple and required little care, such as washes and coupling reactions, others such as the cuprate additions and work-up procedures became more challenging when increasing the number of reactions. These difficulties may help to explain why small optimization studies showed improved results, but when the knowledge gathered from these studies was applied to a large number of reactions, the process did not improve.

1.3 CONCLUSION

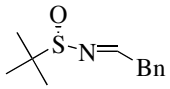
We were able to demonstrate the S_N2'-ring opening of BUS-activated aziridines with organocuprate reagents on solid phase. The study of the reactivity of these aziridines has shown the BUS-activation follows a pattern similar to the nosyl- or tosyl-activated hetereocycles, but leds to a decreased rate and diastereoselectivity. This methodology was used in the solid phase preparation of a small combinatorial library based on L-

685,458. Members of this library were obtained in yields between 20-50% with an average purity before final chromatographic purification of 56%.

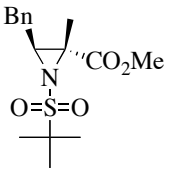
1.4 EXPERIMENTAL SECTION

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. CH_2Cl_2 was dried by distillation over NaH. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ^{o}C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, dd=doublet of doublet, ddd= doublet of doublet of doublet, dt=doublet of triplet, dq=doublet of quartet, m=multiplet, b=broad). LC/MS analyses used a Hewlett Packard Series 1100 MSD. Semi-prepative HPLC was performed on a Varian 215 delivery system in conjuntion with a Varian ProStar 325 UV detector using a Rainin Instrument company

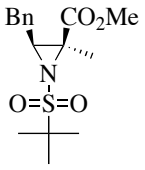
dynamax 60 Å C-18 column (No. 3-211-C). Chiral HPLC analysis was performed on a Dynamax SD-200 delivery system in conjunction with a Dynamax UV-1 absorbance detector. A Chiralcel OD (0.46 cm x 25 cm) or AD-H (0.46 cm x 25 cm) column was used for analytical separation. Infrared spectra were measured on a Nicolet AVATAR 360 FTIR E.S.P. spectrometer. Mass spectra were obtained on a double focusing instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C.



(S_S)-(-)-*N*-(Benzyl)-*t*-butylsulfinamide (101). To a solution of 10.9 g (89.9 mmol) of *t*-butylsulfinamide in 168 mL of CH_2Cl_2 was added 54.1 g (450 mmol) of $MgSO_4$, 11.0 mL (98.9 mmol) of distilled phenylacetaldehyde, and 1.13 g (4.49 mmol) of PPTS at room temperature. The reaction mixture was stirred for 48 h, filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (10-20% EtOAc/Hexanes) to yield 16.9 g (84%) of **101** as an orange oil: $[\alpha]_D^{25}$ +19.8 (*c* 0.96, $CHCl_3$); IR (neat) 3086, 3062, 3029, 2960, 2925, 2867, 1620, 1602, 1496, 1474, 1454, 1363, 1181, 1089 cm^{-1}; ^1H NMR δ 8.14 (t, 1 H, *J* = 5.2 Hz), 7.35-7.24 (m, 5 H), 3.86 (d of AB, 1 H, *J* = 17.0, 5.28 Hz), 3.82 (d of AB, 1 H, *J* = 15.3, 5.15 Hz), 1.20 (s, 9 H); ^{13}C NMR δ 167.4, 134.8, 129.2, 128.8, 127.1, 56.8, 42.6, 22.4; MS (EI) *m/z* (rel intensity) 167 ($[M-C_4H_8]^+$, 32), 153 (7), 118 (5), 117 (10), 105 (12), 104 (27), 91 (22), 77 (10), 65 (7), 57 (100); HRMS (EI) Calcd for C_8H_9NOS ($M-C_4H_8$) 167.0404, found 167.0406.

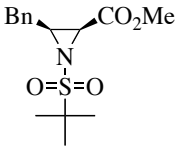


(3*S*)-Benzyl-(2*R*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridine-2-carboxylic acid methyl ester (103). To a solution of 1.59 g (5.18 mmol) of **106** in 60 mL in CH_2Cl_2 at 0 ºC was added 1.34 g (7.77 mmol) of *m*-CPBA. The reaction mixture was stirred for 3 h, gradually warmed to room temperature, quenched with 10 mL 10% $NaHSO_3$, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexane) to yield 1.07 g (63%) of **103** in 87% ee (determined by HPLC) as an off white solid: Mp 62.8-65.7 ºC; $[\alpha]_D^{25}$ –8.8 (*c* 1.1, $CHCl_3$); IR (KBr) 3459, 2984, 1740, 1630, 1497, 1455, 1311, 1160, 1127, 1075, 1015, 950, 891 cm^{-1}; ^1H NMR δ 7.35-7.25 (m, 5 H), 4.05 (dd, 1 H, *J* = 7.8, 5.8 Hz), 3.77 (s, 3 H), 3.04 (dd, 1 H, *J* = 15.2, 5.7), 2.80 (dd, 1 H, *J* = 15.2, 7.8 Hz), 1.66 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR δ 168.8, 136.6, 128.9, 128.7, 127.0, 60.3, 53.1, 50.7, 48.8, 34.2, 23.9, 15.4; MS (ES) *m/z* (rel intensity) 348.1 ($[M+^{23}Na]^+$, 100), 228.1 (20) ; HRMS (ES) Calcd for $C_{16}H_{23}NO_4NaS$ ($M+^{23}Na$) 348.1245, found 348.1235.



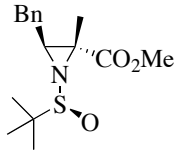
(3*S*)-Benzyl-(2*S*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridine-2-carboxylic acid methyl ester (104). Isolated as a colorless oil in 259 mg (15% yield) as the minor diastereomer from the reaction yielding **103**: $[\alpha]_D^{25}$ –26 (*c* 0.90, $CHCl_3$); IR (neat) 3054,

2987, 1747, 1639, 1421, 1311, 1265, 1129, 896 cm^{-1}; ^1H NMR δ 7.37-7.25 (m, 3 H), 7.18-7.14 (m, 2 H), 3.78 (s, 3 H), 3.17 (dd, 1 H, *J* = 8.4, 4.9 Hz), 3.01 (dd, 1 H, *J* = 14.9, 4.9 Hz), 2.81 (dd, 1 H, *J* = 14.9, 8,4 Hz), 1.88 (s, 3 H), 1.47 (s 9 H); ^{13}C NMR δ 168.8, 136.5, 128.8, 128.7, 127.0, 60.5, 52.8, 51.3, 50.9, 34.4, 23.9, 17.3; MS (EI) *m/z* (rel intensity) 266 ($[M-C_2H_3O_2]^+$, 22), 205 (5), 204 (32), 174 (6), 147 (9), 146 (59), 145 (27), 144 (74), 135 (30), 121 (5), 118 (16), 114 (21), 104 (33), 103 (47); HRMS (EI) Calcd for $C_{14}H_{20}NO_2S$ ($M-C_2H_3O_2$) 266.1214, found 266.1227.



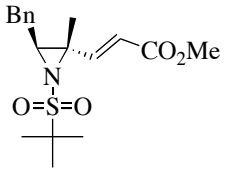
(3*S*)-Benzyl-1-(2-methylpropane-2-sulfonyl)-aziridine-(2*S*)-carboxylic acid methyl ester (105). To a solution of 10.5 mL (49.5 mmol) of HMDS in 500 mL of THF cooled to 0 ºC was added 31.0 mL (49.5 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 1 h, cooled to –78 ºC and treated with 1.60 mL (49.5 mmol) of methylbromoacetate via syringe pump over 1 h. A solution of 5.00 g (22.4 mmol) of **101** in 25 mL of THF was cooled to –78 ºC and added via canula over 30 min. The resulting mixture was stirred for 7 h at –78 ºC, quenched with 100 ml H_2O, extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was redissolved in 140 mL of CH_2Cl_2, cooled to 0 ºC, and 6.76 g (39.2 mmol) of *m*-CPBA was added. The reaction mixture was stirred for 2 h, warmed gradually to room temperature, quenched with 100 mL of a 10% aqueous solution of $NaHSO_3$, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was

purified by chromatography on SiO_2 (100% CH_2Cl_2) to yield 1.63 g (23%) of **105** in 99% ee as a yellow solid: Mp 54.1-62.8 ºC; $[\alpha]_D^{25}$ –7.9 (*c* 1.3, $CHCl_3$); IR (KBr) 2993, 1743, 1602, 1438, 1305, 1234, 1129, 1039 cm^{-1}; ^1H NMR δ 7.36-7.18 (m 5 H), 3.80 (s 3 H), 3.44 (d, 1 H, *J* = 7.2 Hz), 3.26 (ddd, 1 H, 13.2, 7.3, 6.0 Hz), 3.12 (dd, 1 H, *J* = 14.7, 5.8 Hz), 2.93 (dd, 1 H, *J* = 14.7, 7.4 Hz), 1.48 (s, 9 H); ^{13}C NMR δ 166.5, 136.4, 128.7, 128.7, 127.0, 59.9, 52.6, 43.2, 41.3, 33.2, 23.9; MS (ES) *m/z* (rel intensity) 334.1 ($[M+^{23}Na]^+$, 100), 215.1 (6), 214.1 (78); HRMS (ES) Calcd for $C_{15}H_{21}NO_4NaS$ ($M+^{23}Na$) 334.1089, found 334.1097.



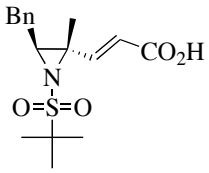
(3*S*)-Benzyl-(2*R*)-methyl-1-(2-methylpropane-2-(*S*)-sulfinyl)-aziridine-2-carboxylic acid methyl ester (106). To a solution of 2.1 mL (9.9 mmol) of HMDS in 32 mL of THF was added at 0 ºC 6.2 mL (9.9 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 1 h, cooled to –78 ºC, treated dropwise with 1.1 mL (9.9 mmol) of methyl bromopropinate and stirred for 2 h. A solution of 1.0 g (4.5 mmol) of **101** in 5 mL of THF was cooled to –78 ºC and added via canula over the course of 30 min. The resulting mixture was stirred for 3 h, quenched with 10 mL H_2O, extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to yield 0.82 g (59%) of **106** as a pale yellow oil: $[\alpha]_D^{25}$ 93 (*c* 0.55, $CHCl_3$); IR (neat) 2952, 1731, 1496, 1455, 1272, 1200, 1160, 1087, 1029, 980, 936 cm^{-1}; ^1H NMR δ 7.35-7.15 (m, 5 H), 3.78 (s, 3 H), 3.53 (dd, 1 H, *J* = 7.5, 5.9 Hz), 2.93 (dd, 1 H, *J* = 15.0, 5.9 Hz), 2.80 (dd, 1 H, *J* = 14.9, 7.4

Hz), 1.58 (s, 3 H), 1.24 (s 9 H); ^{13}C NMR δ 170.6, 137.6, 129.0, 128.9, 127.0, 56.9, 53.3, 49.2, 45.9, 34.7, 22.3, 16.5; MS (ES) *m/z* (rel intensity) 332.2 ([M+^{23}Na]$^{+}$, 100), 227.2 (31), 213.2 (23); HRMS (ES) Calcd for $C_{16}H_{23}NO_3NaS$ (M+^{23}Na) 332.1296, found 332.1296.



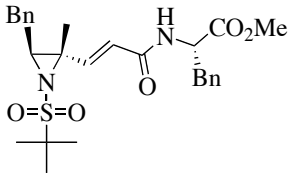
3-[(3*S*)-Benzyl-(2*R*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridin-2-yl]-(*E*)-acrylic acid methyl ester (108). To a solution of 0.20 g (0.61 mmol) of **103** in 4 mL of CH_2Cl_2 at –78 ºC was added 1.2 mL (1.2 mmol) of a 1 M solution of DiBAL in hexanes. The reaction mixture was stirred for 30 min and quenched with 2 mL of a saturated aqueous solution of NH_4Cl. To the resulting solution was added 0.40 g (1.2 mmol) of (methoxycarbonylmethyl) triphenylphosphonium bromide. The reaction mixture was stirred, warmed to room temperature for 15 h, filtered through a pad of Celite, diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30%EtOAc/Hexane) to yield 0.15 g (70%) of **108** as an off white solid: Mp 76.2-77.2 ºC (CH_2Cl_2); $[\alpha]_D^{25}$ –2.3 (*c* 0.96, $CHCl_3$); IR (KBr) 2975, 2949, 1719, 1654, 1440, 1301, 1124 cm^{-1}; ^{1}H NMR δ 7.36-7.15 (m, 5 H), 7.11 (d, 1 H *J* = 15.8 Hz), 6.09 (d, 1 H, *J* = 15.8 Hz), 3.73 (s, 3 H), 3.37 (dd, 1 H, *J* = 8.7, 4.9 Hz), 3.13 (dd, 1 H, *J* = 15.1, 4.9 Hz), 2.83 (dd, 1 H, *J* = 15.1, 8.7), 1.58 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR δ 166.0, 146.7, 136.5, 129.1, 128.6, 127.2, 123.5, 60.1, 53.2, 52.0, 51.1, 34.2, 24.1, 16.3; MS (ES) *m/z* (rel intensity) 374.2 ([M+^{23}Na]$^{+}$, 100), 288.3 (5), 255.2 (8), 254.2 (33),

232.2 (18), 200.2 (4); HRMS (ES) Calcd for $C_{18}H_{25}NO_4NaS$ (M+^{23}Na) 374.1402, found 374.1415.



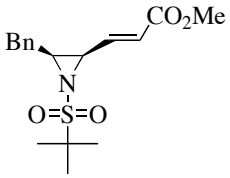
3-[(3*S*)-Benzyl-(2*R*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridin-2-yl]-(*E*)-acrylic acid (109). To a solution of 1.00 g (3.06 mmol) of **103** in 20 mL of CH_2Cl_2 at –78 ºC was added 6.20 mL (6.20 mmol) of a 1 M solution of DiBAL in hexanes. The reaction mixture was stirred for 30 min, quenched with 4 mL of cold (-78 ºC) MeOH, warmed to rt, treated with 4 mL of saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3x), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting aldehyde was washed with benzene, concentrated *in vacuo* (3x) and dried under high vacuum. To a solution of 2.04 g (7.60 mmol) of trimethylsilyl diethylphosphonoacetate in Et_2O at 0 ºC was added 4.80 mL (7.60 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The ice bath was removed, and the reaction mixture was warmed to room temperature, stirred for 1 h, and cooled again to 0 ºC. A solution of the aldehyde in 6 mL of a 1:1 solution of THF/Et_2O was added dropwise. The resulting solution was stirred for 3 h, poured over 20 mL of 2 M aqueous $NaHSO_4$, immediately extracted with EtOAc (3x), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30%-50%EtOAc/Hexane) to yield 630 mg (60%) of **109** as an off white sticky solid: Mp 120.2-124.4 ºC (CH_2Cl_2); $[\alpha]_D^{25}$ –21 (*c* 0.58, CH_2Cl_2); IR (KBr) 3089, 2984, 2659, 1698, 1310, 1128, 931 cm^{-1}; ^{1}H NMR (Acetone-d_6) δ 7.33-7.19 (m, 5 H), 7.11 (d, 1 H, *J* = 15.7 Hz), 6.10 (d, 1 H, *J* = 15.7 Hz), 3.34 (dd, 1 H, *J* = 8.2, 5.3 Hz), 3.19 (dd, 1 H, *J* = 15.0, 5.3 Hz), 2.97 (dd, 1 H,

J = 15.0, 8.2 Hz), 1.61 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR (Acetone-d_6) δ 166.4, 148.0, 137.9, 129.3, 129.3, 127.3, 123.6, 59.9, 53.9, 51.1, 34.3, 23.9, 16.2; MS (ES) *m/z* (rel intensity) 360.2 ([M+^{23}Na]$^+$, 100), 259.2 (3), 240.2 (13); HRMS (ES) Calcd for $C_{17}H_{23}NO_4SNa$ (M+^{23}Na) 360.1245, found 360.1255.



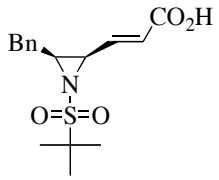
2-{3-[(3*S*)-Benzyl-(2*R*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridin-2-yl]-(*E*)-acryloylamino}-3-phenyl-(*S*)-propionic acid methyl ester (110). To a solution of 0.20 g (0.59 mmol) of **109** in 12 mL DMF was added 0.53 g (1.8 mmol) of DEPBT, 0.62 mL (3.6 mmol) of diisopropyl ethyl amine, and 0.38 mg (1.8 mmol) of L-phenylalanine methyl ester•HCl and was stirred for 3 h at room temperature. The reaction mixture was quenched with 10 mL of a saturated aqueous solution of NH_4Cl and extracted with Et_2O (5x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (30% EtOAc/Hexane) to yield 0.28 g (96%) of **110** as an iridescent foam: $[\alpha]_D^{25}$ 49 (*c* 0.60, $CHCl_3$); IR (KBr) 3290, 2985, 1746, 1668, 1633, 1538, 1455, 1308, 1205, 1126, 982, 936, 848 cm^{-1}; ^{1}H NMR δ 7.36-7.09 (m, 10 H), 6.88 (d, 1 H, *J* = 15.7 Hz), 6.13 (bs, 1 H), 6.07 (d, 1 H, *J* = 15.7 Hz), 4.94 (ddd, 1 H, *J* = 11.8, 6.8, 5.7 Hz), 3.72 (s, 3 H), 3.38 (dd, 1 H, *J* = 8.5, 4.9 Hz), 3.13 (dd, 3 H, *J* = 12.1, 5.6 Hz), 2.83 (dd, 1 H, *J* = 15.1, 8.6 Hz), 1.56 (s, 3 H), 1.43 (s, 9 H) ; ^{13}C NMR δ 171.8, 164.4, 142.2, 136.5, 135.8, 129.3, 128.8, 128.6, 128.5, 127.0, 1267.0, 125.9, 59.8, 53.2, 52.6, 52.3, 51.1, 37.9, 34.1, 24.02,

16.3; MS (ES) *m/z* (rel intensity) 521.6 ([M+^{23}Na]$^{+}$, 100), 499.6 (83), 467.6 (5), 401.5 (5), 379.5 (10), 378.5 (17), 377.5 (30), 260.4 (10), 259.3 (22), 198.3 (8), 168.2 (5); HRMS (ES) Calcd for $C_{27}H_{34}N_2O_5NaS$ (M+^{23}Na) 521.2086, found 521.2067.



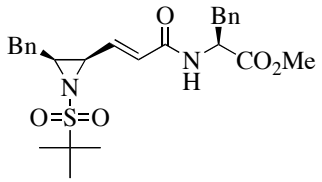
3-[(3*S*)-Benzyl-1-(2-methylpropane-2-sulfonyl)-aziridin-(2*S*)-yl]-(*E*)-acrylic acid methyl ester (111). To a solution of 0.10 g (0.32 mmol) of **105** in 4 mL of CH_2Cl_2 at –78 ºC was added 0.48 mL (0.48 mmol) of a 1 M solution of DiBAL in hexanes. The reaction mixture was stirred for 30 min, quenched with 2 mL of cold (-78 ºC) MeOH, warmed to rt, treated with 2 mL of a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3x), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting aldehyde was washed with benzene, concentrated *in vacuo* (3x) and dried under high vacuum. To a solution of 0.13 g (0.64 mmol) of methyl diethylphosphonoacetate in Et_2O at 0 ºC was added 0.40 mL (0.64 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The ice bath was removed, the reaction mixture was warmed to room temperature, stirred for 1 h, and cooled again to 0 ºC. A solution of the aldehyde in 0.5 mL of a 1:1 mixture of THF/Et_2O was added dropwise. The reaction mixture was stirred for 3 h, quenched with 1 mL of a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3x), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexanes) to yield 58 mg (52%) of **111** as a white solid: Mp 101.1-107.4 ºC (CH_2Cl_2); $[\alpha]_D^{25}$ –52 (*c* 0.71, CH_2Cl_2); IR (KBr) 2985, 1725, 1659, 1440, 1295, 1256, 1126, 979, 936, 859, 751 cm^{-1}; ^{1}H NMR (Acetone-d_6) δ 7.36-7.18 (m, 5 H), 6.89 (dd, 1 H,

J = 15.6, 7.2 Hz), 6.34 (dd, 1 H, *J* = 15.6, 0.8 Hz), 3.73 (s, 3 H), 3.50 (dt, 1 H, *J* = 7.2, 0.8 Hz), 3.19 (ddd, 1 H, *J* = 13.4, 7.2, 6.3 Hz), 3.02 (dd, 1 H, *J* = 14.7, 6.2 Hz), 2.88 (dd, 1 H, *J* = 14.8, 7.2 Hz), 1.39 (s 9 H); ^{13}C NMR (Acetone-d_6) δ 165.5, 140.4, 137.6, 129.2, 128.8, 127.0, 126.43, 59.1, 51.4, 45.5, 43.3, 33.2, 23.6; MS (ES) *m/z* (rel intensity) 360.1 ([M+^{23}Na]$^+$, 100), 262.1 (9), 240.1 (15); HRMS (ES) Calcd for $C_{17}H_{23}NO_4NaS$ (M+^{23}Na) 360.1245, found 360.1253.



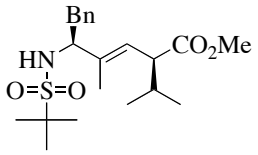
3-[(3*S*)-Benzyl-1-(2-methylpropane-2-sulfonyl)-aziridin-(2*S*)-yl]-(*E*)-acrylic acid (112). To a solution of 0.25 g (0.80 mmol) of **105** in 10 mL of CH_2Cl_2 at –78 ºC was added 1.2 mL (1.2 mmol) of a 1 M solution of DiBAL in hexanes. The reaction mixture was stirred for 30 min, quenched with 1 mL of cold (-78 ºC) MeOH, warmed to rt, treated with 5 mL of a 10% aqueous solution of citric acid and extracted with EtOAc (3x). The combined organic layers were washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting aldehyde was washed with benzene, concentrated *in vacuo* (3x) and placed under high vacuum. To a solution of 0.43 mg (1.6 mmol) of trimethylsilyl diethylphosphonoacetate in Et_2O at 0 ºC was added 1.0 mL (1.6 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The ice bath was removed and the reaction mixture was warmed to room temperature, stirred for 1.5 h and cooled again to 0 ºC. A solution of the aldehyde in 1.3 mL of 1:1 mixture of THF/Et_2O was added dropwise. The resulting solution was stirred for 1.25 h, poured over 10 mL of 2 M aqueous $NaHSO_4$, immediately extracted with EtOAc (3x), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was

purified by chromatography on SiO_2 (30-100% EtOAc/Hexane) to yield 0.15 g (57%) of **112** as an off-white gummy solid: Mp 98.4-108.1 ºC (CH_2Cl_2); $[\alpha]_D^{25}$ –40 (*c* 0.85, CH_2Cl_2); IR (KBr) 2990, 1686, 1651, 1455, 1423, 1308, 1206, 1129, 979, 859 cm^{-1}; ^1H NMR (Acetone d_6) δ 7.38-7.17 (m, 5 H), 6.89 (dd, 1 H, *J* = 15.6, 7.2 Hz), 6.31 (dd, 1 H, *J* = 15.6, .8 Hz), 3.50 (dt, 1 H, *J* = 7.2, 0.8 Hz), 3.19 (dt, 1 H, *J* = 7.2, 6.2 Hz), 3.04 (dd, 1 H, *J* = 14.8, 6.2 Hz), 2.89 (dd, 1 H, *J* = 14.8, 7.3 Hz), 1.40 (s, 9 H); ^{13}C NMR (Acetone d_6) δ 166.3, 141.0, 138.1, 129.8, 129.7, 129.3, 127.5, 59.7, 45.9, 43.9, 33.8, 24.1; MS (ES) *m/z* (rel intensity) 346.1 ([M+^{23}Na]$^+$, 83), 306.1 (13), 275.1 (4), 259.1 (17), 247.1 (43), 226.1 (9), 181.1 (9), 153.0 (9); HRMS (ES) Calcd for $C_{16}H_{21}NO_4NaS$ (M+^{23}Na) 346.1089, found 346.1083.



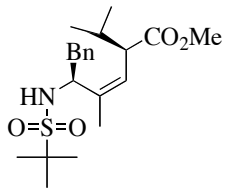
2-{3-[(3*S*)-Benzyl-1-(2-methylpropane-2-sulfonyl)-aziridin-(2*S*)-yl]-(*E*)-acryloyl amino}-3-phenyl-(*S*)-propionic acid methyl ester (113). A solution of 0.21 g (0.63 mmol) of **112**, 0.57 g (1.9 mmol) of DEPBT, 0.67 mL (3.8 mmol) diisopropyl ethylamine, and 0.41 g (1.9 mmol) L-phenylalanine methyl ester•HCl in 13 mL of DMF was stirred for 3 h at room temperature. The reaction mixture was quenched with 10 mL of a saturated aqueous solution of NH_4Cl, and extracted with Et_2O (5x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (30% EtOAc/Hexane) to yield 0.14g (45%) of **113** as an 8:1 mixture of diastereomers as a clear glass. After purification

by semi-preparative reverse phase HPLC (4 mL/min, 2:1 acetonitrile/H_2O) a sample of pure **113** was isolated: $[\alpha]_D^{25}$ 3.6 (*c* 1.4, $CHCl_3$); IR (KBr) 3415, 3054, 2986, 2305, 1742, 1680, 1647, 1510, 1438, 1309, 1266, 1127 cm^{-1}; ^1H NMR (Acetone-d_6) δ 7.69 (d, 1 H, *J* = 8.1 Hz), 7.38- 7.16 (m, 10 H), 6.72 (dd, 1 H, *J* = 15.5, 7.0 Hz), 6.51 (d, 1 H, *J* = 15.3 Hz), 4.80 (ddd, 1 H, *J* = 8.0, 8.0, 2.8 Hz), 3.66 (s, 3 H), 3.41 (t, 1 H, *J* = 13.8 Hz), 3.16 (dd, 2 H, *J* = 13.5, 5.9 Hz), 3.07-2.92 (m, 2 H), 2.82 (dd, 1 H, *J* = 14.6, 7.3 Hz), 1.49 (s, 9 H); characteristic signals for the minor isomer: ^1H NMR (Acetone-d_6) δ 7.55 (d, 1 H, *J* = 7.4 Hz), 4.11 (t, 1 H, *J* = 5.6 Hz), 3.61 (s, 3 H); ^{13}C NMR (Acetone-d_6) δ 171.7, 163.6, 137.4, 137.0, 135.1, 129.2, 129.1, 128.9, 128.5, 128.3, 126.6, 58.7, 53.8, 51.4, 45.0, 43.3, 37.4, 32.8, 23.4; MS (ES) *m/z* (rel intensity) 507.2 ([M+^{23}Na]$^+$, 100), 387.2 (7); HRMS (ES) Calcd for $C_{26}H_{32}N_2O_5NaS$ (M+^{23}Na) 507.1930, found 507.1922.



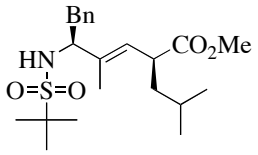
(2*R*)-Isopropyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (114b). To a solution of 50 mg (0.56 mmol) of CuCN in 5.5 mL of THF was added at –78 ºC 0.28 mL (0.56 mmol) of a 2 M solution of *i*-propyl magnesium chloride in THF. The resulting mixture was stirred for 10 min, warmed to 0 ºC, stirred for 15 min, and cooled to –20 ºC. A solution of 50 mg (0.14 mmol) of **108** in 0.6 mL of THF was added. The resulting solution was stirred for 3 h, quenched with 3 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10% EtOAc/Hexanes) to yield 30 mg (55%) of a 9:1 mixture of **114b/115b** as a colorless oil.

After repeated chromatography on SiO_2 a pure sample of **114b** was isolated: $[\alpha]_D^{25}$ 55 (*c* 0.72, $CHCl_3$); IR (neat) 3023, 1727, 1218, 1126, 758 cm^{-1}; ^1H NMR δ 7.37-7.18 (m, 5 H), 5.25 (d, 1 H, *J* = 10.2 Hz), 4.59 (ddd, 1 H, *J* = 9.1, 9.1, 4.5 Hz), 3.84 (d, 1 H, *J* = 9.0 Hz), 3.67 (s, 3 H), 3.11 (t, 1 H, *J* = 9.7 Hz), 2.85 (dd, 1 H, *J* = 13.7, 4.6 Hz), 2.72 (dd, 1 H, *J* = 13.6, 9.22 Hz), 2.07-1.93 (m, 1 H), 1.74 (d, 3 H, *J* = 1.2 Hz), 1.13 (s, 9 H), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.93 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 174.04, 138.63, 137.22, 129.58, 128.66, 126.98, 124.68, 59.79, 56.66, 51.65, 51.52, 41.74, 31.52, 23.94, 20.61, 20.02, 19.09; MS (ES) *m/z* (rel intensity) 418.5 ($[M+^{23}Na]^+$, 100), 298.4 (12), 259.4 (16), 199.3 (11), 143.2 (5); HRMS (ES) Calcd for $C_{21}H_{33}NO_4NaS$ ($M+^{23}Na$) 418.2028, found 418.2025.



(2*S*)-Isopropyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*Z*)-enoic acid methyl ester (115b). Isolated as the minor isomer from the reaction yielding **114b**: $[\alpha]_D^{25}$ 33 (*c* 0.39, $CHCl_3$); IR (neat) 3054, 2986, 1731, 1421, 1265, 1127, 984, 896 cm^{-1}; ^1H NMR δ 7.30-7.10 (m, 4 H), 7.12 (d, 1 H, *J* = 7.1 Hz), 5.19 (d, 1 H, *J* = 9.9 Hz), 4.25-4.08 (m, 1 H), 4.03 (d, 1 H, *J* = 9.4 Hz), 3.63 (s, 3 H), 2.98 (m, 3 H), 1.87 (dq, 1 H, *J* = 17.1, 6.6 Hz), 1.73 (s, 3 H), 1.26 (s, 9 H), 0.81 (d, 3 H, *J* = 6.6 Hz), 0.64 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 173.9, 136.9, 136.6, 129.6, 128.4, 126.8, 125.0, 62.5, 59.73, 52.1, 51.4, 41.4, 31.2, 24.0, 20.6, 19.4, 13.9; MS (ES) *m/z* (rel intensity) 418.48

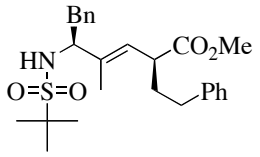
([M+^{23}Na]$^{+}$, 100), 299.42 (5), 298.41 (17), 259.38 (13), 199.31 (10), 143.20 (5); HRMS (ES) Calcd for $C_{21}H_{33}NO_4NaS$ (M+^{23}Na) 418.2028, found 418.2011.



(2*S*)-Isobutyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (114c). To a solution of 50 mg (0.56mmol) of CuCN in 5.5 mL of THF was added at –78 ºC 0.28 mL (0.56 mmol) of a 2 M solution of *i*-butyl magnesium chloride in THF. The resulting mixture was stirred for 10 min, warmed to 0 ºC, stirred for 15 min, and cooled to –20 ºC. A solution of 50 mg (0.14 mmol) of **108** in 0.6 mL of THF was added. The resulting solution was stirred for 3 h, quenched with 3 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (40:1 CH_2Cl_2/Et_2O) to yield 42 mg (73%) of a 4.9:1 mixture of **114c/115c** as a white solid. After repeated chromatography on SiO_2 a pure sample of **114c** was isolated: Mp 92.5-96.6 ºC, $[\alpha]_D^{25}$ 53 (*c* 0.52, $CHCl_3$); IR (KBr) 3318, 2953, 2867, 1722, 1437, 1304, 1125 cm^{-1}; ^{1}H NMR δ 7.30-7.10 (m 5 H), 5.06 (d, 1 H, *J* = 9.6 Hz), 4.14 (dd, 1 H, *J* = 8.1, 5.8 Hz), 3.93 (d, 1 H, *J* = 9.2 Hz), 3.63 (s, 3 H), 3.25 (ddd, 1 H, *J* = 14.9, 8.3, 6.5 Hz), 3.01 (dd, 1 H, *J* = 13.5, 5.7 Hz), 2.87 (dd, 1 H, *J* = 13.5, 7.9 Hz), 1.74 (d, 3 H, *J* = 1.3 Hz), 1.49-1.41 (m, 2 H), 1.35-1.07 (m, 1 H), 1.28 (s, 9 H), 0.81 (d, 3 H, *J* = 6.5 Hz), 0.75 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 174.7, 137.1, 136.4, 129.82, 128.7, 127.0, 126.9, 62.9, 60.0, 51.9, 42.9, 42.0, 41.6, 26.0, 24.4, 23.1, 22.2, 13.7; MS (ES) *m/z* (rel intensity) 432.3

([M+^{23}Na]$^{+}$, 100), 313.3 (5), 312.3 (17), 273.3 (6), 24.3 (5); HRMS (ES) Calcd for $C_{22}H_{35}NO_4NaS$ (M+^{23}Na) 432.2185, found 432.2187.

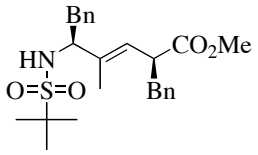
Characteristic signals for **115c**: ^{1}H NMR δ 5.26 (d, 1 H, *J* = 10 Hz), 4.58 (q, 1 H, *J* = 8.4 Hz), 3.62 (s, 3 H), 1.76 (d, 3 H, *J* = 1.2 Hz), 1.27 (s, 9 H).



4-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-(2*S*)-phenethyl-6-phenylhex-3-(*E*)-enoic acid methyl ester (114d). To a solution of 50 mg (0.14 mmol) of CuCN in 5.5 mL of THF was added at –78 ºC 0.56 mL (0.56 mmol) of a 1 M solution of phenethyl magnesium chloride in THF. The resulting mixture was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 50 mg (0.14 mmol) of **108** in 0.6 mL of THF was added. The resulting solution was stirred for 3 h, quenched with 4 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-30% EtOAc/Hexanes) to yield 39 mg (61%) of a 3:1 mixture of **114d/115d** as a colorless oil. After repeated chromatography on SiO_2 a pure sample of **114d** was isolated: $[\alpha]_D^{25}$ 32 (*c* 0.73, $CHCl_3$); IR (neat) 3054, 2986, 1731, 1421, 1265, 1127 cm^{-1}; ^{1}H NMR δ 7.32-7.02 (m, 10 H), 5.17 (d, 1 H, *J* = 1.0 Hz), 4.20-4.10 (m, 1 H), 4.05 (d, 1 H, *J* = 9.5 Hz), 3.63 (s, 3 H), 3.23-3.13 (m, 1 H), 2.99 (dd, 1 H, *J* = 13.5, 5.8 Hz), 2.89 (dd, 1 H, *J* = 13.6, 7.3 Hz), 2.46-2.25 (m, 2 H), 2.04-1.88 (m, 1 H), 1.75-1.60 (m, 1 H), 1.69 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR δ 174.3, 141.6, 137.5, 137.0, 129.9, 128.8, 128.6, 127.2, 126.2, 126.0, 62.8,

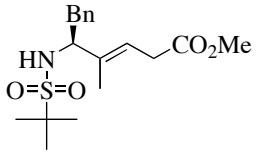
601, 51.9, 44.1, 41.8, 34.1, 33.1, 24.4, 14.1; MS (ES) *m/z* (rel intensity) 480.6 ([M+^{23}Na]$^{+}$, 100), 360.5 (12), 338.5 (7), 321.4 (15), 290.4 (5), 289.4 (15), 261.4 (9), 183.3 (5); HRMS (ES) Calcd for $C_{26}H_{35}NO_4NaS$ (M+^{23}Na) 480.2185, found 480.2173.

Characteristic signals for **115d**: ^{1}H NMR δ 5.28 (d, 1 H, *J* = 11.1 Hz), 4.56 (q, 1 H, *J* = 8.8 Hz), 1.79 (d, 3 H, *J* = 1.2 Hz).

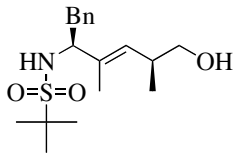


2-Benzyl-4-methyl-5-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (114e). A solution of 24 mg (0.56 mmol) of flame-dried LiCl in 1.0 mL of THF was stirred for 15 min and cooled to 0 ºC. To this solution was added 0.56 mL (0.28mmol) of a 0.5 M solution of $ZnCl_2$ in toluene and 0.14 mL (0.28 mmol) of a 2 M solution of BnMgCl in THF. The resulting mixture was stirred for 30 min and 25 mg (0.28 mmol) of CuCN was added in one portion. The resulting solution was stirred for 30 min and added to a solution of 10 mg (0.028 mmol) of **108** in 0.40 mL of THF cooled to 0 ºC. The reaction mixture was stirred for 7 h, warmed to room temperature overnight, quenched with 1 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexane) to yield 10 mg (81%) of **114e** as a pale yellow oil: $[\alpha]_D^{25}$ 4.6 (*c* 0.50, $CHCl_3$); IR (neat) 3019, 2400, 1731, 1521, 1422, 1215, 1127, 983, 769 cm^{-1}; ^{1}H NMR δ 7.31-7.14 (m, 6 H), 7.09 (t, 4 H, *J* = 6.5 Hz), 5.22 (d, 1 H, *J* = 9.7 Hz), 4.08 (ddd, 1 H, *J* = 9.4, 5.6, 3.9 Hz), 3.99-3.78 (m, 1 H), 3.61 (s, 3 H), 3.52 (ddd, 1 H, *J* = 8.7,

5.9, 4.5 Hz), 2.98 (dd, 1 H, *J* = 13.7, 7.2 Hz), 2.86 (d, 2 H, *J* = 6.21 Hz), 2.63 (dd, 1 H, *J* = 13.7, 7.6 Hz), 1.61 (d, 3 H, *J* = 2.3 Hz), 1.22 (s, 9 H); ^{13}C NMR δ 173.8, 138.9, 137.8, 136.8, 130.0, 129.3, 128.7, 127.2, 126.7, 125.0, 62.4, 60.1, 52.0, 46.8, 41.9, 38.7, 24.3, 14.3; MS (ES) *m/z* (rel intensity) 466.3 (M+^{23}Na^{+}, 100); HRMS (ES) Calcd for $C_{25}H_{33}NO_4NaS$ (M+^{23}Na) 466.2028, found 466.2041.

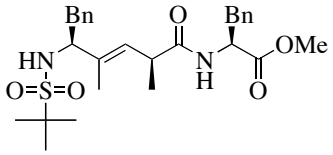


4-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (114f). A solution of 61 mg (1.5 mmol) of flame-dried LiCl in 11 mL of THF was stirred for 15 min and cooled to –78 ºC. To this solution was added 0.24 mL (0.73 mmol) of a 3 M solution of PhMgBr in Et_2O and 66 mg (0.73 mmol) of CuCN. The resulting mixture was stirred for 30 min. A solution of 90 mg (0.28 mmol) of **108** in 1 mL of THF was added dropwise. The reaction mixture was stirred for 3 h, quenched with 5 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (30% EtOAc/Hexane) to yield 75 mg (82%) of **114f** as a brown paste: $[\alpha]_D^{25}$ 0.54 (*c* 1.0, $CHCl_3$); IR (KBr) 3301, 2951, 1738, 1434, 1299, 1126, 946 cm^{-1}; ^{1}H NMR δ 7.30-7.12 (m, 5 H), 5.42 (t, 1 H, *J* = 7.1 Hz), 4.25-3.95 (m, 2 H), 3.65 (s, 3 H), 3.05 (d, 2 H, *J* = 7.1 Hz), 1.71 (s, 3 H), 1.24 (s, 9 H); ^{13}C NMR δ 172.1, 138.0, 137.1, 129.9, 128.7, 127.1, 119.3, 62.7, 60.2, 52.0, 42.0, 33.6, 24.3, 14.0; MS (ES) *m/z* (rel intensity) 376.16 ([M+^{23}Na]$^{+}$, 100), 257.1 (3), 256.1 (20); HRMS (ES) Calcd for $C_{18}H_{27}NO_4NaS$ (M+^{23}Na) 376.1559, found 376.1557.



2-Methylpropane-2-sulfonic acid ((1*S*)-benzyl-5-hydroxy-(2*S*),4-dimethyl-pent-2-enyl)-amide (116). A solution of 76 mg (0.90 mmol) of flame-dried LiCl in 9 mL of THF was stirred for 15 min, cooled to 0 ºC, and treated 0.45 mL (0.90 mmol) of a 2 M solution of Me_2Zn in toluene. The resulting solution was stirred for 15 min, cooled to –78 ºC, and 80 mg (0.90 mmol) of CuCN was added in one portion. The resulting solution was stirred for 30 min, warmed to –20 ºC, and an aliquot of 3.0 mL was added to a solution of 37 mg (0.10 mmol) of **108** in 2 mL of THF cooled to –20 ºC. The reaction mixture was stirred for 2 h, quenched with 3 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexanes) to yield 28 mg (77%) of a 12:1 mixture of **114a/115a** as a colorless oil. To a solution of 27 mg (0.070 mmol) of this mixture in 1 mL of CH_2Cl_2 was added at 0 ºC 0.22 mL (0.22 mmol) of 1 M DiBAL in hexanes. The reaction mixture was stirred for 30 min, quenched with 2 mL of a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3x), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by chromatography on Si_2O (30-50% EtOAc/Hexane) to yield 11 mg (67%) of **116** as a white solid: Mp 128.7-131.5 ºC; $[\alpha]_D^{25}$ –1.0 (*c* 0.38, $CHCl_3$); IR (KBr) 3434, 3140, 2929, 1460, 1367, 1290, 1122, 1058, 1012 cm^{-1}; ^1H NMR δ 7.34-7.18 (m, 5 H), 4.95 (d, 1 H, *J* = 9.8 Hz), 4.19-3.95 (m 2 H), 3.48 (dd, 1 H, *J* = 10.7, 5.3 Hz), 3.26 (dd, 1 H, *J* = 10.6, 8.7 Hz), 2.89 (d, 2 H, *J* = 6.3 Hz), 2.72-2.52 (m, 1 H), 1.77 (s, 3 H), 1.21 (s, 9 H), 0.82 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 137.1, 136.1, 131.2, 129.4, 128.6, 127.0, 67.8, 63.8, 60.1, 53.4, 41.0, 35.3, 24.0, 16.3, 12.8; MS (EI) *m/z* (rel

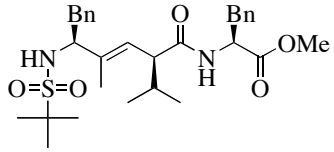
intensity) 248 ([M-C_7H_7]$^+$, 22), 240 (10), 172 (26), 157 (18), 143 (13), 129 (11), 128 (86), 120 (7), 110 (14); HRMS (EI) Calcd for $C_{11}H_{22}NO_3S$ (M-C_7H_7) 248.1320, found 248.1312.



2-[(2*S*),4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoylamino]-3-phenylpropionic acid methyl ester (117a). A solution of 25 mg (0.60 mmol) of flame dried LiCl in 4 mL of THF was stirred for 15 min, cooled to 0 ºC, and treated with 0.15 mL (0.30 mmol) of a 2 M solution of Me_2Zn in toluene. The resulting solution was stirred for 15 min, cooled to –78 ºC, and treated with 27 mg (0.30mmol) of CuCN in one portion. The resulting solution was stirred for 30 min and warmed to –20 ºC. A solution of 50 mg (0.10mmol) of **110** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-50% EtOAc/Hexane) to yield 52 mg (100%) of a 9:1 mixture of **117a/118a** as a colorless oil. After repeated chromatography on SiO_2 a pure sample of **117a** was isolated: $[\alpha]_D^{25}$ 1.4 (*c* 0.71, $CHCl_3$); IR (neat) 3347, 2931, 1748, 1648, 1522, 1455, 1300, 1125, 750 cm^{-1}; ^{1}H NMR δ 7.48-7.04 (m 10 H), 6.67 (d, 1 H, *J* = 8.2 Hz), 5.27 (d, 1 H, *J* = 9.4 Hz), 4.79 (dd, 1 H, *J* = 8.6, 5.5 Hz), 4.07 (dd, 1 H, *J* = 8.3, 6.0 Hz), 3.96 (d, 1 H, *J* = 8.0 Hz), 3.69 (s, 3 H), 3.18 (dd, 1 H, *J* = 13.9, 5.9 Hz), 3.09-2.93 (m, 2 H), 2.84 (dd, 1 H, *J* = 13.5, 5.9 Hz), 2.77 (dd, 1 H, *J* = 13.5, 8.5 Hz), 1.61 (d, 3 H, *J* = 1.2 Hz), 1.16 (s, 9 H), 1.12 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 173.5,

172.3, 138.5, 137.1, 136.9, 129.3, 129.2, 128.3, 127.6, 127.0, 126.6, 64.9, 60.4, 53.6, 52.0, 41.0, 39.1, 37.2, 24.0, 17.1, 11.6; MS (ES) *m/z* (rel intensity) 537..2 ([M+^{23}Na]$^{+}$,100), 515.3 (8), 379.2 (8), 378.2 (18); HRMS (ES) Calcd for $C_{28}H_{38}N_2O_5NaS$ (M+^{23}Na) 537.2365, found 537.2378.

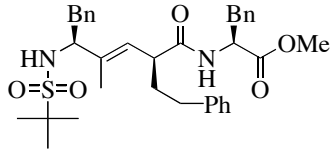
Characteristic signals for **118a**: ^{1}H NMR δ 5.19 (d, 1 H, *J* = 9.2 Hz), 3.70 (s, 3 H), 1.74 (s, 3 H), 1.15 (s, 9 H).



2-[(2*R*)-Isopropyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoylamino]-3-phenyl-(*S*)-propionic acid methyl ester (117b). To a solution of 36 mg (0.40 mmol) of CuCN in 4 mL of THF cooled to –78 ºC was added 0.20 mL (0.40 mmol) of a 2 M solution of *i*-propyl magnesium chloride in THF. The resulting solution was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 50 mg (0.10 mmol) of **110** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-50% EtOAc/Hexane) to yield 46 mg (84%) of a 3:1 mixture of **117b/118b** as a colorless oil. After repeated chromatography on SiO_2 a pure sample of **117b** was isolated: $[\alpha]_D^{25}$ 4.1 (*c* 1.2, $CHCl_3$); IR (neat); ^{1}H NMR δ 7.60-7.01 (m, 10 H), 6.49 (d, 1 H, *J* = 7.4 Hz), 5.33 (d, 1 H, *J* = 9.9 Hz), 4.82 (dd, 1 H, *J* = 7.9, 6.9 Hz), 4.15-3.96 (m, 2 H), 3.68 (s, 3 H), 3.16 (dd, 1 H, *J* = 14.0, 5.9 Hz), 3.01 (dd,

1 H, *J* = 13.9, 8.3 Hz), 2.87-2.76 (m, 3 H), 2.28-2.18 (m, 1 H), 1.60 (s, 3 H), 1.21 (s, 9 H), 0.72 (d, 3 H, *J* = 6.8 Hz), 0.68 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 172.6, 172.3, 139.8, 137.0, 136.8, 129.3, 129.2, 128.7, 128.3, 127.0, 126.7, 123.7, 64.7, 60.2, 53.4, 52.0, 51.5, 41.1, 37.5, 29.8, 24.0, 20.6, 18.0, 12.2; MS (ES) *m/z* (rel intensity) 565.3 ([M+^{23}Na]$^+$, 100), 543.3 (8), 407.3 (8), 406.2 (20); HRMS (ES) Calcd for $C_{30}H_{42}N_2O_5NaS$ (M+^{23}Na) 565.2736, found 565.2726.

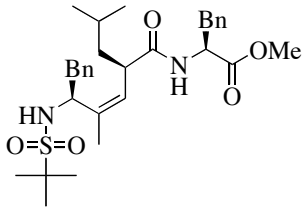
Characteristic signals for **118b**: ^{1}H NMR δ 6.55 (d, 1 H, *J* = 8.3 Hz), 5.28 (d, 1 H, *J* = 9.5 Hz), 3.70 (s, 3 H), 1.71 (s, 3 H), 1.21 (s, 9 H), 0.50 (d, 3 H, *J* = 6.8 Hz).



2-[4-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-(2*S*)-phenethyl-6-phenylhex-3-(*E*)-enoylamino]-3-phenyl-(*S*)-propionic acid methyl ester (117d). To a solution of 36 mg (0.40 mmol) of CuCN in 4 mL of THF cooled to –78 ºC was added 0.40 mL of a 1 M solution of *i*-butyl magnesium chloride in THF. The resulting solution was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 50 mg (0.10 mmol) of **110** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-50% EtOAc/Hexanes) to yield 40 mg (67%) of a 7:1 mixture of **117d/118d** as a white foam. After repeated chromatography on SiO_2 a pure sample of **117d** was isolated: $[\alpha]_D^{25}$ 12 (*c* 0.46 $CHCl_3$); IR (KBr) 3344, 3027, 2928, 1747, 1648, 1521, 1496,

1455, 1300, 1212, 1126, 1058, 942 cm^{-1}; ^1H NMR δ 7.51-7.11 (m, 13 H), 7.05 (d, 2 H), 6.67 (d, 1 H, *J* = 8.0 Hz), 5.30 (d, 1 H, *J* = 9.7 Hz), 4.80 (dd, 1 H, *J* = 8.2, 6.1 Hz), 4.0-4.05 (m, 2 H), 3.68 (s, 3 H), 3.18 (dd, 1 H, *J* = 13.9, 5.7 Hz), 3.00 (dd, 1 H, *J* = 13.9, 8.7 Hz), 2.91 (dt, 1 H, *J* = 9.7, 4.1 Hz), 2.82 (d, 2 H, *J* = 6.3 Hz), 2.43-2.10 (m, 2 H), 1.83-1.57 (m, 2 H), 1.55 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR δ 172.7, 172.2, 141.6, 139.8, 137.0, 129.2, 128.2, 127.1, 126.7, 126.4, 125.8, 64.8, 60.3, 53.5, 52.1, 44.3, 40.9, 37.3, 33.2, 33.0, 24.0, 11.9; MS (ES) *m/z* (rel intensity) 627.3 ($[M+^{23}Na]^+$, 100), 605.3 (11), 469.3 (9), 468.3 (13); HRMS (ES) Calcd for $C_{35}H_{44}N_2O_5NaS$ ($M+^{23}Na$) 627.2869, found 627.2878.

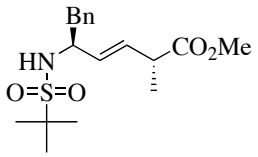
Characteristic signals for **118d**: ^1H NMR δ 6.60 (d, 1 H, *J* = 7.5 Hz), 5.25 (d, 1 H, *J* = 10.4 Hz), 3.69 (s, 3 H), 1.82 (d, 3 H, *J* = 1.2 Hz).



2-[(2*R*)-Isobutyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*Z*)-enoylamino]-3-phenyl-(*S*)-propionic acid methyl ester (108c). To a solution of 36 mg (0.40 mmol) of CuCN in 4 mL of THF was added at –78 ºC 0.20 mL (0.40 mmol) of a 2 M solution of *i*-butyl magnesium chloride in THF. The resulting solution was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 50 mg (0.10mmol) of **110** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc

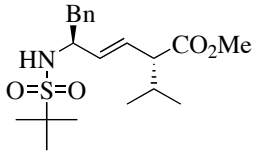
(3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-50% EtOAc/Hexanes) to yield 40 mg (66%) of a 3:1 mixture of **118c/117c** as a colorless solid: Mp 138.7-139.9 ºC; $[\alpha]_D^{25}$ –64 (*c* 0.85, $CHCl_3$); IR (KBr) 3375, 3332, 3200, 3063, 3030, 2952, 2869, 1757, 1735, 1673, 1650, 1559, 1527, 1496, 1455, 1364, 1297 cm^{-1}; ^1H NMR δ 7.50-7.10 (m, 10 H), 7.05 (d, 1 H, *J* = 7.8 Hz), 4.93 (d, 1 H, *J* = 10.6 Hz), 4.74 (dd, 1 H, *J* = 8.8, 5.8 Hz), 4.52 (q, 1 H, *J* = 7.8 Hz), 4.21 (d, 1 H, *J* = 8.6 Hz), 3.66 (s, 3 H), 3.31 (ddd, 1 H, *J* = 14.4, 7.9, 6.5 Hz), 3.12 (dd, 1 H, *J* = 13.7, 5.7 Hz), 2.93 (dd, 1 H, *J* = 13.7, 9.1 Hz), 2.81 (bd, 2 H, *J* = 7.4 Hz), 1.82 (d, 3 H, *J* = 1.0 Hz), 1.75-1.65 (m, 1 H), 1.60-1.35 (m, 1 H), 1.17 (s, 9 H), 0.86 (d, 6 H, *J* = 6.5 Hz), 0.75-0.58 (m, 1 H); ^{13}C NMR δ 172.9, 172.3, 137.1, 136.8, 135.2, 129.4, 128.8, 128.5, 128.2, 127.1, 126.5, 60.3, 56.8, 53.8, 51.8, 42.8, 40.7, 40.3, 37.8, 25.6, 23.8, 22.4, 17.8; MS (ES) *m/z* (rel intensity) 579.3 ($[M+^{23}Na]^+$, 100); HRMS (ES) Calcd for $C_{31}H_{44}N_2O_5NaS$ ($M+^{23}Na$) 579.2869, found 579.2848.

Characteristic signals for **117c**: ^1H NMR δ 6.65 (d, 1 H, *J* = 8.5 Hz), 5.17 (d, 1 H, *J* = 9.7 Hz), 3.68 (s, 3 H), 0.78 (d, 3 H, *J* = 6.6 Hz), 0.68 (d, 3 H, *J* = 6.5 Hz).



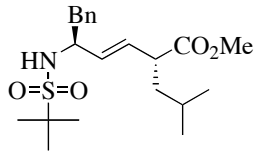
(2*R*)-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (119a). A solution of 23 mg (0.54 mmol) of flame-dried LiCl in 3 mL of THF was stirred for 15 min, cooled to 0 ºC, and treated with 0.14 mL (0.27 mmol) of a 2 M solution of Me_2Zn in toluene. The resulting solution was stirred for 15 min, cooled to

–78 ºC, and 24 mg (0.27 mmol) of CuCN was added in one portion. The resulting solution was stirred for 30 min and warmed to –20 ºC. A solution of 30 mg (0.090 mmol) of **111** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexanes) to yield 31 mg (100%) of **119a** as a colorless oil: $[\alpha]_D^{25}$ – 21 (*c* 1.4, $CHCl_3$); IR (neat) 2978, 1736, 1644, 1496, 1455, 1395, 1365, 1305, 1169, 1127, 1049, 969, 750 cm^{-1}; ^1H NMR δ 7.35-7.10 (m, 5 H), 5.66 (ddd, 1 H, *J* = 15.6, 5.2, 1.0 Hz), 5.54 (dd, 1 H, *J* = 15.6, 5.7 Hz), 4.26-4.17 (m, 1 H), 3.81 (d, 1 H, *J* = 9.7 Hz), 3.67 (s, 3 H), 3.14 (p, 1 H, *J* = 7.0 Hz), 2.94 (d, 2 H, *J* = 6.2 Hz), 1.29 (s, 9 H), 1.23 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 174.6, 136.3, 131.5, 130.4, 130.0, 128.4, 126.9, 59.9, 57.1, 51.8, 43.3, 42.3, 24.0, 17.1; MS (ES) *m/z* (rel intensity) 376.0 ($[M+^{23}Na]^+$, 100), 362.5 (5), 257.1 (5), 256.1 (45), 240.1 (5); HRMS (ES) Calcd for $C_{18}H_{27}NO_4NaS$ ($M+^{23}Na$) 376.1559, found 376.1571.



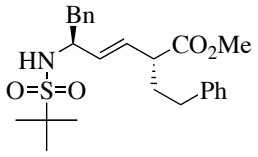
(2*S*)-Isopropyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (119b). To a solution of 32 mg (0.36 mmol) of CuCN in 3 mL of THF was added at –78 ºC 0.18 mL (0.36 mmol) of a 2 M solution of *i*-propyl magnesium chloride in THF. The resulting solution was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 30 mg (0.090 mmol) of **111** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1

solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (50% acetonitrile/H_2O, 4 mL/min) to yield 24 mg (72%) of **119b** as a colorless oil: $[\alpha]_D^{25}$ -35 (*c* 0.56, $CHCl_3$); IR (neat) 3373, 3271, 3020, 2873, 1729, 1496, 1479, 1454, 1435, 1395, 1367, 1311, 1215, 1136, 1126, 750 cm^{-1}; ^1H NMR δ 7.40-7.00 (m, 5 H), 5.58 (dd, 1 H, *J* = 15.5, 8.2 Hz), 5.50 (dd, 1 H, *J* = 15.4, 5.7 Hz), 4.21 (dt, 1 H, *J* = 11.4, 5.9 Hz), 3.78 (d, 1 H, *J* = 11.2 Hz), 3.65 (s, 3 H), 2.93 (bd, 2 H, *J* = 6.4 Hz), 2.68 (t, 1 H, *J* = 8.3 Hz), 1.95 (dq, 1 H, *J* = 14.2, 6.7 Hz), 1.28 (s, 9 H), 0.87 (d, 3 H, *J* = 6.6 Hz), 0.81 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 173.9, 136.3, 133.3, 130.0, 128.6, 128.5, 126.8, 60.0, 57.4, 56.5, 43.3, 30.9, 24.0, 20.7, 19.7; MS (ES) *m/z* (rel intensity) 404.1 ([M+$^{23}Na]^+$, 100), 285.2 (11), 284.1 (72); HRMS (ES) Calcd for $C_{20}H_{31}NO_4NaS$ (M+^{23}Na) 404.1872, found 404.1853.



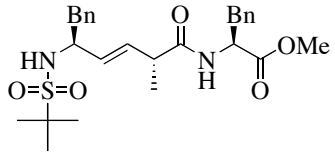
(2*R*)-Isobutyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (119c). To a solution of 32 mg (0.36 mmol) of CuCN in 3 mL of THF was added at –78 ºC 0.18 mL (0.36 mmol) of a 2 M solution of *i*-butyl magnesium chloride in THF. The resulting mixture was stirred for 10 min at –78 ºC, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 30 mg (0.090 mmol) of **111** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (50% acetonitrile/H_2O, 4 mL/min) to yield 33 mg (95%) of **119c** as a colorless oil: $[\alpha]_D^{25}$ –38 (*c* 0.26, $CHCl_3$); IR

(neat) 3019, 1731, 1315, 1215, 1126 cm^{-1}; ^1H NMR δ 7.42-7.16 (m, 5 H), 5.85-5.49 (m, 2 H), 4.29-4.17 (m, 1 H), 3.76 (d, 1 H, *J* = 9.9 Hz), 3.66 (s, 3 H), 3.13-3.05 (m, 1 H), 2.96 (dd, 1 H, *J* = 13.7, 5.9 Hz), 2.94 (dd, 1 H, *J* = 13.1, 6.4 Hz), 1.60-1.54 (m, 1 H), 1.51-1.43 (m, 1 H), 1.42-1.35 (m, 1 H), 1.30 (s, 9 H), 0.88 (d, 3 H, *J* = 6.6 Hz), 0.86 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 174.4, 136.2, 132.3, 130.0, 129.6, 128.4, 126.9, 60.0, 57.1, 51.7, 46.8, 43.3, 41.2, 25.5, 24.0, 22.7, 21.9; MS (ES) *m/z* (rel intensity) 418.2 ($[M+^{23}Na]^+$, 100), 299.2 (12), 298.2 (67); HRMS (ES) Calcd for $C_{21}H_{33}NO_4NaS$ ($M+^{23}Na$) 418.2028, found 418.2029.



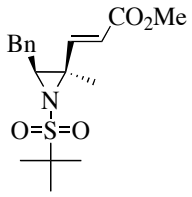
(5*S*)-(2-Methylpropane-2-sulfonylamino)-(2*R*)-phenethyl-6-phenylhex-3-(*E*)-enoic acid methyl ester (119d). To a solution of 32 mg (0.36 mmol) of CuCN in 3 mL of THF was added at –78 ºC 0.36 mL (0.36 mmol) of a 1 M solution of phenethyl magnesium chloride in Et_2O. The resulting mixture was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 30 mg (0.090 mmol) of **111** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (50% acetonitrile/H_2O, 4 mL/min) to yield 31 mg (79%) of **119d** as a colorless oil: $[\alpha]_D^{25}$ –34 (*c* 0.27, $CHCl_3$); IR (neat) 3019, 1731, 1216, 758 cm^{-1}; ^1H NMR δ 7.45-7.08 (m, 10 H), 5.60 (d of AB, 1 H, *J* = 15.5, 8.2 Hz), 5.56 (d of AB, 1 H, *J* = 15.4, 5.4 Hz), 4.24 (dq, 1 H, *J* = 5.8, 2.8 Hz), 3.76 (d, 1 H, *J* = 9.9 Hz), 3.66 (s, 3 H), 3.03 (q, 1 H, *J* = 3.5 Hz), 2.95 (d of AB, 1 H, *J* =

6.2, 2.9 Hz), 2.93 (d of AB, 1 H, *J* = 6.7, 3.3 Hz), 2.65-2.47 (m, 2 H), 2.07 (ddd, 1 H, *J* = 6.7, 4.7, 3.3 Hz), 1.81 (dddd, 1 H, *J* = 8.5, 4.6, 3.9, 3.1 Hz), 1.29 (s, 9 H); ^{13}C NMR δ 179.9, 141.1, 136.2, 133.0, 130.0, 129.0, 128.5, 128.4, 128.4, 126.9, 126.0, 60.0, 57.3, 51.8, 48.0, 43.2, 33.7, 33.1, 24.0; MS (ES) *m/z* (rel intensity) 466.20 ([M+^{23}Na]$^+$, 100), 347.19 (12), 346.18 (52); HRMS (ES) Calcd for $C_{25}H_{33}NO_4NaS$ (M+^{23}Na) 466.2028, found 466.2018.



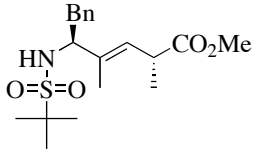
2-[2-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoyl amino]-3-phenyl-(*S*)-propionic acid methyl ester (120). A solution 5.0 mg (0.12 mmol) of flame dried LiCl in 1 mL of THF was stirred for 15 min, cooled to 0 ºC, and treated with 0.030 mL (0.060 mmol) of a 2 M solution of Me_2Zn in toluene. The resulting solution was stirred for 15 min, cooled to –78 ºC, and 6.0 mg (0.060 mmol) of CuCN was added in one portion. The resulting solution was stirred for 30 min and warmed to –20 ºC. A solution of 10 mg (0.020 mmol) of **113** in 0.10 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 1.0 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (50% EtOAc/Hexane) to yield 6.3 mg (61%) of **120** as a colorless oil: $[\alpha]_D^{25}$ 0.96 (*c* 0.28, $CHCl_3$); IR (neat) 3290, 2928, 1744, 1653, 1520, 1454, 1301, 1211, 1125 cm^{-1}; ^{1}H NMR δ 7.37-6.83 (m, 10 H), 6.14 (d, 1 H, *J* = 7.9 Hz), 5.66 (d of AB, 1 H, *J* = 15.7, 6.4 Hz), 5.60 (d of AB, 1 H, *J* = 15.3, 4.9 Hz), 4.81 (ddd, 1 H, *J* = 7.3, 6.9, 6.0 Hz), 4.24-4.11 (m, 1 H), 3.75 (d, 1 H, *J* = 9.6 Hz),

3.72 (s, 3 H), 3.15 (dd, 1 H, J = 13.8, 5.9 Hz), 3.07-2.87 (m, 3 H), 2.81 (dd, 1 H, J = 13.5, 6.8 Hz), 1.24 (s, 9 H), 1.17 (d, 3 H, J = 7.1 Hz); ^{13}C NMR δ 173.3, 172.1, 136.5, 136.2, 133.2, 130.8, 129.8, 129.3, 128.6, 128.4, 127.0, 126.97, 60.0, 57.7, 53.2, 52.2, 43.7, 42.7, 37.7, 24.0, 16.9; MS (ES) *m/z* (rel intensity) 523.2 ([M+^{23}Na]$^+$, 100); HRMS (ES) Calcd for $C_{27}H_{36}N_2O_5NaS$ (M+^{23}Na) 523.2243, found 523.2219.



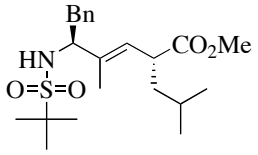
3-[(3*S*)-Benzyl-(2*S*)-methyl-1-(2-methylpropane-2-sulfonyl)-aziridin-2-yl]-(*E*)-acrylic acid methyl ester (121). To a solution of 0.10 g (0.31 mmol) of **104** in 2 mL of CH_2Cl_2 at –78 ºC was added 0.62 mL (0.62 mmol) of a 1 M solution of DiBAL in hexanes. The reaction mixture was stirred for 30 min, quenched with 2 mL of cold (-78 ºC) MeOH, warmed to rt, treated with 2 mL of a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting aldehyde was washed with benzene, concentrated *in vacuo* (3x) and dried under high vacuum. To a solution of 0.13 g (0.62 mmol) of methyl diethylphosphonoacetate in 0.5 mL Et_2O at 0 ºC was added 0.39 mL (0.62 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The ice bath was removed and the reaction mixture was warmed to room temperature, stirred for 1 h and cooled again to 0 ºC. A solution of the aldehyde in 0.5 mL of a 1:1 solution of THF/Et_2O was added dropwise. The reaction mixture was stirred for 3 h, quenched with 2 mL of a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3x), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on

SiO_2 (20-30%EtOAc/Hexane) to yield 76 mg (69%) of **121** as a pale yellow oil: $[\alpha]_D^{25}$ – 57 (*c* 0.61, CH_2Cl_2); IR (neat) 3054, 2986, 1722, 1650, 1421, 1308, 1265, 1127 cm^{-1}; ^1H NMR (Acetone-d_6) δ 7.43-7.17 (m, 5 H), 6.94 (d, 1 H, *J* = 15.5 Hz), 6.18 (d, 1 H, *J* = 15.5 Hz), 3.77 (s, 3 H), 3.24 (dd, 1 H, *J* = 8.5, 5.0 Hz), 3.08 (dd 1 H, *J* = 14.8, 5.0 Hz), 2.77 (dd, 1 H, *J* = 14.8, 8.5 Hz), 1.82 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (Acetone-d_6) δ 165.7, 145.5, 137.5, 128.9, 127.0, 124.1, 60.0, 54.3, 51.3, 51.0, 34.0, 23.6, 18.6; MS (ES) *m/z* (rel intensity) 374.4 ([M+^{23}Na]$^+$, 100), 254.3 (23), 232.3 (21), 200.3 (7); HRMS (ES) Calcd for $C_{18}H_{25}NO_4SNa$ (M+^{23}Na) 374.1402, found 374.1412.



(2*R*)-4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (122a). A solution of 18 mg (0.42 mmol) of flame dried LiCl in 3 mL of THF was stirred for 15 min, cooled to 0 ºC, and 0.21 mL (0.42 mmol) of a 2 M solution of Me_2Zn in toluene was added. The resulting solution was stirred for 15 min, cooled to –78 ºC, and 19 mg (0.21 mmol) of CuCN was added in one portion. The resulting solution was stirred for 30 min and warmed to –20 ºC. A solution of 25 mg (0.071 mmol) of **121** in 0.30 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2 mL of a 1:1 solution of NH_4Cl/NH_4OH, extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (30% EtOAc/Hexanes) to yield 25 mg (97%) of **122a** as a colorless oil: $[\alpha]_D^{25}$ – 18 (*c* 1.2, $CHCl_3$); IR (neat) 2981, 1736, 1454, 1305, 1127, 942 cm^{-1}; ^1H NMR δ 7.37-7.07 (m, 5 H), 5.19 (d, 1 H, *J* = 9.4 Hz), 4.18-4.00 (m, 2 H), 3.60 (s, 3 H), 3.32 (dq, 1 H,

J = 14.0, 9.2 Hz), 2.94 (dd, 1 H, *J* = 13.5, 5.9 Hz), 2.90 (dd, 1 H, *J* = 13.8, 6.7 Hz), 1.73 (d, 3 H, *J* = 1.0 Hz), 1.26 (s, 9 H), 1.17 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 175.0, 136.6, 135.7, 129.8, 128.5, 127.0, 126.9, 62.3, 59.9, 51.9, 41.7, 38.7, 24.1, 17.6, 13.5; MS (ES) *m/z* (rel intensity) 390.2 ([M+^{23}Na]$^{+}$, 100), 270.2 (18), 213.1 (9); HRMS (ES) Calcd for $C_{19}H_{29}NO_4NaS$ (M+^{23}Na) 390.1715, found 390.1708.

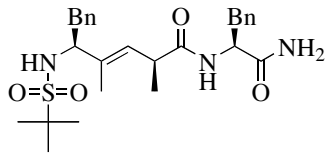


(2*R*)-Isobutyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid methyl ester (122b). To a solution of 25 mg (0.28 mmol) CuCN in 2.8 mL of THF was added at –78 ºC 0.14 mL (0.28 mmol) of a 2 M solution of *i*-butyl magnesium chloride in THF. The resulting solution was stirred for 10 min, warmed to 0 ºC, stirred for 15 min and cooled to –20 ºC. A solution of 30 mg (0.072 mmol) of **121** in 0.3 mL of THF was added. The reaction mixture was stirred for 3 h, quenched with 2.0 mL of a 1:1 solution of NH_4Cl/NH_4OH, and extracted with EtOAc (3x), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10-30% EtOAc/Hexane) to yield 20 mg (70%) of **122b** as a colorless oil: $[\alpha]_D^{25}$ –28 (*c* 0.63, $CHCl_3$); IR (neat) 3054, 2986, 1731, 1421, 1265, 1127, 983, 896 cm^{-1}; ^{1}H NMR δ 7.34-7.18 (m, 3 H), 7.17-7.11 (m, 2 H), 5.13 (d, 1 H, *J* = 9.7 Hz), 4.18-4.09 (m, 1 H), 4.05 (d, 1 H, *J* = 9.5 Hz), 3.59 (s, 3 H), 3.31 (ddd, 1 H, *J* = 9.5, 7.6, 7.6 Hz)), 2.98 (dd, 1 H, *J* = 13.5, 5.9 Hz), 2.91 (dd, 1 H, *J* = 13.5, 6.9 Hz), 1.76 (s, 3 H), 1.60-1.49 (m, 1 H), 1.47-1.31 (m, 2 H), 1.28 (s, 9 H), 0.89 (d, 3 H, *J* = 6.3 Hz), 0.86 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 174.4, 136.5, 136.1, 129.6, 128.4, 126.8, 126.1, 62.3, 59.8, 51.6, 42.6, 41.4, 25.6,

24.0, 22.7, 22.1, 13.6; MS (ES) *m/z* (rel intensity) 432.2 ([M+^{23}Na]$^{+}$, 89), 377.1 (8), 312.2 (9), 213.2 (10); HRMS (ES) Calcd for $C_{22}H_{35}NO_4NaS$ (M+^{23}Na) 432.2185, found 432.2160.

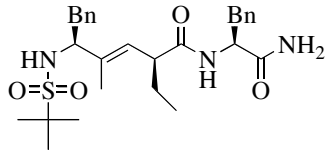
General procedure for solid phase synthesis of compounds 132. To a 3 mL fritted reaction tube placed on the Mini-Bohdan reaction block loaded with 56 mg of Nova-Biochem Fmoc Rink resin (loading: 0.62 mmol/g), was added 1 mL of a 2:8 solution of piperidine / DMF. The reaction block was shaken for 10 min. The solution was drained and the procedure was repeated. The tube was washed with DMF (5 x 1 mL for 5 min). To the resin was added 1 mL of a solution of 0.072 mmol of Fmoc-amino acid, DEPBT (21.5 mg, 0.062 mmol), and DIPEA (12 μL, 0.062 mmol) in DMF. The reaction block was vigorously shaken for 3 h. The solution was drained, the resin was washed with DMF (5 x 1 mL for 5 minutes) and treated with 1 mL of a 2:8 solution of piperidine / DMF and was shook 10 min. The solution was drained and the procedure was repeated. The resin was washed with DMF (5 x 1 mL for 5 min), and 1.2 mL of a solution of 0.056 mmol of aziridine **109** or **112**, TFFH (18.5 mg, 0.072 mmol), and DIPEA (12 μL, 0.072 mmol) in DMF was added. The reaction block was vigorously shaken for 3 h, and the solution was drained, the resin was washed with DMF (5 x 1 mL for 5 min), H_2O (5 x 1 mL for 5 min), DMF (5 x 1 mL for 5 min), MeOH (3 x 3 mL for 5 min), CH_2Cl_2 (3 x 3 mL for 5 min) and dried under high vacuum for 12 h. To a solution of 17 mg (0.36 mmol) of LiCl in 1 mL of THF cooled to 0 °C was added $R^3{}_2Zn$ (0.20 mmol). The mixture was stirred for 10 min, cooled to -78 °C, treated with 18 mg (0.20 mmol) of CuCN and stirred for 30 min. The resulting solution was added to the resin at –20 °C. The reaction block

was shaken for 3 h. The mixture was quenched with 1 mL of a 1:1 solution of NH_4Cl / NH_4OH, shaken for 30 min, and the solution was drained. The resin was washed with a saturated aqueous solution of NH_4Cl (5 x 1 mL for 5 min), H_2O (5 x 1 mL for 5 min), MeOH (5 x 1 mL for 5 min), and CH_2Cl_2 (3 x 1 mL for 5 min) and dried under high vacuum for 12 h. The resulting resin was treated with 1.0 mL of a 3:7 solution of TFA / CH_2Cl_2 at room temperature, and shaken for 10 min. The reaction tube was drained and the solution was collected. This process was repeated and the combined CH_2Cl_2 layers were neutralized with 2 mL of a 10% aqueous solution of NH_4OH, extracted with CH_2Cl_2 (3x), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0-100% EtOAc/Hexane).

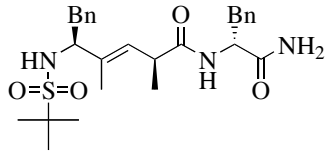


(2*S*),4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-2-phenylethyl)-amide (132a). According to the general procedure, 24 mg of L-Fmoc-Phe-OH (0.062 mmol), 17 mg (0.050 mmol) of aziridine **109** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 7.2 mg (40%) of **132a** as a colorless oil: $[\alpha]_D^{25}$ –1.4 (*c* 0.28, $CHCl_3$); IR (film) 3345, 3028, 2973, 2929, 1654, 1497, 1478, 1455, 1292, 1122, 1057, 952, 752 cm^{-1}; ^1H NMR δ 7.35-7.07 (m, 10 H), 6.72 (d, 1 H, *J* = 8.1 Hz), 6.32 (bs, 1 H), 5.39 (bs, 1 H), 5.23 (d, 1 H, *J* = 9.9 Hz), 4.74-4.65 (m, 1 H), 4.26 (d, 1 H, *J* = 8.3 Hz), 4.03 (dd, 1 H, *J* = 8.7, 6.1 Hz), 3.26 (dd, 1 H, *J* = 14.3, 5.6 Hz), 3.05-2.92 (m, 2 H), 2.87-2.72 (m, 2 H), 1.57 (d, 3 H, *J* = 1.1 Hz), 1.14 (s, 9 H), 1.12 (d, 3 H, *J* = 7.1 Hz) ; ^{13}C NMR δ 173.9, 138.6, 137.5, 137.0,

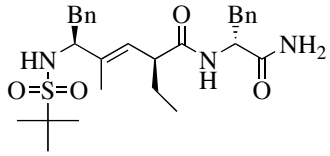
129.2, 128.7, 128.4, 128.0, 127.1, 126.6, 65.3, 60.5, 54.8, 40.5, 39.0, 38.5, 36.8, 23.9, 16.7, 11.1; MS (ES) *m/z* (rel intensity) 522.3 ([M+^{23}Na]$^{+}$, 100), 483.3 (7), 375.2 (5), 318.2 (4); HRMS (ES) Calcd for $C_{27}H_{37}N_3O_4NaS$ (M+^{23}Na) 522.2402, found 522.2380.



(2*S*)-Ethyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-2-phenylethyl)-amide (132b). According to the general procedure, 24 mg of L-Fmoc-Phe-OH (0.062 mmol), 17 mg (0.050 mmol) of aziridine **109** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 5.9 mg (32 %) of impure **132b** as a colorless oil: $[\alpha]_D^{25}$ –0.53 (*c* 0.24, $CHCl_3$); IR (film) 3321, 3028, 2927, 1670, 1653, 1558, 1506, 1455, 1295, 1123 cm^{-1}; ^{1}H NMR δ 7.34-7.16 (m, 10 H), 6.67 (d, 1 H, *J* = 8.0 Hz), 6.25 (bs, 1 H), 5.33 (bs, 1 H), 5.21 (d, 1 H, *J* = 9.9 Hz), 4.70 (ddd, 1 H, *J* = 8.4, 8.0, 5.9 Hz), 4.19 (d, 1 H, *J* = 8.2 Hz), 4.07 (q, 1 H, *J* = 7.2 Hz), 3.26 (dd, 1 H, *J* = 14.4, 5.9 Hz), 2.97 (dd, 1 H, *J* = 14.2, 9.6 Hz), 2.82 (d, 2 H, *J* = 7.5 Hz), 2.81-2.76 (m, 1 H), 1.91-1.82 (m, 2 H), 1.57 (s, 3 H), 1.18 (s, 9 H), 0.64 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 173.8, 173.3, 139.6, 137.5, 135.9, 129.2, 128.7, 128.4, 127.1, 126.6, 65.2, 60.4, 54.6, 46.3, 40.7, 36.8, 29.7, 24.5, 23.9, 11.3; MS (ES) *m/z* (rel intensity) 536.3 ([M+^{23}Na]$^{+}$, 100), 488.3 (20), 332.2 (12); HRMS (ES) Calcd for $C_{28}H_{39}N_3O_4NaS$ (M+^{23}Na) 536.2559, found 536.2558.

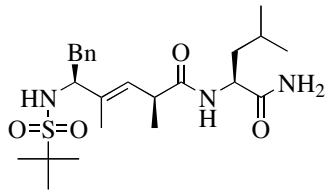


(2*S*),4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-2-phenylethyl)-amide (132d). According to the general procedure, 24 mg of D-Fmoc-Phe-OH (0.062 mmol), 17 mg (0.050 mmol) of aziridine **109** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 6.4 mg (36%) of **132d** as a colorless oil: $[\alpha]_D^{25}$ 0.59 (*c* 0.75, $CHCl_3$); IR (film) 3204, 2925, 1690, 1668, 1552, 1454, 1295, 1119 cm^{-1}; ^1H NMR δ 7.36-7.21 (m, 10 H), 6.68 (d, 1 H, *J* = 8.3 Hz), 6.32 (bs, 1 H), 5.71 (bs, 1 H), 5.14 (d, 1 H, *J* = 8.9 Hz), 4.77 (d, 1 H, *J* = 8.5 Hz), 4.72-4.63 (m, 1 H), 4.02 (q, 1 H, *J* = 8.1 Hz), 3.23 (dd, 1 H, *J* = 14.0, 5.6 Hz), 3.09 (dd, 1 H, *J* = 8.8, 7.1 Hz), 2.91 (dd, 1 H, *J* = 14.0, 10.0 Hz), 2.83 (d, 2 H, *J* = 7.3 Hz), 1.66 (d, 3 H, *J* = 0.9 Hz), 1.14 (s, 9 H), 0.97 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 174.6, 174.5, 140.3, 137.4, 137.3, 129.2, 128.6, 128.4, 127.1, 127.0, 126.7, 67.6, 60.4, 55.2, 40.1, 39.6, 37.5, 23.7, 17.9, 11.4; MS (ES) *m/z* (rel intensity) 522.2 ([M + $^{23}Na]^+$, 100), 488.3 (18); HRMS (ES) Calcd for $C_{27}H_{37}N_3O_4NaS$ (M+^{23}Na) 522.2402, found 522.2379



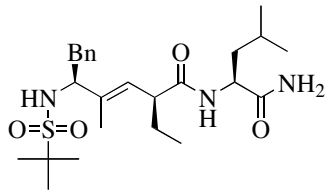
(2*S*)-Ethyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-2-phenylethyl)-amide (132e). According to the general procedure, 24 mg (0.062 mmol) of D-Fmoc-Phe-OH, 17 mg (0.050 mmol) of aziridine **109** and 0.36 mL (0.36 mmol) of a 2 M solution of Et_2Zn in toluene afforded 5.3 mg

(29%) of **132e** as a colorless oil: $[\alpha]_D^{25}$ –2.6 (*c* 0.15, $CHCl_3$); IR (film) 3204, 2960, 2927, 1689, 1659, 1551, 1496, 1455, 1295, 1118 cm^{-1}; ^1H NMR δ 7.35-7.18 (m, 10 H), 6.62 (d, 1 H, *J* = 8.4 Hz), 6.31 (bs, 1 H), 5.53 (bs, 1 H), 5.14 (d, 1 H, *J* = 8.9 Hz), 4.67 (ddd, 1 H, *J* = 10.4, 8.4, 5.4 Hz), 4.44 (d, 1 H, *J* = 8.4 Hz), 4.08 (q, 1 H, *J* = 7.8 Hz), 3.23 (dd, 1 H, *J* = 14.2, 6.2 Hz), 2.97-2.89 (m, 2 H), 2.84 (d, 2 H, *J* = 7.5 Hz), 1.66 (d, 3 H, *J* = 1.0 Hz), 1.19 (s, 9 H), 1.19-1.05 (m, 2 H), 0.55 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 174.7, 173.8, 141.0, 137.3, 129.4, 129.2, 128.6, 128.4, 126.9, 126.6, 125.8, 65.5, 60.3, 55.2, 46.6, 40.1, 37.3, 25.4, 23.7, 11.5, 11.0; MS (ES) *m/z* (rel intensity) 536.2 ($[M+^{23}Na]^+$, 100), 332.2 (10); HRMS (ES) Calcd for $C_{28}H_{39}N_3O_4NaS$ 536.2447 ($M+^{23}Na$), found 536.2465.

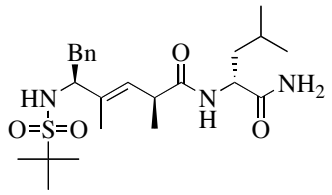


(2*S*),4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-3-methylbutyl)-amide (132g). According to the general procedure, 22 mg (0.062 mmol) of L-Fmoc-Leu-OH, 17 mg (0.050 mmol) of aziridine **109** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene, afforded 6.0 mg (36%) of **132g** as a colorless oil: $[\alpha]_D^{25}$ –1.1 (*c* 0.35, $CHCl_3$); IR (film) 3336, 3209, 2957, 2931, 2871, 1675, 1654, 1517, 1455, 1295, 1123 cm^{-1}; ^1H NMR δ 7.34-7.19 (m, 5 H), 6.76 (d, 1 H, *J* = 8.2 Hz), 6.53 (bs, 1 H), 6.05 (bs, 1 H), 5.32 (d, 2 H, *J* = 8.3 Hz), 4.50-4.40 (m, 1 H), 4.25 (d, 1 H, *J* = 8.4 Hz) 4.10-4.00 (m, 1 H), 3.18 (dd, 1 H, *J* = 13.2, 6.0 Hz), 2.94-2.79 (m, 2 H), 1.71 (s, 3 H), 1.30-1.23 (m, 2 H), 1.12 (d, 3 H, *J* = 7.0 Hz), 1.10 (s, 9 H), 0.93-0.87 (m, 6 H); ^{13}C NMR δ 174.9, 174.2, 138.8, 137.1, 129.3, 128.7, 128.1,

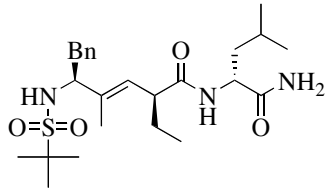
127.2, 65.4, 60.5, 52.2, 40.6, 39.6, 39.3, 24.9, 23.9, 21.6, 17.1, 11.2; MS (ES) *m/z* (rel intensity) 488.3 ([M+^{23}Na]$^{+}$, 100), 459.3 (8), 403.3 (9), 347.2 (6), 284.2 (7); HRMS (ES) Calcd for $C_{24}H_{39}N_3O_4NaS$ (M+^{23}Na) 488.2559, found 488.2545.



(2*S*)-Ethyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-3-methylbutyl)-amide (132h). According to the general procedure, 22 mg (0.062 mmol) of L-Fmoc-Leu-OH, 17 mg (0.050 mmol) of aziridine **109** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 6.2 mg (39%) of **132h** as a colorless oil: $[\alpha]_D^{25}$ –1.2 (*c* 0.31, $CHCl_3$); IR (film) 3326, 2958, 2930, 2871, 1671, 1654, 1455, 1296, 1123 cm^{-1}; ^{1}H NMR δ 7.34-7.17 (m, 5 H), 6.66 (d, 1 H, *J* = 7.8 Hz), 6.37 (bs, 1 H), 5.37 (bs, 1 H), 5.28 (d, 1 H, *J* = 9.6 Hz), 4.45 (q, 1 H, *J* = 7.1 Hz), 4.32 (d, 1 H, *J* = 8.7 Hz), 4.09 (q, 1 H, *J* = 6.8 Hz), 3.01 (dt, 1 H, *J* = 9.1, 3.8 Hz), 2.81 (d, 2 H, *J* = 7.4 Hz), 2.01–1.86 (m, 1 H), 1.74 (s, 3 H), 1.52-1.34 (m, 2 H), 1.16 (s, 9 H), 0.93 (d, 3 H, *J* = 5.7 Hz), 0.89 (d, 3 H, *J* = 5.6 Hz), 0.71 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 175.2, 173.7, 140.0, 137.0, 129.2, 128.7, 127.1, 126.6, 65.5, 60.4, 51.9, 46.3, 40.5, 39.3, 24.8, 23.9, 22.9, 21.5, 11.4, 11.3; MS (ES) *m/z* (rel intensity) 502.3 ([M+^{23}Na]$^{+}$, 100), 298.2 (10); HRMS (ES) Calcd for $C_{25}H_{41}N_3O_4S$ (M+^{23}Na) 502.2715, found 502.2727.

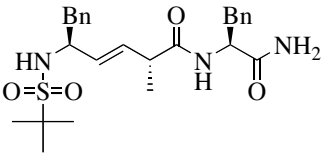


(2*S*),4-Dimethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-3-methylbutyl)-amide (132j). According to the general procedure, 22 mg (0.062 mmol) of D-Fmoc-Leu-OH, 17 mg (0.050 mmol) of aziridine **109** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 4.0 mg (24%) of impure **132j** as a colorless oil: $[\alpha]_D^{25}$ 1.9 (*c* 0.10, $CHCl_3$); IR (film) 3360, 3207, 2962, 2927, 1688, 1669, 1655, 1558, 1540, 1456, 1302, 1120, 1057 cm^{-1}; ^1H NMR δ 7.36-7.18 (m, 5 H), 6.66 (d, 1 H, *J* = 7.5 Hz), 6.30 (bs, 1 H), 5.42 (bs, 1 H), 5.31 (d, 1 H, *J* = 9.1 Hz), 4.48-4.39 (m, 2 H), 4.07 (q, 1 H, *J* = 8.8 Hz), 3.20 (dd, 1 H, *J* = 9.2, 7.2 Hz), 2.90-2.77 (m, 2 H), 1.73 (d, 3 H, *J* = 1.1 Hz), 1.65-1.56 (m, 3 H), 1.23 (d, 3 H, *J* = 7.1 Hz), 1.13 (s, 9 H), 0.93 (d, 3 H, *J* = 6.2 Hz), 0.89 (d, 3 H, *J* = 6.2 Hz); MS (ES) *m/z* (rel intensity) 488.3 ($[M+^{23}Na]^+$, 100); HRMS (ES) Calcd for $C_{24}H_{39}N_3O_4NaS$ ($M+^{23}Na$) 488.2559, found 488.2545.



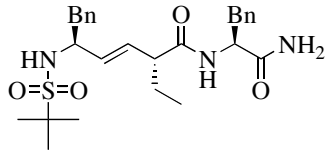
(2*S*)-Ethyl-4-methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-3-methylbutyl)-amide (132k). According to the general procedure, 22 mg (0.062 mmol) of D-Fmoc-Leu-OH, 17 mg (0.050 mmol) of aziridine **109** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 5.2 mg

(30%) of impure **132k** as a colorless oil: $[\alpha]_D^{25}$ 0.28 (*c* 0.49, MeOH); IR (film) 3357, 3203, 2959, 2927, 2872, 1687, 1668, 1655, 1301, 1118 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.63 (d, 1 H, *J* = 8.2 Hz), 7.25-7.13 (m, 5 H), 6.87 (bs, 1 H), 5.12 (d, 1 H, *J* = 9.7 Hz), 4.17 (dd, 1 H, *J* = 14.5, 8.4 Hz), 3.79 (dd, 2 H, *J* = 15.8, 7.6 Hz), 2.96 (dd, 1 H, *J* = 15.8, 6.0 Hz), 2.73 (d, 2 H, *J* = 7.6 Hz), 1.64 (s, 3 H), 1.53-1.31 (m, 4 H), 1.04 (s, 9 H), 0.85-0.78 (m, 6 H), 0.57 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 174.6, 173.3, 139.1, 137.1, 129.7, 128.4, 126.9, 126.5, 64.2, 58.5, 51.1, 47.8, 46.5, 44.7, 26.2, 25.3, 24.6, 24.1, 23.5, 22.1, 19.2, 13.1, 11.7; MS (ES) *m/z* (rel intensity) 502.3 ([M+^{23}Na]$^+$, 100); HRMS (ES) Calcd for $C_{25}H_{41}N_3O_4NaS$ (M+^{23}Na) 5022.2715, found 502.2701.

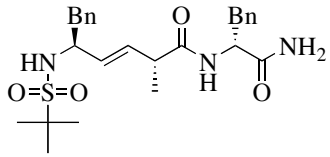


(2*R*)-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-2-phenyl-ethyl)-amide (132m). According to the general procedure, 24 mg (0.062 mmol) of L-Fmoc-Phe-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 5.1 mg (29%) of **132m** as a colorless oil: $[\alpha]_D^{25}$ –1.9 (*c* 0.47, $CHCl_3$); IR (film) 3288, 2974, 2930, 1652, 1520, 1496, 1455, 1296, 1123 cm^{-1}; ^1H NMR δ 7.36-7.17 (m, 10 H), 6.42 (d, 1 H, *J* = 7.8 Hz), 6.10 (bs, 1 H), 5.67 (d of AB, 1 H, *J* = 15.6, 6.5 Hz), 5.61 (d of AB, 1 H, *J* = 15.6, 5.3 Hz), 5.43 (bs, 1 H), 4.64 (q, 1 H, *J* = 8.1 Hz), 4.25-4.03 (m, 1 H), 4.02 (bs, 1 H), 3.17 (dd, 1 H, *J* = 13.9, 6.6 Hz), 3.05-2.86 (m, 3 H), 2.78 (dd, 1 H, *J* = 13.5, 7.3 Hz), 1.20 (s, 9 H), 1.08 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 174.09, 173.32, 137.09, 136.59, 133.58, 130.69, 129.71, 129.31, 128.67, 128.54, 127.10, 126.83, 60.16, 58.17, 54.44, 43.64,

42.44, 37.48, 23.96, 16.60; MS (ES) m/z (rel intensity) 508.2 ([M+^{23}Na]$^{+}$, 100), 304.2 (12); HRMS (ES) Calcd for $C_{26}H_{35}N_3O_4NaS$ (M+^{23}Na) 508.2246, found 508.2223.

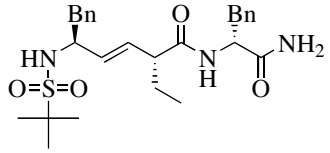


(2*R*)-Ethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-2-phenylethyl)-amide (132n). According to the general procedure, 24 mg (0.062 mmol) of L-Fmoc-Phe-OH, 16 mg of aziridine **112** (0.050 mmol) and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 2.8 mg (17%) of **132n** as a colorless oil: $[\alpha]_D^{25}$ –3.5 (*c* 0.21, $CHCl_3$); IR (Film) 3301, 2926, 1641, 1539, 1496, 1296, 1123 cm^{-1}; ^{1}H NMR δ 7.35-7.17 (m, 10 H), 6.33 (d, 1 H, *J* = 7.7 Hz), 6.05 (bs, 1 H), 5.67-5.53 (m, 2 H), 5.37 (bs, 1 H), 4.64 (q, 1 H, *J* = 7.9 Hz), 4.20-4.11 (m, 1 H), 3.96 (bd, 1 H, *J* = 9.3 Hz), 3.16 (dd, 1 H, *J* = 13.9, 6.6 Hz), 3.02-2.90 (m, 2 H), 2.86-2.71 (m, 2 H), 1.45-1.37 (m, 2 H), 1.23 (s, 9 H), 0.74 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 173.6, 173.4, 137.1, 136.6, 134.7, 129.9, 129.4, 128.8, 128.5, 127.2, 127.0, 60.2, 58.2, 54.5, 51.5, 42.5, 37.6, 24.0, 11.7; MS (ES) *m/z* (rel intensity) 522.2 ([M+^{23}Na]$^{+}$, 100), 318.2 (12); HRMS (ES) Calcd for $C_{27}H_{37}N_3O_4NaS$ (M+^{23}Na) 522.2402, found 522.2393.



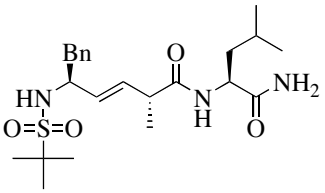
(2*R*)-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid

((1*R*)-carbamoyl-2-phenylethyl)-amide (132p). According to the general procedure, 24 mg (0.062 mmol) of D-Fmoc-Phe-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 4.5 mg (26%) of **132p** as a colorless oil: $[\alpha]_D^{25}$ –0.21 (*c* 0.24, $CHCl_3$); IR (film) 3324, 3202, 3087, 3063, 3028, 2974, 2930, 2873, 1655, 1521, 1497, 1454, 1294, 1123, 752 cm^{-1}; ^1H NMR δ 7.33-7.17 (m, 10 H), 6.56 (bs, 1 H), 6.33 (bs, 1 H), 5.73-5.43 (m, 2 H), 4.71 (q, 1 H, *J* = 7.4 Hz), 4.48 (bs, 1 H), 4.17-4.03 (m, 1 H), 3.18 (dd, 1 H, *J* = 14.0, 6.2 Hz), 3.05-2.85 (m, 3 H), 2.78 (dd, 1 H, *J* = 13.5, 7.8 Hz), 1.25-1.00 (m, 12 H); ^{13}C NMR δ 174.1, 173.7, 137.0, 136.9, 134.0, 130.3, 129.8, 129.3, 128.6, 128.5, 127.0, 126.8, 60.1, 57.9, 54.5, 43.4, 42.0, 37.7, 23.8, 16.8; MS (ES) m/z (rel intensity) 508.3 ([M+^{23}Na]$^+$, 100), 469.3 (5), 361.2 (6), 304.2 (3); HRMS (ES) Calcd for $C_{26}H_{35}N_3O_4NaS$ (M+^{23}Na) 508.2246, found 508.2242.

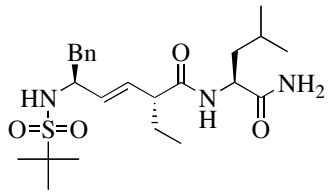


(2*R*)-Ethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-2-phenylethyl)-amide (132q). According to the general procedure, 24 mg (0.062 mmol) of D-Fmoc-Phe-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 5.4 mg (30%) of **132q** as a colorless oil: $[\alpha]_D^{25}$ –1.1 (*c* 0.22, $CHCl_3$); IR (film) 3303, 3028, 2963, 2929, 1661, 1640, 1533, 1454, 1297, 1122 cm^{-1}; ^1H NMR δ 7.33-7.17 (m, 10 H), 6.53 (bd, 1 H, *J* = 6.4 Hz), 6.29 (bs, 1 H), 5.69-5.55 (m, 3 H), 4.75 (dd, 1 H, *J* = 14.5, 7.9 Hz), 4.51 (bs, 1 H), 4.15-4.05 (m, 1 H), 3.16 (dd, 1 H, *J* = 14.0, 6.2 Hz), 3.04-2.89 (m, 2 H), 2.79 (dd, 1 H, *J* = 13.6, 7.6 Hz), 2.68–2.62 (m, 1 H), 1.89-1.69 (m, 1 H), 1.49–1.37 (m, 1 H), 1.19 (s,

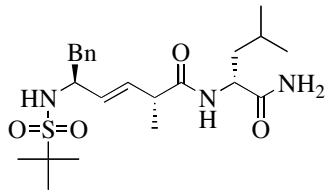
9 H), 0.76 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 173.7, 148.0, 137.3, 137.0, 135.1, 130.1, 129.6, 128.9, 128.8, 127.3, 127.2, 60.4, 58.1, 54.6, 51.6, 42.6, 38.1, 25.1, 24.2, 11.9; MS (ES) m/z (rel intensity) 522.2 ([M+^{23}Na]$^{+}$, 100), 483.2 (12); HRMS (ES) Calcd for $C_{27}H_{37}N_3O_4NaS$ (M+^{23}Na) 522.2402, found 522.2414.



(2*R*)-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-3-methylbutyl)-amide (132s). According to the general procedure, 22 mg (0.062 mmol) of L-Fmoc-Leu-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 4.7 mg (30%) of **132g** as a colorless oil: $[\alpha]_D^{25}$ –2.7 (*c* 0.16, $CHCl_3$); IR (film) 3304, 2957, 2930, 2871, 1654, 1528, 1454, 1295, 1123, 969, 751 cm^{-1}; ^{1}H NMR δ 7.38-7.16 (m, 5 H), 6.38 (d, 2 H, *J* = 7.9 Hz), 5.75 (d of AB, 1 H, *J* = 15.6, 6.6 Hz), 5.73 (d of AB, 1 H, *J* = 15.6, 4.7 Hz), 5.44 (bs, 1 H), 4.48-4.35 (m, 1 H), 4.25-4.08 (m, 2 H), 3.14-3.00 (m, 1 H), 2.96 (dd, 1 H, *J* = 15.2, 5.3 Hz), 2.79 (dd, 1 H, *J* = 13.4, 7.2 Hz), 1.70-1.55 (m, 3 H), 1.29 (d, 3 H, *J* = 7.1 Hz), 1.19 (s, 9 H), 0.93 (d, 3 H, *J* = 5.9 Hz) 0.89 (d, 3 H, *J* = 5.6 Hz) ^{13}C NMR δ 174.6, 174.4, 136.5, 134.1, 130.5, 129.7, 128.7, 127.2, 60.2, 58.3, 51.7, 43.7, 42.3, 39.9, 24.7, 23.9, 22.9, 21.7, 16.9; MS (ES) m/z (rel intensity) 474.3 ([M+^{23}Na]$^{+}$, 100), 435.3 (4), 407.3 (5), 270.2 (5); HRMS (ES) Calcd for $C_{23}H_{37}N_3O_4NaS$ (M+^{23}Na) 474.2402, found 474.2393.

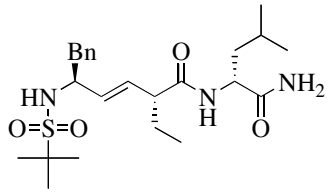


(2*R*)-Ethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*S*)-carbamoyl-3-methylbutyl)-amide (132t). According to the general procedure, 22 mg (0.062 mmol) of D-Fmoc-Leu-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 6.0 mg (36%) of **132t** as a colorless oil: $[\alpha]_D^{25}$ –2.9 (*c* 0.31 , $CHCl_3$); IR (film) 3306, 2959, 2930, 2872, 1668, 1651, 1539, 1455, 1297, 1123 cm^{-1}; ^1H NMR δ 7.34-7.16 (m, 5 H), 6.38 (bs, 1 H), 6.31 (d, 1 H, *J* = 8.0 Hz), 5.71 (d, 2 H, *J* = 5.2 Hz), 5.42 (bs, 1 H), 4.47-4.39 (m, 1 H), 4.17 (s, 2 H), 3.00-2.77 (m, 3 H), 1.95-1.80 (m, 1 H), 1.62-1.48 (m, 4 H), 1.22 (s, 9 H), 0.94-0.85 (m, 9 H); MS (ES) *m/z* (rel intensity) 488.3 ($[M+^{23}Na]^+$, 100), 368.2 (8), 284.2 (10); HRMS (ES) Calcd for $C_{24}H_{39}N_3O_4NaS$ ($M+^{23}Na$) 488.2559, found 488.2554.



(2*R*)-Methyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-3-methylbutyl)-amide (132v). According to the general procedure, 22 mg (0.062 mmol) of D-Fmoc-Leu-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.18 mL (0.36 mmol) of a 2 M solution of Me_2Zn in toluene afforded 4.7 mg (36%) of **132v** as a colorless oil: $[\alpha]_D^{25}$ 0.39 (*c* 0.25, $CHCl_3$); IR (film) 3304, 3206, 2957, 2931, 2871, 1651, 1538, 1294, 1123, 753 cm^{-1}; ^1H NMR δ 7.36-7.18 (m, 5 H), 6.49 (d, 1 H, *J* = 8.5 Hz),

6.45 (bs, 1 H), 5.79-5.74 (m, 2 H), 5.49 (bs, 1 H), 4.55-4.43 (m, 2 H), 4.19-4.09 (m, 1 H), 3.07 (qn, 1 H, *J* = 6.6 Hz), 2.96 (dd, 1 H, *J* = 13.4, 5,5 Hz), 2.80 (dd, 1 H, *J* = 13.5, 8.1 Hz), 1.69-1.55 (m, 3 H), 1.28 (d, 1 H, *J* = 7.1 Hz), 1.16 (s, 9 H), 0.94 (d, 3 H, *J* = 6.0 Hz), 0.92 (d, 3 H, *J* = 6.0 Hz); ^{13}C NMR δ 174.8, 174.2, 136.8, 134.2, 130.6, 129.7, 128.6, 127.1, 60.1, 58.1, 43.4, 41.9, 40.5, 24.9, 23.8, 23.0, 21.8, 17.0; MS (ES) m/z (rel intensity) 474.3 ([M+^{23}Na]$^+$, 100), 453.3 (10), 452.4 (55), 450.4 (10), 435.3 (45), 408.4 (5), 407.3 (22); HRMS (ES) Calcd for $C_{23}H_{37}N_3O_4NaS$ (M+^{23}Na) 474.2402, found 474.2380.



(2*R*)-Ethyl-(5*S*)-(2-methylpropane-2-sulfonylamino)-6-phenylhex-3-(*E*)-enoic acid ((1*R*)-carbamoyl-3-methyl-butyl)-amide (132w). According to the general procedure, 22 mg (0.062 mmol) of D-Fmoc-Leu-OH, 16 mg (0.050 mmol) of aziridine **112** and 0.36 mL (0.36 mmol) of a 1 M solution of Et_2Zn in toluene afforded 4.4 mg (26%) of **132w** as a colorless oil: $[\alpha]_D^{25}$ –1.7 (*c* 0.22, $CHCl_3$); IR (film) 3220, 2959, 2929, 2872, 1651, 1552, 1455, 1296, 1216, 1122 cm^{-1}; ^{1}H NMR δ 7.34-7.19 (m, 5 H), 6.47 (bs, 2 H), 5.75 (d of AB, 1 H *J* = 15.6, 4.7 Hz), 5.67 (d of AB, 1 H, *J* = 15.9, 7.3 Hz), 5.50 (bs, 1 H), 4.58-4.45 (m, 2 H), 4.20-4.10 (m, 1 H), 2.97 (dd, 1 H, *J* = 13.5, 5.6 Hz), 2.87-2.78 (m, 2 H), 1.97-1.82 (m, 2 H), 1.59-1.47 (m, 3 H), 1.16 (s, 9 H), 0.96-0.84 (m, 9 H); ^{13}C NMR δ 175.0, 173.7, 137.0, 135.0, 129.8, 129.1, 128.6, 127.0, 60.1, 58.0 51.7, 51.3, 41.9, 40.7, 29.7, 25.1, 24.9, 23.9, 23.0, 21.8, 11.7; MS (ES) *m/z* (rel intensity) 488.3 ([M+^{23}Na]$^+$,

100), 284.2 (12); HRMS (ES) Calcd for $C_{24}H_{39}N_3O_4NaS$ ($M+^{23}Na$) 488.2559, found 488.2566.

Table 13. Summary of yields and purities of (*E*)-alkene peptide library members (Scheme 15)

Entry	Amino Acid	R^2	R^3	Purity[a]	Yield[b]	Entry	Amino Acid	R^2	R^3	Purity[a]	Yield[b]
132a	L-Phe	Me	Me	ND	40%	**132m**	L-Phe	H	Me	60%	29%
132b	L-Phe	Me	Et	50%	32%	**132n**	L-Phe	H	Et	68%	17%
132d	D-Phe	Me	Me	ND	36%	**132p**	D-Phe	H	Me	66%	26%
132e	D-Phe	Me	Et	55%	29%	**132q**	D-Phe	H	Et	61%	30%
132g	L-Leu	Me	Me	ND	36%	**132s**	L-Leu	H	Me	54%	30%
132h	L-Leu	Me	Et	37%	39%	**132t**	L-Leu	H	Et	55%	36%
132j	D-Leu	Me	Me	47%	24%	**132v**	D-Leu	H	Me	55%	36%
132k	D-Leu	Me	Et	55%	30%	**132w**	D-Leu	H	Et	60%	26%

2.0 SYNTHESIS AND BIOLOGICAL EVALUATION OF *THIO*-HALENAQUINONE AND RELATED ANALOGS

2.1 INTRODUCTION

Halenaquinone (**135**) was isolated in 1983 from the Pacific sponge *Xestospongia exigua*.[95] The structure of **135** was determined by NMR analysis and single crystal X-ray diffraction. The absolute configuration of the molecule was not assigned at the time of isolation but was later determined using a combination of circular dichroism calculations[96,97] and total synthesis.[98] While the pentacyclic structure of halenaquinone was initially unique among known natural products, numerous structurally similar compounds were isolated subsequently such as xestoquinone (**136**),[99] halenaquinol (**137**), xestoquinol (**138**), adociaquinone A (**139**), adociaquinone B (**140**) and 3-ketoadociaquinone A (**141**).[100] Biological assays of **135** revealed a wide array of activities including antibiotic,[95] cardiotonic,[99] cytotoxic,[101,102] antifungal,[102]activities as well as inhibition of protein tyrosine kinase,[103-105] phosphatidylinositol 3 (PI-3) kinase,[106] Cdc25B dual specificity phosphatase.[107] and pfnek-1.[108] Pfenk-1 may be an important target for the treatment of malaria.

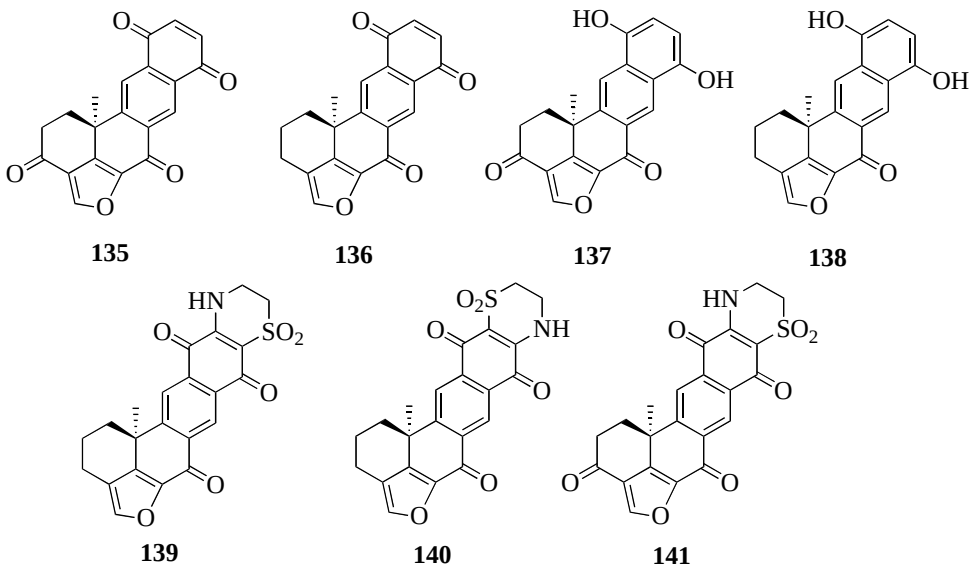


Figure 19. Structures of halenaquinone (**135**) and related compounds.

2.1.1 Malaria

Malaria accounts for more than one million deaths a year.[109] The disease is prevalent in most tropical climates, but the majority of fatalities occur in sub-Saharan Africa (Figure 20).[110] Malaria is caused by a protozoan parasite of the genus *Plasmodium*, and is introducted into humans via several species of female anopheles mosquitoes.[111] There are four *Plasmodium* species that account for almost all human infections: *P. falciparum, P. vivax*, *P. malariae*, and *P. ovale*.[109] Of these species, *P. falciparum* accounts for over 80% of all infections.[112]

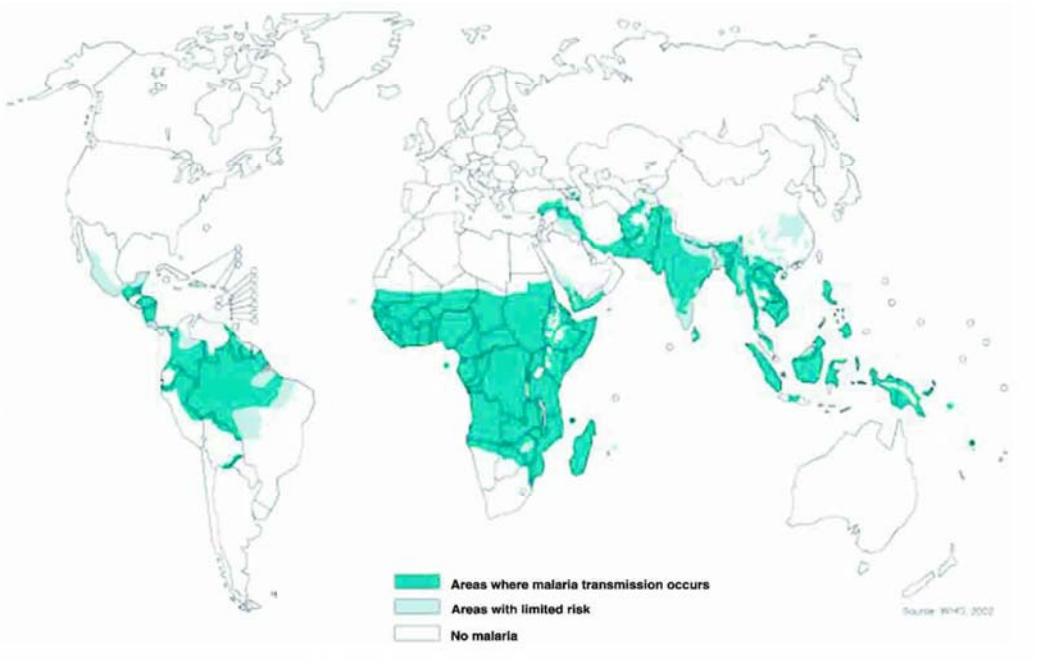


Figure 20. Areas of the world affected by malaria (from Abu-Raddad, L. J.; Patnaik, P.; Kublin J. G. *Science* **2006**, *314*, 1603).

2.1.1.1 The impact of malaria

The exact impact malaria is difficult to quantify.[113] Most deaths occur in the home and not under the care of medical professionals, and as a result, the only way to determine the number of deaths is by post-mortem questionnaires, which lack accuracy.[114,115] Not all malaria infections are fatal but as with the death totals, the morbidity rate is difficult to measure. Extensive work indicates that there are 0.5 billion clinical attacks of malaria each year.[109] Malaria is also believed to be responsible for up to 25% of severe maternal anaemia and 10-20% of low birthweight babies in Africa.[116,117]

Illness and death due to malaria have a severe impact on the economy.[118-120] Malaria infection can limit school attendance, productivity at work and intellectual development.[121] The gross natural product of countries in endemic areas has risen 2% less than in similar countries where malaria is not endemic. The majority of malaria related hardships directly affect the poor and vulnerable.[122]

2.1.1.2 The life cycle of *Plasmodium*

The life cycle of the malaria parasite *Plasmodium* relates to its spread and the course of human infection.[123,124] The parasite is transmitted to its host in the saliva of mosquitoes as sporozoites (Figure 21).[125] These sporozoites then localize themselves in the hepatocyctes and spread by asexual division (exoerythrocytic schizogony). The resulting merozoites enter the bloodstream and invade erythrocytes. Within erythrocytes more asexual division occurs (erythrocytic schizogony) and, at this stage, the resultant daughter cells may be differentiated as either more merozoites or sexed cells - gametocytes. Sexed gametocytes upon ingestion by a new mosquito host become activated in the midgut, leading to the formation of fertilization-competent gametes. After fertilization, the *Plasmodium* zygotes develop into new sporozoites, which, upon accumulation in the insect's salivary glands, may be transmitted to a new human host continuning the life cycle of the parasite.

2.1.1.3 Methods for the prevention of malaria

Malaria prevention is a major area of focus for the international community. Chemoprophylaxis, the treatment with drugs to prevent an infection, is used regularly by those traveling to malaria-

endemic areas.[109] This technique is not currently approved for the treatment of the native people due to the possibility of drug resistance and the delay of the natural immunity.[126] Yet intermittent preventive therapy with sulfadoxine-pyrimethamine is highly effective in the prevention of malaria in pregnant women helping to avoid the related complications.[127-129] Similar treatment of infants less than one year in age lowered the incidence of malaria as well.[130,131]

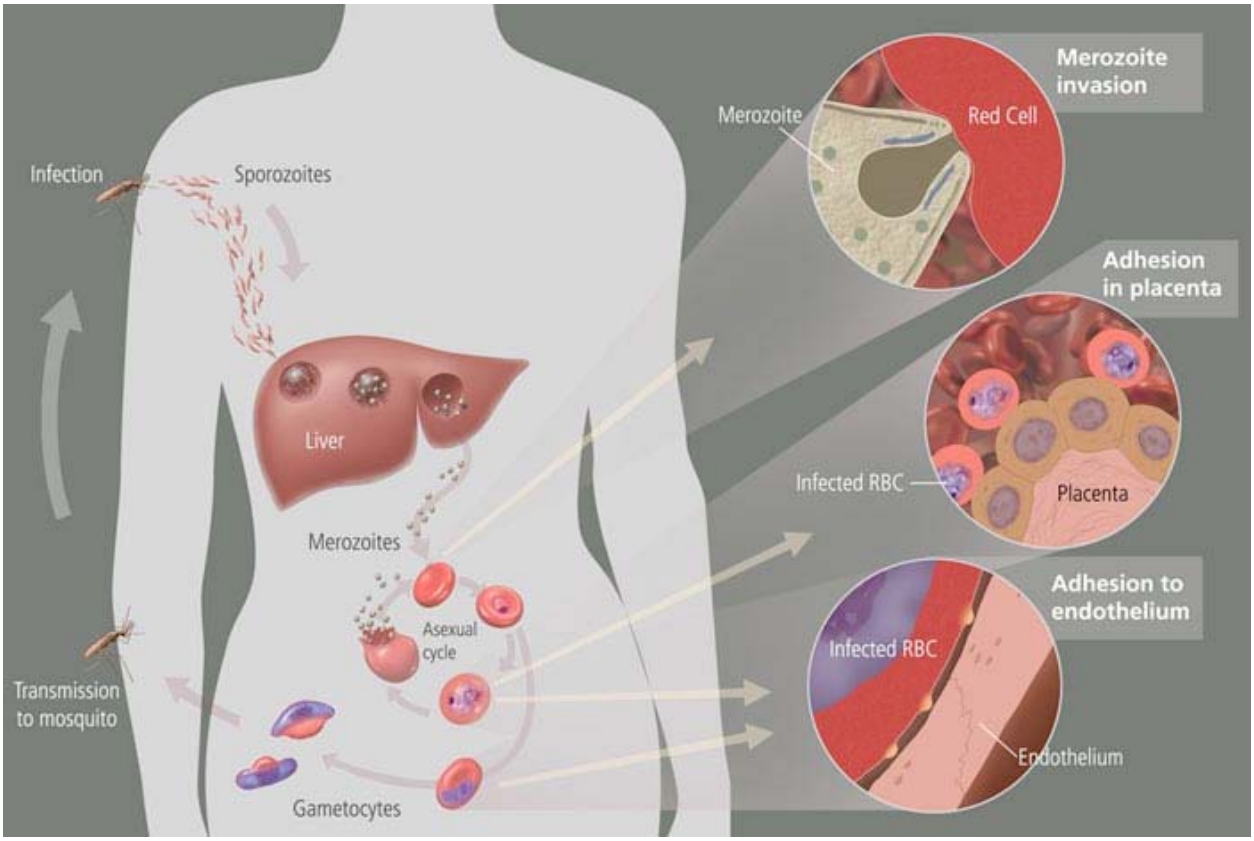


Figure 21. Life cycle of *Plasmodium* (from NIH Aminco-Bowman SPF: Special Spotlights, http://history.nih.gov/exhibits/bowman/SSmalaria.htm).

Control of the mosquito population and limiting their contact with humans is also a major area of interest for the prevention of malaria. There is an ongoing program to develop genetically altered mosquitoes that are resistant to *Plasmodium*[132] but genetic modifications that

are lethal to the female mosquitoes may be more promising.[133] The use of insecticides, such as DDT, to spray the inside surfaces of homes is common.[134] Insecticide-treated nets are a highly effective solution for the prevention of malaria.[135-141] Although inexpensive,[142] they are still outside of the means of many people at the greatest risk of malaria.[143-145]

2.1.1.4 Antimalarial drugs

Drugs are being developed to target the *Plasmodium* parasite at various stages of its life cycle in both human and mosquito hosts. Drugs including chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine and artemisinin belong to a class of molecules known as blood schizontocides, which are used to combat the blood form of the infection and stop clinical symptoms (Figure 22).[146] Primaquine and pyrimethamine are tissue schizontocides that prevent the parasite from transitioning from the liver to the erythrocytic stage.[146] This method of treatment is difficult in practice since malaria cannot be diagnosed until the parasite enters the blood and symptoms are present. Primaquine is also used to prevent the relapse of the infection from *P. vivax* and *P. ovale* hypnozoites that may lie dormant in the liver.[146,147] Gametocytocides kill the sexual form of the parasite in the blood not allowing it to be transmitted to the mosquito. Chloroquine and quinine are effective against *P. vivax* and *P. malariae*. Primaquine is effective against all species of *Plasmodium* in this stage.[146]

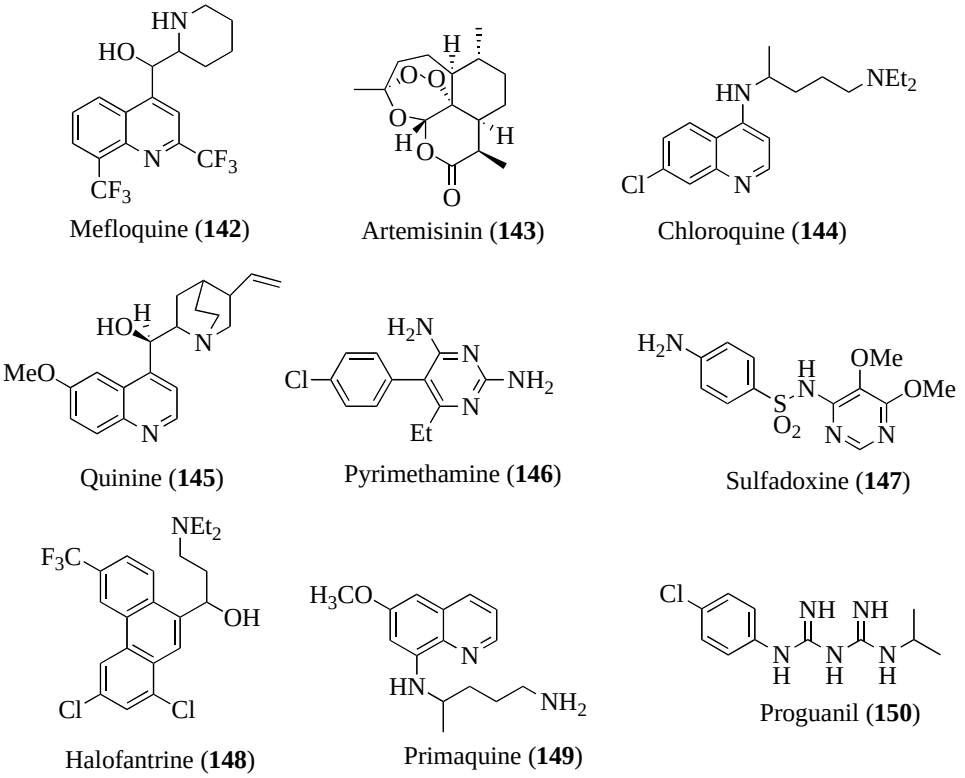


Figure 22. The structures of commonly used antimalarial drugs.

The antimalaria drugs that are currently clinically used have three mechanisms of action. Drugs belonging to the 4-aminoquinoline family, such as chloroquine (**144**), inhibit the polymerization of heme within the parasite, a critical detoxification mechanism during the intraerythrocytic stage.[148] Chloroquine binds to heme and may form a toxic complex which results in cell death. Atemisinin and other endoperoxides generate free radicals in the presence of heme iron, which alkylate proteins within the parasite.[149-151] Finally, the antifolates, which are broken into two classes. Sulfones and sulfonamides are Type-I antifolates, which inhibit dihydropteroate synthase.[152] Pyrimethanmine and proguanil are type-II antifolates that inhibit dihydrofolate reductase.[153]

The development of new malaria drugs has been slow over the past 30 years. Over this time, only two drugs were indentified. Mefloquine is a synthetic antimalarial drug and the natural product artemisinin was isolated, but its medicinal properties had been known for 2000 years.[146] Drugs to treat malaria need to be inexpensive, have low toxicity and be orally available. The lack of new drugs combined with the increasing occurrence of drug resistance is making it difficult to effectively fight the spread of malaria.[154-157]

2.1.1.5 Pfnek-1 as a therapeutic target

Sequencing the genome of *P. falciparum* has offered an increased understanding of the organism and new targets for possible therapeutic intervention.[158,159] One such target is Pfnek-1,[123] a Never-In-Mitosis/*Aspergillus* (NIMA) related protein kinase.[160] Pfnek-1 is present in both the asexual and gametocyte forms of the parasite and is important in the regulation of an atypical *P. falciparum* mitogen-activated protein kinase (MAPK).[160,161] Pfnek-1 phosphorylates Pfmap-2, which is critical for exflagellation *in vitro* and for successful completion of the sexual cycle of the parasite in the mosquito.[161] Working in tandem these two kinases are able to phosphorylate an exogenous substrate, suggesting that phosphorylation by Pfnek-1 activates Pfmap-2.[123,161]

2.1.1.6 Inhibition of Pfnek-1 by xestoquinone and halenaquinone

Xestoquine (**136**) and halenaquinone (**135**) have been reported to be inhibitors of Pfnek-1.[108] Xestoquinone was found to have an IC_{50} of 1.1 μM while halenaquinone was less potent at 3.0 μM. Xestoquine was examined further due to its superior activity and greater abundance.

Screening against a number of *P. falciparum* kinases showed that xestoquinone had modest activity against PfPK5 and no activity toward other screened kinases (Table 14).[108] Screening against kinases from higher eukaryotes revealed activity against Erk2. Xestoquinone was 10-fold less potent against Erk2 than Pfnek-1.

Xestoquinone was also shown to possess antiplasmodial activity with an IC_{50} value of 3 μM. The selectivity index (SI), which is defined as the ratio of cyctotoxicity to antiplasmodial activity, for xestoquinone was found to be 7. Treatment of mice infected with *P. berghei*, an animal malaria, with 5 mg/kg of **136** four times daily lead to a 50% survival rate after 10 days compared to only a 10% survival rate for untreated mice. Also the amount of parasites in the blood was inhibited by 47% by xestoquinone. Mice treated with 10 mg/kg chloroquine had a 100% survival rate and no parasites were detected in their blood after 10 days.

Table 14. Effects of xestoquinone on the activity of several protein kinases.

Protein kinase	IC_{50} (μM)	Protein kinase	IC_{50} (μM)
Pfnek-1	1.1	CDk5/p25	>100
PfPK 5	17	Erk2	11
PfPK 7	>100	PKA	>100
PfGSK-3	160	$pp60^{v\text{-}srcb}$	60
GSK-3α/β	140	EGFR	60
CDK1/cyclin B	60		

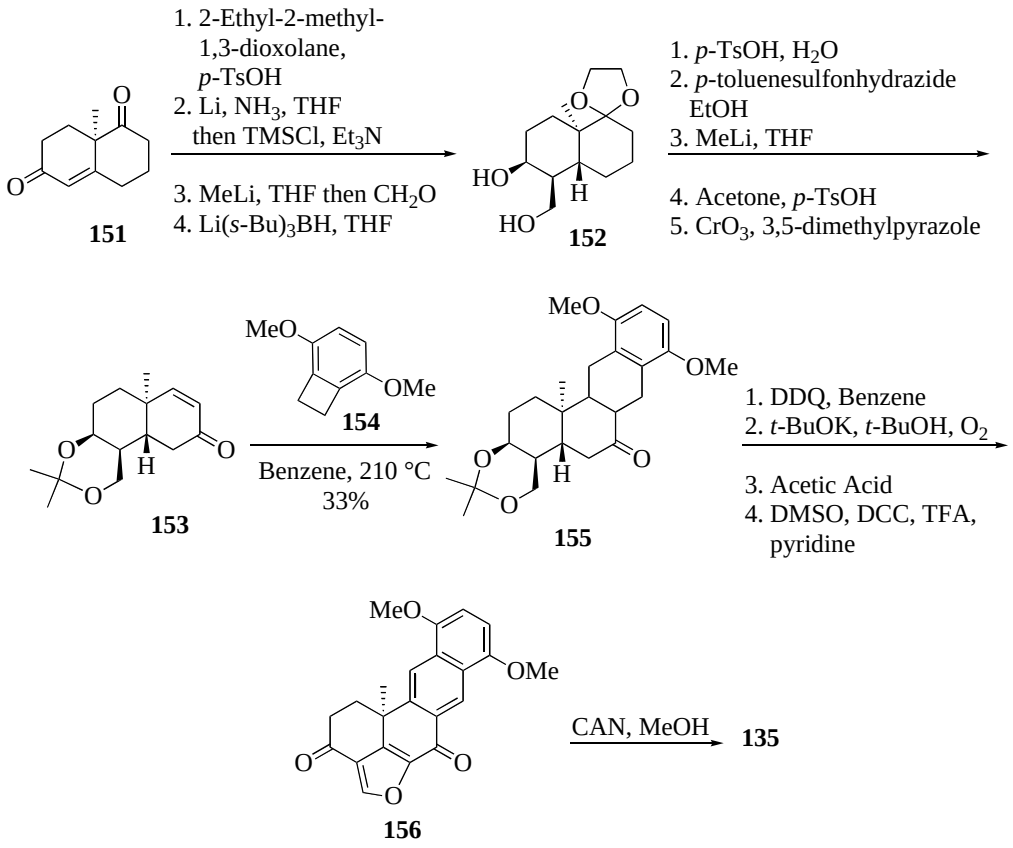
2.1.2 The total and partial syntheses of halenaquinone and xestoquinone

Due to its structure and biological properties, halenaquinone has generated a great deal of interest in the synthetic community. As a result, there are a number of total and partial syntheses found in the literature. Harada and co-workers completed the first total synthesis of

halenaquinone in 1988 (Scheme 19).[98] Their goal was not only the synthesis of the molecule, but also the validation of the computational methods used to assign the absolute stereochemistry.[96,97] The synthesis began with enantiopure Wieland-Miescher ketone **151**, which was protected as the acetal followed by reduction and trapping of the resulting enolate as the TMS-enol ether. Treatment with MeLi, addition of formaldehyde and subsequent reduction of the ketone gave diol **152**. The acetal was cleaved and the resulting ketone was reduced. Protection of the diol as the acetonide followed by allylic oxidation provided enone **153**. Heating this compound in benzene in the presence of benzocyclobutane **154** afforded the Diels-Alder adduct **155**. The resulting cyclohexane ring was oxidized to give the naphthalene and α-oxidation of the ketone by O_2 in the presence of base afforded the enol. The acetonide was removed with aqueous acetic acid and the furan was formed via oxidation of the primary alcohol, cyclization and elimination of water. Finally, CAN oxidation of the naphthalene gave halenaquinone (**135**) in 16 steps.

Shibasaki and co-workers completed the second synthesis of **135** that employed an asymmetric Heck reaction to set the quaterny carbon stereocenter (Scheme 20).[162,163] A five step sequence converted commercially available tetralone **157** to naphthol **158** in 58% overall yield. Compound **158** was then mono-protected as the silyl ether and subsequent treatment with Tf_2O gave **159**. Heck precursor **161** was synthesized via Suzuki cross couping of **159** with alkyl borane **160**, removal of the silyl group and conversion to the triflate. Treatment of this intermediate with $Pd(OAc)_2$, (*S*)-BINAP and K_2CO_3 in THF at 60 °C afforded tricycle **162** in high yield and 87% *ee*. Deprotection of the TBDPS ether, reduction, activation of the alcohol as the triflate and displacement with acyl anion equvalent **163** gave **164**. After protecting group manipulations, the acetal was subjected to benzylic oxidation with DDQ followed by O_2 gave **165**. Iodination and acetyl removal followed by palladium-catalyzed cyclization afforded **166**.

Removal of the silyl group and CAN oxidation gave halenaquinone in 24 steps and 1.9% overall yield.

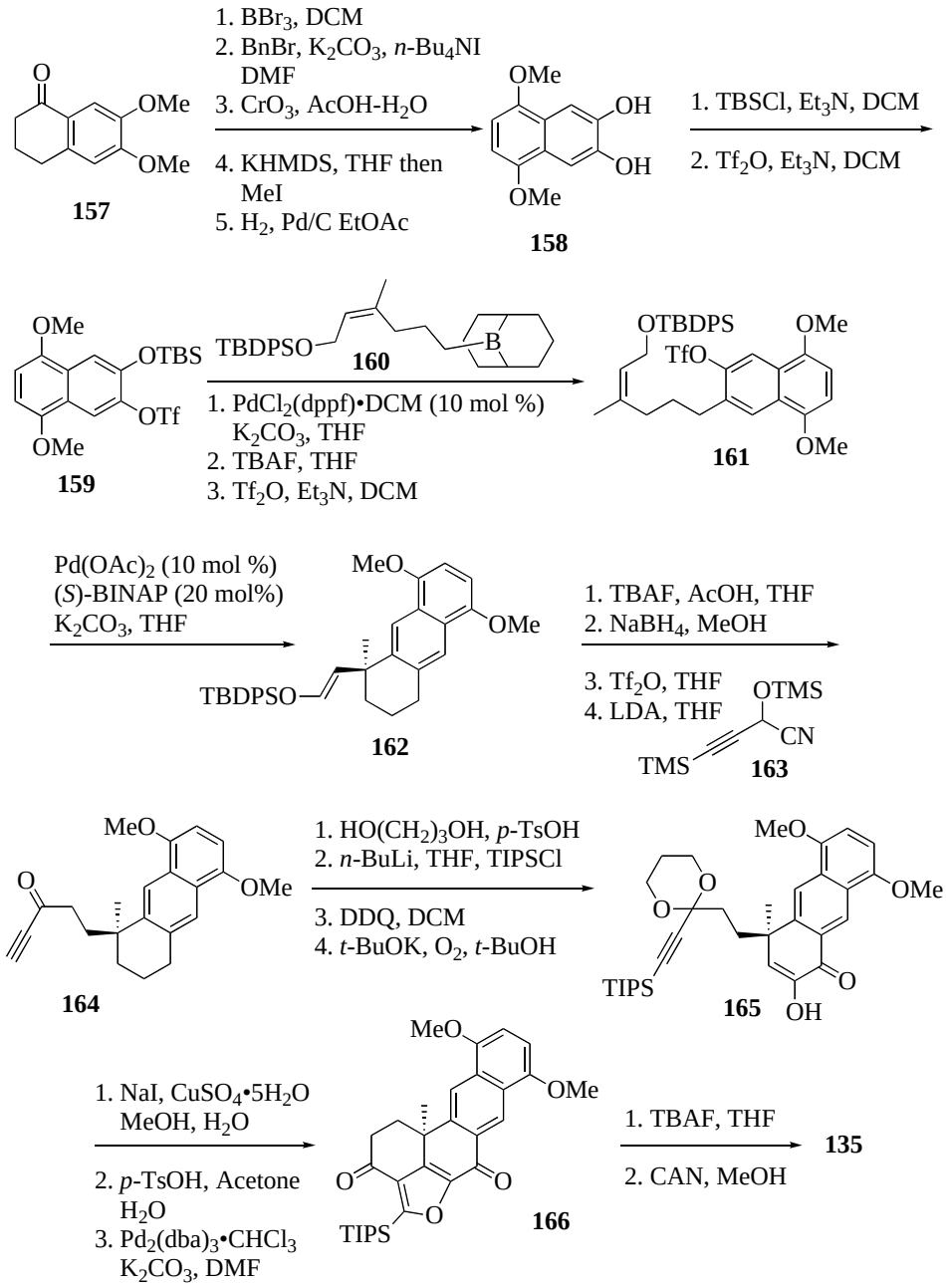


Scheme 19. Harada's synthesis of halenaquinone.

The Trauner group has completed the most recent synthesis of (-)-halenaquinone to date.[164] Protection of known alcohol **167** followed by introduction of the aldehyde and Heck cyclization gave **168** (Scheme 21). Treatment of **169** with *n*-BuLi and addition to aldehyde **168** followed by deprotection, oxidation of the diol and oxidation to the quinone gave **170**. A Diels-Alder reaction at high pressure and oxidation gave (-)-**135**.

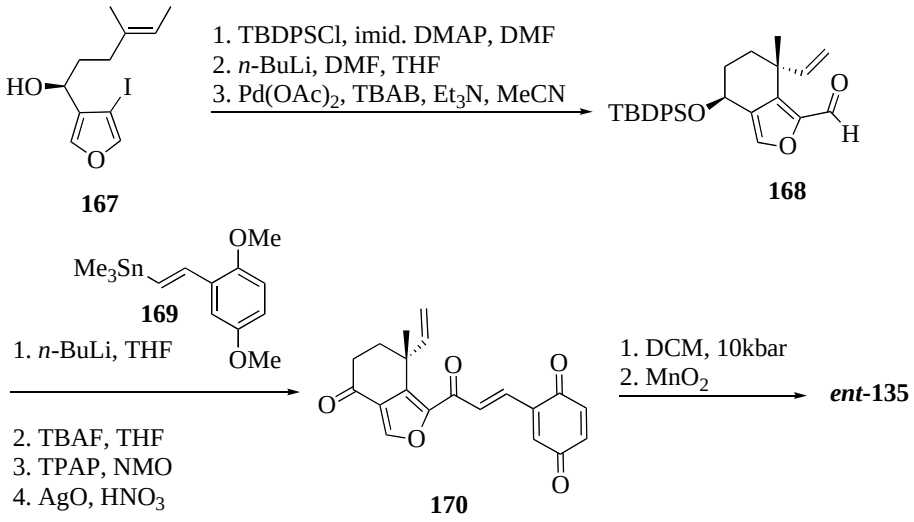
Rodrigo and co-workers applied a different strategy to a formal synthesis of halenaquinone,[165] employing a tandem Diels-Alder-Cope sequence to construct the tricyclic core

of the molecule (Scheme 22).[166] Oxidation of methylguaiacol **171** with [bis(trifluoroacetoxy)iodo)]benzene led to the formation of an *o*-benzoquinone monoketal derivative which participated in a Diels-Alder reaction with diene **172**. Under the reaction

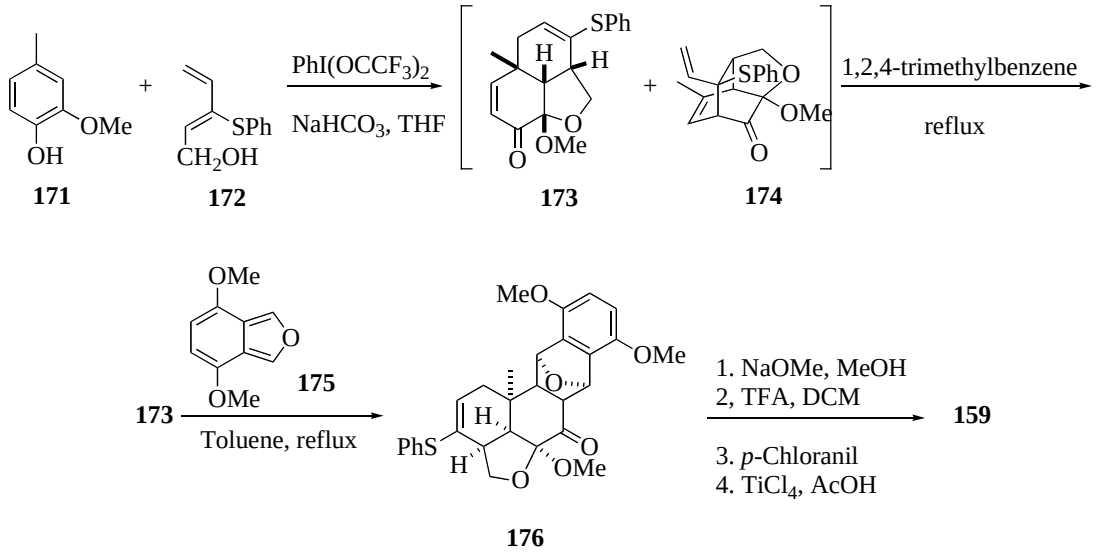


Scheme 20. Shibasaki's synthesis of halenaquinone.

conditions, a mixture of the Cope rearrangement product **173** and the Diels-Alder adduct **174** were isolated. Heating this mixture in 1,2,4 trimethylbenzene gave only **173**. The tricycle was then heated in the presence of naphthofuranone **175** to afford **176**, which contained the entire carbon framework of halenaquinone. Treatment with base facilitated aromatization to the naphthalene and subsequent exposure to TFA and *p*-chloranil oxidized the tetrahydrofuran to the furan. The vinyl sulfide moiety was converted to the ketone by refluxing in AcOH with $TiCl_4$. This compound intersects the Harada intermediate, which was only a single step from **135**.

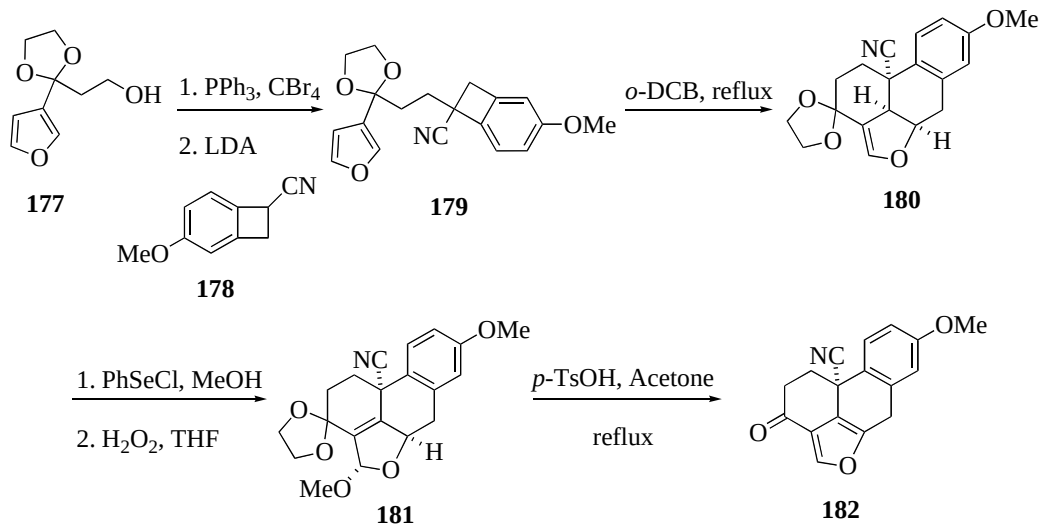


Scheme 21. Truaner's synthesis of (-)-halenaquinone.



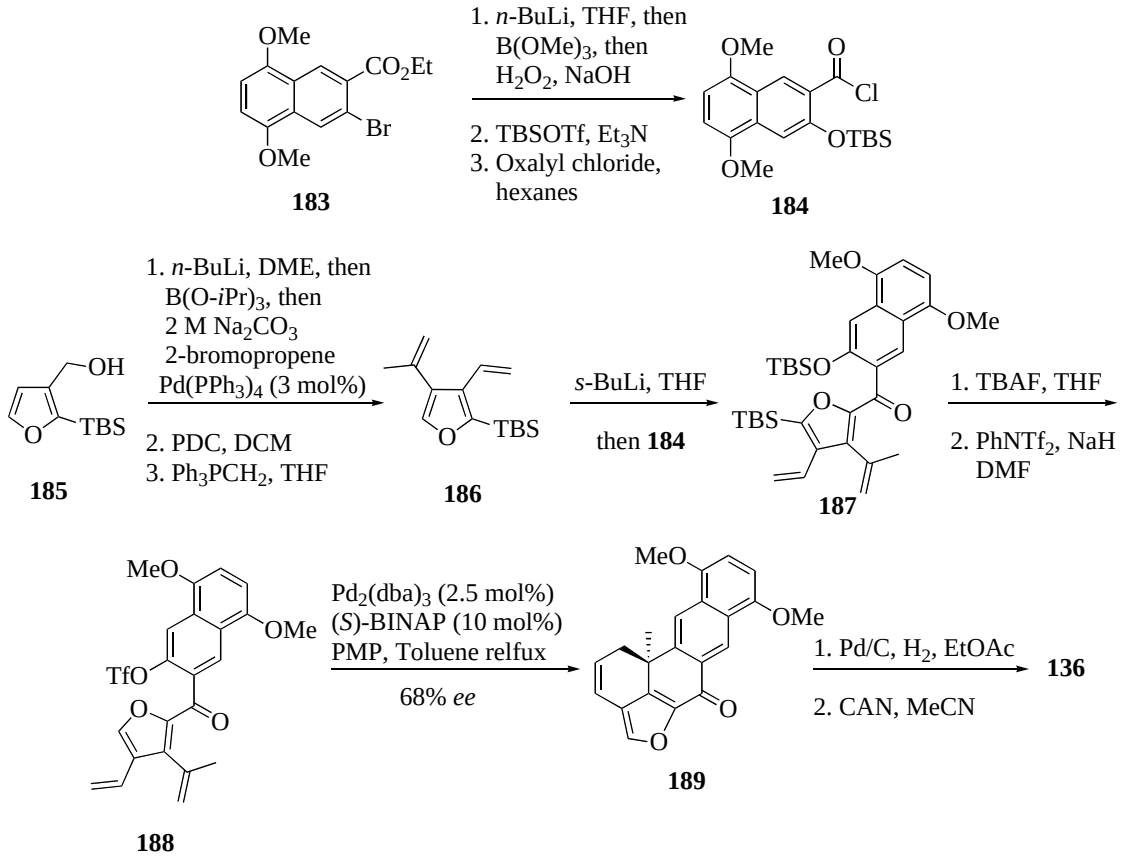
Scheme 22. Rodrigo's formal total synthesis of halenaquinone.

Nemoto and co-workers have published the synthesis of the tetracyclic core of halenaquinone.[167,168] The key step in this route was an intramolecular Diels-Alder reaction between a furan and a benzocyclobutane which constructed the B-ring of halenaquinone (Scheme 23). Conversion of the known alcohol **177** to the bromide followed by alkylation with **178** afforded the Diels-Alder precursor. Heating this compound at reflux in *ortho*-dichlorobenzene (*o*-DCB) led to **180**, which contained the core of halenaquinone. Treatment with PhSeCl in methanol and subsequent elimination gave **181**, which, upon exposure to acid, afforded furan **182**. This compound was not used to complete a total synthesis of halenaquinone, but the Sorensen group employed a similar Diels-Alder strategy in the synthesis of viridin.[169]



Scheme 23. Nemoto's approach to the tricycle core of halenaquinone.

The Keay laboratory realized a synthesis of xestoquinone (**136**) that featured a palladium-catalyzed polyene cyclization to set the quaternary carbon center and construct the A,B-rings of the tricyclic core (Scheme 24).[170,171] The required naphthalene **184** was synthesized in three steps from known **183**.[172] Furan **185** was selectively metalated with *n*-BuLi and the resulting anion was quenched with B(O-*i*Pr)$_3$ and then subjected to Suzuki cross-coupling with 2-bromopropene. Oxidation of the primary alcohol followed by Wittig olefination afforded diene **186**. Deprotonation with *n*-BuLi and addition to **184** gave ketone **187**. Removal of the silyl protecting groups and installation of the aryl triflate gave Heck precursor **188**. Treatment with Pd$_2$(dba)$_3$ and *S*-BINAP afforded the cyclized product in high yield and 68% *ee*. Hydrogenation with Pd/C and CAN oxidation afforded (+)-xestoquinone.

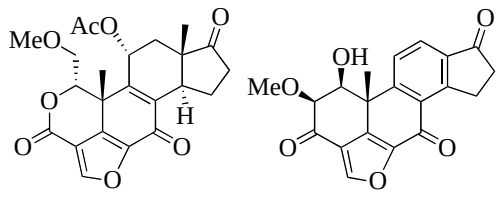


Scheme 24. Keay's synthesis of (+)-xestoquinone.

2.1.3 Replacement of the furan in furanosteroids with thiophene

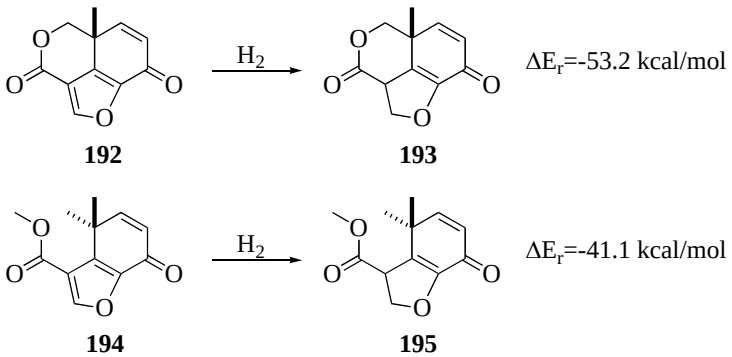
The key structural feature of **135**, wortmannin (**190**) and viridin (**191**) is the strained tricyclic furanodecaline core (Figure 23). The naphtha[1,8-*bc*]furan subunit is flanked by electron-withdrawing carbonyl groups that increase the electrophilicity of the unsubstituted α-carbon of the furan, which, in combination with the strained nature of the tricycle, further enhances furan reactivity. This moiety is responsible for the irreversible conjugation of wortmannin to PI-3 kinase,[173] and this reactivity could also account for the low kinase subtype selectivity, *in vivo* toxicity and poor bioavailability of wortmannin.[174] In the case of wortmannin, the strain of this ring system is approximately 12.1 kcal mol^{-1}, based on a comparison of the relative differences

in the energy of hydrogenation of **192** and **194** (Figure 24).[175] Similar calculations performed on the core of **135** indicate that replacement of the furan with a thiophene decreases the relative energy of hydrogenation of tricycle **196** vs **198** by 2.6 kcal mol^{-1}.[176] This is mainly due to a decrease in the angle strain of the fused ring systems. Isoelectronic replacement of the furan with a thiophene should therefore significantly decrease the electrophilic, alkylating properties of the heterocycle and increase the biological target selectivity. The replacemnt of a furan moiety in natural products, such as salvinorin A[177] and cyclazosin,[178] with other heterocycles has not improved their biological activity relative to the target to interest. To investigate our hypothesis and to gain access to natural product analogs with an improved kinase selectivity profile, we embarked on the preparation of a thiophene analog of halenaquinone.



190 **191**

Figure 23. Structures of wortmannin (**190**) and viridin (**191**).



192 **193**

194 **195**

Figure 24. Approximate reaction ethalpies for partial hydrogenations determined at the B3LYP/6-31G* level in Spartan 04.[175]

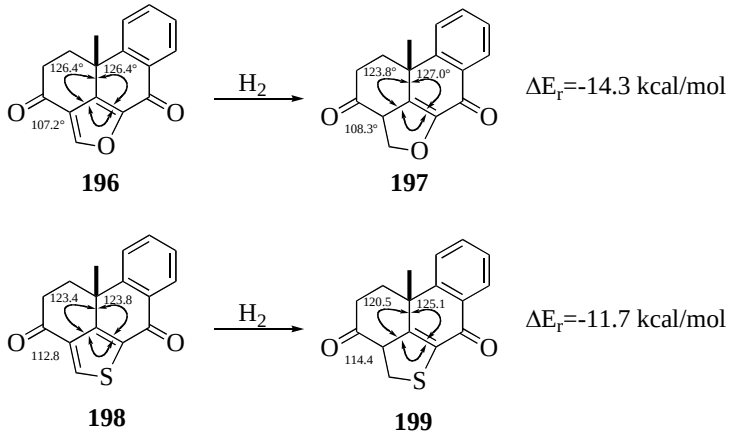


Figure 25. Selected bond angles of furanodecaline (**196**) and thiophenodecaline (**198**), and approximate reaction enthalpies for hydrogenations determined at the B3LYP/6-31G* level in Spartan 04.[176]

2.2 SYNTHESIS OF *THIO*-HALENAQUINONE

2.2.1 Retrosynthetic analysis of *thio*-halenaquinone

The retrosynthetic analysis of *thio*-halenaquinone (**200**) is shown in Figure 26. We envisioned installing the A-ring via a ring closing metathesis of **201**. The key intermediate tetracycle **202** would arise from a Heck cyclization to install the quaternary center. Sequential metalations of the commercially available 3,4-dibromothiophene **206** were envisioned to lead to trisubstituted thiophene **205**. Recently, heterocycle metalations have been used with considerable success for the preparation of polyfunctionalized heteroaromatic systems.[179]

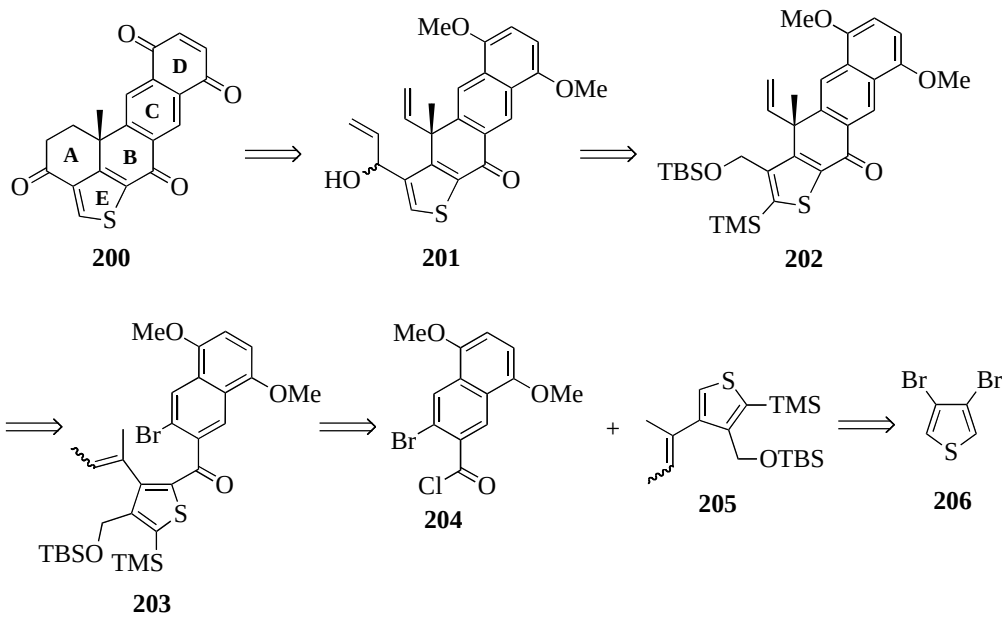
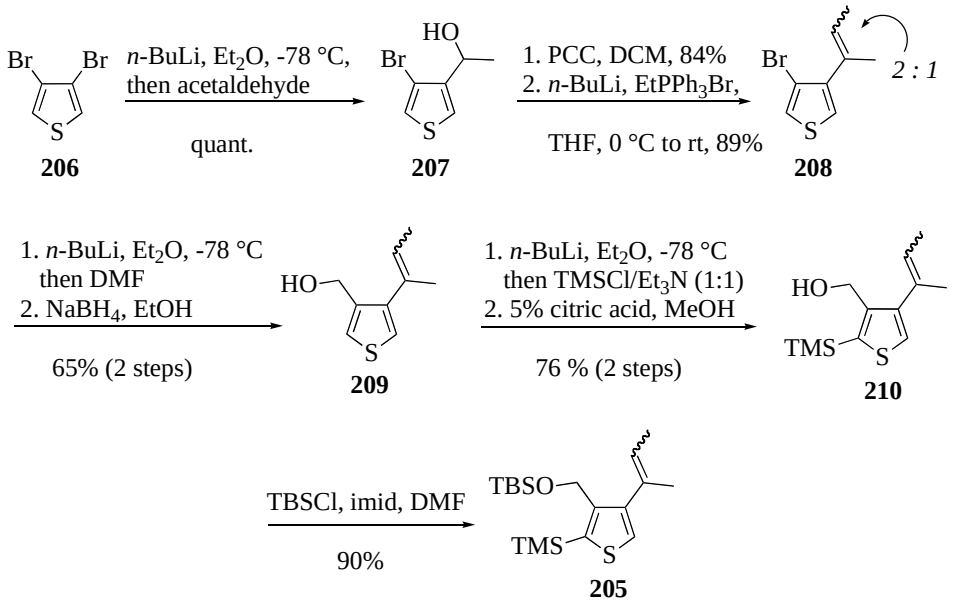


Figure 26. Retrosynthetic analysis of *thio*-halenaquinone (**200**).

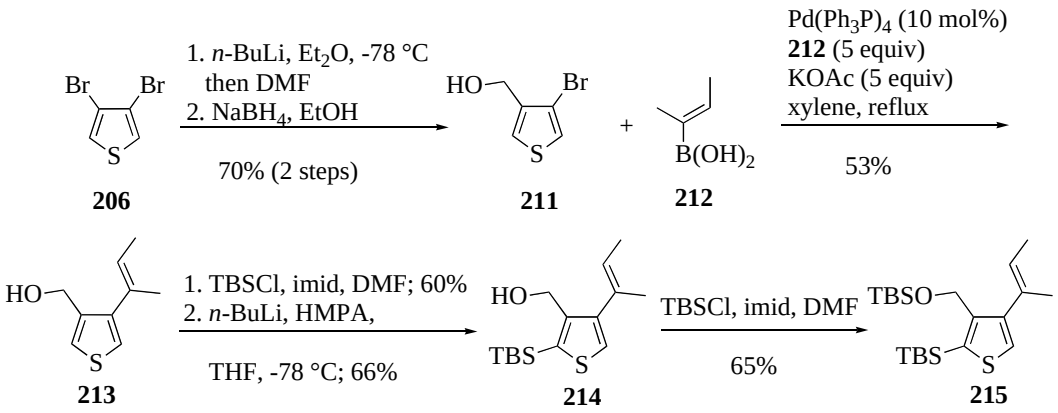
2.2.2 Synthesis of a trisubstituted thiophene fragment

To begin our synthetic efforts towards *thio*-halenaquinone, treatment of 3,4-dibromothiophene with *n*-BuLi and quenching with acetaldehyde gave alcohol **207** in quantative yield (Scheme 25). PCC oxidation and Wittig olefination of the methyl ketone[180] afforded the trisubstituted olefin **208** in 89% yield as a 2:1 mixture of alkene isomers, which were carried on without separation. The thiophene ring was further modified by a bromine-lithium exchange reaction followed by quenching with DMF and subsequent sodium borohydride reduction of the intermediate aldehyde to give 65% of alcohol **209**. The remaing ring substituent was installed by an alkoxide-directed metalation[181] at the 5-position of the thiophene, followed by trapping with TMSCl. The resulting bis-TMS protected compound was treated with citric acid to yield the primary alcohol **210**. Protection of the hydroxyl group with the more robust TBS-ether proceeded in excellent yield to afford the trisubstituted thiophene **205**.



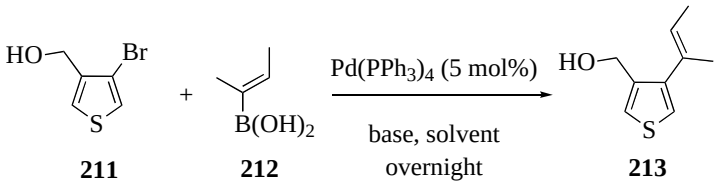
Scheme 25. Synthesis of trisubstituted thiophene **205**.

Although the synthesis of **205** was high yielding, it was lengthy, consisting of 8 steps, and in an attempt to shorten this sequence a Suzuki reaction was employed for the installation of the as a single isomer (Scheme 26). Treatment of **206** with *n*-BuLi and quenching with DMF followed by reduction of the aldehyde with sodium borohydride gave alcohol **211** in 70%. After significant optimization (Table 15), exposure of **211** to 10 mol% $Pd(PPh_3)_4$, 5 equiv of boronic acid **212**[182] and KOAc yielded thiophene **213** as a single olefin isomer in 53% yield. The primary alcohol was protected as the silyl ether and treatment with *n*-BuLi and HMPA facilitated silyl migration from the oxygen to the carbon of the thiophene to give **214**.[170] Protection of the resulting alcohol as the TBS-ether afforded **215**. This route proved to be shorter than the previous synthesis, but it was also less efficient. The yield of the TBS-protections could have been further optimized, but the Suzuki reaction and the conversion from **213** to **214** were not amenable to scale up.



Scheme 26. Synthesis of trisubstituted thiophene **215**.

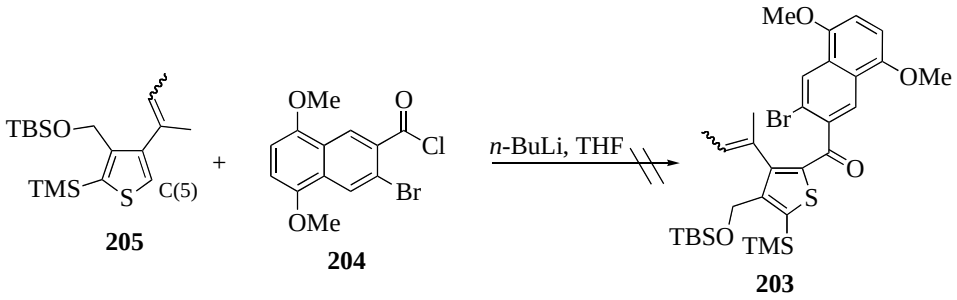
Table 15. Optimization of Suzuki coupling to give **213**.



Entry	Base (equiv)	**212** (equiv)	Solvent	Temp (°C)	Result
1	K_2CO_3 (2)	2	xylenes	130	trace of **213**
2	NaOAc (2)	2	xylenes	130	trace of **213**
3	TlOEt (2)	2	xylenes	130	39%
4	TlOEt (2)	2	THF	rt	Recovered SM
5	TlOEt (2)	2	3:1 THF/H_2O	rt	Recovered SM
6	NaOAc (2)	5	xylenes	130	trace of **213**
7	LiOAc (2)	2	xylenes	130	trace of **213**
8	KOAc (2)	2	xylenes	130	31%
9	AgOAc (2)	2	xylenes	130	dec.
10	NaOEt (2)	2	xylenes	130	trace of **213**
11	NaOAc (2)	2	DMF	130	trace of **213**
12	TlOEt (2)	2	THF	65	trace of **213**
13	TlOEt (2)	2	DMF	130	Recovered SM
14	KOAc (5)	5	xylenes	130	53%
15	KOAc (2)	2	DMF	130	dec.
16	KOAc (2)	2	DME	85	dec.
17	TlOEt (2)	2	DME	85	trace of **213**

2.2.3 First generation approach for the synthesis of the Heck cyclization precursor

Based on work by Keay (Scheme 24), the simplest method for the generation of **203** would be via the addition of metalated **205** to the known acid chloride **204**.[171] However, treatment of **205** with *n*-BuLi followed by addition of **204** did not lead to the desired product but only recovery of the thiophene. Variation of the order of addition did not improve the results. Compound **205** was treated with *n*-BuLi and quenched with D_2O. Dueterium had been incorporated at C(5) as determined by ^1H NMR which confirmed that the anion had been generated. The lack of reactivity of lithitated **205** with the acid chloride could be due to the steric bulk of the trisubstituted olefin at the 4-position.

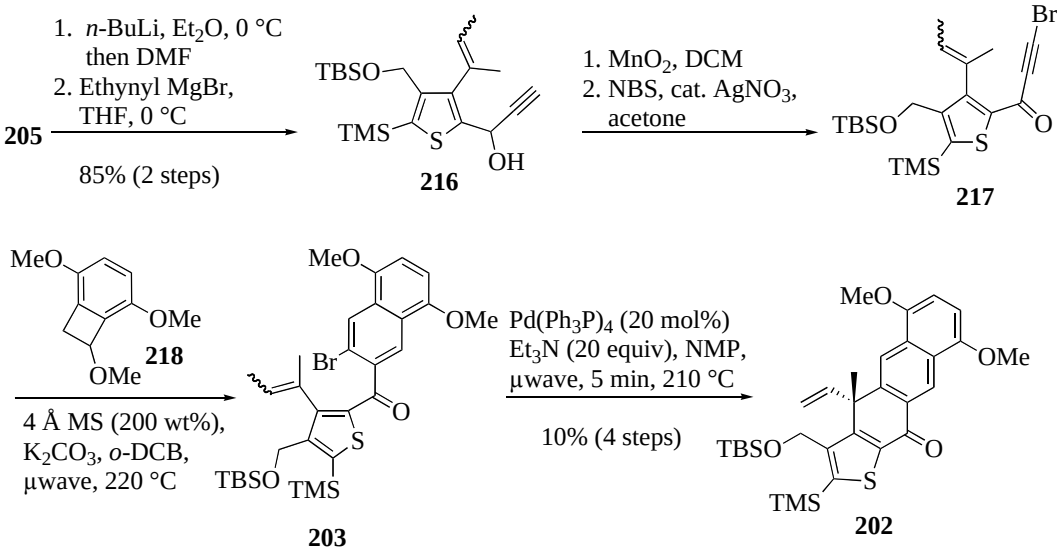


Scheme 27. Attempted addition of **205** to acid chloride **204**.

2.2.4 Diels-Alder approach to the Heck precursor

Due to the steric hindrance near C(5), it was clear that large electrophiles could not be used to install the naphthalene unit of **203**. Instead, the naphthalene moiety could be constructed via a Diels-Alder reaction similar to the method used to synthesize **183**.[172] Metalation at C(5) and introduction of the aldehyde (*n*-BuLi, then DMF) was followed by addition of ethynyl Grignard

reagent to give the desired thiophene **216** in 85% yield from **205** (Scheme 28). Oxidation of thiophene **216** with manganese dioxide and bromination of the alkynyl ketone with NBS in the presence of catalytic silver nitrate[183] provided the Diels-Alder precursor **217**. Microwave irradition in *ortho*-dichlorobenzene (*o*-DCB) was used to mediate the cycloaddition of **217** and benzocyclobutane **218**,[172,184,185] and 4 Å molecular sieves and K_2CO_3 quenched methanol and hydrobromic acid formed during the process. After removal of solvent and other volatiles by distillation, microwave irradiation of a solution of crude **203** in NMP in the presence of 20 mol% $Pd(Ph_3P)_4$ and 20 equiv Et_3N for 5 min at 210 °C gave the desired tetracyclic product 8 in 10% overall yield from **216.** Attempts were made to improve the Heck cyclization by changing the Pd source, solvent, temperature and time; however, the yield was never increased beyond 53% (Table 16). The intermediates in this sequence were not stable to any chromatographic conditions and could not be isolated as pure compounds. Under conventional heating in NMP at reflux, a 36 h reaction time was necessary for the Heck reaction to reach completion.

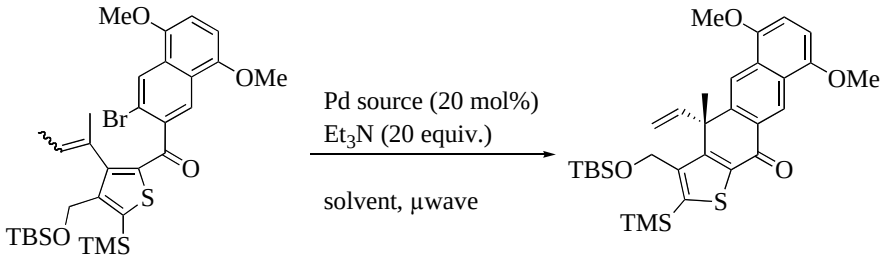


Scheme 28. Diels-Alder-Heck cyclization sequence to give tetracycle **202**.

2.2.5 Completion of the synthesis of *thio*-halenaquinone

After the successful realization of the sequential Diels-Alder – Heck cyclization strategy for the formation of B, C, and E rings of *thio*-halenaquinone, formation of ring A by ring closing metathesis required installing at least an additional two-carbon chain onto intermediate **202**. However, we found that the sequence provided a higher yield of cyclohexene if an allyl group was added instead of the terminal vinyl function. Removal of the silyl-protecting group in **202** with TBAF and oxidation of the primary alcohol gave **219** (Scheme 29). This aldehyde was

Table 16. Optimization of the Heck cyclization.

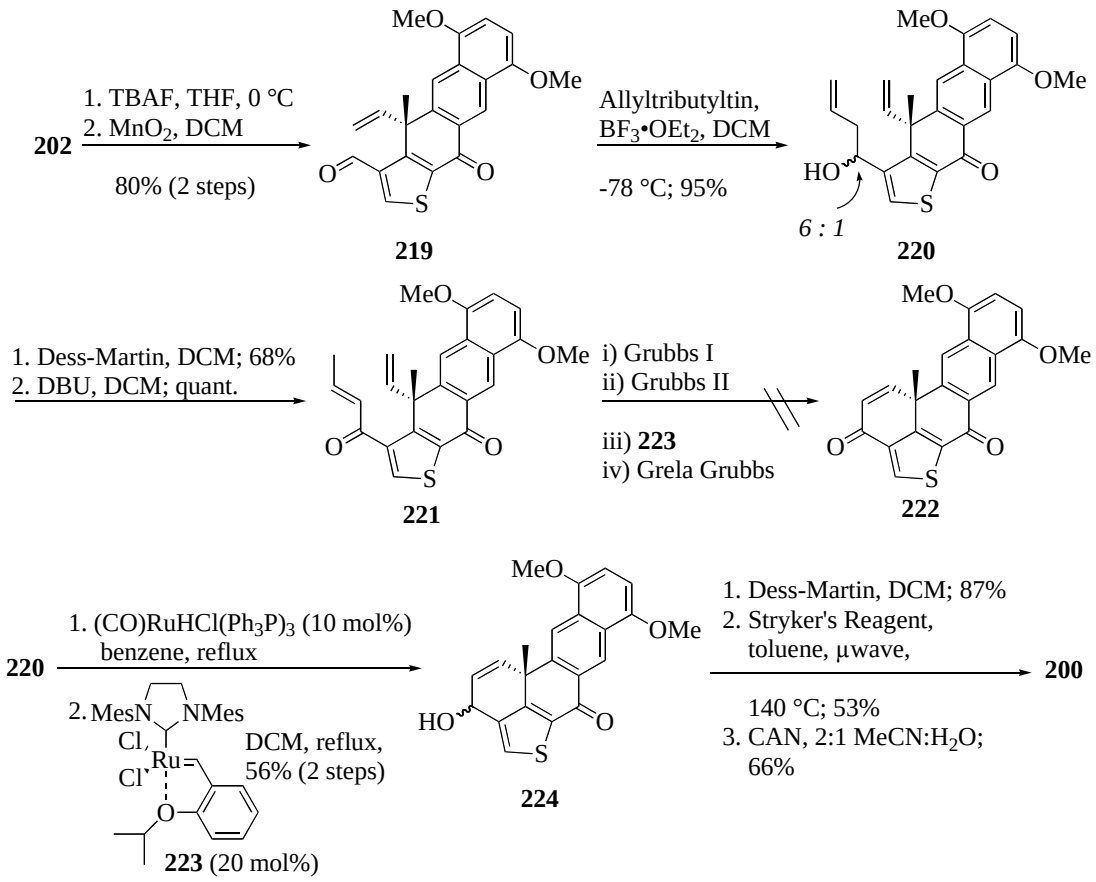


203 **202**

Entry	Pd Complex	Ligand	Solvent	Temp (°C)	Time (min)	Yield
1	$Pd(PPh_3)$	-	NMP	220	30	39%
2	$Pd(PPh_3)$	-	NMP	220	15	48%
3	$Pd(PPh_3)$	-	NMP	220	10	43%
4	$Pd(PPh_3)$	-	*o*-DCB	220	15	33%
5	$Pd(PPh_3)$	-	toluene	170	30	33% conversion of **203**
6	$Pd(PPh_3)$	-	DMF	220	15	48%
7	$Pd(PPh_3)$	-	DMSO	220	15	trace
8	$Pd(PPh_3)$	-	NMP	220	5	53%
9	$Pd(PPh_3)$	-	NMP	220	1	53%
10	$Pd_2(dba)_3$•$CHCl_3$	-	NMP	220	5	10% conversion of **203**
11	$Pd_2(dba)_3$•$CHCl_3$	$(furyl)_3P$	NMP	220	5	dec.
12	$Pd_2(dba)_3$•$CHCl_3$	$^tBu_3P$	NMP	220	5	45%
13	$Pd(P^tBu_3)_2$	-	NMP	220	5	16%
14	$Pd_2(dba)_3$•$CHCl_3$	DPPE	NMP	220	5	55% conversion of **203**

treated with a variety of vinyl organometallics, but difficult to separate product mixtures were obtained in all cases and the desired allylic alcohol could not be isolated in satisfactory yield. Fortunately, treatment with tributylallylstannane in the presence of BF_3•OEt_2[186-188] gave the homoallylic alcohol in 95% yield and a 6:1 diastereoselectivity. The major isomer was not assigned, and the mixture of stereoisomers was carried on without separation. Oxidation of the alcohol with Dess-Martin reagent followed by treatment with DBU gave enone **221**. Exposure of **221** to a variety of metathesis catalysts[189-192] afforded poor mass recovery of the starting material and none of the desired product. As an alternative, the terminal alkene moiety of **220** was readily isomerized in the presence of a Ru-hydride catalyst[193-196] to give the allylic alcohol. Ring closing metathesis with ruthenium catalyst **223**[197,198] afforded cyclohexenol **224** in 56% yield.[199,200] The ring closing metathesis was run at a concentration of 0.006 M to prevent dimerization. Oxidation with Dess-Martin periodane and treatment of the enone with Stryker's reagent[201] afforded the conjugate reduction product. Finally, oxidation of the dimethoxyarene moiety with CAN afforded *thio*-halenaquinone **200**.

In summary, we completed a synthesis of (+/-)-*thio*-halenaquinone in 22 steps and 0.3% overall yield from 3,4-dibromothiophene. Key transformations of this sequence included multiple selective metalations of thiophene hetrocycles to install four different substituents, the Diels-Alder reaction of the highly functionalized alkynyl ketone **217** with benzocyclobutane **218** followed by a Heck cyclization to form the fused B,C,D,E-ring system, and an alkene isomerization - ring closing metathesis reaction to annulate the remaining cyclohexanone. Biological evaluation of **200** along with synthetic intermediates was conducted to determine the Pfnek-1 inhibition profile of these sulfur-containing natural products analogs. Compound **200** was found to be an inhibitor of Pfnek-1 with an IC_{90} value of 2.8-3.9 μM.



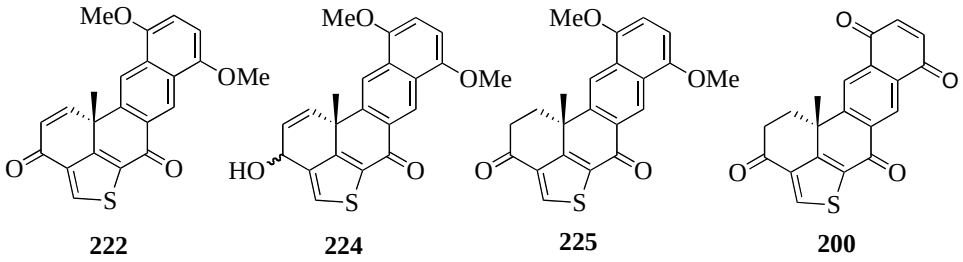
Scheme 29. Alkene isomerization - RCM reaction and completion of the synthesis of *thio*-halenaquinone.

2.3 THE ANTIMALARIAL PROPERTIES OF *THIO*-HALENAQUINONE AND RELATED ANALOGS.

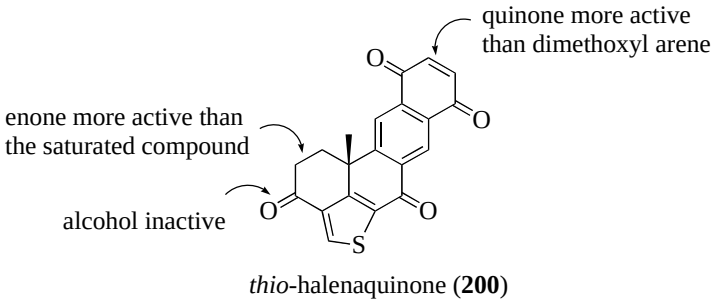
While the synthesis of **200** was gratifying, our biological proposal had not yet been tested. To probe our initial hypothesis, the target compound and several synthetic intermediates were screened for their activity against Pfnek-1 by the Dow laboratory at the Walter Reed Army

Institute of Research (WRAIR) (Table 17).[202-205] Compounds **200** and **222** showed the best activity in this assay with IC_{90} values of 2.8-3.9 and 4.6-6.7 μM, respectively. Compound **225**, which lacks the enone moiety, was inactive, which suggests it is more important for Pfnek-1 inhibition than the quinone. These initial tests provided preliminary structure activity relationship data that guided the development of future analogs.

Table 17. IC_{90} values for **200** and other analogs.



Compound	IC_{90} (μM)
222	2.8-3.9
224	>2500
225	>2500
200	4.6-6.7



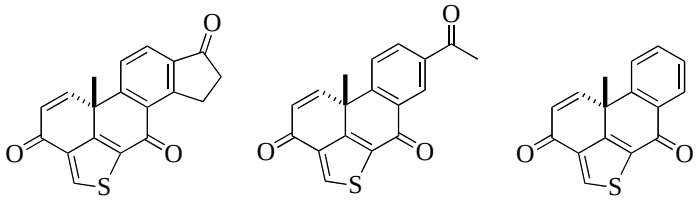
thio-halenaquinone (**200**)

Figure 27. Summary of SAR studies.

2.4 SYNTHESIS OF *THIO*-HALENAQUINONE ANALOGS

2.4.1 Analog selection

Based on the biological results summarized in Table 17, it was decided that new analogs for improved biological activity should be prepared by a synthetic sequence. The targets, **226**-**228**, are closely related to viridin (**191**) and no longer contain the quinone found in **200** since it was shown to not be necessary for Pfnek-1 inhibition (Figure 28). The first analog to be synthesized was **227,** due to the presence of the acetophenone function, which is similar to the carbonyl group found on the D-ring of viridin, wortmannin and *thio*-halenaquinone. Furthermore, the methods developed for the synthesis of **200** should be readily transferred to this target.



226 **227** **228**

Figure 28. Three new analogs of *thio*-halenaquinone.

2.4.2 Retrosynthetic analysis of analog 227

A retrosynthetic analysis of **227** is shown in Figure 29. We envisioned the installation of the A-ring from an alkene isomerization followed by the ring closing metathesis of **229**. The key tricyclic intermediate **230** would arise from a Heck cyclization to install the quaternary center.

Addition of **231** to aldehyde **232** would afford the cyclization precursor. The functionalized aromatic ring could be easily derived from 4-hydroxyacetophenone.

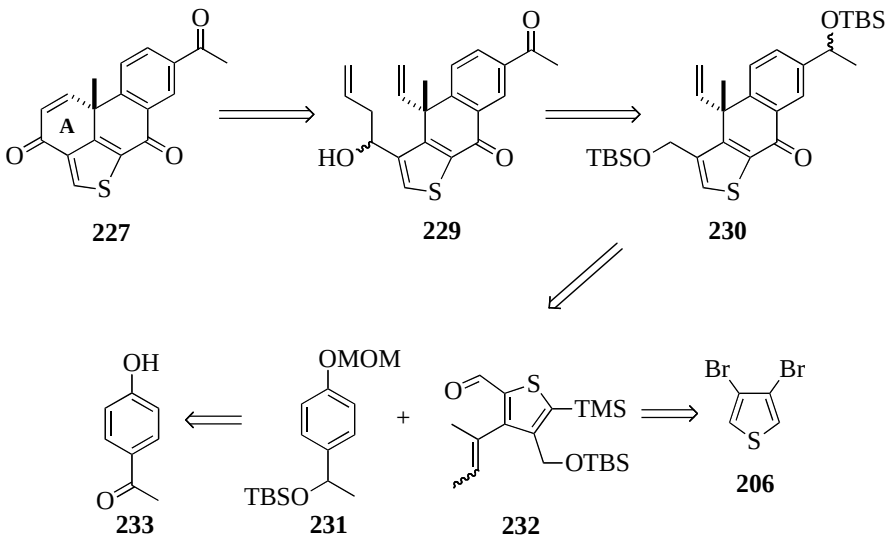
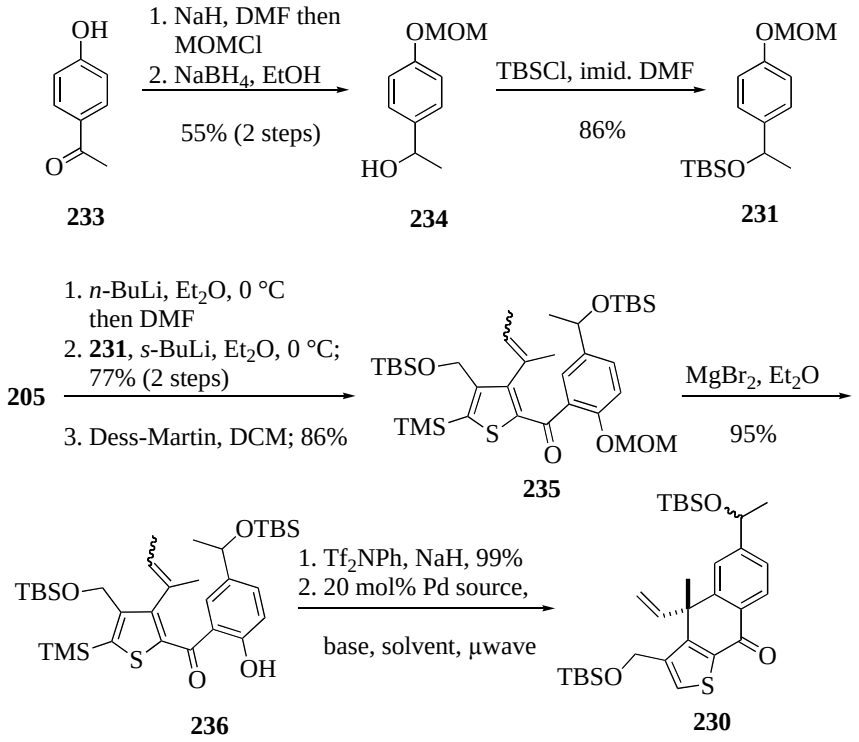


Figure 29. Retrosynthetic analysis of analog **227**.

2.4.3 The attempted synthesis of analog 227

Treatment of 4-hydroxyacetophenone with sodium hydride, quenching with MOMCl and subsequent reduction with sodium borohydride gave alcohol **234** in 55% yield (Scheme 30). Protection of the benzylic alcohol as the TBS-ether gave **231**. Metalation of **205** at C(5) and introduction of the aldehyde was followed by addition of lithiated **231** and oxidation of the resulting alcohol afforded **235**. Removal of the MOM-ether with $MgBr_2$ afforded the free phenol **236**. Introduction of the triflate followed by Heck cyclization did not afford the desired tricycle in high yield (Table 18). The cyclization only yielded trace amounts of product and significant amounts of reduced starting material. Even after significant optimization varying the palladium

source, ligands, base and solvent, the efficiency of this reaction could not be improved. Due to the poor yield of the Heck cyclization, the synthesis of this analog was abandoned.



Scheme 30. Synthesis of **215** and failed route to analog **206**.

2.4.4 Retrosynthetic analysis of analog 228

After abandoning the synthesis of **227**, we turned our focus toward constructing **228**. This compound contains the same core as **200** and **227** but lacks the ketone function, which should simplify the synthesis while maintaining biological activity. The retrosynthetic analysis of **227** is shown in Figure 30. As before, we envisioned the construction of the A-ring though an alkene isomerization and ring closing metathesis of **237**. The quaternary center could be installed by a

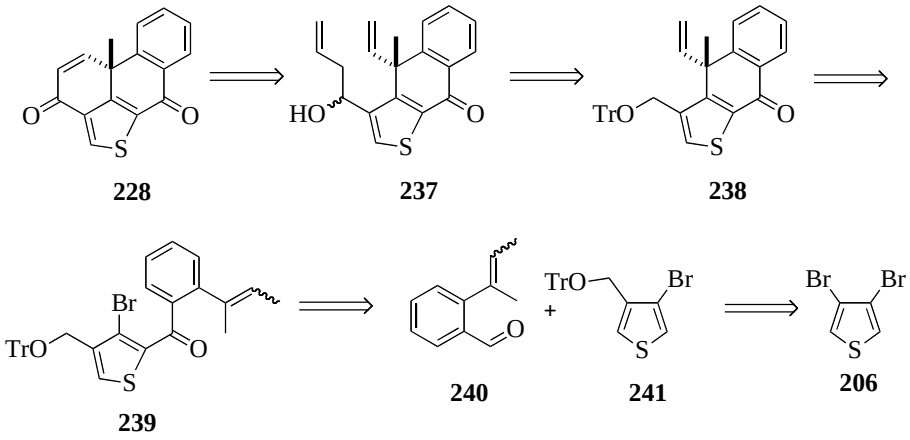
Heck cyclization of **239**. Selective metalation of thiophene **241**[206] and addition to **240** would afford the cyclization precursor. The previous synthesis of the thiophene fragment required eight

Table 18. Conditions for the Heck cyclization to form **230**.

Entry	Pd Complex	Ligand	Base (equiv)	Solvent	Temp (°C)	Time (min)	Yield of **230**/ Result
1	$Pd(PPh_3)$	-	Et_3N (20)	NMP	220	5	trace of **230**
2	$Pd(PPh_3)$	-	Et_3N (20)	THF	120	10	trace of **230**
3	$Pd(PPh_3)$	-	Et_3N (20)	NMP	200	5	trace of **230**
4	$Pd(PPh_3)$	-	Et_3N (20)	toluene	170	5	trace of **230**
5	$Pd(OAc)_2$	dppb	K_2CO_3 (3)	toluene	170	5	trace of **230**
6	$Pd(OAc)_2$	dppb	K_2CO_3 (3)	toluene	170	30	trace of **230**
7	$Pd(OAc)_2$	dppp	K_2CO_3 (3)	toluene	150	5	trace of **230**
8	$Pd(OAc)_2$	dppp	K_2CO_3 (3)	toluene	170	30	trace of **230**
9	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	toluene	170	5	trace of **230**
10	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	THF	120	30	17%
11	$Pd(OAc)_2$	dppp	K_2CO_3 (3)	THF	120	30	-
12	$Pd(OAc)_2$	dppb	K_2CO_3 (3)	THF	120	30	-
13[a]	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	THF	120	30	-
14	$Pd(OAc)_2$	dppf	K_2CO_3 (3)	THF	120	30	-
15	Pd_2•dba_3	BINAP	K_2CO_3 (3)	THF	120	30	trace of **230**
16	$Pd(P^tBu_3)_2$	BINAP	K_2CO_3 (3)	THF	120	30	trace of **230**
17	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	NMP	120	30	trace of **230**
18	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	120	30	34%
19	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMSO	120	30	trace of **230**
20	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	120	10	low conversion
21	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	160	2	25%
22	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	120	15	low conversion
23	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	160	1	28%
24	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	140	2	low conversion
25	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	150	2	low conversion
26	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	155	1	Mixture
27	$Pd(OAc)_2$	BINAP	Cs_2CO_3 (3)	DMA	160	1	28%
28	$Pd(OAc)_2$	BINAP	Li_2CO_3 (3)	DMA	160	1	low conversion
29	$PdCl_2$	BINAP	K_2CO_3 (3)	DMA	160	1	Starting Material
30	PdI_2	BINAP	K_2CO_3 (3)	DMA	160	1	trace of **230**
31	$Pd(OAc)_2$	$(furyl)_3P$	K_2CO_3 (3)	DMA	160	1	-
32[b]	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	95	120	trace of **230**
33[b]	$Pd(OAc)_2$	BINAP	K_2CO_3 (3)	DMA	95	240	trace of **230**
34[b]	$Pd(PPh_3)_4$	-	K_2CO_3 (3)	DMA	95	240	trace of **230**

[a]2 eq KBr added [b]conventional heating

steps and multiple protecting groups; in this new route the functionalized thiophene intermediate is synthesized in only three steps from **206**.



228 **237** **238**

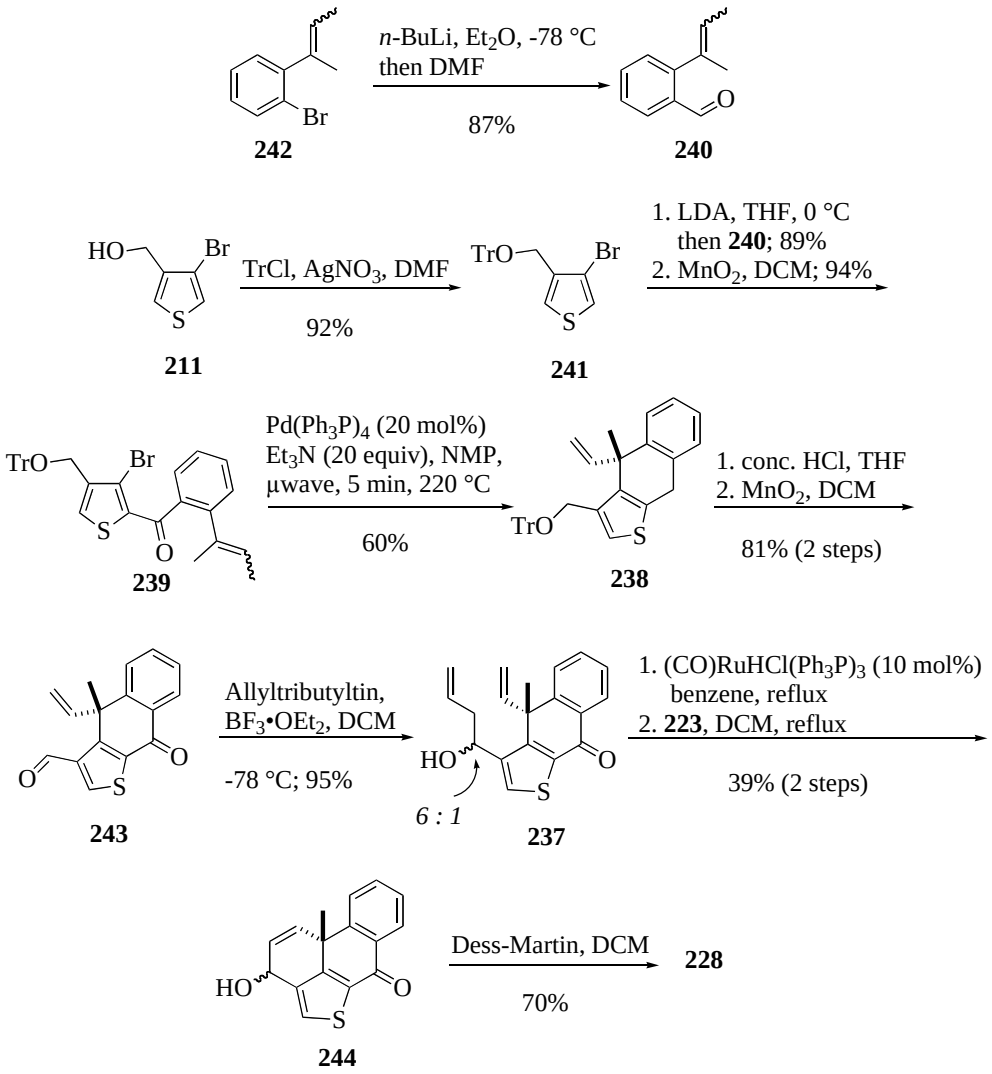
239 **240** **241** **206**

Figure 30. Retrosynthetic analysis of analog **228**.

2.4.5 Synthesis of analog 228

Aldehyde **240** was synthesized by bromine-lithium exchange of known **242**[207] and quenching with DMF (Scheme 31). Protection of alcohol **211** with TrCl afforded **241** in 92%. Selective metalation the 5-position with LDA followed by addition to **240** and oxidation with manganese dioxide gave **239** in excellent yield. Microwave irradiation of a solution of **239** in NMP in the presence of 20 mol % $Pd(PPh_3)_4$ and 20 equiv Et_3N for 5 min at 220 °C afforded the desired tricylic product in 60% yield. Removal of the trityl group in **238** with concentrated HCl and oxidation of the primary alcohol yielded aldehyde **243**. Treatment with tributylallylstannane in the presence of BF_3•OEt_2[186-188] gave homoallylic alcohol **237** in 95% yield in a 6:1 diastereoselectivity. The terminal alkene moiety was isomerized in the presence of a Ru-H catalyst[193-196] to give the allylic alcohol. Ring closing metathesis with ruthenium catalyst **223**[197,198] afforded cyclohexenol **244** in a disappointing 39% yield, and oxidation to the ketone

with Dess-Martin periodinane gave **228** in 70% yield. This synthesis was completed in 12 steps and 6.8% overall yield from 3,4-dibromothiophene.



Scheme 31. Synthesis of analog **228**.

It is interesting to note that treatment of **228** with 10 equiv of diallylamine or thiophenol in DCM for 24 h, does not lead to nucleophilic addition to the thiophene. Even heating the reaction to reflux for 2 h does not give the thiophene addition product by NMR. This is in stark

contrast to wortmannin which readily undergoes addition of these nucleophiles in less than 1 h at 0 °C to room temperature.[174] This results helps to verify our hypothesis that replacement of the furan with a thiophene would reduce the electrophility of this core.

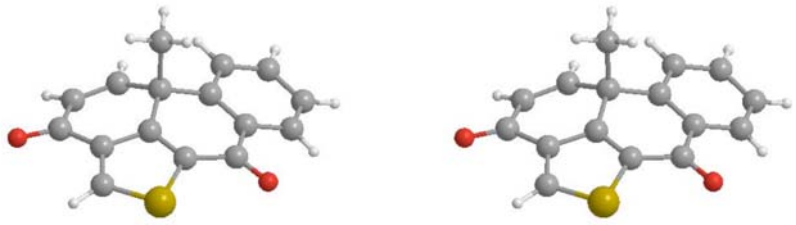


Figure 31. X-ray crystal structure of **228**.

2.4.6 Rationale for the allylation selectivity

The allylation of compounds **220** and **243** with allyltributyltin proceeded with a diastereoselectivity of 6:1, which indicated that the remote quaternary carbon center influenced the approach of the allyl metal reagent. Transition states **245** and **247** show the antiperiplanar orientation of the allylstannane, both should be disfavored due to strong steric interactions between the tin and the quaternary carbon center (Figure 32). These interactions can be avoided if the reaction takes place via the synclinal transition state, **249** and **250**. Approach of the allyl metal syn to the vinyl moiety would give the observed major product, transition state **250**. Rotation of the aldehyde about the single bond and placing oxygen toward the quaternary center is illustrated in models **251**-**254**. In these transition states, there is no clear bias for attack of the aldehyde, which should lead to low selectivity. These transition states may also be disfavored due to steric interactions between the carbon center and the solvated lewis acid. Due to the high

observed selectivity and a minimization of steric interactions, the reaction seems to proceed through transition state **250**.

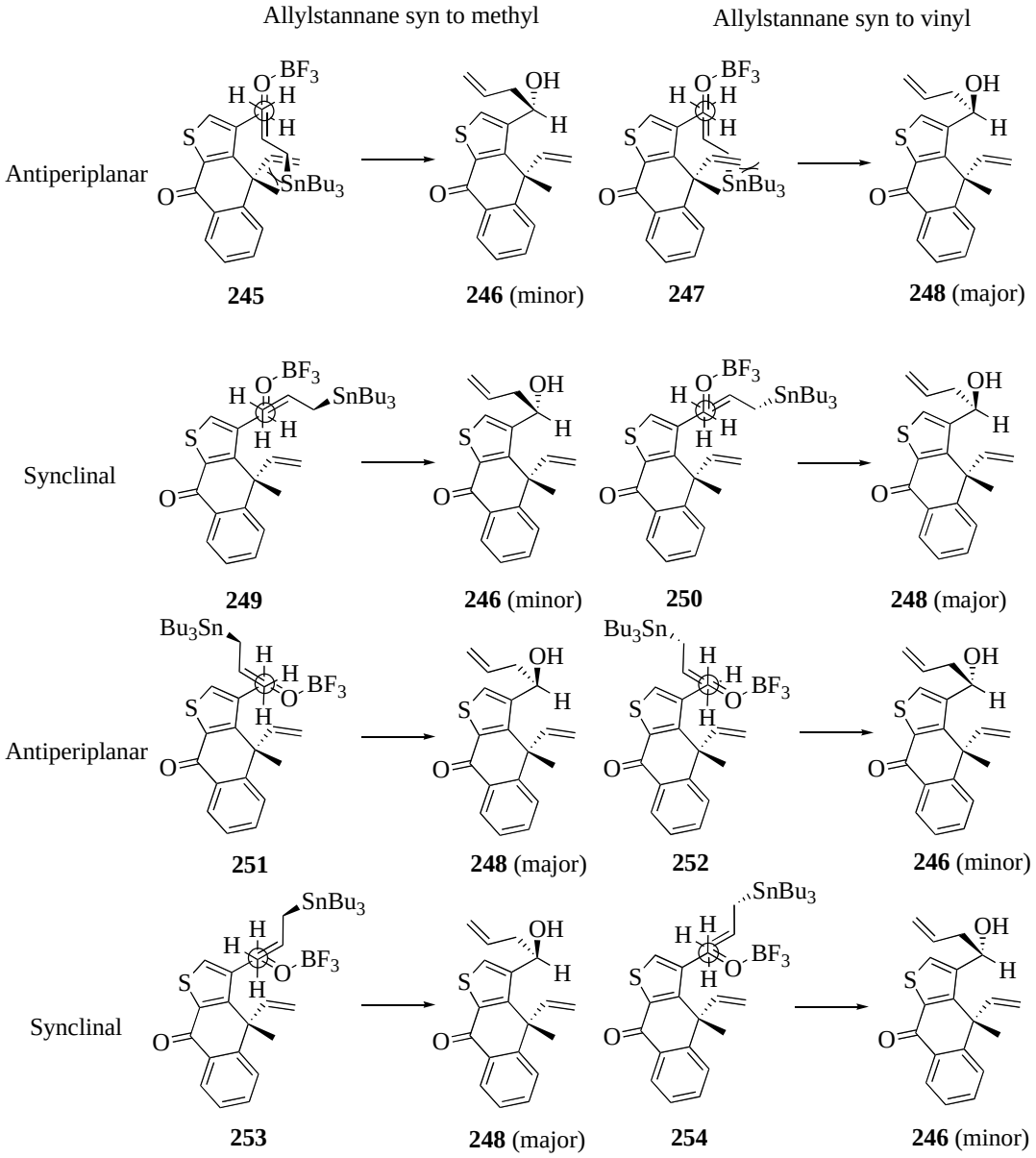
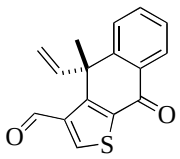


Figure 32. Possible transition states for the allylation of **222.**

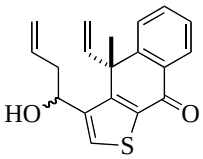
2.4.7 Pfnek-1 inhibtion properties of *thio*-halenaquinone analog 228 and related compounds

Compound **228** and the related compounds **237** and **243** generated during the synthesis were tested for their inhibition of Pfnek-1 by the Dow laboratory at WRAIR (Table 19).[202-205] Compound **228** had an IC_{90} of 3.0-5.3 μM which is similar to that of *thio*-halenaquinone. This supports our hypothesis that the quinone or dimethoxy arene are not needed for biological activity. The two other compounds screened, **237** and **243**, showed lower activity, which was expected since they do not contain the cyclohexenone moiety. Furthermore, **228** showed an selectivity index of 5.1, which is similar to that of 7 by xestoquinone (**136**). Though compound **237** had good activity, it was not taken forward since no other compound without the final cyclohexanone moiety was active and the data may have been an artifact of the assay. Based on this data, **228** was selected to move into animal testing and 200 mg of the compound was required.

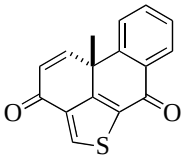
Table 19. Pfenk-1 inhibition by **228** and related compounds.



243



237



228

Compound	IC_{90} (μM)	Seletivity Index
243	>5200	-
237	8.4-14.5	>10
228	3.0-5.3	5.1

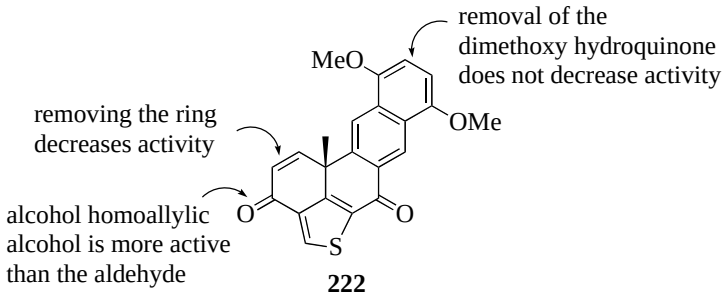


Figure 33. Summary of SAR studies.

2.5 SECOND-GENERATION APPROACH AND SCALE-UP OF ANALOG 228

The isomerization and ring closing metathesis sequence in the synthesis of **228** was very low yielding. Careful monitoring of the isomerization reaction by NMR showed the generation of a major unidentified side product. Varying the reaction temperature, time, and catalyst batch did not eliminate this side product. As in the synthesis of **200**, addition of vinyl metal reagents led to product mixtures that were difficult to separate and the desired allylic alcohol could not be isolated in satisfactory yield. A new route was required to allow for the rapid access to the quantity of material needed for animal testing.

2.5.1 Second-generation retrosynthetic analysis of analog 228

The retrosynthetic analysis of analog **228** is shown in Figure 34. The A-ring could be introduced by ring closing metathesis of **255**. The key tricylic intermediate **256** will be derived from a Heck cyclization. The precursor for this cyclization could be arrived at by selective metalation of **258** and addition to **240**. Thiophene **258**, which already contains the olefin required for the ring closing metathesis, could be synthesized from **206**.

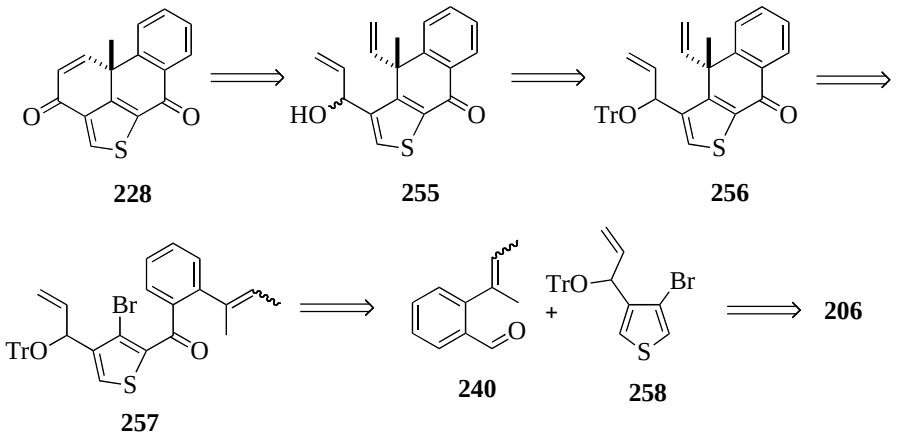
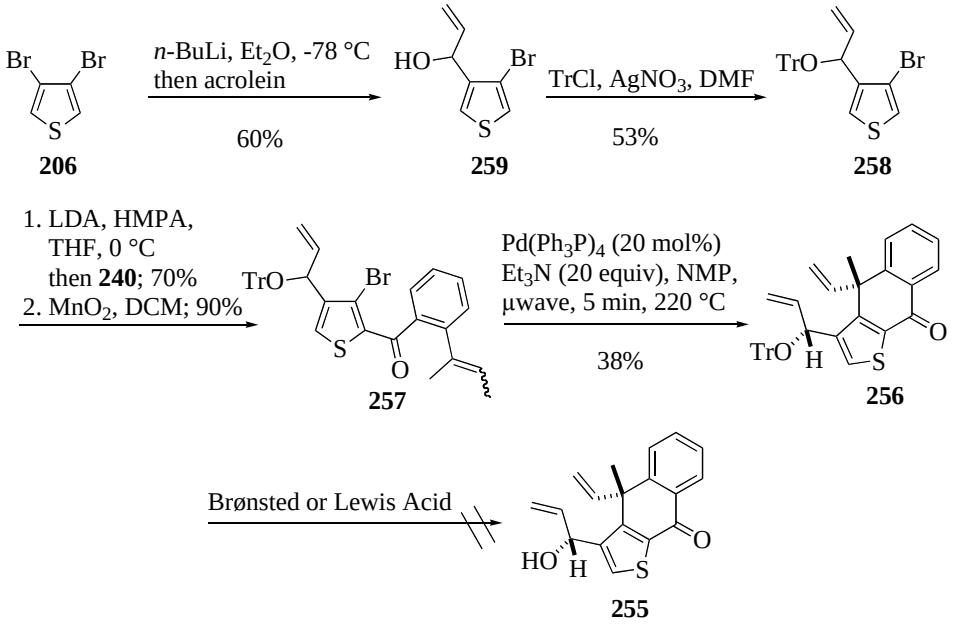


Figure 34. Second-generation retrosynthesis of analog **228**.

2.5.2 Attempted second-generation synthesis of analog 228

Treatment of **206** with *n*-BuLi and quenching with acrolein afforded alcohol **259** in 60% yield. Protection of the hydroxyl group with TrCl gave **258** in 53% yield (Scheme 32).[208] Selective metalation at the 5-position with LDA and HMPA, and addition to **240** followed by manganese dioxide oxidation gave ketone **257**. Subjecting **257** to the previously developed Heck cyclization conditions afforded tricycle **256** in 38% yield. Surprisingly, there was only a single diastereomer isolated from the reaction and the relative configuration was determined by X-ray crystallography (Figure 35). Treatment of **256** with Brønsted or Lewis acids did not afford the desired deprotected product. The material isolated from the reaction of **256** with Brønsted acid resulted from the generation of a cation at the benzylic position of the thiophene. Lewis acids only resulted in recovered starting material from the reaction mixtures. To circumvent this problem, we attempted the ring closing metathesis with the protecting group in place; however, only starting material was recovered.



Scheme 32. Attempted second-generation synthesis of analog **228**.

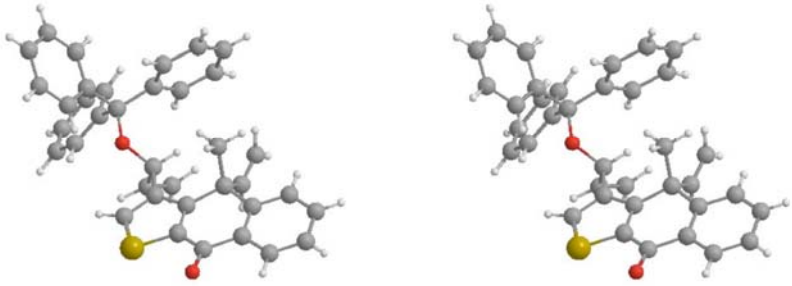
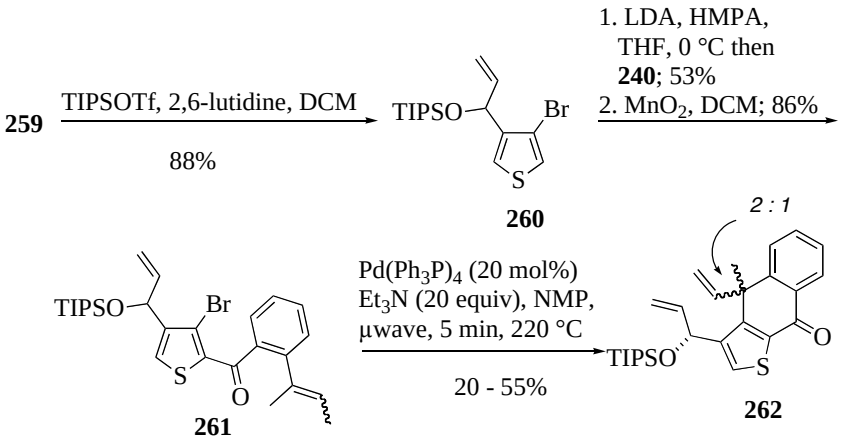


Figure 35. X-ray crystal structure of **256**.

2.5.3 Second-generation synthesis of analog 228 with TIPS-protected alcohol

Because the trityl group of **256** could not be removed, a TIPS-ether, which is similarly large and would shield the 2-position from deprotonation yet could be removed with TBAF or another basic fluoride source, was employed instead. Protection of **259** as the TIPS-ether succeeded in

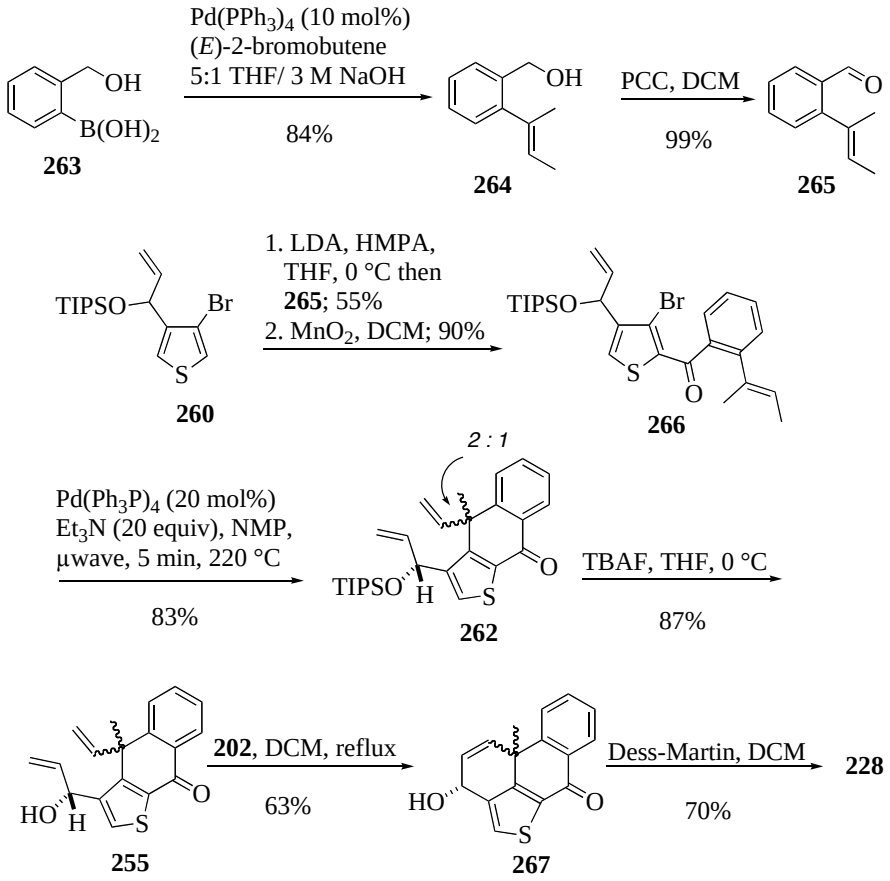
88% yield (Scheme 33). Selective metalation and addition to **240** followed by oxidation with manganese dioxide gave ketone **261**. Microwave irradiation of a solution of **261** in NMP in the presence of 20 mol % of $Pd(Ph_3P)_4$ and 20 equiv of Et_3N gave a tricycle in 20-55% yield as a 2:1 mixture of diastereomers. The yield was greatly impacted by the *E*/*Z* ratio of the olefin in **261**. After multiple purifications, a sample of the pure major isomer of **261**, the (*Z*)-alkene, was isolated and subjected to the cyclization conditions; however, surprisingly no product was observed.



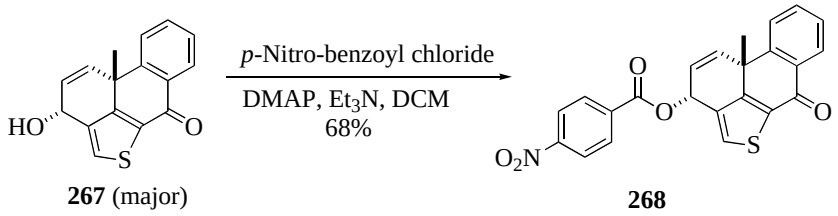
Scheme 33. Progress toward **228**: Heck cyclization with a mixture of olefin isomers.

Since the major olefin isomer did not undergo cyclization, **261** could no longer be prepared as a mixture. Suzuki cross-coupling of commercially available **263** with (*E*)-2-bromobutene gave alcohol **264** in 84% yield (Scheme 34). Oxidation with PCC yielded the aldehyde as a single (*E*)-olefin isomer. Addition of **260** to the aldehyde and oxidation gave the cyclization precursor. Exposure of **266** to the Heck conditions gave the tricyle in 83% yield as a 2:1 mixture of diastereomers at the newly formed quaternary carbon center. Removal of the silyl-protecting group in **262** with TBAF proceeded in 87% yield. Ring closing metathesis with

223 afforded cyclohexenol **267** in a 3:1 ratio of diastereomers and 63% combined yield. The relative stereochemistry of the major isomer was determined by X-ray crystallography (Figure 36) after derivativization (Scheme 35). Oxidation with Dess-Martin periodinane gave enone **228** in 70% yield. This route was used to produce 200 mg of this analog for biological testing in 8 linear steps and 8.3% yield from 3,4-dibromothiophene.



Scheme 34. Heck cyclization with a single olefin isomer and completion of the synthesis of **228.**



267 (major) **268**

Scheme 35. Convertion of the major isomer of **255** to **268**.

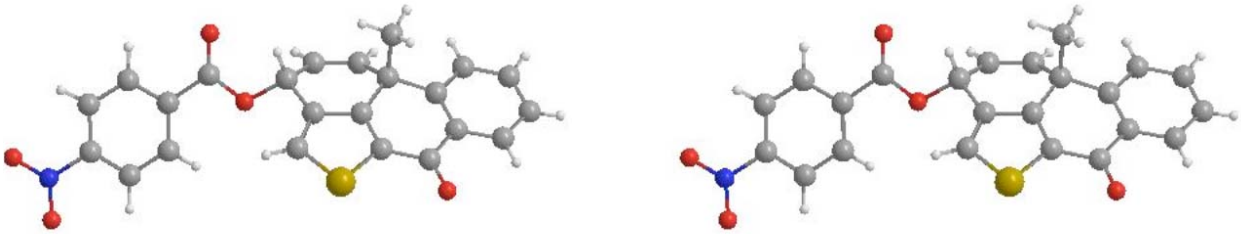


Figure 36. X-ray crystal structure of **268**.

2.5.4 Rationale for the Heck selectivity

The Heck cyclization to form compounds **256** and **262** was interesting due to the fact that only one olefin isomer was reactive and that the reaction was diastereoselective, which can be rationalized by a conformation of the secondary alcohol that minimizes $A_{1,3}$ strain and comparing the four possible transition states (Figure 37). In transition state models **269** and **271**, the olefin coordinates palladium from the same face of the thiophene as the protected alcohol. This approach is disfavored due to strong steric interactions with the large protecting groups (trityl and TIPS) on the alcohol. These problematic interactions are avoid by coordination from the opposite face of the thiophene ring is shown in **273** and **274**. Although transition state **273** minimizes the interaction of the olefin and the protected alcohol, the methyl groups on the olefin are placed directly under the thiophene ring, which would be disfavored due to steric considerations. In model **274**, the olefin is coordinated opposite to the large protecting group

and the olefinic methyl groups are orientated away from the thiophene resulting in the least sterically-encumbered transition state model and leading to the major observed diastereomer. When the alcohol is protected as the TIPS-ether, the olefin is able to coordinate palladium from the same face as the alcohol as shown in **271**, giving rise to the minor isomer, **272**. The *Z*-olefin may not be reactive since there is no way in which it can coordinate to palladium that eliminates the steric interactions between the substitutent at the 4-position of the thiophene and both methyl groups of the olefin as seen in structures **275** and **276**.

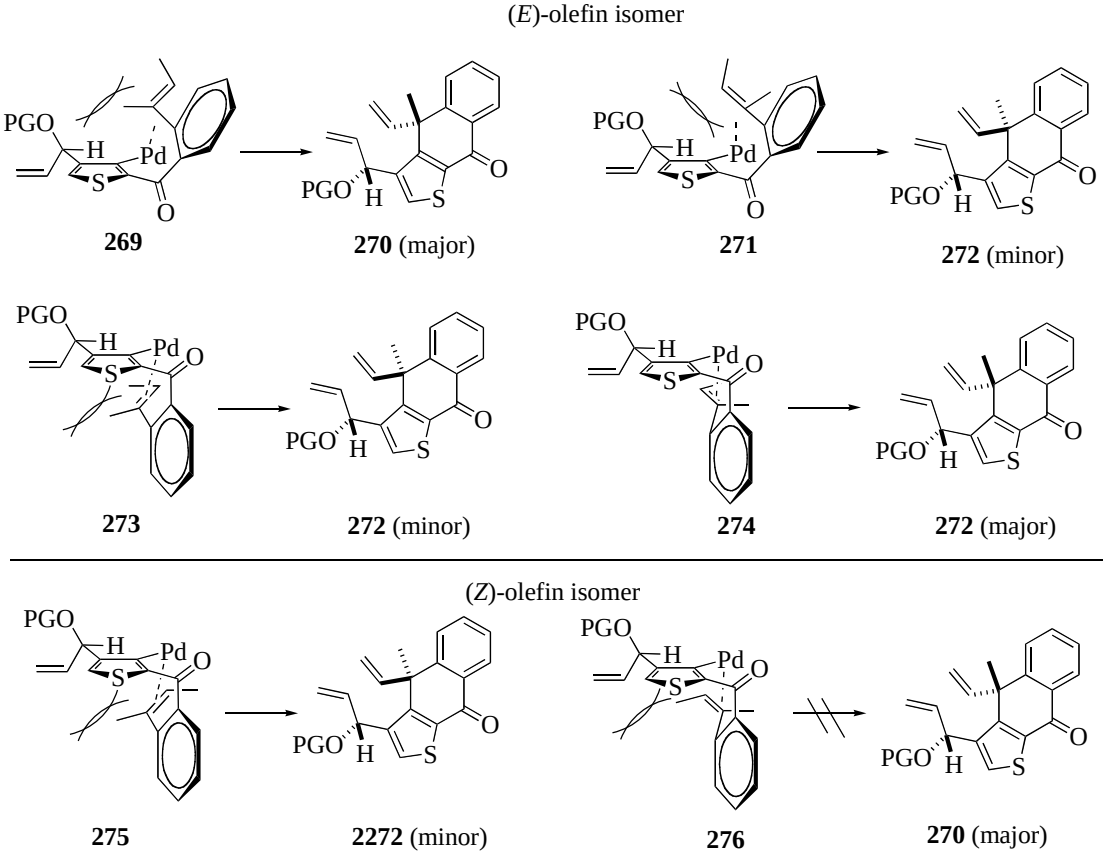
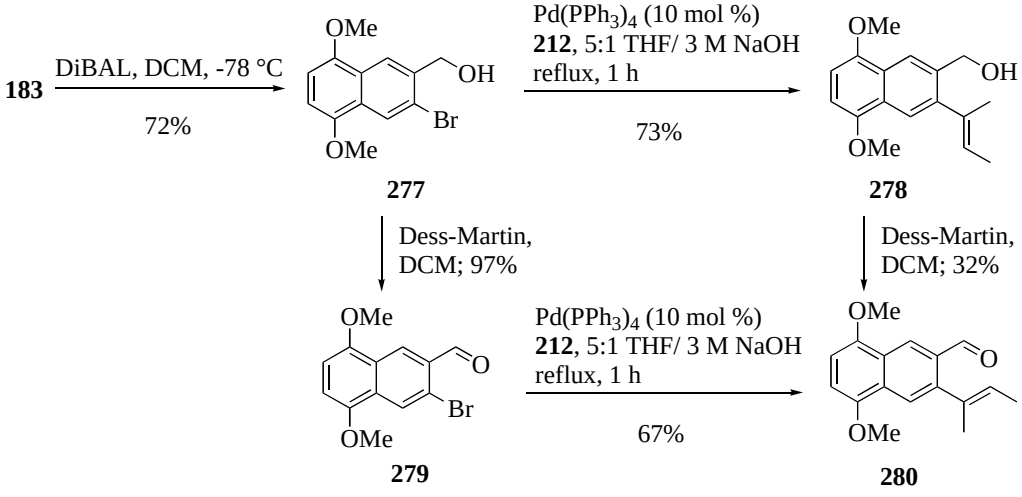


Figure 37. Possible transition states for the Heck cyclization.

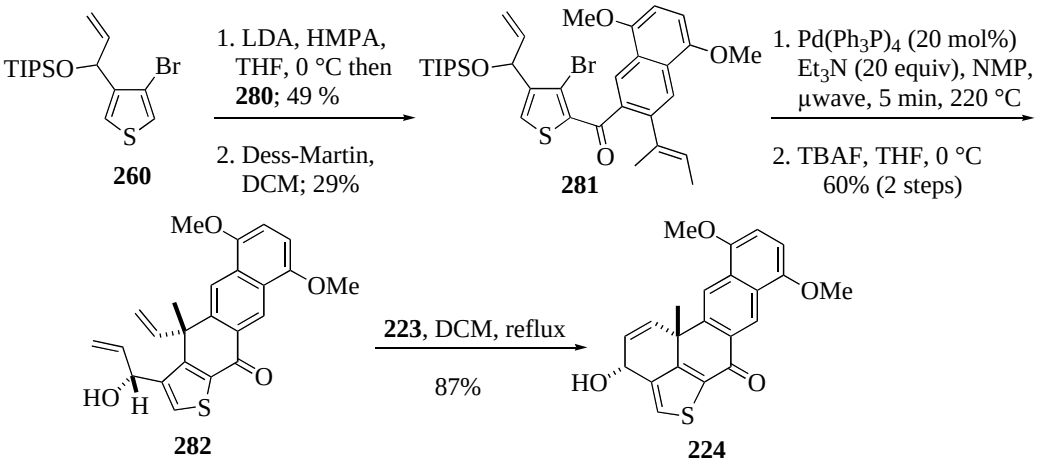
2.6 SECOND GENERATION APPROACH TO *THIO*-HALENAQUINONE

After completing the scale-up of **228**, we decided to revisit the synthesis of *thio*-halenaquinone and apply what we had learned by synthesizing this analog on scale to improve the route. We proposed a formal total synthesis of *thio*-halenaquinone via the synthesis of **200** from key intermediate cyclohexenol **224**. The retrosynthesis is identical to that shown in Figure 27, however thiophene **260** replaced **258** and a functionalized naphthalene replaced **240**. The second-generation approach began with the reduction of known naphthalene **163**[171,172] with DiBAL to afford the alcohol (Scheme 36). Suzuki cross-coupling with boronic acid **212** proceeded in 73% yield. Unfortunately, the subsequent oxidation to aldehyde **280** proceeded in low yield. Switching the order of the oxidation and coupling steps could avoid this low yielding step and oxidation of **277** with Dess-Martin periodane proceded in excellent yield. Finally, installation of the trisubstituted olefin via a Suzuki reaction gave the desired naphthalene **280** in 67% as a single olefin isomer.



Scheme 36. Synthesis of aldehyde **280**.

With the aldehyde in hand, the synthesis of **224** started by treatment of **260** with LDA and HMPA and addition to **280** followed by oxidation to give ketone **281** under unoptimized conditions (Scheme 37). Gratifyingly, the Heck cyclization and removal of the silyl ether gave the desired tetracycle in 60% yield over 2 steps as a 2:1 mixture of diastereomers at the newly formed quaternary carbon center. Ring closing metathesis with **223**[197,198] afforded cyclohexenol **224** in a 3:1 ratio of diastereomers in 87% combined yield. The coupling constants of the vinyl protons for the major diastereomer match those of the major isomer of **267** exactly, allowing for the relative stereochemistry to be assigned as shown. The route to this intermediate is nine steps shorter than the previous synthesis, reducing the total synthesis from 22 to 13 steps and eliminating the low yielding Heck-Diels-Alder sequence. The overall yield of this new sequence could be further improved by optimizing the aldehyde addition and oxidation steps.



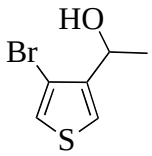
Scheme 37. Second generation synthesis of cyclohexenol **224**.

2.7 CONCLUSION

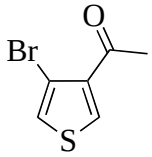
We were able to realize the synthesis of *thio*-halenaquinone and several analogs and evaluate their Pfnek-1 inhibitor profiles. The synthesis of **200** was completed in 13 steps and 0.6% overall yield from 3,4-dibromothiophene. Key transformations of this sequence included multiple selective metalations of thiophene hetrocycles to install four different substituents, the Diels-Alder reaction of the highly functionalized alkynyl ketone **217** with benzocyclobutane **218** followed by a Heck cyclization to form the tetracyclic B,C,D,E-ring system, and an alkene isomerization - ring closing metathesis reaction to annulate the remaining cyclohexanone. This compound was found to have an IC_{90} of ~5 μM while compound **222** had a ~3 μM IC_{90} against Pfnek-1. Based on this data, we embarked on the synthesis of **228**, a simplified analog. We completed the initial synthesis in 12 linear steps from 3,4-dibromothiophene in 6.8% yield. The key steps in this sequence were a directed metalation of a functionalized thiophene and subsequent aldehyde addition, Heck cyclization to form the tricylic core and an alkene isomerization – ring closing metathesis reaction to construct the final cyclohexenone. This compound was found to possess an IC_{90} of ~4 μM and was selected to move into animal studies. A new, more scalable route was developed which allowed access to 200 mg of material in 8 linear steps and 8.3% overall yield from 3,4-dibromothiophene. The biological evaluation of this compound at the WRAIR is still ongoing.

2.8 EXPERIMENTAL SECTION

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. CH_2Cl_2 was dried by distillation over NaH. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated SiO2 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 or 210 nm UV light or by staining with an anisaldehyde solution (7.5mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ^{o}C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublet, ddd= doublet of doublet of doublet, dt=doublet of triplet, dq=doublet of quartet, qq=quartet of quartet, m=multiplet, b=broad, a=apparent). Microwave reactions were conducted using the Biotage Initiator microwave system (absorption level set to “very high”). Infrared spectra were measured on a Nicolet AVATAR 360 FTIR E.S.P. spectrometer. Mass spectra were obtained on a double focusing instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 ^{o}C.

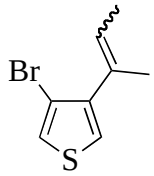


1-(3-Bromo-4-thienyl)-ethanol (207). To a solution of 9.9 g (41 mmol) of **206** in 50 mL of Et_2O at –78 °C was added 20 mL (42 mmol) of a 2.1 M solution of *n*-BuLi in hexanes. The resulting mixture was stirred for 15 min, then 20 mL (360 mmol) of acetaldehyde was added. The solution was stirred for 15 min, warmed to rt, and treated with a saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by Kugelrohr distillation at 75 °C and 0.5 Torr provided 8.4 g (quant.) of **207** as a clear, colorless oil: IR (film) 3351, 3109, 2974, 2927, 1521, 1369 cm^{-1}; ^1H NMR δ 7.30 (dd, 1 H, *J* = 3.3, 0.6 Hz), 7.28 (d, 1 H, *J* = 3.6 Hz), 4.99 (q, 1 H, *J* = 6.3 Hz), 1.97 (bs, 1 H), 1.55 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 144.9, 123.4, 121.1, 109.6, 65.7, 23.3; MS (EI) *m/z* (rel intensity) 208 (35), 206 (M^+, 35), 193 (75), 191 (80), 165 (17), 163 (20), 83 (100); HRMS (EI) Calcd for C_6H_7OSBr 205.9400, found 205.9403.

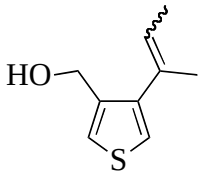


1-(3-Bromo-4-thienyl)ethanone.[180] To a suspension of 22 g of celite and 17 g (79 mmol) of PCC in 100 mL of DCM in a 3-neck flask equipped with a mechanical stirrer was added 11 g (53 mmol) of **207** in 30 mL of DCM. The suspension was stirred for 2.5 h, filtered through a plug of SiO_2, which was washed repeatedly with DCM, and the combined filtrates were concentrated *in vacuo*. Purification by Kugelrohr distillation at 80 °C and 0.5 Torr provided 9.2 g (84%) of 1-(3-

bromo-4-thienyl)-ethanone as a clear oil: IR (film) 3104, 1684, 1488, 1416, 1370, 1227 cm^{-1}; ^1H NMR δ 8.03 (d, 1 H, *J* = 3.6 Hz), 7.33 (d, 1 H, *J* = 3.3 Hz), 2.61 (s, 3 H); ^{13}C NMR δ 191.4, 138.7, 133.8, 125.5, 109.4, 28.8; MS (EI) *m/z* (rel intensity) 206 (30), 204 (M^+, 30), 191 (100), 189 (95), 161 (10), 163 (10), 81 (50); HRMS (EI) Calcd for C_6H_5OSBr 203.9244, found 203.9245.

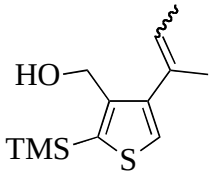


3-Bromo-4-(but-2-en-2-yl)thiophene (208). To a suspension of 22 g (59 mmol) of (ethyl)triphenylphosphonium bromide in 100 mL of THF at 0 °C was added 25 mL (52 mmol) of a 2.1 M solution of *n*-BuLi in hexanes. The resulting solution was stirred for 1 h, then 9.2 g (45 mmol) of 1-(3-bromo-4-thienyl)-ethanone in 40 mL of THF was added via syringe. The solution was stirred overnight, filtered through a plug of SiO_2, and concentrated. After addition of SiO_2 and hexanes, the suspension was filtered through a plug of SiO_2, which was rinsed with hexanes. The combined filtrates were concentrated *in vacuo* to yield 8.7 g (89%) of **208** as a colorless, oily 2:1 mixture of alkene isomers: IR (film) 3109, 2967, 2913, 2854 cm^{-1}; major isomer ^1H NMR δ 7.28 (d, 1 H, *J* = 3.3 Hz), 6.98 (d, 1 H, *J* = 3.3 Hz), 5.69 (q, 1 H, *J* = 5.7 Hz), 1.97 (bs, 3 H), 1.48 (add, 3 H, *J* = 6.6, 1.2 Hz); ^{13}C NMR δ 142.1, 131.0, 125.2, 122.9, 121.8, 111.5, 24.7, 14.9; characteristic signals for minor isomer ^1H NMR δ 7.22 (d, 1 H, *J* = 3.6 Hz), 7.01 (d, 1 H, *J* = 3.3 Hz), 1.78 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 145.4, 130.5, 125.8, 125.2, 123.2, 121.3, 110.8, 16.8, 13.8; MS (EI) *m/z* (rel intensity) 218 (55), 216 (M^+, 55), 191 (55), 189 (45), 122 (100); HRMS (EI) Calcd for C_8H_9SBr 215.9608, found 215.9609.



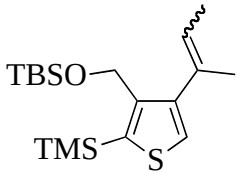
(4-(But-2-en-2-yl)thiophen-3-yl)methanol (209). To a solution of 7.6 g (35 mmol) of **208** in 180 mL of Et_2O at -78 °C was added 25 mL (41 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 30 min, then 27 g (370 mmol) of DMF was added and the resulting solution was removed from the dry ice bath and allowed to warm to room temperature for 45 min. At this time, a saturated aqueous solution of NH_4Cl was added, then the mixture was diluted with brine and the layers were separated. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of 1.3 g (35 mmol) of $NaBH_4$ in 40 mL of EtOH was added a solution of the aldehyde in 60 mL of EtOH. The reaction mixture was stirred for 2 h, quenched by slow addition of conc. HCl, diluted with H_2O and extracted with DCM (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (5→10% EtOAc/hexanes) to yield 3.8 g (65%) of **208** as a colorless, oily 1.5:1 mixture of alkene isomers: IR (film) 3324, 2914, 2857, 1441, 1374 cm^{-1}; ^1H NMR δ 7.29 (d, 1 H, *J* = 3.3 Hz), 6.96 (d, 1 H, *J* = 3.3 Hz), 5.69-5.58 (m, 1 H), 4.56 (s, 2 H), 1.98-1.96 (m, 3 H), 1.64 (s, 1 H), 1.46 (dq, 3 H, *J* = 6.6, 1.5 Hz); characteristic signals for minor isomer: ^1H NMR δ 7.25 (d, 1 H, *J* = 3.3 Hz), 7.03 (d, 1 H, *J* = 3.0 Hz), 4.66 (s, 2 H), 1.77 (add, 3 H, *J* = 6.9, 0.9 Hz); ^{13}C NMR δ 144.7, 141.0, 140.5, 140.1, 131.8, 131.0, 123.9, 123.8, 122.9, 122.3, 121.9, 121.4, 59.9, 59.6, 25.4, 17.2, 14.7, 13.8; MS (EI) *m/z* (rel

intensity) 168 (M^+, 30), 150 (35), 139 (42), 135 (100); HRMS (EI) Calcd for $C_9H_{12}OS$ 168.0608, found 168.0604.

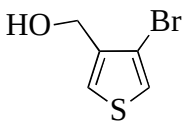


(4-(But-2-en-2-yl)-2-(trimethylsilyl)thiophen-3-yl)methanol (210). To a solution of 3.8 g (22 mmol) of **209** in 20 mL of THF at 0 °C was added 31 mL (50 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was allowed to stir for 15 min, then 15 mL of a 1:1 solution of TMSCl/Et_3N was added. The resulting mixture was stirred for 15 min, removed from the ice bath and allowed to warm to room temperature for 1 h. At this time, a saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with DCM (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* To a solution of the resulting residue in 15 mL of MeOH was added 2.5 mL of a 5% aqueous solution of citric acid. The reaction mixture was stirred for 30 min, diluted with H_2O, and extracted with DCM (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 4.1 g (76%) of **210** as a colorless, oily 1.4:1 mixture of alkene isomers: IR (film) 3321, 2955, 1249 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.23 (s, 1 H), 5.64-5.56 (m, 1 H), 4.53 (d, 2 H, *J* = 5.1 Hz), 3.8 (app q, 1 H, *J* = 4.5 Hz), 1.97-1.93 (m, 3 H), 1.38 (dq, 3 H, *J* = 6.6 Hz, 1.5 Hz), 0.37 (bs, 9 H); characteristic signals for minor isomer: ^1H NMR (acetone-d_6) δ 7.30 (s, 1 H), 4.60 (s, 2 H), 1.74 (app dd, 3 H, *J* = 6.9, 0.9 Hz); ^{13}C NMR (acetone-d_6) δ 149.6, 148.4, 147.9, 145.4, 138.2, 137.7, 133.8, 132.6, 126.6, 126.5, 124.4, 123.9, 59.1, 26.4, 18.2, 15.2,

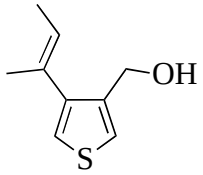
14.2, 0.88; MS (EI) *m/z* (rel intensity) 240 (M^+, 60), 225 (100), 207 (50); HRMS (EI) Calcd for $C_{12}H_{20}OSiS$ 240.1004, found 240.0996.



((4-(But-2-en-2-yl)-2-(trimethylsilyl)thiophen-3-yl)methoxy)(*tert*-butyl)dimethylsilane (205). To a solution of 6.9 g (29 mmol) of **210** in 300 mL of DMF at 0 °C was added 6.6 g (44 mmol) of TBSCl followed by 5.3 g (78 mmol) of imidazole. The reaction mixture was allowed to stir at room temperature overnight and diluted with Et_2O. After addition of brine, the layers were separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→2% EtOAc/hexanes) to yield 9.1 g (90%) of **205** as a colorless, oily 2:1 mixture of alkene isomers: IR (film) 2956, 1471, 1373, 1361, 1251, 1174, 1069 cm^{-1}; ^1H NMR δ 7.10 (s, 1 H), 5.62-5.52 (m, 1 H), 4.51 (s, 2 H), 1.97-1.94 (m, 3 H), 1.40 (dq, 3 H, *J* = 6.6, 1.5 Hz), 0.91 (bs, 9 H), 0.37 (bs, 9 H), 0.09 (s, 6 H); characteristic signals for minor isomer: ^1H NMR δ 7.17 (s, 1 H), 4.59 (s, 2 H), 1.75 (dq, 3 H, *J* = 6.9, 0.9 Hz), 0.10 (s, 6 H); ^{13}C NMR δ 149.4, 146.1, 145.7, 145.2, 138.4, 137.9, 133.1, 131.8, 125.8, 125.7, 123.9, 123.1, 59.0, 58.8, 26.2, 26.1, 26.0, 18.5, 18.3, 18.2, 15.0, 13.9, 0.5, -5.3, -5.4; MS (EI) *m/z* (rel intensity) 354 (M^+, 70), 339 (40), 297 (25), 209 (25), 72 (100); HRMS (EI) Calcd for $C_{18}H_{34}OSi_2S$ 354.1864, found 354.1868.

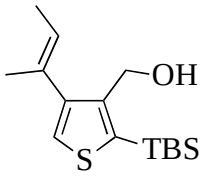


(4-Bromothiophen-3-yl)methanol (211). To a solution of 5.0 g (21 mmol) of **206** in 28 mL of Et_2O at -78 °C was added 15 mL (21 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 20 min, then 10 g (11 mmol) of DMF was added and the resulting solution was stirred for 1 h. At this time, a saturated aqueous solution of NH_4Cl was added and the solution was warmed to room temperature, then the mixture was diluted with brine and the layers were separated. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of 0.92 g (25 mmol) of $NaBH_4$ in 23 mL of EtOH was added a solution of the aldehyde in 37 mL of EtOH. The reaction mixture was stirred for 1 h, quenched by slow addition of a saturated aqueous solution of NH_4Cl, diluted with 10% aqueous HCl and extracted with DCM (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 2.8 g (70%) of **206** as a colorless oil: IR (film) 3392, 3107, 2927, 1318, 1052 cm^{-1}; ^1H NMR δ 7.31 (d, 1 H, J = 3.6 Hz), 7.29 (d, 1 H, J = 3.6 Hz), 4.67 (d, 2 H, J = 5.7 Hz), 1.86 (t, 1 H, J = 5.7 Hz); ^{13}C NMR δ 140.2, 123.7, 123.3, 110.2, 60.1; MS (EI) *m/z* (rel intensity) 194 (90), 193 (20), 192 (90), 191 (M^+, 20), 177 (35), 175 (35), 165 (35), 163 (35), 161 (30), 159 (30), 113 (45); HRMS (EI) Calcd for C_5H_5OSBr 191.9244, found 191.9239.



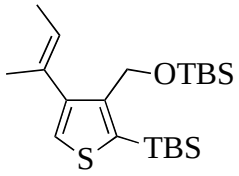
(*E*)-(4-(But-2-en-2-yl)thiophen-3-yl)methanol (213). To a solution of 1.0 g (5.2 mmol) of **211** in 20 mL of xylenes was added 0.60 g (0.52 mmol) of $Pd(PPh_3)_4$, 2.6 g (26 mmol) of **192**,[182] and

2.6 g (26 mmol) of KOAc. The reaction mixture was heated at reflux overnight, cooled, diluted with H_2O, and filtered through celite. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 0.45 g (53%) of **213** as a colorless oil: IR (film) 3332, 3100, 2917, 1380 cm^{-1}; ^1H NMR δ 7.25 (dt, 1 H, *J* = 3.3, 0.7 Hz), 7.03 (d, 1 H, *J* = 3.3 Hz), 5.62 (qq, 1 H, *J* = 6.8, 1.4 Hz), 4.66 (d, 2 H, *J* = 4.8 Hz), 1.97 (m, 3 H), 1.78 (dq, 3 H, *J* = 6.8, 0.9 Hz); ^{13}C NMR δ 144.5, 139.9, 130.9, 123.7, 122.7, 121.2, 59.6, 17.0, 13.7; MS (EI) *m/z* (rel intensity) 168 (M^+, 55), 149 (40), 139 (45), 135 (100); HRMS (EI) Calcd for $C_9H_{12}OS$ 168.0608, found 168.0615.



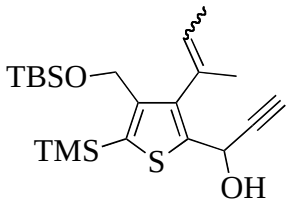
(*E*)-(4-(But-2-en-2-yl)-2-(*tert*-butyldimethylsilyl)thiophen-3-yl)methanol (214). To a solution of 0.17 g (1.0 mmol) of **213** in 10 mL of DMF at 0 °C was added 0.23 g (1.5 mmol) of TBSCl followed by 0.18 g (2.8 mmol) of imidazole. The reaction mixture was allowed to stir overnight at room temperature, quenched with brine, and extracted with Et_2O (3x). The combined organic extracts were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1% Et_2O/hexanes) to yield 0.16 g (60%) of the silyl ether as a colorless oil: IR (film) 2954, 2928, 2856, 1471, 1253 cm^{-1}; ^1H NMR δ 7.21 (dt, 1 H, *J* = 3.6, 1.2 Hz), 6.99 (d, 1 H, *J* = 3.3 Hz), 5.54 (qq, 1 H, *J* = 6.6, 1.5 Hz), 4.65 (d, 2 H, *J* = 0.9 Hz), 1.95-1.93 (m, 3 H), 1.75 (dq, 3 H, *J* = 6.6, 0.9 Hz), 0.94 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR δ

144.6, 140.5, 131.3, 123.7, 122.2, 121.2, 60.9, 25.9, 18.3, 17.2, 13.9, -5.3. To a solution of 46 mg (0.17 mmol) of the silyl ether and 33 mg (0.18 mmol) of HMPA in 1.0 mL of THF at -78 °C was added 0.11 mL (0.18 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The resulting solution was stirred for 2 h, quenched with a saturated aqueous solution of NH_4Cl and diluted with H_2O. The mixture was extracted with DCM (3x) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 30 mg (66%) of **214** as a colorless oil: IR (film) 3299, 2953, 2928, 2856, 1470, 1443, 1252 cm^{-1}; ^1H NMR δ 7.25 (s, 1 H), 5.68 (qq, 1 H, *J* = 6.6, 1.2 Hz), 4.63 (d, 2 H, *J* = 5.3 Hz), 2.01 (m, 3 H), 1.78 (dq, 3 H, *J* = 6.8, 1.1 Hz), 1.58 (t, 1 H, *J* = 5.5 Hz), 0.94 (s, 9 H), 0.40 (s, 6 H); ^{13}C NMR δ 148.4, 146.4, 135.9, 132.0, 127.2, 124.4, 59.3, 26.6, 17.9, 17.4, 14.0, -3.7; MS (EI) *m/z* (rel intensity) 282 (M^+, 10), 267 (15), 253 (85), 225 (100), 207 (90), 75 (60); HRMS (EI) Calcd for $C_{15}H_{26}OSiS$ 282.1473, found 282.1478.



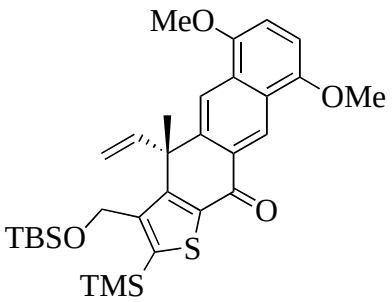
(*E*)-((4-(But-2-en-2-yl)-2-(*tert*-butyldimethylsilyl)thiophen-3-yl)methoxy)(*tert*-butyl)dimethylsilane (215). To a solution of 30 mg (0.11 mmol) of **214** in 1.0 mL of DMF at 0 °C was added 25 mg (0.17 mmol) of TBSCl followed by 20 mg (0.30 mmol) of imidazole. The reaction mixture was allowed to stir at room temperature overnight, quenched with brine, and extracted with Et_2O (3x). The combined organic extracts were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1% Et_2O/hexanes) to yield 29 mg (65%) of **214** as a colorless oil: IR (film) 2928, 2883,

2856, 1471, 1252 cm^{-1}; ^{1}H NMR δ 7.20 (s, 1 H), 5.55 (qq, 1 H, *J* = 6.6, 1.2 Hz), 4.57 (s, 2 H), 1.96 (s, 3 H), 1.75 (dd, 3 H, *J* = 6.9, 0.6 Hz), 0.94 (s, 9 H), 0.91 (s, 9 H), 0.38 (s, 6 H), 0.10 (s, 6 H); ^{13}C NMR δ 149.4, 146.2, 135.4, 132.1, 126.4, 123.4, 58.9, 26.8, 25.9, 18.3, 18.2, 17.4, 13.8, -3.6, -5.4; MS (EI) *m/z* (rel intensity) 396 (M^{+}, 5), 381 (20), 339 (80), 147 (100), 73 (95), 57 (70); HRMS (EI) Calcd for $C_{21}H_{40}OSi_2S$ 396.2338, found 396.2319.



1-(3-(But-2-en-2-yl)-4-((*tert*-butyldimethylsilyloxy)methyl)-5-(trimethylsilyl)thiophen-2-yl)prop-2-yn-1-ol (216). To a solution of 5.0 g (14 mmol) of **205** in 70 mL of THF at 0 °C was added 13 mL (21 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 15 min, then 21 g (280 mmol) of DMF was added and the solution was stirred for 45 min. At this time, a saturated aqueous solution of NH_4Cl was added. The solution was diluted with brine and extracted 3x with Et_2O. The combined organic layers were washed with brine (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of the resulting aldehyde in 75 mL of THF at 0 °C was added 56 mL (28 mmol) of a 0.5 M solution of ethynyl magnesium bromide in THF. The reaction mixture was allowed to stir for 30 min and was then quenched with a saturated aqueous solution of NH_4Cl. The solution was diluted with H_2O, extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5%

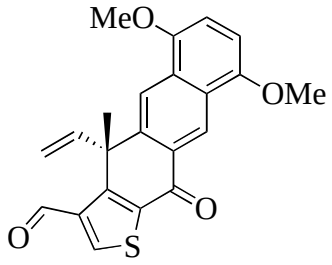
EtOAc/hexanes) to yield 4.9 g (85%) of **216** as a yellow, oily 2.9:1 mixture of alkene isomers: IR (film) 3312, 2956, 2929, 2857, 1251cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.73-5.69 (m, 1 H), 5.48 (ddd, 1 H, *J* = 5.1, 4.4, 2.3 Hz), 5.02 (dd, 1 H, *J* = 11.4, 5.5 Hz), 4.50-4.49 (m, 2 H), 3.02 (dd, 1 H, *J* = 5.6, 2.3 Hz), 1.96-1.93 (m, 3 H), 1.39-1.33 (m, 3 H), 0.91 (s, 9 H), 0.37 (s, 9 H), 0.12 (s, 6 H); characteristic signals for minor isomer: ^{1}H NMR (acetone-d_6) δ 5.56 (dd, 1 H, *J* = 7.9, 5.6 Hz), 5.42-5.34 (m, 1 H), 5.10 (d, 1 H, *J* = 5.2 Hz), 4.53 (s, 2 H), 1.90-1.89 (m, 3 H), 1.76 (dq, 3 H, *J* = 6.7, 1.1 Hz), 0.90 (s, 9 H), 0.35 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 147.0, 146.9, 146.6, 146.5, 145.1, 144.8, 144.6, 143.1, 142.4, 137.7, 137.4, 137.0, 132.9, 132.8, 132.0, 126.3, 125.4, 125.2, 85.5, 85.4, 74.4, 74.3, 74.2, 59.8, 59.7, 58.9, 58.8, 58.6, 26.4, 26.3, 25.7, 25.5, 18.9, 18.8, 18.6, 15.2, 13.9, 0.7, -5.2, -5.3; MS (EI) *m/z* (rel intensity) 393 ([M-C_2H]$^{+}$, 25), 380 (65), 351 (30), 333 (50), 276 (35), 261 (80), 73 (100); HRMS (EI) Calcd for $C_{21}H_{36}O_2Si_2S$ 408.1974, found 408.1979.



3-((*tert*-Butyldimethylsilyloxy)methyl)-4-methyl-2-(trimethylsilyl)-4-vinylanthra[2,3-*b*]thiophen-11(4*H*)-one (202). To a solution of 2.3 g (5.5 mmol) of **216** in 120 mL of DCM was added 24 g (280 mmol) of MnO_2. After 1 h, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the ketone as a 2.7:1 white, solid mixture of olefin isomers: Mp 114.9-119.8 °C; IR (KBr) 3259, 2951, 2928, 2856, 2093, 1632 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.65 (qq, 1 H, *J* = 8.3, 1.5 Hz), 4.55 (s, 2 H), 4.20 (s, 1 H), 1.99 (dq, 3 H, *J* = 1.5, 1.5 Hz), 1.31

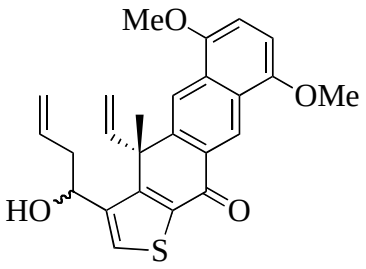
(dq, 3 H, *J* = 6.7, 1.5 Hz), 0.91 (s, 9 H), 0.43 (s, 9 H), 0.12 (s, 6 H); characteristic signals for minor isomer: ^{1}H NMR (acetone-d_6) δ 5.38 (qq, 1 H, *J* = 6.7, 1.5 Hz), 4.24 (s, 1 H), 1.93 (dq, 3 H, *J* = 1.2, 1.2 Hz), 1.76 (dq, 3 H, *J* = 6.8, 1.1 Hz), 0.90 (s, 9 H), 0.40 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 168.9, 168.6, 155.0, 151.4, 150.6, 150.1, 149.4, 149.0, 142.4, 141.6, 132.7, 131.9, 126.3, 124.9, 82.1, 81.7, 81.5, 81.4, 59.3, 59.2, 26.4, 26.3, 25.0, 18.9, 18.8, 18.3, 15.1, 14.0, 0.3, -5.3; MS (EI) *m/z* (rel intensity) 406 (M^+, 25), 391 (35), 349 (30), 274 (30), 147 (40), 73 (100). To a solution of this ketone in 25 mL of acetone was added a catalytic amount of $AgNO_3$ followed by 1.1 g (6.2 mmol) of *N*-bromosuccinimide. The reaction mixture was stirred for 10 min, quenched with H_2O, and filtered through a pad of celite, which was washed with hexanes. The layers were separated and the aqueous layer was extracted with hexanes (3x). The combined organic layers were washed with 10% aqueous HCl, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was dissolved in 10 mL of *o*-DCB and divided evenly between 2 microwave reaction vessels loaded with 490 mg (2.5 mmol) of **218**, 1.05 g of powdered 4 Å molecular sieves and 650 mg (5.0 mmol) of K_2CO_3. The reaction mixtures were heated at 210 ºC for 5 min under microwave irradiation, diluted with hexanes, filtered through a plug of celite and concentrated *in vacuo.* The solvent and other volatiles were removed via Kugelrohr distillation at 120 ºC and 0.5 Torr. The residue was dissolved in 25 mL of NMP and divided evenly among 5 microwave reaction vessels containing 250 mg of $Pd(Ph_3P)_4$ and 1.7 mL of Et_3N. The solutions were heated at 220 °C for 5 min under microwave irradiation, and filtered through a pad of celite, which was washed with DCM, and then concentrated *in vacuo*. The solvent and other volatiles were removed via Kugelrohr distillation at 120 ºC under high vacuum. The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) followed by crystallization from Et_2O to yield 310 mg (10%) of **202** as a yellow solid: Mp 200.7-203.4 °C; IR

(film) 2954, 2856, 1654, 1625, 1585, 1463, 1343, 1298, 1264 cm^{-1}; ^1H NMR (acetone-d_6) δ 9.13 (s, 1 H), 8.42, (s, 1 H), 6.96 (d, 1 H, *J* = 8.4 Hz), 6.87 (d, 1 H, *J* = 8.4 Hz), 6.18 (dd, 1 H, *J* = 17.4, 10.4 Hz), 5.61 (dd, 1 H, *J* = 17.4, 0.7 Hz), 5.46 (dd, 1 H, *J* = 10.4, 0.7 Hz), 5.08 (d, 1 H, *J* = 11.7 Hz), 4.79 (d, 1 H, *J* = 11.7 Hz), 4.02 (s, 3 H), 3.98 (s, 3 H), 1.95 (s, 3 H), 0.94 (s, 9 H), 0.46 (s, 9 H), 0.27 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 178.6, 154.0, 152.1, 150.9, 149.2, 148.0, 145.6, 143.3, 140.9, 128.8, 127.9, 122.5, 122.4, 114.5, 106.1, 103.7, 59.1, 56.0, 46.7, 29.1, 26.2, 18.4, 0.56, -4.8, -4.9; MS (EI) *m/z* (rel intensity) 566 (M^+, 100), 509 (90), 494 (35), 405 (25), 147 (45), 73 (677); HRMS (EI) Calcd for $C_{31}H_{42}O_4Si_2S$ 566.2308, found 566.2326.



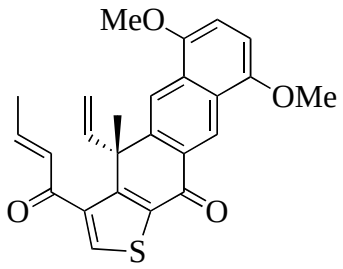
4-Methyl-11-oxo-4-vinyl-4,11-dihydroanthra[2,3-*b*]thiophene-3-carbaldehyde (219). To a solution of 310 mg (0.55 mmol) of **202** in 4.0 mL of THF at 0 ^oC was added 1.7 mL (1.7 mmol) of a 1 M solution of TBAF in THF. After 5 min, the reaction mixture was quenched with H_2O and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was dissolved in 28 mL of DCM and 2.9 g (33 mmol) of MnO_2 was added. The mixture was stirred for 1 h, then filtered through a plug of celite and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→15% EtOAc/hexanes) to yield 166 mg (80%) of **219** as a orange yellow solid: Mp 199.3-202.8 ^oC; IR (film) 2936, 2359, 2341, 1653, 1625, 1592 cm^{-1}; ^1H NMR δ 10.29 (s, 1 H), 9.27 (s, 1 H), 8.60 (s,

1 H), 8.36 (s, 1 H), 6.83 (d, 1 H, *J* = 8.3 Hz), 6.72 (d, 1 H, *J* = 8.3 Hz), 6.35 (dd, 1 H, *J* = 17.3, 10.4 Hz), 5.49 (d, 1 H, *J* = 17.3 Hz), 5.43 (d, 1 H, *J* = 10.4 Hz), 4.01 (s, 3 H), 3.99 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR δ 185.3, 178.7, 152.5, 150.7, 148.8, 144.3, 143.1, 140.8, 139.1, 128.6, 126.9, 125.0, 123.2, 122.3, 115.2, 106.3, 103.6, 55.8, 46.1, 30.5 ; MS (EI) *m/z* (rel intensity) 378 (M^+, 100), 363 (75), 194 (20); HRMS (EI) Calcd for $C_{22}H_{18}O_4S$ 378.0892, found 378.0924.



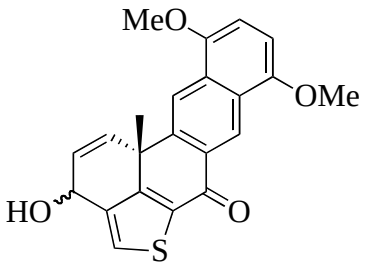
3-(1-Hydroxybut-3-enyl)-6,9-dimethoxy-4-methyl-4-vinylanthra[2,3-*b*]thiophen-11(4*H*)-one (220). To a solution of 170 mg (0.45 mmol) of **219** and 210 mg (0.63 mmol) of allyltributylstanne in DCM at -78 °C was added 47 μL (0.36 mmol) of BF•OEt_2. The resulting solution was stirred for 1.5 h, quenched with sat. aq. $NaHCO_3$ and warmed to room temperature. The aqueous layer was extracted with DCM (3x), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10% Et_2O/ DCM) to yield 180 mg (95%) of **220** as a 6:1 yellow, solid mixture of diastereomers: Mp 184.3-193.1 °C; IR (film) 3435, 2936, 1650, 1622, 1464, 1265 cm^{-1}; ^{1}H NMR δ 9.25 (s, 1 H), 8.30 (s, 1 H), 7.89 (s, 1 H), 6.79 (d, 1 H, *J* = 8.4 Hz), 6.69 (d, 1 H, *J* = 8.4 Hz), 6.11 (dd, 1 H, *J* = 17.4, 10.5 Hz), 5.95-5.80 (m, 1 H), 5.64 (d, 1 H, *J* = 17.4 Hz), 5.48 (d, 1 H, *J* = 10.8 Hz), 5.26-5.16 (m, 3 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 2.67-2.57 (m, 2 H), 2.52-2.40 (m, 1 H), 1.92 (s, 3 H); characteristic signals for minor isomer: ^{1}H NMR 7.91 (s, 1 H), 6.25 (dd, 1 H, *J* = 17.4, 10.5 Hz), 1.85 (s, 3 H); ^{13}C NMR δ 178.8, 150.7, 150.5, 148.7, 145.9, 144.5, 142.9, 137.7, 134.5, 132.6, 128.4, 127.4, 124.9, 122.9,

121.9, 118.8, 114.3, 105.8, 103.3, 66.7, 55.7, 46.2, 43.6, 28.8; MS (EI) *m/z* (rel intensity) 420 (M^+, 100), 339 (25), 147 (35), HRMS (EI) Calcd for $C_{25}H_{24}O_4S$ 420.1395, found 420.1386.



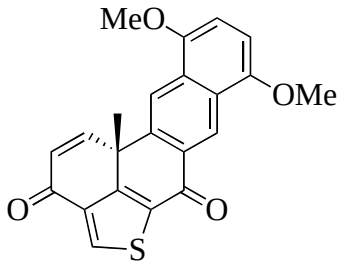
(*E*)-3-But-2-enoyl-6,9-dimethoxy-4-methyl-4-vinylanthra[2,3-*b*]thiophen-11(4*H*)-one (221). To a solution of 30 mg (0.071 mmol) of **220** in 1.0 mL of DCM was added 36 mg (0.089 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 2.5 h at which time an additional 10 mg (0.024 mmol) of Dess-Martin periodinane was added and stirring was continued for 30 min. The mixture was then quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/Hex) to yield 22 mg (74%) of the ketone as a yellow orange foam: IR (film) 3081, 2936, 2834, 1693, 1654, 1625 cm^{-1}; ^1H NMR δ 9.23 (s, 1 H), 8.31 (s, 1 H), 8.23 (s, 1 H), 6.79 (d, 1 H, *J* = 8.1 Hz), 6.69 (d, 1 H, *J* = 8.1 Hz), 6.31 (dd, 1 H, *J* = 17.4, 10.5), 6.02 (dddd, 1 H, *J* = 17.1, 10.2, 6.6 Hz), 5.31-5.18 (m, 3 H), 5.10 (d, 1 H, *J* = 17.4 Hz), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.70 (dd, 1 H, *J* = 17.1, 6.9 Hz), 3.60 (dd, 1 H, *J* = 17.1, 6.6 Hz), 2.02 (s, 3 H); ^{13}C NMR δ 195.0, 179.1, 153.2, 150.7, 148.9, 146.6, 142.3, 142.2, 138.9, 138.8, 130.5, 128.7, 126.9, 124.8, 122.8, 122.4, 119.2, 115.5, 106.0, 103.2, 55.7, 47.7, 46.7, 30.0. To a solution of 22 mg (0.053 mmol) of the ketone in 1.0 mL of DCM was added 0.25 mL (0.025 mmol) of a 0.1 M solution of DBU in DCM. The reaction mixture

was stirred overnight then quenched with a saturated aqueous solution of $CuSO_4$. The aqueous layer was extracted with DCM (3x), the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and *in vacuo*. The residue was purified by chromatography on SiO_2 (10% EtOAc/Hex) to yield 22 mg (quant.) of **221** as a yellow orange foam: IR (film) 3084, 2936, 2834, 1652, 1624 cm^{-1}; ^1H NMR δ 9.24 (s, 1 H), 8.28 (s, 1 H), 7.89 (s, 1 H), 6.84-6.71 (m, 2 H), 6.68 (d, 1 H, *J* = 8.4 Hz), 6.49 (dq, 1 H, *J* = 13.8, 1.8 Hz), 6.10 (dd, 1 H, *J* = 17.1, 10.2 Hz), 5.28 (d, 1 H, *J* = 10.5 Hz), 5.26 (d, 1 H, *J* = 17.4 Hz), 3.99 (s, 3 H), 3.96 (s, 3 H), 2.00 (s, 3 H), 1.97 (dd, 3 H, *J* = 6.9, 1.5 Hz); ^{13}C NMR δ 190.5, 179.0, 153.2, 150.7, 148.8, 147.0, 145.9, 142.1, 141.3, 138.7, 136.8, 133.2, 128.6, 127.3, 124.8, 122.9, 122.1, 115.9, 105.9, 103.3, 55.7, 46.7, 30.3, 18.5; MS (EI) *m/z* (rel intensity) 418 (M^+, 100), 403 (30), 373 (15); HRMS (EI) Calcd for $C_{25}H_{22}O_4S$ 418.1238, found 418.1244.



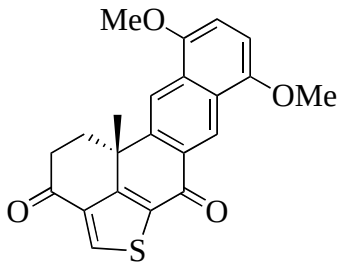
3-Hydroxy-8,11-dimethoxy-12b-methyl-3*H*-tetrapheno[5,4-*bc*]thiophen-6(12b*H*)-one (224). To a solution of 60 mg (0.14 mmol) of **220** in 6.0 mL of degassed benzene was added 14 mg (0.014 mmol) of $(CO)RuHCl(Ph_3P)_3$. The reaction vessel was sealed, lowered into a preheated 80 °C bath, stirred for 30 min, cooled, filtered through florisil and concentrated *in vacuo*. To a solution of the resulting residue in 24 mL of degassed DCM was added 17 mg (0.028 mmol) of catalyst **223**, and the mixture was heated at reflux. After 2 h, an additional 8.5 mg (0.014 mmol) of **223** was added and the mixture was heated overnight, cooled, filtered through florisil and

concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (0→50% EtOAc/hexanes) to yield 29 mg (56%) of **224** as a 8:1 ratio of a red-orange, solid mixture of diastereomers: Mp 198.9-200.1 °C; IR (film) 3583, 3396, 2923, 1651, 1622, 1464, 1436, 1344 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.02 (s, 1 H), 8.54 (s, 1 H), 8.07 (d, 1 H, *J* = 1.2 Hz), 7.57 (d, 1 H, *J* = 8.7 Hz), 6.94 (d, 1 H, *J* = 8.4 Hz), 6.82 (dd, 1 H, *J* = 9.9, 2.7 Hz), 6.16 (dd, 1 H, *J* = 9.9, 1.5 Hz), 5.99 (d, 1 H, *J* = 7.2 Hz), 5.37-5.28 (m, 1 H), 3.99 (s, 6 H), 1.45 (s, 3 H); characteristic signals of minor isomer: ^1H NMR (DMSO-d_6) δ 9.00 (s, 1 H), 7.97 (s, 1 H), 6.35 (d, 1 H, *J* = 13.5 Hz), 5.85 (d, 1 H, *J* = 4.8 Hz), 5.74-5.65 (m, 1 H), 3.33 (s, 6 H), 1.80 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 177.5, 153.8, 149.7, 148.2, 143.8, 143.1, 134.3, 130.6, 130.5, 129.0, 127.0, 124.8, 123.7, 122.6, 118.2, 107.2, 104.5, 63.5, 55.8, 37.8, 30.4; MS (EI) *m/z* (rel intensity) 378 (M^+, 25), 363 (35), 347 (35), 33 (25), 317 (20), 149 (100), 121 (35), 97 (55), 87 (90), 85 (95); HRMS (EI) Calcd for $C_{22}H_{18}O_4S$ 378.0925, found 378.9261.



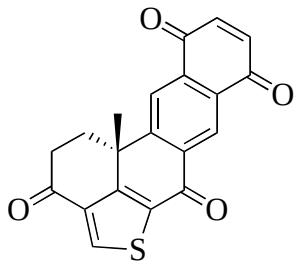
8,11-Dimethoxy-12b-methyl-3*H*-tetrapheno[5,4-*bc*]thiophene-3,6(12b*H*)-dione (222). To a solution of 23 mg (0.06 mmol) of **224** in 3.0 mL of DCM was added 31 mg (0.07 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 30 min, and quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% Et_2O/DCM)

to yield 20 mg (87%) of **222** as a yellow glass: IR (film) 2932, 1654, 1624 cm^{-1}; ^{1}H NMR δ 9.27 (s, 1 H), 8.53 (s, 1 H), 8.50 (s, 1 H), 8.05 (d, 1 H, *J* = 10.2 Hz), 6.87 (d, 1 H, *J* = 8.4 Hz), 6.75 (d, 1 H, *J* = 8.4 Hz), 6.51 (d, 1 H, *J* = 10.2), 4.01 (s, 3 H), 3.99 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR δ 180.3, 177.8, 157.7, 150.8, 149.7, 148.6, 139.8, 137.5, 135.4, 129.6, 129.3, 127.4, 125.3, 124.7, 116.9, 106.8, 104.0, 55.7, 43.3, 42.8; MS (EI) *m/z* (rel intensity) 376 (M^{+}, 50), 361 (100), 331 (25), 303 (20), 84 (30); HRMS (EI) Calcd for $C_{22}H_{16}O_4S$ 376.0769, found 376.0760.

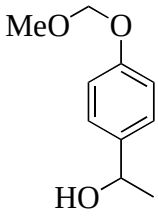


8,11-Dimethoxy-12b-methyl-1*H*-tetrapheno[5,4-*bc*]thiophene-3,6(2*H*,12b*H*)-dione (225). To a solution of 15 mg (0.039 mmol) of **222** in 1.2 mL of toluene in a microwave reaction vessel was added 150 mg (0.040 mmol) of Stryker's reagent. The vessel was sealed and the reaction mixture was heated at 150 °C for 30 min under microwave irradiation. The mixture was diluted with EtOAc and washed with a solution of saturated aqueous NH_4Cl (2x), then $NaHCO_3$ (2x) and brine (2x). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→30% EtOAc/hexanes) to yield 8.0 mg (53%) of **225** as a yellow glass: IR (film) 3088, 2932, 1686, 1656, 1624 cm^{-1}; ^{1}H NMR δ 9.26 (s, 1 H), 8.50 (s, 1 H), 8.36 (s, 1 H), 6.84 (d, 1 H, *J* = 8.4 Hz), 6.73 (d, 1 H, *J* = 8.4 Hz), 4.00 (s, 2 H), 3.99 (s, 3 H), 3.15-2.85 (m, 3 H), 2.47-2.34 (m, 1 H), 1.68 (s, 3 H); ^{13}C NMR δ 192.1, 178.4, 158.6, 150.8, 148.7, 144.8, 138.7, 136.1, 135.4, 129.2, 127.9, 124.8, 124.3, 117.9, 106.4, 103.6, 55.7, 38.9, 35.9, 44.4, 33.3; MS (EI) *m/z* (rel intensity) 347 ($[M-CH_3O]^{+}$, 30), 277 (20), 192

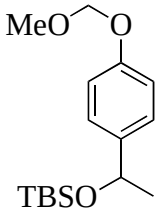
(100), 164 (50), 136 (100), 122 (85), 120 (55), 91 (73); HRMS (EI) Calcd for $C_{22}H_{18}O_4S$ 378.0925, found 378.0930.



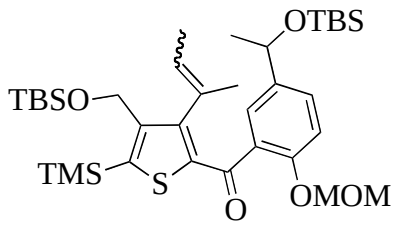
***thio*-Halenaquenone (200).** To a solution of 5.0 mg (0.013 mmol) of **225** in 0.50 mL of acetonitrile and 0.25 mL of DCM was added 22 mg (0.039 mmol) of CAN in 0.25 mL of H_2O. The reaction mixture was stirred for 5 min, diluted with H_2O, and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on C_{18} silica (0→100% MeOH/H_2O) to yield 3.0 mg (66%) of **200** as a white film: IR (film) 2923, 2853, 1657 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.95 (s, 1 H), 8.71 (s, 1 H), 8.38 (s, 1 H), 7.20 (s, 2 H), 3.20-2.96 (m, 2 H), 2.75 (dd, 1 H, *J* = 18.6, 4.5 Hz), 2.27 (dt, 1 H, *J* = 12.9, 4.8 Hz), 1.62 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 191.3, 184.2, 183.8, 176.1, 159.5, 154.8, 141.4, 139.2, 136.0, 134.7, 134.0, 130.3, 124.7, 123.5, 35.4, 31.7, 31.5; MS (EI) *m/z* (rel intensity) 348 (M^+, 45), 239 (65), 78 (75), 63 (100); HRMS (EI) Calcd for $C_{20}H_{12}O_4S$ 348.0456, found 348.0448.



1-(4-(Methoxymethoxy)phenyl)ethanol (234). To a solution of 3.0 g (22 mmol) of 4-hydroxyacetophenone in 220 mL of DMF at 0 °C was added 0.56 g (23 mmol) of 60 % NaH in mineral oil. The reaction mixture was warmed to room temperature, stirred for 30 min, cooled to 0 °C, and treated with 1.8 g (23.2 mmol) of MOMCl. The solution was warmed to room temperature, stirred for 1.5 h, diluted with brine, and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of 0.82 g (22 mmol) of $NaBH_4$ in 25 mL EtOH was added a solution of the ketone in 35 mL of EtOH. The reaction mixture was allowed to stir for 2 h and quenched with a saturated aqueous solution of NH_4Cl, extracted with DCM (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (20% EtOAc/hexanes) to yield 2.2 g (55%) of **234** as a colorless oil: IR (film) 3402, 2970, 2826, 1610, 1586 cm^{-1}; ^1H NMR δ 7.32-7.28 (m, 2 H), 7.05-7.00 (m, 2 H), 5.18 (s, 2 H), 4.86 (q, 1 H, J = 6.0 Hz), 3.48 (s, 3 H), 1.80 (bs, 1 H), 1.48 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 156.0, 139.3, 126.3, 115.8, 94.0, 69.2, 55.5, 24.8; MS (EI) *m/z* (rel intensity) 182 (M^+, 55), 167 (50), 137 (60), 120 (100), 91 (35), 77 (55); HRMS (EI) Calcd for $C_{10}H_{14}O_3$ 182.0942, found 182.0945.



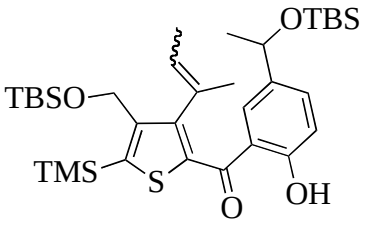
***tert*-Butyl(1-(4-(methoxymethoxy)phenyl)ethoxy)dimethylsilane (231).** To a solution of 1.85 g (10.2 mmol) of **234** in 100 mL of DMF at 0 °C was added 2.37 g (15.8 mmol) of TBSCl followed by 1.91 g (28.1 mmol) of imidazole. The reaction mixture was allowed to stir at room temperature overnight, quenched with brine and extracted with Et_2O (3x). The combined organic layers were washed with brine (2x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1% Et_2O/hexanes) to yield 2.59 g (86%) of **231** as a colorless oil: IR (film) 2955, 2894, 2856, 1510 cm^{-1}; ^1H NMR δ 7.27-7.23 (m, 2 H), 7.02-6.96 (m, 2 H), 5.18 (s, 2 H), 4.80 (q, 1 H, *J* = 6.3 Hz), 3.49 (s, 3 H), 1.39 (d, 3 H, *J* = 6.3 Hz), 0.91 (s, 9 H), 0.05 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR δ 156.1, 140.2, 126.1, 115.7, 94.3, 70.3, 55.6, 27.2, 25.8, 18.1, -4.8, -4.9; MS (EI) *m/z* (rel intensity) 296 (M^+, 4), 239 (40), 209 (50), 165 (100), 133 (25), 75 (40); HRMS (EI) Calcd for $C_{16}H_{28}O_3Si$ 296.1807, found 296.1817.



(3-(But-2-en-2-yl)-4-((*tert*-butyldimethylsilyloxy)methyl)-5-(trimethylsilyl)thiophen-2-yl)(5-(1-(*tert*-butyldimethylsilyloxy)ethyl)-2-(methoxymethoxy)phenyl)methanone (235). To a solution of 1.0 g (2.8 mmol) of **205** in 15 mL of THF at 0 °C was added 2.6 mL (4.3 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 15 min, then 4.0 g (56

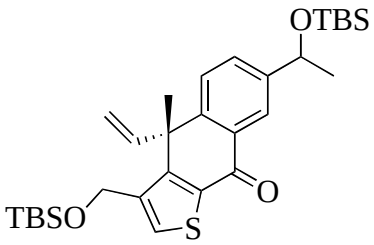
mmol) of DMF was added and the solution was stirred for 15 min. At this time, a saturated aqueous solution of NH_4Cl was added. The solution was diluted with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of 1.2 g (4.2 mmol) of **231** in 35 mL Et_2O at 0 °C was added 3.6 mL (5.0 mmol) of a 1.4 M solution of *s*-BuLi in cyclohexane. The reaction mixture was stirred for 30 min then a solution of the resulting aldehyde in 10 mL of Et_2O was added. The reaction mixture was allowed to stir for 15 min and was then quenched with a saturated aqueous solution of NH_4Cl, and extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 1.5 g (77%) of the alcohol as a colorless oil. To a solution of 0.50 g (0.74 mmol) of the alcohol in 40 mL of DCM was added 0.38 g (0.89 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 2 h at which time an additional 0.20 g (0.44 mmol) of DMP was added. Stirring was continued for 30 min, and the solution was quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by chromatography on Si_2O (5% EtOAc/hexanes) to yield 0.43 g (86%) of **235** as a colorless, oily 2.4:1 mixture of alkene isomers: IR (film) 2954, 2856, 1654, 1607 cm^{-1}; ^1H NMR δ 7.40-7.32 (m, 2 H), 7.09 (d, 1 H, *J* = 8.7 Hz), 5.57-5.46 (m, 1 H), 5.11-5.06 (m, 2 H), 4.88-4.81 (m, 1 H), 4.47 (s, 2 H), 3.37 (d, 3 H, *J* = 3.3 Hz), 1.91 (d, 3 H, *J* = 6 Hz), 1.41-1.33 (m, 6 H), 0.89 (s, 18 H), 0.36 (s, 9 H), 0.10 (s, 6 H), 0.06 (s, 3 H), -0.02 (s, 3 H); characteristic signals for minor isomer: ^1H NMR δ 7.20 (d, 1 H, *J* = 2.1 Hz), 7.07 (d, 1 H, *J* = 8.4 Hz), 5.33-5.28 (m, 1 H), 4.49 (s, 2 H), 3.39 (s, 3 H), 1.51 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 188.7, 187.9, 153.2, 153.1, 152.9,

149.3, 149.2, 147.4, 147.1, 146.7, 146.7, 142.5, 141.8, 141.7, 139.51, 139.48, 139.4, 132.6, 131.3, 131.2, 131.1, 131.0, 128.0, 127.9, 127.7, 125.4, 125.37, 125.32, 123.05, 122.99, 114.8, 114.7, 114.6, 94.8, 94.7, 70.04, 69.97, 58.6, 56.0, 27.0, 25.9, 25.8, 25.7, 24.5, 24.4, 18.3, 18.2, 18.1, 18.0, 14.9, 13.6, 0.1, -4.8, -5.0, -5.6; MS (EI) *m/z* (rel intensity) 676 (M^+, 10), 661 (35), 147 (55), 73 (100); HRMS (EI) Calcd for $C_{35}H_{60}O_5Si_3S$ 676.3469, found 676.3470.



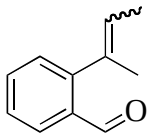
(3-(But-2-en-2-yl)-4-((*tert*-butyldimethylsilyloxy)methyl)-5-(trimethylsilyl)thiophen-2-yl)(5-(1-(*tert*-butyldimethylsilyloxy)ethyl)-2-hydroxyphenyl)methanone (236). To a solution of 69 mg (0.10 mmol) of **235** in 3.0 mL Et_2O at 0 °C was added 40 mg (0.15 mmol) of $MgBr_2 \bullet OEt_2$. The reaction mixture was warmed to room temperature, stirred for 2 h, quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 61 mg (95%) of **236** as a colorless, oily 2.8:1 mixture of alkene isomers: IR (film) 2955, 2928, 2856 cm^{-1}; ^1H NMR δ 11.67 (s, 1 H), 7.80 (dd, 1 H, *J* = 13.5, 1.8 Hz), 7.48-7.43 (m, 1 H), 6.98 (d, 1 H, *J* = 8.7 Hz), 5.66-5.55 (m, 1 H), 4.81 (q, 1 H, *J* = 6.3 Hz), 4.54 (s, 2 H), 1.99 (bd, 3 H, *J* = 15.9 Hz), 1.43-1.35 (m, 6 H), 0.92 (s, 9 H), 0.85 (s, 9 H), 0.41 (s, 9 H), 0.12 (s, 9 H), 0.05 (s, 3 H); characteristic signals of minor isomer: ^1H NMR δ 11.70 (s, 1 H), 7.68 (d, 1 H, *J* = 2.1 Hz), 6.97 (d, 1 H, *J* = 8.4 Hz), 5.48-5.41 (m, 1 H), 4.59 (s, 2 H), 1.62 (d, 3 H, *J* = 6.6 Hz), -0.03 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR δ 195.0, 194.1, 193.9, 161.5, 161.4, 161.2, 151.9, 148.8, 148.7, 146.9, 148.7, 144.5, 144.2, 143.6, 138.2,

137.74, 137.7, 137.0, 136.9, 136.9, 133.2, 133.1, 132.2, 132.1, 131.1, 129.5, 129.3, 129.2, 126.2, 124.3, 124.2, 120.3, 120.2, 120.1, 117.7, 117.6, 117.6, 69.8, 69.7, 58.7, 26.9, 26.8, 26.0, 25.9, 25.8, 25.7, 25.4, 25.2, 18.4, 18.3, 18.3, 18.2, 18.1, 18.0, 15.2, 15.0, 13.8, 0.3, -4.8, -4.9, -5.4, -.5.5; MS (EI) *m/z* (rel intensity) 632 (M^+, 40), 617 (65), 575 (15), 485 (10), 443 (15), 351 (40), 279 (15), 219 (15), 147 (100), 84 (90), 73 (100); HRMS (EI) Calcd for $C_{33}H_{56}O_4Si_3S$ 632.3207, found 632.3199.



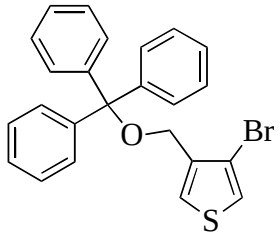
7-(1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-methyl-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (230). To a solution of 0.02 g (0.34 mmol) of **236** in 2 mL of THF was added 15 mg (0.63 mmol) of NaH. The reaction mixture was cooled to 0 °C, treated with 0.45 g (1.26 mmol) of $PhN(Tf)_2$, warmed to room temperature, stirred overnight, quenched with H_2O and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (2% EtOAc/hexanes) to yield 237 mg (99%) of the triflate as a yellow oil. To a solution of 3.0 mg (0.013 mmol) of $Pd(OAc)_2$ in 0.50 mL of degassed DMA in a conical microwave reaction vessel was added 16 mg (0.026 mmol) of racemic BINAP. The resulting solution stirred for 15 min, then 28 mg (0.20 mmol) of K_2CO_3 and a solution of 50 mg (0.065 nmol) of the triflate in 0.30 mL of degassed DMA were added. The solution was heated at 120 °C for 30 min under microwave irradiation, diluted with hexanes, filtered through a plug of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (2%

Et_2O/hexanes) to give 12 mg (34%) of **230** as a colorless oil: IR (film) 2924, 2853, 1651 cm^{-1}; ^1H NMR δ 8.21 (s, 1 H), 7.78 (s, 1 H), 7.65 (d, 1 H, *J* = 8.4 Hz), 7.46 (d, 1 H, *J* = 8.7 Hz), 5.89 (dd, 1 H, *J* = 17.4, 11.2 Hz), 5.49 (d, 1 H, *J* = 17.4 Hz), 5.42 (d, 1 H, *J* = 10.5 Hz), 4.98 (q, 1 H, *J* = 6.0 Hz), 4.89 (d, 1 H, *J* = 14.1 Hz), 4.75 (d, 1 H, *J* = 13.5 Hz), 1.71 (s, 3 H), 1.45 (dd, 3 H, *J* = 8.1, 1.8 Hz), 0.96 (s, 9 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H), 0.07 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR δ 178.9, 150.1, 147.23, 147.19, 146.02, 146.00, 142.8, 141.0, 137.7, 131.1, 129.9, 129.8, 129.59, 129.56, 128.3, 123.18, 123.16, 114.55, 114.54, 70.20, 70.18, 60.7, 45.73, 45.72, 27.04, 27.01, 26.2, 25.9, 25.8, 18.4, 18.2, -4.79, -4.82, -5.3, -5.4; MS (ES) *m/z* (rel intensity) 565 ($[M+^{23}Na]^+$, 60), 413 (100); HRMS (ES) Calcd for $C_{30}H_{46}O_3NaSi_2S$ 565.2604, found 565.2570.

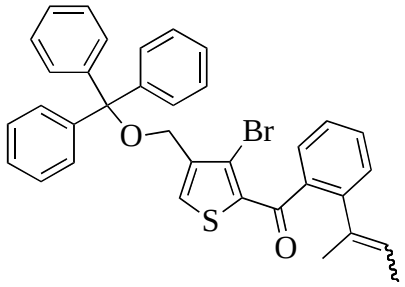


2-(But-2-en-2-yl)benzaldehyde (240). To a solution of 3.0 g (14 mmol) of 1-bromo-2-(but-2-en-2-yl)benzene (**242**)[207] in 90 mL of Et_2O at 0 °C was added 14 mL (20 mmol) of a 1.4 M solution of *s*-BuLi in cyclohexane. The reaction mixture was stirred for 10 min, treated with 10 g (140 mmol) of DMF, allowed to stir at room temperature for 30 min, diluted with brine, and extracted with Et_2O (3x). The combined organic layers were washed with brine (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→5% EtOAc/hexanes) to yield 2.0 g (87%) of **240** as a pale yellow, oily 2.9:1 mixture of alkene isomers: IR (film) 3027, 2975, 2913, 2835, 1693, 1596 cm^{-1}; ^1H NMR δ 10.09 (s, 1 H), 7.95 (dd, 1 H, *J* = 7.8, 0.6 Hz), 7.59 (dt, 1 H, *J* = 7.5, 1.5 Hz), 7.42-7.33 (m, 1 H), 7.20 (d, 1 H, *J* = 7.5 Hz), 5.78 (qq, 1 H, *J* = 6.9, 1.5 Hz), 2.08-2.06 (m, 3 H), 1.39 (dq, 3 H, *J* = 6.6, 1.5 Hz); characteristic signals for minor isomer: ^1H NMR δ 10.11 (s, 1 H), 7.90 (dd, 1 H, *J* = 6.9, 0.9 Hz),

7.53 (dt, 1 H, *J* = 7.5, 1.5 Hz), 7.38-7.35 (m, 1 H), 7.33-7.29 (m, 1 H), 5.42 (qq, 1 H, *J* = 6.6, 1.2 Hz), 1.85 (dq, 3 H, *J* = 6.6, 0.9 Hz); ^{13}C NMR δ 191.5, 149.1, 145.8, 133.6, 133.3, 133.0, 132.8, 132.54, 132.5, 128.9, 128.3, 127.1, 126.7, 126.6, 126.3, 124.4, 26.1, 17.9, 14.22, 13.7; MS (EI) *m/z* (rel intensity) 160 (M^+, 30), 145 (100), 131 (50), 117 (60), 115 (75), 103 (30), 91 (60), 76 (50), 61 (25); HRMS (EI) Calcd for $C_{11}H_{12}O$ 160.0888, found 160.0883.

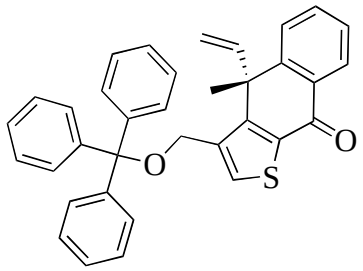


3-Bromo-4-(trityloxymethyl)thiophene (241). To a solution of 1.9 g (9.8 mmol) of **211** in 30 mL of DMF was added 3.2 g (12 mmol) of trityl chloride, 2.0 g (12 mmol) of $AgNO_3$, and 2.8 g (22 mmol) of Et_3N. The reaction mixture was stirred overnight, then diluted with Et_2O and filtered through celite. The filtrate was diluted with brine, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (0→10% EtOAc/hexanes), then crystallized from Et_2O to yield 3.9 g (92%) of **241** as a white solid: Mp 123.3-126.2 °C, IR (film) 3108, 3085, 3058, 3030, 1490, 1447 cm^{-1}; ^{1}H NMR δ 7.60-7.49 (m, 7 H), 7.41-7.26 (m, 10 H), 4.16 (d, 2 H, *J* = 0.6 Hz); ^{13}C NMR δ 143.8, 138.6, 128.6, 127.9, 127.1, 123.0, 122.4, 109.9, 87.2, 62.1.

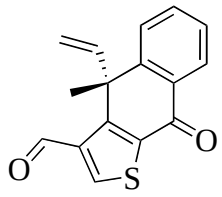


(3-Bromo-4-(trityloxymethyl)thiophen-2-yl)(2-(but-2-en-2-yl)phenyl)methanone (239). To a solution of 1.9 g (19 mmol) of diisopropylamine in 65 mL of THF at 0 °C was added 12 mL (19 mmol) of a 1.6 M solution of n-BuLi. The resulting pale yellow solution was stirred for 30 min then a solution of 4.1 g (9.3 mmol) of **241** in 25 mL of THF was added. The resulting red solution was stirred for 1 h, treated with 1.8 g (11 mmol) of **240** stirred for 1 h and quenched with a saturated aqueous solution of NH_4Cl. The solution was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→15% EtOAc/hexanes) to yield 5.0 g (89%) of the alcohol as a pale yellow oil. To a solution of 5.0 (8.4 mmol) of the resulting alcohol in 240 mL of DCM was added 41 g (461 mmol) of MnO_2. The solution was stirred overnight, filtered through celite and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→10% EtOAc/hexanes) to yield 4.7 g (94%) of **239** as a pale yellow, oily 3.2:1 mixture of alkene isomers: IR (film) 3058, 1646, 1446 cm^{-1}; ^1H NMR δ 7.73 (s, 1 H), 7.51-7.47 (m, 7 H), 7.36-7.27 (m, 12 H), 5.47 (q, 1 H, J = 6.6 Hz), 4.17 (s, 2 H), 1.92 (s, 3 H), 1.40 (dq, 3 H, J = 5.7, 1.2 Hz); characteristic signals for minor isomer: ^1H NMR δ 7.67 (s, 1 H), 4.15 (s, 2 H), 1.87 (s, 3 H), 1.58 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 190.2, 188.9, 144.5, 143.6, 141.2, 141.1, 140.9, 138.7, 138.5, 138.3, 137.7, 135.3, 134.7, 130.7, 130.4, 129.2, 128.4, 128.3, 128.2, 127.8, 127.44, 127.4, 127.0, 126.1, 123.6, 114.6, 114.2, 87.2, 62.1, 25.6, 17.2, 15.1,

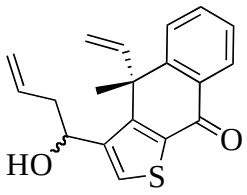
14.21; MS (ES) *m/z* (rel intensity) 617.2 ([M+^{23}Na]$^+$, 95), 615.2 (90), 595.2 (100), 593.2 ([M+H]$^+$, 90); HRMS (ES) Calcd for $C_{35}H_{30}O_2SBr$ 593.1150, found 593.1158.



4-Methyl-3-(trityloxymethyl)-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (238). A solution of 1.6 g (2.7 mmol) of **239** in 18 mL of NMP was divided evenly among 5 microwave reaction vessels containing 0.12 g (0.11 mmol) $Pd(Ph_3P)_4$ and 1.1 g (11 mmol) of Et_3N. The solutions were heated at 220 °C for 5 min under microwave irradiation and filtered through a pad of celite, which was washed with DCM. The combined filtrates were diluted with brine and extracted with Et_2O (3x) the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 0.84 g (60%) of **238** as a white foam: IR (film) 3059, 3030, 2247, 1649, 1598, 1490 cm^{-1}; ^{1}H NMR δ 8.32 (dd, 1 H, *J* = 6.6, 1.2 Hz), 8.10 (bs, 1 H), 7.59-7.50 (m, 7 H), 7.45-7.19 (m, 11 H), 5.61 (dd, 1 H, *J* = 17.4, 10.5 Hz), 5.03 (d, 1 H, *J* = 17.4 Hz), 4.99 (d, 1 H, *J* = 10.5 Hz), 4.29 (dd, 1 H, *J* = 12.6, 0.9 Hz), 4.17 (dd, 1 H, *J* = 12.6, 0.6 Hz), 1.49 (s, 3 H); ^{13}C NMR δ 178.6, 150.6, 148.7, 143.7, 140.1, 140.0, 137.1, 132.7, 131.7, 129.8, 128.5, 128.2, 127.9, 127.1, 126.9, 126.6, 114.6, 87.3, 61.5, 45.7, 26.0; MS (ES) *m/z* (rel intensity) 513 ([M+H]$^+$, 50), 443 (100), 365 (10), 362 (10), 243 (15), 165 (40); HRMS (ES) Calcd for $C_{35}H_{29}O_2S$ 513.1888, found 513.1861.

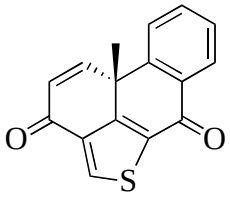


4-Methyl-9-oxo-4-vinyl-4,9-dihydronaphtho[2,3-*b*]thiophene-3-carbaldehyde (243). To a solution of 0.78 g (1.5 mmol) of **238** in 14 mL of THF was added 4.7 mL (56 mmol) of conc. HCl. The reaction mixture was stirred for 1 h, then quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of the resulting alcohol in 33 mL of DCM was added 3.8 g (44 mmol) of MnO_2. After 45 min, the mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→20% EtOAc/hexanes) to yield 0.33 g (81%) of **243** as a white solid: Mp 112.9-115.0 °C; IR (film) 1683, 1651, 1519 cm^{-1}; ^1H NMR δ 10.23 (s, 1 H), 8.56 (s, 1 H), 8.34 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.66 (dt, 1 H, *J* = 8.1, 1.2 Hz), 7.57 (d, 1 H, *J* = 7.8 Hz), 7.50 (dt, 1 H, *J* = 8.1, 1.2 Hz), 6.23 (dd, 1 H, *J* = 17.4, 10.5 Hz), 5.42 (d, 1 H, *J* = 17.4 Hz), 5.38 (d, 1 H, *J* = 10.5 Hz), 1.93 (s, 3 H); ^{13}C NMR δ 184.6, 178.1, 152.0, 148.8, 143.5, 141.7, 140.5, 138.2, 133.2, 129.1, 128.5, 127.1, 126.4, 115.3, 45.7, 28.7; MS (EI) *m/z* (rel intensity) 268 (M^+, 40), 253 (90), 225 (25), 80 (50), 68 (100); HRMS (EI) Calcd for $C_{16}H_{12}O_2S$ 268.0558, found 268.0568.



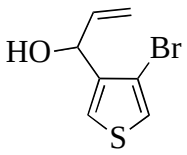
3-(1-Hydroxybut-3-enyl)-4-methyl-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (237). To a solution of 0.16 g (0.58 mmol) of **243** and 270 mg (0.82 mmol) of allyltributylstanne in 9 mL of

DCM at -78 °C was added 0.15 mL (1.2 mmol) of BF_3•OEt_2. The resulting solution was stirred for 30 min, quenched with a saturated aqueous solution of $NaHCO_3$ and warmed to room temperature. The aqueous layer was extracted with DCM (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→20% EtOAc/hexanes) to yield 0.18 g (95%) of **237** as a 10:1 white, pasty mixture of diastereomers: IR (film) 3443, 3078, 2978, 2938, 1642, 1598, 1525, 1453 cm^{-1}; ^1H NMR δ 8.31 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.63 (s, 1 H), 7.59 (dd, 1 H, *J* = 6.9, 1.2 Hz), 7.51 (d, 1 H, *J* = 7.2 Hz), 7.44 (dt, 1 H, *J* = 8.1, 1.2 HZ), 5.97 (dd, 1 H, *J* = 17.4, 10.5 Hz), 5.92-5.71 (m, 1 H), 5.56 (d, 1 H, *J* = 17.4 Hz), 5.44 (d, 1 H, *J* = 10.5 Hz), 5.24-5.14 (m, 3 H), 2.63-2.54 (m, 1 H), 2.51-2.39 (m, 1 H), 2.14-2.10 (m, 1 H), 1.83 (s, 3 H); characteristic signals for minor isomer: ^1H NMR δ 7.64 (s, 1 H), 6.10 (dd, 1 H, *J* = 17.4, 10.5), 1.76 (s, 3 H); ^{13}C NMR δ 178.6, 150.6, 150.4, 148.9, 146.1, 141.8, 141.6, 136.6, 134.4, 134.3, 132.8, 132.5, 129.4, 128.3, 126.9, 126.3, 118.0, 114.8, 114.7, 66.5, 66.3, 45.9, 45.7, 43.3, 43.0, 27.9, 27.2; MS (ES) *m/z* (rel intensity) 311 ($[M+H]^+$, 25), 255 (20), 237 (15); HRMS (ES) Calcd for $C_{19}H_{19}O_2S$ 311.1106, found 311.1104.



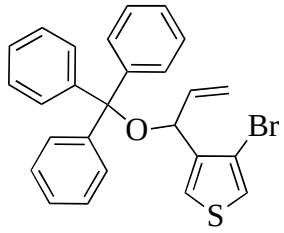
10b-Methyl-3*H*-phenanthro[10,1-*bc*]thiophene-3,6(10b*H*)-dione (228). To a solution of 0.17 g (0.53 mmol) of **237** in 21 mL of benzene was added 51 mg (0.053 mmol) of $(CO)RuHCl(Ph_3P)_3$. The reaction vessel was sealed, lowered into a preheated 80 °C bath, stirred for 30 min, cooled, filtered through florisil and concentrated *in vacuo*. To a solution of the

resulting residue in 90 mL of DCM was added 66 mg (0.11 mmol) of **223**, and the mixture was heated at reflux for 4 h. The solution was cooled, filtered through florisil, which was washed with EtOAc, and concentrated *in vacuo*. The residue was purified by chromatography on Si_2O (0→50% EtOAc/hexanes) to yield 55 mg (39%) of the cyclohexenol. To a solution of 55 mg (0.21 mmol) of the cyclohexenol in 10 mL of DCM was added 0.11 g (0.25 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 30 min, and quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 39 mg (70%) of **228** as a white solid: Mp (dec) 145.1 °C, IR (film) 2926, 2854, 1658, 1265, 1198 cm^{-1}; ^1H NMR δ 8.52 (s, 1 H), 8.36 (d, 1 H, *J* = 7.8 Hz), 7.82 (d, 1 H, *J* = 9.9 Hz), 7.77 (d, 1 H, *J* = 7.8 Hz), 7.67 (t, 1 H, *J* = 7.5 Hz), 7.51 (t, 1 H, *J* = 7.5 Hz), 6.46 (d, 1 H, *J* = 10.2 Hz), 1.68 (s, 3 H); ^{13}C NMR δ 180.1, 177.5, 157.8, 149.0, 144.8, 137.7, 135.5, 135.0, 133.1, 132.2, 129.8, 128.8, 127.7, 123.7, 43.2, 42.9; MS (EI) *m/z* (rel intensity) 266 (M^+, 35), 251 (100), 223 (30), 195 (15), 151 (10), 61 (15); HRMS (EI) Calcd for $C_{16}H_{10}O_2S$ 266.0401, found 266.0398.



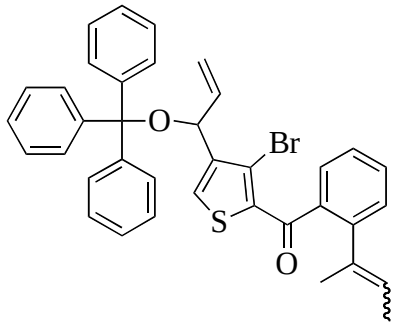
1-(4-Bromothiophen-3-yl)prop-2-en-1-ol (259). To a solution of 1.0 g (4.1 mmol) of **206** in 5.0 mL of Et_2O at -78 °C was added 2.6 mL (4.1 mmol) of a 1.6 M solution of n-BuLi in hexanes. The reaction mixture was stirred for 20 min and then 0.37 g (6.2 mmol) of acrolein was added. The solution was stirred for 1 h, diluted with H_2O and warmed to room temperature. The

layers were separated, and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were washed with brine (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 0.54 g (60%) of **259** as a pale yellow oil: IR (film) 3356, 3108 cm^{-1}; ^1H NMR δ 7.31 (s, 2 H), 6.09 (ddd, I H, *J* = 17.1, 10.5, 5.7 Hz), 5.43 (dt, 1 H, *J* = 17.1, 1.2 Hz), 5.33 (bd, 1 H, *J* = 5.7 Hz), 5.28 (dt, 1 H, *J* = 10.5, 1.2 Hz), 2.11 (bs, 1 H); ^{13}C NMR δ 141.8, 138.0, 123.9, 123.0, 116.0, 110.3, 70.3; MS (EI) *m/z* (rel intensity) 217 (M^+, 10), 204 (50), 203 (85), 202 (45), 201 (80), 191 (65), 189 (60), 177 (25), 175 (25), 122 (100), 84 (50); HRMS (EI) Calcd for C_7H_7OSBr 217.9400, found 217.9407.



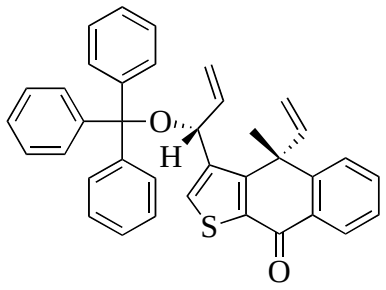
3-Bromo-4-(1-(trityloxy)allyl)thiophene (258). To a solution of 2.4 g (11 mmol) of **259** in 8 mL pyridine was added 3.7 g (13 mmol) of trityl chloride. The reaction mixture was heated at 75 °C overnight, cooled, diluted with H_2O, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 2.7 g (53%) of **258** as a white solid: Mp 108.8-112.4 °C; IR (film) 3085, 3058, 3030, 1490, 1447 cm^{-1}; ^1H NMR δ 7.51-7.45 (m, 6 H), 7.30-7.14 (m, 9 H), 7.05 (d, 1 H, *J* = 3.3 Hz), 6.94 (d, 1 H, *J* = 3.6 Hz), 5.85 (ddd, 1 H, *J* = 17.1, 10.5, 3.6 Hz), 5.15 (s, 1 H), 5.11 (d, 1 H, *J* = 9.3 Hz), 4.99 (d, 1 H, *J* = 10.5 Hz); ^{13}C NMR δ 144.3, 141.7, 138.1, 128.8, 128.6, 127.6, 122.7, 122.1, 114.4, 109.2, 88.3, 73.3; MS (EI) *m/z* (rel intensity) 460 (M^+, 10), 406 (30), 404 (30), 385 (20), 383 (20), 259 (35), 244 (85),

243 (100), 241 (50), 239 (45), 228 (40), 215 (35), 165 (95), 122 (90), 77 (90); HRMS (EI) Calcd for $C_{26}H_{21}OSBr$ 460.0496, found 460.0501.



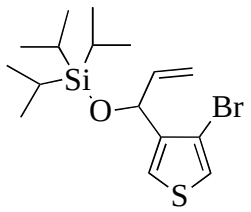
(3-Bromo-4-(1-(trityloxy)allyl)thiophen-2-yl)(2-(but-2-en-2-yl)phenyl)methanone (257). To a solution of 0.11 g (1.1 mmol) of diisopropylamine and 0.20 g (1.1 mmol) of HMPA in 6.0 mL of THF at 0 °C was added 0.67 mL (1.1 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. The resulting pale yellow solution was stirred for 30 min and then a solution of 0.25 g (0.54 mmol) of **258** in 1.0 mL of THF was added. The resulting red solution was stirred for 1 h, treated with 0.10 g (0.65 mmol) of **240**, stirred for 2 h and quenched with a saturated aqueous solution of NH_4Cl. The solution was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→5% EtOAc/hexanes) to yield 0.10 g (70%) of the alcohol as a yellow oil. To a solution of the alcohol in 15 mL of DCM was added 2.5 g (28 mmol) of MnO_2. The mixture was stirred overnight, filtered through celite and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 0.21 g (90%) of **257** as a yellow, oily 3:1 mixture of alkene isomers: IR (film) 3086, 3059, 3024, 2977, 2913, 1643, 1595, 1490, 1446, 1404 cm^{-1}; ^1H NMR δ 7.55-7.50 (m, 7 H), 7.47 (dd, 1 H, *J* = 7.2, 1.5 Hz), 7.39 (d, 1 H, *J* = 6.6 Hz), 7.34 (d, 1 H, *J* = 7.5 Hz), 7.31-7.17 (m, 10 H), 5.95 (ddd, 1 H, *J* = 17.1,

10.2, 6.0 Hz), 5.51 (qq, 1 H, *J* = 6.6, 1.2 Hz), 5.28 (d, 1 H, *J* = 17.1 Hz), 5.24 (d, 1 H, *J* = 6.0 Hz), 5.14 (d, 1 H, *J* = 13.5 Hz), 1.95 (d, 3 H, *J* = 0.9 Hz), 1.43 (dd, 3 H, *J* = 6.6, 1.2 Hz); characteristic signals of minor isomer: ^{1}H NMR δ 1.88 (s, 3 H), 1.63 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 190.0, 188.5, 144.6, 144.4, 144.0, 141.5, 138.3, 137.4, 136.5, 135.5, 134.9, 130.7, 130.4, 129.5, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.7, 126.9, 126.1, 126.0, 123.2, 115.0, 114.2, 113.8, 88.4, 73.03, 72.97, 34.6, 34.5, 31.5, 25.8, 25.2, 22.6, 20.7, 17.4, 15.1, 14.3, 14.1; MS (ES) *m/z* (rel intensity) 641 ([M+^{23}Na]$^{+}$, 25), 621 (80), 619 (75), 243 (75), 165 (100); HRMS (ES) Calcd for $C_{37}H_{31}O_2NaSBr$ 641.1126, found 641.1144.

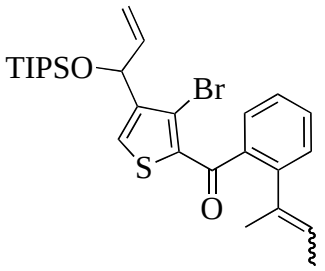


4-Methyl-3-(1-(trityloxy)allyl)-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (256). To a solution of 0.72 g (1.2 mmol) of **257** in 10 mL of NMP divided evenly among 2 microwave reaction vessels was added 0.12 g of $Pd(Ph_3P)_4$ and 1.7 mL of Et_3N. The solutions were heated at 220 °C for 5 min under microwave irradiation, and filtered through a plug of celite, which was washed with Et_2O. The filtrate was washed with brine (2x), and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 0.24 g (38%) of **256** as a white foam: IR (film) 3059, 3029, 1648 cm^{-1}; ^{1}H NMR δ 8.32 (d, 1 H, *J* = 6.9 Hz), 8.19 (s, 1 H), 7.56-7.22 (m, 18 H), 5.68 (dd, 1 H, *J* = 17.4, 10.2 Hz), 5.41-5.17 (m, 4 H), 4.70 (d, 1 H, *J* = 10.5 Hz), 4.64 (d, 1 H, *J* = 17.1 Hz), 1.16 (s, 3 H); ^{13}C NMR δ 178.7, 149.6, 148.6, 144.7, 144.5, 142.0, 139.7, 133.6, 132.7, 130.0, 129.1, 128.1,

127.7, 127.2, 127.0, 126.6, 144.9, 114.4, 88.4, 70.7, 46.0, 27.4; MS (ES) *m/z* (rel intensity) 539 ($[M+H]^+$, 100), 527 (20), 443 (20), 365 (20), 243 (10), 165 (25); HRMS (ES) Calcd for $C_{37}H_{31}O_2S$ 539.2045, found 539.2026.

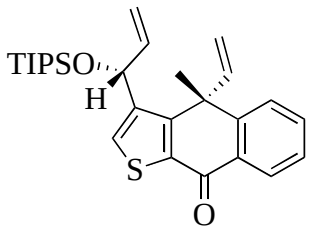


(1-(4-Bromothiophen-3-yl)allyloxy)triisopropylsilane (260). To a solution of 2.0 (9.3 mmol) of **259** in 35 mL of DCM was added 2.0 g (19 mmol) of 2,6-lutidine followed by 4.4 g (14 mmol) of triisopropylsilyl trifluoromethanesulfonate. The reaction mixture was stirred overnight, quenched with a saturated aqueous solution of NH_4Cl, diluted with H_2O, and extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→1% EtOAc/hexanes) to yield 3.1 g (88%) of **260** as pale yellow oil: IR (film) 2943, 2866, 1463, 1384 cm^{-1}; ^1H NMR δ 7.34 (d, 1 H, *J* = 3.3 Hz), 7.23 (d, 1 H, *J* = 3.3 Hz), 5.92 (ddd, 1 H, *J* = 17.1, 10.2, 5.7 Hz), 5.37 (d, 1 H, *J* = 7.5 Hz), 5.33 (d, 1 H, *J* = 17.1 Hz), 5.08 (d, 1 H, *J* = 10.2 Hz), 1.15-1.01 (m, 21 H); ^{13}C NMR δ 143.6, 139.8, 123.0, 122.2, 113.8, 109.2, 72.0, 18.0, 17.9, 12.2; MS (EI) *m/z* (rel intensity) 335 (5), 334 (20), 333 (85), 331 ($[M-C_3H_7]^+$, 85), 203 (20), 201 (20), 122 (100), 121 (20); HRMS (EI) Calcd for $C_{13}H_{20}OSiSBr$ 331.0187, found 331.0186.



(3-Bromo-4-(1-(triisopropylsilyloxy)allyl)thiophen-2-yl)(2-(but-2-en-2-yl)phenyl)methanone (261). To a solution of 81 mg (0.80 mmol) of diisopropylamine and 0.14 g (0.80 mmol) of HMPA in 3.0 mL THF at 0 °C was added 0.50 mL (0.80 mmol) of a 1.6 M solution n-BuLi in hexanes. The resulting pale yellow solution was stirred for 30 min then a solution of 0.10 g (0.27 mmol) of **260** in 0.50 mL of THF was added. The resulting red solution was stirred for 1 h., treated with 0.51 mg (0.31 mmol) of **240**, stirred for 2 h, and quenched with a saturated aqueous solution of NH_4Cl. The solution was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→5% EtOAc/hexanes) to yield 76 mg (53%) of the alcohol as a yellow oil. To a solution of the alcohol in 18 mL of DCM was added 2.2 g (98 mmol) of MnO_2. The mixture was stirred overnight, filtered through celite and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 0.15 g (86%) of **261** as a yellow, oily 3:1 mixture of alkene isomers: IR (film) 2942, 2891, 2866, 1648 cm^{-1}; ^1H NMR δ 7.62 (s, 1 H), 7.49 (d, 2 H, *J* = 7.2 Hz), 7.35 (t, 1 H, *J* = 6.6 Hz), 7.20 (d, 1 H, *J* = 7.2 Hz), 5.89 (ddd, 1 H, *J* = 13.5, 10.2, 5.4), 5.46-5.28 (m, 3 H), 5.10 (d, 1 H, *J* = 10.2 Hz), 1.89 (s, 3 H), 1.38 (d, 3 H, *J* = 6.6 Hz), 1.16-1.00 (m, 21 H); characteristic signals for minor isomer: ^1H NMR δ 7.56 (s, 1 H), 7.45 (d, 2 H, *J* = 7.5 Hz), 1.84 (s, 3 H), 1.54 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 190.6, 189.4, 146.3, 146.2, 144.5, 141.2, 139.0, 138.9, 137.9, 135.3, 134.6, 130.7, 130.5, 129.2, 128.3, 128.2, 127.9, 127.8, 127.6, 127.1, 126.3, 123.9, 114.2, 114.1, 113.7,

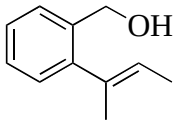
113.2, 71.6, 71.5, 25.5, 17.9, 17.8, 17.0, 15.1, 14.2, 12.0; MS (ES) *m/z* (rel intensity) 533($[M+H]^+$, 100), 527 (40), 443 (20), 365 (40), 362 (10); HRMS (ES) Calcd for $C_{27}H_{38}SiSBr$ 533.1545, found 533.1553.



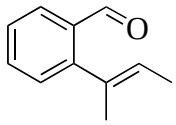
4-methyl-3-(1-(triisopropylsilyloxy)allyl)-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (262).

A solution of 0.63 g (1.2 mmol) of **261** in 12 mL of NMP was divided evenly among 3 microwave reaction vessels containing 84 mg of $Pd(Ph_3P)_4$ and 1.2 mL of Et_3N. The solutions were heated at 220 °C for 5 min under microwave irradiation, and filtered through a plug of celite, which was washed with Et_2O. The filtrate was washed with brine (2x), and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→2% EtOAc/hexanes) to yield 0.70 g (55%) of **262** as a yellow, oily 2.2:1 mixture of diastereomers: IR (film) 2942, 2865, 1652, 1455 cm^{-1}; ^1H NMR δ 8.32 (d, 1 H, *J* = 7.5 Hz), 7.88 (s, 1 H), 7.58 (d, 1 H, *J* = 6.9 Hz), 7.50 (d, 1 H, *J* = 6.9 Hz), 7.44 (t, 1 H, *J* = 7.2 Hz), 6.10-5.88 (m, 3 H), 5.70 (d, 1 H, *J* = 4.5 Hz), 5.62 (d, 1 H, *J* = 17.4 Hz), 5.47 (d, 1 H, *J* = 10.5 Hz), 5.20 (d, 1 H, *J* = 18.3 Hz), 5.04 (d, 1 H, *J* = 10.5 Hz), 1.77 (s, 3 H), 1.17-0.95 (m, 21 H); characteristic signals for minor isomer: ^1H NMR δ 7.96 (s, 1 H), 5.78 (d, 1 H, *J* = 6.0 Hz), 5.65 (d, 1 H, *J* = 17.4 Hz), 5.12 (d, 1 H, *J* = 5.1 Hz); ^{13}C NMR δ 178.7, 178.6, 149.4, 148.6, 148.5, 146.6, 146.5, 142.7, 141.7, 141.3, 141.2, 137.1, 136.9, 133.4, 133.3, 132.8, 130.1, 130.0, 128.4, 128.2, 127.1, 126.7, 126.6, 115.3, 115.1, 114.7, 113.5, 69.4, 46.2, 46.1, 27.9, 27.6, 18.0,

17.9, 12.5, 12.3; MS (ES) *m/z* (rel intensity) 453 (M^+, 100), 365 (20); HRMS (ES) Calcd for $C_{27}H_{37}O_2SSi$ 453.2284, found 453.2260.

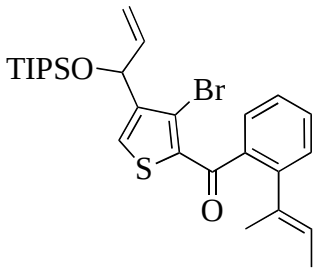


(*E*)-(2-(But-2-en-2-yl)phenyl)methanol (264). To a solution of 0.10 g (0.66 mmol) of 2-(hydroxymethyl)phenylboronic acid (**263**) in 5.0 mL of THF and 1.0 mL of 3 M NaOH was added 0.10 g (0.73 mmol) of (*E*)-2-bromobutene and 76 mg (0.07 mmol) of $Pd(Ph_3P)_4$. The reaction was heated at reflux for 2 h, cooled, diluted with H_2O, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 90 mg (84%) of **264** as a colorless oil: IR (film) 3331, 3020, 2917, 1483, 1444 cm^{-1}; ^1H NMR δ 7.47-7.41 (m, 1 H), 7.31-7.22 (m, 2 H), 7.15-7.10 (m, 1 H), 5.42 (qq, 1 H, *J* = 6.9, 1.5 Hz), 4.67 (s, 2 H), 2.18 (s, 1 H), 1.96 (q, 3 H, *J* = 0.9 Hz), 1.78 (dq, 3 H, *J* = 6.6, 1.2 Hz); ^{13}C NMR δ 144.4, 137.5, 135.4, 128.1, 127.4, 126.9, 126.5, 123.9, 62.3, 18.0, 13.6; MS (EI) *m/z* (rel intensity) 162 (M^+, 65), 117 (40), 115 (100), 105 (65), 91 (95); HRMS (EI) Calcd for $C_{11}H_{14}O$ 162.1044, found 162.1055.



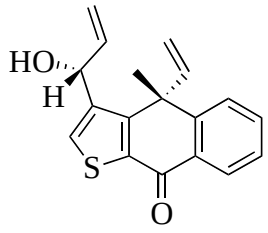
(*E*)-2-(But-2-en-2-yl)benzaldehyde (265). To a suspension of 0.97 g (4.5 mmol) of PCC and 1.2 g of celite in 20 mL of DCM was added a solution of 0.490 g (3.0) mmol of **264** in 10 mL of DCM. The resulting mixture was stirred for 30 min, filtered through a plug of SiO_2, which was

washed with DCM, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 90 mg (99%) of **265** as a colorless oil: IR (film) 3061, 3020, 2982, 2917, 2856, 2744, 1691, 1650, 1596 cm^{-1}; ^1H NMR δ 10.12 (s, 1 H), 7.90 (d, 1 H, *J* = 7.8 Hz), 7.53 (dt, 1 H, *J* = 7.2, 0.9 Hz), 7.37 (d, 1 H, *J* = 7.5 Hz), 7.32 (d, 1 H, *J* = 8.1 Hz), 5.43 (q, 1 H, *J* = 6.9 Hz), 2.08 (s, 3 H), 1.85 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 191.3, 148.9, 133.2, 132.6, 132.4, 128.2, 128.1, 127.0, 126.2, 17.8, 13.6; MS (EI) *m/z* (rel intensity) 160 (M^+, 20), 159 (10), 146 (20), 145 (100), 131 (25), 117 (50), 115 (60), 103 (20), 91 (40); HRMS (EI) Calcd for $C_{11}H_{12}O$ 160.0888, found 160.0887.



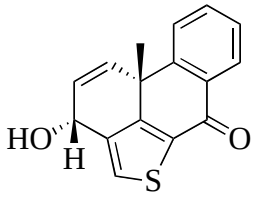
(*E*)-(3-Bromo-4-(1-(triisopropylsilyloxy)allyl)thiophen-2-yl)(2-(but-2-en-2-yl)phenyl)methanone (266). To a solution of 0.49 g (4.8 mmol) of diisopropylamine and 0.87 g (4.8 mmol) of HMPA in 25 mL of THF at 0 °C was added 3.0 mL (4.8 mmol) of a 1.6 M solution *n*-BuLi in hexanes. The resulting pale yellow solution was stirred for 30 min then a solution of 0.9 g (2.4 mmol) of **260** in 4.0 mL of THF was added. The resulting red solution was stirred for 1 h, treated with 0.46 g (2.9 mmol) of the **265** stirred for 2 h, and quenched with a saturated aqueous solution of NH_4Cl. The solution was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5% EtOAc/hexanes) to yield 0.70 g (55%) of the alcohol as a yellow oil. To a solution of the alcohol in 80 mL of DCM was added

8.7 g (98 mmol) of MnO_2. The mixture was stirred overnight, filtered through celite and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 0.63 g (90%) of **266** as a yellow oil: IR (film) 2942, 2891, 2865, 1646 cm^{-1}; ^1H NMR δ 7.57 (s, 1 H), 7.45 (d, 2 H, *J* = 7.5 Hz), 7.34 (dd, 1 H, *J* = 8.1, 1.8 Hz), 7.30 (d, 1 H, *J* = 7.2 Hz), 5.88 (ddd, 1 H, *J* = 17.1, 10.2, 5.7 Hz), 5.44 (qq, 1 H, *J* = 6.9, 1.5 Hz), 5.39 (d, 1 H, *J* = 5.7 Hz), 5.31 (d, 1 H, *J* = 17.1 Hz), 5.09 (d, 1 H, *J* = 10.2 Hz), 1.84 (s, 3 H), 1.55 (dd, 3 H, *J* = 6.9, 0.9 Hz), 1.16-1.08 (m, 3 H), 1.04 (d, 9 H, *J* = 7.2 Hz), 1.02 (d, 9 H, *J* = 6.9 Hz); ^{13}C NMR δ 190.5, 146.1, 144.5, 138.9, 138.7, 138.6, 134.6, 130.4, 128.2, 127.9, 127.6, 127.0, 126.3, 114.0, 113.1, 71.6, 17.82, 17.80, 17.0, 14.2, 12.0; MS (ES) *m/z* (rel intensity) 535 (100), 533 ($[M+H]^+$, 100); HRMS (ES) Calcd for $C_{27}H_{38}O_2SiSBr$ 533.1545, found 533.1552.

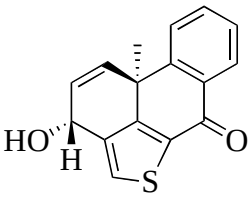


3-(1-Hydroxyallyl)-4-methyl-4-vinylnaphtho[2,3-*b*]thiophen-9(4*H*)-one (255). To a solution of 0.16 g (0.35 mmol) of **262** in 3.0 mL of THF at 0 °C was added 0.71 mL (0.71 mmol) of a 1 M solution of TBAF in THF. After 15 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, diluted with H_2O, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (25% EtOAc/hexanes) to yield 91 mg (87%) of **255** as an off-white, sticky foam 2.2:1 mixture of diastereomers: IR (film) 3424, 1640, 1597 cm^{-1}; ^1H NMR δ 8.33 (d, 1 H, *J* = 7.5 Hz), 7.79 (s, 1 H), 7.61 (d, 1 H, *J* = 7.5 Hz), 7.55 (d, 1 H, *J* = 6.9 Hz), 7.45 (dd, 1 H, *J* = 7.8, 6.9 Hz), 6.20-6.08 (m, 1 H), 6.01 (dd, 1 H, *J* = 17.4, 10.5 Hz),

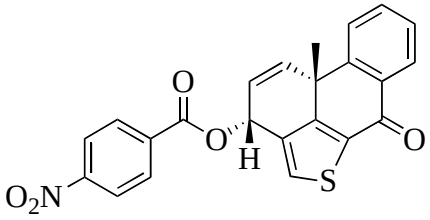
5.72 (s, 1 H), 5.61-5.50 (m, 2 H), 5.46-5.37 (m, 2 H), 5.27 (d, 1 H, *J* = 10.5 Hz), 1.92 (s, 3 H); characteristic signals of minor isomer: ^{1}H NMR δ 7.85 (s, 1 H), 1.76 (s, 3 H); ^{13}C NMR δ 178.7, 178.6, 151.1, 150.6, 149.2, 148.8, 144.7, 144.4, 141.8, 139.4, 137.2, 137.0, 134.2, 133.0, 129.5, 129.4, 128.3, 127.0, 126.9, 126.5, 115.7, 115.1, 115.0, 114.3, 67.6, 67.4, 46.0, 45.8, 27.9, 27.6; MS (EI) *m/z* (rel intensity) 296 (M^+, 25), 281 (35), 267 (40), 253 (30), 237 (35), 94 (100), 83 (45); HRMS (EI) Calcd for $C_{18}H_{16}O_2S$ 296.0871, found 296.0871.



3-Hydroxy-10b-methyl-3*H*-phenanthro[10,1-*bc*]thiophen-6(10b*H*)-one (267). To a solution of 106 mg (0.36 mmol) of **255** in 50 mL of DCM was added 45 mg (0.07 mmol) of **223**. The reaction mixture was heated at reflux for 3 h, cooled, filtered through florisil and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→30% EtOAc/hexanes) to yield 46 mg (48%) of **267** as the major and less polar diastereomer as a white foam and 14 mg (15%) of a minor and more polar diastereomer: Characteristic signals for major diastereomer: IR (film) 3404, 1644, 1565, 1451, 1416 cm^{-1}; ^{1}H NMR δ 8.35 (d, 1 H, *J* = 8.1 Hz), 7.82 (s, 1 H), 7.76 (d, 1 H, *J* = 6.8 Hz), 7.66 (dt, 1 H, *J* = 7.5, 1.2 Hz), 7.49 (t, 1 H, *J* = 7.2 Hz), 6.75 (dd, 1 H, *J* = 9.9, 2.7 Hz), 6.19 (dd, 1 H, *J* = 10.2, 1.8 Hz), 5.35 (s, 1 H), 2.15 (bs, 1 H), 1.47 (s, 3 H); ^{13}C NMR δ 178.7, 153.4, 147.6, 142.0, 132.92, 132.89, 132.6, 132.0, 131.7, 129.7, 128.0, 127.1, 125.0, 65.1, 41.3, 37.5; MS (EI) *m/z* (rel intensity) 268 (M^+, 10), 266 (30), 253 (85), 251 (100), 223 (30), 195 (20); HRMS (EI) Calcd for $C_{16}H_{12}O_2S$ 268.0558, found 268.0556.

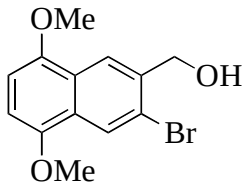


Characteristic signals for minor diastereomer: IR (film) 3401, 1645, 1596, 1452, 1328 cm^{-1}; ^1H NMR δ 8.35 (dd, 1 H, *J* = 6.6, 1.5 Hz), 7.81 (s, 1 H), 7.76 (d, 1 H, *J* = 7.8 Hz), 7.64 (ddd, 1 H, 7.8, 7.5, 1.5 Hz), 7.47 (ddd, 1 H, *J* = 7.8, 7.2, 1.2 Hz), 6.99 (d, 1 H, *J* = 9.9 Hz), 6.30 (dd, 1 H, *J* = 9.6, 5.1 Hz), 5.32 (d, 1 H, *J* = 5.4 Hz), 1.72 (s, 3 H); ^{13}C NMR δ 178.2, 156.9, 147.7, 138.6, 136.7, 133.3, 132.8, 132.7, 132.1, 128.4, 128.1, 127.0, 124.3, 62.1, 41.9, 41.8; MS (EI) *m/z* (rel intensity) 268 (M^+, 10), 254 (50), 253 (100); HRMS (EI) Calcd for $C_{16}H_{12}O_2S$ 268.0558, found 268.0541.

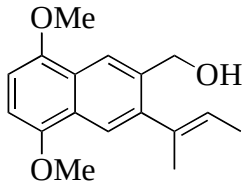


10b-Methyl-6-oxo-6,10b-dihydro-3*H*-phenanthro[10,1-*bc*]thiophen-3-yl 4-nitrobenzoate (268). To a solution of 35 mg (0.13 mmol) of **267** in 2.0 mL of DCM was added 5.0 mg (0.039 mmol) of DMAP, 40 mg (0.39 mmol) of Et_3N and 50 mg (0.26 mmol) of 4-nitrobenzoyl chloride. The reaction mixture was stirred overnight, quenched with H_2O and extracted with DCM (3x). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl, H_2O and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→15% EtOAc/hexanes) to yield 37 mg (68%) of **268** as a white foam: IR (film) 3108, 2969, 2921, 1725, 1650, 1598, 1527, 1453 cm^{-1}; ^1H NMR δ 8.37 (dd, 1 H, *J* = 7.8, 0.6 Hz), 8.31 (s, 4 H), 7.78 (d, 1 H, *J* = 7.8 Hz), 7.70-7.65 (m, 2 H), 7.50 (t, 1

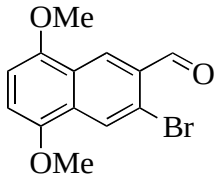
H, *J* = 7.5 Hz), 6.94 (dd, 1 H, *J* = 9.9, 2.4 Hz), 6.73 (s, 1 H), 6.20 (dd, 1 H, *J* = 10.2, 1.8 Hz), 1.56 (s, 3 H); ^{13}C NMR δ 178.2, 164.4, 152.9, 150.9, 146.9, 136.1, 134.8, 134.1, 133.4, 133.0, 131.8, 131.0, 129.7, 128.2, 127.31, 127.29, 124.7, 123.7, 67.8, 41.3, 38.5; MS (EI) *m/z* (rel intensity) 417 (M^+, 65), 368 (10), 83 (50), 69 (85), 57 (100); HRMS (EI) Calcd for $C_{23}H_{15}NO_5S$ 417.0670, found 417.0668.



(3-Bromo-5,8-dimethoxynaphthalen-2-yl)methanol (277). To a solution of 145 mg (0.42 mmol) of **183**[171,172] in 4.0 mL of DCM at -78 °C was added 0.94 mL (0.94 mmol) of DiBAL. The resulting solution was stirred for 15 min, quenched with a saturated aqueous solution of NH_4Cl and warmed to room temperature. The solution was then diluted with H_2O and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→25% EtOAc/hexanes) to yield 91 mg (72%) of **277** as a white solid: Mp 139.9-140.3 °C; IR (film) 3583, 3333, 2925 cm^{-1}; ^{1}H NMR δ 8.42 (s, 1 H), 8.27 (s, 1 H), 6.75 (s, 2 H), 4.90 (s, 2 H), 3.96 (s, 6 H), 2.10 (t, 1 H, *J* = 6.3 Hz); ^{13}C NMR δ 149.4, 148.4, 136.8, 126.7, 125.8, 125.2, 122.0, 120.8, 104.3, 103.9, 65.5, 55.71, 55.67; MS (EI) *m/z* (rel intensity) 296 (M^+, 50), 283 (40), 281 (40), 111 (35), 109 (25); HRMS (EI) Calcd for $C_{13}H_{13}O_3Br$ 296.0048, found 296.0045.

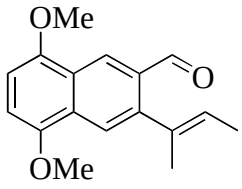


(*E*)-(3-(But-2-en-2-yl)-5,8-dimethoxynaphthalen-2-yl)methanol (278). To a solution of 90 mg (0.30 mmol) of **277** in 3.0 mL of 5:1 THF/ 3 M NaOH was added 45 mg (0.45 mmol) **212**[182] and 32 mg (0.030 mmol) of $Pd(PPh_3)_4$. The resulting solution was heated at reflux for 1 h, cooled, diluted with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→25% EtOAc/hexanes) to yield 60 mg (73%) of **278** as a yellow oil: IR (film) 3384, 2936, 2833, 1598, 1461, 1434 cm^{-1}; ^1H NMR δ 8.26 (s, 1 H), 7.93 (s, 1 H), 6.68 (s, 2 H), 5.53 (qq, 1 H, *J* = 6.6, 1.2 Hz), 4.82 (d, 2 H, *J* = 5.7 Hz), 3.96 (s, 6 H, 2.03 (s, 3 H), 1.95 (t, 1 H, *J* = 6.0 Hz), 1.81 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 149.4, 149.2, 142.9, 136.5, 136.1, 125.5, 125.1, 124.5, 121.1, 120.5, 103.2, 102.9, 63.7, 55.59, 55.55, 18.3, 13.9; MS (EI) *m/z* (rel intensity) 272 (M^+, 100), 257 (100), 213 (45), 115 (50); HRMS (ES) Calcd for $C_{17}H_{20}O_3Na$ 295.1310, found 295.1314.

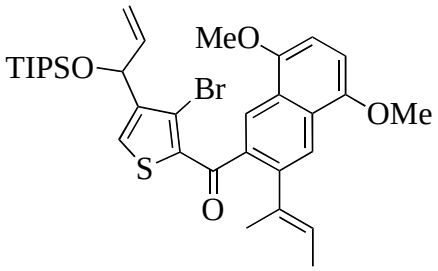


3-Bromo-5,8-dimethoxy-2-naphthaldehyde (279). To a solution of 50 mg (0.17 mmol) of **277** in 2.0 mL of DCM was added 86 mg (0.2 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 30 min, and quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the

combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to yield 48 mg (97%) of **279** as a yellow solid: Mp 164.0-166.2 °C; IR (film) 2962, 2836, 1739, 1688, 1620, 1574, 1461, 1430 cm^{-1}; ^1H NMR δ 10.62 (s, 1 H), 8.69 (s, 1 H), 8.36 (s, 1 H), 6.78 (d, 1 H, *J* = 8.4 Hz), 6.69 (d, 1 H, *J* = 8.4 Hz), 3.93 (s, 6 H); ^{13}C NMR δ 191.9, 150.6, 147.9, 129.9, 129.3, 126.9, 126.5, 124.4, 120.9, 107.6, 104.3, 55.7, 55.6; MS (EI) *m/z* (rel intensity) 294 ($[M]^+$, 80), 281 (100), 279 (100).

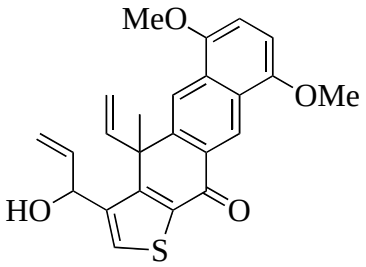


(*E*)-3-(but-2-en-2-yl)-5,8-dimethoxy-2-naphthaldehyde (280). To a solution of 52 mg (0.17 mmol) of **279** in 1.3 mL of 5:1 THF/ 3 M NaOH was added 26 mg (0.26 mmol) of **212**[182] and 19 mg (0.018 mmol) $Pd(PPh_3)_4$. The resulting solution was heated at reflux for 1 h, cooled, diluted with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (0→25% EtOAc/hexanes) to yield 32 mg (67%) of **280** as a yellow oil: IR (film) 2936, 2835, 1688, 1637, 1625, 1462, 1433 cm^{-1}; ^1H NMR δ 10.24 (s, 1 H), 8.79 (s, 1 H), 8.05 (s, 1 H), 6.80 (d, 1 H, *J* = 8.4 Hz), 6.68 (d, 1 H, *J* = 8.4 Hz), 5.52 (qq, 1 H, *J* = 6.9, 1.2 Hz), 3.96 (s, 6 H), 2.11 (d, 3 H, *J* = 0.6 Hz), 1.86 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 192.8, 150.6, 148.9, 144.3, 134.3, 131.6, 128.4, 127.3, 125.1, 124.4, 121.9, 106.4, 103.4, 55.7, 55.6, 18.9, 14.2; MS (EI) *m/z* (rel intensity) 270(M^+, 60), 255 (100), 237 (50), 227 (55), 139 (55); HRMS (EI) Calcd for $C_{17}H_{18}O_3$ 270.1255, found 270.1260.



(*E*)-(3-Bromo-4-(1-(triisopropylsilyloxy)allyl)thiophen-2-yl)(3-(but-2-en-2-yl)-5,8-dimethoxynaphthalen-2-yl)methanone (281). To a solution of 64 mg (0.63 mmol) of diisopropylamine and 0.11 g (0.63 mmol) of HMPA in 3.0 mL of THF at 0 °C as added 0.40 mL (0.63 mmol) of a 1.6 M solution *n*-BuLi in hexanes. The resulting pale yellow solution was stirred for 30 min and then a solution of 0.12 g (0.31 mmol) of **260** in 1.0 mL of THF was added. The resulting red solution was stirred for 1 h. Then, a solution of 0.10 g (0.37 mmol) of **280** in 1.0 mL of THF was added. The reaction mixture was stirred for 2 h, quenched with a saturated aqueous solution of NH_4Cl, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→5% EtOAc/hexanes) to yield 0.10 g (49%) of the alcohol as a yellow oil. To a solution of 0.10 g (0.15 mmol) of the alcohol in 2.0 mL of DCM was added 0.080 g (0.18 mmol) of Dess-Martin periodinane at room temperature. The reaction mixture was stirred for 30 min, and quenched with a 1:1 solution of saturated aqueous $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM (3x), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (0→5% EtOAc/hexanes) to yield 29 mg (29%) of **281** as a yellow oil: IR (film) 2941, 2865, 1657, 1626, 1589, 1462 cm^{-1}; ^1H NMR δ 8.35 (s, 1 H), 8.09 (s, 1 H), 7.59 (s, 1 H), 6.78 (d, 1 H, *J* = 8.4 Hz), 6.70 (d, 1 H, *J* = 8.4 Hz), 5.89 (ddd, 1 H, *J* = 17.1, 10.2, 5.7 Hz), 5.54 (qq, 1 H, *J* = 6.9, 1.5 Hz), 5.40 (d, 1 H, *J* = 5.7 Hz), 5.31 (ddd, 1 H, *J* = 17.1, 1.2 Hz), 5.09 (d, 1 H, *J* = 10.2

Hz), 3.98 (s, 3 H), 3.94 (s, 3 H), 1.94 (s, 3 H), 1.60 (dd, 3 H, *J* = 6.6, 0.6 Hz), 1.17-1.08 (m, 3 H), 1.05 (d, 9 H, *J* = 7.2 Hz), 1.03 (d, 9 H, *J* = 6.6 Hz); ^{13}C NMR δ 190.5, 150.0, 149.1, 146.2, 141.6, 139.1, 138.8, 137.2, 135.2, 127.5, 127.3, 127.1, 124.2, 123.4, 120.8, 114.1, 113.6, 105.1, 103.4, 71.6, 55.67, 55.65, 17.92, 17.89, 17.6, 14.3, 12.1; MS (ES) *m/z* (rel intensity) 667 (100), 665 ([M+^{23}Na]$^{+}$, 65); HRMS (ES) Calcd for $C_{33}H_{43}O_4NaSiSBr$ 665.1732, found 665.1715.



3-(1-Hydroxyallyl)-6,9-dimethoxy-4-methyl-4-vinylanthra[2,3-*b*]thiophen-11(4*H*)-one (282). To a solution of 29 mg (0.045 mmol) of **281** in 0.50 mL of NMP in a microwave reaction vessel was added 9.0 mg (0.085 mmol) of $Pd(Ph_3P)_4$ and 0.13 mL (of Et_3N. The solution was heated at 220 °C for 5 min under microwave irradiation, and filtered through a plug of celite, which was washed with Et_2O. The filtrate was washed with brine (2x), and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by chromatography on SiO_2 (0→3% EtOAc/hexanes) to give 18 mg of the alcohol as a yellow oil. To a solution of 18 mg (0.031 mmol) of the alcohol in 0.50 mL of THF at 0 °C was added 0.10 mL (0.10 mmol) of a 1 M solution of TBAF in THF. The solution was stirred for 15 min, quenched with a saturated aqueous solution of NH_4Cl, diluted with H_2O and, extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→20% EtOAc/hexanes) to yield 11 mg (60%) of **282** as a yellow, oily 2.1:1 mixture of diastereomers: IR (film) 3428, 2928, 1649, 1622, 1468, 1434, 1396 cm^{-1}; ^{1}H NMR δ 9.25 (s, 1 H), 8.34 (s, 1 H), 7.81 (s, 1 H), 6.80 (d, 1 H, *J* = 8.4

Hz), 6.70 (d, 1 H, *J* = 8.4 Hz), 6.21-6.07 (m, 2 H), 5.78 (bs, 1 H), 5.65 (d, 1 H, *J* = 12.6 Hz), 5.56 (d, 1 H, *J* = 9.6 Hz), 5.48-5.39 (m, 1 H), 5.27 (d, 1 H, *J* = 10.2 Hz), 4.00 (s, 3 H), 3.98 (s, 3 H), 1.99 (s, 3 H); characteristic signals for minor isomer: ^{1}H NMR δ 8.32 (s, 1 H), 7.87 (s, 1 H), 6.29 (dd, 1 H, *J* = 17.1, 10.2 Hz), 1.84 (s, 3 H); ^{13}C NMR δ 178.8, 151.1, 150.8, 150.6, 148.8, 144.8, 144.5, 144.4, 143.2, 142.9, 139.5, 139.3, 138.2, 134.3, 134.2, 128.5, 128.46, 127.4, 125.03, 125.00, 123.0, 122.9, 121.9, 115.7, 114.8, 114.7, 114.5, 105.93, 105.89, 103.4, 103.3, 67.8, 67.7, 55.8, 55.7, 46.3, 46.1, 29.4, 29.1; MS (ES) *m/z* (rel intensity) 429 ([M+^{23}Na]$^{+}$, 100); HRMS (ES) Calcd for $C_{24}H_{22}O_4NaS$ 429.1137, found 429.1134.

Convertion of **282** to **224.** To a solution of 11 mg (0.027 mmol) of **282** in 11 mL of DCM was added 3.4 mg (0.0054 mmol) of **223**. The reaction mixture was heated at reflux for 2 h, cooled filtered through florisil, which was washed with EtOAc and the combined filtrates were concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (0→40% EtOAc/hexanes) to give 9 mg (87%) of **224** as a 3.5:1 yellow, glassy mixture of diastereomers.

APPENDIX A

X-RAY CRYSTAL DATA FOR 106

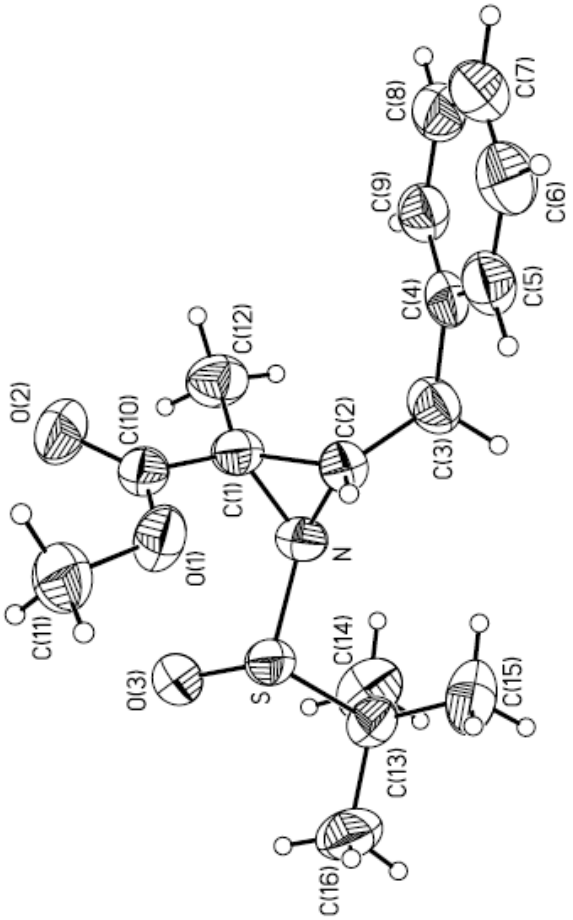


Table A1. Crystal data and structure refinement for bw0407t.

Identification code	bw0407t	
Empirical formula	C16 H23 N O3 S	
Formula weight	309.41	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.4576(7) Å	a= 90°.
	b = 13.6267(12) Å	b= 108.086(2)°.
	c = 8.6904(8) Å	g = 90°.
Volume	839.51(13) $Å^3$	
Z	2	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.202 mm^{-1}	
F(000)	332	
Crystal size	0.27 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.47 to 30.00°.	
Index ranges	-10<=h<=10, -19<=k<=18, -12<=l<=12	
Reflections collected	9774	
Independent reflections	4740 [R(int) = 0.0416]	
Completeness to theta = 30.00°	99.80%	
Absorption correction	None	
Max. and min. transmission	0.9607 and 0.9475	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4740 / 1 / 191	
Goodness-of-fit on F^2	0.956	
Final R indices [I>2sigma(I)]	R1 = 0.0579, wR2 = 0.1207	
R indices (all data)	R1 = 0.0898, wR2 = 0.1328	
Absolute structure parameter	0.07(8)	
Largest diff. peak and hole	0.280 and -0.149 $e.Å^{-3}$	

Table A2. Atomic coordinates ($x\ 10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for bw0407t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	1064(1)	3901(1)	9130(1)	47(1)
N	1364(3)	5038(2)	10073(3)	47(1)
O(1)	399(3)	3521(2)	12086(3)	58(1)
C(1)	558(4)	5202(2)	11429(3)	45(1)
O(2)	-1925(3)	4494(2)	12230(3)	71(1)
C(2)	2648(4)	5110(2)	11757(3)	47(1)
O(3)	-963(3)	3869(2)	8249(3)	68(1)
C(3)	3971(4)	5983(2)	12096(4)	57(1)
C(4)	4553(4)	6313(2)	13834(4)	49(1)
C(5)	5841(4)	5777(2)	15037(4)	58(1)
C(6)	6434(4)	6081(3)	16606(4)	69(1)
C(7)	5744(5)	6940(3)	17026(4)	70(1)
C(8)	4496(4)	7488(2)	15881(4)	63(1)
C(9)	3884(4)	7183(2)	14285(4)	55(1)
C(10)	-464(4)	4375(2)	11955(3)	46(1)
C(11)	-627(5)	2672(2)	12332(5)	72(1)
C(12)	-396(5)	6171(3)	11364(4)	63(1)
C(13)	2315(4)	4195(2)	7665(3)	50(1)
C(14)	1526(5)	5095(3)	6679(4)	75(1)
C(15)	4382(4)	4292(3)	8641(5)	79(1)
C(16)	2001(6)	3277(3)	6610(5)	81(1)

Table A3. Bond lengths [Å] and angles [°] for bw0407t.

S-O(3)	1.468(2)	C(10)-O(1)-C(11)	117.1(2)
S-N	1.734(2)	C(12)-C(1)-N	113.9(2)
S-C(13)	1.841(3)	C(12)-C(1)-C(2)	122.4(3)
N-C(2)	1.483(3)	N-C(1)-C(2)	59.34(16)
N-C(1)	1.496(3)	C(12)-C(1)-C(10)	113.1(2)
O(1)-C(10)	1.318(3)	N-C(1)-C(10)	119.5(2)
O(1)-C(11)	1.439(4)	C(2)-C(1)-C(10)	118.2(2)
C(1)-C(12)	1.493(4)	N-C(2)-C(1)	60.22(16)
C(1)-C(2)	1.499(4)	N-C(2)-C(3)	115.2(2)
C(1)-C(10)	1.508(4)	C(1)-C(2)-C(3)	123.2(3)
O(2)-C(10)	1.196(3)	C(4)-C(3)-C(2)	113.4(2)
C(2)-C(3)	1.514(4)	C(5)-C(4)-C(9)	117.6(3)
C(3)-C(4)	1.505(4)	C(5)-C(4)-C(3)	121.0(3)
C(4)-C(5)	1.388(4)	C(9)-C(4)-C(3)	121.4(3)
C(4)-C(9)	1.388(4)	C(6)-C(5)-C(4)	121.9(3)
C(5)-C(6)	1.361(5)	C(5)-C(6)-C(7)	119.6(3)
C(6)-C(7)	1.374(5)	C(8)-C(7)-C(6)	120.2(3)
C(7)-C(8)	1.356(5)	C(7)-C(8)-C(9)	120.6(3)
C(8)-C(9)	1.383(5)	C(8)-C(9)-C(4)	120.3(3)
C(13)-C(14)	1.506(4)	O(2)-C(10)-O(1)	123.5(3)
C(13)-C(15)	1.517(4)	O(2)-C(10)-C(1)	122.5(3)
C(13)-C(16)	1.526(4)	O(1)-C(10)-C(1)	114.0(2)
O(3)-S-N	103.55(12)	C(14)-C(13)-C(15)	113.4(3)
O(3)-S-C(13)	107.85(13)	C(14)-C(13)-C(16)	111.4(3)
N-S-C(13)	96.53(12)	C(15)-C(13)-C(16)	110.3(3)
C(2)-N-C(1)	60.44(16)	C(14)-C(13)-S	112.2(2)
C(2)-N-S	118.33(18)	C(15)-C(13)-S	106.1(2)
C(1)-N-S	118.74(18)	C(16)-C(13)-S	102.7(2)

Table A4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw0407t. The anisotropic displacement factor exponent take the form: $-2p^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	53(1)	41(1)	52(1)	-6(1)	24(1)	-3(1)
N	50(1)	47(1)	43(1)	-9(1)	14(1)	-2(1)
O(1)	53(1)	52(1)	78(1)	10(1)	34(1)	4(1)
C(1)	46(1)	45(2)	42(1)	-5(1)	12(1)	4(1)
O(2)	52(1)	77(2)	96(2)	-8(1)	38(1)	2(1)
C(2)	45(1)	47(1)	49(1)	-3(1)	17(1)	-6(1)
O(3)	54(1)	76(1)	78(1)	-29(1)	26(1)	-17(1)
C(3)	58(2)	57(2)	56(2)	-3(1)	17(1)	-15(1)
C(4)	39(1)	49(2)	62(2)	-5(1)	17(1)	-13(1)
C(5)	43(2)	51(2)	74(2)	-4(2)	12(2)	-2(1)
C(6)	49(2)	78(2)	71(2)	3(2)	6(2)	1(2)
C(7)	62(2)	84(3)	62(2)	-14(2)	17(2)	-20(2)
C(8)	54(2)	55(2)	83(2)	-16(2)	26(2)	-7(2)
C(9)	48(2)	49(2)	67(2)	0(1)	17(1)	-3(1)
C(10)	43(1)	55(2)	41(1)	-7(1)	13(1)	-3(1)
C(11)	78(2)	58(2)	91(2)	0(2)	43(2)	-15(2)
C(12)	67(2)	55(2)	67(2)	-6(1)	19(2)	13(2)
C(13)	52(2)	51(2)	52(2)	2(1)	23(1)	3(1)
C(14)	91(3)	72(2)	70(2)	20(2)	35(2)	16(2)
C(15)	51(2)	107(3)	84(2)	7(2)	28(2)	-4(2)
C(16)	105(3)	72(2)	88(2)	-20(2)	62(2)	-7(2)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bw0407t.

	x	y	z	U(eq)
H(2A)	3217	4477	12259	56
H(3B)	5114	5809	11806	68
H(3C)	3345	6536	11395	68
H(5A)	6321	5180	14757	69
H(6A)	7321	5701	17406	83
H(7A)	6142	7151	18122	84
H(8A)	4038	8086	16177	75
H(9A)	3003	7569	13493	66
H(11A)	154	2085	12406	108
H(11B)	-1788	2604	11419	108
H(11C)	-946	2749	13337	108
H(12A)	329	6678	11018	95
H(12B)	-471	6335	12440	95
H(12C)	-1670	6137	10592	95
H(14A)	2232	5224	5919	113
H(14B)	1638	5659	7401	113
H(14C)	194	4985	6074	113
H(15A)	5117	4451	7914	118
H(15B)	4831	3671	9195	118
H(15C)	4533	4816	9443	118
H(16A)	2618	3358	5774	122
H(16B)	645	3176	6096	122
H(16C)	2537	2707	7283	122

APPENDIX B

X-RAY CRYSTAL DATA FOR 114

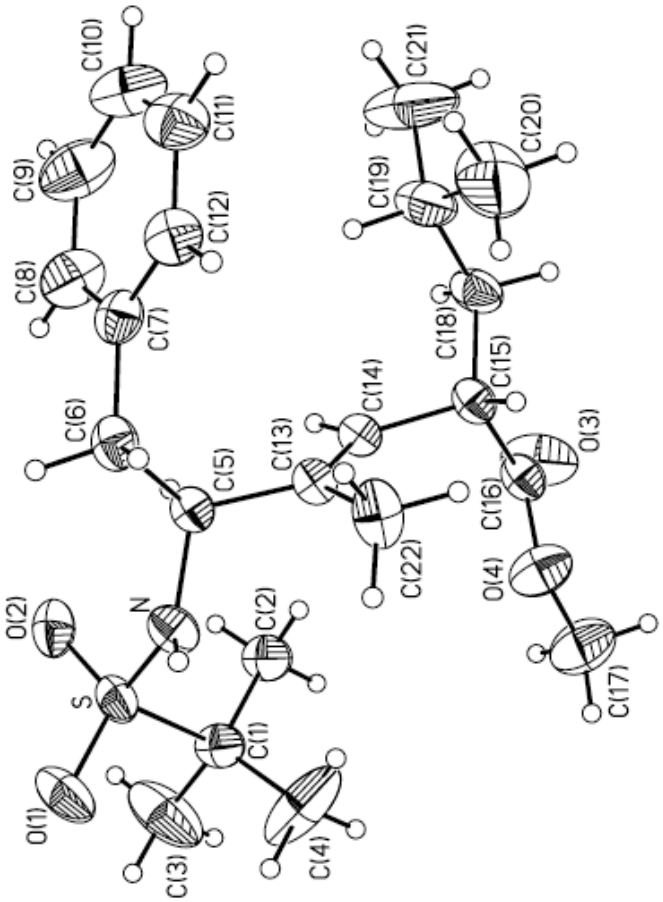


Table B1. Crystal data and structure refinement for bw929s.

Identification code	bw929s	
Empirical formula	C22 H35 N O4 S	
Formula weight	409.57	
Temperature	228(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P4(1)	
Unit cell dimensions	a = 12.8025(4) Å	α= 90°.
	b = 12.8025(4) Å	β= 90°.
	c = 14.9383(11) Å	γ = 90°.
Volume	2448.4(2) Å3	
Z	4	
Density (calculated)	1.111 Mg/m3	
Absorption coefficient	0.156 mm-1	
F(000)	888	
Crystal size	0.29 x 0.27 x 0.21 mm3	
Theta range for data collection	1.59 to 32.50°.	
Index ranges	-19<=h<=19, -19<=k<=19, -22<=l<=22	
Reflections collected	32521	
Independent reflections	8717 [R(int) = 0.0327]	
Completeness to theta = 32.50°	99.10%	
Absorption correction	Sadabs	
Max. and min. transmission	0.9679 and 0.9561	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	8717 / 1 / 258	
Goodness-of-fit on F2	0.966	
Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.1312	
R indices (all data)	R1 = 0.0900, wR2 = 0.1518	
Absolute structure parameter	0.00(6)	
Largest diff. peak and hole	0.307 and -0.125 e.Å-3	

Table B2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bw929s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	8355(1)	2599(1)	2051(1)	49(1)
O(1)	8369(2)	2044(1)	2886(1)	76(1)
O(2)	7500(1)	2445(1)	1443(1)	64(1)
O(3)	10946(2)	5566(2)	-855(1)	94(1)
O(4)	11307(1)	5317(2)	566(1)	72(1)
N	8409(2)	3818(1)	2305(1)	49(1)
C(1)	9545(2)	2257(2)	1457(1)	53(1)
C(2)	9566(2)	2777(2)	560(2)	59(1)
C(3)	9514(4)	1073(2)	1338(3)	122(2)
C(4)	10462(2)	2607(4)	2020(2)	122(2)
C(5)	7982(1)	4659(1)	1748(1)	41(1)
C(6)	7027(2)	5155(2)	2211(1)	51(1)
C(7)	6462(2)	5923(2)	1619(1)	52(1)
C(8)	5886(2)	5572(2)	889(2)	77(1)
C(9)	5374(3)	6269(3)	338(2)	95(1)
C(10)	5434(3)	7331(3)	502(2)	90(1)
C(11)	5994(2)	7676(2)	1219(2)	72(1)
C(12)	6509(2)	6983(2)	1766(2)	58(1)
C(13)	8821(1)	5443(1)	1506(1)	41(1)
C(14)	9035(1)	5605(1)	652(1)	40(1)
C(15)	9828(2)	6348(1)	257(1)	45(1)
C(16)	10752(2)	5721(2)	-96(1)	49(1)
C(17)	12196(2)	4676(3)	325(2)	92(1)
C(18)	9332(2)	6989(2)	-497(2)	61(1)
C(19)	8401(2)	7633(2)	-190(2)	76(1)
C(20)	8732(4)	8484(3)	473(4)	135(2)
C(21)	7816(4)	8062(4)	-1007(3)	146(2)
C(22)	9360(2)	5983(2)	2275(2)	64(1)

Table B3. Bond lengths [Å] and angles [°] for bw929s.

S-O(2)	1.4367(18)	C(18)-H(18A)	0.98
S-O(1)	1.4361(17)	C(18)-H(18B)	0.98
S-N	1.6075(18)	C(19)-C(21)	1.533(5)
S-C(1)	1.816(2)	C(19)-C(20)	1.531(6)
O(3)-C(16)	1.177(3)	C(19)-H(19A)	0.99
O(4)-C(16)	1.323(3)	C(20)-H(20A)	0.97
O(4)-C(17)	1.449(3)	C(20)-H(20B)	0.97
N-C(5)	1.465(2)	C(20)-H(20C)	0.97
N-H(1N)	0.82(3)	C(21)-H(21A)	0.97
C(1)-C(2)	1.496(3)	C(21)-H(21B)	0.97
C(1)-C(4)	1.512(4)	C(21)-H(21C)	0.97
C(1)-C(3)	1.527(4)	C(22)-H(22A)	0.97
C(2)-H(2A)	0.97	C(22)-H(22B)	0.97
C(2)-H(2B)	0.97	C(22)-H(22C)	0.97
C(2)-H(2C)	0.97	O(2)-S-O(1)	119.41(11)
C(3)-H(3A)	0.97	O(2)-S-N	108.36(10)
C(3)-H(3B)	0.97	O(1)-S-N	105.97(11)
C(3)-H(3C)	0.97	O(2)-S-C(1)	107.31(10)
C(4)-H(4A)	0.97	O(1)-S-C(1)	107.12(10)
C(4)-H(4B)	0.97	N-S-C(1)	108.26(10)
C(4)-H(4C)	0.97	C(16)-O(4)-C(17)	117.2(2)
C(5)-C(13)	1.514(2)	C(5)-N-S	124.31(14)
C(5)-C(6)	1.542(3)	C(5)-N-H(1N)	118.3(17)
C(5)-H(5A)	0.99	S-N-H(1N)	115.6(17)
C(6)-C(7)	1.507(3)	C(2)-C(1)-C(4)	110.6(2)
C(6)-H(6A)	0.98	C(2)-C(1)-C(3)	109.7(2)
C(6)-H(6B)	0.98	C(4)-C(1)-C(3)	112.3(3)
C(7)-C(12)	1.375(3)	C(2)-C(1)-S	110.19(14)
C(7)-C(8)	1.391(3)	C(4)-C(1)-S	107.93(16)
C(8)-C(9)	1.380(4)	C(3)-C(1)-S	105.94(19)
C(8)-H(8A)	0.94	C(1)-C(2)-H(2A)	109.5
C(9)-C(10)	1.384(5)	C(1)-C(2)-H(2B)	109.5
C(9)-H(9A)	0.94	H(2A)-C(2)-H(2B)	109.5
C(10)-C(11)	1.362(4)	C(1)-C(2)-H(2C)	109.5
C(10)-H(10A)	0.94	H(2A)-C(2)-H(2C)	109.5
C(11)-C(12)	1.375(4)	H(2B)-C(2)-H(2C)	109.5
C(11)-H(11A)	0.94	C(1)-C(3)-H(3A)	109.5
C(12)-H(12A)	0.94	C(1)-C(3)-H(3B)	109.5
C(13)-C(14)	1.321(2)	H(3A)-C(3)-H(3B)	109.5
C(13)-C(22)	1.507(3)	C(1)-C(3)-H(3C)	109.5
C(14)-C(15)	1.511(2)	H(3A)-C(3)-H(3C)	109.5
C(14)-H(14A)	0.94	H(3B)-C(3)-H(3C)	109.5
C(15)-C(16)	1.523(3)	C(1)-C(4)-H(4A)	109.5

Table B3. Cont'd

C(15)-C(18)	1.531(3)	C(1)-C(4)-H(4B)	109.5
C(15)-H(15A)	0.99	H(4A)-C(4)-H(4B)	109.5
C(17)-H(17A)	0.97	C(1)-C(4)-H(4C)	109.5
C(17)-H(17B)	0.97	H(4A)-C(4)-H(4C)	109.5
C(17)-H(17C)	0.97	H(4B)-C(4)-H(4C)	109.5
C(18)-C(19)	1.521(3)	N-C(5)-C(13)	111.00(15)
N-C(5)-C(6)	110.15(15)	C(18)-C(15)-H(15A)	109
C(13)-C(5)-C(6)	113.34(15)	O(3)-C(16)-O(4)	122.7(2)
N-C(5)-H(5A)	107.4	O(3)-C(16)-C(15)	125.8(2)
C(13)-C(5)-H(5A)	107.4	O(4)-C(16)-C(15)	111.39(17)
C(6)-C(5)-H(5A)	107.4	O(4)-C(17)-H(17A)	109.5
C(7)-C(6)-C(5)	112.76(16)	O(4)-C(17)-H(17B)	109.5
C(7)-C(6)-H(6A)	109	H(17A)-C(17)-H(17B)	109.5
C(5)-C(6)-H(6A)	109	O(4)-C(17)-H(17C)	109.5
C(7)-C(6)-H(6B)	109	H(17A)-C(17)-H(17C)	109.5
C(5)-C(6)-H(6B)	109	H(17B)-C(17)-H(17C)	109.5
H(6A)-C(6)-H(6B)	107.8	C(19)-C(18)-C(15)	113.22(18)
C(12)-C(7)-C(8)	117.8(2)	C(19)-C(18)-H(18A)	108.9
C(12)-C(7)-C(6)	121.9(2)	C(15)-C(18)-H(18A)	108.9
C(8)-C(7)-C(6)	120.2(2)	C(19)-C(18)-H(18B)	108.9
C(7)-C(8)-C(9)	120.7(3)	C(15)-C(18)-H(18B)	108.9
C(7)-C(8)-H(8A)	119.7	H(18A)-C(18)-H(18B)	107.7
C(9)-C(8)-H(8A)	119.7	C(21)-C(19)-C(18)	109.7(2)
C(10)-C(9)-C(8)	120.2(3)	C(21)-C(19)-C(20)	113.3(3)
C(10)-C(9)-H(9A)	119.9	C(18)-C(19)-C(20)	111.3(3)
C(8)-C(9)-H(9A)	119.9	C(21)-C(19)-H(19A)	107.5
C(9)-C(10)-C(11)	119.1(3)	C(18)-C(19)-H(19A)	107.4
C(9)-C(10)-H(10A)	120.4	C(20)-C(19)-H(19A)	107.5
C(11)-C(10)-H(10A)	120.4	C(19)-C(20)-H(20A)	109.5
C(12)-C(11)-C(10)	120.7(3)	C(19)-C(20)-H(20B)	109.5
C(12)-C(11)-H(11A)	119.6	H(20A)-C(20)-H(20B)	109.5
C(10)-C(11)-H(11A)	119.6	C(19)-C(20)-H(20C)	109.5
C(11)-C(12)-C(7)	121.4(2)	H(20A)-C(20)-H(20C)	109.5
C(11)-C(12)-H(12A)	119.3	H(20B)-C(20)-H(20C)	109.5
C(7)-C(12)-H(12A)	119.3	C(19)-C(21)-H(21A)	109.5
C(14)-C(13)-C(5)	118.83(15)	C(19)-C(21)-H(21B)	109.5
C(14)-C(13)-C(22)	124.64(17)	H(21A)-C(21)-H(21B)	109.5
C(5)-C(13)-C(22)	116.53(16)	C(19)-C(21)-H(21C)	109.5
C(13)-C(14)-C(15)	128.01(16)	H(21A)-C(21)-H(21C)	109.5
C(13)-C(14)-H(14A)	116	H(21B)-C(21)-H(21C)	109.5
C(15)-C(14)-H(14A)	116	C(13)-C(22)-H(22A)	109.5
C(14)-C(15)-C(16)	108.98(15)	C(13)-C(22)-H(22B)	109.5
C(14)-C(15)-C(18)	110.30(17)	H(22A)-C(22)-H(22B)	109.5
C(16)-C(15)-C(18)	110.52(16)	C(13)-C(22)-H(22C)	109.5

Table B3. Cont'd

C(14)-C(15)-H(15A)	109	H(22A)-C(22)-H(22C)	109.5
C(16)-C(15)-H(15A)	109	H(22B)-C(22)-H(22C)	109.5

Table B4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw929s. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	54(1)	44(1)	48(1)	6(1)	13(1)	-4(1)
O(1)	103(1)	61(1)	64(1)	22(1)	29(1)	4(1)
O(2)	55(1)	62(1)	77(1)	-6(1)	7(1)	-17(1)
O(3)	134(2)	102(2)	46(1)	6(1)	29(1)	49(1)
O(4)	67(1)	91(1)	56(1)	-12(1)	-3(1)	24(1)
N	66(1)	49(1)	34(1)	0(1)	3(1)	-2(1)
C(1)	57(1)	60(1)	43(1)	2(1)	6(1)	11(1)
C(2)	60(1)	69(1)	48(1)	5(1)	14(1)	12(1)
C(3)	183(4)	56(2)	127(3)	20(2)	85(3)	40(2)
C(4)	53(1)	252(5)	63(2)	-47(2)	-9(1)	33(2)
C(5)	46(1)	42(1)	33(1)	-3(1)	5(1)	-1(1)
C(6)	53(1)	53(1)	47(1)	-4(1)	14(1)	-3(1)
C(7)	47(1)	57(1)	51(1)	-10(1)	10(1)	3(1)
C(8)	75(2)	72(2)	84(2)	-26(1)	-18(1)	6(1)
C(9)	86(2)	114(2)	85(2)	-28(2)	-32(2)	23(2)
C(10)	92(2)	99(2)	79(2)	-1(2)	-8(2)	41(2)
C(11)	83(2)	66(1)	68(2)	-5(1)	14(1)	16(1)
C(12)	64(1)	58(1)	51(1)	-13(1)	9(1)	6(1)
C(13)	48(1)	40(1)	35(1)	-3(1)	3(1)	-2(1)
C(14)	46(1)	38(1)	34(1)	-3(1)	2(1)	0(1)
C(15)	54(1)	42(1)	38(1)	0(1)	9(1)	-2(1)
C(16)	61(1)	44(1)	43(1)	-1(1)	12(1)	-3(1)
C(17)	70(2)	110(2)	95(2)	-8(2)	4(2)	31(2)
C(18)	72(1)	55(1)	57(1)	18(1)	18(1)	10(1)
C(19)	86(2)	64(1)	79(2)	23(1)	24(1)	23(1)
C(20)	126(3)	69(2)	209(5)	-36(3)	49(3)	14(2)
C(21)	145(4)	177(4)	115(3)	69(3)	33(3)	103(3)
C(22)	77(2)	78(1)	37(1)	-11(1)	3(1)	-29(1)

Table B5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bw929s.

	x	y	z	U(eq)
H(1N)	8551(17)	3948(18)	2826(17)	50(6)
H(2A)	10205	2590	250	89
H(2B)	9538	3528	638	89
H(2C)	8969	2549	211	89
H(3A)	10134	846	1019	183
H(3B)	8897	881	999	183
H(3C)	9492	739	1921	183
H(4A)	11108	2436	1715	183
H(4B)	10442	2254	2594	183
H(4C)	10424	3356	2113	183
H(5A)	7734	4338	1184	49
H(6A)	6541	4601	2389	61
H(6B)	7258	5514	2756	61
H(8A)	5844	4852	771	92
H(9A)	4984	6021	-151	114
H(10A)	5093	7809	123	108
H(11A)	6028	8395	1340	87
H(12A)	6901	7238	2250	69
H(14A)	8646	5210	240	48
H(15A)	10075	6827	731	53
H(17A)	12531	4418	864	138
H(17B)	12690	5090	-16	138
H(17C)	11962	4090	-35	138
H(18A)	9861	7459	-747	73
H(18B)	9107	6515	-974	73
H(19A)	7919	7156	129	91
H(20A)	9093	8166	975	202
H(20B)	8118	8850	687	202
H(20C)	9194	8974	176	202
H(21A)	7637	7491	-1405	219
H(21B)	8259	8555	-1321	219
H(21C)	7184	8411	-812	219
H(22A)	9882	6461	2043	96
H(22B)	9694	5467	2653	96
H(22C)	8849	6370	2622	96

APPENDIX C

X-RAY CRYSTAL DATA FOR 116

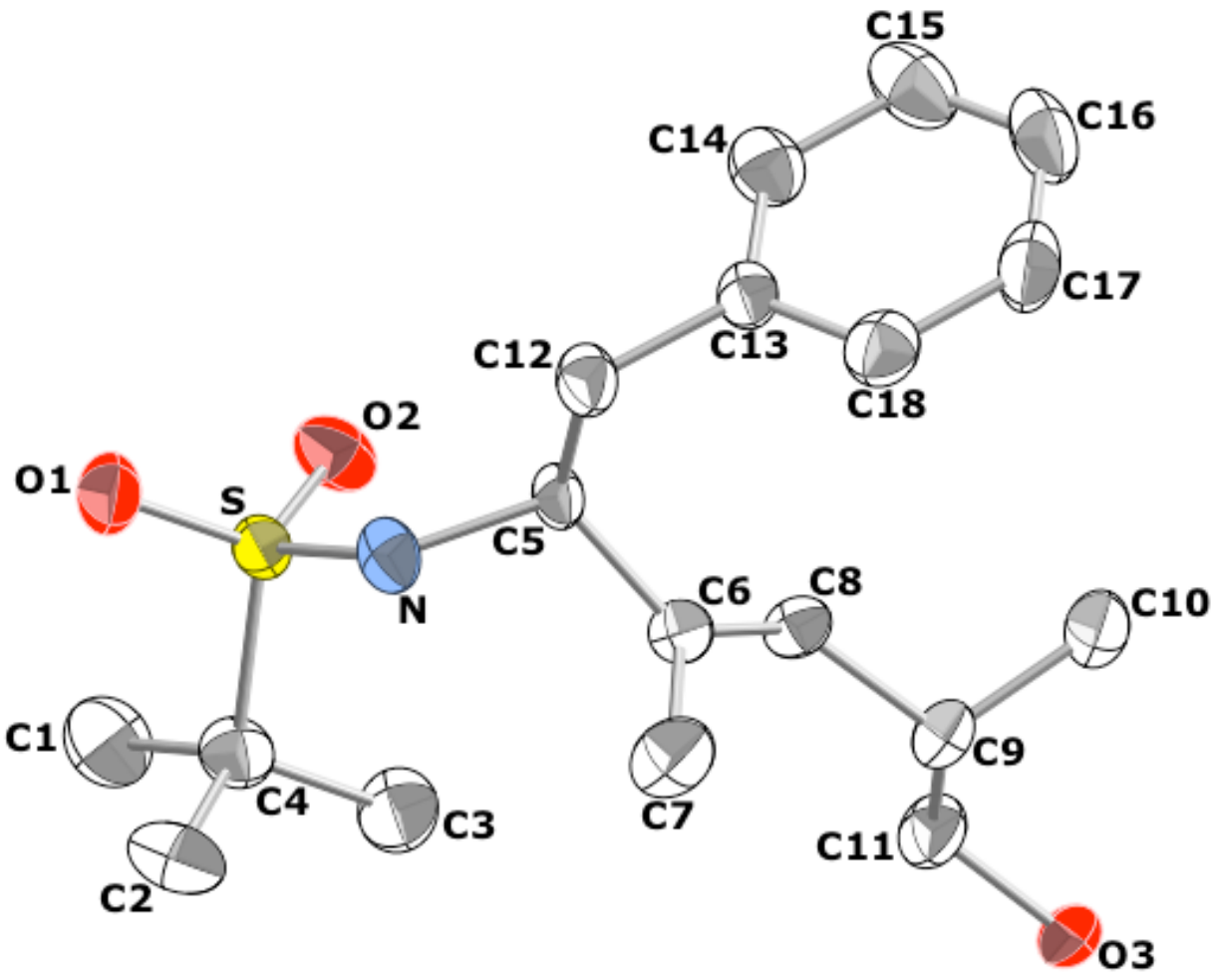


Table C1. Crystal data and structure refinement for bw0419s.

Identification code	bw0419s	
Empirical formula	C18 H29 N O3 S	
Formula weight	339.48	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 6.3998(8) Å	a= 70.719(3)°.
	b = 8.4297(11) Å	b= 88.743(3)°.
	c = 10.0584(13) Å	g = 75.346(3)°.
Volume	494.41(11) $Å^3$	
Z	1	
Density (calculated)	1.140 Mg/m^3	
Absorption coefficient	0.177 mm^{-1}	
F(000)	184	
Crystal size	0.28 x 0.14 x 0.09 mm^3	
Theta range for data collection	2.15 to 25.00°.	
Index ranges	-7<=h<=7, -10<=k<=10, -11<=l<=11	
Reflections collected	3974	
Independent reflections	3284 [R(int) = 0.0224]	
Completeness to theta = 25.00°	99.90%	
Absorption correction	Multi-scan (Sadabs)	
Max. and min. transmission	0.9843 and 0.9522	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3284 / 3 / 222	
Goodness-of-fit on F^2	0.915	
Final R indices [I>2sigma(I)]	R1 = 0.0602, wR2 = 0.1385	
R indices (all data)	R1 = 0.0766, wR2 = 0.1492	
Absolute structure parameter	0.22(12)	
Largest diff. peak and hole	0.230 and -0.190 e.$Å^{-3}$	

Table C2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bw0419s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	-1254(1)	5796(1)	4359(1)	50(1)
N	-1980(6)	4580(5)	5777(4)	54(1)
O(1)	-2594(6)	7521(4)	4046(4)	78(1)
O(2)	1050(5)	5533(5)	4520(3)	73(1)
O(3)	3628(6)	-3817(4)	6364(4)	62(1)
C(5)	-494(6)	3263(5)	6944(4)	43(1)
C(1)	-1150(11)	6251(9)	1606(6)	94(2)
C(2)	-4153(9)	5091(9)	2879(6)	89(2)
C(3)	-351(10)	3180(7)	3288(6)	90(2)
C(4)	-1740(8)	5007(6)	2951(5)	64(1)
C(6)	-401(6)	1433(5)	7038(4)	47(1)
C(7)	-2493(8)	923(7)	7120(7)	76(2)
C(8)	1536(6)	326(5)	7143(4)	48(1)
C(9)	2093(7)	-1591(5)	7410(5)	52(1)
C(10)	3687(11)	-2530(6)	8707(6)	86(2)
C(11)	3089(8)	-1995(6)	6152(5)	64(1)
C(12)	-1154(7)	3593(6)	8328(4)	57(1)
C(13)	445(7)	2483(5)	9545(4)	50(1)
C(14)	2299(8)	2912(7)	9693(5)	69(1)
C(15)	3826(9)	1920(9)	10794(6)	86(2)
C(16)	3496(11)	452(9)	11751(6)	89(2)
C(17)	1678(11)	-34(7)	11613(6)	81(2)
C(18)	128(9)	965(6)	10510(5)	68(1)

Table C3. Bond lengths [Å] and angles [°] for bw0419s.

S-O(1)	1.423(3)	C(8)-C(6)-C(5)	118.2(3)
S-O(2)	1.439(3)	C(7)-C(6)-C(5)	117.8(4)
S-N	1.596(4)	C(6)-C(8)-C(9)	129.1(4)
S-C(4)	1.815(5)	C(8)-C(9)-C(11)	110.4(3)
N-C(5)	1.472(5)	C(8)-C(9)-C(10)	109.3(4)
O(3)-C(11)	1.430(5)	C(11)-C(9)-C(10)	109.6(4)
C(5)-C(6)	1.500(6)	O(3)-C(11)-C(9)	112.0(4)
C(5)-C(12)	1.537(6)	C(13)-C(12)-C(5)	112.7(3)
C(1)-C(4)	1.521(7)	C(14)-C(13)-C(18)	118.2(4)
C(2)-C(4)	1.530(7)	C(14)-C(13)-C(12)	119.9(4)
C(3)-C(4)	1.501(7)	C(18)-C(13)-C(12)	121.8(4)
C(6)-C(8)	1.332(5)	C(13)-C(14)-C(15)	121.9(5)
C(6)-C(7)	1.499(6)	C(16)-C(15)-C(14)	119.8(6)
C(8)-C(9)	1.495(5)	C(17)-C(16)-C(15)	119.7(5)
C(9)-C(11)	1.504(6)	C(16)-C(17)-C(18)	120.8(5)
C(9)-C(10)	1.529(7)	C(17)-C(18)-C(13)	119.6(5)
C(12)-C(13)	1.495(6)		
C(13)-C(14)	1.349(7)		
C(13)-C(18)	1.387(6)		
C(14)-C(15)	1.380(7)		
C(15)-C(16)	1.357(9)		
C(16)-C(17)	1.351(9)		
C(17)-C(18)	1.391(7)		
O(1)-S-O(2)	118.0(2)		
O(1)-S-N	108.5(2)		
O(2)-S-N	107.7(2)		
O(1)-S-C(4)	108.2(2)		
O(2)-S-C(4)	106.7(2)		
N-S-C(4)	107.3(2)		
C(5)-N-S	125.1(3)		
N-C(5)-C(6)	113.0(3)		
N-C(5)-C(12)	108.7(3)		
C(6)-C(5)-C(12)	111.7(3)		
C(3)-C(4)-C(1)	112.3(5)		
C(3)-C(4)-C(2)	111.9(5)		
C(1)-C(4)-C(2)	110.8(4)		
C(3)-C(4)-S	108.3(3)		
C(1)-C(4)-S	106.0(4)		
C(2)-C(4)-S	107.2(3)		
C(8)-C(6)-C(7)	123.8(4)		

Table C4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw0419s. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	54(1)	46(1)	44(1)	-16(1)	-5(1)	-4(1)
N	40(2)	57(2)	54(2)	-22(2)	2(2)	8(2)
O(1)	104(3)	53(2)	61(2)	-18(2)	-9(2)	5(2)
O(2)	63(2)	98(3)	58(2)	-17(2)	0(2)	-33(2)
O(3)	63(2)	46(2)	76(2)	-32(2)	-12(2)	3(2)
C(5)	39(2)	39(2)	42(2)	-10(2)	-4(2)	2(2)
C(1)	118(5)	105(5)	57(4)	-22(3)	7(3)	-31(4)
C(2)	84(4)	116(5)	81(4)	-50(4)	-11(3)	-23(4)
C(3)	114(5)	75(4)	75(4)	-45(3)	-3(3)	10(3)
C(4)	72(3)	69(3)	51(3)	-29(2)	4(2)	-10(3)
C(6)	43(2)	48(2)	51(2)	-19(2)	5(2)	-11(2)
C(7)	55(3)	68(3)	110(5)	-36(3)	13(3)	-18(3)
C(8)	46(2)	44(2)	58(3)	-23(2)	9(2)	-14(2)
C(9)	53(3)	39(2)	61(3)	-18(2)	6(2)	-7(2)
C(10)	126(5)	48(3)	72(4)	-17(3)	-23(3)	-5(3)
C(11)	78(3)	47(3)	65(3)	-25(2)	5(2)	-4(2)
C(12)	65(3)	49(3)	49(3)	-18(2)	-2(2)	3(2)
C(13)	59(3)	45(2)	42(2)	-21(2)	2(2)	3(2)
C(14)	72(3)	77(3)	56(3)	-22(3)	5(2)	-15(3)
C(15)	59(3)	117(5)	80(4)	-44(4)	-7(3)	-1(3)
C(16)	93(5)	84(4)	65(4)	-31(3)	-21(3)	33(4)
C(17)	119(5)	48(3)	56(3)	-9(2)	0(3)	3(3)
C(18)	85(4)	62(3)	61(3)	-24(3)	10(3)	-18(3)

Table C5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for bw0419s.

	x	y	z	U(eq)
H(1N)	-3010(60)	4960(50)	5950(40)	21(10)
H(3)	2820(80)	-4050(70)	5900(60)	72(18)
H(5A)	961	3431	6776	52
H(1A)	-1421	5913	817	141
H(1B)	355	6213	1687	141
H(1C)	-2012	7413	1465	141
H(2A)	-4987	6273	2683	134
H(2B)	-4517	4374	3766	134
H(2C)	-4469	4680	2143	134
H(3A)	-528	2763	2528	135
H(3B)	-776	2443	4143	135
H(3C)	1138	3165	3408	135
H(7A)	-2462	189	6562	114
H(7B)	-3671	1950	6766	114
H(7C)	-2687	304	8084	114
H(8)	2707	814	7035	57
H(9)	772	-1994	7588	62
H(10A)	5026	-2208	8511	128
H(10B)	3947	-3765	8932	128
H(10C)	3089	-2206	9492	128
H(11A)	2082	-1377	5329	77
H(11B)	4389	-1585	5969	77
H(12A)	-1296	4808	8200	68
H(12B)	-2556	3364	8544	68
H(14)	2555	3905	9034	83
H(15)	5079	2256	10879	104
H(16)	4515	-217	12500	107
H(17)	1461	-1049	12264	98
H(18)	-1114	617	10419	82

APPENDIX D

X-RAY CRYSTAL DATA FOR 118C

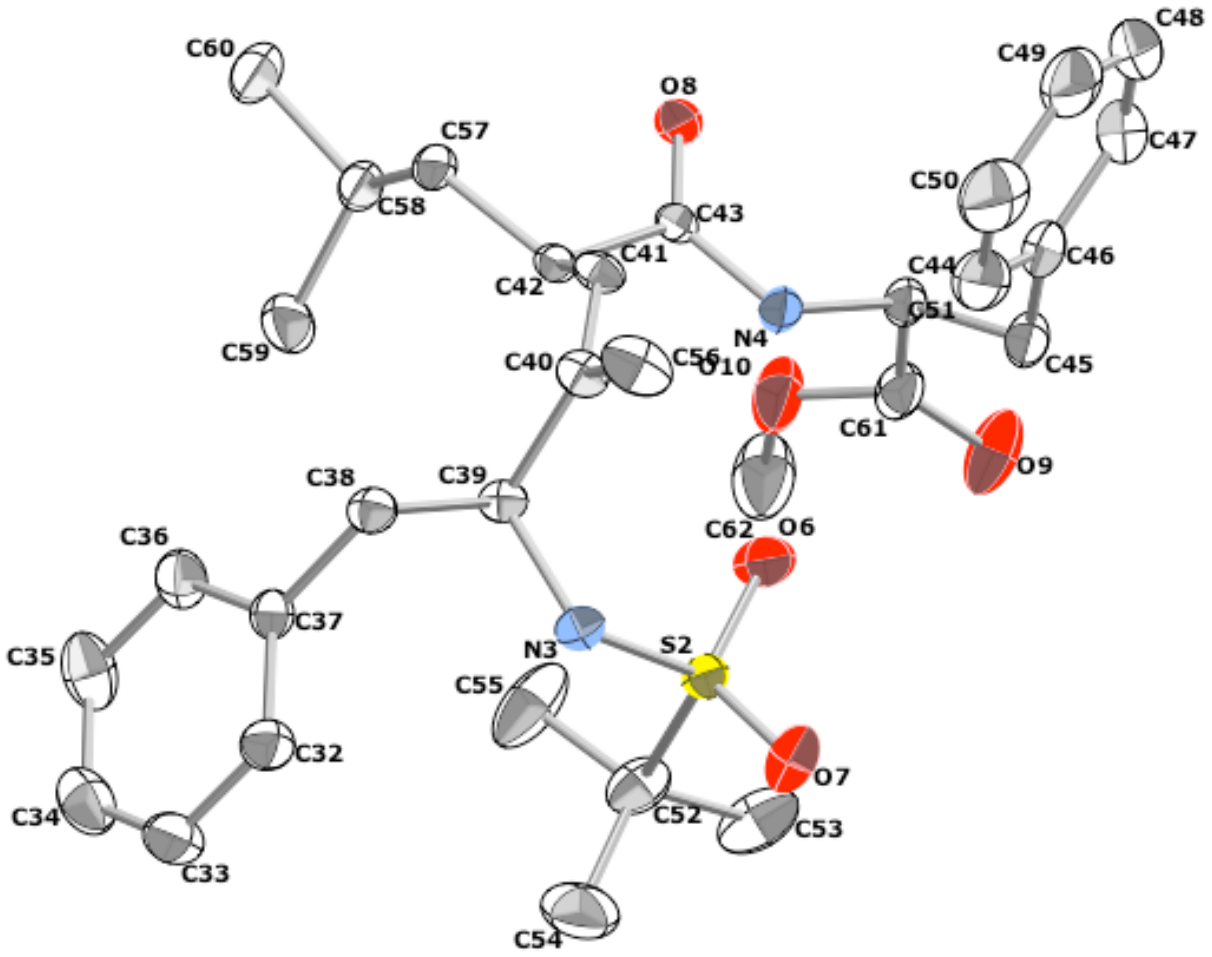


Table D1. Crystal data and structure refinement for bw927s.

Identification code	bw927s	
Empirical formula	C31 H44 N2 O5 S	
Formula weight	556.74	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.9411(4) Å	a= 90°.
	b = 24.7469(10) Å	b= 90°.
	c = 25.9473(11) Å	g = 90°.
Volume	6383.3(5) $Å^3$	
Z	8	
Density (calculated)	1.159 Mg/m^3	
Absorption coefficient	0.140 mm^{-1}	
F(000)	2400	
Crystal size	0.30 x 0.22 x 0.20 mm^3	
Theta range for data collection	1.57 to 32.58°.	
Index ranges	-15<=h<=15, -36<=k<=37, -38<=l<=39	
Reflections collected	85322	
Independent reflections	22718 [R(int) = 0.0657]	
Completeness to theta = 32.58°	99.20%	
Absorption correction	None	
Max. and min. transmission	0.9725 and 0.9592	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	22718 / 0 / 720	
Goodness-of-fit on F^2	1.02	
Final R indices [I>2sigma(I)]	R1 = 0.0724, wR2 = 0.1376	
R indices (all data)	R1 = 0.1279, wR2 = 0.1594	
Absolute structure parameter	0.02(5)	
Largest diff. peak and hole	0.481 and -0.259 $e.Å^{-3}$	

Table D2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bw927s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4507(1)	7866(1)	2907(1)	31(1)
C(1)	8473(3)	7026(1)	2675(1)	55(1)
N(1)	6106(2)	7951(1)	2861(1)	32(1)
O(1)	3871(2)	8147(1)	2488(1)	47(1)
C(2)	8554(4)	6471(1)	2640(1)	77(1)
N(2)	3458(2)	8803(1)	4247(1)	39(1)
O(2)	4100(2)	7990(1)	3427(1)	40(1)
S(2)	7270(1)	9662(1)	-39(1)	39(1)
C(3)	8636(4)	6162(1)	3078(1)	80(1)
N(3)	8885(2)	9692(1)	-4(1)	35(1)
O(3)	4714(2)	9344(1)	4733(1)	49(1)
C(4)	8663(4)	6409(1)	3553(1)	70(1)
N(4)	6484(2)	8851(1)	1354(1)	42(1)
O(4)	2337(2)	8557(1)	5202(1)	69(1)
C(5)	8598(3)	6964(1)	3589(1)	51(1)
O(5)	1101(2)	9306(1)	5155(1)	77(1)
C(6)	8510(2)	7282(1)	3152(1)	40(1)
O(6)	6735(2)	9477(1)	438(1)	67(1)
C(7)	8408(2)	7886(1)	3190(1)	42(1)
O(7)	6809(2)	10173(1)	-227(1)	62(1)
C(8)	6978(2)	8093(1)	3302(1)	31(1)
O(8)	7335(2)	8239(1)	1904(1)	46(1)
C(9)	6998(2)	8693(1)	3412(1)	34(1)
O(9)	3120(2)	8551(1)	1067(1)	91(1)
C(10)	6547(2)	8908(1)	3847(1)	37(1)
O(10)	4938(2)	8050(1)	1019(1)	82(1)
C(11)	5855(2)	8617(1)	4286(1)	35(1)
C(12)	4642(2)	8954(1)	4444(1)	34(1)
C(13)	2228(2)	9061(1)	4406(1)	39(1)
C(14)	1039(3)	8887(1)	4066(1)	46(1)
C(15)	1087(2)	9135(1)	3535(1)	42(1)
C(16)	1454(2)	8840(1)	3105(1)	45(1)
C(17)	1484(3)	9073(1)	2623(1)	58(1)
C(18)	1145(3)	9604(1)	2562(1)	66(1)
C(19)	787(4)	9905(1)	2981(2)	75(1)
C(20)	761(3)	9673(1)	3465(1)	62(1)
C(21)	4174(3)	7156(1)	2810(1)	40(1)
C(22)	2659(3)	7087(1)	2856(1)	57(1)
C(23)	4674(4)	7001(1)	2272(1)	65(1)
C(24)	4902(3)	6831(1)	3230(1)	55(1)
C(25)	7598(3)	9048(1)	2999(1)	44(1)

Table D2. Cont'd

C(26)	6781(3)	8524(1)	4749(1)	48(1)
C(27)	6122(3)	8217(1)	5195(1)	65(1)
C(28)	7102(5)	8199(3)	5651(2)	131(2)
C(29)	5656(6)	7663(2)	5039(2)	108(2)
C(30)	1922(3)	8932(1)	4966(1)	46(1)
C(31)	581(5)	9212(2)	5666(1)	103(2)
C(32)	11441(3)	9370(1)	-785(1)	50(1)
C(33)	11697(3)	9084(2)	-1238(1)	70(1)
C(34)	11947(3)	8542(2)	-1214(1)	68(1)
C(35)	11976(3)	8283(1)	-747(1)	69(1)
C(36)	11735(3)	8567(1)	-303(1)	53(1)
C(37)	11458(2)	9114(1)	-314(1)	38(1)
C(38)	11190(2)	9411(1)	183(1)	38(1)
C(39)	9707(2)	9374(1)	363(1)	32(1)
C(40)	9565(2)	9553(1)	918(1)	37(1)
C(41)	9217(2)	9218(1)	1297(1)	35(1)
C(42)	8818(2)	8634(1)	1264(1)	30(1)
C(43)	7477(2)	8549(1)	1542(1)	30(1)
C(44)	5103(2)	8839(1)	1520(1)	45(1)
C(45)	4508(3)	9412(1)	1537(1)	58(1)
C(46)	5246(3)	9786(1)	1893(1)	62(1)
C(47)	4875(4)	9836(2)	2407(1)	89(1)
C(48)	5584(6)	10194(2)	2731(2)	103(2)
C(49)	6634(5)	10479(2)	2547(2)	93(1)
C(50)	7015(5)	10433(1)	2048(2)	87(1)
C(51)	6318(4)	10094(1)	1720(1)	67(1)
C(52)	6848(3)	9173(1)	-524(1)	56(1)
C(53)	5315(3)	9127(1)	-517(2)	76(1)
C(54)	7354(4)	9370(2)	-1037(1)	93(1)
C(55)	7480(4)	8625(1)	-368(2)	96(2)
C(56)	9902(4)	10134(1)	1024(1)	61(1)
C(57)	9902(2)	8247(1)	1466(1)	39(1)
C(58)	9736(3)	7664(1)	1300(1)	44(1)
C(59)	9936(4)	7593(1)	717(1)	61(1)
C(60)	10733(3)	7299(2)	1582(1)	73(1)
C(61)	4263(3)	8471(1)	1182(1)	55(1)
C(62)	4209(4)	7674(2)	698(2)	104(2)

Table D3. Bond lengths [Å] and angles [°] for bw927s.

S(1)-O(1)	1.4372(18)	C(9)-C(10)	1.325(3)
S(1)-O(2)	1.4417(16)	C(9)-C(25)	1.509(3)
S(1)-N(1)	1.608(2)	O(9)-C(61)	1.191(3)
S(1)-C(21)	1.807(2)	C(10)-C(11)	1.513(3)
C(1)-C(2)	1.377(4)	C(10)-H(10A)	0.95
C(1)-C(6)	1.392(4)	O(10)-C(61)	1.310(4)
C(1)-H(1A)	0.95	O(10)-C(62)	1.444(4)
N(1)-C(8)	1.477(3)	C(11)-C(12)	1.521(3)
N(1)-H(1N)	0.77(2)	C(11)-C(26)	1.531(3)
C(2)-C(3)	1.372(5)	C(11)-H(11A)	1
C(2)-H(2A)	0.95	C(13)-C(30)	1.519(4)
N(2)-C(12)	1.336(3)	C(13)-C(14)	1.537(3)
N(2)-C(13)	1.440(3)	C(13)-H(13A)	1
N(2)-H(2N)	0.85(3)	C(14)-C(15)	1.510(4)
S(2)-O(6)	1.4224(19)	C(14)-H(14A)	0.99
S(2)-O(7)	1.430(2)	C(14)-H(14B)	0.99
S(2)-N(3)	1.6101(19)	C(15)-C(20)	1.381(4)
S(2)-C(52)	1.796(3)	C(15)-C(16)	1.381(4)
C(3)-C(4)	1.376(4)	C(16)-C(17)	1.378(4)
C(3)-H(3A)	0.95	C(16)-H(16A)	0.95
N(3)-C(39)	1.479(3)	C(17)-C(18)	1.366(5)
N(3)-H(3N)	0.85(2)	C(17)-H(17A)	0.95
O(3)-C(12)	1.226(3)	C(18)-C(19)	1.365(5)
C(4)-C(5)	1.378(4)	C(18)-H(18A)	0.95
C(4)-H(4A)	0.95	C(19)-C(20)	1.381(5)
N(4)-C(43)	1.331(3)	C(19)-H(19A)	0.95
N(4)-C(44)	1.439(3)	C(20)-H(20A)	0.95
N(4)-H(4N)	0.82(3)	C(21)-C(22)	1.520(4)
O(4)-C(30)	1.187(3)	C(21)-C(23)	1.529(3)
C(5)-C(6)	1.386(4)	C(21)-C(24)	1.535(4)
C(5)-H(5A)	0.95	C(22)-H(22A)	0.98
O(5)-C(30)	1.326(3)	C(22)-H(22B)	0.98
O(5)-C(31)	1.444(4)	C(22)-H(22C)	0.98
C(6)-C(7)	1.502(3)	C(23)-H(23A)	0.98
C(7)-C(8)	1.538(3)	C(23)-H(23B)	0.98
C(7)-H(7A)	0.99	C(23)-H(23C)	0.98
C(7)-H(7B)	0.99	C(24)-H(24A)	0.98
C(8)-C(9)	1.512(3)	C(24)-H(24B)	0.98
C(8)-H(8A)	1	C(24)-H(24C)	0.98
O(8)-C(43)	1.221(3)	C(25)-H(25A)	0.98

Table D3. Cont'd

C(25)-H(25B)	0.98	C(42)-H(42A)	1
C(25)-H(25C)	0.98	C(44)-C(61)	1.515(4)
C(26)-C(27)	1.532(4)	C(44)-C(45)	1.537(4)
C(26)-H(26A)	0.99	C(44)-H(44A)	1
C(26)-H(26B)	0.99	C(45)-C(46)	1.502(5)
C(27)-C(29)	1.501(6)	C(45)-H(45A)	0.99
C(27)-C(28)	1.533(5)	C(45)-H(45B)	0.99
C(27)-H(27A)	1	C(46)-C(51)	1.384(5)
C(28)-H(28A)	0.98	C(46)-C(47)	1.390(5)
C(28)-H(28B)	0.98	C(47)-C(48)	1.410(7)
C(28)-H(28C)	0.98	C(47)-H(47A)	0.95
C(29)-H(29A)	0.98	C(48)-C(49)	1.347(7)
C(29)-H(29B)	0.98	C(48)-H(48A)	0.95
C(29)-H(29C)	0.98	C(49)-C(50)	1.354(6)
C(31)-H(31A)	0.98	C(49)-H(49A)	0.95
C(31)-H(31B)	0.98	C(50)-C(51)	1.381(5)
C(31)-H(31C)	0.98	C(50)-H(50A)	0.95
C(32)-C(37)	1.378(3)	C(51)-H(51A)	0.95
C(32)-C(33)	1.394(4)	C(52)-C(54)	1.504(5)
C(32)-H(32A)	0.95	C(52)-C(53)	1.528(4)
C(33)-C(34)	1.365(5)	C(52)-C(55)	1.548(5)
C(33)-H(33A)	0.95	C(53)-H(53A)	0.98
C(34)-C(35)	1.373(5)	C(53)-H(53B)	0.98
C(34)-H(34A)	0.95	C(53)-H(53C)	0.98
C(35)-C(36)	1.371(4)	C(54)-H(54A)	0.98
C(35)-H(35A)	0.95	C(54)-H(54B)	0.98
C(36)-C(37)	1.382(4)	C(54)-H(54C)	0.98
C(36)-H(36A)	0.95	C(55)-H(55A)	0.98
C(37)-C(38)	1.507(3)	C(55)-H(55B)	0.98
C(38)-C(39)	1.549(3)	C(55)-H(55C)	0.98
C(38)-H(38A)	0.99	C(56)-H(56A)	0.98
C(38)-H(38B)	0.99	C(56)-H(56B)	0.98
C(39)-C(40)	1.515(3)	C(56)-H(56C)	0.98
C(39)-H(39A)	1	C(57)-C(58)	1.513(4)
C(40)-C(41)	1.332(3)	C(57)-H(57A)	0.99
C(40)-C(56)	1.500(3)	C(57)-H(57B)	0.99
C(41)-C(42)	1.502(3)	C(58)-C(60)	1.528(4)
C(41)-H(41A)	0.95	C(58)-C(59)	1.535(4)
C(42)-C(43)	1.530(3)	C(58)-H(58A)	1
C(42)-C(57)	1.534(3)	C(59)-H(59A)	0.98

Table D3. Cont'd

C(59)-H(59B)	0.98	C(5)-C(4)-H(4A)	119.9
C(59)-H(59C)	0.98	C(43)-N(4)-C(44)	125.8(2)
C(60)-H(60A)	0.98	C(43)-N(4)-H(4N)	118.2(19)
C(60)-H(60B)	0.98	C(44)-N(4)-H(4N)	115.1(19)
C(60)-H(60C)	0.98	C(4)-C(5)-C(6)	120.9(3)
C(62)-H(62A)	0.98	C(4)-C(5)-H(5A)	119.5
C(62)-H(62B)	0.98	C(6)-C(5)-H(5A)	119.5
C(62)-H(62C)	0.98	C(30)-O(5)-C(31)	116.6(3)
O(1)-S(1)-O(2)	118.84(11)	C(5)-C(6)-C(1)	118.1(2)
O(1)-S(1)-N(1)	108.37(11)	C(5)-C(6)-C(7)	121.1(2)
O(2)-S(1)-N(1)	108.56(10)	C(1)-C(6)-C(7)	120.8(2)
O(1)-S(1)-C(21)	106.49(11)	C(6)-C(7)-C(8)	114.0(2)
O(2)-S(1)-C(21)	106.67(10)	C(6)-C(7)-H(7A)	108.7
N(1)-S(1)-C(21)	107.37(11)	C(8)-C(7)-H(7A)	108.7
C(2)-C(1)-C(6)	120.7(3)	C(6)-C(7)-H(7B)	108.7
C(2)-C(1)-H(1A)	119.7	C(8)-C(7)-H(7B)	108.7
C(6)-C(1)-H(1A)	119.7	H(7A)-C(7)-H(7B)	107.6
C(8)-N(1)-S(1)	123.67(15)	N(1)-C(8)-C(9)	112.83(18)
C(8)-N(1)-H(1N)	118.5(19)	N(1)-C(8)-C(7)	108.48(18)
S(1)-N(1)-H(1N)	110.3(19)	C(9)-C(8)-C(7)	110.53(18)
C(3)-C(2)-C(1)	120.4(3)	N(1)-C(8)-H(8A)	108.3
C(3)-C(2)-H(2A)	119.8	C(9)-C(8)-H(8A)	108.3
C(1)-C(2)-H(2A)	119.8	C(7)-C(8)-H(8A)	108.3
C(12)-N(2)-C(13)	121.0(2)	C(10)-C(9)-C(25)	120.4(2)
C(12)-N(2)-H(2N)	114.3(19)	C(10)-C(9)-C(8)	123.4(2)
C(13)-N(2)-H(2N)	124.6(19)	C(25)-C(9)-C(8)	116.2(2)
O(6)-S(2)-O(7)	117.51(14)	C(9)-C(10)-C(11)	127.2(2)
O(6)-S(2)-N(3)	109.76(11)	C(9)-C(10)-H(10A)	116.4
O(7)-S(2)-N(3)	107.37(11)	C(11)-C(10)-H(10A)	116.4
O(6)-S(2)-C(52)	107.76(15)	C(61)-O(10)-C(62)	116.2(3)
O(7)-S(2)-C(52)	106.40(13)	C(10)-C(11)-C(12)	107.59(18)
N(3)-S(2)-C(52)	107.62(12)	C(10)-C(11)-C(26)	112.9(2)
C(2)-C(3)-C(4)	119.6(3)	C(12)-C(11)-C(26)	110.42(19)
C(2)-C(3)-H(3A)	120.2	C(10)-C(11)-H(11A)	108.6
C(4)-C(3)-H(3A)	120.2	C(12)-C(11)-H(11A)	108.6
C(39)-N(3)-S(2)	124.27(15)	C(26)-C(11)-H(11A)	108.6
C(39)-N(3)-H(3N)	118.7(16)	O(3)-C(12)-N(2)	120.4(2)
S(2)-N(3)-H(3N)	108.7(16)	O(3)-C(12)-C(11)	123.3(2)
C(3)-C(4)-C(5)	120.2(3)	N(2)-C(12)-C(11)	116.30(19)
C(3)-C(4)-H(4A)	119.9	N(2)-C(13)-C(30)	110.5(2)

Table D3. Cont'd

N(2)-C(13)-C(14)	111.38(19)	H(22B)-C(22)-H(22C)	109.5
C(30)-C(13)-C(14)	109.7(2)	C(21)-C(23)-H(23A)	109.5
N(2)-C(13)-H(13A)	108.4	C(21)-C(23)-H(23B)	109.5
C(30)-C(13)-H(13A)	108.4	H(23A)-C(23)-H(23B)	109.5
C(14)-C(13)-H(13A)	108.4	C(21)-C(23)-H(23C)	109.5
C(15)-C(14)-C(13)	112.7(2)	H(23A)-C(23)-H(23C)	109.5
C(15)-C(14)-H(14A)	109.1	H(23B)-C(23)-H(23C)	109.5
C(13)-C(14)-H(14A)	109.1	C(21)-C(24)-H(24A)	109.5
C(15)-C(14)-H(14B)	109.1	C(21)-C(24)-H(24B)	109.5
C(13)-C(14)-H(14B)	109.1	H(24A)-C(24)-H(24B)	109.5
H(14A)-C(14)-H(14B)	107.8	C(21)-C(24)-H(24C)	109.5
C(20)-C(15)-C(16)	117.8(3)	H(24A)-C(24)-H(24C)	109.5
C(20)-C(15)-C(14)	120.3(2)	H(24B)-C(24)-H(24C)	109.5
C(16)-C(15)-C(14)	121.9(2)	C(9)-C(25)-H(25A)	109.5
C(17)-C(16)-C(15)	121.2(3)	C(9)-C(25)-H(25B)	109.5
C(17)-C(16)-H(16A)	119.4	H(25A)-C(25)-H(25B)	109.5
C(15)-C(16)-H(16A)	119.4	C(9)-C(25)-H(25C)	109.5
C(18)-C(17)-C(16)	120.1(3)	H(25A)-C(25)-H(25C)	109.5
C(18)-C(17)-H(17A)	120	H(25B)-C(25)-H(25C)	109.5
C(16)-C(17)-H(17A)	120	C(27)-C(26)-C(11)	114.2(2)
C(19)-C(18)-C(17)	119.8(3)	C(27)-C(26)-H(26A)	108.7
C(19)-C(18)-H(18A)	120.1	C(11)-C(26)-H(26A)	108.7
C(17)-C(18)-H(18A)	120.1	C(27)-C(26)-H(26B)	108.7
C(18)-C(19)-C(20)	120.2(3)	C(11)-C(26)-H(26B)	108.7
C(18)-C(19)-H(19A)	119.9	H(26A)-C(26)-H(26B)	107.6
C(20)-C(19)-H(19A)	119.9	C(29)-C(27)-C(26)	112.3(3)
C(15)-C(20)-C(19)	120.9(3)	C(29)-C(27)-C(28)	112.2(4)
C(15)-C(20)-H(20A)	119.5	C(26)-C(27)-C(28)	109.0(3)
C(19)-C(20)-H(20A)	119.5	C(29)-C(27)-H(27A)	107.7
C(22)-C(21)-C(23)	111.4(2)	C(26)-C(27)-H(27A)	107.7
C(22)-C(21)-C(24)	110.7(2)	C(28)-C(27)-H(27A)	107.7
C(23)-C(21)-C(24)	111.3(2)	C(27)-C(28)-H(28A)	109.5
C(22)-C(21)-S(1)	106.2(2)	C(27)-C(28)-H(28B)	109.5
C(23)-C(21)-S(1)	108.16(18)	H(28A)-C(28)-H(28B)	109.5
C(24)-C(21)-S(1)	108.86(17)	C(27)-C(28)-H(28C)	109.5
C(21)-C(22)-H(22A)	109.5	H(28A)-C(28)-H(28C)	109.5
C(21)-C(22)-H(22B)	109.5	H(28B)-C(28)-H(28C)	109.5
H(22A)-C(22)-H(22B)	109.5	C(27)-C(29)-H(29A)	109.5
C(21)-C(22)-H(22C)	109.5	C(27)-C(29)-H(29B)	109.5
H(22A)-C(22)-H(22C)	109.5	H(29A)-C(29)-H(29B)	109.5

Table D3. Cont'd

C(27)-C(29)-H(29C)	109.5	C(40)-C(39)-H(39A)	108.1
H(29A)-C(29)-H(29C)	109.5	C(38)-C(39)-H(39A)	108.1
H(29B)-C(29)-H(29C)	109.5	C(41)-C(40)-C(56)	121.3(2)
O(4)-C(30)-O(5)	124.7(3)	C(41)-C(40)-C(39)	123.0(2)
O(4)-C(30)-C(13)	126.1(2)	C(56)-C(40)-C(39)	115.7(2)
O(5)-C(30)-C(13)	109.3(2)	C(40)-C(41)-C(42)	128.7(2)
O(5)-C(31)-H(31A)	109.5	C(40)-C(41)-H(41A)	115.7
O(5)-C(31)-H(31B)	109.5	C(42)-C(41)-H(41A)	115.7
H(31A)-C(31)-H(31B)	109.5	C(41)-C(42)-C(43)	109.53(18)
O(5)-C(31)-H(31C)	109.5	C(41)-C(42)-C(57)	113.27(18)
H(31A)-C(31)-H(31C)	109.5	C(43)-C(42)-C(57)	111.43(18)
H(31B)-C(31)-H(31C)	109.5	C(41)-C(42)-H(42A)	107.4
C(37)-C(32)-C(33)	120.8(3)	C(43)-C(42)-H(42A)	107.4
C(37)-C(32)-H(32A)	119.6	C(57)-C(42)-H(42A)	107.4
C(33)-C(32)-H(32A)	119.6	O(8)-C(43)-N(4)	123.4(2)
C(34)-C(33)-C(32)	119.7(3)	O(8)-C(43)-C(42)	123.31(19)
C(34)-C(33)-H(33A)	120.2	N(4)-C(43)-C(42)	113.34(18)
C(32)-C(33)-H(33A)	120.2	N(4)-C(44)-C(61)	111.4(2)
C(33)-C(34)-C(35)	120.1(3)	N(4)-C(44)-C(45)	110.9(2)
C(33)-C(34)-H(34A)	120	C(61)-C(44)-C(45)	111.0(2)
C(35)-C(34)-H(34A)	120	N(4)-C(44)-H(44A)	107.8
C(36)-C(35)-C(34)	120.0(3)	C(61)-C(44)-H(44A)	107.8
C(36)-C(35)-H(35A)	120	C(45)-C(44)-H(44A)	107.8
C(34)-C(35)-H(35A)	120	C(46)-C(45)-C(44)	113.5(2)
C(35)-C(36)-C(37)	121.3(3)	C(46)-C(45)-H(45A)	108.9
C(35)-C(36)-H(36A)	119.4	C(44)-C(45)-H(45A)	108.9
C(37)-C(36)-H(36A)	119.4	C(46)-C(45)-H(45B)	108.9
C(32)-C(37)-C(36)	118.2(3)	C(44)-C(45)-H(45B)	108.9
C(32)-C(37)-C(38)	122.2(2)	H(45A)-C(45)-H(45B)	107.7
C(36)-C(37)-C(38)	119.6(2)	C(51)-C(46)-C(47)	117.8(4)
C(37)-C(38)-C(39)	113.37(19)	C(51)-C(46)-C(45)	121.2(3)
C(37)-C(38)-H(38A)	108.9	C(47)-C(46)-C(45)	121.0(3)
C(39)-C(38)-H(38A)	108.9	C(46)-C(47)-C(48)	119.6(4)
C(37)-C(38)-H(38B)	108.9	C(46)-C(47)-H(47A)	120.2
C(39)-C(38)-H(38B)	108.9	C(48)-C(47)-H(47A)	120.2
H(38A)-C(38)-H(38B)	107.7	C(49)-C(48)-C(47)	120.5(4)
N(3)-C(39)-C(40)	113.82(19)	C(49)-C(48)-H(48A)	119.8
N(3)-C(39)-C(38)	107.54(17)	C(47)-C(48)-H(48A)	119.8
C(40)-C(39)-C(38)	110.93(18)	C(48)-C(49)-C(50)	120.7(5)
N(3)-C(39)-H(39A)	108.1	C(48)-C(49)-H(49A)	119.7

Table D3. Cont'd.

C(50)-C(49)-H(49A)	119.7	C(58)-C(57)-H(57B)	108.6
C(49)-C(50)-C(51)	120.0(5)	C(42)-C(57)-H(57B)	108.6
C(49)-C(50)-H(50A)	120	H(57A)-C(57)-H(57B)	107.5
C(51)-C(50)-H(50A)	120	C(57)-C(58)-C(60)	110.8(2)
C(50)-C(51)-C(46)	121.5(4)	C(57)-C(58)-C(59)	112.1(2)
C(50)-C(51)-H(51A)	119.3	C(60)-C(58)-C(59)	108.7(2)
C(46)-C(51)-H(51A)	119.3	C(57)-C(58)-H(58A)	108.4
C(54)-C(52)-C(53)	111.6(3)	C(60)-C(58)-H(58A)	108.4
C(54)-C(52)-C(55)	112.2(3)	C(59)-C(58)-H(58A)	108.4
C(53)-C(52)-C(55)	109.6(3)	C(58)-C(59)-H(59A)	109.5
C(54)-C(52)-S(2)	108.9(2)	C(58)-C(59)-H(59B)	109.5
C(53)-C(52)-S(2)	106.0(2)	H(59A)-C(59)-H(59B)	109.5
C(55)-C(52)-S(2)	108.3(2)	C(58)-C(59)-H(59C)	109.5
C(52)-C(53)-H(53A)	109.5	H(59A)-C(59)-H(59C)	109.5
C(52)-C(53)-H(53B)	109.5	H(59B)-C(59)-H(59C)	109.5
H(53A)-C(53)-H(53B)	109.5	C(58)-C(60)-H(60A)	109.5
C(52)-C(53)-H(53C)	109.5	C(58)-C(60)-H(60B)	109.5
H(53A)-C(53)-H(53C)	109.5	H(60A)-C(60)-H(60B)	109.5
H(53B)-C(53)-H(53C)	109.5	C(58)-C(60)-H(60C)	109.5
C(52)-C(54)-H(54A)	109.5	H(60A)-C(60)-H(60C)	109.5
C(52)-C(54)-H(54B)	109.5	H(60B)-C(60)-H(60C)	109.5
H(54A)-C(54)-H(54B)	109.5	O(9)-C(61)-O(10)	122.7(3)
C(52)-C(54)-H(54C)	109.5	O(9)-C(61)-C(44)	124.8(3)
H(54A)-C(54)-H(54C)	109.5	O(10)-C(61)-C(44)	112.5(2)
H(54B)-C(54)-H(54C)	109.5	O(10)-C(62)-H(62A)	109.5
C(52)-C(55)-H(55A)	109.5	O(10)-C(62)-H(62B)	109.5
C(52)-C(55)-H(55B)	109.5	H(62A)-C(62)-H(62B)	109.5
H(55A)-C(55)-H(55B)	109.5	O(10)-C(62)-H(62C)	109.5
C(52)-C(55)-H(55C)	109.5	H(62A)-C(62)-H(62C)	109.5
H(55A)-C(55)-H(55C)	109.5	H(62B)-C(62)-H(62C)	109.5
H(55B)-C(55)-H(55C)	109.5		
C(40)-C(56)-H(56A)	109.5		
C(40)-C(56)-H(56B)	109.5		
H(56A)-C(56)-H(56B)	109.5		
C(40)-C(56)-H(56C)	109.5		
H(56A)-C(56)-H(56C)	109.5		
H(56B)-C(56)-H(56C)	109.5		
C(58)-C(57)-C(42)	114.86(19)		
C(58)-C(57)-H(57A)	108.6		
C(42)-C(57)-H(57A)	108.6		

Table D4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw927s. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	32(1)	34(1)	26(1)	1(1)	2(1)	-2(1)
C(1)	69(2)	58(2)	38(1)	5(1)	4(1)	24(2)
N(1)	34(1)	36(1)	26(1)	2(1)	4(1)	-4(1)
O(1)	42(1)	56(1)	43(1)	12(1)	-1(1)	1(1)
C(2)	116(3)	66(2)	48(2)	-14(2)	-10(2)	42(2)
N(2)	38(1)	41(1)	37(1)	-12(1)	-5(1)	0(1)
O(2)	36(1)	49(1)	36(1)	-10(1)	6(1)	-7(1)
S(2)	31(1)	49(1)	38(1)	11(1)	1(1)	-4(1)
C(3)	129(3)	45(2)	66(2)	-5(2)	-19(2)	34(2)
N(3)	34(1)	33(1)	38(1)	9(1)	1(1)	-5(1)
O(3)	41(1)	42(1)	64(1)	-24(1)	-9(1)	1(1)
C(4)	108(3)	52(2)	49(2)	12(1)	-12(2)	28(2)
N(4)	34(1)	50(1)	41(1)	19(1)	11(1)	8(1)
O(4)	88(2)	67(1)	51(1)	9(1)	10(1)	13(1)
C(5)	64(2)	52(2)	39(1)	1(1)	-8(1)	17(1)
O(5)	78(2)	96(2)	59(1)	-6(1)	14(1)	36(1)
C(6)	39(1)	41(1)	40(1)	1(1)	0(1)	10(1)
O(6)	38(1)	112(2)	50(1)	27(1)	1(1)	-11(1)
C(7)	31(1)	45(1)	48(1)	5(1)	2(1)	4(1)
O(7)	47(1)	51(1)	89(2)	11(1)	-3(1)	7(1)
C(8)	29(1)	34(1)	31(1)	4(1)	2(1)	0(1)
O(8)	42(1)	59(1)	36(1)	17(1)	10(1)	10(1)
C(9)	27(1)	34(1)	42(1)	5(1)	-5(1)	-4(1)
O(9)	33(1)	99(2)	140(2)	1(2)	-14(1)	8(1)
C(10)	37(1)	28(1)	47(1)	-2(1)	-6(1)	-5(1)
O(10)	45(1)	95(2)	104(2)	-33(1)	-16(1)	18(1)
C(11)	37(1)	34(1)	35(1)	-5(1)	-5(1)	-1(1)
C(12)	37(1)	33(1)	33(1)	-3(1)	-1(1)	-2(1)
C(13)	36(1)	43(1)	40(1)	-7(1)	-2(1)	0(1)
C(14)	39(1)	53(2)	46(1)	-2(1)	-5(1)	-4(1)
C(15)	32(1)	47(1)	47(1)	-4(1)	-10(1)	0(1)
C(16)	35(1)	50(2)	50(2)	-1(1)	-6(1)	0(1)
C(17)	49(2)	74(2)	51(2)	-4(2)	-5(1)	-3(2)
C(18)	62(2)	73(2)	63(2)	16(2)	-20(2)	-14(2)
C(19)	88(3)	46(2)	91(3)	10(2)	-29(2)	2(2)
C(20)	72(2)	54(2)	59(2)	-11(2)	-16(2)	9(2)
C(21)	47(1)	37(1)	36(1)	-6(1)	2(1)	-12(1)
C(22)	51(2)	65(2)	55(2)	0(1)	-3(1)	-22(1)
C(23)	84(2)	60(2)	50(2)	-25(1)	12(2)	-17(2)
C(24)	62(2)	38(1)	64(2)	9(1)	-1(1)	-9(1)

Table D4. Cont'd.

C(25)	43(1)	34(1)	55(2)	9(1)	4(1)	-7(1)
C(26)	39(1)	58(2)	48(1)	-8(1)	-7(1)	12(1)
C(27)	68(2)	85(2)	41(2)	8(2)	-7(1)	20(2)
C(28)	106(4)	231(6)	56(2)	29(3)	-21(2)	39(4)
C(29)	165(5)	66(2)	92(3)	30(2)	25(3)	-1(3)
C(30)	43(1)	54(2)	42(1)	-10(1)	0(1)	2(1)
C(31)	102(3)	149(4)	59(2)	-10(2)	32(2)	35(3)
C(32)	49(2)	58(2)	45(2)	9(1)	2(1)	2(1)
C(33)	59(2)	110(3)	41(2)	2(2)	3(1)	8(2)
C(34)	54(2)	88(3)	63(2)	-27(2)	7(2)	4(2)
C(35)	62(2)	55(2)	89(2)	-12(2)	28(2)	4(2)
C(36)	50(2)	51(2)	57(2)	10(1)	14(1)	5(1)
C(37)	26(1)	47(1)	41(1)	1(1)	3(1)	-1(1)
C(38)	33(1)	44(1)	37(1)	2(1)	-3(1)	-5(1)
C(39)	31(1)	34(1)	31(1)	2(1)	-3(1)	-7(1)
C(40)	38(1)	38(1)	35(1)	-5(1)	-1(1)	-10(1)
C(41)	37(1)	43(1)	26(1)	-8(1)	-2(1)	-7(1)
C(42)	28(1)	38(1)	23(1)	-1(1)	1(1)	-2(1)
C(43)	32(1)	36(1)	23(1)	-2(1)	2(1)	0(1)
C(44)	35(1)	59(2)	41(1)	17(1)	11(1)	12(1)
C(45)	46(2)	72(2)	56(2)	17(2)	12(1)	26(2)
C(46)	62(2)	68(2)	56(2)	3(2)	1(2)	38(2)
C(47)	74(2)	129(3)	63(2)	-2(2)	9(2)	48(2)
C(48)	114(4)	139(4)	57(2)	-25(2)	-6(2)	74(3)
C(49)	112(4)	81(3)	88(3)	-22(2)	-20(3)	52(3)
C(50)	115(3)	49(2)	96(3)	-10(2)	-16(3)	24(2)
C(51)	86(2)	50(2)	64(2)	-2(2)	-3(2)	21(2)
C(52)	47(2)	57(2)	66(2)	0(1)	-23(1)	-5(1)
C(53)	52(2)	76(2)	99(3)	22(2)	-37(2)	-16(2)
C(54)	75(2)	155(4)	48(2)	-14(2)	-13(2)	-5(3)
C(55)	84(3)	50(2)	152(4)	-25(2)	-64(3)	3(2)
C(56)	87(2)	43(2)	52(2)	-11(1)	3(2)	-21(2)
C(57)	26(1)	54(1)	37(1)	5(1)	0(1)	3(1)
C(58)	42(1)	45(1)	45(1)	12(1)	5(1)	11(1)
C(59)	80(2)	51(2)	53(2)	-1(1)	12(2)	18(2)
C(60)	64(2)	84(2)	71(2)	26(2)	7(2)	33(2)
C(61)	33(1)	71(2)	60(2)	21(2)	10(1)	3(1)
C(62)	61(2)	124(4)	125(4)	-51(3)	-20(2)	3(2)

Table D5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bw927s.

	x	y	z	U(eq)
H(1A)	8391	7235	2369	66
H(1N)	6290(30)	8062(10)	2592(10)	31(7)
H(2A)	8553	6302	2312	92
H(2N)	3500(30)	8543(11)	4036(11)	44(7)
H(3A)	8674	5779	3053	96
H(3N)	9140(20)	10011(10)	-80(9)	30(6)
H(4A)	8727	6196	3857	84
H(4N)	6620(30)	9022(10)	1090(10)	41(7)
H(5A)	8614	7130	3919	62
H(7A)	8724	8047	2863	50
H(7B)	9015	8013	3467	50
H(8A)	6632	7903	3615	38
H(10A)	6672	9286	3888	45
H(11A)	5531	8259	4159	42
H(13A)	2344	9461	4372	47
H(14A)	1043	8488	4033	55
H(14B)	188	8993	4236	55
H(16A)	1691	8471	3143	54
H(17A)	1740	8863	2332	70
H(18A)	1158	9763	2229	79
H(19A)	555	10274	2939	90
H(20A)	516	9887	3754	74
H(22A)	2423	6707	2804	85
H(22B)	2211	7309	2593	85
H(22C)	2366	7202	3199	85
H(23A)	4503	6616	2212	97
H(23B)	5642	7072	2248	97
H(23C)	4197	7216	2013	97
H(24A)	4732	6445	3179	82
H(24B)	4568	6941	3569	82
H(24C)	5871	6900	3209	82
H(25A)	7564	9426	3110	66
H(25B)	7085	9005	2679	66
H(25C)	8536	8943	2939	66
H(26A)	7581	8319	4633	58
H(26B)	7097	8878	4878	58
H(27A)	5313	8427	5306	78
H(28A)	6683	8006	5939	196
H(28B)	7323	8568	5758	196
H(28C)	7925	8011	5547	196
H(29A)	5232	7485	5334	161
H(29B)	6429	7450	4923	161

Table D5. Cont'd.

H(29C)	5003	7695	4758	161
H(31A)	9	9516	5769	155
H(31B)	1331	9178	5909	155
H(31C)	51	8878	5669	155
H(32A)	11252	9746	-802	60
H(33A)	11697	9265	-1560	84
H(34A)	12101	8344	-1522	82
H(35A)	12163	7907	-731	82
H(36A)	11760	8384	19	63
H(38A)	11432	9796	137	45
H(38B)	11777	9260	456	45
H(39A)	9419	8987	339	39
H(41A)	9222	9369	1634	42
H(42A)	8671	8547	891	36
H(44A)	5082	8690	1878	54
H(45A)	4522	9566	1184	69
H(45B)	3557	9389	1647	69
H(47A)	4147	9630	2540	106
H(48A)	5319	10235	3080	124
H(49A)	7113	10715	2771	112
H(50A)	7762	10634	1923	104
H(51A)	6579	10072	1369	80
H(53A)	5027	8864	-777	113
H(53B)	4917	9480	-594	113
H(53C)	5018	9007	-175	113
H(54A)	7129	9105	-1304	139
H(54B)	8333	9416	-1021	139
H(54C)	6931	9717	-1119	139
H(55A)	7264	8353	-629	144
H(55B)	7119	8511	-34	144
H(55C)	8459	8665	-343	144
H(56A)	9780	10209	1392	91
H(56B)	9306	10368	822	91
H(56C)	10839	10203	927	91
H(57A)	10791	8377	1347	47
H(57B)	9899	8261	1847	47
H(58A)	8804	7545	1389	53
H(59A)	9293	7822	531	92

Table D5. Cont'd.

H(59B)	9788	7214	624	92
H(59C)	10855	7698	624	92
H(60A)	10614	7341	1955	110
H(60B)	11653	7401	1487	110
H(60C)	10571	6922	1485	110
H(62A)	4808	7379	594	155
H(62B)	3878	7861	390	155
H(62C)	3446	7526	891	155

APPENDIX E

X-RAY CRYSTAL DATA FOR 228

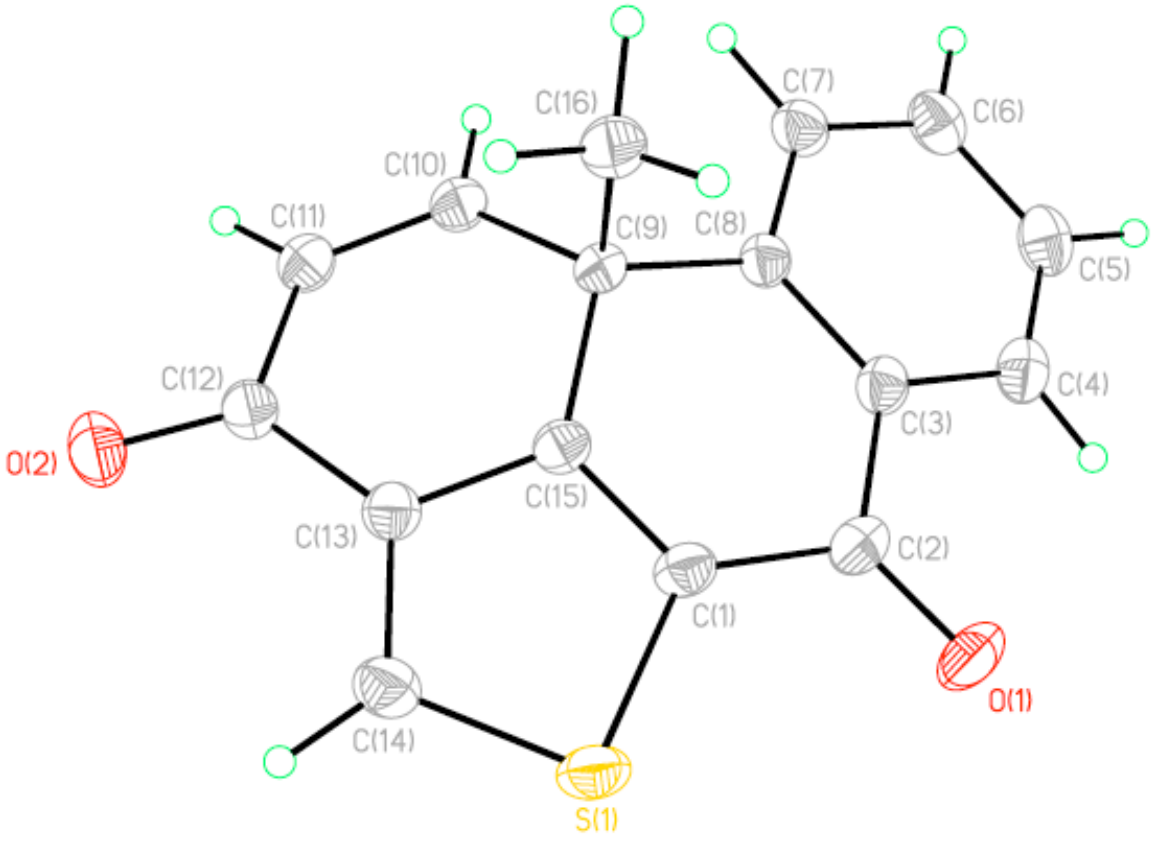


Table E1. Crystal data and structure refinement for bw612s.

Identification code	bww612s	
Empirical formula	C16 H10 O2 S	
Formula weight	266.3	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3598(9) Å	a= 100.717(2)°.
	b = 7.9274(10) Å	b= 96.314(2)°.
	c = 11.2447(14) Å	g = 108.545(2)°.
Volume	600.99(13) $Å^3$	
Z	2	
Density (calculated)	1.472 Mg/m^3	
Absorption coefficient	0.262 mm^{-1}	
F(000)	276	
Crystal size	? x ? x ? mm^3	
Theta range for data collection	1.87 to 32.60°.	
Index ranges	-10<=h<=11, -11<=k<=11, -16<=l<=17	
Reflections collected	7843	
Independent reflections	4090 [R(int) = 0.0169]	
Completeness to theta = 32.60°	93.40%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4090 / 0 / 213	
Goodness-of-fit on F^2	1.176	
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1238	
R indices (all data)	R1 = 0.0529, wR2 = 0.1321	
Extinction coefficient	0.000(4)	
Largest diff. peak and hole	0.496 and -0.267 $e.Å^{-3}$	

Table E2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bww612s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-1313(1)	-11762(1)	-1364(1)	28(1)
C(1)	30(2)	-10139(2)	-2060(1)	22(1)
O(1)	1981(2)	-11720(1)	-2938(1)	35(1)
O(2)	-4831(1)	-7809(1)	-961(1)	32(1)
C(2)	1398(2)	-10417(2)	-2855(1)	24(1)
C(3)	1901(2)	-9071(2)	-3644(1)	22(1)
C(4)	2928(2)	-9432(2)	-4581(1)	26(1)
C(5)	3420(2)	-8264(2)	-5358(1)	29(1)
C(6)	2915(2)	-6699(2)	-5193(1)	28(1)
C(7)	1904(2)	-6319(2)	-4267(1)	25(1)
C(8)	1345(2)	-7512(2)	-3498(1)	20(1)
C(9)	265(2)	-7060(2)	-2467(1)	20(1)
C(10)	-1281(2)	-6267(2)	-2816(1)	24(1)
C(11)	-2923(2)	-6555(2)	-2356(1)	25(1)
C(12)	-3472(2)	-7773(2)	-1505(1)	23(1)
C(13)	-2304(2)	-8960(2)	-1424(1)	22(1)
C(14)	-2807(2)	-10562(2)	-1022(1)	28(1)
C(15)	-645(2)	-8710(2)	-1995(1)	20(1)
C(16)	1799(2)	-5566(2)	-1403(1)	27(1)

Table E3. Bond lengths [Å] and angles [°] for bww612s.

S(1)-C(14)	1.6986(14)	C(4)-C(3)-C(2)	117.42(11)
S(1)-C(1)	1.7261(12)	C(8)-C(3)-C(2)	122.81(10)
C(1)-C(15)	1.3682(15)	C(5)-C(4)-C(3)	120.75(12)
C(1)-C(2)	1.4590(17)	C(5)-C(4)-H(4)	121.9(11)
O(1)-C(2)	1.2308(15)	C(3)-C(4)-H(4)	117.2(11)
O(2)-C(12)	1.2240(15)	C(4)-C(5)-C(6)	119.44(12)
C(2)-C(3)	1.4951(17)	C(4)-C(5)-H(5)	120.8(11)
C(3)-C(4)	1.4021(16)	C(6)-C(5)-H(5)	119.7(11)
C(3)-C(8)	1.4074(16)	C(7)-C(6)-C(5)	120.54(12)
C(4)-C(5)	1.3814(19)	C(7)-C(6)-H(6)	118.4(13)
C(4)-H(4)	0.936(18)	C(5)-C(6)-H(6)	121.1(13)
C(5)-C(6)	1.3906(19)	C(6)-C(7)-C(8)	120.68(12)
C(5)-H(5)	0.960(18)	C(6)-C(7)-H(7)	119.8(10)
C(6)-C(7)	1.3885(18)	C(8)-C(7)-H(7)	119.6(10)
C(6)-H(6)	0.92(2)	C(7)-C(8)-C(3)	118.78(11)
C(7)-C(8)	1.3947(16)	C(7)-C(8)-C(9)	120.14(10)
C(7)-H(7)	1.014(18)	C(3)-C(8)-C(9)	120.96(10)
C(8)-C(9)	1.5283(15)	C(15)-C(9)-C(10)	108.80(9)
C(9)-C(15)	1.4900(15)	C(15)-C(9)-C(8)	110.64(9)
C(9)-C(10)	1.5134(16)	C(10)-C(9)-C(8)	114.67(10)
C(9)-C(16)	1.5600(17)	C(15)-C(9)-C(16)	108.86(9)
C(10)-C(11)	1.3366(17)	C(10)-C(9)-C(16)	106.30(9)
C(10)-H(10)	0.921(18)	C(8)-C(9)-C(16)	107.34(9)
C(11)-C(12)	1.4795(17)	C(11)-C(10)-C(9)	123.72(11)
C(11)-H(11)	0.95(2)	C(11)-C(10)-H(10)	116.7(11)
C(12)-C(13)	1.4712(17)	C(9)-C(10)-H(10)	119.5(11)
C(13)-C(14)	1.3801(17)	C(10)-C(11)-C(12)	123.34(11)
C(13)-C(15)	1.4166(16)	C(10)-C(11)-H(11)	122.7(12)
C(14)-H(14)	0.98(2)	C(12)-C(11)-H(11)	113.9(12)
C(16)-H(16A)	0.988(17)	O(2)-C(12)-C(13)	124.05(11)
C(16)-H(16B)	0.978(19)	O(2)-C(12)-C(11)	121.79(11)
C(16)-H(16C)	0.94(2)	C(13)-C(12)-C(11)	114.10(10)
C(14)-S(1)-C(1)	92.01(6)	C(14)-C(13)-C(15)	112.06(11)
C(15)-C(1)-C(2)	122.71(11)	C(14)-C(13)-C(12)	126.79(11)
C(15)-C(1)-S(1)	111.20(9)	C(15)-C(13)-C(12)	120.16(10)
C(2)-C(1)-S(1)	124.69(9)	C(13)-C(14)-S(1)	111.96(9)
O(1)-C(2)-C(1)	123.11(12)	C(13)-C(14)-H(14)	124.7(12)
O(1)-C(2)-C(3)	122.61(12)	S(1)-C(14)-H(14)	122.9(12)
C(1)-C(2)-C(3)	114.09(10)	C(1)-C(15)-C(13)	112.72(10)
C(4)-C(3)-C(8)	119.75(11)	C(1)-C(15)-C(9)	123.85(10)

Table E3. Cont'd.

C(13)-C(15)-C(9)	123.43(10)
C(9)-C(16)-H(16A)	109.5(10)
C(9)-C(16)-H(16B)	114.2(11)
H(16A)-C(16)-H(16B)	106.8(14)
C(9)-C(16)-H(16C)	110.1(11)
H(16A)-C(16)-H(16C)	108.0(15)
H(16B)-C(16)-H(16C)	108.0(16)

Table E4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bww612s. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	38(1)	21(1)	30(1)	11(1)	10(1)	12(1)
C(1)	27(1)	20(1)	23(1)	7(1)	5(1)	10(1)
O(1)	44(1)	30(1)	44(1)	13(1)	14(1)	25(1)
O(2)	30(1)	38(1)	36(1)	12(1)	15(1)	16(1)
C(2)	26(1)	21(1)	26(1)	4(1)	2(1)	11(1)
C(3)	19(1)	23(1)	22(1)	3(1)	2(1)	8(1)
C(4)	23(1)	30(1)	26(1)	3(1)	5(1)	12(1)
C(5)	24(1)	39(1)	24(1)	5(1)	6(1)	11(1)
C(6)	24(1)	35(1)	26(1)	12(1)	6(1)	9(1)
C(7)	24(1)	26(1)	28(1)	11(1)	6(1)	9(1)
C(8)	18(1)	21(1)	21(1)	5(1)	4(1)	7(1)
C(9)	21(1)	18(1)	24(1)	7(1)	6(1)	8(1)
C(10)	26(1)	23(1)	29(1)	11(1)	8(1)	12(1)
C(11)	25(1)	24(1)	31(1)	10(1)	7(1)	13(1)
C(12)	22(1)	23(1)	24(1)	5(1)	6(1)	7(1)
C(13)	24(1)	21(1)	21(1)	5(1)	6(1)	8(1)
C(14)	33(1)	26(1)	26(1)	10(1)	11(1)	9(1)
C(15)	21(1)	19(1)	19(1)	4(1)	3(1)	8(1)
C(16)	26(1)	22(1)	29(1)	1(1)	4(1)	7(1)

Table E5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bww612s.

	x	y	z	U(eq)
H(4)	3190(20)	-10530(20)	-4689(16)	32(4)
H(5)	4130(30)	-8500(20)	-5996(16)	41(5)
H(6)	3260(30)	-5880(30)	-5683(18)	50(5)
H(7)	1570(30)	-5160(20)	-4143(16)	38(4)
H(10)	-1070(20)	-5480(20)	-3337(15)	33(4)
H(11)	-3870(30)	-6030(30)	-2573(17)	48(5)
H(14)	-3980(30)	-11050(30)	-682(18)	49(5)
H(16A)	1180(30)	-5330(20)	-686(15)	31(4)
H(16B)	2370(30)	-4390(30)	-1611(16)	40(5)
H(16C)	2810(30)	-5980(20)	-1158(17)	43(5)

APPENDIX F

X-RAY CRYSTAL DATA FOR 256

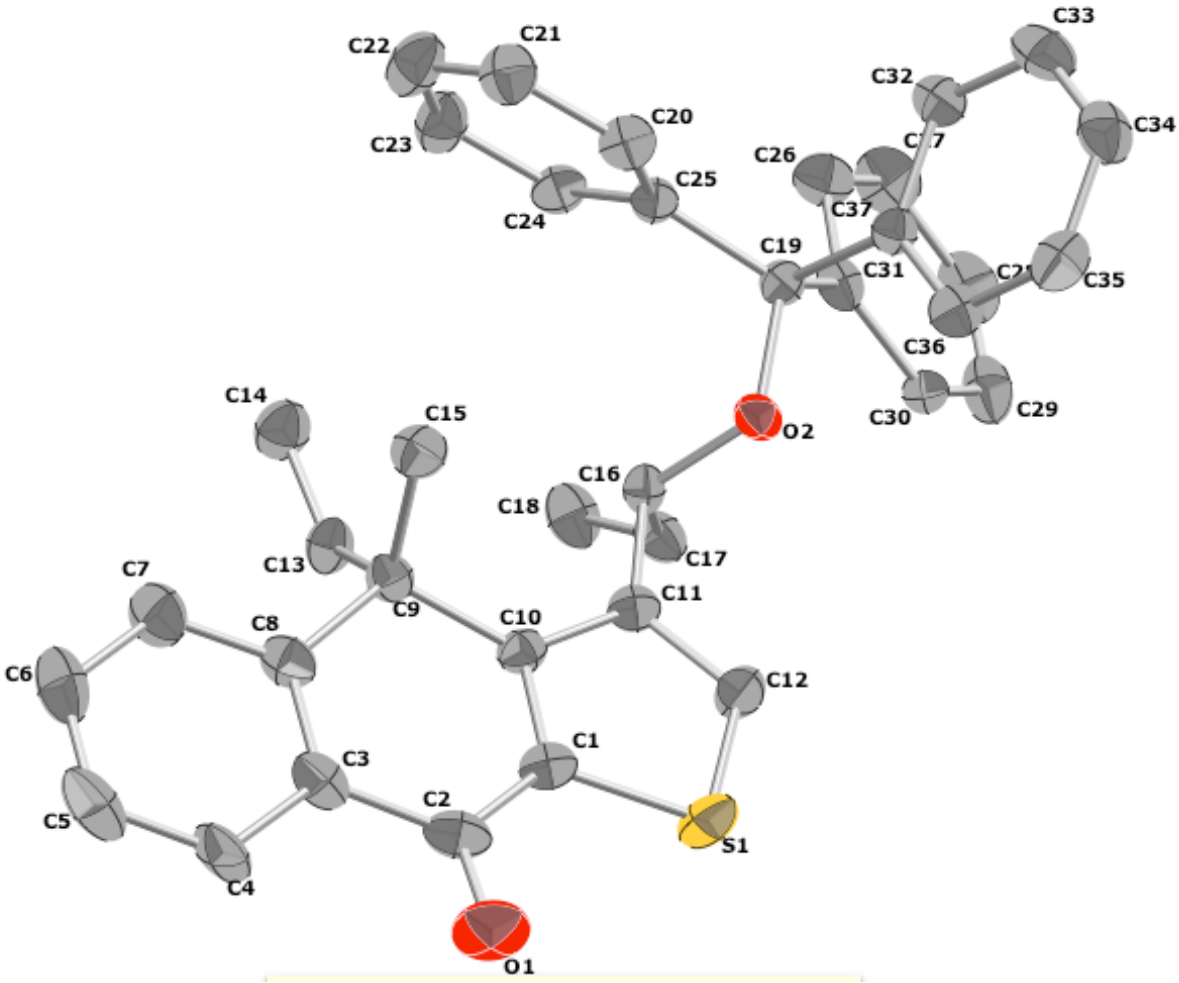


Table F1. Crystal data and structure refinement for bw31308.

Identification code	bw31308
Empirical formula	C37 H30 O2 S
Formula weight	538.67
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pna2(1)
Unit cell dimensions	a = 14.0848(8) Å a= 90°. b = 12.0300(7) Å b= 90°. c = 33.068(2) Å g = 90°.
Volume	5603.0(6) $Å^3$
Z	8
Density (calculated)	1.277 Mg/m^3
Absorption coefficient	0.149 mm^{-1}
F(000)	2272
Crystal size	0.38 x 0.35 x 0.18 mm^3
Theta range for data collection	1.80 to 32.63°.
Index ranges	-21<=h<=21, -17<=k<=18, -50<=l<=49
Reflections collected	70149
Independent reflections	19605 [R(int) = 0.0681]
Completeness to theta = 32.63°	98.20%
Absorption correction	Multi-scan (Sadabs)
Max. and min. transmission	0.9737 and 0.9457
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	19605 / 1 / 778
Goodness-of-fit on F^2	1.01
Final R indices [I>2sigma(I)]	R1 = 0.0681, wR2 = 0.1432
R indices (all data)	R1 = 0.1202, wR2 = 0.1704
Absolute structure parameter	0.55(8)
Largest diff. peak and hole	0.605 and -0.226 e.$Å^{-3}$

Table F2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bw31308. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3896(1)	-747(1)	2346(1)	37(1)
S(2)	3591(1)	4265(1)	2560(1)	36(1)
O(1)	5016(2)	944(2)	1862(1)	51(1)
O(2)	2901(1)	-600(2)	3609(1)	25(1)
O(3)	2467(2)	5953(2)	3039(1)	49(1)
O(4)	4601(1)	4430(2)	1297(1)	25(1)
C(1)	4633(2)	293(2)	2512(1)	29(1)
C(2)	5129(2)	1001(3)	2230(1)	35(1)
C(3)	5788(2)	1807(3)	2418(1)	33(1)
C(4)	6387(5)	2433(3)	2161(2)	40(2)
C(5)	7003(3)	3203(3)	2326(1)	51(1)
C(6)	7018(3)	3377(3)	2738(1)	49(1)
C(7)	6438(3)	2764(4)	2991(1)	41(1)
C(8)	5821(2)	1958(2)	2838(1)	30(1)
C(9)	5188(2)	1312(2)	3135(1)	26(1)
C(10)	4659(2)	365(2)	2928(1)	25(1)
C(11)	4069(2)	-446(2)	3113(1)	25(1)
C(12)	3627(2)	-1097(3)	2829(1)	32(1)
C(13)	5824(2)	855(2)	3469(1)	29(1)
C(14)	5879(2)	1234(3)	3841(1)	36(1)
C(15)	4438(2)	2117(3)	3303(1)	32(1)
C(16)	3917(2)	-648(2)	3559(1)	23(1)
C(17)	4341(2)	-1756(2)	3673(1)	29(1)
C(18)	5058(2)	-1879(3)	3922(1)	36(1)
C(19)	2503(2)	-533(2)	4013(1)	24(1)
C(20)	2647(2)	1517(2)	4189(1)	31(1)
C(21)	3099(5)	2414(3)	4371(2)	37(1)
C(22)	3895(3)	2246(4)	4603(1)	42(1)
C(23)	4237(2)	1180(3)	4653(1)	37(1)
C(24)	3790(2)	282(3)	4475(1)	29(1)
C(25)	2981(2)	434(2)	4240(1)	24(1)
C(26)	2590(3)	-1793(4)	4642(1)	35(1)
C(27)	2541(3)	-2833(4)	4818(1)	41(1)
C(28)	2459(3)	-3777(3)	4577(1)	43(1)
C(29)	2388(3)	-3657(3)	4162(2)	39(1)
C(30)	2425(4)	-2610(3)	3970(2)	28(1)
C(31)	2542(2)	-1672(3)	4226(1)	26(1)
C(32)	850(2)	-154(3)	4278(1)	33(1)
C(33)	-112(2)	12(3)	4227(1)	40(1)
C(34)	-505(2)	46(3)	3845(1)	38(1)

Table F2. Cont'd.

C(35)	78(2)	-92(3)	3515(1)	36(1)
C(36)	1044(2)	-269(3)	3562(1)	31(1)
C(37)	1443(2)	-299(2)	3944(1)	25(1)
C(38)	2857(2)	5301(2)	2391(1)	28(1)
C(39)	2352(2)	6018(3)	2672(1)	34(1)
C(40)	1695(2)	6820(3)	2483(1)	34(1)
C(41)	1087(5)	7443(3)	2730(2)	46(2)
C(42)	484(3)	8215(3)	2570(1)	52(1)
C(43)	469(3)	8381(3)	2157(1)	48(1)
C(44)	1047(3)	7755(4)	1908(1)	39(1)
C(45)	1665(2)	6961(2)	2062(1)	31(1)
C(46)	2301(2)	6312(2)	1766(1)	25(1)
C(47)	2833(2)	5382(2)	1977(1)	22(1)
C(48)	3427(2)	4563(2)	1791(1)	25(1)
C(49)	3870(2)	3917(3)	2075(1)	32(1)
C(50)	1663(2)	5849(2)	1434(1)	29(1)
C(51)	1616(3)	6220(3)	1061(1)	38(1)
C(52)	3059(2)	7120(3)	1596(1)	31(1)
C(53)	3583(2)	4360(2)	1346(1)	24(1)
C(54)	3170(2)	3244(2)	1232(1)	29(1)
C(55)	2462(2)	3121(3)	975(1)	37(1)
C(56)	4999(2)	4486(2)	895(1)	24(1)
C(57)	3706(2)	5251(3)	432(1)	31(1)
C(58)	3238(2)	6131(3)	244(1)	38(1)
C(59)	3572(3)	7204(4)	289(1)	42(1)
C(60)	4358(5)	7400(3)	525(3)	43(2)
C(61)	4838(2)	6514(2)	709(1)	34(1)
C(62)	4519(2)	5425(2)	659(1)	27(1)
C(63)	6643(2)	4890(3)	629(1)	36(1)
C(64)	7611(2)	5060(3)	675(1)	41(1)
C(65)	8002(2)	5078(3)	1059(1)	41(1)
C(66)	7432(2)	4919(3)	1389(1)	39(1)
C(67)	6458(2)	4737(2)	1343(1)	31(1)
C(68)	6057(2)	4733(2)	962(1)	26(1)
C(69)	4936(3)	3190(3)	276(1)	35(1)
C(70)	4965(3)	2110(5)	115(2)	50(1)
C(71)	5054(3)	1209(3)	358(2)	52(1)
C(72)	5116(3)	1347(3)	766(1)	39(1)
C(73)	5084(4)	2405(3)	915(2)	33(1)
C(74)	4970(3)	3339(3)	693(1)	26(1)

Table F3. Bond lengths [Å] and angles [°] for bww31308.

S(1)-C(12)	1.697(3)	C(17)-C(18)	1.312(4)
S(1)-C(1)	1.717(3)	C(17)-H(17)	1.01(3)
S(2)-C(49)	1.706(3)	C(18)-H(18A)	0.93(3)
S(2)-C(38)	1.713(3)	C(18)-H(18B)	0.95(3)
O(1)-C(2)	1.229(4)	C(19)-C(37)	1.537(4)
O(2)-C(16)	1.442(3)	C(19)-C(25)	1.539(4)
O(2)-C(19)	1.451(3)	C(19)-C(31)	1.542(4)
O(3)-C(39)	1.228(3)	C(20)-C(21)	1.389(6)
O(4)-C(56)	1.444(3)	C(20)-C(25)	1.396(4)
O(4)-C(53)	1.445(3)	C(20)-H(20A)	0.95
C(1)-C(10)	1.380(4)	C(21)-C(22)	1.374(8)
C(1)-C(2)	1.442(4)	C(21)-H(21A)	0.95
C(2)-C(3)	1.480(5)	C(22)-C(23)	1.381(5)
C(3)-C(8)	1.401(4)	C(22)-H(22A)	0.95
C(3)-C(4)	1.416(6)	C(23)-C(24)	1.382(4)
C(4)-C(5)	1.381(7)	C(23)-H(23A)	0.95
C(4)-H(4A)	0.95	C(24)-C(25)	1.390(4)
C(5)-C(6)	1.376(5)	C(24)-H(24A)	0.95
C(5)-H(5A)	0.95	C(26)-C(27)	1.380(5)
C(6)-C(7)	1.384(5)	C(26)-C(31)	1.387(5)
C(6)-H(6A)	0.95	C(26)-H(26A)	0.95
C(7)-C(8)	1.396(5)	C(27)-C(28)	1.392(6)
C(7)-H(7A)	0.95	C(27)-H(27A)	0.95
C(8)-C(9)	1.537(4)	C(28)-C(29)	1.385(6)
C(9)-C(10)	1.524(4)	C(28)-H(28A)	0.95
C(9)-C(13)	1.524(4)	C(29)-C(30)	1.411(6)
C(9)-C(15)	1.538(4)	C(29)-H(29A)	0.95
C(10)-C(11)	1.421(4)	C(30)-C(31)	1.420(6)
C(11)-C(12)	1.372(4)	C(30)-H(30A)	0.95
C(11)-C(16)	1.510(4)	C(32)-C(33)	1.379(4)
C(12)-H(12)	0.88(3)	C(32)-C(37)	1.396(4)
C(13)-C(14)	1.313(4)	C(32)-H(32A)	0.95
C(13)-H(13)	1.00(3)	C(33)-C(34)	1.381(5)
C(14)-H(14A)	0.98(3)	C(33)-H(33A)	0.95
C(14)-H(14B)	1.04(4)	C(34)-C(35)	1.377(5)
C(15)-H(15A)	0.98	C(34)-H(34A)	0.95
C(15)-H(15B)	0.98	C(35)-C(36)	1.386(4)
C(15)-H(15C)	0.98	C(35)-H(35A)	0.95
C(16)-C(17)	1.508(4)	C(36)-C(37)	1.383(4)
C(16)-H(16A)	1	C(36)-H(36A)	0.95

Table F3. Cont'd.

C(38)-C(47)	1.373(4)	C(58)-C(59)	1.382(6)
C(38)-C(39)	1.453(4)	C(58)-H(58A)	0.95
C(39)-C(40)	1.475(5)	C(59)-C(60)	1.374(9)
C(40)-C(41)	1.401(7)	C(59)-H(59A)	0.95
C(40)-C(45)	1.403(4)	C(60)-C(61)	1.400(6)
C(41)-C(42)	1.366(8)	C(60)-H(60A)	0.95
C(41)-H(41A)	0.95	C(61)-C(62)	1.394(4)
C(42)-C(43)	1.381(5)	C(61)-H(61A)	0.95
C(42)-H(42A)	0.95	C(63)-C(64)	1.387(4)
C(43)-C(44)	1.381(5)	C(63)-C(68)	1.388(4)
C(43)-H(43A)	0.95	C(63)-H(63A)	0.95
C(44)-C(45)	1.390(5)	C(64)-C(65)	1.384(5)
C(44)-H(44A)	0.95	C(64)-H(64A)	0.95
C(45)-C(46)	1.540(4)	C(65)-C(66)	1.370(5)
C(46)-C(47)	1.517(4)	C(65)-H(65A)	0.95
C(46)-C(50)	1.523(4)	C(66)-C(67)	1.398(4)
C(46)-C(52)	1.548(4)	C(66)-H(66A)	0.95
C(47)-C(48)	1.431(4)	C(67)-C(68)	1.380(4)
C(48)-C(49)	1.369(4)	C(67)-H(67A)	0.95
C(48)-C(53)	1.509(4)	C(69)-C(74)	1.394(5)
C(49)-H(49)	0.99(3)	C(69)-C(70)	1.405(5)
C(50)-C(51)	1.315(4)	C(69)-H(69A)	0.95
C(50)-H(50)	0.95(3)	C(70)-C(71)	1.356(7)
C(51)-H(51A)	0.99(4)	C(70)-H(70A)	0.95
C(51)-H(51B)	1.00(4)	C(71)-C(72)	1.361(6)
C(52)-H(52A)	0.98	C(71)-H(71A)	0.95
C(52)-H(52B)	0.98	C(72)-C(73)	1.366(5)
C(52)-H(52C)	0.98	C(72)-H(72A)	0.95
C(53)-C(54)	1.511(4)	C(73)-C(74)	1.351(6)
C(53)-H(53A)	1	C(73)-H(73A)	0.95
C(54)-C(55)	1.317(5)		
C(54)-H(54)	1.04(4)		
C(55)-H(55A)	1.02(3)		
C(55)-H(55B)	1.00(3)		
C(56)-C(62)	1.530(4)		
C(56)-C(74)	1.533(4)		
C(56)-C(68)	1.536(4)		
C(57)-C(62)	1.387(4)		
C(57)-C(58)	1.393(4)		
C(57)-H(57A)	0.95		

Table F4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw31308. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	49(1)	37(1)	25(1)	-6(1)	-6(1)	-2(1)
S(2)	48(1)	37(1)	25(1)	6(1)	-5(1)	1(1)
O(1)	71(2)	60(2)	23(1)	6(1)	3(1)	-2(1)
O(2)	21(1)	31(1)	24(1)	1(1)	1(1)	2(1)
O(3)	65(2)	58(2)	25(1)	-6(1)	1(1)	2(1)
O(4)	24(1)	30(1)	21(1)	1(1)	1(1)	0(1)
C(1)	34(2)	28(1)	24(1)	-1(1)	0(1)	5(1)
C(2)	41(2)	39(2)	24(1)	4(1)	5(1)	9(1)
C(3)	32(2)	34(2)	31(2)	11(1)	4(1)	5(1)
C(4)	37(3)	50(3)	33(3)	16(2)	15(3)	1(1)
C(5)	44(2)	59(2)	51(2)	23(2)	12(2)	-11(2)
C(6)	42(2)	41(2)	65(2)	11(2)	5(2)	-13(2)
C(7)	45(2)	40(2)	39(2)	8(2)	5(2)	-10(2)
C(8)	32(2)	29(1)	30(2)	7(1)	5(1)	2(1)
C(9)	29(1)	24(1)	24(1)	3(1)	3(1)	-1(1)
C(10)	25(1)	24(1)	25(1)	-3(1)	0(1)	3(1)
C(11)	27(1)	23(1)	26(1)	0(1)	0(1)	4(1)
C(12)	36(2)	30(2)	30(2)	-4(1)	-3(1)	-5(1)
C(13)	30(2)	26(1)	31(2)	2(1)	-3(1)	-3(1)
C(14)	40(2)	37(2)	31(2)	1(1)	-4(1)	-4(1)
C(15)	37(2)	23(2)	37(2)	0(1)	4(1)	2(1)
C(16)	22(1)	23(1)	25(1)	2(1)	-2(1)	-4(1)
C(17)	26(1)	26(1)	35(2)	4(1)	6(1)	2(1)
C(18)	29(2)	34(2)	45(2)	9(1)	-1(1)	4(1)
C(19)	22(1)	28(1)	21(1)	0(1)	-1(1)	-1(1)
C(20)	35(2)	27(1)	30(2)	3(1)	-1(1)	2(1)
C(21)	42(3)	28(2)	39(3)	4(1)	1(2)	-1(1)
C(22)	57(3)	33(2)	37(2)	0(2)	-4(2)	-13(2)
C(23)	41(2)	40(2)	31(2)	2(1)	-7(1)	-9(1)
C(24)	33(2)	30(2)	24(1)	0(1)	-1(1)	1(1)
C(25)	26(1)	27(1)	20(1)	1(1)	0(1)	-3(1)
C(26)	34(2)	38(2)	33(2)	1(2)	2(2)	5(2)
C(27)	45(2)	41(2)	39(2)	13(2)	-1(2)	0(2)
C(28)	37(2)	31(2)	60(2)	14(2)	3(2)	2(1)
C(29)	26(2)	30(2)	61(3)	2(2)	1(2)	-1(1)
C(30)	24(2)	30(2)	30(2)	-10(1)	4(2)	-3(1)
C(31)	23(2)	23(2)	32(2)	6(1)	0(1)	1(1)
C(32)	30(2)	38(2)	31(2)	-1(1)	4(1)	0(1)
C(33)	32(2)	41(2)	47(2)	3(2)	12(2)	7(1)
C(34)	25(1)	36(2)	54(2)	0(2)	1(1)	6(1)

Table F4. Cont'd.

C(35)	35(2)	34(2)	40(2)	-1(1)	-10(1)	4(1)
C(36)	31(2)	31(1)	31(2)	0(1)	-2(1)	3(1)
C(37)	25(1)	24(1)	26(1)	-1(1)	1(1)	-1(1)
C(38)	35(2)	26(1)	23(1)	0(1)	2(1)	-3(1)
C(39)	41(2)	38(2)	23(1)	-3(1)	3(1)	-7(1)
C(40)	35(2)	32(2)	33(2)	-8(1)	7(1)	-5(1)
C(41)	53(4)	49(3)	37(3)	-18(2)	3(3)	-5(2)
C(42)	47(2)	50(2)	58(2)	-25(2)	8(2)	8(2)
C(43)	42(2)	46(2)	58(2)	-12(2)	1(2)	15(2)
C(44)	36(2)	39(2)	41(2)	-4(2)	1(2)	9(2)
C(45)	30(2)	28(1)	35(2)	-5(1)	2(1)	0(1)
C(46)	28(1)	22(1)	25(1)	-1(1)	1(1)	-2(1)
C(47)	23(1)	21(1)	23(1)	-1(1)	1(1)	-3(1)
C(48)	27(1)	24(1)	24(1)	2(1)	-1(1)	-2(1)
C(49)	39(2)	31(2)	26(2)	2(1)	2(1)	1(1)
C(50)	28(2)	29(1)	31(2)	-4(1)	0(1)	2(1)
C(51)	39(2)	40(2)	33(2)	-1(1)	-5(1)	6(2)
C(52)	36(2)	22(2)	35(2)	0(1)	4(1)	-3(1)
C(53)	22(1)	26(1)	23(1)	-1(1)	2(1)	0(1)
C(54)	26(1)	26(2)	34(2)	-2(1)	5(1)	1(1)
C(55)	32(2)	36(2)	45(2)	-8(2)	2(1)	-5(1)
C(56)	27(1)	23(1)	20(1)	-3(1)	0(1)	-2(1)
C(57)	34(2)	29(2)	29(2)	-3(1)	-2(1)	3(1)
C(58)	40(2)	45(2)	29(2)	-1(1)	-9(1)	5(1)
C(59)	50(2)	42(2)	33(2)	9(2)	-5(2)	14(2)
C(60)	59(4)	25(2)	44(3)	8(2)	-2(3)	2(2)
C(61)	37(2)	32(2)	33(2)	-1(1)	0(1)	-1(1)
C(62)	29(1)	29(1)	22(1)	1(1)	3(1)	2(1)
C(63)	34(2)	41(2)	31(2)	-4(1)	2(1)	-3(1)
C(64)	32(2)	40(2)	50(2)	-8(2)	13(2)	-4(1)
C(65)	26(2)	34(2)	63(2)	-8(2)	-2(2)	-2(1)
C(66)	35(2)	35(2)	46(2)	0(1)	-13(2)	-5(1)
C(67)	29(2)	30(1)	33(2)	-1(1)	-4(1)	-4(1)
C(68)	25(1)	21(1)	32(1)	-3(1)	0(1)	2(1)
C(69)	38(2)	35(2)	32(2)	-9(2)	-3(2)	5(2)
C(70)	46(2)	58(3)	46(2)	-31(2)	2(2)	0(2)
C(71)	42(2)	38(2)	76(3)	-26(2)	7(2)	-2(2)
C(72)	29(2)	29(2)	59(3)	-4(2)	12(2)	2(1)
C(73)	19(2)	33(2)	47(3)	-10(1)	2(2)	1(1)
C(74)	22(2)	33(2)	24(1)	-3(1)	1(1)	3(1)

Table F5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bw31308.

	x	y	z	U(eq)
H(4A)	6366	2324	1877	48
H(5A)	7416	3613	2156	62
H(6A)	7431	3923	2848	59
H(7A)	6459	2893	3274	49
H(12)	3210(20)	-1630(30)	2872(10)	34(9)
H(13)	6210(20)	210(30)	3374(10)	36(9)
H(14A)	5500(20)	1880(30)	3928(10)	35(9)
H(14B)	6340(30)	860(30)	4049(11)	41(9)
H(15A)	4043	2394	3081	48
H(15B)	4755	2743	3436	48
H(15C)	4037	1727	3500	48
H(16A)	4225	-42	3720	28
H(17)	4170(30)	-2430(30)	3507(12)	28(11)
H(18A)	5270(30)	-2610(30)	3935(12)	24(11)
H(18B)	5340(20)	-1240(30)	4039(10)	34(9)
H(20A)	2102	1644	4026	37
H(21A)	2856	3144	4335	44
H(22A)	4207	2858	4727	50
H(23A)	4789	1061	4812	45
H(24A)	4038	-445	4513	35
H(26A)	2656	-1154	4809	42
H(27A)	2564	-2904	5104	50
H(28A)	2451	-4495	4696	51
H(29A)	2312	-4303	4000	47
H(30A)	2373	-2537	3685	33
H(32A)	1111	-170	4542	40
H(33A)	-507	104	4457	48
H(34A)	-1167	162	3810	46
H(35A)	-185	-64	3250	44
H(36A)	1435	-370	3330	37
H(41A)	1094	7326	3015	56
H(42A)	79	8636	2741	62
H(43A)	59	8926	2044	58
H(44A)	1021	7871	1624	47
H(49)	4320(20)	3300(30)	2015(10)	34(9)
H(50)	1250(20)	5260(30)	1514(10)	32(9)
H(51A)	2040(30)	6820(30)	960(10)	39(9)
H(51B)	1160(30)	5910(30)	859(11)	48(10)
H(52A)	3470	6722	1406	46
H(52B)	3442	7413	1819	46

Table F5. Cont'd.

H(52C)	2743	7736	1456	46
H(53A)	3269	4960	1185	29
H(54)	3530(30)	2550(30)	1336(13)	42(14)
H(55A)	2120(30)	2410(30)	894(12)	30(12)
H(55B)	2180(20)	3730(30)	806(10)	36(9)
H(57A)	3463	4518	404	37
H(58A)	2689	5994	85	46
H(59A)	3260	7803	158	50
H(60A)	4576	8140	564	51
H(61A)	5385	6656	868	41
H(63A)	6376	4880	365	43
H(64A)	8003	5163	444	49
H(65A)	8664	5200	1093	49
H(66A)	7701	4933	1653	46
H(67A)	6071	4615	1574	37
H(69A)	4893	3814	101	42
H(70A)	4922	2009	-170	60
H(71A)	5073	484	245	63
H(72A)	5180	727	941	47
H(73A)	5147	2492	1199	39

APPENDIX G

X-RAY CRYSTAL DATA FOR 268

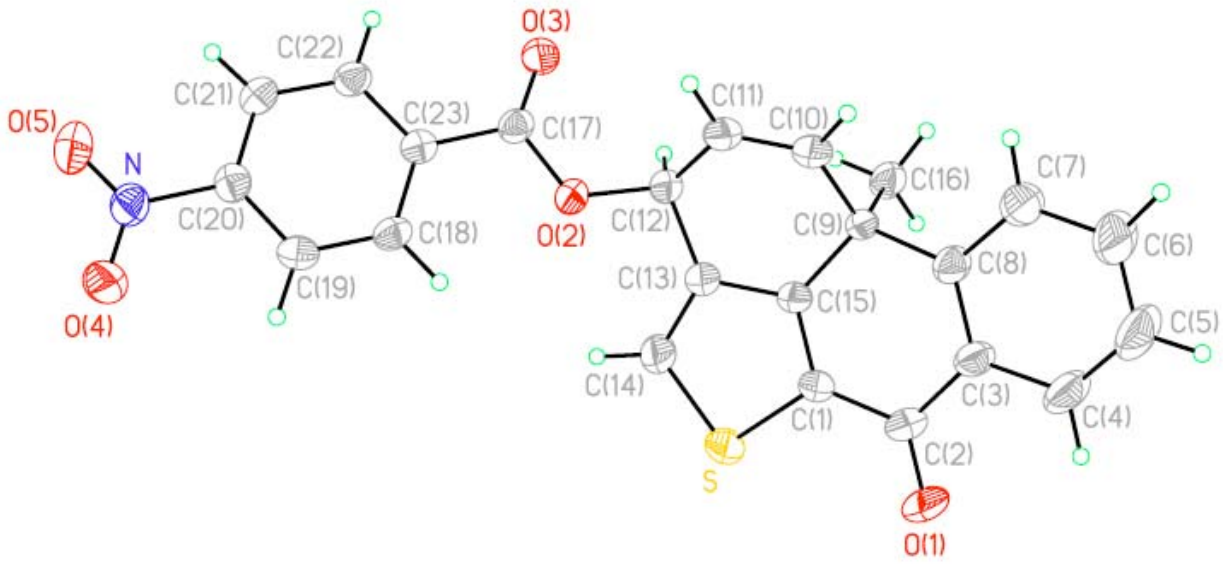


Table G1. Crystal data and structure refinement for bw32608s.

Identification code	bw32608s	
Empirical formula	C23 H15 N O5 S	
Formula weight	417.42	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.8826(11) Å	a= 90°.
	b = 23.289(4) Å	b= 105.618(3)°.
	c = 12.400(2) Å	g = 90°.
Volume	1914.2(5) $Å^3$	
Z	4	
Density (calculated)	1.448 Mg/m^3	
Absorption coefficient	0.206 mm^{-1}	
F(000)	864	
Crystal size	0.34 x 0.25 x 0.25 mm^3	
Theta range for data collection	3.54 to 30.70°.	
Index ranges	-9<=h<=9, -33<=k<=32, -17<=l<=17	
Reflections collected	19064	
Independent reflections	5624 [R(int) = 0.0619]	
Completeness to theta = 30.70°	94.90%	
Absorption correction	None	
Max. and min. transmission	0.9502 and 0.9331	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5624 / 0 / 331	
Goodness-of-fit on F^2	1.008	
Final R indices [I>2sigma(I)]	R1 = 0.0659, wR2 = 0.1415	
R indices (all data)	R1 = 0.1225, wR2 = 0.1701	
Largest diff. peak and hole	0.406 and -0.279 $e.Å^{-3}$	

Table G2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bw32608s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	353(1)	2603(1)	5985(1)	54(1)
O(1)	2140(3)	1737(1)	4568(2)	62(1)
O(2)	2328(2)	4408(1)	6974(1)	34(1)
O(3)	1894(3)	5340(1)	6478(1)	37(1)
O(4)	2793(3)	5000(1)	12399(1)	59(1)
O(5)	2046(3)	5883(1)	11994(2)	53(1)
N	2437(3)	5402(1)	11740(2)	37(1)
C(1)	1813(4)	2700(1)	5068(2)	34(1)
C(2)	2606(4)	2243(1)	4515(2)	39(1)
C(3)	4097(4)	2432(1)	3912(2)	34(1)
C(4)	4976(4)	2014(1)	3381(3)	52(1)
C(5)	6334(5)	2164(1)	2800(3)	72(1)
C(6)	6880(5)	2730(1)	2764(4)	75(1)
C(7)	6036(4)	3151(1)	3279(3)	54(1)
C(8)	4613(3)	3013(1)	3847(2)	34(1)
C(9)	3468(3)	3489(1)	4238(2)	27(1)
C(10)	4706(4)	3993(1)	4827(2)	34(1)
C(11)	4060(4)	4333(1)	5510(2)	34(1)
C(12)	2118(4)	4243(1)	5809(2)	31(1)
C(13)	1537(3)	3623(1)	5709(2)	31(1)
C(14)	445(4)	3321(1)	6286(2)	46(1)
C(15)	2294(3)	3262(1)	4999(2)	27(1)
C(16)	1936(4)	3721(1)	3171(2)	37(1)
C(17)	2155(3)	4968(1)	7181(2)	28(1)
C(18)	2515(3)	4620(1)	9145(2)	28(1)
C(19)	2601(3)	4728(1)	10251(2)	30(1)
C(20)	2437(3)	5290(1)	10575(2)	29(1)
C(21)	2223(3)	5749(1)	9844(2)	31(1)
C(22)	2179(3)	5634(1)	8746(2)	30(1)
C(23)	2302(3)	5071(1)	8389(2)	26(1)

Table G3. Bond lengths [Å] and angles [°] for bww32608s.

S-C(14)	1.711(3)	C(18)-C(23)	1.390(3)
S-C(1)	1.723(2)	C(18)-H(18)	0.97(2)
O(1)-C(2)	1.227(3)	C(19)-C(20)	1.382(3)
O(2)-C(17)	1.340(2)	C(19)-H(19)	0.98(2)
O(2)-C(12)	1.464(3)	C(20)-C(21)	1.383(3)
O(3)-C(17)	1.208(2)	C(21)-C(22)	1.380(3)
O(4)-N	1.222(2)	C(21)-H(21)	0.94(2)
O(5)-N	1.214(2)	C(22)-C(23)	1.393(3)
N-C(20)	1.468(3)	C(22)-H(22)	0.97(2)
C(1)-C(15)	1.360(3)	C(14)-S-C(1)	91.26(12)
C(1)-C(2)	1.450(3)	C(17)-O(2)-C(12)	117.12(16)
C(2)-C(3)	1.490(3)	O(5)-N-O(4)	123.5(2)
C(3)-C(4)	1.399(3)	O(5)-N-C(20)	118.5(2)
C(3)-C(8)	1.406(3)	O(4)-N-C(20)	118.0(2)
C(4)-C(5)	1.370(4)	C(15)-C(1)-C(2)	123.3(2)
C(4)-H(4)	0.96(3)	C(15)-C(1)-S	111.30(16)
C(5)-C(6)	1.375(4)	C(2)-C(1)-S	125.17(17)
C(5)-H(5)	0.91(4)	O(1)-C(2)-C(1)	122.9(2)
C(6)-C(7)	1.380(4)	O(1)-C(2)-C(3)	122.4(2)
C(6)-H(6)	0.89(4)	C(1)-C(2)-C(3)	114.70(19)
C(7)-C(8)	1.390(3)	C(4)-C(3)-C(8)	119.6(2)
C(7)-H(7)	0.95(3)	C(4)-C(3)-C(2)	118.3(2)
C(8)-C(9)	1.514(3)	C(8)-C(3)-C(2)	122.1(2)
C(9)-C(15)	1.494(3)	C(5)-C(4)-C(3)	120.9(3)
C(9)-C(10)	1.516(3)	C(5)-C(4)-H(4)	120.9(16)
C(9)-C(16)	1.551(3)	C(3)-C(4)-H(4)	118.2(16)
C(10)-C(11)	1.321(3)	C(4)-C(5)-C(6)	119.5(3)
C(10)-H(10)	0.94(2)	C(4)-C(5)-H(5)	121(2)
C(11)-C(12)	1.495(3)	C(6)-C(5)-H(5)	120(2)
C(11)-H(11)	0.96(2)	C(5)-C(6)-C(7)	120.9(3)
C(12)-C(13)	1.494(3)	C(5)-C(6)-H(6)	123(2)
C(12)-H(12)	0.97(2)	C(7)-C(6)-H(6)	116(2)
C(13)-C(14)	1.365(3)	C(6)-C(7)-C(8)	120.8(3)
C(13)-C(15)	1.413(3)	C(6)-C(7)-H(7)	117.4(16)
C(14)-H(14)	0.95(3)	C(8)-C(7)-H(7)	121.8(16)
C(16)-H(15A)	0.99(3)	C(7)-C(8)-C(3)	118.4(2)
C(16)-H(16B)	0.98(2)	C(7)-C(8)-C(9)	119.4(2)
C(16)-H(16C)	0.95(3)	C(3)-C(8)-C(9)	121.70(19)
C(17)-C(23)	1.492(3)	C(15)-C(9)-C(8)	111.09(17)
C(18)-C(19)	1.381(3)	C(15)-C(9)-C(10)	107.37(17)

Table G3. Cont'd.

C(8)-C(9)-C(10)	116.60(18)	C(9)-C(16)-H(16B)	111.0(13)
C(15)-C(9)-C(16)	107.63(19)	H(15A)-C(16)-H(16B)	107.4(19)
C(8)-C(9)-C(16)	105.96(18)	C(9)-C(16)-H(16C)	110.2(15)
C(10)-C(9)-C(16)	107.82(18)	H(15A)-C(16)-H(16C)	110(2)
C(11)-C(10)-C(9)	122.0(2)	H(16B)-C(16)-H(16C)	107(2)
C(11)-C(10)-H(10)	118.6(14)	O(3)-C(17)-O(2)	124.2(2)
C(9)-C(10)-H(10)	119.3(14)	O(3)-C(17)-C(23)	124.45(19)
C(10)-C(11)-C(12)	123.5(2)	O(2)-C(17)-C(23)	111.35(17)
C(10)-C(11)-H(11)	122.4(15)	C(19)-C(18)-C(23)	120.0(2)
C(12)-C(11)-H(11)	114.1(15)	C(19)-C(18)-H(18)	120.4(13)
O(2)-C(12)-C(13)	106.86(16)	C(23)-C(18)-H(18)	119.5(13)
O(2)-C(12)-C(11)	110.48(19)	C(18)-C(19)-C(20)	118.5(2)
C(13)-C(12)-C(11)	110.63(19)	C(18)-C(19)-H(19)	120.8(13)
O(2)-C(12)-H(12)	107.1(13)	C(20)-C(19)-H(19)	120.6(13)
C(13)-C(12)-H(12)	111.7(13)	C(19)-C(20)-C(21)	122.9(2)
C(11)-C(12)-H(12)	110.0(13)	C(19)-C(20)-N	118.33(19)
C(14)-C(13)-C(15)	111.6(2)	C(21)-C(20)-N	118.7(2)
C(14)-C(13)-C(12)	128.8(2)	C(22)-C(21)-C(20)	117.8(2)
C(15)-C(13)-C(12)	119.39(19)	C(22)-C(21)-H(21)	122.9(15)
C(13)-C(14)-S	112.47(19)	C(20)-C(21)-H(21)	119.3(15)
C(13)-C(14)-H(14)	125.4(18)	C(21)-C(22)-C(23)	120.7(2)
S-C(14)-H(14)	122.1(18)	C(21)-C(22)-H(22)	119.8(14)
C(1)-C(15)-C(13)	113.36(19)	C(23)-C(22)-H(22)	119.4(14)
C(1)-C(15)-C(9)	124.22(19)	C(18)-C(23)-C(22)	120.1(2)
C(13)-C(15)-C(9)	122.41(18)	C(18)-C(23)-C(17)	121.39(19)
C(9)-C(16)-H(15A)	111.1(14)	C(22)-C(23)-C(17)	118.51(18)

Table G4. Anisotropic displacement parmeters ($Å^2 x\ 10^3$) for bw32608s. The anisotropic displacement factor exponent take the form: $-2\pi^2[h^2\ a^{*2}U^{33} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	83(1)	36(1)	59(1)	-7(1)	47(1)	-22(1)
O(1)	96(2)	22(1)	84(2)	-5(1)	50(1)	-10(1)
O(2)	49(1)	24(1)	30(1)	-2(1)	14(1)	2(1)
O(3)	52(1)	28(1)	35(1)	5(1)	16(1)	7(1)
O(4)	96(2)	45(1)	31(1)	2(1)	10(1)	-17(1)
O(5)	69(1)	50(1)	41(1)	-13(1)	19(1)	0(1)
N	38(1)	40(1)	32(1)	-6(1)	8(1)	-9(1)
C(1)	44(1)	26(1)	37(1)	0(1)	20(1)	-7(1)
C(2)	50(2)	22(1)	45(1)	1(1)	15(1)	-2(1)
C(3)	36(1)	24(1)	45(1)	3(1)	14(1)	4(1)
C(4)	52(2)	26(1)	84(2)	-4(1)	32(2)	7(1)
C(5)	70(2)	41(2)	126(3)	-19(2)	62(2)	6(2)
C(6)	75(2)	52(2)	128(3)	-18(2)	78(2)	-6(2)
C(7)	56(2)	37(2)	84(2)	-8(1)	46(2)	-7(1)
C(8)	31(1)	28(1)	46(1)	-2(1)	17(1)	2(1)
C(9)	31(1)	20(1)	34(1)	0(1)	15(1)	0(1)
C(10)	37(1)	28(1)	40(1)	0(1)	16(1)	-8(1)
C(11)	43(1)	26(1)	34(1)	0(1)	13(1)	-8(1)
C(12)	42(1)	26(1)	26(1)	0(1)	11(1)	0(1)
C(13)	37(1)	26(1)	33(1)	-2(1)	14(1)	-5(1)
C(14)	62(2)	36(1)	50(2)	-11(1)	34(1)	-13(1)
C(15)	30(1)	24(1)	31(1)	1(1)	11(1)	-3(1)
C(16)	53(2)	28(1)	31(1)	3(1)	11(1)	8(1)
C(17)	27(1)	25(1)	36(1)	-2(1)	12(1)	1(1)
C(18)	27(1)	22(1)	37(1)	0(1)	10(1)	1(1)
C(19)	28(1)	28(1)	35(1)	4(1)	8(1)	-3(1)
C(20)	24(1)	34(1)	28(1)	-3(1)	5(1)	-4(1)
C(21)	32(1)	26(1)	35(1)	-3(1)	7(1)	1(1)
C(22)	32(1)	24(1)	32(1)	2(1)	7(1)	2(1)
C(23)	23(1)	25(1)	31(1)	1(1)	7(1)	0(1)

Table G5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bw32608s.

	x	y	z	U(eq)
H(4)	4580(40)	1623(12)	3420(20)	49(7)
H(5)	6820(60)	1894(16)	2410(30)	98(12)
H(6)	7660(60)	2855(16)	2340(30)	100(13)
H(7)	6430(40)	3535(11)	3210(20)	48(7)
H(10)	5950(40)	4078(9)	4677(18)	34(6)
H(11)	4790(40)	4665(11)	5850(20)	41(7)
H(12)	1070(40)	4485(10)	5342(19)	32(6)
H(14)	-150(50)	3477(12)	6830(20)	66(9)
H(15A)	1050(40)	3409(11)	2760(20)	43(7)
H(16B)	1060(30)	4015(10)	3361(19)	37(6)
H(16C)	2630(40)	3898(11)	2690(20)	50(8)
H(18)	2530(30)	4229(9)	8881(18)	27(6)
H(19)	2710(30)	4412(10)	10791(19)	35(6)
H(21)	2120(30)	6121(10)	10110(20)	39(7)
H(22)	2120(30)	5948(10)	8225(19)	36(6)

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