CATALYTIC, ASYMMETRIC ACYL HALIDE-ALDEHYDE CYCLOCONDENSATIONS IN COMPLEX MOLECULE SYNTHESIS AND APPLICATION TO THE INSTALLATION OF QUATERNARY CARBON STEREOCENTERS

by

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Andrew J. Kassick, Ph. D.

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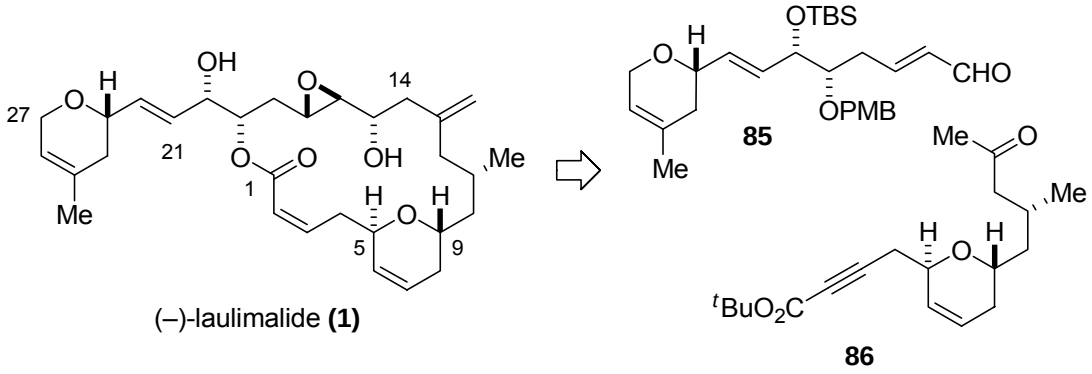
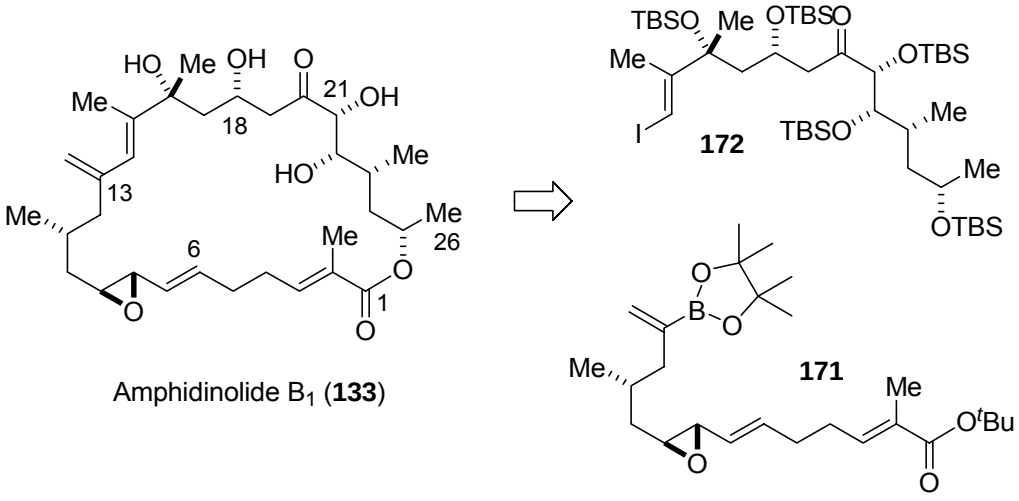
The synthetic utility of recently developed catalytic, asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions has been successfully demonstrated in complex molecule total synthesis. Extensive use of the enantiomerically enriched β-lactone products of AAC methodology has led to the enantioselective total synthesis of the potent microtubule-stabilizing agent, (–)-laulimalide (**1**). Additional highlights of the synthesis include a diastereoselective aldol reaction that united major fragments **85** and **86** and a remarkably high-yielding modified Yamaguchi macrolactonization. Novel methodology was also developed to effect both the one-pot interconversion of β-lactones to dihydropyranones and the Lewis acid-mediated addition of allenylstannane reagents to glycal acetates.



(–)-laulimalide **(1)**

86

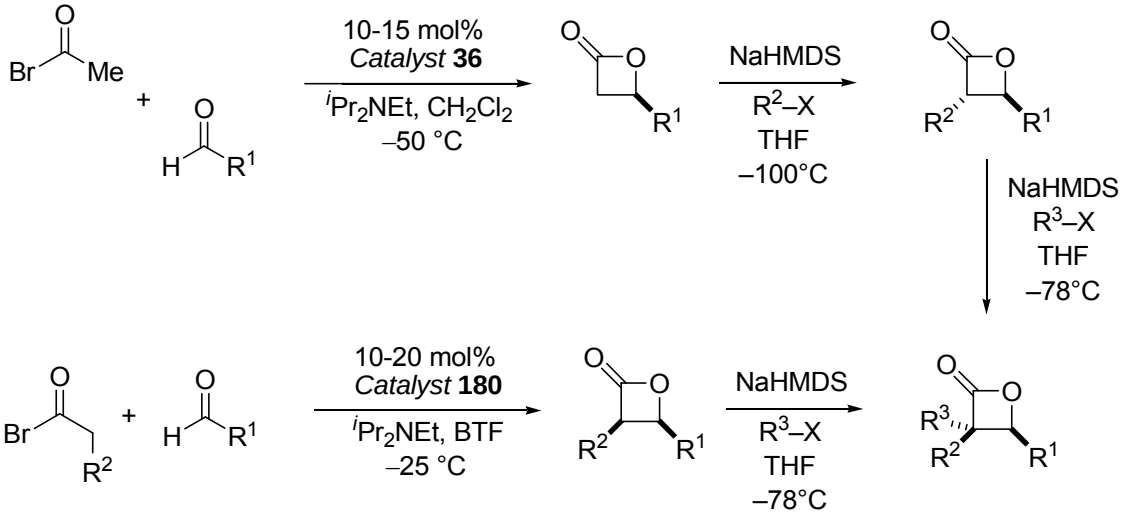
Asymmetric AAC reactions have also been instrumental in recent studies toward the total synthesis of the cytotoxic marine natural product, amphidinolide B_1 (**133**). By exploiting AAC methodology, several key stereochemical relationships present in major fragments **171** and **172** were established. A highly enantioselective installation of the C_{16} tertiary carbinol stereocenter was acheived through the application of Mukaiyama's Sn(IV)-allylation protocol, and a rapid synthesis of sulfone subunit **174** was realized from commercially available γ-butyrolactone. Regioselective β-lactone ring opening by phosphonate anions was also documented.

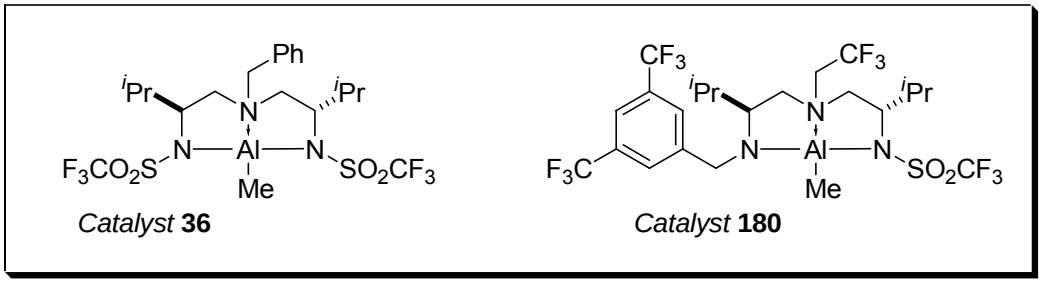


Amphidinolide B_1 (**133**)

The enantiomerically enriched β-lactone products of AAC methodology have also been demonstrated to serve as useful templates for the installation of asymmetric quaternary carbon stereocenters. Treatment of β-lactones with NaHMDS in the presence of an in situ electrophile at low temperature resulted in enolization and subsequent alkylation to afford to afford *trans*-3,4-disubstituted lactones in moderate to good yield with good levels of diastereoselectivity. Resubjecting the monoalkylated products to the reaction conditions and a different electrophile resulted in the efficient production of α,α-disubstituted-β-lactones in high yield with high *trans*-diastereoselectivity. A more efficient route to α,α-disubstituted β-lactones was realized starting from the *cis*-3,4-disubstituted β-lactones products of the recently developed second generation

AAC reaction. Asymmetric quaternary carbon formation was accomplished in two steps affording the desired α,α-disubstituted-β-lactones in high yield with excellent diastereoselectivity.





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CHAPTER 1. ENANTIOSELECTIVE TOTAL SYNTHESIS OF (–)-LAULIMALIDE

1.1 BACKGROUND

1.1.1 Isolation

(–)-Laulimalide **(1)**, originally known as fijianolide B, is a macrocyclic marine natural product that was first isolated in 1988 by Crews and coworkers from the Vanuatu chocolate sponge *Cacospongia mycofijiensis* (Figure 1).[1] Independent efforts by a team of Hawaiian scientists led by Moore coincided with this discovery, culminating in the isolation of **1** from the Indonesian sponge *Hyatella* sp.[2] The genesis of the name laulimalide is the Hawaiian word *laulima*, meaning "people working together," and is reflective of the highly collaborative research effort that led to its isolation. Laulimalide has since been found in the crude lipophilic extracts of several other species of marine sponge native to the Pacific region including *Fasciospongia rimosa*[3] and most recently *Dactylospongia* sp.[4] Structure elucidation and relative stereochemical assignments for **1** were achieved by NMR spectroscopy,[1,2] while its absolute configuration was determined through X-ray diffraction studies by Higa and coworkers in 1996.[3]

[1] Quiñoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642.
[2] Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644.
[3] Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.
[4] Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.

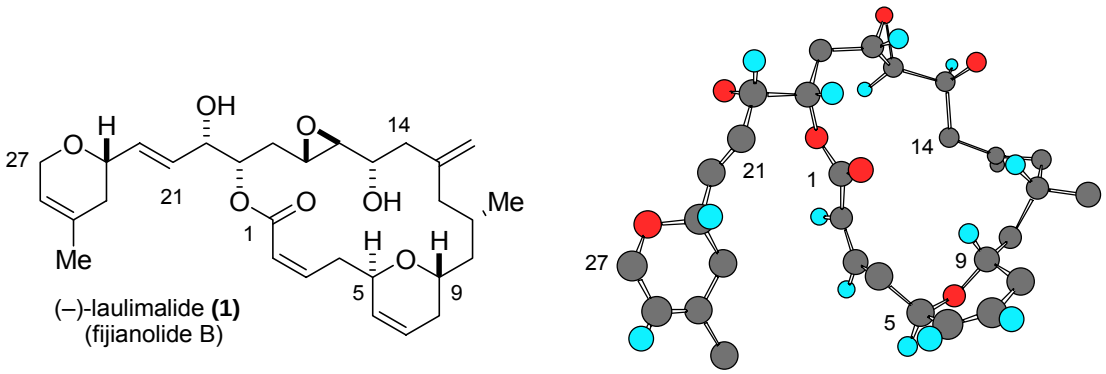

Figure 1. (–)-Laulimalide **(1)**

As depicted in Figure 2, laulimalide is isolated along with its constitutional isomers, isolaulimalide **(2)** and neolaulimalide **(3)**. Isolaulimalide (fijianolide A) is a trisubstituted tetrahydrofuran-containing metabolite of **1** that arises from the S_N2 ring opening of the laulimalide C_{16}–C_{17} epoxide by the C_{20} hydroxyl function under weakly acidic conditions.[5] Neolaulimalide was obtained by Higa et al. from the Okinawan sponge *Fasciospongia rimosa*, and exists as a ring-expanded regioisomer of **1** resulting from lactonization onto the distal C_{20} hydroxyl group of the *syn* diol moiety.[6] It also appears to be less susceptible to acid-mediated cyclization than laulimalide **(1)**, isomerizing to **2** only after several days.

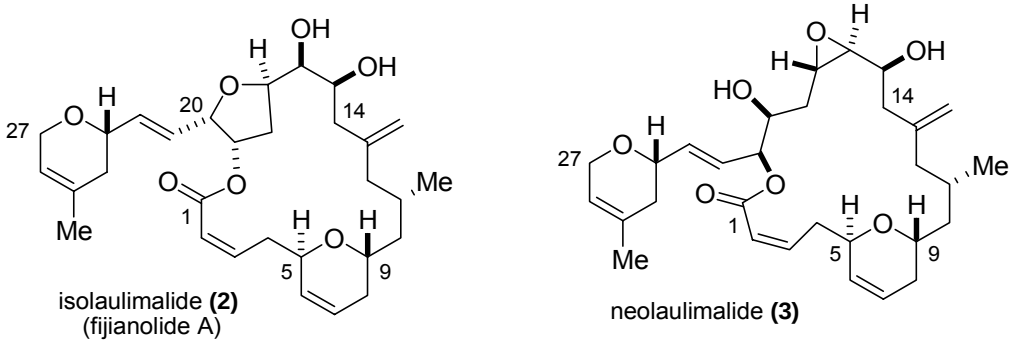

Figure 2. Isolaulimalide **(2)** and Neolaulimalide **(3)**

[5] Upon treatment of **1** with 0.01 N HCl in acetone (4 h, ambient temperature), complete isomerization to **2** is observed. See ref. 2.
[6] Tanaka, J.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chem. Lett*, **1996**, 255.

1.1.2 Biological Activity

Soon after its isolation, laulimalide **(1)** was found to be a highly cytotoxic chemical entity.[1,2] It exhibits low nanomolar activity against the human epidermoid carcinoma KB cell line (IC_{50} = 15 ng/mL), and has also proven to effectively inhibit growth in several other human tumor cell lines including A549 (human lung), HT29 (human colon), MEL28 (human skin), and MDA-MB-435 (human breast) cell lines (IC_{50} = 10–50 ng/mL).[2,3] Isolaulimalide exhibits substantially weaker levels of activity against the KB cell line (IC_{50} >200 ng/mL) as well as MDA-MB-435 cells (IC_{50} = 2 μM) potentially owing to its lack of the C_{16}–C_{17} epoxide moiety. The ring-expanded neolaulimalide **(3)**, however, displays commensurate levels of cytotoxicity as **1** against A549, HT29, and MEL28 cell lines (IC_{50} = 10–50 ng/mL).[6]

Recent studies have shown that the mechanism of action of laulimalide is similar to that of the popular anticancer agent paclitaxel (Taxol™).[7] Both compounds promote the polymerization of tubulin and the stabilization of cellular microtubules, events that disrupt normal mitotic cell division and lead, ultimately, to premature apoptosis.[7] As a result, **1** has been recognized as a new member of a limited collection of nontaxane microtubule-stabilizing natural products with high anticancer potential that includes discodermolide, elutherobin, and the epothilones. However, a recent report strongly suggests that while laulimalide exhibits similar microtubule stabilizing activity as paclitaxel, it does not bind to the taxoid site on the αβ-tubulin dimer.[8] Competitive binding assays by Hamel et al. have demonstrated the failure of (–)-laulimalide to inhibit binding of either [^{3}H]-paclitaxel or the fluorescent Taxol derivative, 7-*O*-[*N*-(2,7-difluoro-4'-fluoresceincarbonyl)-L-alanyl]paclitaxel (Flutax 2), to the tubulin polymer.

[7] Mooberry, S. L.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res*. **1999**, *59*, 653.
[8] Pryor, D. E.; O'Brate, A.; Bilcer, G.; Diaz, J. F.; Wang, Yu; Wang, Yo; Kabaki, M.; Jing, M. K. ; Andreu, J. M.; Ghosh, A. K.; Giannakakou, P.; Hamel, E. *Biochemistry* **2002**, *41*, 9109.

Additionally, HPLC analysis of microtubule pellets formed in the presence of both laulimalide and paclitaxel revealed a near stoichiometric amount of both compounds. This simultaneous binding of paclitaxel and laulimalide to tubulin provided further evidence for the existence of a binding site distinct from that recognized by the taxoids. Another notable difference between the two microtubule-stabilizing agents is the superior ability of laulimalide to inhibit cellular proliferation in multidrug-resistant cell lines overexpressing P-glycoprotein such as the human ovarian carcinoma SKVLB-1 cell line.[6] Such impressive biological activity along with its limited natural abundance makes laulimalide an attractive synthetic target.

1.1.3 Structural Features

In addition to its intriguing and potentially useful biological activity, laulimalide displays a high degree of molecular complexity with many key structural features. One of the most notable features is its highly functionalized 18-membered macrolide. Located within laulimalide's macrolactone is a *trans*-2, 6-disubstituted dihydropyran ring (C_5–C_9) along with some particularly sensitive functionality in the form of an acid-labile epoxide ring[9] at C_{16}–C_{17} and an easily isomerized *Z*-enoate ester linkage spanning C_1–C_4 (Figure 1).[10] A second dihydropyran moiety is incorporated into a side chain that is tethered to the macrolide at C_{19}. Laulimalide possesses ten oxygenated carbons, nine stereogenic centers (eight hydroxyl-bearing stereocenters and an isolated methyl-bearing stereocenter at C_{11}), as well as five C–C double bonds. This

[9] Isolaumalide can be easily prepared from **1** under acidic conditions (CSA, $CDCl_3$). See Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 213.

[10] Base-mediated scrambling of the (Z)-enoate ester was observed under traditional macrolactonization conditions. See (a) Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 213. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989. Boden, E. P.; Keck, G. E. *J. Org. Chem*. **1985**, *50*, 2394.

combination of structural complexity and potential chemotherapeutic utility has made laulimalide an extremely attractive target molecule for synthetic organic chemists.[11,12]

1.1.4 Previous Synthetic Work

To date, ten total syntheses of (–)-laulimalide have been reported by seven different synthetic groups. The first total synthesis of laulimalide was achieved in 2000 by Ghosh and Wang.[11a] Ghosh's approach features two olefin forming reactions that unite the two major fragments **4** and **5** to furnish the requisite macrocycle. First, a Julia olefination between sulfone fragment **4** and aldehyde **5** affords the *trans*-alkene which is later fashioned into the C_{16}–C_{17} epoxide functionality. An intramolecular Still-Gennari coupling between a C_{19} phosphonoacetate and C_3 aldehyde forms the requisite C_2–C_3 *Z* olefin (*E*/*Z* 2:1) and closes the macrocycle.[13] Assembly of **4** was accomplished through the nucleophilic addition of the organolithium species derived from vinyl dibromide **6** into α-alkoxyaldehyde **7**. Both dihydropyran rings were synthesized using Grubbs' ring closing metathesis strategy,[14] and the sensitive epoxide ring was installed in the final stages of the synthesis via the Sharpless asymmetric epoxidation (Figure 3).

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[11] (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. (b) Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149. (c) Enev, V. S.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764. (d) Mulzer, J.; Öhler, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3842. (e) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2002**, *43*, 3381. (f) Ahmed, A.; Hoegenauer, E. K.; Enev, V. E.; Hanbauer, J. Kahlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026. (g) Mulzer, J.; Öhler, E. *Chem. Rev*. **2003**, *103*, 3753. (h) Ghosh, A. K.; Wang, Y.; Kim, J. *J. Org. Chem.* **2001**, *66*, 8973. (i) Wender, P. A.; Hedge, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956. (j) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958. (k) Williams, D. R.; Mi, L.; Mullins, R. J. Stites, R. E. *Tetrahedron Lett*. **2002**, *43*, 4841.

[12] (a)Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011. (b) Shimizu, A.; Nishiyama, S. *Synlett*. **1998**, 1209. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett*. **1997**, *38*, 2427. (d) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett*. **2000**, *41*, 2319. (e) Mulzer, J; Hanbauer, M. *Tetrahedron Lett*. **2000**, 41, 33. (f) Dorling, E. K.; Öhler, E.; Mulzer, J. *Tetrahedron Lett*. **2000**, *41*, 6323. (g) Dorling, E. K.; Öhler, E.; Mantouidis, A.; Mulzer, J. *Synlett*. **2001**, 1105. (h) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett*. **2001**, *42*, 797. (i) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett*. **2001**, *42*, 801.

[13] Still, W. C.; Gennari, C.; *Tetrahedron Lett*. **1983**, *24*, 4405.

[14] Grubbs, R. H.; Chang, S. *Tetrahedron*, **1998**, *54*, 4413, and references therein.

Ghosh et al. later reported a modified approach to (–)-laulimalide that incorporated an improved method for macrocycle construction (Figure 4).[15] Following the fragment uniting Julia olefination reaction between major subunits **4** and **5** employed in the original total synthesis of **1**, Ghosh elected to pursue the Yamaguchi macrolactonization of hydroxy alkynoic acid **8** to close the 18-membered ring. Subsequent Z-enoate ester installation was achieved by Lindlar reduction of the C_2–C_3 triple bond to furnish a highly functionalized laulimalide precursor.

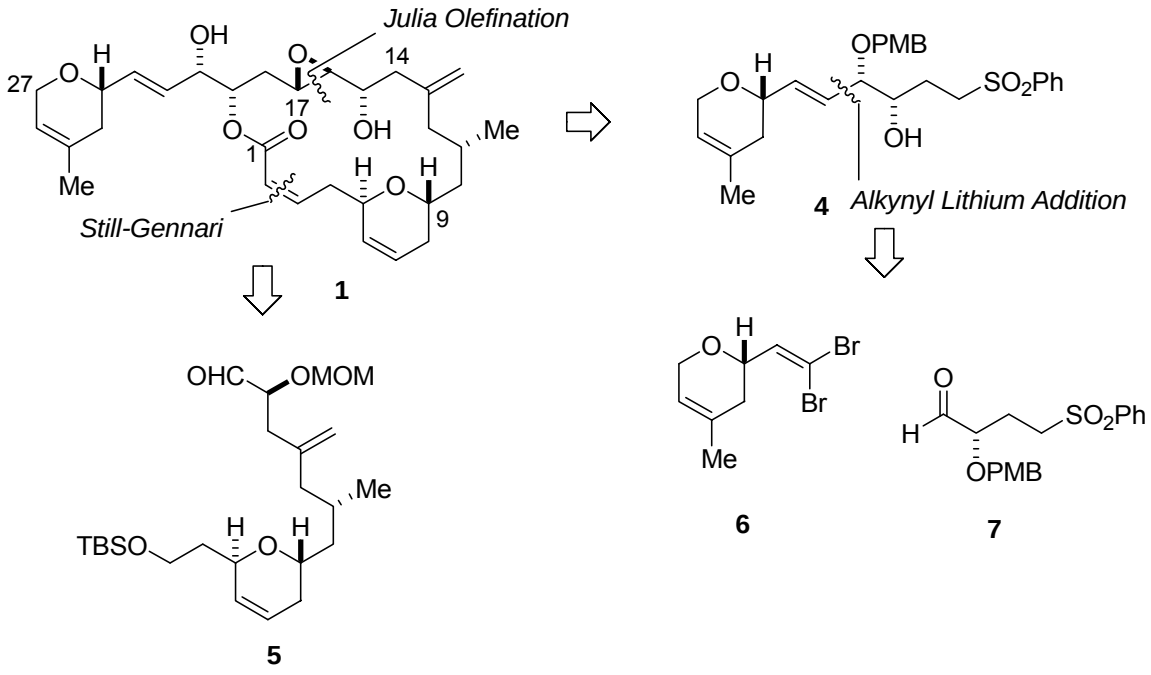


Figure 3. Retrosynthesis of (–)-laulimalide: Ghosh approach

[15] Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem*. **2001**, *66*, 8973.

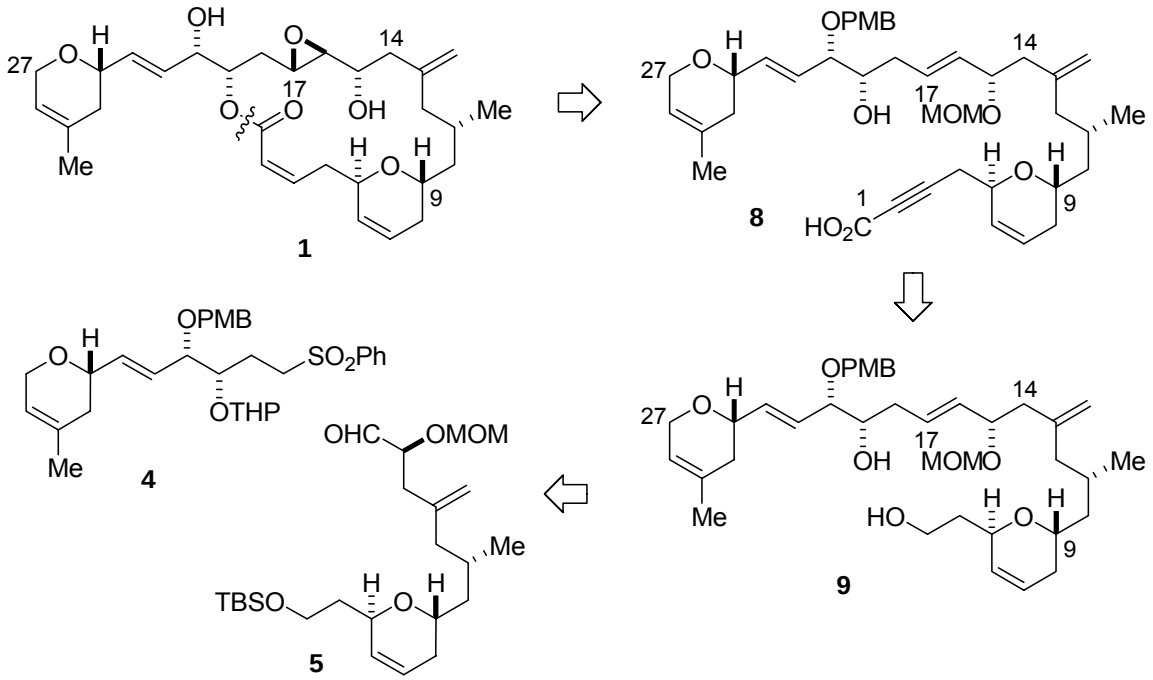


Figure 4. Revised Ghosh Retrosynthesis

Shortly after Ghosh and Wang published their first total synthesis of (–)-laulimalide, Paterson[11b] disclosed a second approach to the potent, microtubule-stabilizing natural product (Figure 5). Paterson's approach relied on his previously developed asymmetric aldol methodology employing chiral diisopinocampheyl-boron enolates.[16] This methodology is used to achieve the C_{14}–C_{15} bond formation between fragments **10** and **11** as well as in the preparation of the dihydropyran ring in fragment **11**.[17] The side chain dihydropyran fragment **12** was prepared in highly enantioenriched form via a hetero-Diels-Alder reaction using Jacobsen's chiral tridentate Cr (III) catalyst **14**.[18] In the late stages of the synthesis, a Mitsunobu macrolactonization protocol was required to complete the macrolide in order to preserve the

[16](a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett*. **1986**, *27*, 4787. (b) Paterson, I; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron Lett*. **1990**, *46*, 4663.
[17] Paterson, I. and Smith, J. D. *Tetrahedron Lett*. **1993**, *34*, 5351.
[18]Dossetter, A. G; Jamison, T.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2398.

integrity of the Z-enoate ester due to undesired scrambling of the olefin geometry at C_2–C_3 under traditional based-mediated macrolactonization conditions.[6]

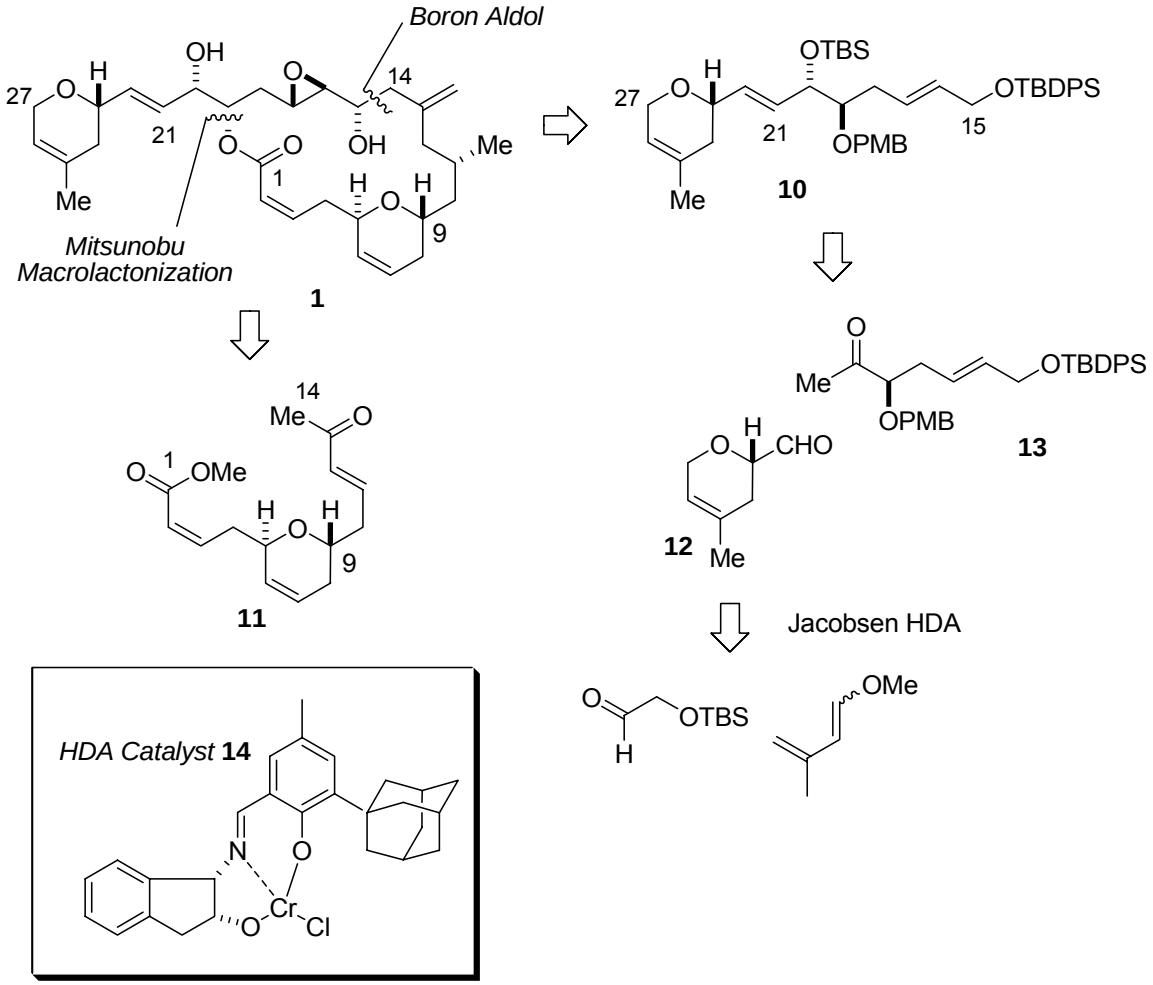


Figure 5. Retrosynthesis of (–)-Laulimalide: Paterson Approach

For Mulzer and coworkers, the total synthesis of (–)-laulimalide has been the subject of intense study since 1999. A total of three different approaches to the synthesis of **1** have been achieved in the Mulzer laboratories.[11c-e] In perhaps the most elegant of these strategies, a highly selective Still-Gennari coupling between the C_3 aldehyde in fragment **15** and the C_{19} phosphonoacetate in fragment **16** established the Z-enoate linkage. Subsequent macrolide ring

closure was accomplished with an unprecedented allylsilane addition into a chiral acetal moiety in **16** derived from (2*R*, 4*R*)-(–)-pentanediol. This is reported as being the first example of macrocycle formation by an allyl transfer reaction. As in Ghosh's approach, dihydropyran ring formation in subunits **15** and **17** was achieved by ring-closing metathesis using Grubbs' catalyst (Figure 6).

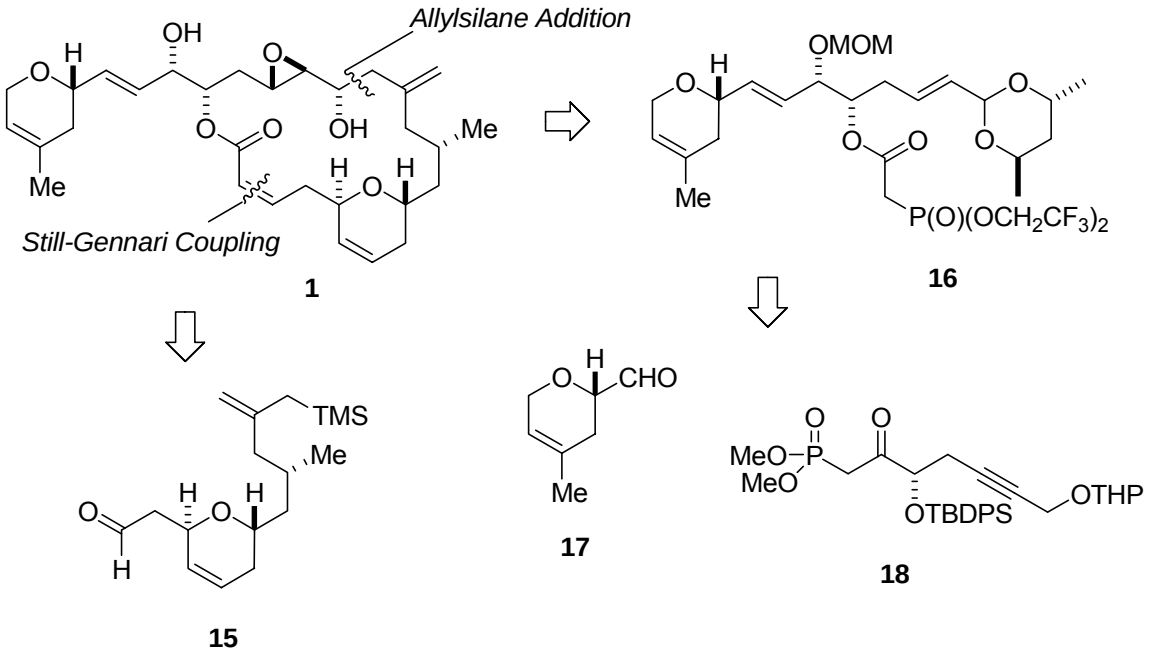


Figure 6. Retrosynthesis of (–)-Laulimalide: Mulzer Approach

In 2002, several total syntheses of (–)-laulimalide were completed in close succession beginning with a highly convergent route published by Wender (Figure 7). Analysis of Wender's synthesis reveals major fragments **19** and **20**. In the formation of the 18-membered macrolactone, Yamamoto's (acyloxy)-borane **21**[19] was employed to effect an intermolecular asymmetric Sakurai reaction uniting allylsilane **20** and aldehyde **19** with concomitant establishment of the C_{15} stereocenter. Wender then relied on a highly regioselective Yamaguchi

[19] Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

macrolactonization of an alkynoic acid onto the unprotected C_{19}, C_{20}-diol to deliver the intact macrolide. Desymmetrization of commercially available isopropylidene tartrate led to α-chiral aldehyde **22**, while asymmetric hetero-Diels-Alder technology using Jacobsen's (*S*, *S*)-Cr-salen catalyst **24**[20] and Mikami's (*S*)-BINOL-$TiCl_2$ system **25**[21] provided dihydropyran subunits **20** and **23**, respectively.

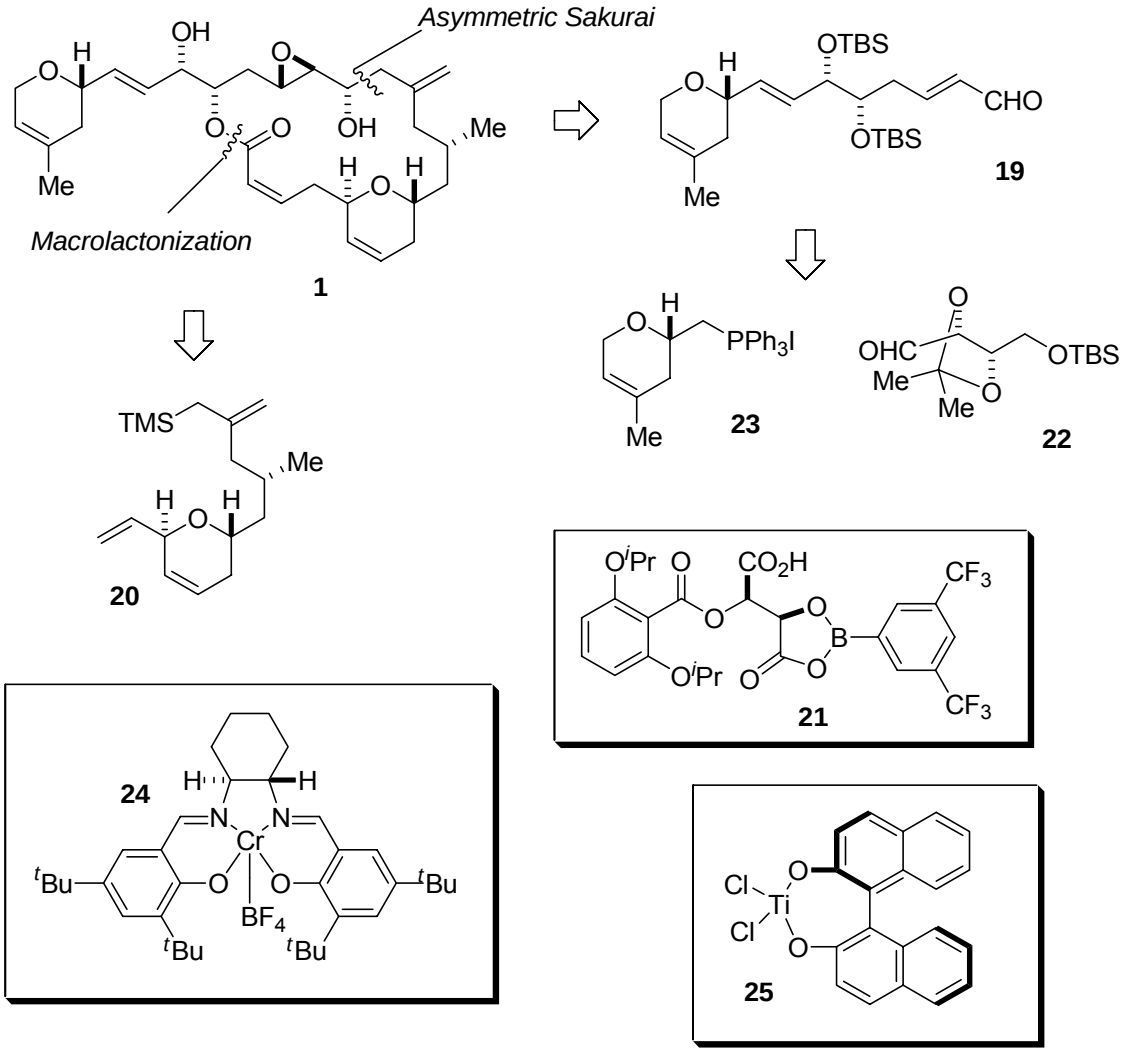


Figure 7. Retrosynthesis of (–)-Laulimalide: Wender Approach

[20] Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.
[21] Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2391.

Up to this point, the C_{16}–C_{17} epoxide of (–)-laulimalide was viewed as an extremely sensitive functional group that warranted its installation very late, if not in the final step of all previously reported total syntheses. This notion was challenged in Crimmins' approach to laulimalide where the sensitive epoxide moiety was introduced at a much earlier stage in the synthesis.[10f] Fragment union and macrolide formation was accomplished with a diastereoselective allylstannane addition between the C_1–C_{14} fragment **26** and the epoxide containing C_{15}–C_{27} subunit **27**, followed by a Mitsunobu macrolactonization of seco acid **28** to preserve the integrity of the (*Z*)-enoate ester linkage (Figure 8). To establish elements of stereochemistry in each of the three major fragments **26**, **29**, and **30**, Crimmins relied heavily on his previously developed asymmetric alkylation methodology employing chiral oxazolidinone glycolates.[22]

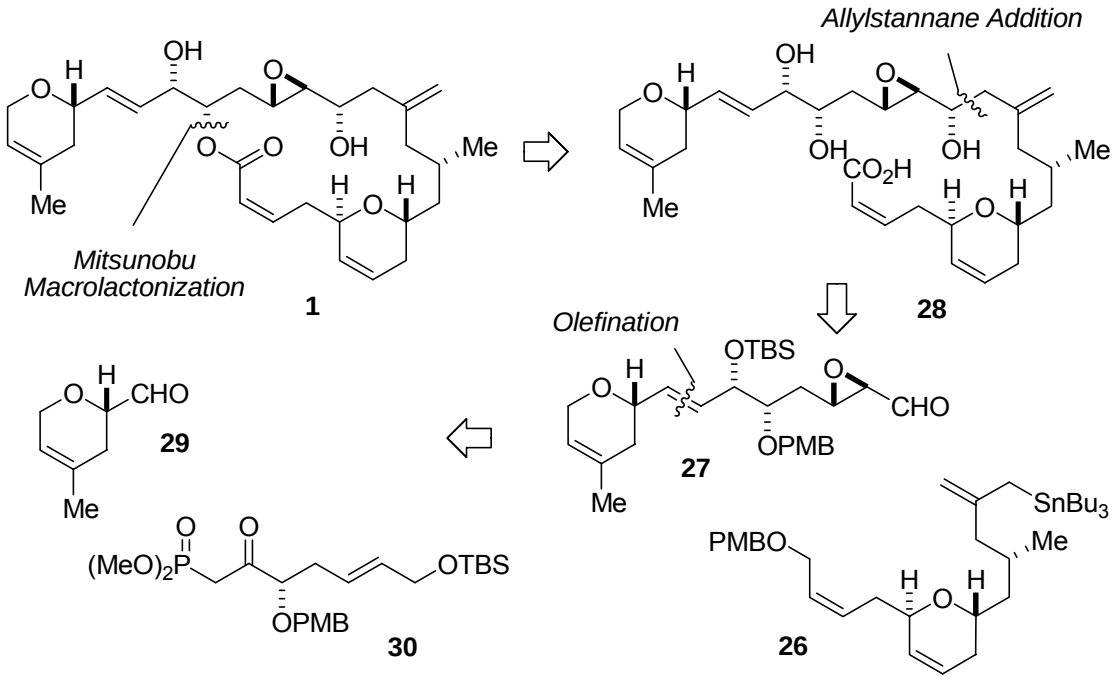


Figure 8. Retrosynthesis of (–)-Laulimalide: Crimmins Approach

[22] Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett*. **2000**, *2*, 2165.

In the most recently reported total synthesis of (–)-laulimalide, Williams described a highly diastereoselective coupling of allylsilane fragment **31** and Crimmins' epoxyaldehyde **27**. Subunit **27** was constructed through a chelation-controlled addition of *E*-alkenyl zincate **32** to α-alkoxyaldehyde **33** followed by Grubbs' ring-closing metathesis to form the requisite dihydropyran side chain. A novel allenylstannane Ferrier reaction between **34** and glycal acetate **35** was employed to directly install the C_1–C_4 propargylic sidearm necessary for the safe installation of the required C_2–C_3 *Z*-olefin via the Yamaguchi macrolactonization and subsequent Lindlar reduction protocol initially described by Ghosh and coworkers (Figure 9).

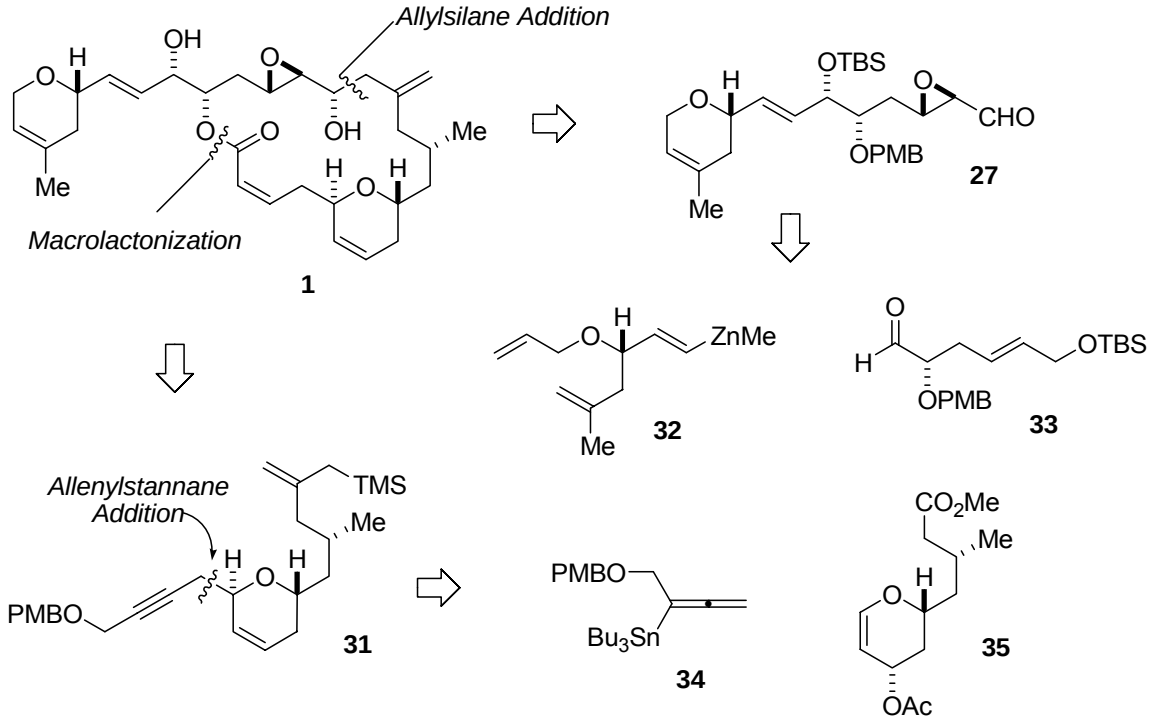
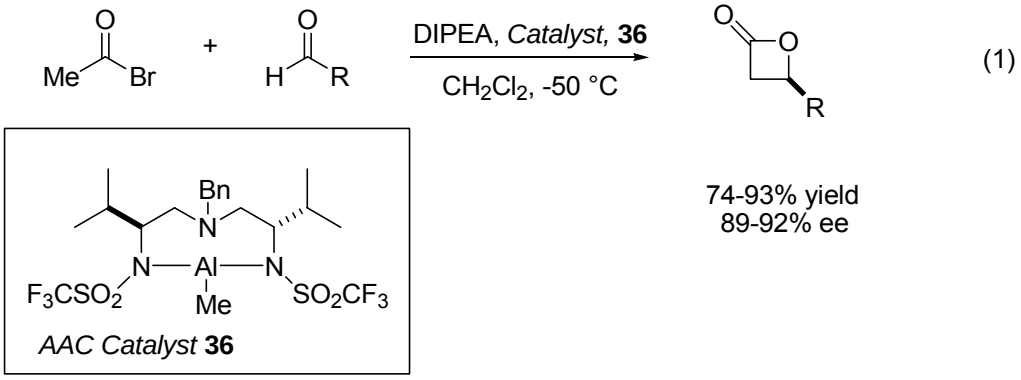


Figure 9. Retrosynthesis of (–)-Laulimalide: Williams Approach

1.2 AAC REACTION TECHNOLOGY IN THE TOTAL SYNTHESIS OF (–)-LAULIMALIDE

Methodology developed recently in our research group encouraged our pursuit of the total synthesis of (–)-laulimalide. Catalytic, asymmetric acyl halide-aldehyde cyclocondensation (AAC) reaction technology allows for the efficient preparation of masked aldol products in the form of β-lactones from a wide variety of aldehydes (Equation 1). Employing substoichiometric amounts (10-15 mol %) of a chiral aluminum triamine catalyst **36**, a variety of enantiomerically enriched β-lactones have been produced, making these synthons readily available and easily prepared for use in synthesis endeavors. [23]



(1)

Enantioenriched β-lactones are useful building blocks in organic synthesis due to their unique electrophilicity (Figure 10).[24] By exploiting the reactivity of these β-lactone templates, synthetic and stereochemical challenges associated with the total synthesis of (–)-laulimalide can be addressed. For example, the creation of hydroxyl-bearing stereocenters, a prominent architectural feature of laulimalide, can be accomplished by the addition of hard nucleophiles

[23] (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742. (b) Nelson, S. G.; Kim, B. K.; Peelen, T. J. *J. Am. Chem. Soc*. **2000**, *122*, 9318. (c) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470.
[24] Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441.

such as alkoxides, alkyl Grignard reagents, and metal amide species into the carbonyl of the β-lactone.[25] Installing alkyl-bearing stereocenters, such as the methyl-bearing stereocenter at C_{11} of laulimalide, can be achieved by utilizing soft nucleophiles. Dialkylcuprate reagents undergo nucleophilic attack in an S_N2 fashion at the C_4 position of the lactone to generate optically active β-disubstituted carboxylic acids.[26] Use of the asymmetric AAC reaction in an iterative fashion leads to the formation of 1,3-stereochemical relationships, yet another important structural feature in our planned total synthesis. It was therefore speculated that the versatile reactivity demonstrated by enantiomerically enriched β-lactones would provide a novel and efficient approach to the total synthesis of (–)-laulimalide.

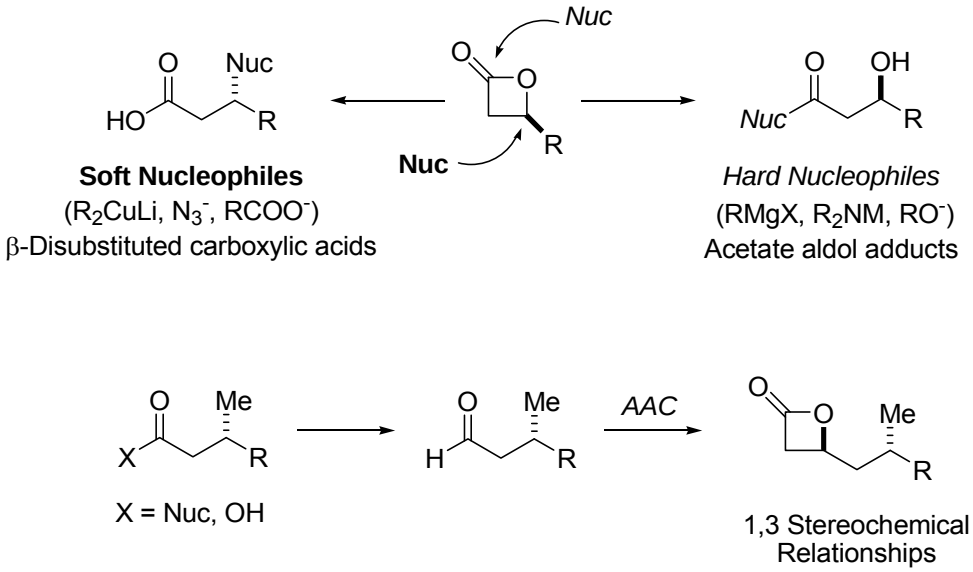


Figure 10. Accessible Structural Motifs from Enantiomerically Enriched β-Lactones

[25] (a) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett*. **1999**, *40*, 6535. (b) Stuckwisch, C. G.; Bailey, J. V. *J. Org. Chem*. **1963**, *28*, 2362. (c) Gresham, T. L.; Jansen, J. E. Shaver, F. W.; Bankert, R. A. *J. Am. Chem. Soc*. **1949**, *71*, 2807.

[26] (a) Sato, T.; Kawara, T.; Kawashima, M.; Fujisawa, T. *Chem. Lett*. **1980**, 571. (b) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett*. **1980**, *21*, 3377. (c) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823. (d) Sato, T.; Naruse, K.; Fujisawa, T. *Tetrahedron Lett*. **1982**, *23*, 3587. (e) Sato, T.; Itoh, T.; Hattori, C.; Fujisawa, T. *Chem. Lett*. **1983**, 1391. (f) Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403.

1.3 RETROSYNTHETIC ANALYSIS

Our original retrosynthetic approach to (–)-laulimalide is outlined in Figure 11. Removal of the C_{16}–C_{17} epoxide followed by a disconnection at C_{20}–C_{21} via a diastereoselective vinyl metal addition would deliver dihydropyran subunit **37** along with the highly functionalized macrocycle **38**. Construction of **38** would be accomplished through propargylic acid esterification and subsequent intramolecular asymmetric allylsilane addition of the lower C_1–C_{14} dihydropyran fragment **39** and the C_{15}–C_{20} α,β-unsaturated aldehyde **40**. Stereoselective synthesis of fragments **39** and **40** was predicated on exploiting the unique reactivity demonstrated by the enantiomerically enriched β-lactone products of AAC reaction technology.

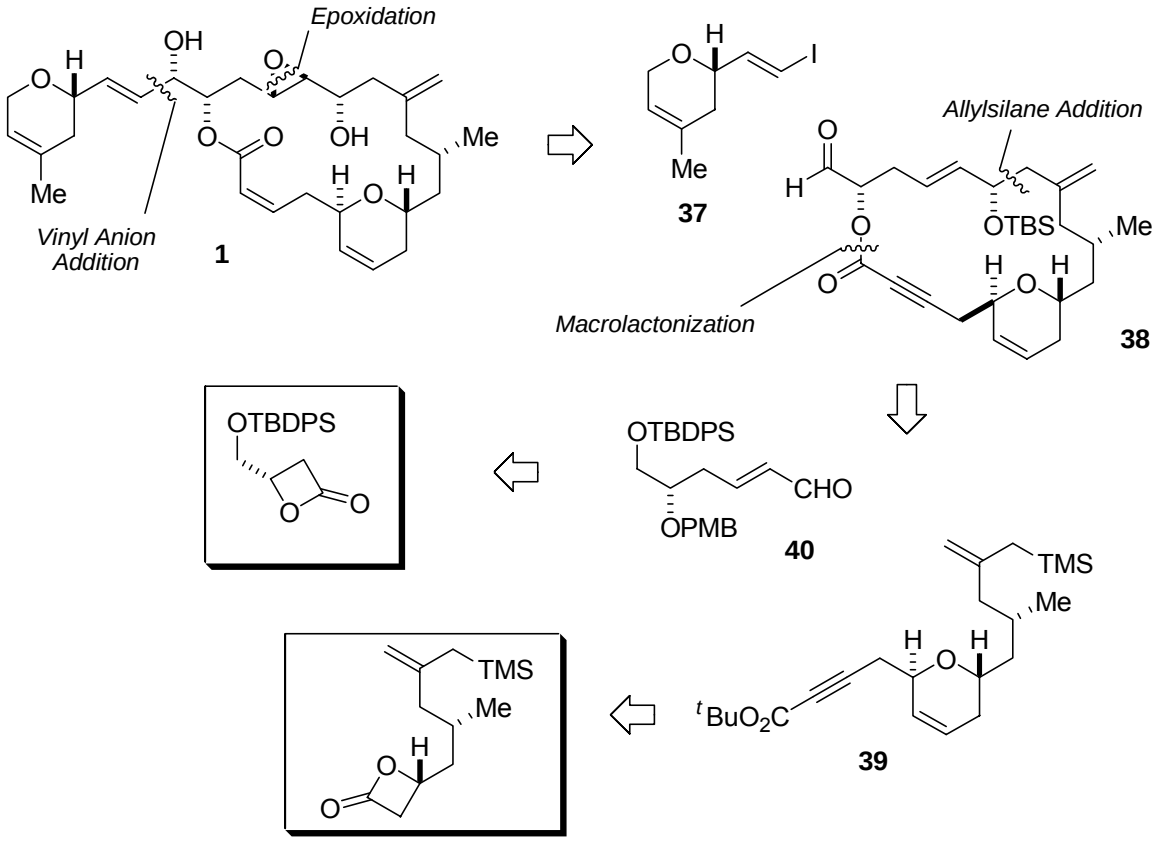


Figure 11. Retrosynthesis of (–)-Laulimalide: Nelson Approach

1.4 THE C_1–C_{14} DIHYDROPYRAN FRAGMENT

1.4.1 Retrosynthetic Analysis

Through further retrosynthetic analysis of the lower dihydropyran fragment **39**, we recognized the potential for applying AAC-based reaction technology and developing new methods for addressing key synthetic challenges (Figure 12). We had envisaged the novel stereoselective installation of the entire C_1–C_4 ynoate ester sidearm of **39** occurring via a Lewis acid-mediated allenylstannane addition of **41** to glycal acetate **42**.[27] Glycal **42** would be readily accessible through the typical 1,2-reduction and acylation sequence available to the corresponding dihydropyranone **43**. Preparation of **43** was then anticipated from the regioselective ring opening of β-lactone **44** with subsequent acid- mediated cyclization and elimination.

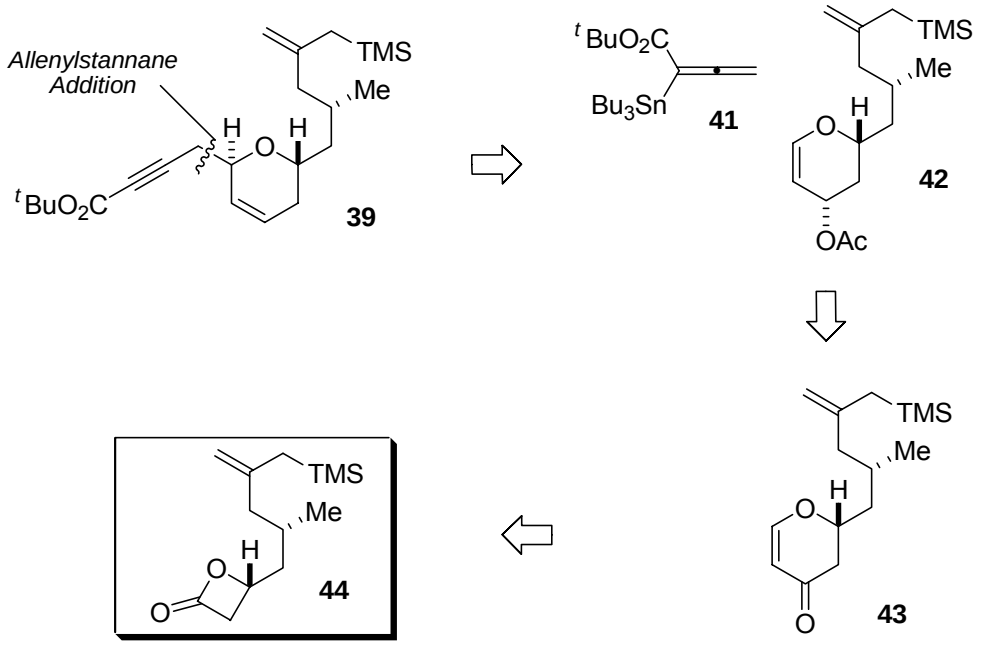


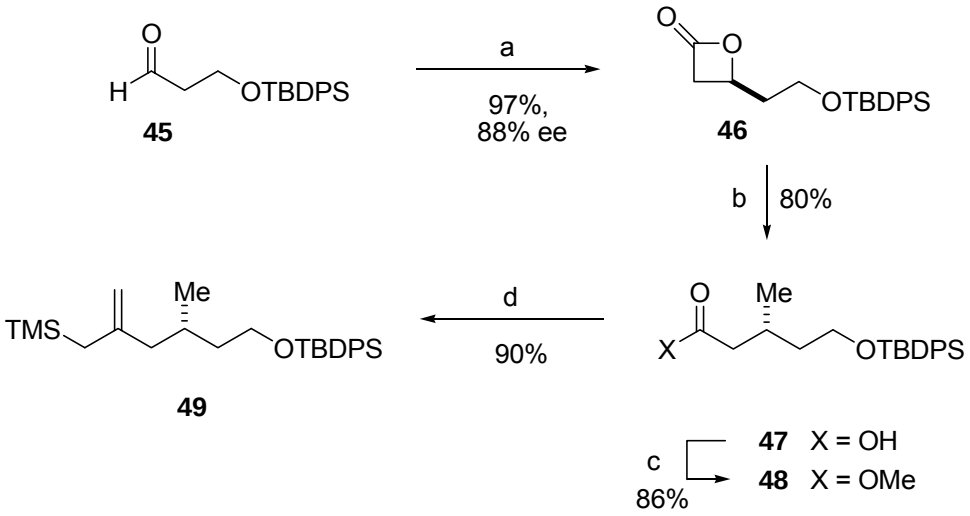
Figure 12. Retrosynthetic Approach to the C_1–C_{14} fragment of (–)-laulimalide

[27] For a similar approach to this bond construction see ref 11k.

1.4.2 First Generation Synthesis of the C_1–C_{14} Fragment of (–)-Laulimalide

The synthesis of the C_1–C_{14} fragment of (–)-laulimalide (Scheme 1) began from the known aldehyde **45**.[28] Lactone **46** was prepared in 97% yield from aldehyde **45** under standard asymmetric AAC conditions (AcBr, iPr_2NEt, CH_2Cl_2, –50 °C) employing 10 mol % of the *S*,*S* Al(III)-triamine catalyst **36** and was recrystallized to high enantiopurity (98% ee). Regioselective S_N2 ring opening of **46** to the carboxylic acid via dimethylmagnesiocuprate addition (80% yield) efficiently set the requisite methyl-bearing C_{11} stereocenter. Acid **47** was then converted to methyl ester **48** (DCC, DMAP, MeOH) in 86% yield. Treating ester **48** with an excess of an organocerium reagent derived from $CeCl_3$ and trimethylsilylmethylmagnesium chloride ($TMSCH_2MgCl$) delivered the corresponding allylsilane **49**.[29]

Scheme 1. Synthesis of Allylsilane **49**[a]

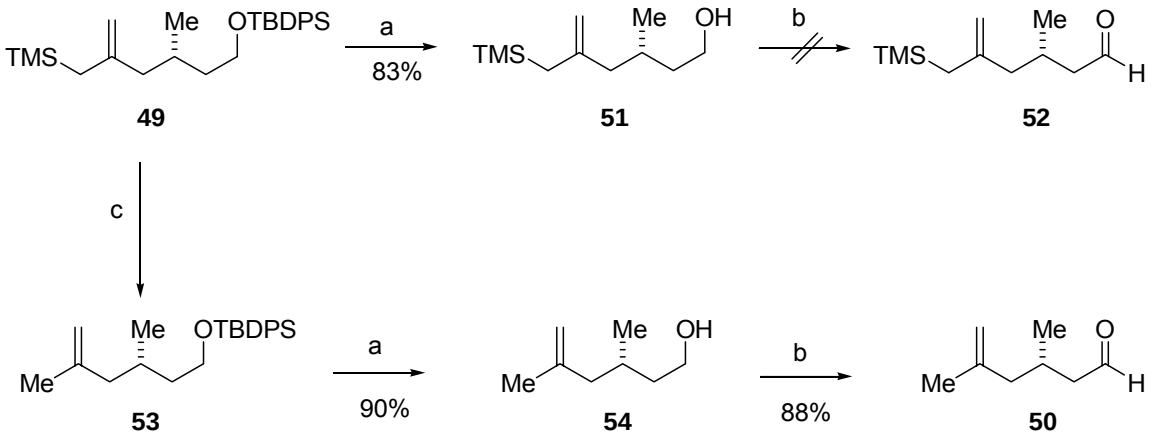


[a]Conditions: a) 10 mol% *Catalyst* **2**, AcBr, DIPEA, CH_2Cl_2, –50 °C. b) CuBr, MeMgBr, TMSCl, THF/DMS, –50 °C to rt. c) DCC, DMAP, MeOH. d) $CeCl_3$, $TMSCH_2MgCl$, THF, –78 °C to rt.

[28] Aldehyde **36** was prepared by ozonolysis of 3-(*tert*-butyldiphenylsilyloxy)-1-butene. See Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc*. **1991**, *113*, 5337.
[29] Narayanan, B. A. and Bunnelle, W. H. *Tetrahedron Lett*. **1987**, *28*, 6261.

Further elaborating allylsilane **49** to the target molecule **39** required its transformation into lactone **44** (Eq 2). The aldehyde **52** required for generating **44** was to be produced by silyl deprotection and oxidation of **49** (Scheme 2). Treatment of silane **49** with tetra-*n*-butylammonium fluoride (TBAF) resulted in the cleavage of the TBDPS ether in forming alcohol **51** (83% yield); however, oxidation with tetra-*n*-propylammonium perruthenate (TPAP, NMO, 4Å molecular sieves) afforded none of the desired aldehyde product **52**. Additional attempts to oxidize the primary alcohol employing Swern conditions[30] and Dess-Martin periodinane[31] were also unsuccessful. This problem was circumvented by removal of the trimethylsilyl (TMS) group with Amberlyst-15 resin in THF to form **53**, although loss of the allylsilane at this stage now required a new approach for the coupling of major fragments **39** and **40**. Silyl deprotection and subsequent TPAP oxidation provided the volatile aldehyde **50** in 79% yield from silyl ether **49**.

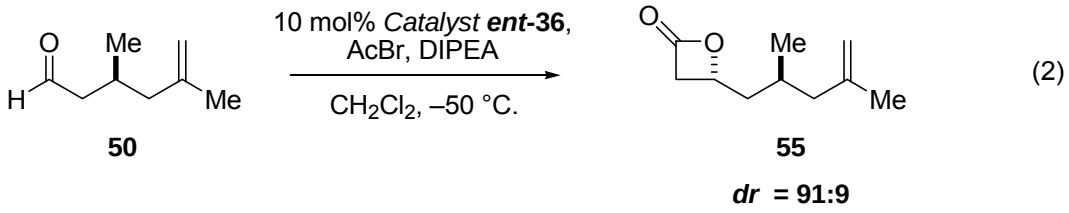
Scheme 2. Preparation of AAC-Precursor **50**[a]



[a]Conditions: a) TBAF, THF. b) TPAP, NMO, 4 Å MS, CH_2Cl_2. Amberlyst-15, THF.

[30] (a) Swern, D. *J. Org. Chem*. **1976**, *41*, 3329-3331. (b) Swern, D. *J. Org. Chem*. **1978**, *43*, 2480. (c) Swern, *Synthesis*. **1978**, 297.
[31] (a) Dess, P. B.; Martin , J. C. *J. Am. Chem. Soc*. **1978**, *100*, 300. (b) Dess, P. B.; Martin , J. C. *J. Am. Chem. Soc.* **1979**, *101*, 5294. (c) Dess, P. B.; Martin , J. C. *J. Org. Chem*. **1983**, *48*, 4155.

Aldehyde **50** was then used as the coupling partner in a second AAC reaction. Subjecting aldehyde **50** to standard AAC reaction conditions (AcBr, $^{i}Pr_2NEt$, CH_2Cl_2, –50 °C) employing 10 mol% of the (*R*, *R*) aluminum-triamine catalyst ***ent*-36** furnished lactone **55** as a 91:9 mixture of (2′*S*,4*R*):(2′*S*,4*S*) diastereomers based on ^{1}H NMR analysis (500 MHz). Unfortunately, intermediate **55** also proved to be very volatile and attempts to completely remove solvent from the product resulted in the substantial loss of material. After separation of the lactone diastereomers by column chromatography, steps were taken to convert **55** to the requisite dihydropyranone.



50 **55**

***dr* = 91:9**

(2)

We envisioned a possible synthetic route to dihydropyranones from simple enantiomerically enriched β-lactone precursors. The initial strategy for arriving at these pyranone intermediates involved the direct nucleophilic addition of vinyl anions of type **56** into β-lactones (Figure 13). These hard nucleophiles would preferentially add into the carbonyl of the lactone with subsequent ring opening to produce the corresponding enol ether **57**. Under acidic conditions, this enol ether would hydrolyze to the β-ketoaldehyde **58** with probable cyclization to form hemiacetal **59**. Subsequent dehydration would then provide the desired dihydropyranone product **60**.

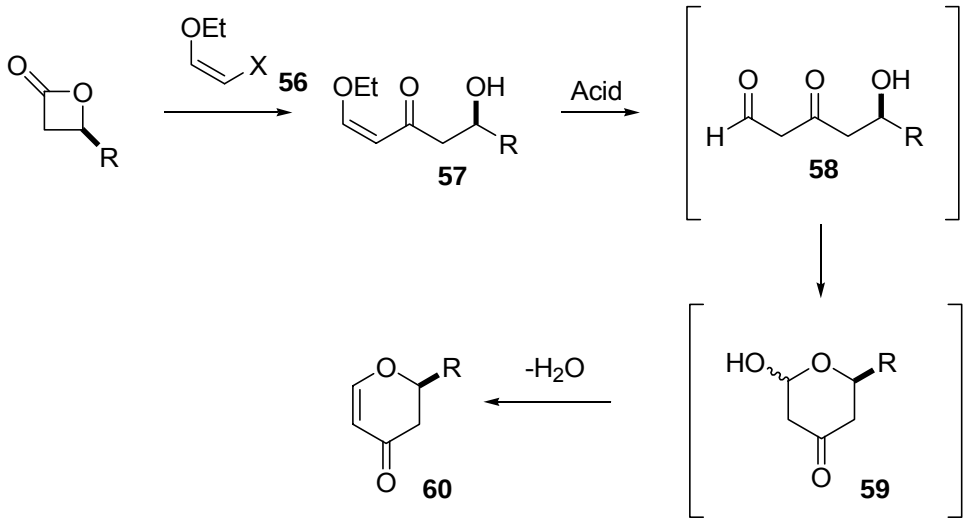
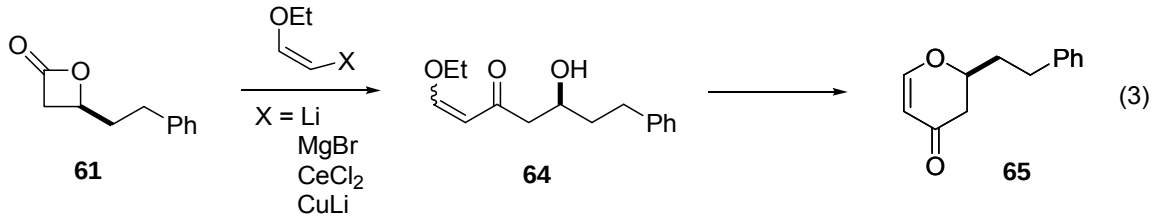


Figure 13. Pyranone Formation Via Direct Vinyl Anion Addition to β-Lactones

To explore the feasibility of this direct vinyl anion addition route, a model study was undertaken employing (4*S*)-4-phenethyloxetan-2-one **61** (Eq 3).[23a] Metallating (*Z*)-1-ethoxy-2-tributylstannylethylene **62**[32] with *n*-butyllithium afforded vinyl anion **63**[33] which was then slowly treated with β-lactone **61**. The desired product **64** was obtained as an approximately 3:1 mixture of *cis/trans* vinyl ether isomers in a combined 23% yield, along with many unidentifiable products. Transmetallation of the reactive organolithium species **63** to the corresponding Grignard and organocerium reagents afforded similar mixtures of olefin isomers but in slightly lower yields (18%). Forming the cuprate of the organolithium species provided compound **64** again in low yield (15%). Despite these low yields, it was discovered that, upon standing at ambient temperature, the enol ether intermediate does cyclize to the desired pyranone product **65**, proving the viability of the route; however, extensive optimization was necessary to achieve synthetically useful chemical yields.

[32] Prepared by the hydrostannylation of ethyl ethynyl ether. See: Leusink, A. J.; Budding, A.; Marsman, J. W. *J. Organometal. Chem*. **1967**, *9*, 285, 294.
[33] (a) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc*. **1977**, *99*, 7365. (b) Ficini, J.; Falou, S.; Touzin, A. M.; d'Angelo, J. *Tetrahedron Lett*. **1977**, 3589.

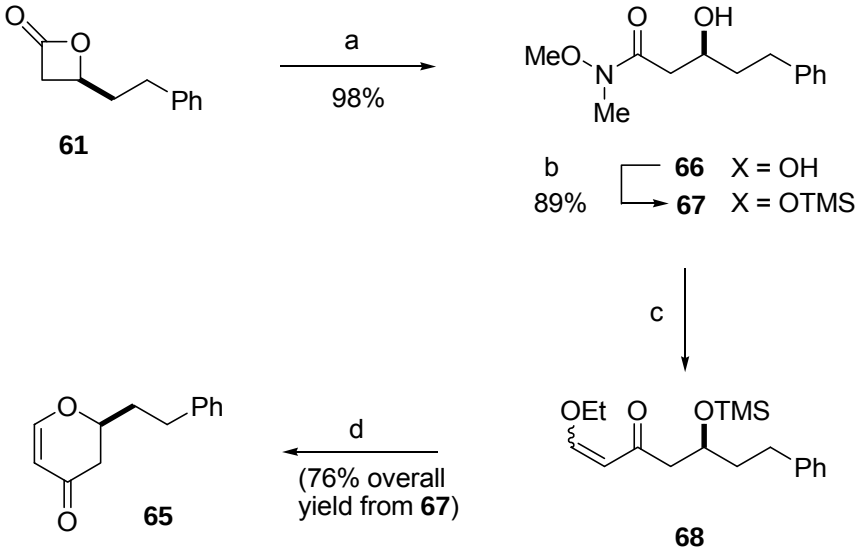


(3)

Due to the unsatisfactory results obtained from the direct addition of vinyl anions to β-lactones, a modified strategy to achieve pyranone formation was devised (Scheme 3). Prior ring opening of the β-lactone to a species more tolerant of the reaction conditions followed by vinyl anion addition was anticipated to result in higher yields. To test this strategy, Weinreb amide **66** was prepared from the corresponding β-lactone in 98% yield under conditions developed by Shimizu and Nakata.[34] Protection of the resulting secondary alcohol with *N,O*-bis(trimethylsilyl)acetamide (BSA) afforded the TMS-protected Weinreb amide **67** in 89% isolated yield. Subjecting amide **67** to lithium anion **63** at –78 °C provided enol ether **68** as a mixture of cis/trans isomers (15:1) in a combined 65% yield. In subsequent experiments, the enol ether was not isolated but, rather, was dissolved in tetrahydrofuran (THF), treated with Amberlyst-15 ion exchange resin (100 mass%), and maintained at ambient temperature overnight to effect the acid-mediated cyclization. After purification, dihydropyran **65** was obtained in 76% overall yield from amide **67**.

[34] Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett*. **1997**, *38*, 2685.

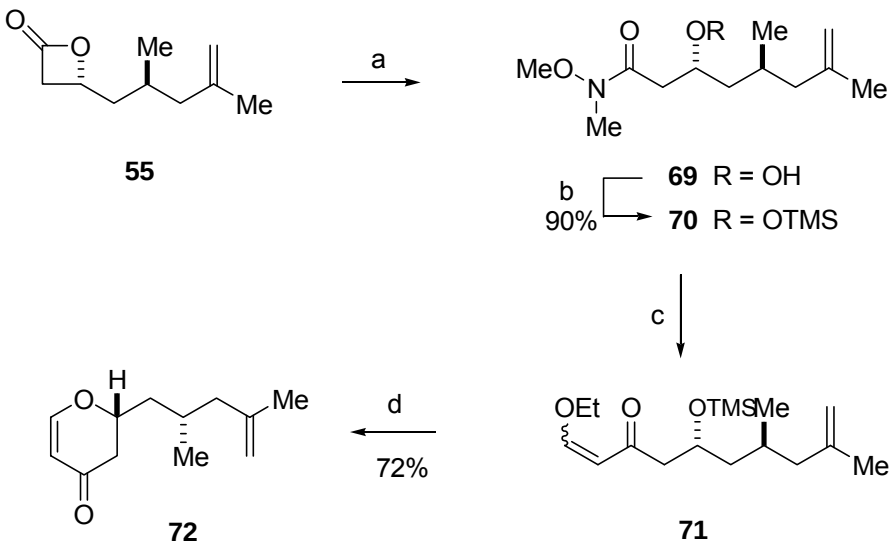
Scheme 3. Lactone to Dihydropyranone Interconversion[a]



[a]Conditions: a) MeON(Me)H•HCl, Me_2AlCl, CH_2Cl_2. b) BSA, CH_2Cl_2, rt. c) **62**, ^{n}BuLi, THF, –78 °C. d) Amberlyst-15, THF, rt

Using this strategy, lactone **55** was efficiently converted to Weinreb amide **69** by ring opening with the aluminum-amide species derived from *N, O*-dimethylhydroxylamine and dimethylaluminum chloride (Scheme 4). Amide **69** was then treated with *N, O*-bis(trimethylsilyl)acetamide (BSA) providing the corresponding TMS ether **70** in 90% yield. The resulting β-siloxyamide **70** was subjected to the *cis*-ethoxyvinyllithium-mediated protocol for pyranone synthesis and the resulting mixture of enones **71** was then treated with 100 mass % of Amberlyst-15 resin in THF at ambient temperature to effect the cyclization to pyranone **72** in good yield (72% from amide **70**).

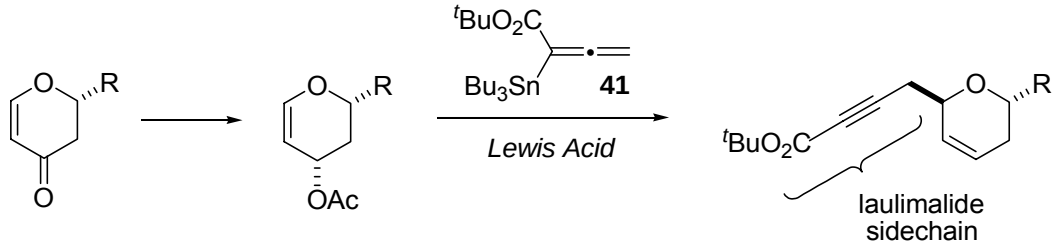
Scheme 4. Synthesis of Dihydropyranone **72**[a]



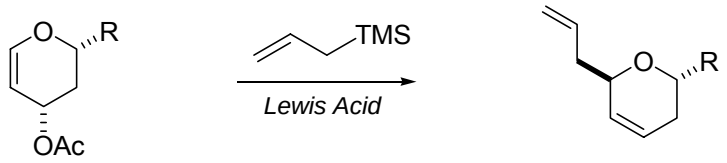
aConditions: a) MeON(Me)H•HCl, Me_2AlCl, CH_2Cl_2. b) BSA, CH_2Cl_2. c) **62**, ^{n}BuLi, THF, –78°C. d) Amberlyst-15, THF.

Having arrived at a working synthetic route to the desired dihydropyranone intermediate **72**, we next initiated model studies focused on installing the ynoate ester sidearm of the C_1–C_{14} fragment. A Lewis acid-mediated allenylstannane addition of reagent **41** into glycal acetates derived from the corresponding pyranone intermediates was an intriguing possibility (Scheme 5).

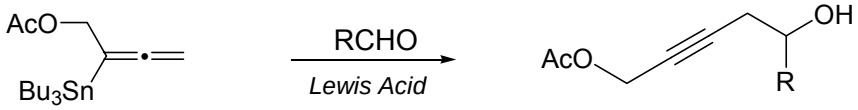
Scheme 5. Proposed Lewis Acid Activated Allenylstannane Addition of C_1–C_4 laulimalide sidechain



The requisite allenylstannane reagent **41** for exploring this strategy was previously unreported; however, there were several examples of similar compounds in the literature that instilled confidence in achieving the desired reactivity with glycal acetate intermediates. For example, Danishefsky has demonstrated, under appropriately Lewis acidic conditions, that allylsilanes serve as good nucleophiles for the regio- and stereoselective addition into glycal acetates to provide 2,6-*trans*-disubstituted dihydropyran rings (Eq 4).[35] Additionally, synthetic studies by Marshall have shown that allenylstannane reagents are capable of Lewis acid-mediated nucleophilic addition into aldehydes, affording the corresponding homopropargylic alcohol adducts (Eq 5).[36] Based on these precedents, the successful nucleophilic addition of allenylstannane **41** to glycal acetates was anticipated.



(4)

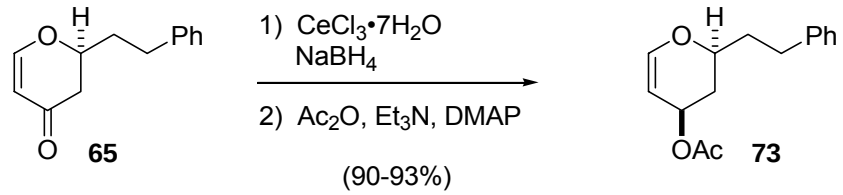


(5)

To examine the proposed nucleophilic allenylstannane addition, model glycal acetate **73** as well as stannane reagent **41** was prepared. Glycal acetate **73** was synthesized via a standard two step reaction sequence involving the reduction of pyranone **65** under Luche conditions[37]

[35] Danishefsky, S.; Kerwin, J. *J. Org. Chem*. **1982**, *47*, 3803.
[36] (a) Marshall, J.; Wang, X. *J. Org. Chem*. **1990**, *55*, 6246. (b) Marshall, J.; Wang, X. *J. Org. Chem*. **1991**, *56*, 3211. (c) Marshall, J. *Chem. Rev*. **1996**, *96*, 31.
[37] Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.

($CeCl_3$•$7H_2O$, $NaBH_4$) with subsequent protection of the resulting allylic alcohol as the corresponding acetate to furnish glycal acetate **73** in 90-93% overall yield (Eq 6).[38]

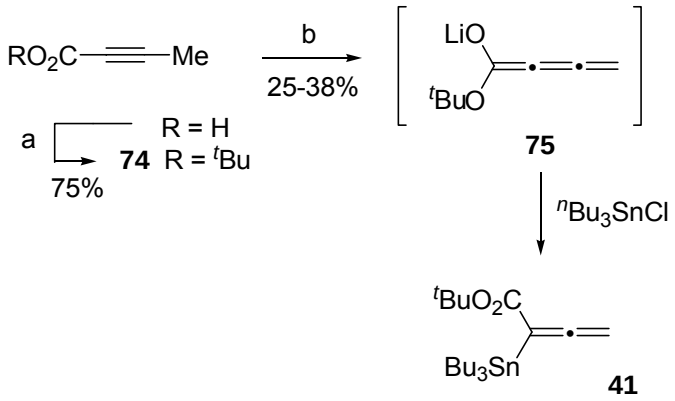


(6)

The synthesis of allenylstannane **41**, as depicted in Scheme 6, commenced with the acid-catalyzed esterification of commercially available 2-butynoic acid (H_2SO_4, isobutylene) to afford the desired *tert*-butyl ester **74** in good yield. Deprotonation of **74** with LDA at –78 °C followed by quenching with $^nBu_3SnCl$ then furnished allenylstannane **41** (25-38%). These modest isolated yields have recently been attributed to the original preparation of **41** in which $^nBu_3SnCl$ was added dropwise to a solution of enolate **75**. Under such reaction conditions, the potential Michael accepting product **41**, was generated in the presence of excess nucleophile leading to an increased propensity for anionic polymerization. Upon addition of the electrophile, the solution became deep red in color indicative of the presence of a highly conjugated species. A reverse addition of enolate to electrophile at low temperature was envisioned to prevent the undesired Michael addition and increase the isolated yield of the allenylstannane **41**.[39] Indeed, reverse addition of nucleophile to electrophile proved to be the most effective method for enolate quenching as it cleanly afforded **41** in 75% yield.

[38] Due to the high acid sensitivity of **73**, purification was performed by flash chromatography on deactivated silica gel eluting with hexanes/Et_3N (50:1).
[39] Optimization was performed by Dr. Junfa Fan (Postdoctoral fellow, Department of Chemistry, Univeristy of Pittsburgh).

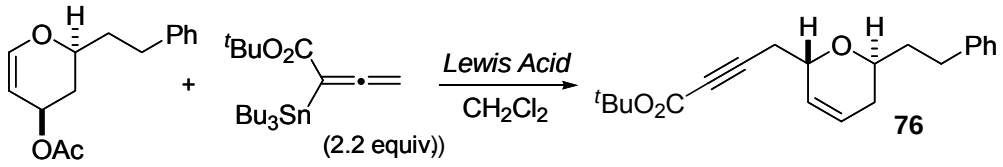
Scheme 6. Synthesis of Allenylstannane **41**[a]



[a]Conditions: (a) isobutylene, H_2SO_4. (b) i. LDA, THF, –78 °C, ii. ^{n}BuSnCl.

With model glycal acetate **73** and allenylstannane **41** in hand, a variety of Lewis acids were screened to establish the optimal reaction conditions for effecting the introduction of the requisite ynoate ester sidechain (Table 1). Treatment of a –78 °C methylene chloride solution of acetate **73** and stannane **41** (2.2 equiv) with stoichiometric Lewis acids was envisioned to result in nucleophilic attack of **41** at C_6 of glycal **73** with concomitant elimination of acetate to form **76** (Eq 4). Boron trifluoride diethyletherate provided the desired 2,6-dihydropyran product **76**, but in modest yield (38%). Montmorillonite K10 clay was also employed to mediate the reaction between glycal acetate **73** and allenylstannane **41**; however, a yield of only 33% was achieved. Reactions with titanium-based Lewis acids afforded only moderate reactivity (entries c-e). The low isolated yields of **76** obtained in these reactions prompted the investigation of other means of promoting this transformation

Table 1. Lewis Acid Activated Allenylstannane Additions to Glycal Acetates

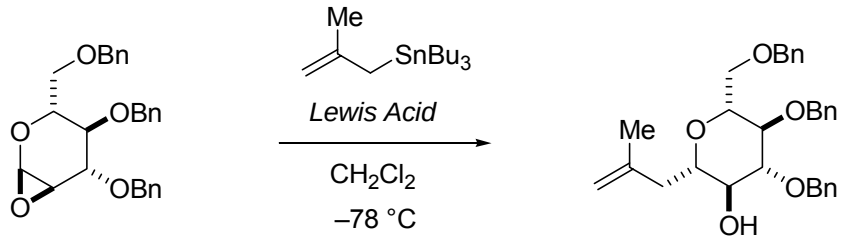


entry	Lewis Acid	Conditions	Yield (%)[a]
a	$BF_3{\bullet}OEt_2$	1.1 equiv, –78 °C	38
b	Montmorillonite K10	100 mass %, –78 °C	33
c	$TiCl_4$	1.1 equiv, –78 °C	45
d	$TiCl_2(O^iPr)_2$[b]	1.1 equiv, –78 °C	35
e	$TiCl_4(THF)_2$	1.1 equiv, –78 °C	40
f	$SnCl_4$[b]	1.1 equiv, –78 °C	20

[a]Isolated yields of purified products. [b]Addition of glycal acetate to allene/Lewis acid.

A similar reaction involving Lewis acid mediated allylstannane addition into glycal epoxides was recently described in Evans' total synthesis of altohyrtin C (Eq 7).[40] This nucleophilic addition sequence utilized various silyl and stannyl triflate Lewis acids for the introduction of propenyl sidechains into glycal epoxides in moderate to good yield (51-63%). These results led to the examination of silyl and stannyl triflate Lewis acids in the context of our allenylstannane addition reactions.

[40] Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, N. A. *Tetrahedron* **1999**, *55*, 8671.

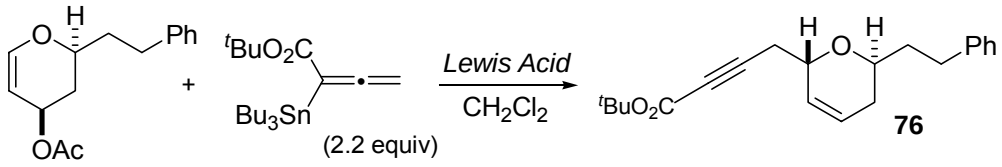


(7)

Lewis Acid: TMSOTf = 51%, TESOTf = 56%, $^{n}Bu_3SnOTf$ = 63%

Initial attempts to promote the allenylstannane addition to glycal acetate **73** under the silyl triflate conditions afforded the desired product **76** in yields higher than those observed in previous investigations (Table 2). Use of trimethylsilyl triflate generated propargyl ester **76** in 56% yield while treatment with triethylsilyl triflate afforded the desired dihydropyran product in 63% yield. Additional trials with triisopropylsilyl triflate were comparable to earlier studies where titanium(IV)-based Lewis acids were employed (40%). However, tributyltin triflate proved to be the optimal Lewis acid for the nucleophilic addition of allenylstannane **41** into glycal acetate **73**, furnishing dihydropyran **76** in 65% yield.

Table 2. Lewis Acid Activated Allenylstannane Addition to Glycal Acetate



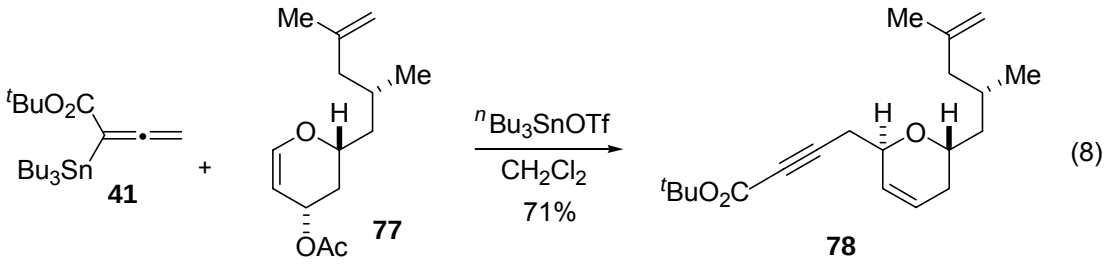
entry	Lewis Acid	Conditions	Yield (%)[a]
a	TMSOTf	1.1 equiv, –78 °C	56
b	TESOTf	1.1 equiv, –78 °C	63
c	TIPSOTf	1.1 equiv, –78 °C	40
d	^{n}Bu$_3$SnOTf	1.1 equiv, –78 °C	65
e	^{n}Bu$_3$SnOTf[b]	1.1 equiv, –78 °C	75

[a] Isolated yields of purified products. [b] Reaction was performed using 5.0 equiv of the allenylstannane reagent and warmed slowly to ambient temperature.

Due to the previously experienced acid sensitivity of glycal acetates,[38] we hypothesized that the lower isolated yields of **76** resulted from the undesired decomposition of **73** prior to allenylstannane addition. We envisioned that excess tin reagent would intercept the glycal acetate electrophile prior to its participation in destructive side reactions. To test this hypothesis, a large excess (5.0 equiv) of the allenylstannane reagent **41** was employed in the ^{n}BuSnOTf-mediated addition reaction. The desired adduct **76** was now obtained as a single diastereomer in 75% yield.

We were now prepared to introduce the ynoate ester sidechain of the C_1–C_{14} fragment of **1** employing the optimized conditions for nucleophilic allenylstannane addition. Glycal acetate **77**, prepared according to the reaction sequence outlined in Eq 6, and allenylstannane **41** were cooled to –78 °C and slowly treated with 1.1 equiv of ^{n}Bu$_3$SnOTf. Upon warming the reaction to

ambient temperature, the C_1–C_4 α, β-unsaturated ester sidearm of (–)-laulimalide was efficiently installed in one step in 71% yield completing fragment **78** (Eq 8). The *trans*-substitution across the dihydropyran ring was confirmed by a 2D-NOESY spectrum (Figure 14) in which a cross-peak between H_9 and the C_4 methylene was observed. Additionally, the absence of a cross-peak between H_5 and H_9 provided further evidence for a 2,6-*trans* arrangement of ring substituents.

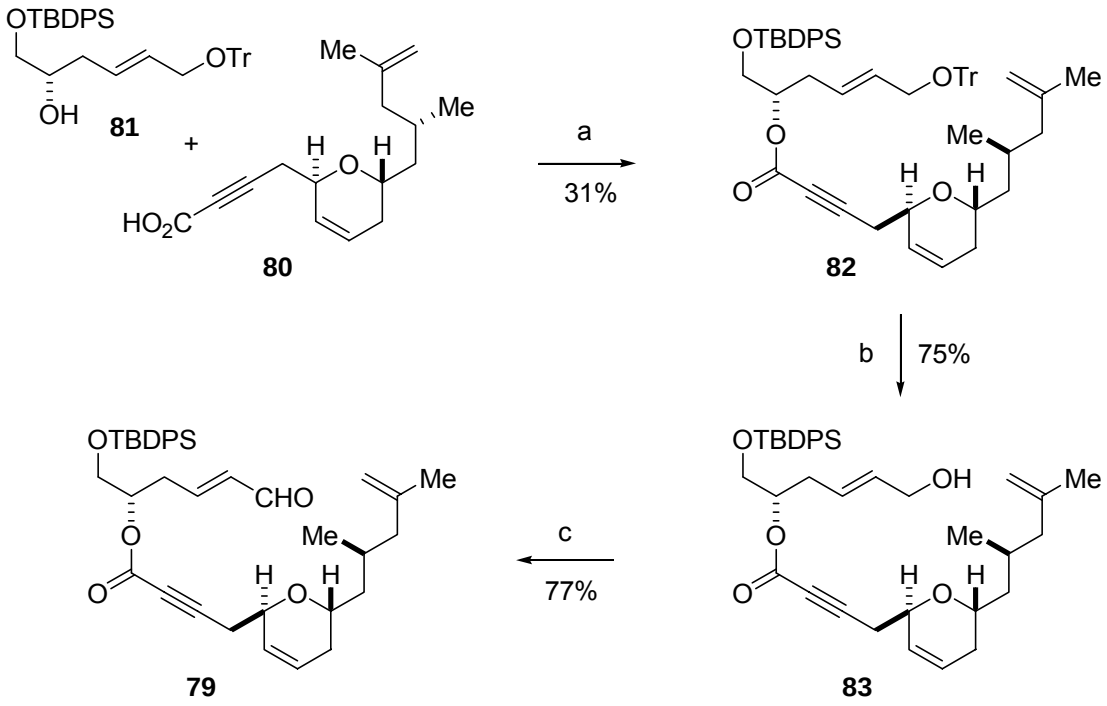


(8)

1.5 FRAGMENT UNION AND MACROLIDE FORMATION

According to the retrosynthetic strategy outlined in Figure 11**,** assembly of the asymmetric ene precursor **79** required first formatting dihydropyran subunit **78** as the corresponding carboxylic acid. After a brief survey of reaction conditions for the deprotection of *tert*-butyl esters, TMSOTf and 2,6-lutidine was identified as a suitable reagent system, cleanly affording carboxylic acid **80** in 90% yield. Acid **80** and alcohol **81** were then united through a carbodiimide coupling reaction (DCC, DMAP) to generate ester **82** in moderate yield (31%). Subjecting the coupled product **82** to 2% triflic acid (TfOH) in $CHCl_3$/MeOH (7:3) resulted in trityl ether deprotection providing allylic alcohol **83** which was then oxidized to the requisite α, β-unsaturated aldehyde substrate for intramolecular ene macrocyclization (Scheme 7).

Scheme 7. Synthesis of Ene Substrate **79**[a]



[a]Conditions: a) DCC, DMAP, CH_2Cl_2. b) 2% TfOH in $CHCl_3$/MeOH. c) TPAP, NMO, 4Å MS, CH_2Cl_2.

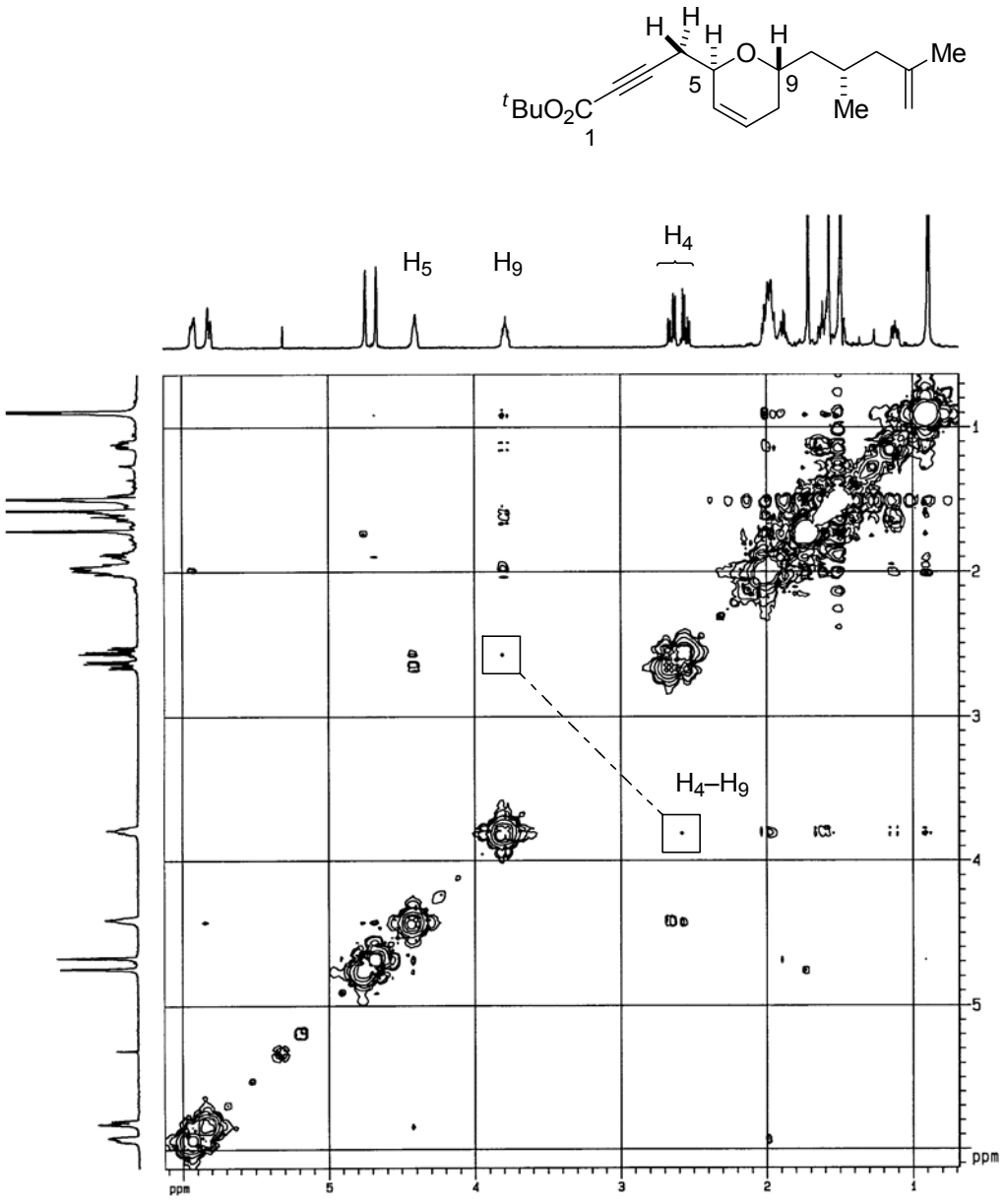
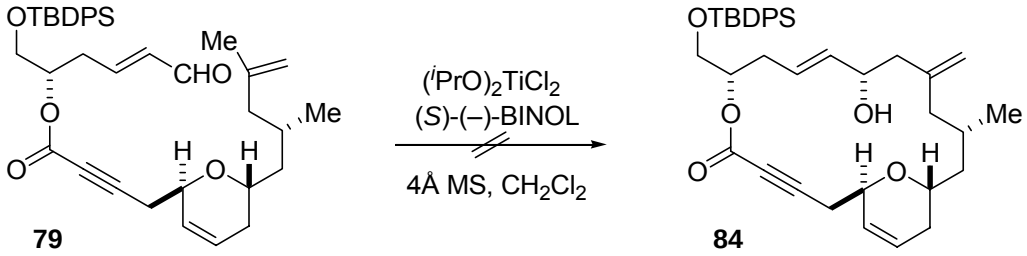


Figure 14. ^{1}H 2D-NOESY NMR Spectrum of Dihydropyran **78** (500 MHz)

The synthesis at this stage had arrived at the critical intramolecular ene macrocyclization event (Eq 9). We sought to construct the C_{14}–C_{15} bond and concomitantly establish the requisite C_{15} hydroxyl-bearing stereocenter under reaction conditions described by Mikami for the intermolecular ene reaction of olefins and activated glyoxylate electrophiles.[41] Employing Mikami's protocol, a –78 °C solution of Ti(IV)-(*S*)-(–)-BINOL catalyst was treated with the enal substrate **79**. No reaction was observed by TLC analysis after 2 h at –78 °C and, as a result, the reaction was allowed to warm slowly to ambient temperature while being carefully monitored by TLC. Even after being maintained for several hours at ambient temperature, no product formation was observed. Unfortunately, the electrophilic aldehyde portion of ene substrate **79** proved to be insufficiently activated to achieve the desired bond construction.



(9)

Despite our inability to close the macrocycle through an intramolecular ene reaction, the previously described synthetic route provided a suitable arena for the evaluation of catalytic, asymmetric AAC reaction technology in complex molecule synthesis as well as the development of additional novel methodology aimed at addressing some of the key challenges in the synthesis of the lower C_1–C_{14} fragment of (–)-laulimalide. For example, a working synthetic route to useful dihydropyranone intermediates from enantiomerically enriched β-lactones was achieved. In addition, a novel, one-step installation of the C_1–C_4 ynoate ester sidechain of **78** was realized

[41] Mikami, K.; Shimizu, M. *Chem. Rev*. **1992**, *92*, 1021, and references therein.

via a Lewis acid-mediated allenylstannane addition to glycal acetate **73**. However, the present approach did suffer from several other problems. Aldehyde **50** and lactone **55** were discovered to be rather volatile intermediates which hindered their preparation in large quantities. Additionally, although we had arrived at a route that accessed dihydropyranones from enantiomerically enriched β-lactone templates, we still desired a more direct strategy to streamline the current synthesis. As a result, we elected to pursue an alternate route to the C_1–C_{14} fragment of (–)-laulimalide.

1.6 REVISED RETROSYNTHETIC ANALYSIS

Our revised retrosynthetic approach to (–)-laulimalide is illustrated in Figure 15. Coupling of major fragments **85** and **86** was now envisioned to occur by an asymmetric aldol reaction between the C_{15} α,β-unsaturated aldehyde in fragment **85** and a suitable chiral enolate derived from the methyl ketone moiety in fragment **86**. To avoid the base- mediated scrambling of the Z-enoate ester linkage observed by Paterson, we would perform the requisite macrolactonization step on the corresponding propargylic carboxylic acid to close the 18-membered ring. Subsequent partial hydrogenation of the alkyne would unveil the sensitive Z-alkene. As outlined in our initial strategy, the C_1–C_4 propargylic acid side arm would be installed via a Lewis acid-mediated addition of allenylstannane **41** to glycal acetate **87** which in turn would be accessed through a dihydropyranone intermediate derived from the corresponding enantiomerically enriched β-lactone. Completion of the upper fragment **85** and concomitant introduction of the C_{19},C_{20} *syn*-diol arrangment would be accomplished via a diastereoselective vinyl metal addition between an anion derived from dihydropyran subunit **88** and α-alkoxyaldehyde **89**.

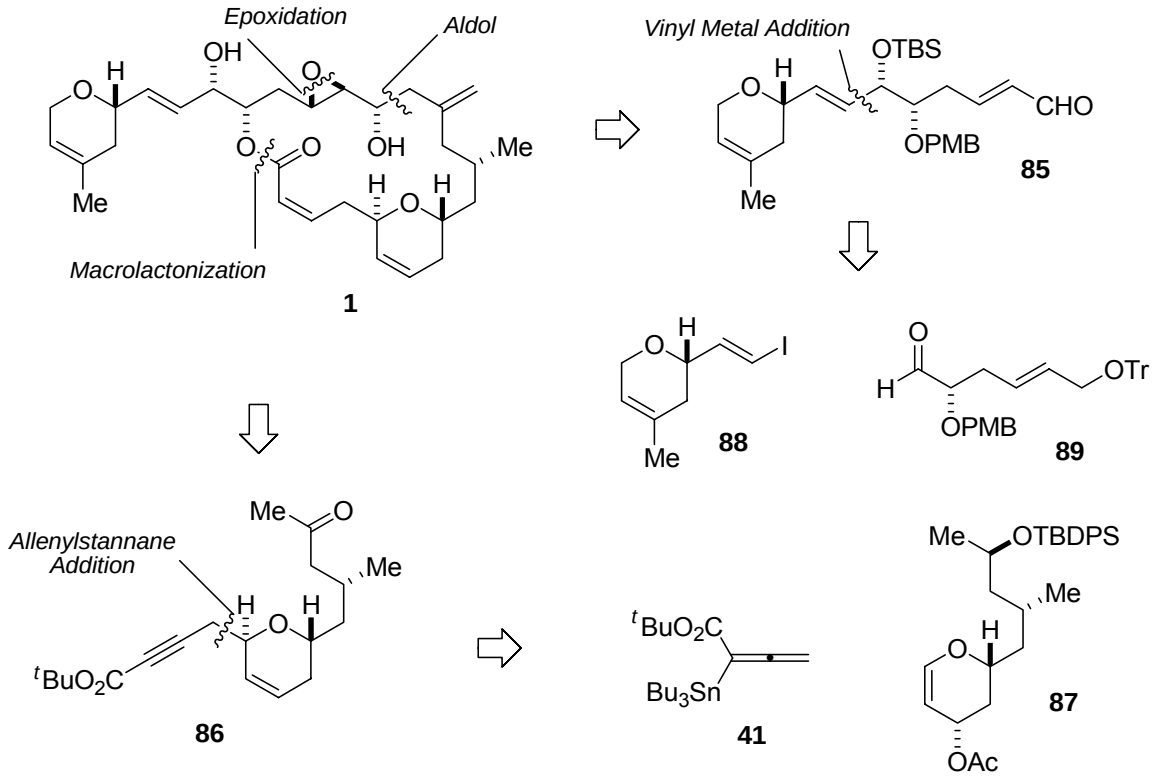


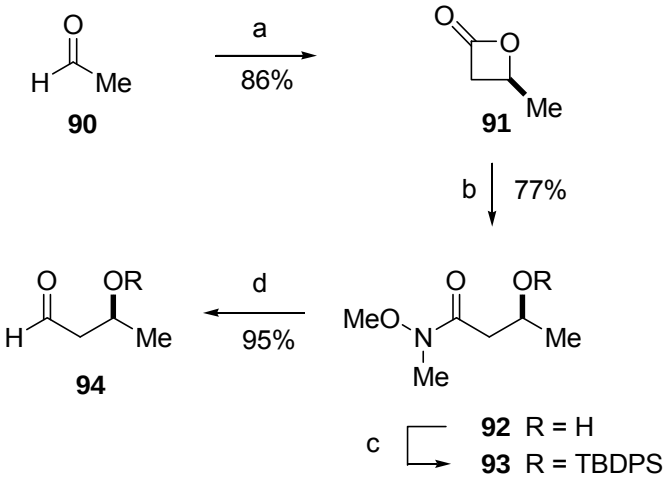
Figure 15. Revised Nelson Retrosynthesis

1.7 SECOND GENERATION SYNTHESIS OF THE C_1–C_{14} DIHYDROPYRAN FRAGMENT

The synthesis of the lower C_1–C_{14} dihydropyran subunit of (–)-laulimalide was initiated by an asymmetric AAC reaction with acetaldehyde (**90**) in the presence of tetrabutylammonium bromide at –78 °C to provide the known compound (*S*)-β-butyrolactone **91** in 86% yield and greater than 99% ee as determined by chiral GC analysis (Scheme 8). Ring opening of **91** with *N*,*O*-dimethylhydroxylamine and dimethylaluminum chloride[34] followed by protection of the resulting secondary alcohol as its *tert*-butyldiphenylsilyl ether furnished Weinreb amide **93** in 77% overall yield from lactone **91**. Amide **93** was then efficiently reduced with

diisobutylaluminum hydride (DIBAL-H) at –78 °C to deliver the corresponding β-siloxyaldehyde **94** in excellent yield.

Scheme 8. Synthesis of β-Silyloxyaldehyde **94**[a]



[a]Conditions: (a) *Catalyst* **X**, AcBr, DIPEA, Bu_4NBr, CH_2Cl_2, –78 °C. (b) Me_2AlCl, (MeO)MeNH·HCl, CH_2Cl_2. (c) TBDPSCl, DIPEA, DMAP, CH_2Cl_2, rt. (d) DIBAL-H, Et_2O, –78 °C.

From our revised retrosynthesis, it can be seen that the silyl-protected secondary alcohol possessed by aldehyde **94** represents a latent C_{13} methyl ketone moiety anticipating the crucial asymmetric aldol reaction to unite major fragments **85** and **86**. Although this stereocenter would eventually be destroyed in the oxidative unmasking of the ketone, judicious choice of the absolute stereochemistry at this position is imperative as the iterative application of AAC reaction technology enters into the realm of double stereodifferentiation.

In double diastereodifferentiating reactions, both reacting partners (or one reacting partner and a catalyst) possess stereocontrolling elements. These chiral controllers can either interact favorably with one another in a "matched pair" to afford the desired product with

enhanced selectivity or alternatively an unfavorable interaction can result leading to a "mismatched pair" and diminished levels of diastereoselectivity.[42] Previous investigations from our group regarding the establishment of 1,3 stereochemical relationships via sequential AAC reactions have demonstrated the propensity of the chiral Al(III)-triamine catalyst **36** to exert a strong influence over the preexisting β-stereocenter in the aldehyde component of the reaction, leading to good to excellent levels of diastereoselectivity for both the "mismatched" and "matched" substrate/catalyst pairs, respectively.[43] These observations have been rationalized by employing the following model (Figure 16). In the matched AAC reaction of a β-chiral aldehdye containing an (*S*)-stereocenter and catalyst **36**, the apically coordinated aldehyde adopts a conformation such that the β-methyl substituent orients itself away from the incoming ketene nucleophile. This arrangment acts in concert with the stereocontrolling trifluoromethyl group present in the triamine backbone of **36** to further shield the *Si* diastereoface of the aldehyde resulting in excellent levels of diastereoselectivity (>94% de). In contrast, when catalyst ***ent*-36** is employed, the corresponding mismatched case is obtained. The methyl substituent of the β-stereocenter is now directed toward the ketene nucleophile creating a more hindered approach to the *Si* face of the aldehyde electrophile. Although the observed diastereoselection is lower in this case, it is still synthetically useful (>85% de).

[42] Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 1.
[43] For a more detailed discussion of double diastereodifferentiating AAC reactions, see Magdalena A. Stan Ph. D. thesis, University of Pittsburgh, 2003.

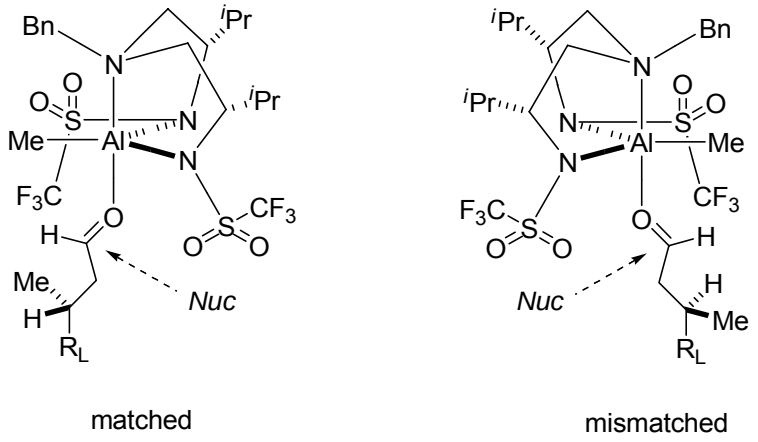
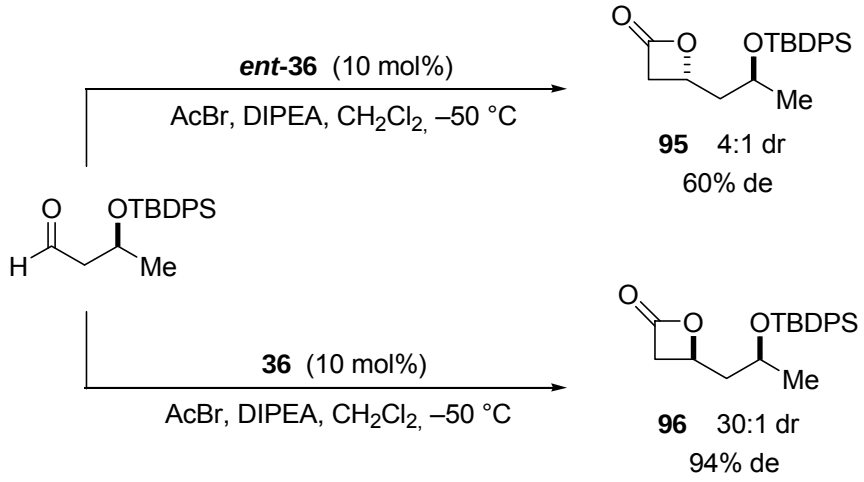


Figure 16. Proposed Model for Observed Selectivity in Double Diastereodifferentiating AAC Reactions[43]

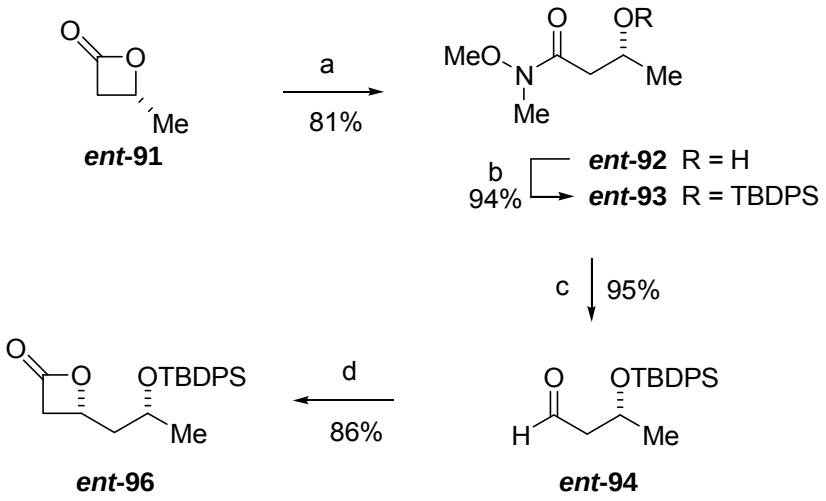
We sought to exploit this observation by establishing the C_{11} stereocenter in β-lactone intermediate **95** by iterative AAC application (Scheme 9). Unfortunately, subjecting aldehyde **94** to standard AAC reaction conditions (AcBr, $^{i}Pr_2NEt$, CH_2Cl_2, –50 °C) and employing 10 mol% of the necessary (*R*, *R*) aluminum-triamine catalyst ***ent*-36** resulted in unexpectedly low levels of diastereoselection (60% de) along with poor yields, and undesirably long reaction times. It appeared from this exceedingly apparent "mismatched" substrate/catalyst pairing that the sterically demanding *tert*-butyldiphenylsilyl protecting group was more capable of influencing the diastereoselectivity of the AAC reaction than in previously studied aldehydes. Based on this outcome, we expected that performing the reaction with (*S*,*S*) catalyst **36** would result in much increased levels of diastereoselectivity and faster reaction time indicative of the matched pair. Indeed, this was the case as the combination of aldehyde **94** and 10 mol% of catalyst **36** at –50 °C rapidly afforded *syn*-β-lactone **96** as a 97:3 mixture of (2′*S*,4*S*):(2′*S*:4*R*) diastereomers.

Scheme 9. Double Diastereodifferentiation in Iterative AAC Application



Arriving at the desired 1,3-*syn*-β-lactone ***ent*-96** necessary for (–)-laulimalide required the preparation of aldehyde ***ent*-94** in the opposite enantiomeric series starting from (*R*)-β-butyrolactone (Scheme 10). Lactone ***ent*-91** was obtained in identical yield as essentially a single enantiomer (99% ee), and application of the previously described three step sequence of ring-opening, protection, and reduction arrived at (3*R*)-3-(*tert*-butyldiphenylsilyloxy)-butyraldehyde (***ent*-94)**. When subjected to the iterative AAC reaction with 10 mol % of the *R*,*R*-Al(III)-triamine catalyst ***ent*-36**, lactone ***ent*-96** was obtained in 86% isolated yield with excellent levels of diastereoselectivity [(2′*R*,4*R*):(2′*R*:4*S*) = 97:3] as determined by 500 MHz ^{1}H NMR analysis.

Scheme 10. Synthesis of 1,3-*syn* β-lactone ***ent*-96**[a]



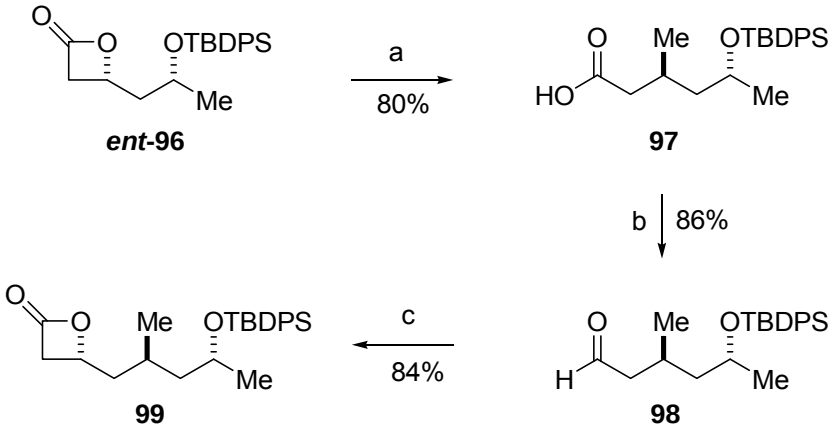
***ent*-91** ***ent*-92** ***ent*-93** ***ent*-96** ***ent*-94**

[a]Conditions: (a) (Me_2AlCl, (MeO)MeNH·HCl, CH_2Cl_2. b) TBDPSCl, DIPEA, DMAP, CH_2Cl_2, rt. (c) DIBAL-H, Et_2O, –78 °C. (d) *Catalyst* ***ent*-36**, AcBr, DIPEA, CH_2Cl_2, –50 °C.

After generating β-lactone ***ent*-96** with the correct absolute stereochemistry, we could then further elaborate this intermediate to the lower subunit of (–)-laulimalide (Scheme 11). Treating ***ent*-96** with the soft nucleophile dimethylmagnesiocuprate resulted in the expected S_N2 ring opening to establish the requisite C_{11} methyl-bearing stereocenter in carboxylic acid **97**. Acid **97** was then efficiently converted to the corresponding aldehyde **98** in high yield (86%) according to a one-pot reduction/oxidation sequence developed by Brown.[44] Aldehyde **98** then served as the coupling partner in a third AAC reaction that afforded the *anti*, *anti*-β-lactone **99** in 84% isolated yield with acceptable levels of diastereoselectivity (dr = 92:8).

[44] Brown, H. C.; Rao, C. G.; Kulkarni, S. U. *Synthesis* **1979**, 704.

Scheme 11. Preparation of *anti,anti*-β-lactone **99**[a]



[a]Conditions: (a) CuBr, MeMgBr, TMSCl, THF/DMS, –50 °C to rt. (b) i. $BH_3{\cdot}SMe_2$, Et_2O; ii. PCC, CH_2Cl_2. (c) 15 mol% *Catalyst* ***ent*-36**, AcBr, DIPEA, CH_2Cl_2, –50 °C.

With lactone **99** in hand, attention was then focused on the preparation of pyranone **100**. Although a synthetic route to dihydropyranones from β-lactones had been previously established, a more direct conversion was still desired. Recently, a streamlined approach for the preparation of dihydropyranones via direct nucleophilic addition of hydrazone anions into β-lactones was described (Figure 17).[45] The method involved lithiation of acetaldehyde *N*-piperidine hydrazone **101** at –78 °C, followed by treatment with a β-lactone electrophile which resulted in regioselective ring opening to the corresponding β-ketohydrazone. Subjecting the crude hydrazones to Amberlyst-15 acidic ion exchange resin in refluxing THF then resulted in cyclization and subsequent dehydroamination to provide the desired dihydropyranone products in good yield (72-81%).

[45] Zipp, G. G.; Hilfiker, M. A.; Nelson, S. G. *Org. Lett.* **2002**, *4*, 1823.

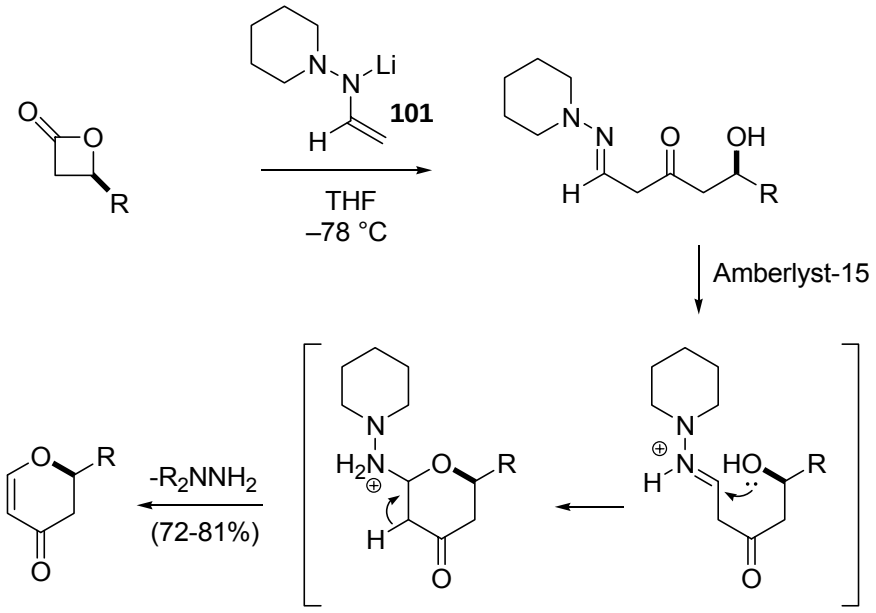
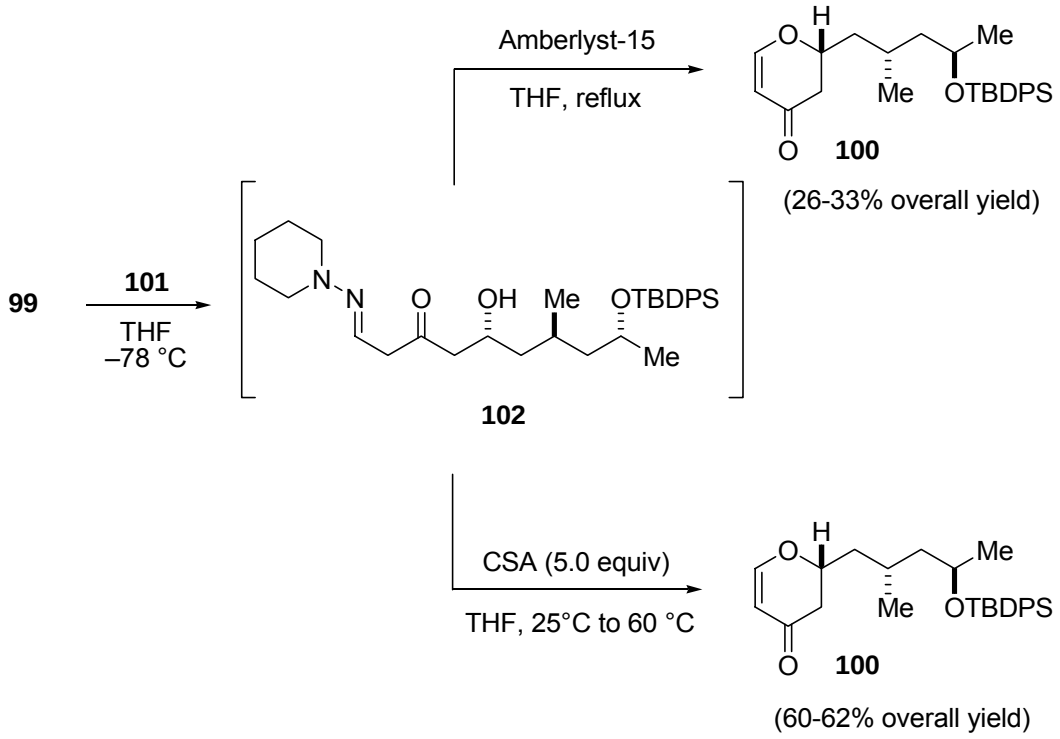


Figure 17. Hydrazone Anion Mediated Dihydropyranone Formation from β-lactones

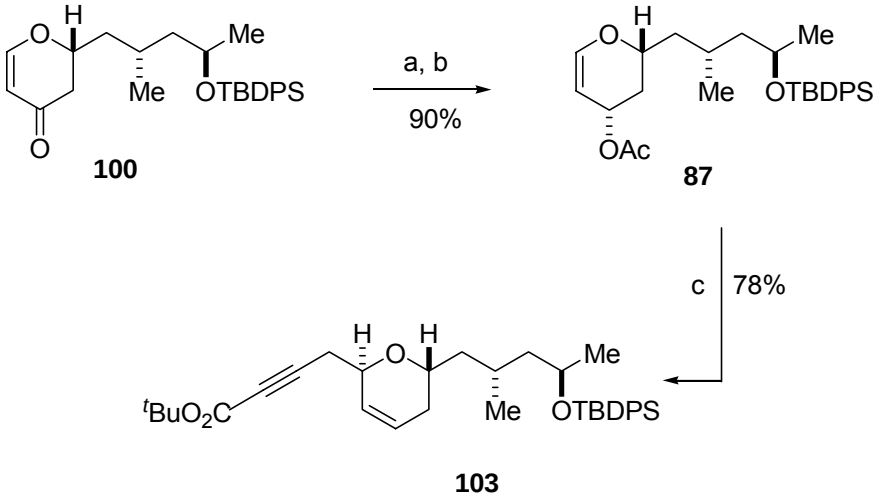
Attempts to apply the hydrazone anion methodology to the more complex lactone intermediate **99** proved to be problematic. Treating an excess of lithium anion derived from acetaldehyde *N*-piperidine hydrazone at –78 °C with lactone **99** cleanly generated the corresponding β-ketohydrazone **102**; however, when **102** was subjected to the cyclization conditions (Amberlyst-15, THF, reflux) unexpected cleavage of the *tert*-butyldiphenylsilyl protecting group was observed. The desired pyranone product was isolated in 26-38% yield along with considerable amounts of *tert*-butyldiphenylsilanol and other unidentified materials. By choosing a milder acid source to effect the cyclization, it was believed that this silyl deprotection/decomposition problem could be circumvented. Treatment of **102** with CSA (5.0 equiv) in THF at ambient temperature followed by gently warming to 60 °C resulted in cyclization of ketohydrazone **102** to the desired pyranone **100** in 62% yield from lactone **99** without any observed loss of the TBDPS group (Scheme 12).

Scheme 12. One Pot β-Lactone to Dihdyropyranone Interconversion



Having adapted the acid-mediated cyclization conditions to arrive at the requisite dihydropyranone intermediate, attention was then focused on preparing **100** for ynoate ester sidearm installation. Pyranone **100** was further elaborated into glycal acetate **87** according to the previously described sequence of Luche reduction followed by acylation of the resultant allylic alcohol to furnish acetate **87** in 90% overall yield. Lewis acid-mediated allenylstannane addition with $^{n}Bu_3SnOTf$ then delivered the *trans*-2, 6-disubstituted dihydropyran **103** as a single diastereomer in 74% yield (Scheme 13).

Scheme 13. Synthesis of *trans*-2,6-Dihydropyran **103**[a]



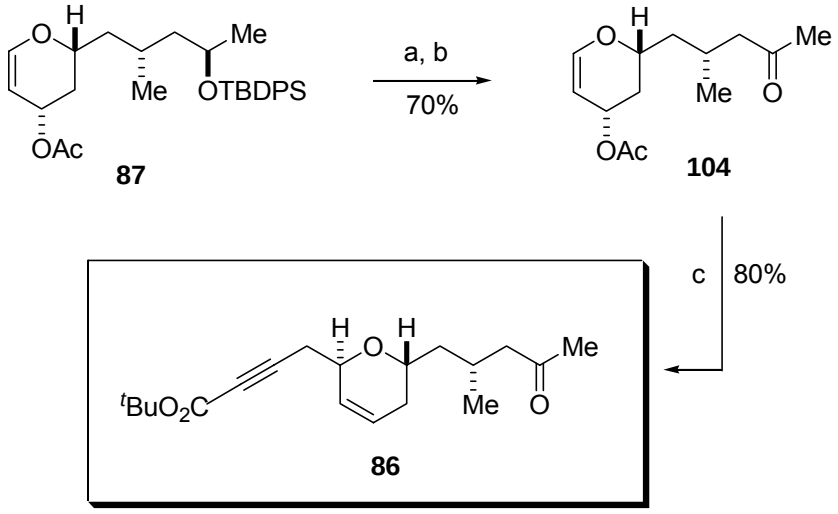
[a]Conditions: a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$. b) Ac_2O, Et_3N, DMAP. c) **41**, Bu_3SnOTf, CH_2Cl_2, –78 °C

Formatting subunit **103** for the fragment uniting aldol reaction required removal of the secondary silyl group at C_{13} followed by oxidation to the corresponding methyl ketone. However, these seemingly trivial functional group manipulations proved to be quite challenging as attempted deprotection of the TBDPS ether under standard fluoride- based reaction conditions (TBAF, THF) resulted in decomposition of the starting material. This problematic decomposition may arise from either the deprotonation of a propargylic hydrogen at C_4 or potential 1,4-addition of fluoride ion into the α,β-unsaturated ester. Both pathways would lead to a reactive allene intermediate which could engage in unwanted side reactions. As a result of this unexpected sensitivity of advanced intermediate **103** to TBAF deprotection conditions, a modification of the present scheme was required.

Given the observed incompatibility of the α, β-unsaturated ester moiety in **103** with fluoride-based deprotection agents, it was decided to unveil the latent methyl ketone moiety at C_{13} prior to introducing the ynoate ester sidechain. Compound **87** was treated with excess TBAF

(5.0 equiv) at 0 °C to successfully effect silyl group deprotection, and the crude reaction product was then oxidized to methyl ketone **104** (80% overall yield from **87)** employing pyridinium dichromate (PDC). Exposing glycal acetate **104** to excess allenylstannane reagent **41** under the optimized conditions (Bu_3SnOTf, –78 °C) resulted in the efficient installation of the C_1–C_4 sidearm in one step (80%), thus completing the synthesis of the lower C_1–C_{14} dihydropyran subunit **86** (Scheme 14).

Scheme 14. Completion of the C_1–C_{14} Dihydropyran Fragment **86**[a]



[a]Conditions: (a) TBAF, THF. (b) PDC, CH_2Cl_2. (c) **41,** Bu_3SnOTf, CH_2Cl_2, –78 °C

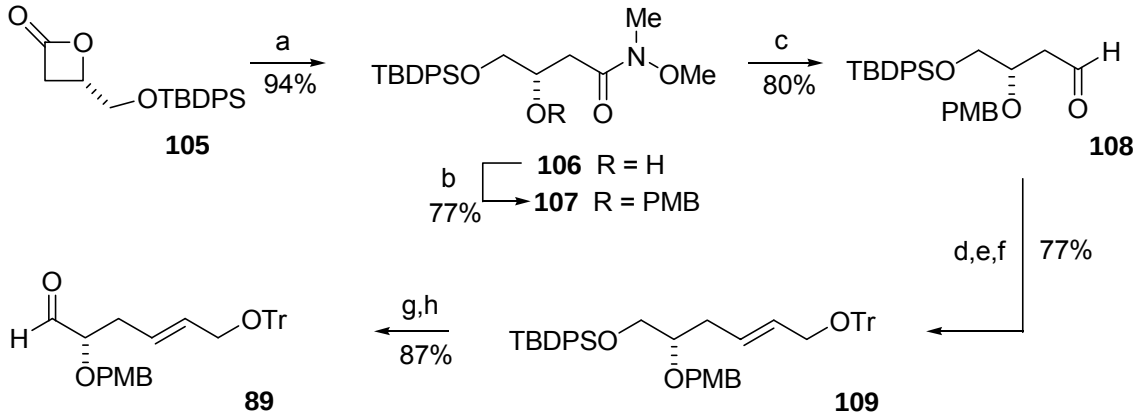
1.8 SYNTHESIS OF THE C_{15}–C_{20} SUBUNIT[46]

As illustrated in Scheme 15, construction of the C_{15}–C_{20} α-alkoxyaldehyde subunit **89** again relied on the enantiomerically enriched β-lactone products of asymmetric AAC technology.

[46] The synthetic work described in this section was performed by Dr. Wing S. Cheung. and Dr. Mark A. Hilfiker, University of Pittsburgh.

Lactone **105** was prepared from aldehyde in 92% yield under the usual conditions (AcBr, $^{i}Pr_2NEt$, 10 mol% Catalyst ***ent*-36**, CH_2Cl_2, –50 °C) efficiently setting the C_{19} hydroxyl-bearing stereocenter with an enantiomeric excess of 92% as determined by chiral HPLC analysis. Ring opening of **105** with *N*, *O*-dimethylhydroxylamine and dimethylaluminum chloride[34] to the corresponding Weinreb amide **106** followed by protection of the resulting secondary alcohol with *p*-methoxybenzyltrichloroacetimidate and triflic acid (TfOH) at 0 °C afforded amide **107** in 77% yield from lactone **105**. Amide to aldehyde interconversion with DIBAL-H provided aldehyde **108** (80%) which was then subjected to the three step sequence of Wittig olefination, DIBAL-H reduction, and trityl protection to furnish the protected triol **109** in 60% yield. Deprotection of the *tert*-butyldiphenylsilyl ether (TBAF, THF) followed by alcohol oxidation with Dess-Martin periodinane then provided the α-alkoxyaldehyde subunit **89** in 87% overall yield from the fully protected triol **109**.

Scheme 15. Synthesis of the C_{15}–C_{20} Subunit **89**[a]

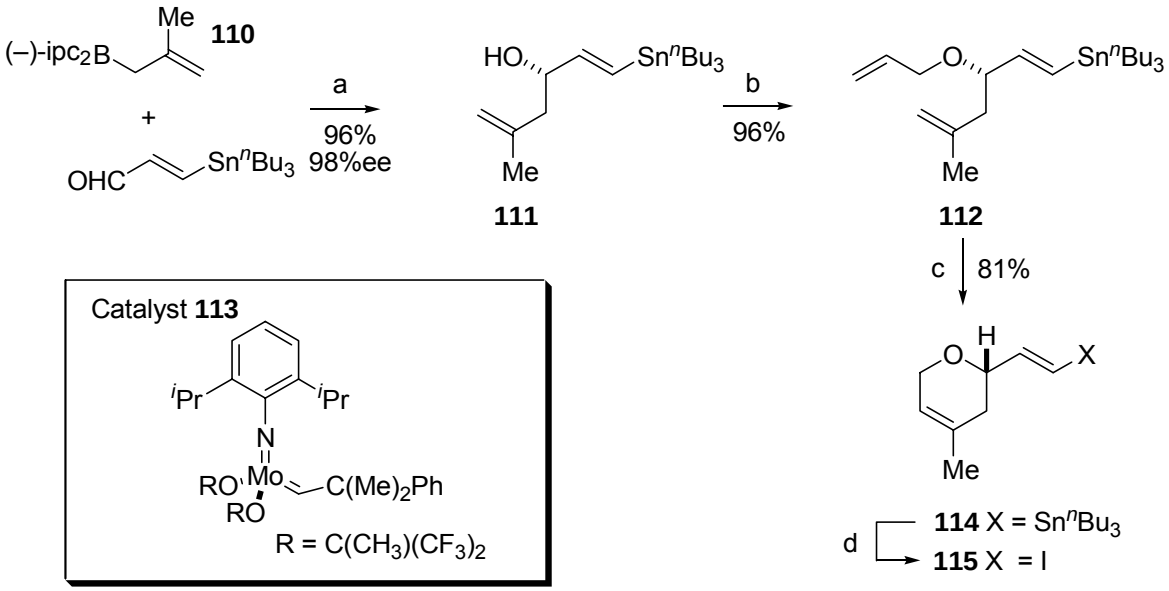


[a]Conditions: (a) Me_2AlCl, (MeO)MeNH·HCl, CH_2Cl_2. b) $PMBOC(=NH)CCl_3$, TfOH, Et_2O, rt. (c) DIBAL-H, THF, –78 °C. (d) (e) DIBAL-H, THF, –78 °C. (f) (g) TBAF, THF. (h) Dess-Martin periodinane, CH_2Cl_2, rt.

1.9 SYNTHESIS OF THE C_{21}–C_{28} DIHYDROPYRAN SIDECHAIN[47]

Having arrived at the α-alkoxyaldehyde portion of the upper synthon **85**, an efficient synthetic route to the corresponding dihydropyran coupling partner **88** was required. The synthesis of the requisite C_{21}–C_{28} dihydropyran subunit **88**, depicted in Scheme 16, was initiated by an asymmetric Brown allylation[48] of β-tributylstannyl acrolein with (–)-diisopinocampheylallylborane **110** to afford the chiral homoallylic alcohol **111** in high yield with excellent levels of enantioselectivity (98% ee). Etherification of alcohol **111** provided triene **112** which was then exposed to 14 mol% of Schrock's Mo(VI)-based ring closing metathesis catalyst **113** to effect dihydropyran ring formation.[49] Vinyl iodide **115** was then obtained upon treatment of stannane **114** with *N*-iodosuccinimide (NIS) at –20 °C.

Scheme 16. Synthesis of the C_{21}–C_{28} Dihydropyran Sidechain **88**[a]



[a]Conditions: (a) **110**, CH_2Cl_2. (b) KHMDS, CH_2CHCH_2Br, THF. (c) Catalyst **113** (14 mol%), $PhCH_3$. (d) NIS, THF.

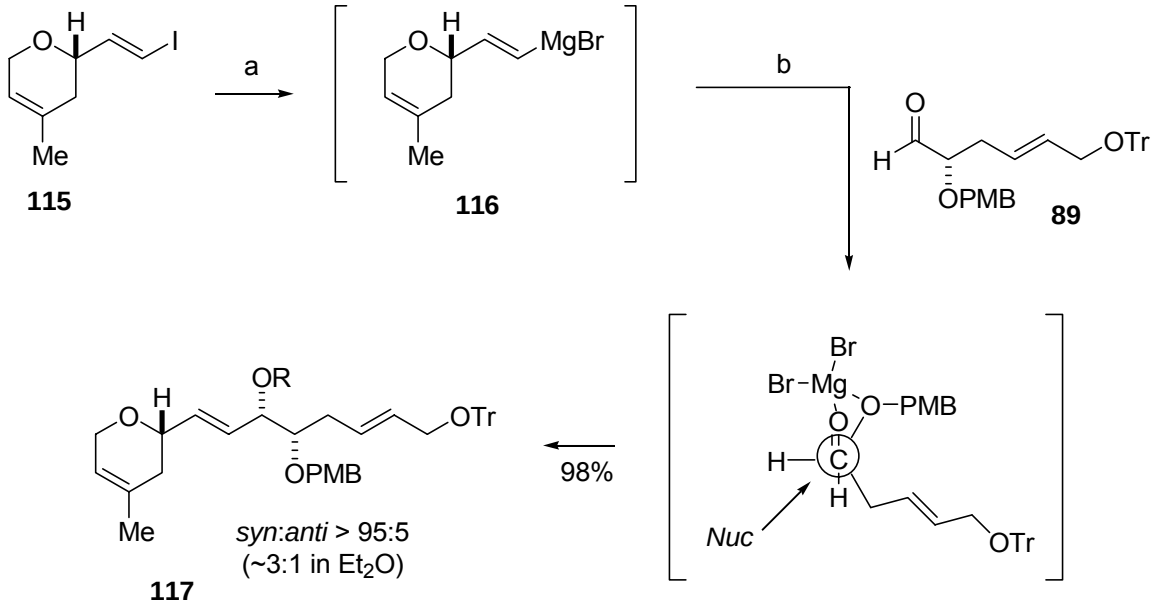
[47] All synthetic work described in this section was performed by Dr. Wing Cheung.
[48] Brown, H. C.; Jadhav, P. K.; Perumal, P. T. J. *Tetrahedron Lett.* **1984**, *25*, 5111.
[49] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

1.10 COMPLETION OF THE C_{15}–C_{28} FRAGMENT

The assembly of the intact C_{15}–C_{28} fragment of (–)-laulimalide was predicated on the diastereoselective addition of a vinyl metal species derived from dihydropyran **115** into α-alkoxyaldehyde **89**. It was postulated that metal chelation between the carbonyl oxygen and the neighboring *p*-methoxybenzyl substituent would serve to create an organized transition state capable of governing the formation of the desired C_{19}–C_{20} *syn* diol relationship. Preliminary experimentation revealed that the necessary Cram-chelate stereocontrol could be realized by employing vinyl Grignard **116** (Scheme 17). Lithiation of iodide **115** at –78 °C with ^{t}BuLi (2 equiv) followed by transmetallation with an ethereal solution of $MgBr_2$ afforded the necessary vinyl Grignard species **116** which was then treated with α-alkoxyaldehyde **89**. Ensuing nucleophilic addition resulted in the formation of the C_{15}–C_{28} fragment **117** in 89% yield as a 3:1 mixture of *syn*:*anti* diastereomers favoring the desired *syn*-diol arrangement.[50] Despite our arrival at the requisite C_{19}–C_{20} *syn*-stereochemical relationship, the low levels of diastereoselectivity obtained in the vinyl Grignard addition prompted further optimization in order to be incorporated into the present total synthesis.

[50] The (19*R*,20*S*) configurational assignment of **117** was confirmed by NOE analysis of the corresponding dimethyl acetal.

Scheme 17. Diastereoselective Vinyl Grignard Addition to α-Alkoxyaldehyde **89**[a]



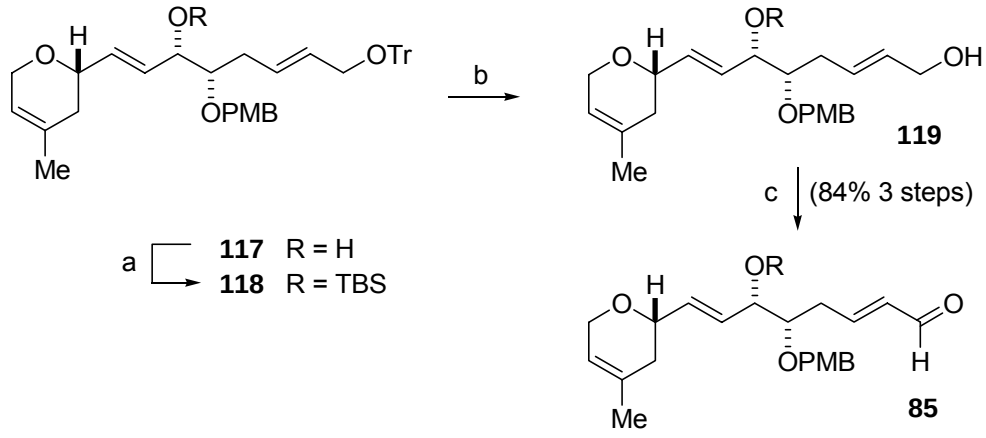
[a]Conditions: (a) i. ^{t}BuLi, THF, –78 °C. ii. $MgBr_2$. (b) **89**, CH_2Cl_2.

Solvent polarity was believed to play a major role in the modest diastereoselectivity observed in the previously described vinyl Grignard addition. It has been well documented that the use of Lewis basic solvents such as Et_2O and THF in diastereoselective Grignard-aldehyde addition reactions disrupts chelate organization by coordination to the metal center leading, ultimately, to lower diastereoselectivity. To avoid this undesired solvent effect, the diethyl ether was removed under reduced pressure at –78 °C after formation of the reactive Grignard species and was replaced with the noncoordinating solvent CH_2Cl_2.[51,52] Treatment of the CH_2Cl_2 solution of vinyl Grignard **116** with α-alkoxyaldehyde **89** then resulted in nucleophilic addition along the chelate-Cram trajectory depicted in Scheme 17 to afford exclusively the requisite C_{19}–C_{20} *syn*-diol diastereomer **117** in 98 % yield.

[51] Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.
[52] Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

Completion of the upper C_{15}–C_{28} synthon of laulimalide required only a few routine synthetic manipulations (Scheme 18). Silylation of the newly formed C_{20} hydroxyl group with TBSCl and imidazole furnished the fully protected upper synthon **118** which was subsequently exposed to formic acid in nitromethane to effect trityl ether deprotection. Treatment of allylic alcohol **119** with Dess-Martin periodinane then provided the completed α,β-unsaturated aldehyde fragment **85** in 84% overall yield from alcohol **117**.

Scheme 18. Completion of the C_{15}–C_{28} Fragment **85**[a]



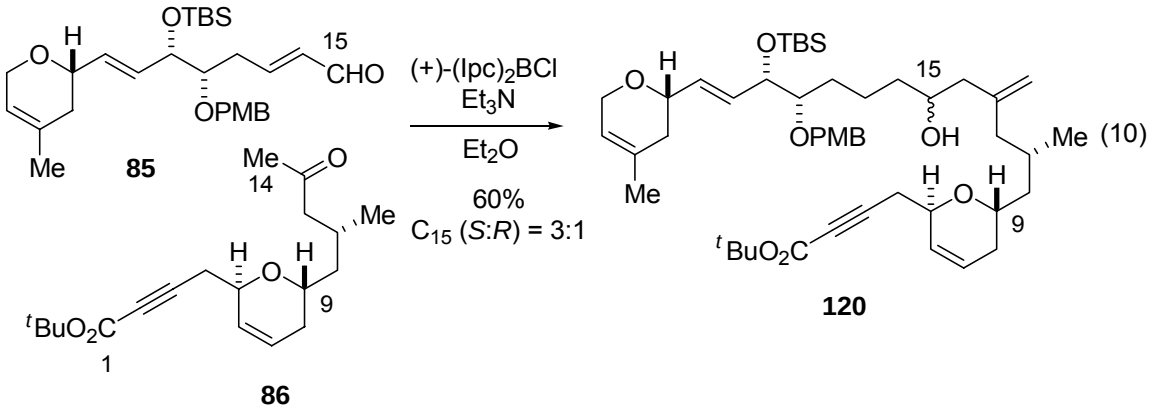
(a) TBSCl, imidazole CH_2Cl_2. (b) HCOOH, $MeNO_2$. (c) Dess-Martin periodinane, CH_2Cl_2.

1.11 FRAGMENT UNION AND MACROLIDE FORMATION

1.11.1 Asymmetric Aldol Reaction

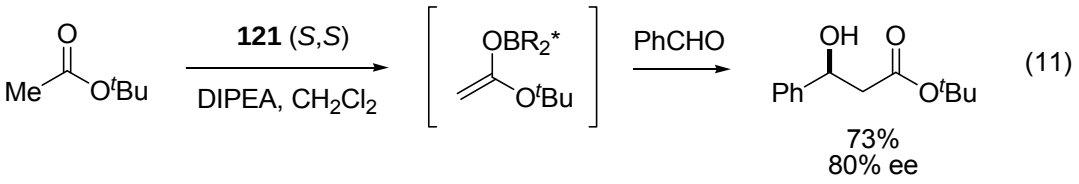
With sufficient quantities of both major fragments of laulimalide in hand, steps toward the union of the two halves were investigated. Initial attempts at achieving the desired C_{14}–C_{15} bond construction between aldehyde fragment **85** and methyl ketone **86** employed a chiral boron aldol

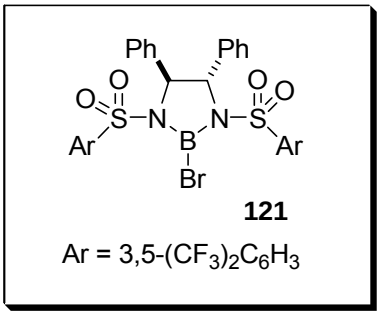
protocol described by Paterson (Eq 10).[53] Generation of the (+)-diisopinocampheyl boron enolate of methyl ketone **86** followed by treatment with aldehyde **85** at –78 °C afforded the desired aldol adduct **120** in 60% yield albeit as a 3:1 mixture of C_{15} (*S*:*R*) diastereomers.



The poor levels of diastereoselectivity obtained in the previously described aldol reaction forced us to evaluate other methods for achieving acceptable levels of stereocontrol.[54] We recognized an attractive alternative to (+)-DIPCl in Corey's chiral diazaborolidine **121**. In 1993, Corey described the aldol reaction of the chiral boron enolate derived from bromoborane **121** and *tert*-butyl acetate with benzaldehyde (Eq 11) that successfully delivered the desired β-hydroxyester product in 73% yield and 80% ee.[55] However, application of bromoborane reagent **121** to the construction of the C_{14}–C_{15} bond in laulimalide, did not increase diastereoselectivity from what was previously observed (3:1).

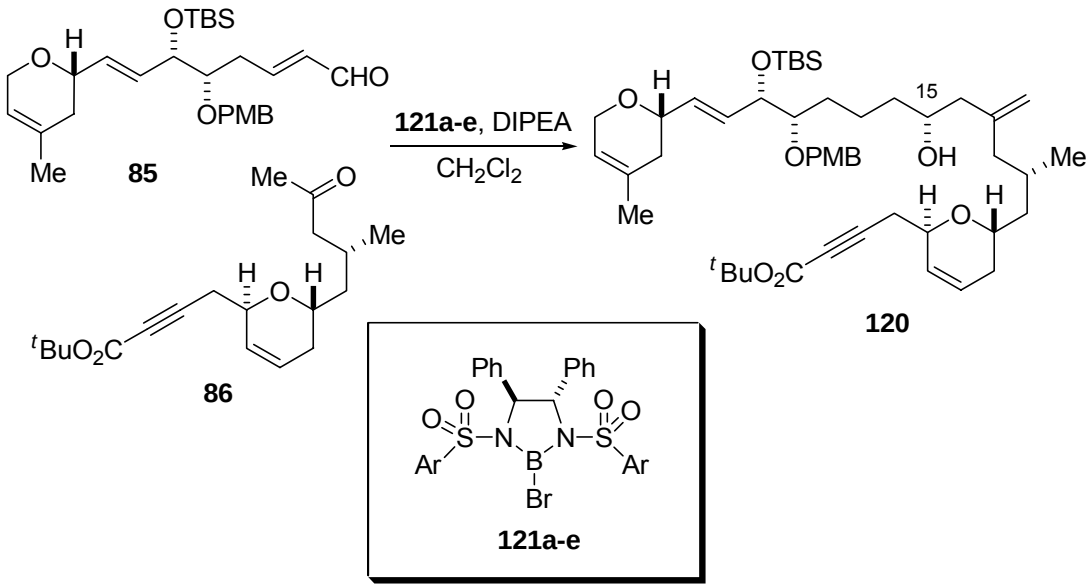
[53] Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.
[54] Further opitmization of the asymmetric aldol reaction described in this section was performed by Dr. Wing S. Cheung (Postdocoral Researcher, Department of Chemistry, University of Pittsburgh).
[55] Corey, E. J.; Lee, D.-H. *Tetrahedron Lett.* **1993**, *34*, 1737.

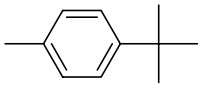
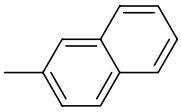
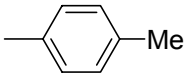
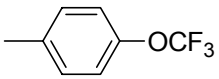
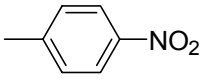




Further attempts at optimization of diastereoselectivity were made by modifying the structure of the Corey diazaborolidine reagent. Reacting 1,2-diphenylethylenediamine with a variety of sulfonyl chlorides provided a range of bis-sulfonamide ligands that were evaluated in the asymmetric aldol reaction to stereoselectively unite fragments **85** and **86**. The results of this survey of modified Corey reagents are summarized in Table 3. More sterically bulky sulfonamide groups (entries a and b) produced aldol adducts with higher levels of diastereoselection (~5:1) than previously observed. Examining electron donating *p*-tolyl sulfonyl substituents on the diamine backbone (entry c) led to only marginally increased diastereoselectivity. The use of electron withdrawing substituents, however, proved to be much more effective. While *p*-trifluoromethoxyphenyl groups resulted in commensurate levels of selectivity as previously observed, the bis-*p*-nitrophenyl-substituted diazaborolidine reagent **121e** afforded the desired aldol adduct as an 8.7:1 (*S*):(*R*) mixture of diastereomers. Scale-up and subsequent protection of the resulting secondary alcohol as the corresponding *tert*-butyldimethylsilyl ether furnished aldol adduct **122** in 89% yield with a synthetically useful diastereomer ratio (C_{15} (*S*):(*R*) = 9:1).

Table 3. Asymmetric Aldol Reaction Employing Modified Corey Diazaborolidines

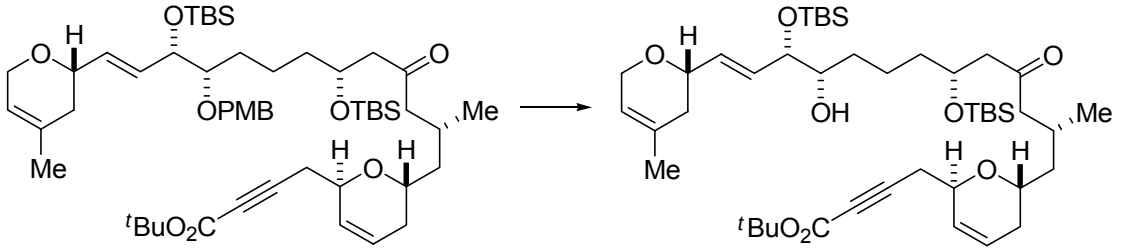


entry	Ar	Diastereoselectivity C_{15} (*S*):(*R*)
a		4.8 : 1
b		5.2 : 1
c		5.7 : 1
d		6.4 : 1
e		9.0 : 1

1.11.2 Seco Acid Formation and Macrolactonization

Once suitable conditions were established for uniting major fragments **85** and **86** with good levels of diastereoselectivity, we turned our attention to the critical macrocylcization event. According to our planned retrosynthesis, ring closure to form the 18-membered macrolide would occur via the Yamaguchi macrolactonization of propargylic seco acid **123** in order to prevent the undesired base-mediated scrambling of the C_2–C_3 (*Z*)-olefin observed previously by Paterson.[10a] Arriving at **123**, however, required the sequential deprotection of the *p*-methoxybenzyl (PMB) ether and the *tert*-butyl ester in the fully protected aldol adduct **122**. Initial attempts aimed at removing the C_{19} PMB ether focused on traditional oxidative deprotection with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Treating **122** with 1.5 equiv of DDQ in a CH_2Cl_2/H_2O mixture resulted in the cleavage of the desired PMB protecting group; however, the yield of alcohol **124** was not always reproducible (70-83%). The varied isolated yields of **124** were attributed to the strongly acidic dihydroquinone by-product of the deprotection reaction. Under the reaction conditions, the acidic nature of the dihydroquinone may also to serve to deprotect the secondary TBS groups present in **124** resulting in an extremely polar triol species. Conducting the deprotection reaction under neutral conditions was viewed as a means of avoiding the unwanted cleavage of the silyl ether linkages. Subjecting *p*-methoxybenzyl ether **122** to DDQ in the presence of pH 7 phosphate buffer then provided alcohol **124** in quantitative yield (Scheme 19).

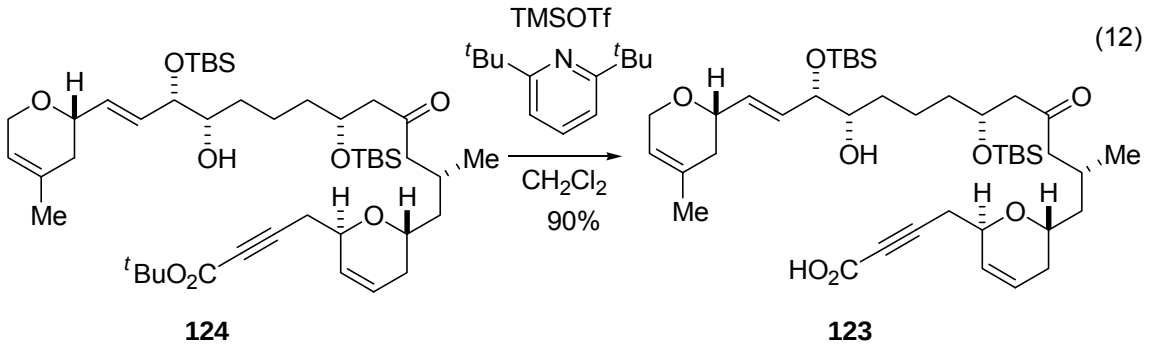
Scheme 19. Deprotection of C_{19} *p*-Methoxybenzyl Ether **122**[a]



122 **124**

Conditions	% Yield **124**
DDQ, CH_2Cl_2/H_2O	70-83
DDQ, CH_2Cl_2, pH 7 buffer	100

Removal of the *tert*-butyl ester was next accomplished by adapting the previously described protocol in Scheme 7. Ester **124** was treated with 2, 6-di-*tert*-butylpyridine and TMSOTf at –50 ºC followed by a pH 5 buffer solution at 0 ºC to effect silyl ester deprotection to obtain seco acid **123** in 90% yield after column chromatography (Eq 12). With the requisite seco acid in hand, cyclization conditions for the construction of the 18-membered macrolactone could be explored.



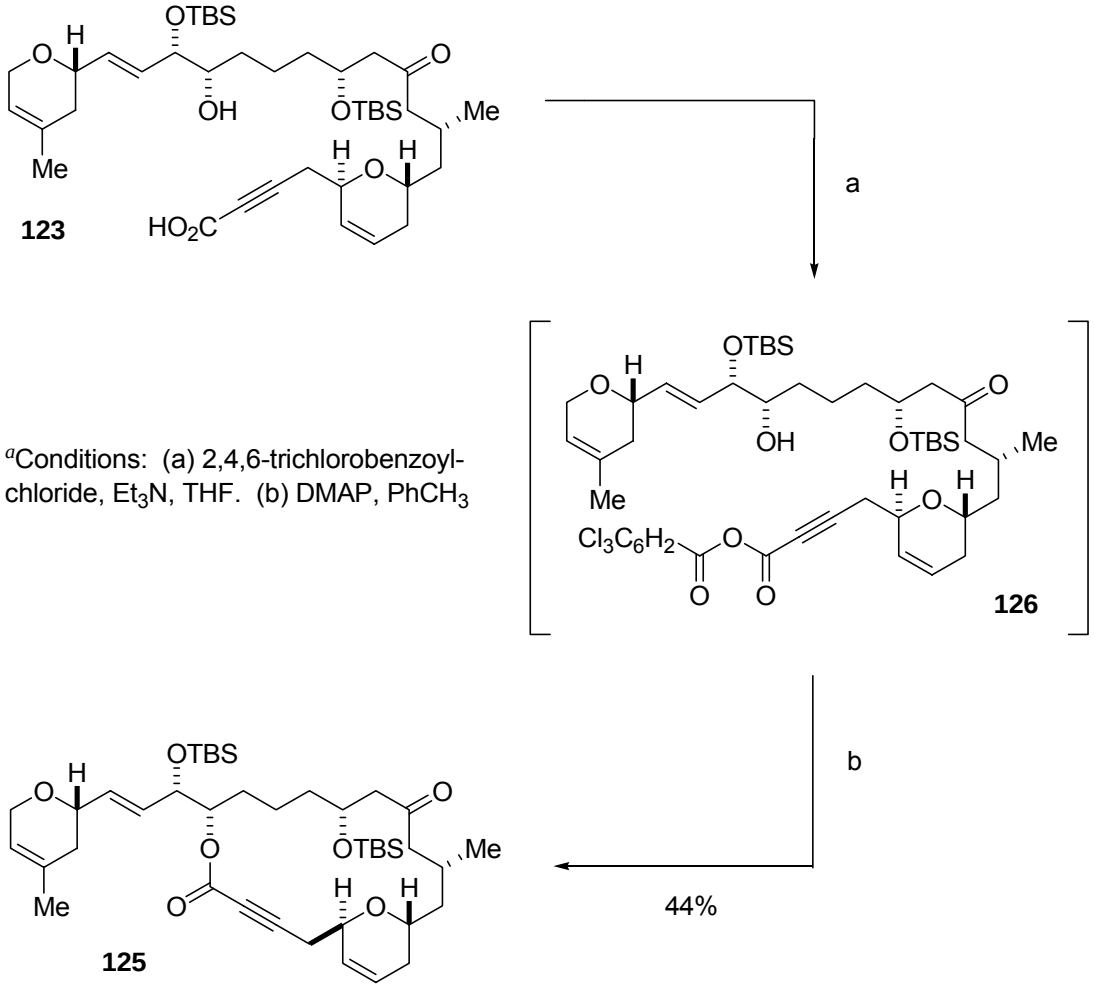
(12)

124 **123**

Pursuit of macrolactone **125** began by employing traditional Yamaguchi macrolactonization conditions (Scheme 20). Seco acid **123** was first treated with Et_3N and 2,4,6-trichlorobenzoyl chloride in THF to generate the corresponding mixed anhydride **126**. Following the removal of solvent, the crude reaction mixture was diluted with toluene (0.0006 M) to attain the "high-dilution" conditions necessary to avoid intermolecular lactonization. Syringe pump addition of DMAP over the course of 2 h to a solution of mixed anhydride **126** at ambient temperature resulted in acyl-pyridinium formation and subsequent lactonization to afford the desired macrolactone **125** in 44 % yield. Although preparation of the highly functionalized 18-membered macrolactone of (–)-laulimalide with the commonly used Yamaguchi protocol was successful, a more efficient macrolactonization method was still desired. Additional reagent systems were investigated to achieve the desired propargylic acid macrolactonization. Carbodiimide coupling reagents DCC[56] and EDC[57] as well diphenyl chlorophosphate,[58] and *p*-nitrobenzoyl anhydride with $Sc(OTf)_3$[59] were selected for activating the carboxylic acid moiety, unfortunately, the high reaction temperatures required by these macrolactonization protocols resulted in decomposition of the seco acid starting material.

[56] Boden, E. P.; Keck, G. E. *J. Org. Chem*. **1985**, *50*, 2394.
[57] Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberan, T.; Doller, D.; Wong, J.; Leone, D. McPhail, A. T. *J. Org. Chem*. **1999**, *64*, 1932.
[58] Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem*. **1982**, *47*, 1612.
[59] Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem*. **1996**, *61*, 4560.

Scheme 20. Yamaguchi Macrolactonization of Seco Acid **123**[a]

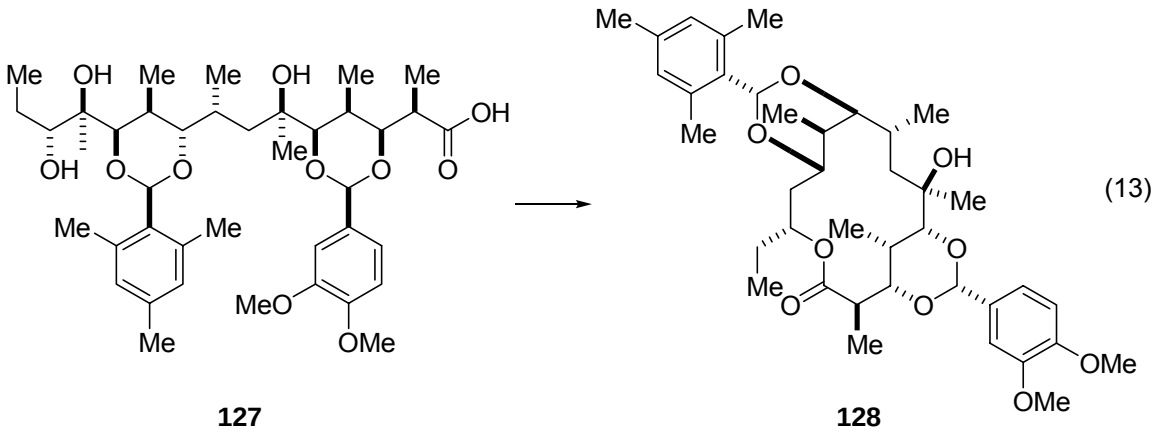


[a]Conditions: (a) 2,4,6-trichlorobenzoyl-chloride, Et_3N, THF. (b) DMAP, $PhCH_3$

An interesting and highly efficient Yamaguchi macrolactonization was reported in 1990 by Yonemitsu in the total synthesis of erythronolide A (Eq 13).[60] The 14-membered erythronolide macrocycle was formed by treating a concentrated benzene solution (0.01 M) of the mixed anhydride of seco acid **127** with DMAP at ambient temperature. The ensuing macrolactonization proceeded rapidly (1 h) to afford lactone **128** in near quantitative yield. Surprisingly, this reaction was successful even without the high dilution conditions which are

[60] Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahdron Lett.* **1990**, *31*, 6367.

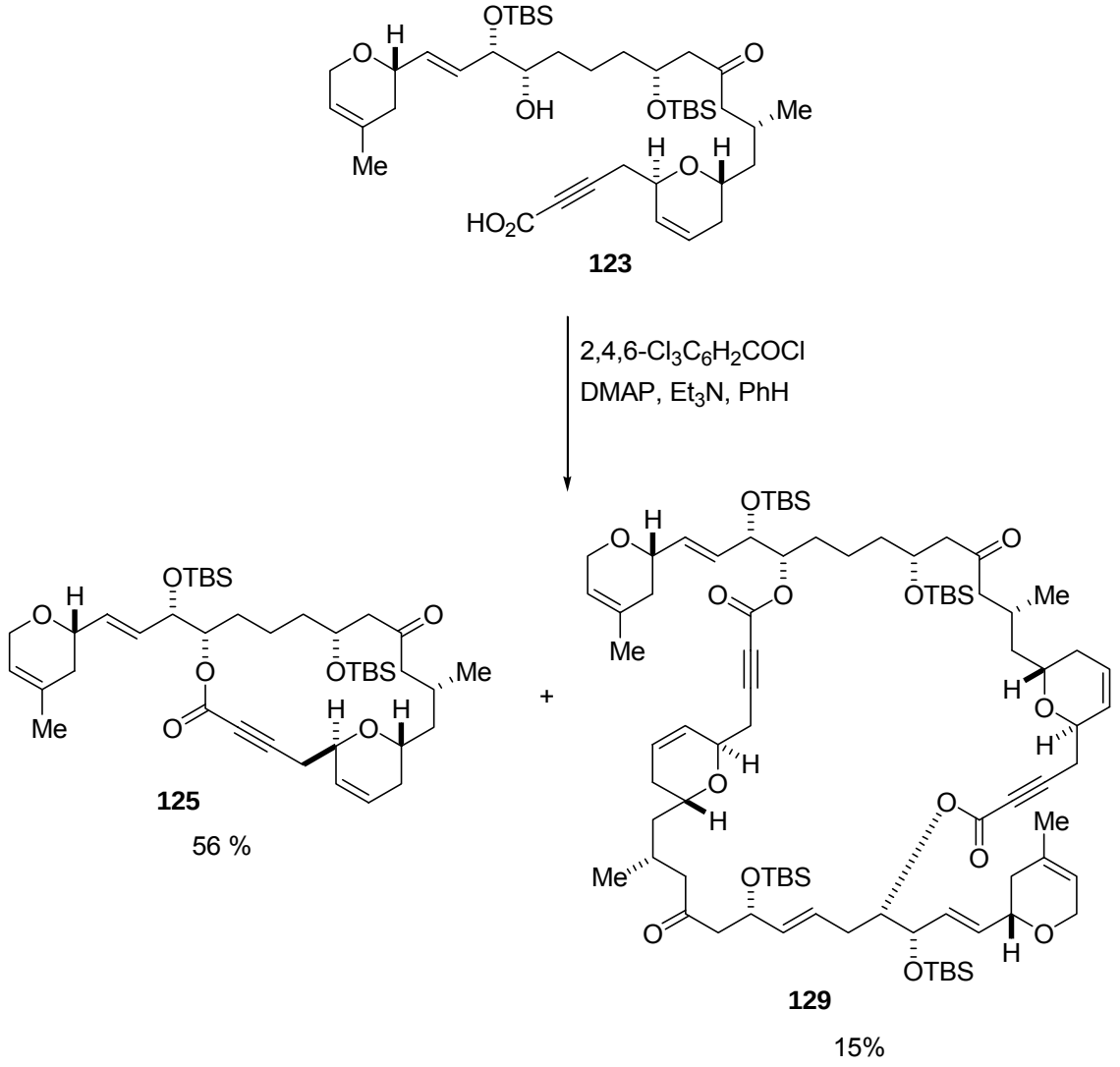
generally required in the conventional Yamaguchi macrolactonization. The success of this method has been attributed to the favorable conformation adopted by seco acid **127**, which greatly enhances its propensity for cyclization.



127 **128** (13)

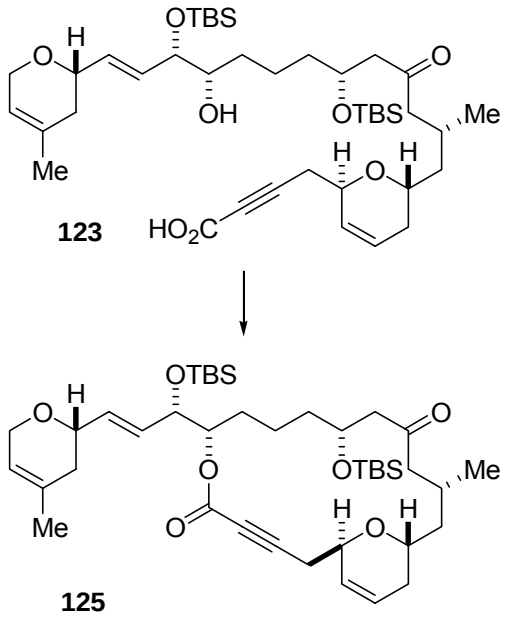
Given the success enjoyed by Yonemitsu in the previously described Yamaguchi macrocyclization, we elected to incorporate similar lactonization conditions into our own synthetic strategy (Scheme 21). Treating a benzene solution of seco acid **123**, DMAP, and Et_3N at ambient temperature with 2,4,6-trichlorobenzoyl chloride resulted in the complete consumption of starting material and the formation of two products as observed by TLC analysis. The major product, isolated in 56% yield, was determined to be the desired macrocycle **125** by ^1H NMR and high resolution ESI-MS analysis. The minor component of the reaction mixture was identified as the dimer **129** based on similar spectroscopic techniques and was obtained in 15% yield. While this result would suggest that seco acid **123** does not adopt an optimal conformation for macrolactonization, it was believed that the formation of dimer could be prevented by the commonly employed high dilution technique for traditional Yamaguchi macrolactonization.

Scheme 21. Synthesis of **125** via Yonemitsu Modified Yamaguchi Macrolactonization



To test this hypothesis, a series of macrolactonization reactions were performed at varying concentrations and the results are presented in Table 8. Despite our attempts at lowering reaction concentration, we could not inhibit dimer formation. Even at 0.001 M, the concentration typically employed in conventional Yamaguchi macrolactonizations, the undesired dimeric product **129** was still observed.

Table 4. Concentration Studies in Yamaguchi Macrolactonization



Concentration (M)	Result
0.007	**125** + dimer
0.004	**125** + dimer
0.001	**125** + dimer

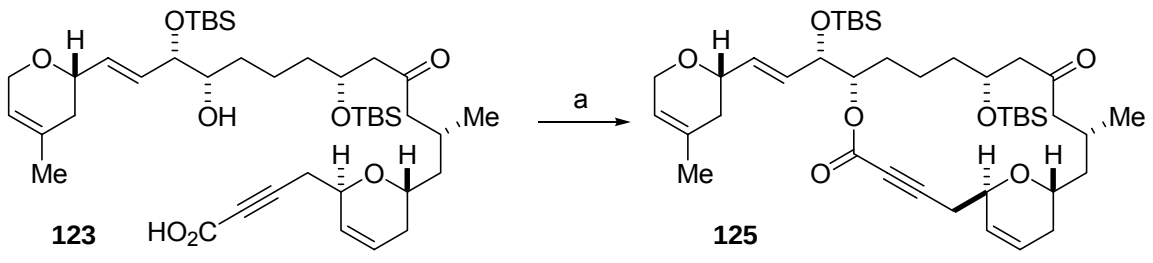
Our inability to suppress the formation of dimer **129** led to the examination of several other variables.[61] In our previous attempts at macrocyclization, the Yamaguchi reagent, 2,4,6-trichlorobenzoyl chloride, was added to a solution of seco acid **123**. Under these reaction conditions, a small amount of the activated acyl pyridinium pecies would be generated in the presence of a relatively high concentration of hydroxy-acid thereby increasing the likelihood of dimer formation. By reversing the order of addition, slow addition of **123** to a large excess of reagents, the effective concentration of seco acid would be minimized and the likelihood for dimer formation should be diminished. In these modified macrolactonization reactions, a benzene suspension containing a large excess of 2,4,6-trichlorobenzoyl chloride (100 equiv), Et_3N (500 equiv), and 4-pyrrolidinopyridine (30 equiv) was slowly treated with seco acid **123** in benzene via syringe pump. Monitoring reaction progress by TLC revealed the complete

[61] These optimization studies were the work of Dr. Wing S. Cheung (Postdocoral Researcher, Department of Chemistry, University of Pittsburgh).

consumption of the starting acid **123** and the formation of three products: the desired macrolactone **125**, the dimer **129**, although to a much lesser extent than previously observed, and a more polar, unidentified product. Although another undesired by-product was formed during the course of the reaction, we were pleased to be able to suppress the formation of dimer **129**.

The final variable to be explored in the optimization of our propargylic acid macrolactonization was reaction temperature. All previous attempts at macrolactonization had been performed at ambient temperature, and determination of any temperature dependence on dimer/by-product formation was pursued. Cyclization reactions were now conducted at 0 ºC in toluene employing the previously described slow addition of seco acid to excess reagents protocol. Gratifyingly, dimer formation was completely eliminated at the lower temperature; however, the unidentified by-product still remained. In an attempt to avoid this polar by-product, the large excess of reagents was dramatically reduced. Treating a 0 ºC toluene suspension of DIPEA (40 equiv), 4-pyrrolidinopyridine (20 equiv), and 2,4,6-trichlorobenzoyl chloride (20 equiv) with seco acid **123** via syringe pump now cleanly afforded the desired 18-membered macrolactone **125** as the only observable product by TLC analysis. The optimized Yamaguchi macrolactonization conditions provided macrolide **125** in 93% isolated yield (Scheme 22).

Scheme 22. Optimized Conditions for Modified Yamaguchi Macrolactonization[a]

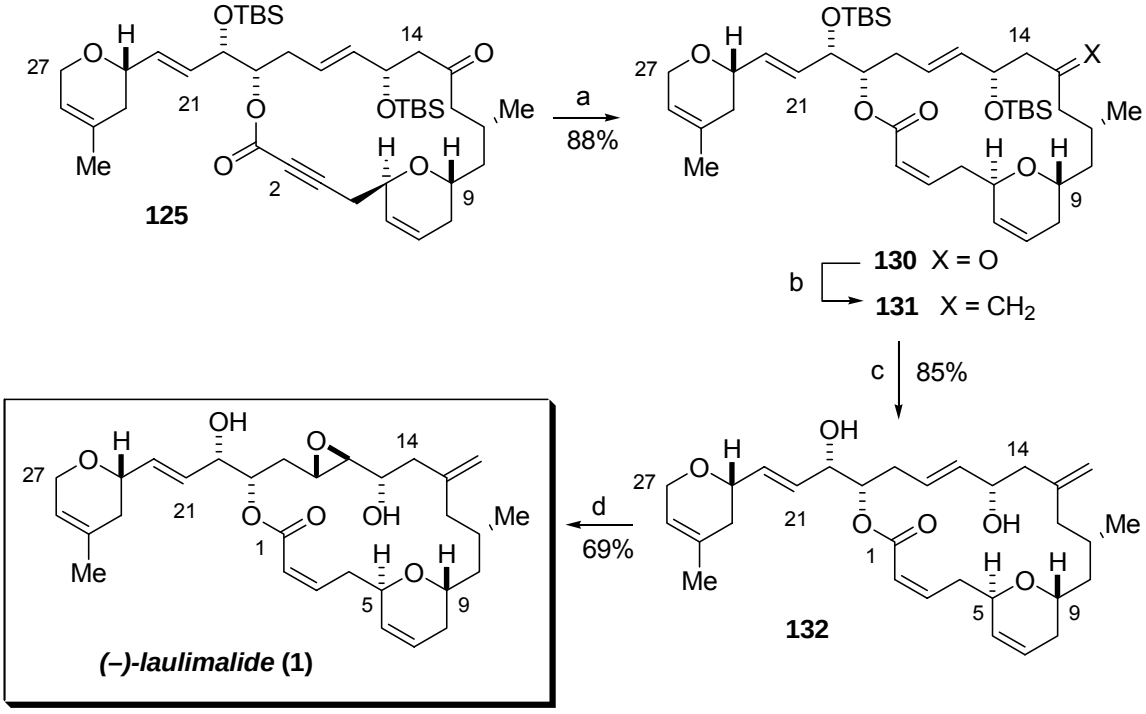


[a]Conditions: (a) 2,4,6-trichlorobenzoyl chloride (20 equiv), 4-pyrrolidinopyridine (20 equiv), DIPEA (40 equiv), $PhCH_3$

1.12 COMPLETION OF THE TOTAL SYNTHESIS OF (–)-LAULIMALIDE

Having prepared the highly functionalized macrolide **125**, only a few additional functional group manipulations were necessary to complete the total synthesis of (–)-laulimalide (Scheme 23). Partial hydrogenation of the C_2–C_3 alkyne under Lindlar conditions (H_2, $BaSO_4$) successfully unveiled the requisite (*Z*)-enoate ester **130** as a single regioisomer in 88% yield. Arriving at alkene **130**, we had intercepted an intermediate previously described in Paterson's laulimalide synthesis, and thus an equivalent approach was pursued. Takai methylenation of the C_{13} ketone residue efficiently installed the desired exocyclic olefin (**131**), and subsequent silyl deprotection at 0 ºC with HF•py provided desepoxylaulimalide (**132**) in good yield. The completion of our total synthesis of **1** was finally realized with a regio- and stereoselective Sharpless asymmetric epoxidation of the C_{16}–C_{17} olefin employing (+)-diisopropyltartrate to afford synthetic (–)-laulimalide (**1**) in 69% isolated yield. All physical and spectroscopic data exhibited by **1** ($[\alpha]_D$ = –198 (*c* 0.1, $CHCl_3$), ^1H, ^{13}C, IR, HRMS) were in agreement with that previously reported in the literature by Ghosh, Paterson, and Mulzer.[11]

Scheme 23. Completion of the Total Synthesis of (–)-Laulimalide **(1)**[a]



[a]Conditions: (a) H_2, $BaSO_4$, EtOAc/1-hexene. (b) CH_2I_2, Zn, PbI_2, $TiCl_4$, THF. (c) HF•py, THF (d) 20 mol% $Ti(O^iPr)_4$, 20 mol% (+)-DIPT, ^{t}BuOOH, CH_2Cl_2, –20 °C.

1.13 CONCLUSIONS

Catalytic, asymmetric acyl halide–aldehyde cyclocondensation methodology has been successfully applied to the total synthesis of the potent microtubule-stabilizing marine natural product (–)-laulimalide. This achievement represents the first example of the application of AAC-based reaction technology to complex molecule synthesis. The route encompassed 23 steps along the longest linear sequence and afforded **1** in 5.1% overall yield from the inexpensive and readily available starting material acetaldehyde. Asymmetric AAC reactions were instrumental in directly establishing the C_9, C_{11}, and C_{19} stereogenic centers in (–)-laulimalide. Highlights of the synthesis include a diastereoselective aldol reaction that united major fragments **85** and **86** and a remarkably high-yielding modified Yamaguchi macrolactonization. Additionally, novel methodology was developed to effect both the one-pot interconversion of β-lactones to dihydropyranones and the Lewis acid activated allenylstannane addition to glycal acetates which was employed to stereoselectively introduce the C_1–C_4 sidearm of laulimalide in one step. A highly diastereoselective vinyl Grignard addition to α-alkoxyaldehyde **89** was also achieved which effectively generated the C_{19},C_{20}-*syn*-diol arrangement.

1.14 EXPERIMENTAL SECTION

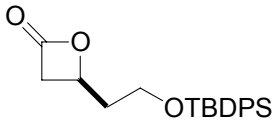
General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100mL, solvent) with units of degree•g•cm^{-3}. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker DPX 301 and DPX 302 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (C**H**Cl$_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on Bruker DPX 301 and DPX 302 spectrometers (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[62] Analytical gas liquid chromatography (GLC) was performed on a Hewlet-Packard 5890 Series II gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Chiraldex™ G-TA column (20 m x 0.25 mm) (Advanced Separation Technologies Inc.). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using either a Daicel Chiralcel™ OD-H column (250 × 4.6 mm)

[62] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

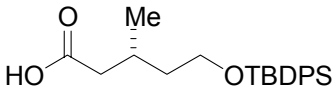
or a Daicel Chiralpak™ AS-H column (250 × 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl. Diethyl ether (Et_2O), toluene and benzene were distilled from sodium benzophone ketyl. Dichloromethane (CH_2Cl_2), dimethylsulfide (DMS), *N*,*N*-diisopropylethylamine (DIPEA), and triethylamine (Et_3N) were distilled from CaH_2 under N_2.

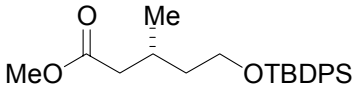


(4*S*)-(*tert*-Butyldiphenylsilyloxyethyl)oxetan-2-one (46): To a –50 °C solution of 0.745 g of aluminum triamine catalyst **36** (1.28 mmol) in 60 mL of CH_2Cl_2 was added 3.8 mL of diisopropylethylamine (21.8 mmol) followed by 1.80 mL of acetyl bromide (24.3 mmol). The resulting light yellow solution was maintained at –50 °C for 5-10 min, then treated with 4.0 g of aldehyde **45** (12.8 mmol) in 5 mL of CH_2Cl_2 slowly dropwise. The reaction was maintained overnight at –50 °C, then poured into 400 mL of cold hexanes. The mixture was filtered through silica gel, and the silica was washed with 30% EtOAc/hexanes. The combined filtrate was concentrated to afford 4.4 g (97%, crude) of lactone **46** as a white crystalline solid (88% ee). Recrystallization from hexanes/CH_2Cl_2 mixtures provided the title compound in 98% ee: $[\alpha]_D$ = –14.3 (*c* 4.0, $CHCl_3$); IR (thin film) 3069, 3046, 2958, 2931, 2851, 2883, 1830, 1735, 1426, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.9 Hz, 4H), 7.48–7.20 (m, 6H), 4.71 (m, 1H), 4.76–4.60 (m, 2H), 3.74 (dd, *J* = 4.5, 11.5 Hz, 1H), 3.45 (dd, *J* = 5.9, 16.5 Hz, 1H), 2.12–1.85 (m, 2H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 135.7, 133.4, 130.1, 128.0, 69.3, 59.9, 43.4, 37.4, 27.0, 19.3; EI-MS *m/z* 297 (M^+-^{t}Bu), 255, 241,

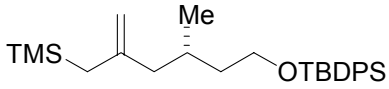
225, 211, 199, 183, 117, 105; HRMS calcd for $C_{21}H_{26}O_3Si$: 297.0947, found 297.0947; HPLC (95:5 hexanes/^{i}PrOH, 1.0 mL/min) T_r (min) = 8.13 (*S*), 9.26 (*R*).



(3*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylpentanoic acid (47): To a –50 °C solution of 1.82 g of CuBr (12.7 mmol) in 120 mL of THF and 13 mL of dimethylsulfide was added 8.5 mL of a 3 M ethereal solution of methylmagnesium bromide (25.4 mmol) slowly dropwise via syringe. The resulting heterogeneous mixture was stirred at –50 °C for 30 min then warmed to –30 °C for 30 min. The reaction was then cooled to –50 °C and 3.0 g of lactone **46** (8.47 mmol) in 10 mL of THF was added via cannula. The resulting mixture was maintained at –50 °C for 45 min, then 1.65 mL of TMSCl (12.7 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. Saturated aqueous NH_4Cl (300 mL) and 1 M HCl (100 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organics were washed with saturated aqueous NH_4Cl and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford 2.5 g (80%) of **47** as a pale yellow viscous oil: $[\alpha]_D$ = +3.7 (*c* 2.7, $CHCl_3$); IR (thin film) 3071, 2959, 2931, 2858, 1708, 1428, 1112, 909, 735, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 1.6, 7.5 Hz, 4H), 7.47–7.28 (m, 6H), 3.74 (t, *J* = 6.2 Hz, 2H), 2.41 (dd, *J* = 4.1, 8.1 Hz, 1H), 2.28–2.10 (m, 2H), 1.63 (m, 1H), 1.50 (m, 1H), 1.05 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 135.8, 134.0, 129.8, 127.9, 61.9, 41.7, 39.2, 27.2, 27.0, 19.9, 19.4; HRMS calcd for $C_{22}H_{30}O_3Si$: 353.1937, found 353.1934.

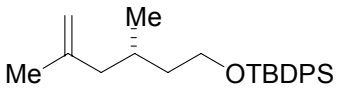


(3*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylpentanoic acid methyl ester (48): To a solution of 4.88 g of carboxylic acid **47** (13.2 mmols) in 80 mL of CH_2Cl_2 was added 0.165 g of DMAP (1.35 mmol), 3.27 g of dicyclohexylcarbodiimide (15.8 mmols), and 2.7 mL of MeOH (65.4 mmol). The reaction was maintained at ambient temperature for 3 h, then diluted with pentane and filtered through Celite. The filtrate was then concentrated and the crude material was purified by silica gel chromatography (5% EtOAc/hexanes) to provide 4.3 g of methyl ester **48** (86%) as a clear, colorless oil: $[\alpha]_D$ = +4.7 (*c* 2.3, $CHCl_3$); IR (thin film) 3069, 3050, 2958, 2931, 2855, 1739, 1426, 1386, 1358, 1295, 1259, 1220, 1168, 1109, 994, 820, 737, 705, 614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 1.3, 7.0 Hz, 4H), 7.45-7.37 (m, 6H), 3.73 (t, *J* = 6.3 Hz, 2H), 3.68 (s, 3H), 2.37 (dd, *J* = 4.7, 8.7 Hz, 1H), 2.23–2.11 (m, 2H), 1.64 (m, 1H), 1.48 (m 1H), 1.08 (s, 9H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 135.7, 134.0, 129.7, 127.8, 61.9, 51.5, 41.7, 39.3, 27.4, 27.0, 19.9, 19.3; EI-MS *m/z* 353 (M^+-OMe), 327 (M^+-^{t}Bu), 213, 197, 183, 135; HRMS calcd for $C_{23}H_{32}O_3Si$: 353.1937, found 353.1937.

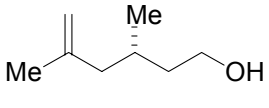


(3*S*)-*tert*-Butyldiphenylsilylmethyl-5-(trimethylsilylmethyl)hex-5-ene ether (49): To a –78 °C suspension of 6.26 g of $CeCl_3$ (25.4 mmol) in 50 mL of dry THF was added 25 mL of a 1.0 M ethereal solution of $TMSCH_2MgCl$ (25.4 mmol). The resulting beige suspension was stirred for 1.5 h at –78 °C whereupon a solution of 1.95 g of methyl ester **48** (5.08 mmol) in 10 mL of THF was added slowly dropwise via cannula. The reaction mixture was maintained at –78 °C for 2 h and then allowed to warm slowly to ambient temperature. The reaction was quenched with 100 mL of 1 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were dried

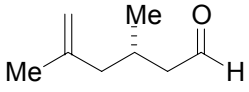
over Na_2SO_4, filtered, and concentrated. The crude residue was then dissolved in 60 mL of CH_2Cl_2 and 10 g of silica gel was added. After stirring at ambient temperature for 1.5 h, the mixture was filtered and concentrated. Purification by flash chromatography on silica gel (2% EtOAc/hexanes) yielded 2.0 g (90%) of allylsilane **49** as a clear, colorless liquid: $[\alpha]_D$ = +7.4 (*c* 2.7, $CHCl_3$); IR (thin film) 3069, 3053, 2951, 2931, 2855, 1628, 1430, 1259, 1113, 859 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 4 H), 7.43–7.34 (m, 6 H), 4.55 (brs, 2 H), 3.72 (d, *J* = 5.6, 6.8 Hz, 1 H), 3.65 (dd, *J* = 5.2, 7.1 Hz, 1 H), 1.90–1.63 (m, 2 H), 1.45–1.22 (m, 2 H), 1.06 (s, 9 H), 0.81 (d, *J* = 6.1 Hz, 3 H), 0.041 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 135.8, 134.3, 129.7, 127.8, 108.8, 62.3, 46.5, 39.6, 27.0, 26.4, 19.8, –1.1; EI-MS *m/z* 423 (M^+), 381, 271, 231, 199, 135, 84, 73, 58; HRMS calcd for $C_{27}H_{42}OSi_2$: 381.2068, found 381.2066.



(3*S*)-*tert*-Butyl-(3,5-dimethylhex-5-enyloxy)diphenyl-silane (53): To a solution of 4.4 g of allylsilane **49** (10.0 mmol) in 50 mL of THF was added 4.4 g of Amberlyst-15 ion exchange resin. The reaction was maintained at ambient temperature for 16 h then filtered and concentrated to afford 3.4 g (92%) of **53** as a yellow oil: IR (thin film): 3071, 3050, 2959, 2930, 2858, 1472, 1428, 1111, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.65 (m, 4H), 7.45–7.35 (m, 6H), 4.74 (s, 1H), 4.65 (s, 1H), 3.76–3.63 (m, 2H), 2.01–1.96 (m, 1H), 1.88–1.78 (m, 2H), 1.69 (s, 3H), 1.65–1.59 (m, 1H), 1.37–1.25 (m, 1H), 1.05 (s, 9H), 0.81 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 135.5, 134.0, 129.5, 127.6, 111.4, 68.0, 62.0, 46.0, 39.4, 26.9, 22.1, 19.5; EI-MS *m/z* 309 (M+-tBu), 271, 199, 183, 84, 77; HRMS *m/z* calcd for $C_{20}H_{25}OSi$: 309.1675; found 309.1684.

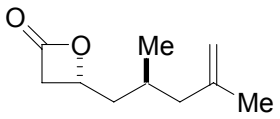


(*3S*)-3,5-Dimethylhex-5-en-1-ol (54): To a 0 °C solution of 1.7 g of silyl ether **53** (4.64 mmol) in 22 mL of dry THF was added 5.6 mL of a 1.0 M THF solution of tetrabutylammonium fluoride (5.57 mmol). The reaction was then warmed to ambient temperature and stirred for 1 h. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography on silica gel (30% Et_2O/pentane) to afford 0.530 g (90%) of the title compound as a clear, colorless liquid. $[\alpha]_D = -26$ (*c* 2.24, $CHCl_3$). IR (thin film): 3343, 3074, 2961, 2928, 1650, 1456, 1378, 1058, 887 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (s, 1H), 4.68 (s, 1H), 3.80–3.65 (m, 2H), 2.02 (dd, *J* = 5.9, 13 Hz, 1H), 1.91–1.75 (m, 2H), 1.70 (s, 3H), 1.67–1.58 (m, 1H), 1.45–1.30 (m, 1H), 1.19 (t, *J* = 5.3 Hz, 1H), 0.89 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 111.9, 61.4, 46.3, 39.9, 27.5, 22.4, 19.7. EI-MS *m/z* 128 (M+), 110, 95, 86, 83, 73, 59, 55; HRMS *m/z* calcd for $C_8H_{16}O$: 128.1201; found 128.1197.

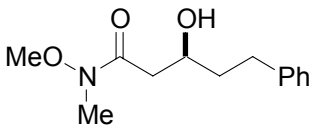


(*3S*)-3,5-Dimethylhex-5-enal (50): To a suspension of 2.0 g of 4Å molecular sieves and 0.728 g of *N*-methylmorpholine *N*-oxide (6.21 mmol) in 15 mL of CH_2Cl_2 at ambient temperature was added 0.530 g of alcohol **54** (4.1 mmol) in 5 mL of CH_2Cl_2. After several minutes, 0.075 g of tetrapropylammonium perruthenate (0.207 mmol) was added. The resulting green-black suspension was stirred 30 min at ambient temperature, then filtered through a plug of silica gel. The filtrate was concentrated to afford 0.460 g (88%) of the title compound as a clear, colorless liquid. $[\alpha]_D = -9.8$ (*c* 3.43, $CHCl_3$). IR (thin film): 3425, 3069, 2962, 2926, 2871, 2827, 2720, 1726, 1651, 1453, 1378, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.77 (t, *J* = 2.3 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 2.47–2.41 (m, 1H), 2.32–

2.15 (m, 2H), 2.01–1.97 (m, 2H), 1.71 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7, 143.5, 112.1, 50.5, 45.6, 26.0, 25.6, 22.0, 20.0; EI-MS *m/z* 111 (M+-Me), 108, 93, 82, 73, 61, 55; HRMS *m/z* calcd for $C_7H_{11}O$: 111.0809; found 1110808.



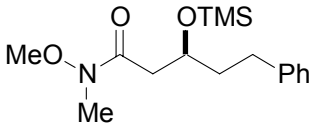
(4*R*, 2′*S*)-4-(2,4-Dimethylpent-4-enyl)oxetan-2-one (55) To a –50 °C solution of 0.405 g of aluminum triamine catalyst ***ent*-36** (0.697 mmol) in 30 mL of CH_2Cl_2 was added 2.0 mL of diisopropylethylamine (11.8 mmol) followed by 0.98 mL of acetyl bromide (13.2 mmol). The resulting light yellow solution was maintained at –50 °C for 5-10 min, then treated with 0.878 g of aldehyde **50** (6.97 mmol) in 5 mL of CH_2Cl_2 slowly dropwise. The reaction was stirred overnight at –50 °C and was poured into 150 mL of cold pentane, filtered through silica gel, and concentrated. The residue was purified by flash chromatography on silica gel (20% ether/pentane) to afford the title compound as a colorless liquid: IR (thin film): 3073, 2966, 2919, 1830, 1647, 1457, 1374, 1124, 887 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79–4.78 (m, 1H), 4.69–4.68 (m, 1H), 4.67–4.59 (m, 1H), 3.56 (dd, J = 5.7, 16.0 Hz, 1H), 3.07 (dd, J = 4.3, 16.0 Hz, 1H), 2.06–1.93 (m, 2H), 1.92–1.84 (m, 2H), 1.70 (s, 3H), 1.54–1.44 (m, 1H), 0.95 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 143.5, 112.2, 69.8, 46.0, 43.4, 41.5, 27.5, 22.0, 19.1; EI-MS *m/z* 168 (M+), 153, 135, 125, 109, 93, 82, 71, 67, 55; HRMS *m/z* calcd for $C_{10}H_{16}O_2$: 168.1150; found 168.1146.



(3*S*)-3-Hydroxy-5-phenylpentanoic acid *N*-methoxy-*N*-methylamide (66):[63] To a 0 °C suspension of 0.937 g of *N*,*O*-dimethylhydroxylamine (9.66 mmol) in 20 mL of CH_2Cl_2 was added 9.66 mL (9.66 mmol) of

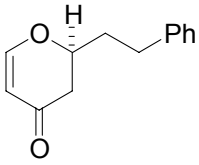
[63] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

dimethylaluminum chloride (1.0 M solution in hexanes). The suspension was warmed to ambient temperature and stirred for 2 h. To this suspension was added a solution of lactone **61** in 5 mL of CH_2Cl_2 via cannula. The reaction mixture was maintained overnight at ambient temperature and then quenched with 36 mL (3 mL/mmol Me_2AlCl) of pH 8 phosphate buffer. The resulting suspension was stirred at ambient temperature for 15 min, filtered through Celite, and the filtrate was extracted with $CHCl_3$ (3 × 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 1.12 g (98%) of the title compound as a pale yellow liquid: $[\alpha]_D$ = +28 (*c* 0.96, $CHCl_3$); IR (thin film): 3437, 3058, 2940, 1639, 1496, 1450, 1183, 1076, 994, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 4.08–4.02 (m, 1H), 3.92 (brs, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 2.85–2.75 (m, 1H), 2.74–2.64 (m, 2H), 2.53–2.49 (m, 1H), 1.91–1.84 (m, 1H), 1.81–1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 142.1, 128.62, 128.58, 128.55, 128.48, 125.9, 67.3, 61.4, 60.2, 43.0, 38.3, 31.9; LRMS (EI, 70 eV): *m/z* 237.



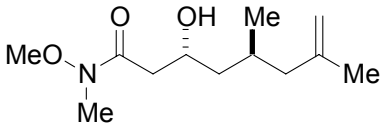
(3*S*)-5-Phenyl-3-trimethylsilyloxypentanoic acid *N*-methoxy-*N*-methylamide (67): To a solution of 0.725 g (3.06 mmol) of amide **66** in 25 mL of CH_2Cl_2 was added 1.2 mL (4.6 mmol) of *N, O*-bis(trimethylsilyl)acetamide at ambient temperature. The reaction was maintained for 90 min, then concentrated and purified by flash chromatography on silica gel (20% EtOAc/hexanes) to yield 0.838 g (89%) of the title compound as a pale yellow oil: $[\alpha]_D$ = +17 (*c* 2.1, $CHCl_3$); IR (thin film) 3062, 3027, 1662, 1250, 1094, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.22–7.16 (m, 3H), 4.31 (dddd, *J* = 5.1, 5.1, 7.3, 7.3 Hz, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.84–2.71 (m, 2H), 2.66–2.58 (m, 1H), 2.47 (dd, *J* = 5.2, 15 Hz, 1H), 1.95–1.72 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 172.0, 142.0, 128.3 (4C), 125.6, 69.1, 61.1, 39.9, 39.5, 31.8, 0.81 (3C); LRMS (EI, 70 eV): *m/z* 309; HRMS calcd for $C_{16}H_{27}NO_3Si$: 309.1760, found 309.1754.

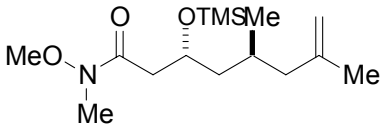


(2*S*)-2-Phenethyl-2,3-dihydropyran-4-one (65):[64] To a –78 °C solution of 0.390 g of *cis*-2-ethoxyvinylstannane **63** (1.08 mmol) in 8 mL of THF was slowly added 0.62 mL of a 1.6 M hexane solution of ^{n}BuLi. The clear solution was stirred at –78 °C for 75 min and a solution of 0.160 g of amide **67** (0.52 mmol) in 2 mL of THF was added via cannula. The reaction mixture was allowed to warm slowly to 0 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 6 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to afford **68** as a yellow oil. The crude product mixture was dissolved in 2 mL of THF and Amberlyst-15 resin was added. The reaction was stirred at ambient temperature overnight, filtered, and concentrated. Purification by flash chromatography on silica gel (20% EtOAc/hexanes) afforded 81 mg (76%) of **65** as a pale yellow oil: $[\alpha]_D$ = – 89 (*c* 1.0, $CHCl_3$); IR (thin film) 1672, 1593 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.0 Hz, 1H), 7.28–7.22 (m, 2H), 7.21–7.10 (m, 3H), 5.36 (dd, *J* = 1.1, 6.0 Hz, 1H), 4.35 (ddd, *J* = 4.3, 8.3, 13 Hz, 1H), 2.82–2.65 (m, 2H), 2.51 (dd, *J* = 13, 17 Hz, 1H), 2.38 (ddd, *J* = 1.1, 4.0, 17 Hz, 1H), 2.11 (dtd, *J* = 5.8, 8.8, 17 Hz, 1H), 1.90 (dddd, *J* = 4.6, 7.1, 9.4, 17 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 162.9, 140.7, 128.6, 128.3, 126.2, 107.1, 78.5, 41.9, 36.0, 31.0, 29.6; HRMS *m/z* calcd for $C_{13}H_{14}O_2$: 202.0994, found 202.0998.

[64] Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.

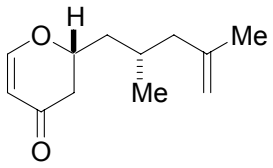


(3*R*,5*S*)-3-Hydroxy-5,7-dimethyloct-7-enoic acid *N*-methoxy-*N*-methyl-amide (69): To a 0 °C suspension of 1.15 g (11.9 mmol) of in 25 mL of CH_2Cl_2 was added 11.9 mL (11.9 mmol) of dimethylaluminum chloride (1.0 M solution in hexanes). The suspension was warmed to ambient temperature and stirred for 2 h. To this suspension was added a solution of lactone **55** in 5 mL of CH_2Cl_2 via cannula. The reaction mixture was allowed to stir overnight at ambient temperature and then quenched with 36 mL (3 mL/mmol Me_2AlCl) of pH 8 phosphate buffer. The resulting suspension was stirred for 15 min, filtered through Celite, and the filtrate was extracted with $CHCl_3$ (3 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.820 g of the title compound as a pale yellow liquid. $[\alpha]_D = -25$ (*c* 2.3, $CHCl_3$). IR (thin film): 3449, 3069, 2962, 2926, 1647, 1441, 1386, 1176, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (m, 1H), 4.65 (m, 1H), 4.18–4.09 (m, 1H), 3.73 (brs, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.61 (brd, *J* = 16.0 Hz, 1H), 2.44 (dd, *J* = 9.4, 16.9 Hz, 1H), 2.03–1.84 (m, 3H), 1.67 (s, 3H), 1.59 (ddd, *J* = 3.4, 9.9, 13.6 Hz, 1H), 1.04 (ddd, *J* = 3.1, 9.3, 12.5 Hz, 1H), 0.89 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 144.5, 111.5, 65.4, 61.2, 46.6, 43.5, 39.0, 31.8, 26.7, 22.1 18.9. HRMS *m/z* calcd for $C_{12}H_{23}NO_3$: 229.1678; found 229.1678.



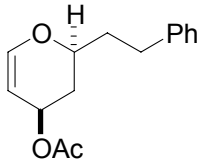
(3*R*,5*S*)-5,7-Dimethyl-3-trimethylsilyloxyoct-7-enoic acid-*N*-methoxy-*N*-methylamide (70): To a solution of 0.815 g (3.56 mmol) of amide **69** in 25 mL of CH_2Cl_2 was added 1.5 mL (6.05 mmol) of *N,O*-bis(trimethylsilyl)acetamide at ambient temperature. The reaction was maintained for 90 min, then concentrated and purified by flash chromatography on silica gel (20% EtOAc/hexanes) to yield 0.960 g (90%) of the title compound as a pale yellow oil. $[\alpha]_D = +2.6$ (*c* 2.4, $CHCl_3$). IR

(thin film): 3073, 2954, 2926, 1663, 1445, 1386, 1247, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.74–4.73 (m, 1H), 4.66 (br s, 1H), 4.32 (m, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.74 (dd, *J* = 7.4, 15.0 Hz, 1H), 2.42 (dd, *J* = 5.3, 15.0 Hz, 1H), 1.69 (s, 3H), 1.56 (ddd, *J* = 3.1, 9.4, 12.8 Hz, 1H), 1.19 (ddd, *J* = 3.1, 9.5, 12.8 Hz, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 144.4, 111.6, 67.5, 61.3, 46.5, 44.9, 40.8, 31.9, 26.7, 22.0, 19.2, 0.60. HRMS *m/z* calcd for $C_{15}H_{31}NO_3Si$: 301.2073; found 301.2073.

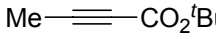


(2*R*, 2′*S*)-(2,4-Dimethylpent-4-enyl)-2,3-dihydropyran-4-one (72): To a –78 °C solution of 1.00 g of cis-2-ethoxyvinylstannane (2.79 mmol) **62** in 8 mL of dry THF was slowly added 1.66 mL of a 1.6 M hexane solution of ^{n}BuLi. The clear solution was stirred at –78 °C for 75 min and a solution of 0.400 g of amide **70** (1.33 mmol) in 2 mL of THF was added via cannula. The reaction mixture was allowed to warm slowly to 0 °C. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was dissolved in 10 mL of THF and Amberlyst-15 resin was added. The reaction was stirred at ambient temperature overnight. The reaction was filtered and the filtrate was concentrated. Purification by flash chromatography on silica gel (15% EtOAc/hexanes) afforded 0.186 g (72%) of **72** a pale yellow oil: $[\alpha]_D$ = +120 (*c* 2.6, $CHCl_3$). IR (thin film): 3073, 2962, 2926, 1683, 1600, 1406, 1275, 1215, 1037, 895 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 6.0 Hz, 1H), 5.39 (d, *J* = 6.0 Hz, 1H), 4.76 (s, 1H), 4.67 (s, 1H), 4.50 (ddt, *J* = 3.7, 7.4, 13.3 Hz, 1H), 2.51 (dd, *J* = 13.2, 16.8 Hz, 1H), 2.38 (dd, *J* = 3.8, 17.0 Hz, 1H), 1.99–1.85 (m, 4H), 1.69 (s, 3H), 1.28–1.20 (m, 1H), 0.91 (d, *J* = 5.9 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 163.3, 143.8, 112.2, 107.0, 78.0, 46.1, 42.5, 41.4, 26.3, 22.0, 19.1. HRMS *m/z* calcd for $C_{12}H_{18}O_2$: 194.1306; found 194.1300.



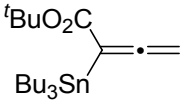
(2*S*, 4*R*)-2-Phenethyl-3, 4-dihydro-2*H*-pyran-4-yl acetate (73): To a 0 °C solution of 75 mg of pyranone **72** (0.37 mmol) and 0.166 g of $CeCl_3 \cdot 7H_2O$ (0.445 mmol) in 2 mL of MeOH was added 15 mg of $NaBH_4$ (0.39 mmol) in portions. After 30 min at 0°C, the reaction was quenched by adding 3 mL of water. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude alcohol (66 mg, 0.337 mmol) was then dissolved in CH_2Cl_2 and cooled to 0 °C. To this solution was added 0.153 mL of Et_3N (1.10 mmol), 4 mg of dimethylaminopyridine (DMAP) (0.037 mmol), and 0.052 mL of acetic anhydride (0.551 mmol). The resulting clear, colorless solution was then stirred 2 h at ambient temperature. The reaction was concentrated and purified by flash chromatography (3% EtOAc/hexanes, with 5% Et_3N) to afford 85 mg (94%) of the title compound as a clear colorless oil: $[\alpha]_D = -5.6$ (*c* 1.2, $CHCl_3$); IR (thin film) 3064, 3027, 2931, 2864, 1731, 1645, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 2H), 7.23–7.20 (m, 3H), 6.50 (d, *J* = 6.3 Hz, 1H), 5.41–5.36 (m, 1H), 4.78–4.75 (m, 1H), 4.08–3.96 (m, 1H), 2.81–2.71 (m, 2H), 2.29–2.22 (m, 1H), 2.06–2.00 (m, 4H), 1.87–1.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 146.6, 141.4, 128.4 (4C), 125.9, 100.9, 73.4, 65.6, 36.3, 33.3, 31.3, 21.2; LRMS (EI, 70eV): *m/z* 246; HRMS calcd for $C_{15}H_{18}O_3$: 246.1256, found 246.1247.



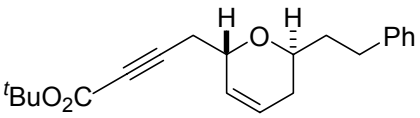
***tert*-Butyl but-2-ynoate (74):**[65] Into a pressure tube charged with 5.0 g of tetrolic acid (59.5 mmol) was condensed ~ 60 mL of isobutylene at –40 °C. The mixture was

[65] Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem*. **2000**, *65*, 4888.

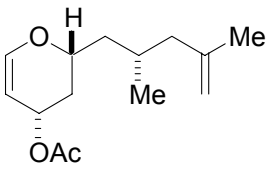
then treated with 0.66 mL of H_2SO_4 dropwise via syringe and sealed. The reaction was warmed to ambient temperature and maintained for 24 h. Saturated aqueous K_2CO_3 (100 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (2% EtOAc/hexanes) to afford 6.2 g (75%) of the title compound **74** as a light yellow liquid: IR (thin film): 2981, 2935, 2874, 2249, 1705, 1370, 1280, 1163, 1073; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H), 1.50 (s, 9H).



***tert*-Butyl 2-(tributylstannyl)buta-2,3-dienoate (41):** To a 0 °C solution of 1.40 mL of diisopropylamine (10.0 mmol) in 30 mL of THF was added 5.35 mL of a 1.6 M solution of ^{n}BuLi in hexanes dropwise via syringe. The pale yellow solution was cooled to –78 °C then treated with 1.00 g of ester **74** (7.14 mmol) in THF (5mL). The resulting orange-red solution was maintained at –78 °C for 1 h then 1.94 mL of ^{n}Bu$_3$SnCl (7.14 mmol) was added dropwise via syringe. After maintaining for an additional 2 h at –78 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with Et_2O. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification of the crude product by flash chromatography (hexanes) afforded 1.16 g (38%) of the title compound as a clear, colorless liquid: IR (thin film): 2957, 2928, 2872, 2854, 1920, 1709, 1685, 1457, 1254, 1151, 801 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 2H), 1.60–1.47 (m, 6H), 1.47 (s, 9H), 1.34 (tq, J = 7.3, 7.3 Hz, 6H), 1.05 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 167.7, 92.5, 80.7, 68.4, 28.8, 28.1, 27.1, 13.6, 10.9; LRMS (EI, 70eV): *m/z* 373 [M-^{t}Bu]$^+$; HRMS calcd for $C_{16}H_{29}O_2{}^{120}Sn$: 373.1190, found 373.1187.

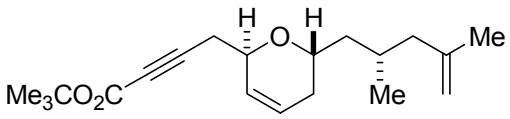


(6*R*,2*S*)-4-(6-Phenethyl-5,6-dihydro-2*H*-pyran-2-yl)but-2-ynoic acid *tert*-butyl ester (76): To a –78 °C solution of 70 mg of glycal acetate **73** (0.284 mmol) in 3 mL of CH_2Cl_2 was slowly added 0.610 g of allenylstannane **41** (1.42 mmol) and a solution of 0.150 mg of tributyltin trifluoromethanesulfonate (0.341 mmol) in 1 mL of CH_2Cl_2 via cannula. The reaction was allowed to slowly warm to ambient temperature. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 12 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography (1% EtOAc/Hex) to afford 70 mg (75%) of the title compound as a clear colorless oil: IR (thin film) 3028, 2979, 2928, 2239, 1706, 1603, 1455, 1369, 1279, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 5.92–5.87 (m, 1H), 5.85–5.80 (m, 1H), 4.47–4.42 (m, 1H), 3.63 (tt, *J* = 4.2, 8.2 Hz, 1H), 2.86 (ddd, *J* = 5.3, 9.1, 14.0 Hz, 1H), 2.76–2.68 (m 1H), 2.64 (dd, *J* = 7.1, 16.8 Hz, 1H), 2.50 (dd, *J* = 7.0, 16.8 Hz, 1H), 2.01–1.96 (m, 2H), 1.93–1.72 (m, 2H), 1.49 (s, 9H); LRMS (EI, 70 eV): *m/z* 326, 270 $[M-^tBu]^+$; HRMS calcd for $C_{21}H_{26}O_3$: 326.1882, found 326.1887.



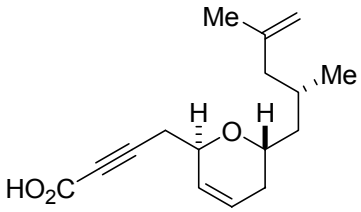
(2*R*, 2′*S*, 4*S*)-(2,4-Dimethylpent-4-enyl)-3,4-dihydro-2*H*-pyran-4-yl acetate (77): To a 0 °C solution of 66 mg of pyranone **72** (0.34 mmol) and 0.152 g of $CeCl_3 \cdot 7H_20$ (0.408 mmol) in 2 mL of MeOH was added 14 mg of $NaBH_4$ (0.36 mmol) in portions. After 30 min at 0°C, the reaction was quenched by adding 3 mL of water. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated to afford the corresponding allylic alcohol. The crude alcohol (0.066 g, 0.337 mmol) was then dissolved in CH_2Cl_2 and cooled to 0

°C. To this solution was added 0.140 mL of Et_3N (1.01 mmol), 4 mg of dimethylaminopyridine (0.0337 mmol), and 0.048 mL of acetic anhydride (0.505 mmol). The resulting clear, colorless solution was then stirred 2 h at ambient temperature. The reaction was concentrated and purified by flash chromatography (3% EtOAc/hexanes, with 5% Et_3N) to afford 0.074 g (92%) of the title compound as a clear colorless residue. $[\alpha]_D$ = +6.8 (*c* 2.3, $CHCl_3$). IR (thin film): 3069, 2958, 2926, 2871, 1734, 1643, 1441, 1370, 1231, 1041, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.45 (d, *J* = 6.2 Hz, 1H), 5.43–5.35 (m, 1H), 4.77–4.71 (m, 2H), 4.67 (brs, 1H), 4.14–4.04 (m, 1H), 2.27–2.16 (m, 1H), 2.05 (s, 3H), 2.00–1.85 (m, 3H), 1.84–1.73 (m, 2H), 1.72 (s, 3H), 1.18–1.09 (m, 1H), 0.89 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 146.7, 144.3, 111.8, 100.9, 72.3, 65.8, 46.5, 41.8, 34.2, 26.5, 22.2, 21.4, 19.1; EI-MS *e/v* 238 (M+), 178, 160, 145, 121, 109, 91, 81, 66.



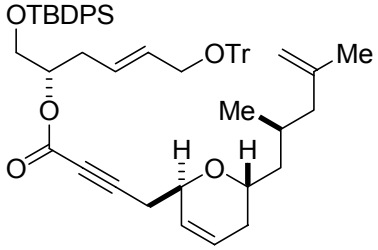
(2*R*,6*R*,2′*S*)-4-[6-(2,4-Dimethylpent-4-enyl)-5,6-dihydro-2*H*-pyran-2-yl]but-2-ynoic acid *tert*-butyl ester (78): To a –78 °C solution of 42 mg of glycal acetate **77** (0.176 mmol) in 1 mL of CH_2Cl_2 was slowly added 0.378 g of allenylstannane **41** (0.882 mmol) and a solution of 85 mg of tributyltin trifluoromethanesulfonate (0.194 mmol) in 1 mL of CH_2Cl_2 via cannula. The reaction was allowed to slowly warm to ambient temperature. Saturated aqueous $NaHCO_3$ (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography (1% EtOAc/Hex) to afford 0.040 g (71%) of the title compound as a clear colorless oil: $[\alpha]_D$ = –74 (*c* 2.1, $CHCl_3$). IR (thin film): 3069, 3034, 2974, 2935, 2242, 1707, 1457, 1370, 1275, 1164, 1073, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.95–5.89 (m, 1H),

5.84–5.79 (m, 1H), 4.75–4.74 (m, 1H), 4.67 (br s, 1H), 4.43–4.38 (m, 1H), 3.82–3.76 (m, 1H), 2.65 (dd, *J* = 7.1, 16.8 Hz, 1H), 2.54 (dd, *J* = 6.8, 16.8 Hz, 1H), 2.04–1.87 (m, 5H), 1.71 (s, 3H), 1.62 (ddd, *J* = 3.5, 9.9, 13.6 Hz, 1H), 1.49 (s, 9H), 1.11 (ddd, *J* = 3.1, 9.2, 13.9 Hz, 1H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 144.6, 127.6, 126.2, 111.7, 83.3, 83.1, 75.9, 70.4, 66.0, 46.6, 42.4, 31.1, 28.0, 26.6, 24.7, 22.2, 19.2; EI-MS *e/v* 317 (M+-H), 261, 219, 179, 161, 109, 95, 67, 57.

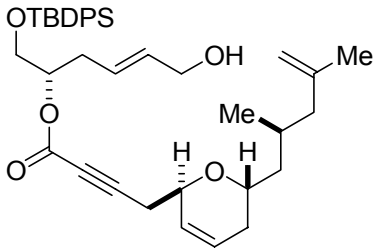


4-((2*R*,6*R*)-5,6-dihydro-6-((4*S*)-2,4-dimethylpent-4-enyl)-2*H*-pyran-2-yl)but-2-ynoic acid (80):[66] To a 0 °C solution of 0.026 g of ester **78** (0.082 mmol) in 2.0 mL of CH_2Cl_2 was added 0.095 mL of 2,6-lutidine (0.82 mmol) followed by 0.075 mL of *tert*-butyldimethyltrifluoromethane sulfonate (0.41 mmol). The resulting yellow solution was maintained at 0 °C for 1.5 h before being quenched with H_2O. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were subsequently washed with 0.1 M citric acid (20 mL) and brine (20 mL). The organics were then dried over Na_2SO_4, filtered, and concentrated to afford 0.020 g (95%) of a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (br s, 1H), 5.96–5.89 (m, 1H), 5.85–5.75 (m, 1H), 4.80–4.70 (m, 1H), 4.66 (br s, 1H), 4.48–4.35 (m, 1H), 3.79 (1H), 2.68 (dd, *J* = 7.0, 16.9 Hz, 1H), 2.58 (dd, *J* = 6.9, 16.9 Hz, 1H), 2.10–1.80 (m, 5H), 1.70 (s, 3H), 1.62 (ddd, *J* = 3.4, 9.8, 13.6 Hz, 1H), 1.12 (ddd, *J* = 3.2, 9.1, 13.8 Hz, 1H), 0.88 (d, *J* = 6.2, Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 144.9, 127.6, 126.5, 111.9, 87.0, 70.6, 66.5, 46.8, 42.6, 31.4, 26.9, 25.0, 22.4, 19.5, 2.2.

[66] Full characterization was not obtained for compounds **80**, **83**, and **79** as they were a part of a failed route to macrocycle **84**.

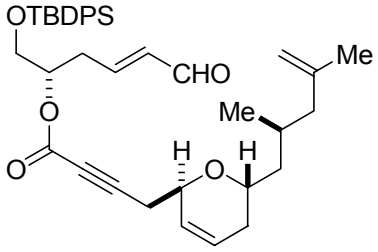


1-(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-5-trityloxy-pent-3-enyl-4-(2*R*,6*R*)-[6-(4*S*)-(2,4-dimethylpent-4-enyl)-5,6-dihydro-2*H*-pyranyl]but-2-ynoate (82): To a 0 °C solution of 42 mg of alcohol **40** (68.7 μmol), 9 mg of acid **80** (34.3 μmol), and 2.7 mg of DMAP (6.87 μmol) in 450 μL of CH_2Cl_2 was added 9 mg of DCC (41.2 μmol) in one portion. The reaction was maintained at ambient temperature overnight. After diluting with pentane, the reaction mixture was filtered through Celite and concentrated. Purification by flash chromatography (2% EtOAc/hexanes) afforded 9 mg (31 %) of the title compound as a clear, colorless residue: $[\alpha]_D$ = –177 (*c* 0.9, $CHCl_3$); IR (thin film): 3062, 3029, 2955, 2928, 2853, 2238, 1709, 1488, 1446, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.3 Hz, 4H), 7.50–7.20 (m, 21H), 5.95–5.85 (m, 1H), 5.85–5.77 (m, 1H), 5.75–5.55 (m, 2H), 5.10 (dddd, *J* = 6.2, 6.2, 6.2, 6.2 Hz, 1H), 4.73 (br s, 1H), 4.66 (br s, 1H), 4.46–4.35 (m, 1H), 3.82–3.75 (m, 1H), 3.74 (d, *J* = 7.0 Hz, 2H), 3.54 (d, *J* = 3.1 Hz, 2H), 2.68 (dd, *J* = 6.6, 16.8 Hz, 1H), 2.59 (dd, *J* = 7.4, 16.8 Hz, 1H), 2.49–2.32 (m, 2H), 2.05–1.85 (m, 5H), 1.69 (s, 3H), 1.62 (ddd, *J* = 3.3, 9.9, 13.6 Hz, 1H), 1.18–1.02 (s+m, 10H), 0.88 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 147.2, 144.8, 144.5 (2C), 135.9 (2C), 133.6, 131.0, 130.0, 129.0 (4C), 128.2, 128.1, 128.0, 127.5, 127.2, 126.4, 111.9, 87.1, 86.2, 77.5, 75.7, 75.1, 70.5, 66.4, 64.9, 64.4, 46.8, 42.6, 33.8, 31.4, 27.1 (3C), 27.0, 25.1, 22.5, 19.5; LRMS (EI, 70eV): *m/z* 856.



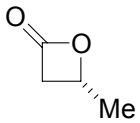
1-(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-5-hydroxy-pent-3-enyl-4-(2*R*,6*R*)-[6-(4*S*)-(2,4-dimethylpent-4-enyl)-5,6-dihydro-2*H*-pyranyl]but-2-ynoate (83): A solution of 13 mg of trityl ether **82** (15.2 μmol) in 200 μL of 2% TfOH in $CHCl_3$/MeOH

was maintained for 30 min at ambient temperature. Saturated aqueous $NaHCO_3$ was added (1 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel provided 7 mg (75%) of the title compound as a pale yellow residue: IR (thin film): 3417, 2957, 2925, 2855, 2237, 1712, 1463, 1248, 1186, 1080, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.64 (m, 4H), 7.49–7.36 (m, 6H), 5.97–5.89 (m, 1H), 5.85–5.79 (m, 1H), 5.71 (dt, *J* = 5.5, 15.4 Hz, 1H), 5.59 (dt, *J* = 6.7, 15.3 Hz, 1H), 5.08 (app quintet, *J* = 5.5 Hz, 1H), 4.73 (br s, 1H), 4.66 (br s, 1H), 4.46–4.38 (m, 1H), 4.06 (br d, 2H), 3.82–3.73 (m, 1H), 3.72 (dd, *J* = 5.7, 11.0 Hz, 1H), 3.67 (dd, *J* = 4.9, 11.0 Hz, 1H), 2.69 (dd, *J* = 6.7, 16.9 Hz, 1H), 2.60 (dd, *J* = 7.1, 16.8 Hz, 1H), 2.51–2.32 (m, 2H), 2.04–1.85 (m, 5H), 1.69 (s, 3H), 1.62 (ddd, *J* = 3.4, 10.0, 13.7 Hz, 1H), 1.12 (ddd, *J* = 3.1, 9.0, 12.3 Hz, 1H), 1.06 (s, 9H), 0.88 (d, *J* = 6.3 Hz, 3H); HRMS calcd for $C_{38}H_{50}O_5SiNa$: 637.3325, found 637.3353.

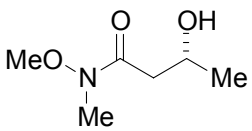


1-(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-5-oxo-pent-3-enyl-4-(2*R*,6*R*)-[6-(2,4-dimethylpent-4-enyl)-5,6-dihydro-2*H*-pyranyl]but-2-ynoate (79): To a mixture of 13 mg of allylic alcohol **83** (21.2 μmol), 4 mg of *N*-methylmorpholine *N*-oxide (31.8 μmol), and 11 mg of 4Å molecular sieves in 150 μL of CH_2Cl_2 at ambient temperature was added 1 mg of tetrapropylammonium perrhuthenate (1.06 μmol). The reaction was maintained for 30 min, then filtered through silica gel (40% EtOAc/hexanes). The filtrate was concentrated to afford 10 mg (77%) of the title compound **79** as a light yellow residue: ^1H NMR (300 MHz, $CDCl_3$): δ 9.46 (d, *J* = 7.8 Hz, 1H), 7.67–7.61 (m, 4H), 7.46–7.35 (m, 6H), 6.71 (dt, *J* = 7.2, 15.6 Hz, 1H), 6.14 (dd, *J* = 7.8 Hz, 15.6 Hz, 1H), 5.95–5.89 (m, 1H), 5.83–5.74 (m, 1H), 5.16

(dddd, J = 5.3, 5.3, 5.3, 5.3 Hz, 1H), 4.71 (br s, 1H), 4.65 (br s, 1H), 4.49–4.35 (m, 1H), 3.85–3.69 (m, 3H), 2.75–2.50 (m, 3H), 2.05–1.84 (m, 5H), 1.66 (s, 3H), 1.05 (s, 9H), 0.96 (d, *J* = 6.6 Hz, 3H).

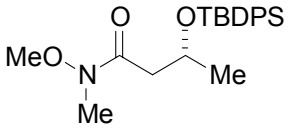


(4*R*)-4-Methyloxetan-2-one (*ent*-91): To a –78 °C solution of 1.3 g of aluminum triamine catalyst ***ent*-36** (2.27 mmol) and 14.6 g of tetrabutylammonium bromide (45.4 mmol) in 91 mL of CH_2Cl_2 was added 6.72 mL of DIPEA (38.6 mmol) followed by 3.20 mL of acetyl bromide (43.1 mmol). The resulting yellow solution was stirred several minutes at –78 °C whereupon 1.27 mL of acetaldehyde (22.7 mmol) was added slowly dropwise via syringe. The reaction was maintained at –78 °C overnight, and was quenched by pouring into cold hexanes (300 mL). The resulting mixture was filtered through silica gel (40% EtOAc/Hex) and concentrated to yield 1.7 g (87%, crude) of ***ent*-91** as a pale yellow liquid: Separation of the enantiomers by chiral GC [Chiraldex G-TA column, flow rate 1.5 mL/min, method: 80 °C for 5.0 min, ramp at 5.0 °C/min to 100 °C for 10.0 min, ramp at 5.0 °C to 130 °C for 5 min. T_r 8.04 min (*R*) and 9.05 min (*S*)] determined the enantiomeric excess to be 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (ddq, *J* = 4.2, 6.0, 12.0 Hz, 1H), 3.48 (dd, *J* = 5.7, 16.3 Hz, 1H), 2.98 (dd, *J* = 4.3, 16.3 Hz, 1H), 1.47 (d, *J* = 8.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 67.7, 44.0, 20.2.



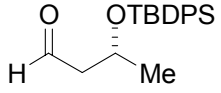
(3*R*)-3-Hydroxy-*N*-methoxy-*N*-methylbutyramide (*ent*-92): To a 0 °C solution containing 6.32 g of *N*,*O*-methoxymethylamine hydrochloride (65.1 mmol) in 30 mL CH_2Cl_2 was added 65 mL of dimethylaluminum chloride (65 mmol) as a 1 M solution in hexanes. The solution was allowed to warm to ambient temperature and stirred for 2 h. The resulting suspension was treated with a solution of ***ent*-91** in 5 mL of CH_2Cl_2 via

cannula. The reaction mixture was maintained at ambient temperature overnight and then quenched with 36 mL (3 mL/mmol Me_2AlCl) of pH 8 phosphate buffer. The reaction was filtered through Celite to remove the solid aluminum salts. The resulting mixture was separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (Et_2O) to provide 3.8 g (81%) of the β-hydroxy amide ***ent*-92** as a pale yellow oil: $[\alpha]_D$ = –58 (*c* 3.0, $CHCl_3$); IR (thin film): 3448, 3008, 2974, 2938, 1642, 1420, 1389, 1216, 1002, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.21 (ddq, *J* = 2.6, 6.3, 9.0 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.67 (d, *J* = 16.7 Hz, 1H), 2.44 (dd, *J* = 9.5, 16.8 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 64.0, 61.2, 39.7, 31.7, 22.2; HRMS calcd for $C_6H_{13}NO_3$: 147.0895, found 147.0895.

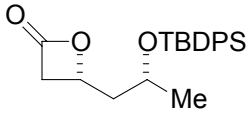


(3*R*)-3-(*tert*-Butyldiphenylsilyloxy)-*N*-methoxy-*N*-methyl-butyramide (*ent*-93): To a 0 °C solution of 0.730 g of the β-hydroxy amide ***ent*-92** (4.96 mmol) in 8 mL of CH_2Cl_2 was added 1.73 mL of DIPEA (9.93 mmol), 1.42 mL of TBDPSCl (5.46 mmol), and 0.607 g of DMAP (4.96 mmol). The resulting solution was warmed to ambient temperature and maintained for 18 h. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with 1 M HCl (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford 1.8 g (94%) of ***ent*-93** as a pale yellow oil: $[\alpha]_D$ = –9.1 (*c* 3.8, $CHCl_3$); IR (thin film): 3069, 3045, 2964, 2930, 2856, 1660, 1472, 1385, 1178, 1002, 940 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.71 (m, 4H), 7.46–7.36 (m, 6H), 4.45 (sextet, *J* = 6.0 Hz, 1H), 3.61

(s, 3H), 3.14 (s, 3H), 2.84 (dd, J = 6.0, 15.0 Hz, 1H), 2.44 (dd, J = 6.0, 15.0 Hz, 1H), 1.16 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 135.8, 135.7, 134.5, 134.0, 129.5, 129.4, 127.4, 127.3, 66.9, 61.1, 41.8, 31.4, 26.9, 23.7, 19.1; HRMS calcd for $C_{22}H_{30}NO_3Si$: 384.1995, found 384.1976.

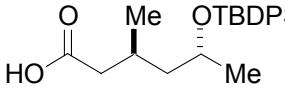


(3*R*)-3-(*tert*-Butyldiphenylsilyloxy)butyraldehyde (*ent*-94): To a –78 °C solution of 0.700 g of ***ent*-93** (1.82 mmol) in 11 mL of dry Et_2O was added a 1.0 M hexanes solution of DIBAL-H (2.00 mmol) dropwise. The resulting colorless solution was maintained at –78 °C for 30 min. The reaction was quenched with 1 M HCl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (30 mL) and filtered through Celite. The filtrate was then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 0.569 g (95%) of the aldehyde as a clear, colorless liquid: $[\alpha]_D$ = +7.5 (*c* 2.9, $CHCl_3$); IR (thin film) 3069, 3048, 2961, 2930, 2893, 2859, 2720, 1728, 1425, 1379, 1110, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (t, J = 2.6 Hz, 1H), 7.75–7.69 (m, 4H), 7.49–7.38 (m, 6H), 4.38 (sextet, J = 6.0 Hz, 1H), 2.57 (ddd, J = 2.9, 6.0, 15.8 Hz, 1H), 2.49 (ddd, J = 2.2, 5.6, 15.8 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 136.1, 134.4, 134.0, 130.2, 130.0, 128.0, 127.9, 66.0, 53.1, 27.2, 24.1, 19.5; HRMS calcd for $C_{16}H_{17}O_2Si$: 269.0998, found 269.0999.



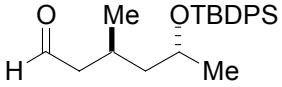
(4*R*,2′*R*)-4-[2-(*tert*-Butyldiphenylsilyloxy)propyl]oxetan-2-one (*ent*-96): To a –50 °C solution of 0.870 g of aluminum triamine catalyst ***ent*-36** (1.50 mmol) in 25 mL of CH_2Cl_2 was added 4.43 mL of DIPEA (25.4 mmol) followed by 2.10 mL of

acetyl bromide (28.4 mmol). The resulting yellow solution was stirred at –50 °C whereupon 4.88 g of the aldehyde ***ent*-94** (15.0 mmol) in 5 mL of CH_2Cl_2 was added dropwise via syringe. The reaction was maintained at –50 °C overnight, and was quenched by pouring into cold hexanes (150 mL). The resulting mixture was filtered through silica gel (50% EtOAc/hexanes) and concentrated. The crude product was then purified by flash chromatography on silica gel (3% EtOAc/hexanes) to afford 4.77 g (86%) of ***ent*-96** as a viscous, colorless oil: $[\alpha]_D$ = +17 (*c* 2.6, $CHCl_3$); IR (thin film): 3072, 3051, 2964, 2930, 2893, 2859, 1824, 1425, 1376, 1110, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.66 (m, 4H), 7.45–7.38 (m, 6H), 4.69 (dq, *J* = 4.4, 6.7 Hz, 1H), 4.04 (sextet, *J* = 6.1 Hz, 1H), 3.29 (dd, *J* = 5.8, 16.3 Hz, 1H), 2.95 (dd, *J* = 4.3, 16.3 Hz, 1H), 2.13 (dt, *J* = 6.3, 14.0 Hz, 1H), 1.81 (ddd, *J* = 5.0, 7.0, 14.0 Hz, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 136.2, 136.1, 134.3, 134.0, 130.2, 130.1, 128.1, 127.9, 68.8, 66.7, 44.0, 43.6, 27.3, 23.6, 19.5; HRMS calcd for $C_{18}H_{19}O_3Si$: 311.1103, found 311.1107.



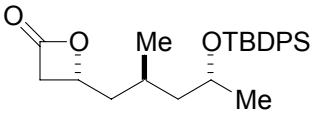
(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylhexanoic acid (97): To a –50 °C solution of 2.69 g of CuBr (18.8 mmol) in 185 mL of THF and 20 mL of dimethylsulfide was added 12.5 mL of a 3.0 M ethereal solution of methylmagnesium bromide (37.5 mmol) slowly dropwise. The resulting clear, faint green solution was stirred at –50 °C for 30 min then warmed to –30 °C for 30 min. The reaction was then cooled to –50 °C and 4.6 g of ***ent*-96** (12.5 mmol) in 15 mL of THF was added via cannula. After maintaining the reaction at –50 °C for 45 min, 2.4 mL of TMSCl (18.8 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. A mixture of saturated NH_4Cl (500 mL) and 1 M HCl (200 mL) was added and the mixture was extracted with Et_2O (4

× 150 mL). The combined organics were washed with saturated NH_4Cl and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford 3.85 g (80%) of **97** as a pale yellow viscous oil: $[\alpha]_D$ = +6.7 (*c* 2.2, $CHCl_3$); IR (thin film): 3070, 3045, 2961, 2928, 2853, 1704, 1426, 1373, 1108, 909, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–7.77 (m, 4H), 7.52–7.41 (m, 6H), 4.02–3.92 (m, 1H), 2.32–2.20 (m, 2H), 2.15–2.06 (m, 1H), 1.69 (ddd, *J* = 5.1, 7.5, 13.0 Hz, 1H), 1.32 (ddd, *J* = 4.6, 7.7, 13.0 Hz, 1H), 1.15-1.18 (m, 12H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 135.9, 134.8, 134.2, 129.6, 129.4, 127.5, 127.4, 67.5, 46.7, 41.9, 27.0, 26.7, 24.0, 19.7, 19.3; HRMS calcd for $C_{19}H_{23}O_3Si$: 327.1416, found 327.1419.

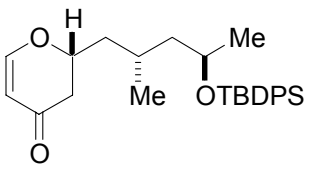


(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methylhexanal (98): To a solution of 3.75 g of carboxylic acid **97** (9.76 mmol) in 50 mL of Et_2O at ambient temperature was added 7.3 mL of a 2.0 M THF solution of $H_3B{\bullet}SMe_2$ (14.6 mmol) slowly dropwise. The resulting clear, colorless solution was heated to reflux and maintained 1 h. After cooling to ambient temperature, the solvent was removed, and the remaining viscous residue was dissolved in 50 mL of CH_2Cl_2. To this colorless solution was added 5.26 g of pyridinium chlorochromate (24.4 mmol), and the resulting brown suspension was heated to reflux and maintained for 2.5 h. The reaction was then cooled to ambient temperature, diluted with Et_2O, filtered through Celite, and concentrated. The crude product was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to afford 3.05 g (85%) of **98** as a pale yellow oil: $[\alpha]_D$ = –1.0 (*c* 2.6, $CHCl_3$); IR (thin film): 3067, 3048, 2959, 2928, 2853, 2708, 1726, 1426, 1373, 1111, 1067, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.63 (t, *J* = 2.5 Hz, 1H), 7.72–7.67 (m, 4H), 7.44–7.36 (m, 6H), 3.91–3.81 (m, 1H), 2.23–2.07 (m, 2H), 1.55 (ddd, *J* = 5.0, 7.7, 13.0

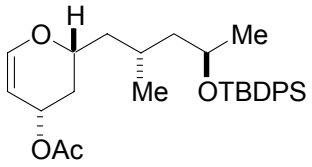
Hz, 1H), 1.23 (ddd, J = 4.7, 8.2, 13.4 Hz, 1H), 1.09 (d, J = 6.0 Hz, 3H), 1.06 (s, 9H), 0.78 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6, 135.9, 134.7, 134.2, 129.6, 129.5, 127.6, 127.4, 67.5, 51.3, 47.1, 27.1, 24.9, 24.0, 20.0, 19.3.



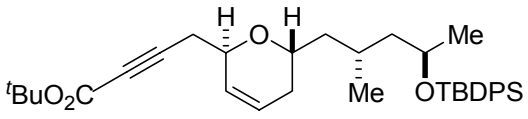
(4*R*,2′*S*,4′*R*)-4-[4′-(*tert*-Butyldiphenylsilyloxy)-2-methylpentyl]oxetan-2-one (99): To a –50 °C solution of 0.704 g of aluminum triamine catalyst ***ent*-36** (1.21 mmol) in 16 mL of CH_2Cl_2 was added 2.40 mL of DIPEA (13.7 mmol) followed by 1.13 mL of acetyl bromide (15.3 mmol). The resulting yellow solution was stirred at –50 °C whereupon 2.97 g of the aldehyde **98** (8.07 mmol) in 5 mL of CH_2Cl_2 was added slowly dropwise via syringe. The reaction was maintained at –50 °C overnight, and was quenched by pouring into cold hexanes (100 mL). The resulting mixture was filtered through silica gel (50% EtOAc/Hex) and concentrated. The crude product was then purified by flash chromatography on silica gel (11% hexanes/benzene) to afford 2.76 g (84%) of **99** as a white solid: $[\alpha]_D$ = +21 (*c* 2.3, $CHCl_3$); IR (thin film): 3070, 3048, 2965, 2931, 2853, 1828, 1426, 1376, 1200, 1111, 1061, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.66 (m, 4H), 7.47–7.35 (m, 6H), 4.45 (dtd, J = 4.5, 5.6, 8.0 Hz, 1H), 3.90–3.80 (m, 1H), 3.45 (dd, J = 5.7, 16.2 Hz, 1H), 2.95 (dd, J = 4.3, 16.2 Hz, 1H), 1.84-1.73 (m, 1H), 1.67 (ddd, J = 5.2, 7.8, 13.7 Hz, 1H), 1.54 (ddd, J = 5.2, 7.6, 13.4 Hz, 1H), 1.37 (ddd, J = 5.3, 7.9, 13.6 Hz, 1H), 1.20 (ddd, J = 4.9, 8.2, 12.7 Hz, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05 (s, 9H), 0.76 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 135.9, 134.7, 134.3, 129.6, 129.5, 127.6, 127.4, 69.7, 67.4, 47.2, 43.4, 42.2, 27.0, 26.7, 24.1, 19.6, 19.3; HRMS calcd for $C_{21}H_{25}O_3Si$: 353.1572, found 353.1559.



(2*R*,2′*S*,4′*R*)-2-[4-(*tert*-Butyldiphenylsilyloxy)-2-methyl-pentyl]-2,3-dihydropyran-4-one (100): To a 0 °C solution of 0.690 mL of diisopropylamine (4.93 mmol) in 20 mL of THF was added 2.95 mL of a 1.6 M solution of ^{n}BuLi in hexanes (4.68 mmol) slowly dropwise. The solution was maintained at 0 °C for 30 min, then treated with 0.590 mL of acetaldehyde *N*-piperidine hydrazone (4.93 mmol). The resulting heterogeneous mixture was stirred at 0 °C for 1 h, then cooled to –78 °C whereupon 1.01 g of **99** (2.46 mmol) in 2 mL of THF was added via cannula. The resultant yellow solution was maintained at –78 °C overnight. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The remaining residue was dissolved in THF and treated with 2.8 g of camphorsulfonic acid (12.1 mmol). The reaction was warmed to 60 °C over the course of 1 h and then allowed to cool to ambient temperature. The reaction was quenched with with saturated $NaHCO_3$ and extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (8% EtOAc/hexanes) afforded 0.665 g (62%) of **100** as a yellow oil: $[\alpha]_D$ = +68 (*c* 2.1, $CHCl_3$); IR (thin film): 3073, 3051, 2962, 2931, 2860, 1673, 1593, 1429, 1274, 1114, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.68 (m, 4H), 7.47–7.35 (m, 6H), 7.29 (d, *J* = 6.0 Hz, 1H), 5.39 (dd, *J* = 1.0, 6.0 Hz, 1H), 4.40 (ddt, *J* = 4.0, 8.3, 13.2 Hz, 1H), 3.94-3.84 (m, 1H), 2.43 (dd, *J* = 12.5, 16.8 Hz, 2H), 1.97-1.81 (m, 1H), 1.67 (ddd, *J* = 4.5, 9.5, 14.2 Hz, 1H), 1.52 (ddd, *J* = 5.7, 7.3, 13.4 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H), 0.76 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 163.0, 135.9, 134.7, 134.3, 129.5, 129.4, 127.5, 127.4, 106.9, 67.5, 47.6, 47.1, 42.4, 41.9, 27.0, 25.3, 24.0, 19.4, 19.2; HRMS calcd for $C_{23}H_{27}O_3Si$: 379.1729, found 379.1729.

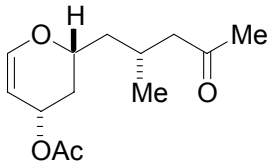


(2*R*,2′*S*,4′*R*, 4*S*)-2-[4-(*tert*-Butyldiphenylsilyloxy)-2-methylpentyl]-3,4-dihydro-2*H*-pyran-4-yl acetate (87): To a 0 °C solution of 0.408 g of **100** (0.936 mmol) and 0.418 g of $CeCl_3 \cdot 7H_20$ (1.12 mmol) in 10 mL of MeOH was added 0.039 g of $NaBH_4$ (1.03 mmol) portionwise. After 40 min at 0 °C, the reaction was quenched by adding 10 mL of water. The mixture was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated to afford the corresponding allylic alcohol. The crude alcohol (0.410 g, 0.936 mmol) was then dissolved in 8 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 0.391 mL of Et_3N (2.81 mmol), 0.011 g of DMAP (0.0936 mmol), and 0.135 mL of acetic anhydride (1.40 mmol). The resulting clear, colorless solution was then maintained at ambient temperature for 2 h. The reaction was concentrated and purified by flash chromatography (hexanes/ Et_3N 50:1) to afford 0.404 g (90%) of the allylic acetate as a clear colorless oil: $[\alpha]_D$ = +17.1 (*c* 2.0, $CHCl_3$); IR (thin film): 3070, 3048, 2961, 2931, 2856, 1729, 1645, 1429, 1370, 1231, 1108, 1040, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.68 (m, 4H), 7.43–7.35 (m, 6H), 6.41 (d, *J* = 6.2 Hz, 1H), 5.38 (tq *J* = 1.5, 6.6 Hz, 1H), 4.72 (ddd, *J* = 2.2, 3.8, 6.2 Hz, 1H), 4.03–3.95 (m, 1H), 3.94–3.83 (m, 1H), 2.16–2.10 (m, 1H), 2.05 (s, 3H), 1.95–1.78 (m, 1H), 1.69–1.57 (m, 1H), 1.56–1.47 (m, 1H), 1.19 (ddd, *J* = 5.3, 8.0, 13.5 Hz, 1H), 1.10–1.06 (m, 12H), 0.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 146.7, 135.9, 134.9, 134.4, 129.5, 129.4, 127.5, 127.3, 100.8, 72.2, 67.6, 65.7, 47.7, 42.2, 34.0, 27.0, 25.5, 24.0, 21.2, 19.5, 19.2; EI-MS *m/z* 423 (M^+-^{t}Bu), 363 (M^+-^{t}Bu-AcOH), 253, 199, 147; HRMS calcd for $C_{23}H_{27}O_2Si$: 363.1780, found 363.1765.



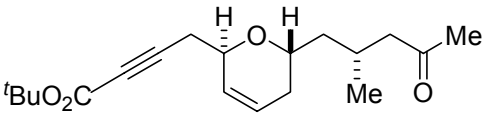
(2*R*,4*R*,2′*S*,4′*R*)-*tert*-Butyl 4-{6-[4-(*tert*-butyldiphenylsiloxy)-2-methylpentyl]-5,6-dihydro-

2*H*-pyran-2-yl}but-2-ynoate (103): To a –78 °C solution of 0.065 g of **87** (0.135 mmol) in 1 mL of dry CH_2Cl_2 was slowly added 0.290 g of **41** (0.677 mmol) in 0.5 mL of CH_2Cl_2 followed by a solution of 0.065 g of tributyltin trifluoromethanesulfonate (0.149 mmol) in 1 mL of CH_2Cl_2 via cannula. The reaction was maintained at –78 °C for 2 h, then allowed to slowly warm to ambient temperature. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography (1% EtOAc/hexanes) to afford 0.056 g (74%) of **103** as a clear colorless oil: $[\alpha]_D$ = –25 (*c* 1.2, $CHCl_3$); IR (thin film): 3071, 3045, 2963, 2930, 2857, 2240, 1708, 1427, 1369, 1279, 1160, 1074, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80–**7**.60 (m, 4H), 7.50–7.32 (m, 6H), 5.95–5.80 (m, 2H), 4.40–4.29 (m, 1H), 3.75–3.20 (m, 1H), 3.88 (dq, *J* = 6.0, 12.0 Hz, 1H), 2.58 (dd, *J* = 6.6, 16.7 Hz, 1H), (dd, *J* = 6.0, 16.5 Hz, 1H) 2.00–1.70 (m, 4H), 1.60 (s, 3H), 1.49 (s, 9H), 1.38 (ddd, *J* = 4.5, 9.1, 13.9 Hz, 1H), 1.25–1.14 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 1H), 1.05 (s, 9H), 0.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 135.9, 134.9, 134.4, 129.4, 129.3, 127.5, 127.4, 127.3, 126.0, 83.2, 83.0, 76.0, 70.1, 67.6, 66.0, 47.7, 42.4, 31.6, 30.8, 29.7, 28.0 (3C), 27.0 (3C), 25.4, 24.7, 24.0, 22.6, 19.7, 19.3, 14.1; HRMS *m/z* calcd for $C_{35}H_{48}O_4Si$ $[M+Na]^+$: 583.3220, found 583.3203.



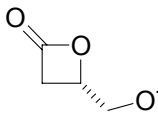
(2*R*,4*S*,2′*S*)-(2-methyl-4-oxopentyl)-3,4-dihydro-2*H*-pyran-4-yl acetate (104): To a 0 °C solution of 0.400 g of allylic acetate **87** (0.833 mmol) in 0.25 mL of THF was added 1.95 mL of a 1.0 M THF solution of tetrabutylammonium fluoride (1.95 mmol) slowly dropwise. The reaction was warmed to ambient temperature, maintained for 6 h, then diluted with EtOAc (100 mL). The solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude alcohol was

dissolved in 6 mL of CH_2Cl_2 and 1.0 g of 4 Å molecular sieves was added followed by 0.784 g of pyridinium dichromate (2.08 mmol). The resulting brown suspension was maintained at ambient temperature for 1.5 h before being diluted with Et_2O (100 mL) and filtered through Celite. The filtrate was concentrated and the crude product mixture was purified by flash chromatography on silica gel (hexanes/Et_3N 50:1) to afford 0.160 g (80%) of **104** as a clear, colorless residue: $[\alpha]_D$ = +9.8 (*c* 2.5, $CHCl_3$); IR (thin film): 3067, 2960, 2930, 1729, 1644, 1372, 1232, 1042, 1023, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.40 (d, *J* = 6.2 Hz, 1H), 5.38–5.33 (m, 1H), 4.72–4.69 (m, 1H), 4.05–3.97 (m, 1H), 2.50–2.22 (m, 3H), 2.20–2.13 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.73–1.61 (m, 2H), 1.27 (ddd, *J* = 3.3, 8.4, 14.0 Hz, 1H), 0.92 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1, 170.7, 146.4, 100.9, 72.2, 65.5, 51.4, 41.7, 34.0, 30.2, 25.7, 21.1, 19.6.

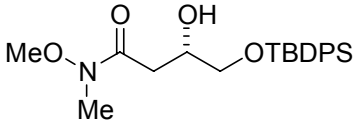


(2*R*,6*R*,2′*S*)-4-[6-(2-Methyl-4-oxo-pentyl)-5,6-dihydro-2*H*-pyran-2-yl]but-2-ynoic acid *tert*-butyl ester (86): To a –78 °C solution of 0.064 g of **104** (0.267 mmol) in 1 mL of dry CH_2Cl_2 was slowly added 0.457 g of **41** (1.07 mmol) in 0.5 mL of CH_2Cl_2 followed by a solution of 0.129 g of tributyltin trifluoromethanesulfonate (0.293 mmol) in 1 mL of CH_2Cl_2 via cannula. The reaction was maintained at –78 °C for 2 h, then allowed to slowly warm to ambient temperature. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 6 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography (2% EtOAc/hexanes) to afford 0.068 g (80%) of **86** as a clear colorless oil: $[\alpha]_D$ = –72 (*c* 1.5, $CHCl_3$); IR (thin film): 3039, 2980, 2931, 2241, 1706, 1369, 1282, 1160, 1074, 912, 732 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ 5.92–5.85 (m, 1H), 5.79–5.74 (m, 1H), 4.46–4.34 (m, 1H), 3.74 (dtd, *J* = 3.6, 8.5, 12.5 Hz, 1H), 2.61 (dd, *J* = 7.0, 16.9 Hz, 1H), 2.50 (dd, *J* = 6.9, 17.0 Hz, 1H), 2.44 (dd, *J* = 6.9, 17.0 Hz, 1H), 2.33–2.22 (m, 2H), 2.11 (s, 3H), 2.02–1.82 (m, 3H), 1.53 (ddd, *J* = 4.5, 9.7, 14.0 Hz, 1H), 1.45 (s, 9H), 1.22 (ddd, *J* = 3.1, 8.3, 12.9 Hz, 1H), 0.92 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6, 152.5, 127.4, 125.9, 83.3, 82.9, 75.9, 70.1, 66.1, 51.6, 42.1, 30.8, 30.0, 28.0, 26.0, 24.6, 19.6; EI-MS *m/z* 321 (M^++H), 265, 181, 163, 123, 105, 57; HRMS calcd for $C_{19}H_{28}O_4$ $[M+Na]^+$: 343.1885, found 343. 1900.

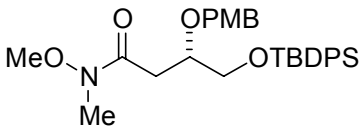


(4*S*)-(*tert*-Butyldiphenylsiloxymethyl)oxetan-2-one (105):[23a] To a –50 °C solution of 58 mg of aluminum triamine catalyst ***ent*-36** (0.10 mmol) in 5.7 mL of CH_2Cl_2 was added 0.30 mL of DIPEA (1.7 mmol) followed by 0.14 mL of acetyl bromide (1.9 mmol). The resulting yellow solution was stirred at –50 °C whereupon 0.298 g of 2-*tert*-butyldiphenylsilyloxyacetaldehyde (1.0 mmol) was added dropwise via syringe. After maintaining at –50 °C for 12 h, the reaction mixture was diluted with 10 mL of pentane, filtered through silica gel (30% EtOAc/hexanes), and concentrated. The resulting residue was purified by silica gel chromatography (10% EtOAc/hexanes) to provide 0.30 g of **105** (92%) as a white crystalline solid: ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.66 (m, 4H), 7.45–7.38 (m, 6H), 4.64–4.57 (m, 1H), 4.05 (dd, *J* = 2.6, 12.4 Hz. 1H), 3.84 (dd, *J* = 3.1, 12.4 Hz, 1H), 1.08 (s, 9H). Separation of the enantiomers by chiral HPLC (90/10 hexanes/^{i}PrOH, 1.0 mL/min) $T_{r\ (min)}$ = 7.63 (*R*), 13.27 (*S*) determined the enantiomeric excess to be 89%.



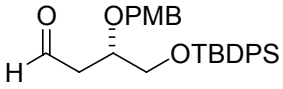
4-(*tert*-Butyldiphenylsilanyloxy)-(3*S*)-hydroxy-*N*-methoxy-*N*-methylbutyramide (106): To a 0 °C solution of 1.36 g of *N*, *O*-

methoxymethylamine hydrochloride (14 mmol) in 30 mL of CH_2Cl_2 was added 14 mL of dimethylaluminum chloride (14 mmol) as a 1 M solution in hexanes. The solution was allowed to warm to ambient temperature and maintained for 1 h. To this suspension was added a solution of 2.39 g of **105** (7.0 mmol) in 5 mL of CH_2Cl_2 via cannula. The reaction mixture was maintained for 2 h at ambient temperature, and then quenched with 42 mL of pH 8 hydrogen phosphate buffer. The reaction was filtered through a pad of Celite to remove the solid aluminum salts. The resulting biphasic solution was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 2.64 g (94%) of the β-hydroxy amide as a white solid: $[\alpha]_D$ = –16 (*c* 1.1, $CHCl_3$); IR (thin film): 3441.6, 3069, 3046, 2954, 2931, 2891, 2855, 1640, 1465, 1426, 1386, 1184, 1109, 998, 828, 741, 705, 610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 1.8, 5.0 Hz, 4H), 7.44–7.36 (m, 6H), 4.24 (m, 1H), 3.85 (d, *J* = 3.2 Hz, 1H), 3.80 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.72 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.64 (s, 3H), 3.16 (s, 3H), 2.78 (d, *J* = 15.6 Hz, 1H), 2.67 (dd, *J* = 8.3, 15.2 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 135.4, 133.2, 129.7, 127.7, 68.6, 67.0, 61.1, 53.4, 34.9, 31.7, 26.8, 19.2; HRMS calcd for $C_{22}H_{31}NO_4Si$: 344.1322, found 344.1318.



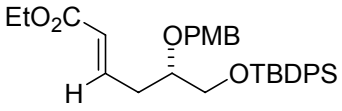
4-(*tert*-Butyldiphenylsilanyloxy)-*N*-methoxy-(3*S*)-(4-methoxybenzyloxy)-*N*-methylbutyramide (107): To a solution of 0.511 g of β-hydroxy amide **106** (1.27 mmol) in 2.5 mL of diethyl ether at ambient temperature was added 0.790 mL of *p*-methoxybenzyltrichloroacetimidate (3.82 mmol) and 0.010 mL of trifluoromethanesulfonic acid via syringe. After stirring for 30 min, saturated

aqueous $NaHCO_3$ (5 mL) was added to the reaction. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (20% EtOAc/hexane). Elution of the title compound from the silica column was coincident with trichloroacetamide. The product was triturated from the white solid using pentane (5 × 10 mL). The combined pentane washings were concentrated to provide **107** as a clear, colorless oil in 77% yield: $[\alpha]_D$ = –9.5 (*c* 1.1, $CHCl_3$); IR (thin film): 3006, 2954, 2931, 2851, 1707, 1655, 1509, 1461, 1422, 1244, 1109, 820, 756, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 1.1, 7.5 Hz, 4H), 7.46–7.35 (m, 6H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.53 (dd, *J* = 5.7, 16.5 Hz, 2H), 4.12 (m, 1H), 3.79 (s, 3H), 3.76 (dd, *J* = 5.2, 7.2 Hz, 1H), 3.68 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.61 (s, 3H), 3.20 (s, 3H), 2.95–2.55 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 156.8, 135.6, 133.3, 130.9, 129.7, 129.4, 127.7, 113.6, 76.5, 72.3, 65.6, 61.2, 55.2, 34.7, 32.0, 26.8, 19.2; HRMS calcd for $C_{30}H_{39}NO_5Si$: 464.1893, found 464.1893.



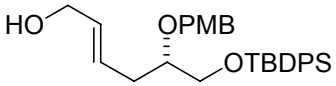
4-(*tert*-Butyldiphenylsilanyloxy)-(3*S*)-(4-methoxybenzyloxy) butyraldehyde (108): To a –78 °C solution of 61 mg of **107** (0.117 mmol) in 1.0 mL of THF was added 0.129 mL of DIBAL-H (0.129 mmol) as a 1 M solution in hexanes. After stirring at –78 °C for 45 min, the reaction was poured into 5 mL of a 0 °C mixture of 1:1 diethyl ether and 1 M HCl. The resulting biphasic mixture was stirred at ambient temperature for 30 min and the organic layer was separated and washed with brine (1 × 5 mL). The ether layer was dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel chromatography (20% EtOAc/hexanes) provided 0.044 g (80%) of the

aldehyde as a clear, colorless oil: $[\alpha]_D$ = –20 (*c* 0.7, $CHCl_3$); IR (thin film): 3065, 3050, 2994, 2954, 2931, 2855, 2725, 1723, 1608, 1584, 1513, 1469, 1422, 1248, 1113, 1034, 820, 737, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.78 (t, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 1.7, 6.1 Hz, 4H), 7.43–7.37 (m, 6H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.48 (dd, *J* = 11.1, 34.1 Hz, 2H), 4.03 (m, *J* = 5.5 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 4.9, 10.6 Hz, 1H), 3.67 (dd, *J* = 5.7, 10.5 Hz, 1H), 2.70 (dd, *J* = 1.9, 6.1 Hz, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 159.4, 135.7, 133.2, 130.3, 130.0, 129.5, 127.9, 113.9, 74.6, 71.9, 65.3, 55.3, 46.4, 26.9, 19.3; EI-MS (70 eV) 419 (M^+-CH_2CHO), 405 (M^+-^{t}Bu), 391, 333, 327, 309, 267, 241, 199, 181, 163, 135, 121, 105.

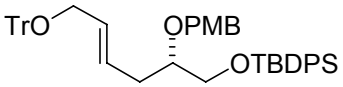


6-(*tert*-Butyldiphenylsilanyloxy)-(5*S*)-(4-methoxybenzyloxy)hex-2-enoic acid ethyl ester: To a 0 °C suspension containing 1.06 g of methyltriphenylphosphonium bromide (3.0 mmol) in 5 mL of THF was added 4.53 mL of KHMDS (2.27 mmol) as a 0.5 M solution in toluene dropwise via syringe. A solution of 0.700 g of the aldehyde **108** (1.5 mmol) in 5 mL of THF was transferred via cannula to the orange Wittig reagent at 0 °C. The reaction mixture was warmed to ambient temperature and maintained for 1 h. The reaction was then concentrated and purified by silica gel chromatography (25% EtOAc/hexanes) to provide 0.758 g (95%) of the *E*-enoate ester as a colorless oil: $[\alpha]_D$ = –16 (*c* 2.5, $CHCl_3$); IR (thin film): 3069, 3050, 2954, 2931, 2851, 1719, 1655, 1612, 1584, 1513, 1469, 1430, 1362, 1299, 1248, 1172, 1113, 1034, 820, 741, 705, 610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.8 Hz, 4H), 7.56–7.40 (m, 6H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.95 (dt, *J* = 7.9, 15.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.87 (d, *J* = 15.6 Hz, 1H), 4.46 (dd, *J* = 11.4, 31.2 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.74 (m, 1H), 3.60 (dd, *J* = 5.2, 6.0 Hz, 2H), 2.49 (dd,

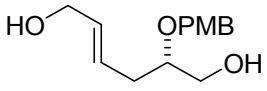
J = 6.9, 14.3 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 159.3, 145.5, 135.7, 133.4, 133.3, 130.5, 129.9, 129.5, 127.9, 123.6, 113.8, 78.1, 71.8, 65.4, 60.3, 55.3, 34.8, 26.9, 19.3, 14.4; EI-MS (70 *eV*) 475 (M^+-^{t}Bu), 429, 337 (475-OPMB), 309, 267, 241, 227, 223, 199, 121 (PMB).



6-(*tert*-Butyldiphenylsiloxy)-(5*S*)-(4-methoxybenzyloxy)hex-2-en-1-ol: To a –78 °C solution of 0.328 g of the *E*-enoate ester (0.617 mmol) in 3.1 mL of THF was added 1.3 mL of a 1.0 M solution of DIBAL-H in hexanes (1.29 mmol). The reaction was allowed to warm slowly to 0 °C over a 90 min period. The reaction mixture was poured into a 0 °C mixture containing 10 mL of diethyl ether and 10 mL of 1 M HCl and was maintained for 15 min. The organic and aqueous layers were separated, and the aqueous layer was saturated with brine and washed with diethyl ether (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (15% EtOAc/hexanes) to provide 0.267 g (89%) of the allylic alcohol as a colorless oil: $[\alpha]_D$ = –13 (*c* 1.1, $CHCl_3$); IR (thin film): 3418, 3065, 3046, 2954, 2931, 2851, 1612, 1509, 1461, 1422, 1244, 1109, 1030, 820, 741, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 6.2 Hz, 4H), 7.44–7.36 (m, 6H), 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5Hz, 2H), 5.66–5.63 (m, 2H), 4.51 (dd, J = 11.3, 34.1 Hz, 2H), 4.04 (dd, J = 4.3, 9.4 Hz, 2H), 3.81 (s, 3H), 3.72 (dd, J = 5.7, 10.7 Hz, 1H), 3.64 (dd, J = 5.1, 10.5 Hz, 1H), 3.53 (m, J = 5.9 Hz, 1H), 2.34 (ddd, J = 6.6, 9.2, 9.9 Hz, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 135.8, 135.7, 133.6, 133.5, 131.7, 130.9, 129.9, 129.8, 129.6, 129.5, 128.7, 127.8, 113.8, 79.0, 71.6, 65.5, 63.6, 55.3, 34.4, 27.0, 19.3; EI-MS (70 *eV*) 433 (M^+-^{t}Bu), 415 (433-H_2O), 333, 295, 279, 241, 223, 211, 199, 181, 163, 135, 121, 105.

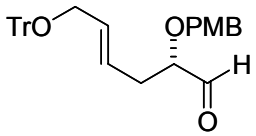


6-*tert*-Butyldiphenylsiloxy-(5*S*)-(4-methoxybenzyloxy)-hex-2-enyl triphenylmethyl ether (109): To a solution containing 0.181 mL of 2,6-lutidine (1.56 mmol), 0.289 g of chlorotriphenylmethane (1.04 mmol), and 0.383 g of tetra-*n*-butylammonium iodide (1.04 mmol) in 2 mL of CH_2Cl_2 was added a 1 mL methylene chloride solution containing 0.508 g of the allylic alcohol (1.04 mmol) via syringe at ambient temperature. The golden-brown reaction solution was maintained at ambient temperature for 5.5 h. The reaction mixture was then concentrated and purified by silica gel chromatography (10% EtOAc/hexanes) to provide 0.678 g (92%) of **109** as a clear, colorless oil: IR (thin film): 3057, 3026, 2955, 2927, 2856, 1960, 1881, 1818, 1616, 1509, 1450, 1426, 1386, 1362, 1299, 1248, 1176, 1109, 1054, 1034, 820, 760, 744, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 6.5 Hz, 4H), 7.53 (d, *J* = 7.3 Hz, 6H), 7.48–7.28 (m, 15H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.88–5.65 (m, 2H), 4.58 (dd, *J* = 11.3, 26.5 Hz, 2H), 3.87–3.65 (m, 3H), 3.83 (s, 3H), 3.60 (d, *J* = 4.6 Hz, 2H), 2.43 (ddd, *J* = 6.4, 9.63, 10.0 Hz, 2H), 1.13 (s, 9H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 159.2, 144.6, 135.8, 133.7, 131.1, 130.0, 129.8, 129.5, 129.4, 128.8, 128.6, 128.0, 127.9, 127.1, 113.9, 86.9, 79.3, 71.8, 65.7, 65.0, 55.4, 34.9, 27.0, 19.4;

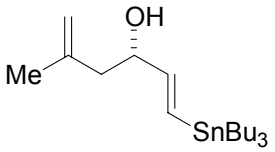


(2*S*)-(4-Methoxybenzyloxy)-6-(triphenylmethyloxy)hex-4-en-1-ol: To a solution of 0.100 g of **109** (0.137 mmols) in 1.4 mL of THF was added 0.164 mL of TBAF (0.164 mmol) as a 1 M solution in THF via syringe at ambient temperature. The reaction was maintained for 2 h, then added directly to a silica gel column and eluted with 30% EtOAc/hexanes. The alcohol was isolated as a colorless oil in 99% yield**:** $[\alpha]_D$ = +8.0 (0.8,

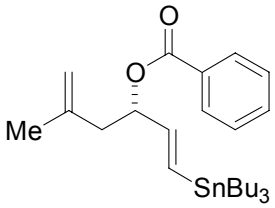
$CHCl_3$); IR (thin film): 3434, 3081, 3061, 3030, 2931, 2867, 1640, 1612, 1513, 1446, 1244, 1172, 1030, 824, 745, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.2 Hz, 6H), 7.35–7.23 (m, 11H), 6.89 (d, *J* = 6.6 Hz, 2H), 5.95–5.65 (m, 2H), 4.57 (dd, *J* = 11.1, 41.0 Hz, 2H), 3.80 (s, 3H), 3.74–3.40 (m, 3H), 2.39 (ddd, *J* = 6.5, 9.8, 13.0 Hz, 2H), 1.95 (m, 1H); ^{13}C NMR (75 MHz**,** $CDCl_3$): δ 159.4, 144.3, 130.5, 129.9, 129.6, 128.8, 128.0, 127.6, 127.1, 114.1, 86.9, 79.1, 71.5, 64.8, 64.3, 55.4, 34.2; HRMS calcd for $C_{33}H_{34}O_4$: 493.2373, found 493.2379.



(2*S*)-(4-methoxybenzyloxy)-6-(triphenylmethyloxy)hex-4-en-1-al (89): To a solution of 0.133 g of alcohol (0.19 mmol) in 15 mL of CH_2Cl_2 at ambient temperature was added 0.094 g of Dess-Martin periodinane (0.22 mmol) portionwise. The resulting turbid white mixture was stirred 30 min. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford 0.124 g (94%) of **89** as a colorless oil: $[\alpha]_D$ = –8.3 (0.8, $CHCl_3$); IR (thin film): 3550, 3085, 3058, 3032, 2932, 2860, 1732, 1612, 1513, 1490, 1448, 1248, 1174, 1035, 763, 738, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.67 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 6H), 7.42–7.18 (m, 11H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.90–5.71 (m, 2H), 4.62 (dd, *J* = 11.3, 21.7 Hz, 2H), 3.88–3.73 (m, 4H), 3.61 (d, *J* = 4.2 Hz, 2H), 2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 144.3, 134.9, 130.8, 129.9, 129.7, 128.8, 128.0, 128.0, 127.3, 127.1, 125.9, 114.1, 87.0, 82.8, 72.4, 64.7, 55.4, 33.6, 29.9. FAB-MS *m/z* 515 $[M+Na]^+$.

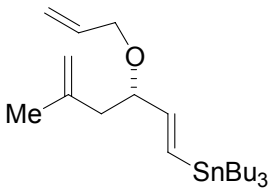


(1*E*)-(3*S*)-5-Methyl-1-tributylstannylhexa-1,5-dien-3-ol (111): To a –78 ºC solution of 0.119 g of allyl-(–)-Ipc_2B **110** (0.348 mmol) in 1.5 mL of Et_2O was added 0.100 g of β-tributylstannyl acrolein (0.290 mmol) slowly dropwise. The resulting colorless solution was maintained for 1 h at –78 ºC and then slowly warmed to 0 ºC. An aqueous solution of 3 N NaOH (0.3 mL) and 30% H_2O_2 (0.3 mL) were added, the colorless, biphasic solution was then stirred for 2 h at ambient temperature. The mixture was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (2% EtOAc/hexanes) to afford 0.112 g (96%) of the homoallylic alcohol as a colorless oil: $[\alpha]_D$ = –9.3 (*c* 1.1, $CHCl_3$); IR (thin film): 3365, 2957, 2926, 2871, 2853, 1460, 1376, 1073, 989, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.12 (dd, *J* = 1.1, 19.1 Hz, 1H), 6.04 (dd, *J* = 5.1, 19.1 Hz, 1H), 4.86 (dd, *J* = 1.2, 79.5 Hz, 1H), 4.24–4.23 (m, 1H), 2.28–2.24 (m, 2H), 1.93 (d, *J* = 3.4 Hz, 1H), 1.80 (s, 3H), 1.55–1.47 (m, 6H), 1.36–1.34 (m, 6H), 0.94–0.89 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.1, 142.2, 127.6, 113.6, 72.4, 46.0, 30.0, 27.2, 22.4, 13.6, 9.4; HRMS calcd for $C_{15}H_{29}OSn$ $[M-^nBu]^+$: 345.1240, found 345.1251.



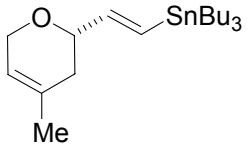
(1*E*)-(3*S*)-Benzoic acid 3-methyl-1-(2-tributylstannylvinyl)-but-3-enyl ester (111a): To a 25 ºC solution of 0.092 g of the homoallylic alcohol **111** (0.23 mmol) in 0.1 mL pyridine was added 0.03 mL of benzoyl chloride (0.28 mmol) and 0.001 g of DMAP (0.01 mmol) sequentially. The resulting white suspension was maintained for 20 min at ambient temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (2 mL), and the aqueous layer was extracted with Et_2O (3 × 6 mL). The combined organics were washed with brine (4 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (2%

EtOAc/Hex) to afford 0.113g (97%) of the ester as a colorless oil: $[\alpha]_D = -9.2$ (*c* 7.1, $CHCl_3$); IR (thin film): 2956, 2926, 2871, 2853, 1721, 1271, 1111, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.59 (m, 1H), 7.50–7.45 (m, 2H), 6.32 (d, *J* = 18.9 Hz, 1H), 6.07 (dd, *J* = 5.5, 19.1 Hz, 1H), 5.70–5.68 (m, 1H), 4.83 (s, 1H), 2.57–2.48 (m, 2H), 1.84 (s, 1H), 1.53 (m, 6H), 1.33 (m, 7H), 0.91 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 145.3, 141.1, 132.7, 130.6, 129.6, 128.3, 113.6, 75.3, 43.1, 29.0, 27.6, 27.2, 22.6, 13.7, 9.4; HRMS calcd for $C_{22}H_{33}O_2Sn$ $[M-^nBu]^+$: 449.1503, found 449.1484. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H colume, flow rate 0.5 mL/min, 0.5% ^{i}PrOH, 99.5% hexane, T_r: 9.7 min (*R*), 10.8 min (*S*)] provided the enantiomer ratio: *S* : *R* = 98 : 1 (98% ee).

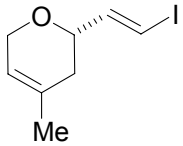


(1*E*, 3*S*)-3-Allyloxy-5-methylhexa-1,5-dienyltributylstannane (112): To a –78 °C solution of 0.662 g of the homoallylic alcohol **111** (1.65 mmol) in 10 mL of THF was added 7.90 mL of 0.5 M toluene solution of KHMDS (1.82 mmol) slowly dropwise. After 15 min, 0.94 mL of allyl bromide (4.95 mmol) was added into the pale yellow reaction mixture. The resulting solution was slowly warmed to ambient temperature and maintained for 2 h. The reaction was quenched with brine and the aqueous layer was extracted with Et_2O (3 × 12 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded 0.699 g (97%) of the title compound **112** as a colorless oil: $[\alpha]_D = -38$ (*c* 2.3, $CHCl_3$); IR (thin film): 3077, 2957, 2926, 2871, 2852, 1460, 1077, 992, 920, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.10 (d, *J* = 9.5 Hz, 1H), 5.96-5.87 (m, 1H), 5.79 (dd, *J* = 7.2, 19.0 Hz, 1H), 5.25 (dd, *J* = 1.6, 17.1 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 2H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.06 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.87–3.79 (m, 2H), 2.39 (dd *J* = 7.1, 13.9 Hz, 1H), 2.21 (dd, *J* =

6.3, 13.9 Hz, 1H), 1.75 (s, 3H), 1.56–1.46 (m, 6H), 1.37–1.25 (m, 7H), 0.96–0.82 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 142.2, 135.1, 131.2, 116.5, 112.6, 82.0, 69.1, 44.0, 29.1, 27.2, 22.9, 13.7, 9.4; HRMS calcd for $C_{18}H_{33}OSn$ [M-^{n}Bu]$^+$: 377.1580, found 377.1597.

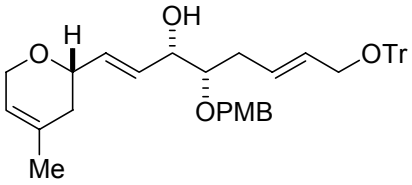


Tributyl[(*E*)-2-[(2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]-vinyl]stannane (114): To a brown solution of 0.081 g of freshly prepared Schrock's catalyst (0.11 mmol) in 11 mL of degassed toluene was added 0.661 g of **112** (1.5 mmol) at ambient temperature. After maintaining the reaction for 25 min, the resulting dark solution was added another portion of 0.081 g of Schrock's catalyst (0.11 mmol). After 30 min, the reaction was exposed to air for 2 h. The reaction mixture was concentrated to provide the crude product, which was purified by flash chromatography on silica gel (0.6% EtOAc/hexanes) to afford 0.465 g (81%) of **114** as a brown oil: $[\alpha]_D$ = –73 (*c* 1.1, $CHCl_3$); IR (thin film): 2957, 2926, 2872, 2851, 1460, 1378, 1123, 988 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (d, *J* = 19.2 Hz, 1H), 6.09 (dd, *J* = 4.8, 19.2 Hz, 1H), 5.43 (s, 1H), 4.22 (s, 2H), 4.00 (m, 1H), 2.10–1.91 (m, 2H), 1.73 (s, 3H), 1.61–1.47 (m, 6H), 1.39–1.27 (m, 6H), 0.94–0.86 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 131.5, 128.5, 119.6, 76.4, 65.6, 35.5, 29.0, 27.2, 22.9, 13.6, 9.3; HRMS calcd for $C_{16}H_{29}OSn$ [M-^{n}Bu]$^+$: 357.1240, found 357.1248.



(2*S*)-2-[(*E*)-2-Iodovinyl]-4-methyl-3,6-dihydro-2*H*-pyran (115): To a –20 ºC solution of 0.226 g of **114** (0.55 mmol) in 10 mL of THF was added a mixture of 0.123 g of NIS (0.55 mmol) and 0.8 mL of THF slowly dropwise. The resulting yellow solution was maintained for 30 min at –20 ºC, at which point brine was added (6 mL) and the mixture was extracted with Et_2O (3 × 15 mL). The combined organics were washed with saturated

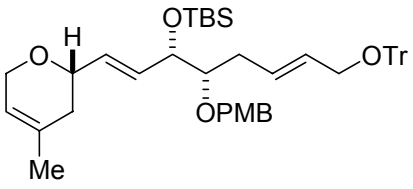
$Na_2S_2O_3$ (8 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% CH_2Cl_2/pentane) to afford 0.131 g (96%) of the title compound **115** as a yellow oil: $[\alpha]_D$ = –107 (*c* 0.76, $CHCl_3$); IR (thin film): 3026, 2963, 2908, 2823, 1381, 1368, 1124, 1059, 1013, 667, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.61 (dd, *J* = 5.5, 14.5 Hz, 1H), 6.39 (dd, *J* = 0.9, 14.6 Hz, 1H), 5.39 (s, 1H), 4.16 (s, 2H), 3.97 (m, 1H), 2.04-1.87 (m, 2H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 131.0, 119.7, 78.0, 75.5, 65.6, 35.0, 23.0; HRMS calcd for $C_8H_{11}OI$: 249.9855, found 249.9860.



(1*E*,6*E*)(3*S*,4*S*)-4-(4-Methoxybenzyloxy)-1-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-8-trityloxy-octa-1,6-dien-3-ol (117): To a mixture of 0.173 g of magnesium powder (7.1 mmol) in 5 mL of Et_2O at ambient temperature was added 0.57 mL of 1,2-dibromoethane (6.7 mmol) in 1.70 mL of benzene slowly dropwise. After heat generation and gas evolution ceased, the slightly turbid gray solution was maintained for an additional 30 min then allowed to stand for 1.5 h without stirring. The molarity of magnesium bromide in Et_2O was approximately 1.0 M.

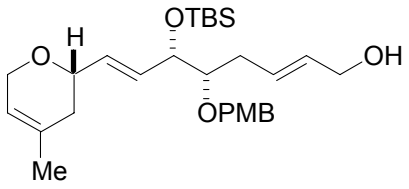
To a –78 °C solution of 0.104 g of **115** (0.42 mmol) in 3.5 mL of Et_2O was added 0.60 mL of 1.39 M pentane solution of ^{t}BuLi (0.83 mmol) slowly dropwise. After maintaining the pale yellow reaction at –78 °C for 1h, 1.00 mL of 1.0 M ethereal magnesium bromide (1.0 mmol) was added dropwise. The diethyl ether was pumped off completely under reduced pressure at –78 °C and 6.0 mL of precooled (–78 °C) CH_2Cl_2 was added via cannula to dissolve the white residue (**116**). To this clear colorless solution, 0.158 g of **89** (0.33 mmol) in 0.7 mL of CH_2Cl_2 was added dropwise. After stirring for 20 min at –78 °C, water (1.5 mL) and brine (2.5 mL)

were added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (35% EtOAc/hexanes) to afford 1.91 g (96%) of **117** as a colorless oil: $[\alpha]_D$ = –32 (*c* 3.0, $CHCl_3$); IR (thin film): 3436, 3013, 2928, 2856, 1513, 1249, 1216, 1034, 757, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58–7.56 (m, 6H), 7.38–7.26 (m, 11H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.97–5.78 (m, 4H), 5.48 (s, 1H), 4.65 (dd, *J* = 10.9, 44.7 Hz, 2H), 4.25 (s, 3H), 4.14 (m, 1H), 3.78 (s, 3H), 3.69 (d, *J* = 4.4 Hz, 2H), 3.52 (m, 1H), 2.93 (s, 1H), 2.56 (m, 1H), 2.43 (s, 1H), 2.16 (m, 1H), 2.08 (s, .6H), 1.99 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 144.1, 133.1, 131.2, 130.0, 129.7, 129.6, 129.4, 128.4, 127.6, 127.5, 126.8, 119.5, 113.7, 86.6, 81.2, 73.1, 72.1, 65.4, 64.5, 60.2, 55.0, 35.5, 33.4, 22.8, 20.9, 14.0; FAB-MS *e*/ν 639 $[M+Na]^+$. Separation of the diastereomers by HPLC [Zorbax column, flow rate 0.3 mL/min, 3.5 % ^{i}PrOH, 96.5% hexane, T_r: 65.2 (*S*), 67.8 (*R*)] provided the diastereomer ratio: *S*:*R* = 9:1.



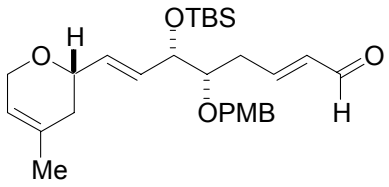
***tert*-Butyl-{(4*E*)(1*S*, 2*S*)-2-(4-methoxy-benzyloxy)-1-[(1*E*)-2-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-vinyl]-6-trityloxyhex-4-enyloxy}dimethylsilane (118):** To a 0 °C solution of 0.682 g of **117** (1.1 mmol) and 0.238 g of imidazole (3.4 mmol) in 5 mL of DMF was added 0.513 g of TBSCl (3.4 mmol). After maintaining the reaction at 25 °C for 4.5 h, the resulting yellow solution was treated with saturated $NaHCO_3$ (15 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% EtOAc/Hex) to afford 0.799 g (98%) of the

silyl ether **118** as a yellow oil: $[\alpha]_D$ = –52 (*c* 2.1, $CHCl_3$); IR (thin film): 3058, 3005, 2954, 2929, 2855, 1513, 1448, 1249, 1105, 1036, 836, 775, 758, 706, 632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.62 (m, 6H), 7.49–7.37 (m, 11H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.05–5.77 (m, 4H), 5.58 (s, 1H), 4.73 (dd, *J* = 11.3, 19.0 Hz, 2H), 4.47 (t, *J* = 4.6 Hz, 1H), 4.30 (s, 2H), 4.20 (m, 1H), 3.90 (s, 3H), 3.71 (d, *J* = 4.9 Hz, 2H), 3.54 (m, 1H), 2.52 (m,1H), 2.32–2.21 (m, 2H), 2.07 (m,1H), 1.06 (s, 9H), 0.2 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 144.3, 131.6, 131.4, 130.8, 130.2 129.6, 129.4 128.6, 127.7, 126.8, 119.7, 113.7, 86.6, 82.1, 73.6, 73.1, 72.5, 65.5, 64.8, 55.2, 35.7, 33.2, 25.9, 25.6, 23.0, 18.1, –4.5, –4.9; FAB-MS *e*/ν 753 $[M+Na]^+$.

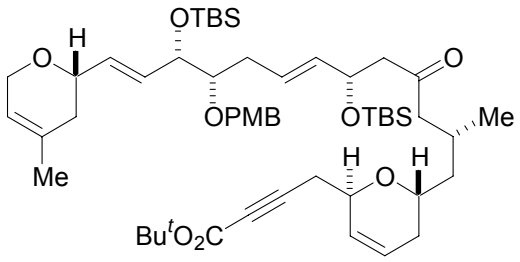


(2*E*,7*E*)(5*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-8-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)octa-2,7-dien-1-ol (119): To a 0 °C solution of 0.440 g of the silyl ether **118** (0.61 mmol) in 28.0 mL of nitromethane was added 3.9 mL of formic acid slowly dropwise. The resulting yellow solution was stirred for another 20 min after the completed addition. 40 mL of cold saturated $NaHCO_3$ and then 30 mL of EtOAc were added. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organics were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (35% EtOAc/Hex) to afford 0.250 g (86%) of the allylic alcohol **119** as a yellow oil: $[\alpha]_D$ = –83 (*c* 4.0, $CHCl_3$); IR (thin film): 3442, 2999, 2929, 2856, 1513, 1249, 1098, 1037, 972, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.87 (m, 2H), 5.72 (m, 2H), 5.50 (s, 1H), 4.62 (dd, *J* = 11.5, 29.6 Hz, 2H), 4.37 (t, *J* = 4.5 Hz, 1H), 4.26 (s, 2H), 4.13 (s, 3H), 3.89 (s, 3H), 3.44 (m, 1H), 2.37 (m, 1H), 2.16–2.11 (m, 2H), 1.79 (m, 1H), 0.98 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 159.2, 131.5, 131.4, 130.9, 130.8, 130.2, 130.1, 129.5, 119.7, 113.6, 81.8, 73.5, 73.1, 72.3, 65.6, 63.8, 55.3, 35.7, 32.8, 25.9, 23.0, 18.1, -4.5, -4.9; HRMS calcd for $C_{24}H_{35}O_5Si$ $[M-^tBu]^+$: 431.2253, found 431.2275.



(2*E*,7*E*)(5*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-8-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)octa-2,7-dienal (85): To a solution of 0.117 g of the allylic alcohol (0.16 mmol) in 10 mL of CH_2Cl_2 was added 0.139 g of Dess-Martin periodinane (0.33 mmol) portionwise at ambient temperature. The resulting turbid white mixture was stirred 30 min, then quenched with 8 mL of saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford 0.117 g (100%) of **85** as a pale yellow oil: $[\alpha]_D$ = –86 (*c* 3.9, $CHCl_3$); IR (thin film): 2955, 2930, 2887, 2856, 1692, 1513, 1250, 1111, 1036, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 6.2 Hz, 2H), 6.89 (dt, *J* = 7.3, 15.6 Hz, 1H), 6.22 (dd, *J* = 7.9, 15.6 Hz, 1H), 5.96 (t, *J* = 3.0 Hz, 2H), 5.56 (s, 1H), 4.68 (dd, *J* = 11.5, 41.5 Hz, 2H), 4.32 (m, 1H), 4.19 (m, 1H), 3.95 (s, 3H), 3.26 (m, 1H), 2.68 (m, 1H), 2.48 (m, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 159.4, 156.6, 134.1, 132.2, 131.3, 130.0, 129.7, 129.0, 119.7, 113.8, 80.5, 73.3, 72.4, 65.6, 55.3, 35.7, 33.4, 25.8, 22.9, 18.1, –4.6, –5.0; HRMS calcd for $C_{24}H_{33}O_5Si$ $[M-^tBu]^+$: 429.2097, found 429.2077.

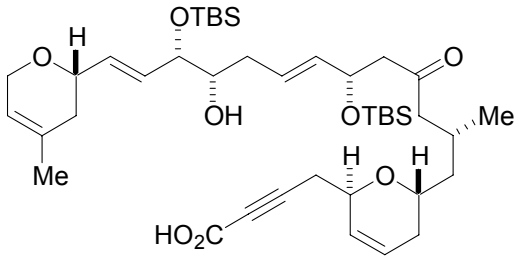


4-{(2*R*, 6*R*)-6-[(7*E*, 12*E*)(2*R*, 6*S*, 10*S*, 11*S*)-6,11-Bis-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-2-methyl-13-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-4-oxo-trideca-7,12-dienyl]-5,6-dihydro-2*H*-pyran-2-yl}but-2-ynoic acid *tert*-butyl ester (122): To a white suspension of 0.800g of disulfonamide (1.4 mmol) in 71 mL of 1,2-dichloroethane at 0 ºC was added 2.75 mL of a 1.0 M CH_2Cl_2 solution of boron tribromide (2.8 mmol) slowly dropwise via syringe. After 5 min, the reaction mixture was warmed to 50 ºC and maintained for 8 h. The resulting clear yellow solution was evaporated under reduced pressure. The yellow residue was dissolved in toluene (50 mL) and then the clear yellow solution was evaporated again. A procedure of dissolution and subsequent evaporation repeated two times until the white powder formed.

To a –78 ºC solution of 0.117 g of the prepared boron reagent **121f** (0.17 mmol) in 4 mL of CH_2Cl_2 was added 0.056 g of **86** (0.17 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added slowly. After maintaining the resulting colorless solution at –78 ºC for 2 h, 0.072 g of **85** (0.15 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added slowly. After 1 h, 1 mL of MeOH and 5 mL of phosphate buffer (pH 7) were injected sequentially. The reaction mixture was allowed to warm to ambient temperature and maintained for an additional 30 min. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 9 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated to provide the crude alcohol **120**.

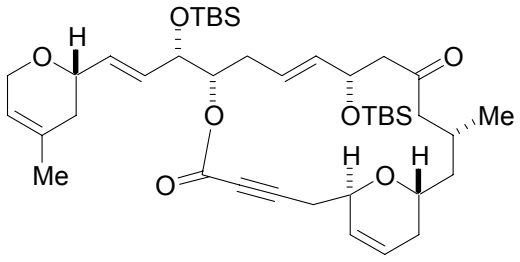
To a 0 ºC solution of the resulting yellow residue **120** and 0.059 g of imidazole (1.1 mmol) in 4 mL of DMF was added 0.126 g of TBSCl (1.0 mmol). After stirring the reaction for 7 h at ambient temperature, the resulting yellow solution was added 10 mL of saturated $NaHCO_3$

and 20 mL of CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford 0.141 g (89%) of the silyl protected aldol adduct **122** as a yellow oil: $[\alpha]_D$ = –82 (*c* 2.1, $CHCl_3$); IR (thin film): 2955, 2929, 2856, 2239, 1708, 1253, 1704, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.93–5.61 (m, 5H), 5.48–5.41 (m, 2H), 4.56–4.44 (m, 3H), 4.39 (bt, 1H), 4.27 (t, *J* = 4.3 Hz, 1H), 4.17 (s, 2H), 4.06–4.00 (m, 1H), 3.79 (s, 3H), 3.79–3.76 (m, 1H), 3.30 (m, 1H), 2.63–2.55 (m, 3H), 2.38–2.28 (m, 5.5H), 2.03–1.92 (m, 6.5H), 1.70 (s, 3H), 1.48 (s, 9H), 0.93 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.7, 159.2, 152.7, 134.3, 131.6, 131.5, 130.9, 130.1, 129.5, 128.1, 127.5, 125.9, 119.8, 113.8, 83.2, 82.4, 76.2, 73.6, 72.8, 72.5, 70.2, 70.0, 66.2, 65.7, 55.4, 52.4, 51.5, 42.1, 35.8, 32.7, 30.9, 28.1, 26.0, 25.3, 24.8, 23.1, 19.7, 18.7, 18.3, 18.2, –4.1, –4.4, –4.8, –4.8; HRMS calcd for $C_{53}H_{84}O_9Si_2$ $[M+Na]^+$: 943.5552, found 943.5579.



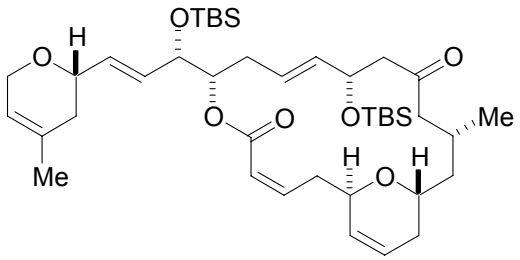
4-{(2*R*,6*R*)-6-[(7*E*,12*E*)(2*R*,6*S*,10*S*,11*S*)-6,11-Bis(*tert*-butyldimethylsilyloxy)-10-hydroxy-2-methyl-13-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)-4-oxotrideca-7,12-dienyl]-5,6-dihydro-2*H*-pyran-2-yl}but-2-ynoic acid (123): To a solution of 0.063 g of the silyl protected aldol adduct **122** (0.069 mmol) in 12 mL of CH_2Cl_2 at ambient temperature was added 6 mL of a pH 7 phosphate buffer followed by 0.134 g of DDQ (0.48 mmol) portionwise. The reaction was maintained for 4 h then diluted with CH_2Cl_2 (20 mL). The separated organic layer was washed

with saturated $NaHCO_3$ (2 × 15 mL) until it was colorless. The extract was dried over Na_2SO_4, filtered, and concentrated to give yellow oil, which was then dissolved in 8 mL of CH_2Cl_2. To this yellow solution, 0.34 mL of 2, 6-di-*tert*-butylpyridine (1.4 mmol) and 0.15 mL of trimethylsilyl trifluoromethanesulfonate (0.7 mmol) were added sequentially at –50 ºC. The reaction mixture was then warmed up to 0 ºC and stirred for 2.5 h. A pH 5 buffer solution (2 mL) was added at 0 ºC and the reaction was stirred vigorously for an additional 1 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (20% EtOAc/Hex to 15% EtOH/EtOAc) to afford 0.050 g (94%) of **123** as a yellow oil: $[\alpha]_D$ = –70 (*c* 2.5, $CHCl_3$); IR (thin film): 3395, 3035, 2953, 2929, 2852, 2237, 1713, 1470, 1359, 1252, 1091, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.95–5.85 (m, 1H), 5.80–5.46 (m, 5H), 5.42 (brs, 1H), 4.62 (m, 1H), 4.42 (m, 1H), 4.19 (brs, 2H), 4.13–3.95 (m, 3H), 3.74 (m, 1H), 3.55 (m, 1H), 2.80–2.55 (m, 2H), 2.54–2.37 (m, 2H), 2.35–2.20 (m, 2H), 2.13–1.88 (m, 6H), 1.71 (s, 3H), 1.65–1.50 (m, 1H), 1.36–1.20 (m, 2H), 0.95 (d, *J* = 5.7 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.04 (brs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 154.8, 135.3, 134.3, 133.6, 131.2, 130.5, 127.4, 126.3, 125.6, 119.5, 86.3, 75.7, 74.5, 73.4, 70.4, 69.4, 66.0, 65.4, 52.3, 50.3, 42.3, 35.4, 35.1, 31.0, 25.9, 24.3, 22.9, 20.0, 18.1, 0.44, –3.9, –4.3, –4.8, –5.0; HRMS calcd for $C_{41}H_{68}O_8Si_2$ $[M+Na]^+$: 767.4370, found 767.4345.

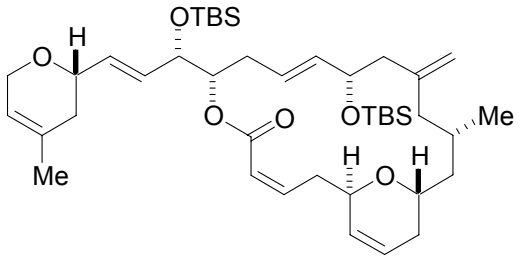


(9*E*,19*Z*)(1*R*, 7*S*, 11*S*, 15*R*, 17*R*)-11-(*tert*-Butyldimethylsilyloxy)-7-[(1*S*)-1-(*tert*-butyl-

dimethylsilyloxy)-3-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)allyl]-15-methyl-6,21-dioxabicyclo[15.3.1]henicosa-9,19-dien-3-yne-5,13-dione (125): To a 0 ºC solution of 0.0228 g of 4-pyrrolidinopyridine (0.15 mmol) and 0.050 mL of DIPEA (0.30 mmol) in 5.8 mL of toluene was added 0.024 mL of 2,4,6-trichlorobenzoyl chloride (0.15 mmol) slowly dropwise. The resulting pale yellow suspension was stirred for 15 min at 0 ºC then slowly treated with 0.0056 g of seco acid **123** (0.077 mmol) in 2.4 mL of toluene via syringe pump over 2 h. The pale yellow suspension was maintained for 16 h. The reaction was quenched with brine (5 mL) and the separated aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (15% EtOAc/hexanes) afforded 0.0051 g (93%) of the title compound **125** as a yellow oil: $[\alpha]_D$ = – 67 (*c* 2.2, $CHCl_3$); IR (thin film): 3033, 2956, 2929, 2856, 2237, 1713, 1471, 1361, 1250, 1094, 1067, 964, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.91–5.79 (m, 2H), 5.70 (dd, *J* = 6.0, 15.6 Hz, 1H), 5.65–5.51 (m, 3H), 5.43 (brs, 1H), 4.95 (ddd, *J* = 2.4, 6.8, 9.3 Hz, 1H), 4.66 (brd, *J* = 9.0 Hz, 1H), 4.43 (brd, *J* = 9.0 Hz, 1H), 4.20-4.16 (m, 3H), 4.07 (ddd, *J* = 3.0, 9.1 Hz, 1H), 3.61–3.53 (m, 1H), 2.67 (dd, *J* = 11.1, 17.6 Hz, 2H), 2.45–2.25 (m, 5H), 2.20–2.02 (m, 4H), 1.72 (s, 3H), 1.95–1.89 (m, 2H), 1.39 (dd, *J* = 10.1, 12.5 Hz, 1H), 1.14 (dd, *J* = 7.6, 13.5 Hz, 1H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 153.2, 137.1, 133.6, 131.3, 128.9, 127.5, 126.7, 123.6, 119.8, 86.7, 73.8, 73.6, 73.2, 71.4, 68.4, 65.9, 65.5, 54.1, 49.8, 41.8, 35.7, 31.6, 26.8, 25.9, 25.8, 23.9, 22.9, 22.6, 21.4, 18.1, 18.0, 14.1, 4.4, –4.4, –4.9, –5.2; ESI-MS: 749.3 $(M^+Na)^+$; HRMS calcd for $C_{41}H_{66}O_7Si_2$ $[M+Na]^+$: 749.4245, found 749.4279.

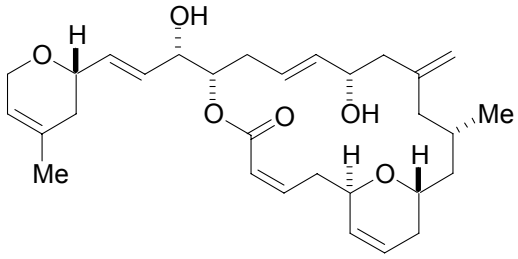


(3*Z*, 9*E*, 19*Z*)(1*R*, 7*S*, 11*S*, 15*R*, 17*R*) - 11-(*tert*-Butyldimethylsilyloxy)-7-[(1*S*)-(*tert*-butyldimethylsilyloxy)-3-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl)allyl]-15-methyl-6, 21-dioxa-bicyclo[15.3.1]henicosa-3, 9, 19-triene-5, 13-dione (130): To a solution of 8.5 mg of **29** (11.7 μmol) in EtOAc (3 mL) and 1-hexene (3 mL) under H_2 was added 0.014 mL of quinoline followed by 15 mg of Lindlar catalyst (5% Pd by wt.). The resulting black suspension was maintained for 1 h at ambient temperature, then filtered through Celite and concentrated. Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded 7.5 mg (88%) of **130** as a clear, colorless oil: $[\alpha]_D$ = –155 (*c* 1.2, $CHCl_3$); IR (thin film): 2955, 2927, 2855, 1720, 1651, 1419, 1111, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (ddd, *J* = 4.1, 9.6, 11.4 Hz, 1H), 5.90–5.77 (m, 3H), 5.73–5.49 (m, 4H), 5.43 (brs, 1H), 4.86 (ddd, *J* = 2.1, 6.0, 11.1 Hz, 1H), 4.59 (app q, *J* = 6.0 Hz, 1H), 4.31,(brd, *J* = 9.8 Hz, 1H), 4.23–4.19 (m, 3H), 4.06 (ddd, *J* = 4.4, 9.3 Hz, 1H), 3.79–3.65 (m, 2H), 2.61 (dd, *J* = 6.2, 16.2 Hz, 1H), 2.46 (dd, *J* = 6.6, 16.3 Hz, 1H), 2.41–2.31 (m, 2H), 2.25 (app dq, *J* = 2.6, 16.6 Hz, 1H), 2.16–2.01 (m, 5H), 1.95–1.85 (m, 2H), 1.72 (s, 3H), 1.51 (pentet, *J* = 7.7 Hz, 1H), 1.27 (ddd, *J* = 3.6, 6.1, 9.9 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 165.3, 148.4, 135.8, 132.9, 131.3, 129.0, 128.8, 125.7, 124.9, 121.4, 119.8, 75.1, 73.3, 73.2, 73.0, 68.6, 66.9, 65.5, 51.8, 51.3, 42.5, 35.7, 33.6, 31.6, 31.3, 28.7, 25.8, 25.7, 22.9, 21.0, 18.1, 18.0, –4.5 (2C), –4.9, –5.0; HRMS *m/z* calcd for $C_{41}H_{68}O_7Si_2$ $[M+K]^+$: 767.4141, found 767.4158.

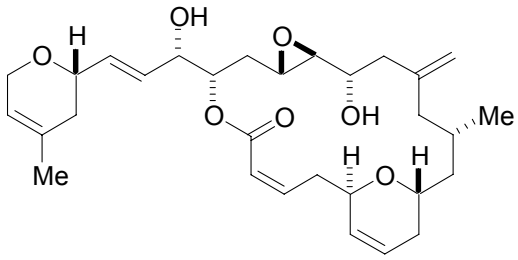


(3*Z*, 9*E*, 19*Z*)(1*R*, 7*S*, 11*S*, 15*R*, 17*R*) - 11-(*tert*-Butyldimethylsilyloxy)-7-[(1*S*)-(*tert*-butyldimethylsilyloxy)-3-((2*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl-)-allyl]-15-methyl-13-methylene-6, 21-dioxa-bicyclo[15.3.1]-henicosa-3,9,19-trien-5-one (131): To a suspension of 0.365 g of zinc (5.58 mmol) and 0.025 g of lead (II) iodide (0.054 mmol) in THF (5 mL) was added 0.250 mL of CH_2I_2 (3.10 mmol). The resulting pale yellow suspension was maintained for 30 min at ambient temperature, cooled to 0 °C, then treated with 0.25 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.25 mmol). The resulting dark brown suspension was warmed to ambient temperature and maintained for an additional 30 min. A 0 ºC solution of **130** in THF (1 mL) was then treated with the previously described suspension until the starting ketone was completely consumed as observed by TLC. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organics were washed with brine, dried over $NaSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 9.1 mg (85%) of 1**31** as a clear, colorless oil: $[\alpha]_D$ = –118 (*c* 1.4, $CHCl_3$); IR (thin film): 2955, 2928, 2856, 1723, 1074, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (ddd, *J* = 4.8, 10.2 Hz, 1H), 5.91-5.82 (m, 2H), 5.80–5.67 (m, 3H), 5.53–5.49 (m, 2H), 5.43 (brs, 1H), 4.89 (ddd, *J* = 2.4, 6.1, 10.4 Hz, 1H), 4.77 (brs, 1H), 4.75 (brs, 1H), 4.30–4.15 (m, 5H), 4.06 (ddd, *J* = 4.3, 9.2 Hz, 1H), 3.80 (m, 1H), 3.68 (ddd, *J* = 10.0, 15.2 Hz, 1H), 2.37–2.22 (m, 3H), 2.19–2.02 (m, 6H), 1.94–1.82 (m, 3H), 1.71 (s, 3H), 1.62–1.54 (m, 1H), 1.17 (ddd, *J* = 4.9, 6.8, 12.0 Hz, 1H), 0.88 (brs, 21H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 147.0, 144.7, 136.3, 132.8, 131.3, 129.0, 128.6, 125.3, 124.9, 121.6, 119.7, 113.4, 75.6, 73.3,

73.1, 72.2, 72.1, 67.0, 65.5, 45.0, 44.7, 43.1, 35.7, 33.8, 31.6, 31.4, 28.8, 25.9, 25.7, 22.9, 20.3, 18.2, 18.0, –4.3, –4.5, –4.8, –4.9; HRMS *m/z* calcd for $C_{42}H_{70}O_6Si_2$ $[M+Na]^+$: 749.4609, found 749.4586.



Desepoxylaulimalide (132): To a 0 ºC solution of 13 mg of silyl ether **131** (17.9 μmol) in THF (2 mL) was added 1.0 mL of HF•pyridine complex dropwise via syringe. The reaction was maintained for 1 h at ambient temperature, then poured into a 0 ºC mixture of saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (30 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried over $NaSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography on silica gel (40% EtOAc/hexanes) afforded 8.0 mg (90%) of desepoxylaulimalide **132** as a pale yellow oil: $[\alpha]_D$ = –171 (*c* 0.7, $CHCl_3$); IR (thin film): 3415, 2924, 2853, 1720, 1415, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (ddd, *J* = 5.3, 9.9, 11.4 Hz, 1H), 5.94–5.82 (m, 3H), 5.79–5.69 (m, 2H), 5.64–5.61 (m, 2H), 5.42 (brs, 1H), 5.00 (app q, *J* = 6.6 Hz, 1H), 4.87 (brs, 2H), 4.23–4.12 (m, 5H), 4.05 (ddd, *J* = 4.4, 9.1 Hz, 1H), 3.92–3.84 (m, 1H), 3.56 (dddd, *J* = 1.3, 8.0, 9.9, 18 Hz, 1H), 2.39–2.32 (m, 2H), 2.31–2.22 (m, 2H), 2.20–2.08 (m, 3H), 2.07–1.97 (m, 1H), 1.96–1.84 (m, 3H), 1.83–1.74 (m, 3H), 1.70 (s, 3H), 1.67–1.61 (m, 1H), 1.14 (ddd, *J* = 4.0, 7.5, 11.7 Hz, 1H), 0.87 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 147.3, 144.9, 135.4, 133.9, 131.3, 129.0, 128.3, 126.5, 124.8, 121.2, 119.7, 114.3, 75.3, 73.7, 73.1, 71.3, 69.8, 67.6, 65.6, 44.8, 43.3, 42.3, 35.7, 34.4, 33.6, 30.9, 28.3, 22.9, 19.7; HRMS *m/z* calcd for $C_{30}H_{42}O_6$ $[M+Na]^+$: 512.2879, found 521.2880.



(–)-Laulimalide (1): To a –20 ºC suspension of 0.130 g of powdered 4 Å molecular sieves in 4 mL of CH_2Cl_2 was added 5 μl of (+)-DIPT (22.5 μmol) followed by 5 μL of titanium tetraisopropoxide (16.1 μmol). The reaction mixture was maintained at –20 ºC for 30 min, then treated with a 4.3 M solution of ^{t}BuOOH in toluene. The reaction was maintained for an additional 30 min at –20 ºC, then a solution of 7.8 mg of desepoxylaulimalide **132** (15.7 μmol) in CH_2Cl_2 (2 mL) was added dropwise via syringe. The reaction was maintained for 2 h. A mixture of 4 N NaOH (0.5 mL) and brine (1.5 mL) was added, and the reaction was maintained for 90 min at 0 ºC. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and filtered through Celite. The filtrate was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to provide a pale yellow oil that was then triturated with 5% ^{i}PrOH/hexanes to afford 5.5 mg (69%) of (–)-laulimalide **(1)** as a white solid: $[\alpha]_D = -198$ (*c* 0.1, $CHCl_3$); IR (thin film): 3423, 3071, 3032, 2917, 2846, 1719, 1642, 1422, 1383, 1213, 1169, 894 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.45 (ddd, *J* = 3.8, 10.1, 11.4 Hz, 1H), 5.94–5.83 (m, 3H), 5.77 (dd, *J* = 5.7, 15.7 Hz, 1H), 5.72–5.69 (m, 2H), 5.43 (brs, 1H), 5.17 (ddd, *J* = 1.6, 5.2, 11.2 Hz, 1H), 4.88 (brs, 1H), 4.86 (br s, 1H), 4.32 (br d, *J* = 9.4 Hz, 1H), 4.24 (app q, *J* = 5.5 Hz, 1H), 4.19 (m, 2H), 4.07 (m, 1H), 4.04 (ddd, *J* = 4.5, 9.7 Hz, 1H), 3.79–3.72 (m, 2H), 3.08 (ddd, *J* = 3.3, 9.1 Hz, 1H), 2.91 (t, *J* = 2.6 Hz, 1H), 2.40–2.37 (m, 2H), 2.22 (app dq, *J* = 2.7, 16.8 Hz, 1H), 2.13 (brd, *J* = 15.3 Hz, 1H), 2.07–1.85 (m, 7H), 1.79 (dd, *J* = 10.0, 12.8 Hz, 1H), 1.70 (brs, 3H), 1.54–1.43 (m, 2H), 1.37–1.31 (m, 1H), 0.84 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 150.3, 144.8, 133.9, 131.2, 128.7, 128.5, 125.2, 120.5, 119.7, 112.5, 73.4, 73.2, 73.1, 72.3, 67.9, 66.5, 65.6, 60.7, 52.1, 45.5, 43.4, 37.1, 35.6,

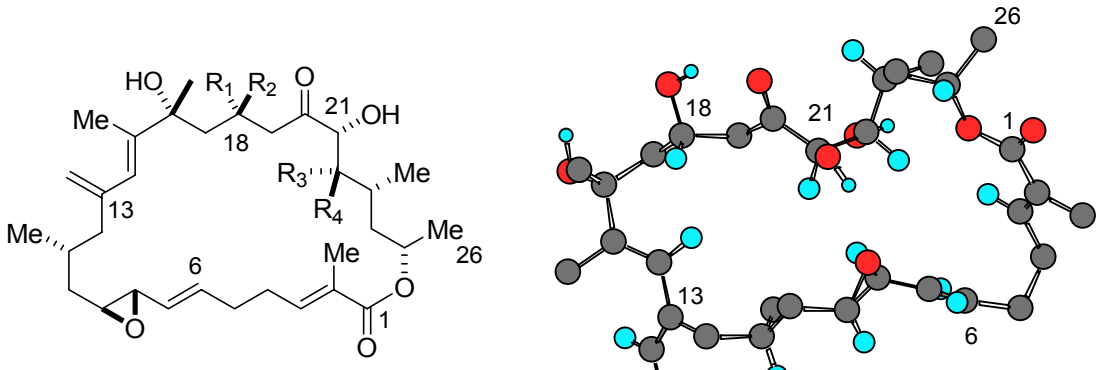
33.8, 33.3, 31.6, 29.7, 22.9, 20.7; HRMS *m/z* calcd for $C_{30}H_{42}O_7$ $[M+Na]^+$: 537.2828, found 537.2816

CHAPTER 2. STUDIES TOWARD THE TOTAL SYNTHESIS OF AMPHIDINOLIDE B

2.1 BACKGROUND

2.1.1 Isolation

The amphidinolides represent an expansive and structurally diverse class of macrocyclic marine natural products that exhibit potentially useful biological activity. Their common origin is the cultured symbiotic dinoflagellate *Amphidinium* sp. isolated from the Okinawan flatworm of the genus *Amphiscolops*.[67] Emerging as one of the most pharmacologically impressive constituents of this family of bioactive microagal metabolites is the highly functionalized, 26-membered macrolide, amphidinolide B_1 **(133)**.



Amphidinolide B_1 **(133)** $R_1 = R_3 = OH$, $R_2 = R_4 = H$
Amphidinolide B_2 **(134)** $R_2 = R_3 = OH$, $R_1 = R_4 = H$
Amphidinolide B_3 **(135)** $R_1 = R_4 = OH$, $R_2 = R_3 = H$

Figure 18. The Amphidinolide B Group

[67] Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun*. **1987**, 1127.

Amphidinolide B_1 **(133)** was originally isolated in 1987 by Kobayashi and coworkers from cultured dinoflagellates obtained from the Okinawan flatworm, *Amphiscolops breviviridis*. Its gross structure was elucidated by 2D-NMR analysis; however, its relative and absolute stereochemical assignments remained unclear. Shimizu et al. later disclosed the isolation of **133** along with two other isomeric macrolides, denoted amphidinolides B_2 **(134)** and B_3 **(135)**,[68] from a larger free-swimming dinoflagellate collected off the coast of the U.S. Virgin Islands in 1994.[69] As a result of the efforts of both Shimizu and Kobayashi, the relative and absolute stereochemistry of the amphidinolide B group was established through X-ray diffraction studies[69] as well as the independent synthesis and chiral HPLC analysis of the C_{22}–C_{26} subunit, a known chemical degradation product of amphidinolide B_1.[70]

2.1.2 Structural Features

Amphidinolide B_1 **(133)** exhibits a high degree of molecular complexity with many key structural features. The molecule itself is a highly decorated 26-membered macrolide that contains two distinct regions of functionality. The C_{14}–C_{26} portion of **133** is highly oxygenated and includes a *syn* diol relationship, a tertiary carbinol stereocenter at C_{16} and a β-hydroxy carbonyl moiety while the C_1–C_{13} portion remains relatively devoid of oxygenated functionality with the exception of the C_8–C_9 allylic epoxide and the (*E*)-enoate ester linkage. Overall, amphidinolide B_1 (**133**) possesses nine stereogenic centers (seven hydroxyl-bearing stereocenters and two isolated methyl-bearing stereocenters) in addition to four double bonds which include a potentially acid sensitive *s-cis* diene.

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[68] Amphidinolides B_2 and B_3 were later identified as the C_{18} and C_{22} epimers of **133**, respectively. See Figure 15.
[69] Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R. W.; Cornell, L.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 2657.
[70] Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett.* **1994**, *35*, 8241.

2.1.3 Biological Activity

In addition to possessing a synthetically challenging molecular architecture, amphidinolide B_1 (**133**) is among the most biologically active members of the amphidinolide family of natural products. It exhibits very potent cytotoxicity against the human epidermoid carcinoma KB cell line (IC_{50} = 4.2 ng/mL) as well as human colon HCT 116 and murine lymphoma L1210 cells (IC_{50} = 0.14 ng/mL). As in the case of (−)-laulimalide (**1**), the C_8–C_9 epoxide moiety is believed to play a critical role in the biological activity expressed by **133**. Single crystal X-ray analysis of amphidinolide B_1 confirms the presence of an intraannular hydrogen bond between the epoxide functionality and the C_{21} hydroxyl group giving **133** a seemingly well-defined rectangular structure.[69] Comparison of the activity displayed by **133** and its C_{21} epimer (amphidinolide D) strongly suggests the importance of the allylic epoxide in the observed biological activity as amphidinolide D is 100 times less potent than **133**. The necessity of the epoxide residue was also demonstrated via structural modification of **133**; epoxide ring opening with MeOH resulted in a derivative of amphidinolide B_1 that displayed a 600-fold decrease in biological activity compared to the parent compound.[71]

Presently, there have been no literature reports regarding the mechanism of action of amphidinolide B_1. Limited natural supply coupled with the current lack of a synthetic route to **133** has severely hampered such investigations. Although no total synthesis of **133** has been communicated to date, the combination of its structural complexity, potential chemotherapeutic utility, and limited natural abundance has made amphidinolide B_1 an extremely attractive target

[71] Kobayashi, J.; Ishibashi, M, *Chem. Rev.* **1993**, *93*, 1753.

molecule for synthetic organic chemists and has led to several reports describing the syntheses of major fragments.[72]

2.1.4 Previous Synthetic Work

The first synthetic approach toward the total synthesis of amphidinolide B_1 (**133**), depicted in Figure 19, was disclosed by Chakraborty et al. in 1997. From a retrosynthetic standpoint, Chakraborty envisioned the assembly of **133** occurring via a Stille coupling to form the C_{13}–C_{14} s-*cis* diene moiety with subsequent macrolactonization to close the 26-membered ring. These disconnections led to the lower C_1–C_{13} fragment **136** and the upper C_{14}–C_{26} fragment **137**. Fragment **137** was constructed through an aldol reaction between aldehyde **138** and methyl ketone **139** (dr = 3:2). The lower C_1–C_{13} fragment **136** was prepared via the Nozaki-Hiyama-Kishi coupling of aldehyde subunit **140** and vinyl iodide **141** (*syn*:*anti* 3:7) to set the requisite *anti*-diol relationship for epoxide formation. Subsequent Wittig homologation then installed the *E*-α,β-unsaturated carboxylate ester.

[72] (a) Cid, B.; Pattenden, G. *Tetrahedron Lett*. **2000**, *41*, 7373. (b) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 571. (c) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 573. (d) Eng, H. M.; Myles, D. C. *Tetrahedron Lett*. **1999**, *40*, 2275. (e) Eng, H. M.; Myles, D. C. *Tetrahedron Lett*. **1999**, *40*, 2279. (f) Chakraborty, T. K.; Thippewamy, D. *Synlett* **1999**, 150. (g)Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1163. (h) Chakraborty, T. K.; Thippewamy, D.; Suresh, V. R. *Chem. Lett*. **1997**, 563. (i) Chakraborty, T. K.; Suresh, V. R. *Chem. Lett*. **1997**, 565. (j) Lee, D. H.; Lee, S. –W. *Tetrahedron Lett*. **1997**, *38*, 7909. (k) Ohi, K.; Shima, K.; Hamada, K.; Saito, Y.; Yamada, N.; Ohba, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 2433.

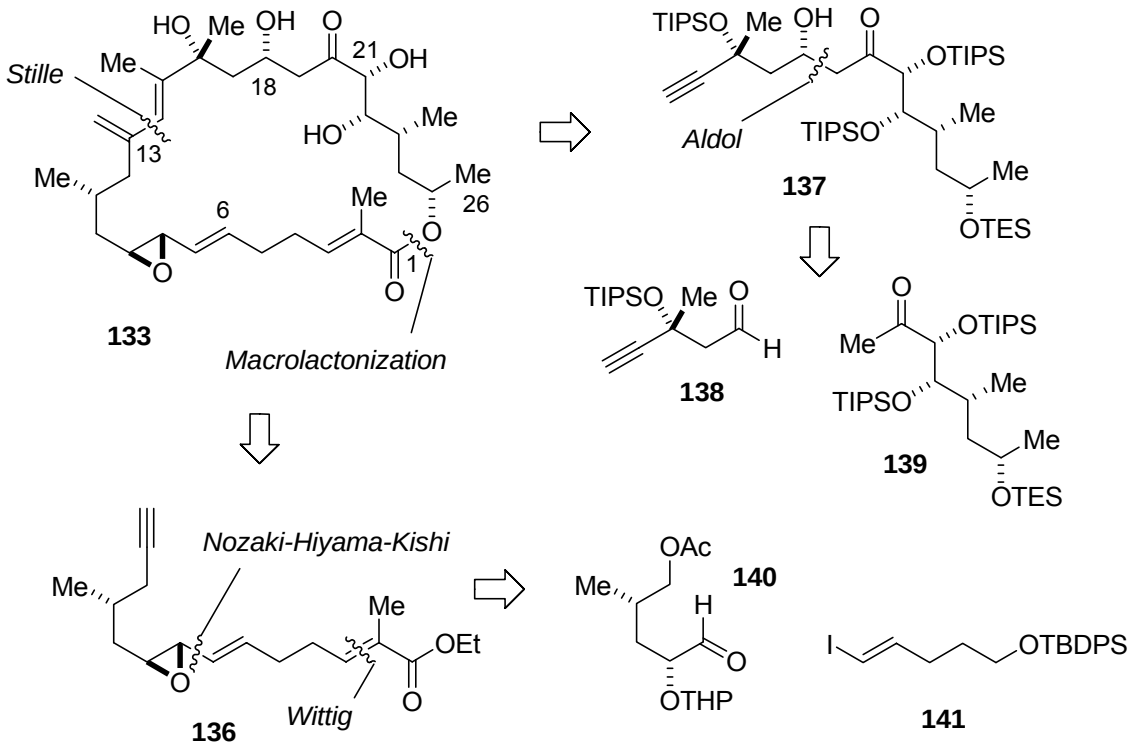


Figure 19. Chakraborty Approach to the Major Fragments of Amphidinolide B_1

Following the initial report by Chakraborty, Nishiyama and coworkers described a second strategy aimed at the enantioselective total synthesis of **133** that made extensive use of the chiral pool (Figure 20). Retrosynthetically, Nishiyama's approach resembles that of Chakraborty calling for the Pd(0)-mediated synthesis of the s-*cis* diene as well as ring closure via the macrocyclization of the resulting seco acid and arriving at the C_1–C_{13} and C_{14}–C_{26} fragments **142** and **143**, respectively. Fragment **142** was prepared by Claisen rearrangement and subsequent Wittig reaction of allyl vinyl ether **144** which in turn was synthesized in 18 steps, including an asymmetric Evans alkylation to install the C_{11} methyl-bearing stereocenter, from commercially available D-erythrose. Fragment **143** was assembled via a dithiane anion addition to primary iodide **145**. Dithiane **146** was prepared via Wittig reaction of the known (2*S*, 4*S*)-(+)-

pentanediol derived aldehyde **147**[73] and iodide **145** was synthesized from (3*S*)-methyl 3,4-dihydroxybutanoate.

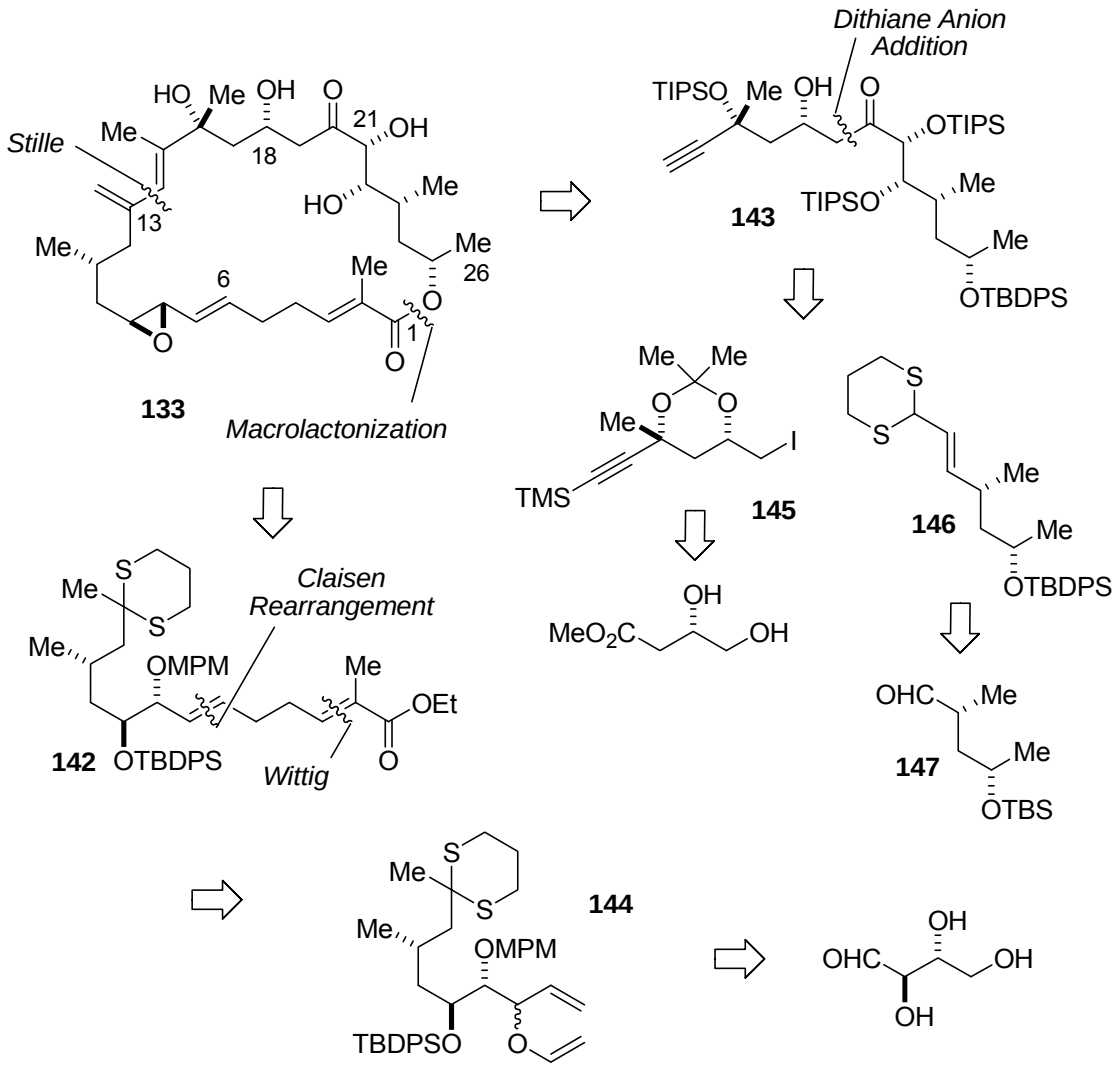


Figure 20. Nishiyama Approach to the Major Fragments of Amphidinolide B_1

In 1999, several partial syntheses of amphidinolide B_1 were completed in close succession beginning with a highly convergent route published by Myles. Macrolide formation was envisioned to proceed through a fragment uniting nucleophilic addition between a vinyl

[73]Shioiri, T.; Imaeda, T.; Hamada, Y. *Heterocycles* **1997**, *46*, 421.

anion derived from ketone **148** and aldehyde **149** followed by macrolactonization. The C_1–C_{13} fragment **148** was synthesized from sulfone **150** and chiral ester **151** via a Trost/Julia olefination. Construction of the upper C_{14}–C_{26} fragment **149** was achieved by employing a Roush-Masamune olefination of β-ketophosphonate **152** and the (*S*)-ethyl-(L)-(+)-lactate derived α-chiral aldehyde **153**. Sharpless asymmetric dihydroxylation of the resulting *E*-olefin then installed the C_{21},C_{22}-*syn*-diol relationship (Figure 21).

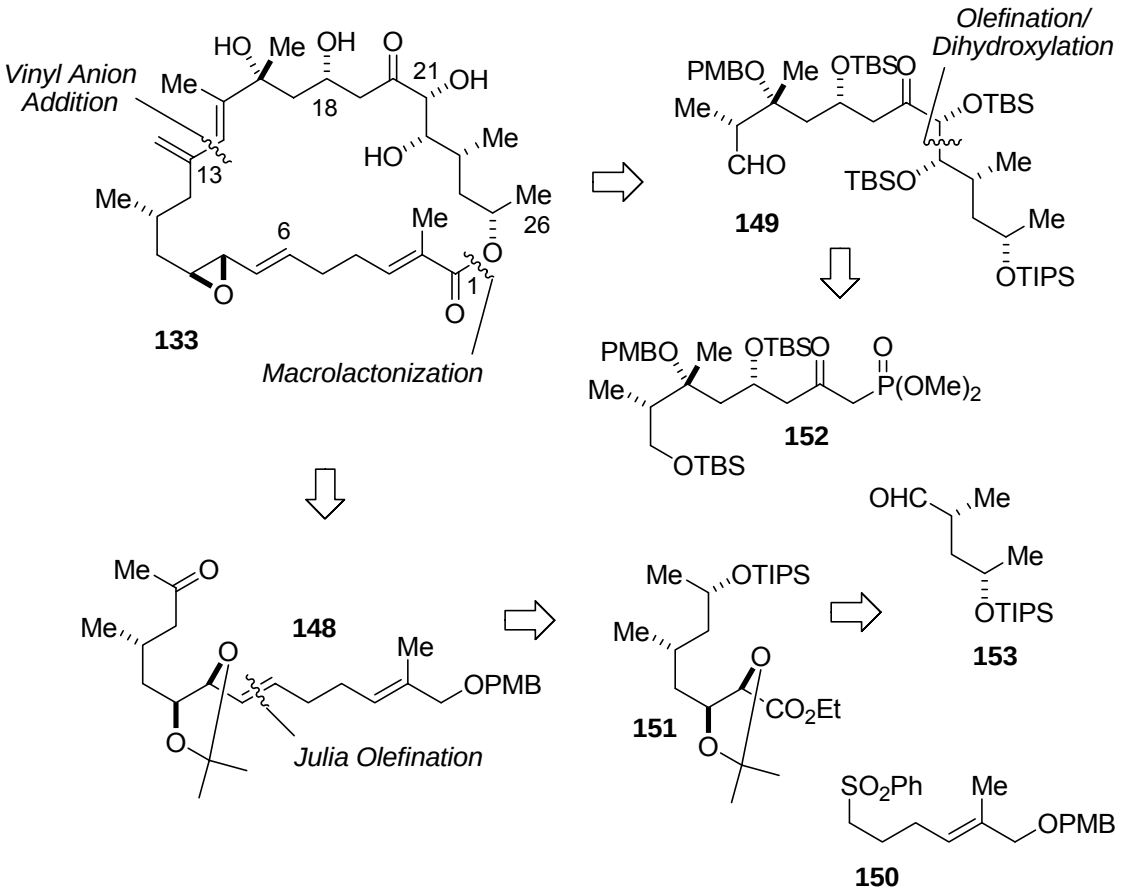


Figure 21. Myles Approach to the Major Fragments of Amphidinolide B_1

Twelve years after first isolating and establishing the absolute stereochemistry of amphidinolide B_1, Kobayashi et al. published synthetic approaches to both the lower C_1–C_{13}

fragment **154** and the upper C_{14}–C_{26} of **155** (Figure 22). Fragment **154** was prepared by the addition of an organocerium reagent derived from alkyne **156** into aldehyde **157** followed by Wittig olefination to introduce the (*E*)-α,β-unsaturated ester moiety. Subunits **156** and **157**, in turn, were obtained from 1,4-butanediol and (2*S*, 4*S*)-(+)-pentanediol, respectively. To arrive at upper fragment **155**, Kobayashi employed an aldol reaction between aldehyde **138** and methyl ketone **158** to form the C_{18}–C_{19} bond. Aldehyde **138** was synthesized from commercially available 3-methylbut-3-en-1-ol employing Sharpless asymmetric dihydroxylation technology to install the C_{16} tertiary carbinol stereocenter. Construction of the highly oxygenated C_{19}–C_{26} ketone subunit **158** was achieved by Wittig olefination and subsequent dihydroxylation of Shioiri's pentanediol derived aldehyde.

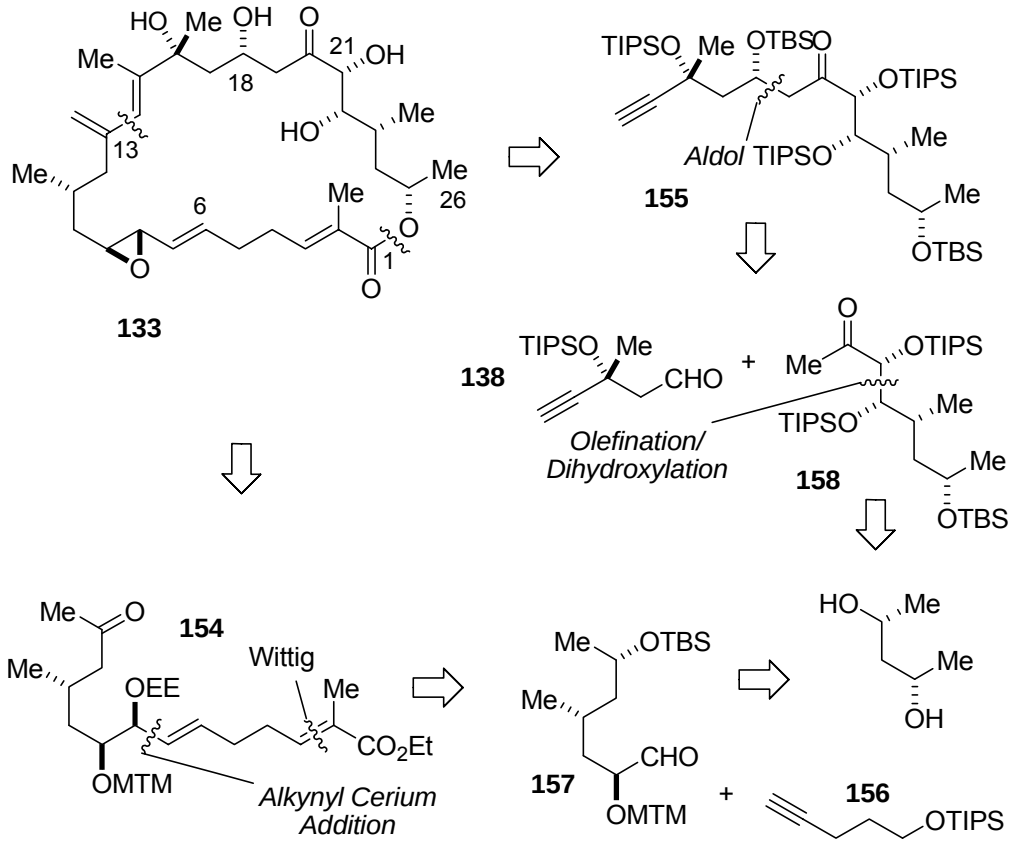


Figure 22. Kobayashi Approach to the Major Fragments of Amphidinolide B_1

Synthetic efforts by Lee et al. (Figure 23) arrived at the enantioselective preparation of major fragments **159** and **160** of amphidinolide B_1. The synthesis of the C_1–C_{13} fragment **159**, first disclosed in 1997, incorporated the asymmetric allylation of an Evans oxazolidinone with 2,3-dibromopropene to successfully install the C_{11} methyl-bearing stereocenter. A more recent report described Lee's approach to the C_{14}–C_{26} fragment **160** that involved construction of the C_{20}–C_{21} bond via nucleophilic addition of a vinyl lithium species derived from iodide **161** to aldehyde **162**. Vinyl iodide **161** was prepared by Takai olefination of α-chiral aldehyde **163** which in turn was manufactured from ethyl-(*S*)-lactate. The C_{16} tertiary carbinol stereocenter in aldehyde **162** was generated via Sharpless asymmetric epoxidation with subsequent ring opening with dimethyl cuprate.

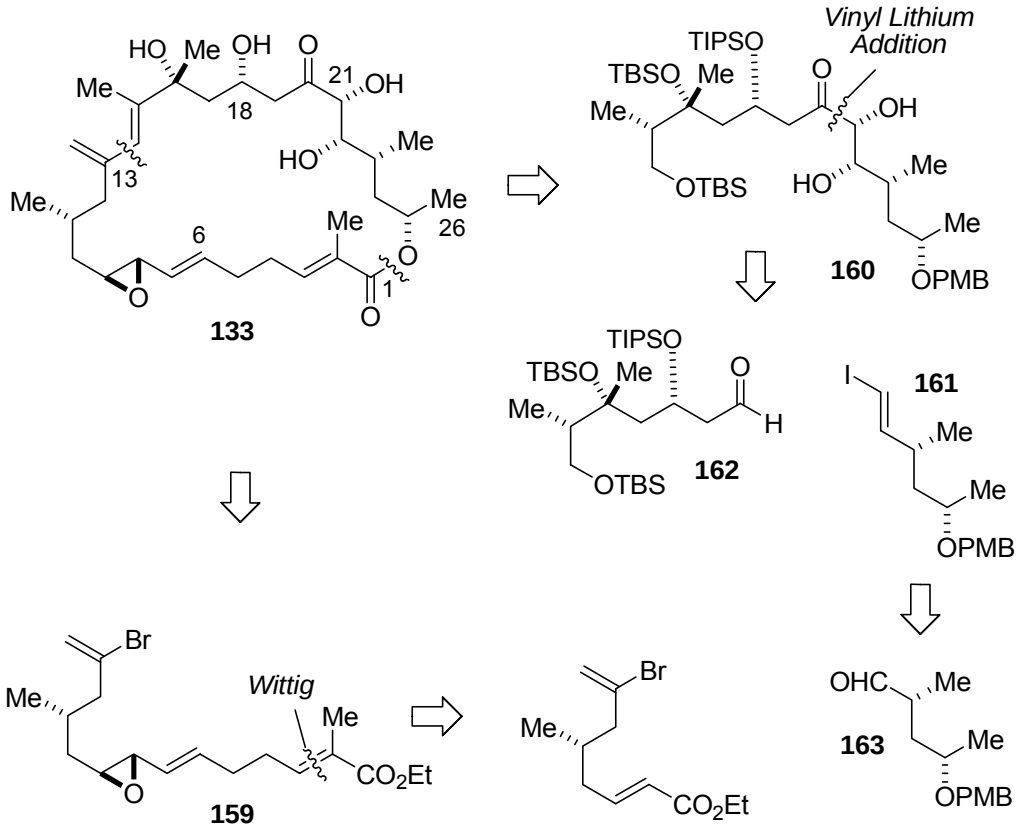


Figure 23. Lee Approach to the Major Fragments of Amphidinolide B_1

The most advanced route to the total synthesis of amphidinolide B_1 has been recently described by Pattenden and Cid (Figure 24). The retrosynthetic strategy called for the union of the major C_1–C_{13} and C_{14}–C_{26} fragments, **164** and **165**, respectively, via an esterification of carboxylic acid **164** and the C_{25} secondary alcohol in fragment **165**. A subsequent intramolecular Stille coupling would then close the 26-membered macrocycle. The synthesis of fragment **165** was accomplished through an aldol coupling of ketone **166**, derived from (2*S*, 4*S*)-pentanediol, and aldehyde **167**. Aldehyde **167** was prepared from 3-methyl-2-penten-4-yn-1-ol via Sharpless epoxidation to install the C_{16} tertiary carbinol and silylstannylation with subsequent cuprate addition to form the requisite trisubstituted olefin. The lower fragment **164** was assembled via Julia olefination of (*R*)-3-methylglutarate derived epoxyaldehyde **168** and sulfone **169**. Unfortunately, after having united major fragments **164** and **165** by esterification to form **170**, the critical intramolecular Stille reaction was unsuccessful in closing the macrolide.

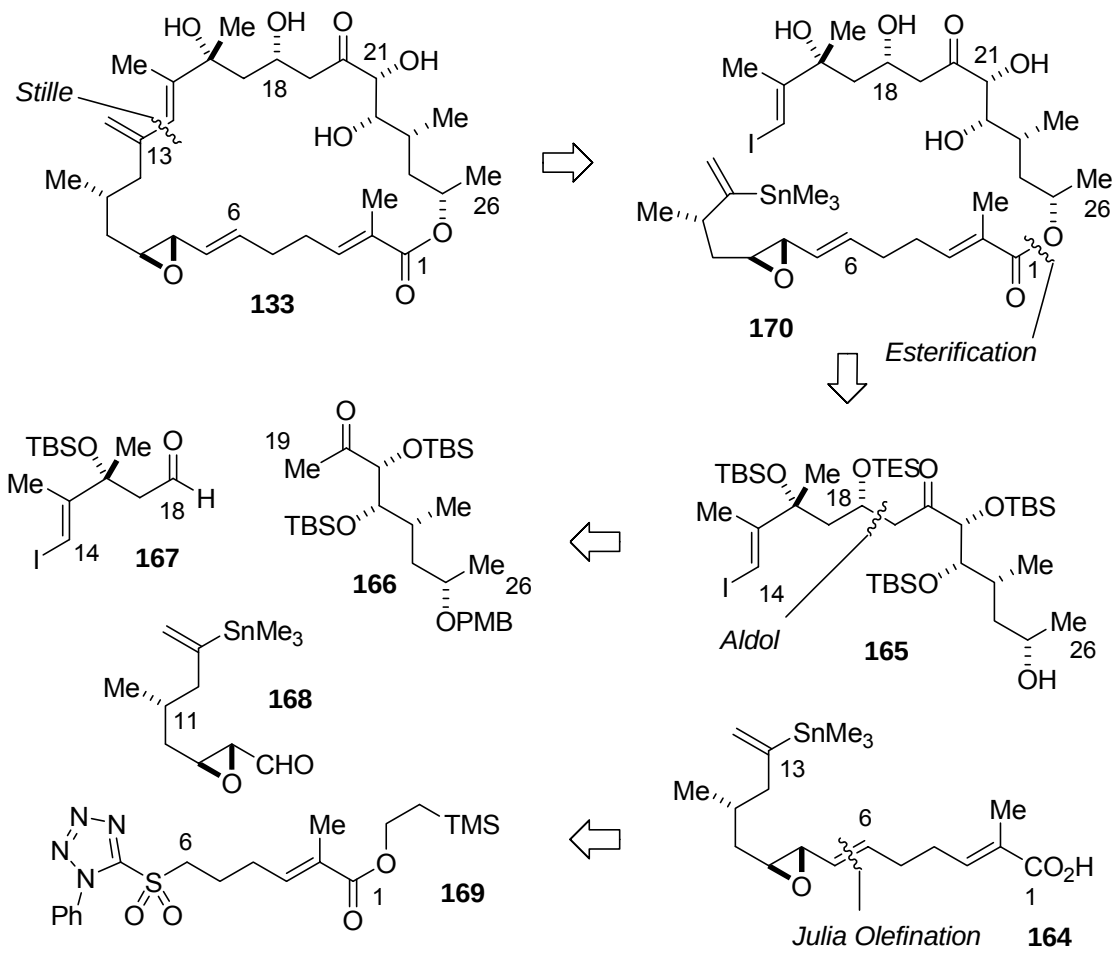


Figure 24. Pattenden Approach to the Major Fragments of Amphidinolide B_1

2.2 RETROSYNTHETIC ANALYSIS

Our retrosynthetic approach to amphidinolide B_1 is outlined in Figure 25. As in previous approaches, bond cleavage along the C_1-macrolactone as well as C_{14}–C_{15} of the s-*cis* diene were recognized as strategic disconnections that would enhance the convergency of the synthesis by effectively dividing the target molecule into two equally complex halves, the lower C_1–C_{13} fragment **171** and the upper C_{14}–C_{26} fragment **172**. Palladium-mediated coupling of vinyl iodide **172** and the pinacol boronate ester moiety in **171** was envisioned to unite the major fragments,

forming the acid-sensitive diene moiety, and subsequent Yamaguchi macrolactonization would be employed to close the 26-membered ring.

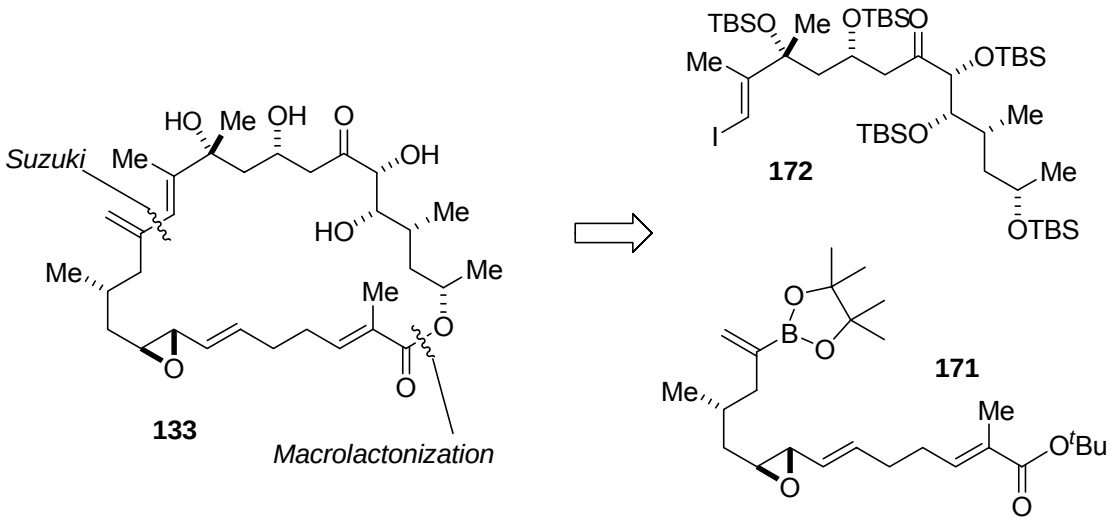


Figure 25. Retrosynthetic Approach to Amphidinolide B_1

2.3 THE C_1–C_{13} FRAGMENT

2.3.1 Retrosynthesis

The lower C_1–C_{13} fragment of amphidinolide B_1 (**133**) can be further dissected at the C_6–C_7 olefin to deliver sulfone **173** and epoxyaldehyde **174** as illustrated in Figure 26. Subunit **173** would be readily accessible from the reduction and subsequent olefination of commercially available γ-butyrolactone, while the enantioselective synthesis of **174** would be predicated on the synthetic elaboration of optically active β-lactone products of asymmetric AAC reaction technology.

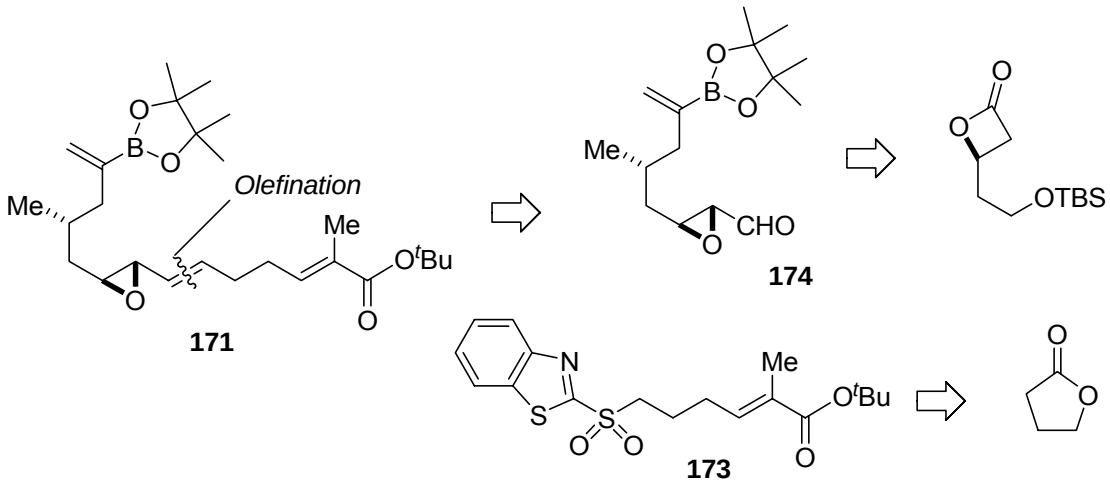


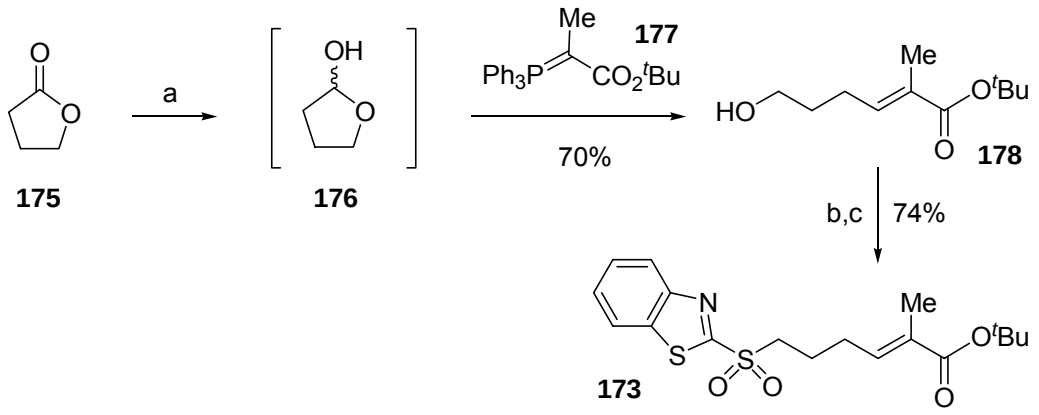
Figure 26. Retrosynthesis for the C_1–C_{13} fragment of amphidinolide B_1

2.3.2 Synthesis of the C_1-C_6 Subunit

We had envisaged a rapid synthesis of the C_1–C_6 subunit of amphidinolide B_1 occurring from commercially available γ-butyrolactone (Scheme 24). The synthesis of **173** commenced with the DIBAL-H reduction of **175** to the corresponding lactol **176** and subsequent trapping of the open form of **176** with phosphorane **177** to arrive at (*E*)-α,β-unsaturated carboxylate ester **178** in good yield.[74] Primary alcohol **178** was recognized as a versatile synthon that could be transformed into a variety coupling partners for either a Wittig or Julia olefination reaction. Electing to pursue the Julia olefination strategy, sulfone formation was achieved through a Mitsunobu reaction of alcohol **178** (DEAD, PPh_3, THF) with 2-mercaptobenzothiazole followed by oxidation of the resulting thioether with catalytic $MnSO_4$•H_2O and 30% H_2O_2 (74% yield).[75]

[74] The geometry of the (*E*)-olefin in ester **178** was confirmed via 1D NOE spectroscopy (500 MHz). Irradiation of the C_3 vinyl hydrogen resulted no observable NOE enhancement in the adjacent methyl group.
[75] Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett*. **2002**, *43*, 3459.

Scheme 24. Synthesis of the C_1–C_6 Subunit **173**[a]



[a]Conditions: (a) i. DIBAL-H, CH_2Cl_2, ii. **177**, THF. (b) DEAD, PPh_3, 2-mercaptobenzothiazole, THF, 0 °C → rt. (d) 30 % H_2O_2, $NaHCO_3$, $MnSO_4$•H_2O (5 mol %) CH_3CN.

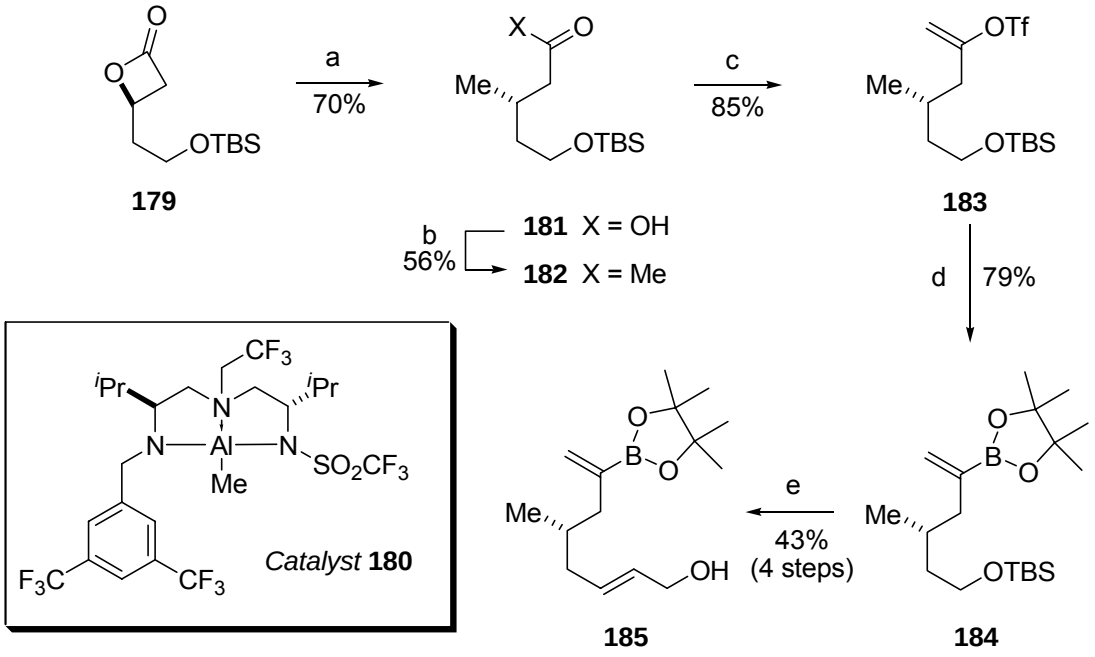
2.3.3 Synthesis of the C_7–C_{13} Subunit[76]

Having arrived at a convenient synthetic route to the C_1–C_6 sulfone subunit, we turned our attention toward the synthesis of epoxy aldehyde **174**. Once again, the aid of the catalytic AAC reaction was enlisted to prepare the highly enantiomerically enriched β-lactone **179** in 95% ee employing 20 mol % of the second generation unsymmetrical Al (III)-triamine catalyst **180**. Cuprate mediated S_N2 ring opening of lactone **179** afforded the corresponding carboxylic acid **181** in good yield and efficiently installed the C_{11} methyl-bearing stereocenter. Acid to enol triflate interconversion was then accomplished by first treating **181** with 2 equiv of MeLi in THF to provide the requisite methyl ketone (56%). Enolization of **182** with potassium hexamethyldisilazide (KHMDS) at –78 °C followed by electrophilic capture of the enolate oxygen atom with *N*-phenyltrifluoromethanysulfonimide ($PhNTf_2$) then furnished vinyl triflate **183** in 85% yield. In anticipation of the planned fragment uniting Suzuki reaction, triflate **183**

[76] All synthetic work described in this section was accomplished by Apsara Gopalarathnam (unpublished results).

was transformed into the corresponding pinacol boronate ester **184** by a palladium catalyzed coupling with bis(pinacolato)diborane in good yield. Silyl ether **184** was then elaborated to allylic alcohol **185** via the four step sequence of deprotection, oxidation, Horner-Wadsworth-Emmons olefination, and ester reduction. Sharpless asymmetric epoxidation of allylic alcohol **185** with subsequent oxidation of the primary alcohol would then provide epoxyaldehyde fragment **174** (Scheme 25).

Scheme 25. Synthesis of the C_7–C_{13} Subunit **185**[a]



[a]Conditions: (a) CuBr, MeMgBr, TMSCl, THF/DMS –50 °C → rt. (b) i. 2MeLi, Et_2O, 0 °C, ii. H_2O. (c) KHMDS, $PhNTf_2$. (d) bis(pinacolato)diborane, $Pd(PPh_3)_2Cl_2$, $_2PPh_3$, PhOK, $PhCH_3$, 50 °C. (e) i. 10 mol% DDQ, THF/H_2O. ii. Dess-Martin periodinane/py. iii.NaH, $(^iPrO)_2P(O)CH_2CO_2Et$. iv. DIBAL-H.

2.4 THE C_{14}–C_{26} FRAGMENT

2.4.1 Retrosynthetic Analysis

The hydrophilic C_{14}–C_{26} fragment of amphidinolide B_1 (**133**) represents the most densely functionalized portion of the natural product. Fragment **172** would be prepared by Sharpless asymmetric dihydroxylation of the α,β-unsaturated ketone **186** followed by carbostannylation and tin-halogen exchange to generate the vinyl iodide to be used in the fragment uniting Suzuki reaction. Further dissection of the C_{14}–C_{26} fragment along the C_{21}–C_{22} olefin would deliver β-ketophosphonate **187** and α-chiral aldehyde **147** as target subunits. The installation of the C_{18} hydroxyl-bearing stereocenter in fragment **187** would result from the strategic use of AAC reaction technology (Figure 27).

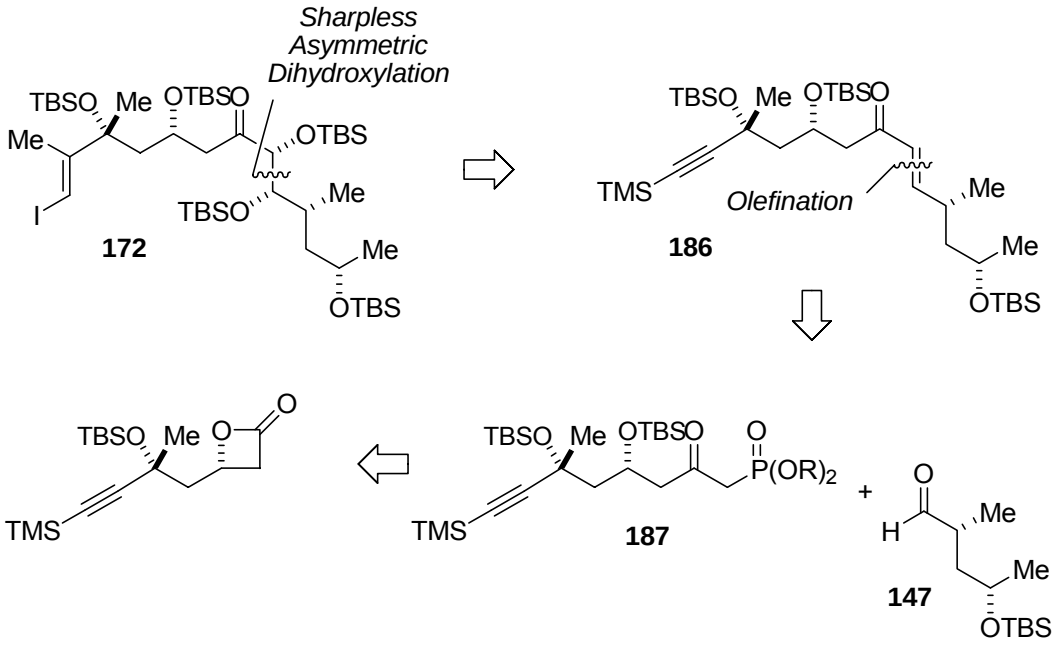


Figure 27. Retrosynthesis for the C_{14}–C_{26} fragment of amphidinolide B_1

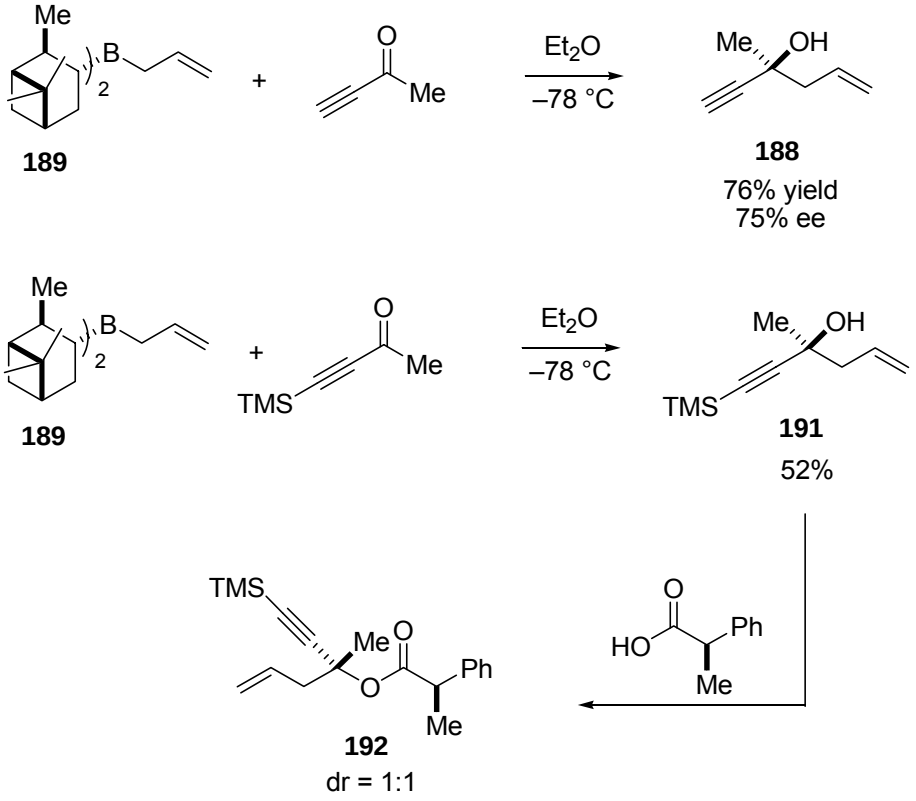
2.4.2 Installation of the C_{16} Tertiary Carbinol Stereocenter

The most synthetically straightforward approach for establishing the C_{16} tertiary carbinol stereocenter in fragment **172**, aside from the commonly employed Sharpless asymmetric epoxidation strategy, was envisioned to be an asymmetric allylation of the commercially available acetylenic ketone, 4-trimethylsilyl-3-butyn-2-one. However, unlike the asymmetric allylation of aldehydes which has enjoyed much success in the literature,[77] the corresponding reaction involving ketone substrates has remained a far more challenging synthetic endeavor due to the marked difference in reactivity between aldehydes and ketones.

One of the few examples of the asymmetric allylation of ketones was described by H. C. Brown.[78] While most of the methyl ketone substrates examined by Brown resulted in poor levels of asymmetric induction, the allylboration of 3-butyn-2-one resulted in moderate enantioselectivity furnishing the corresponding homoallylic alcohol **188** in 75% ee. Encouraged by this result, we applied Brown's asymmetric allylboration conditions to 4-trimethylsilyl-3-butyn-2-one (**190)**. Treating a –78 °C solution of allyldiisopinocampheylborane **189** in Et_2O with acetylenic ketone **190** afforded the desired allyl addition product **191** in 52% yield. In order to assay the enantioselectivity of the reaction, the tertiary alcohol product was derivatized as the ester of (*R*)-methoxyphenylacetic acid (DCC, DMAP). Unfortunately, ^{1}H NMR analysis of the crude product mixture revealed a 1:1 mixture of ester diastereomers (**192**).

[77] Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467.
[78] Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem*. **1986**, *51*, 432.

Scheme 26. Attempted C_{16} Tertiary Carbinol Installation via Asymmetric Brown Allylation

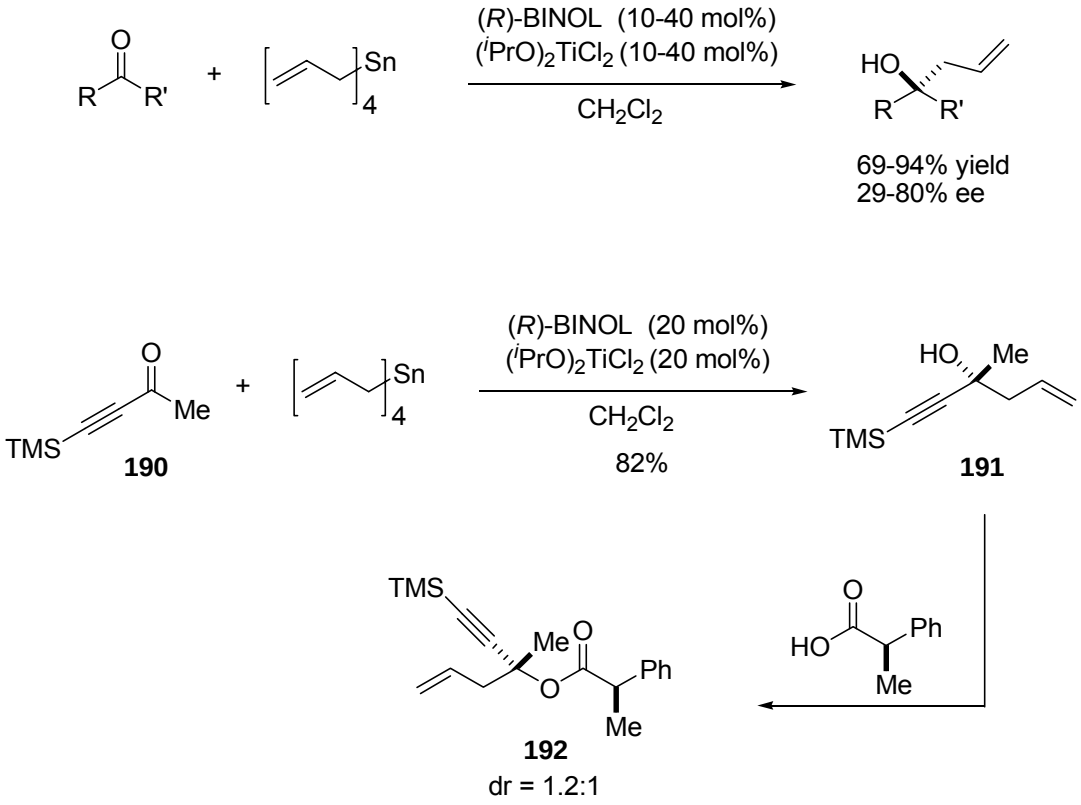


A survey of the more recent literature concerning the synthesis of chiral homoallyic alcohols via catalytic, asymmetric ketone allylation led to our investigation of the Ti(IV)-BINOL based systems of Tagliavini[79] and Walsh.[80] In 1999, Tagliavini et al. published the first example of a catalytic, asymmetric ketone allylation for the enantioselective preparation of tertiary homoallylic alcohols (Scheme 27). Employing a Ti(IV)-(*R*)-BINOL catalyst **ent-25** (20 mol%) and tetraallyltin as the allylating agent (40 mol%), moderate to good enantioselectivities (29-80% ee) were obtained for a variety of aromatic, aliphatic, and α,β-unsaturated ketone substrates. Although no examples of acetylenic ketones were reported, we sought to examine the effectiveness of these reaction conditions for the installation of the C_{16} tertiary carbinol stereocenter of amphidinolide B_1. Treating a solution of Cl_2Ti(IV)-(*R*)-BINOL catalyst ***ent*-25** in

[79] Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061.
[80] Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3697.

CH_2Cl_2 with **190** at ambient temperature resulted in the formation of alcohol **191** in 82% isolated yield. As described previously in the case of Brown allylboration, the resulting tertiary alcohol product was then converted to its corresponding (*R*)-methoxyphenyl acetate ester and assayed by 500 MHz ^{1}H NMR spectroscopy. Unfortunately, a disappointing 1.2:1 ratio of ester diastereomers was observed.

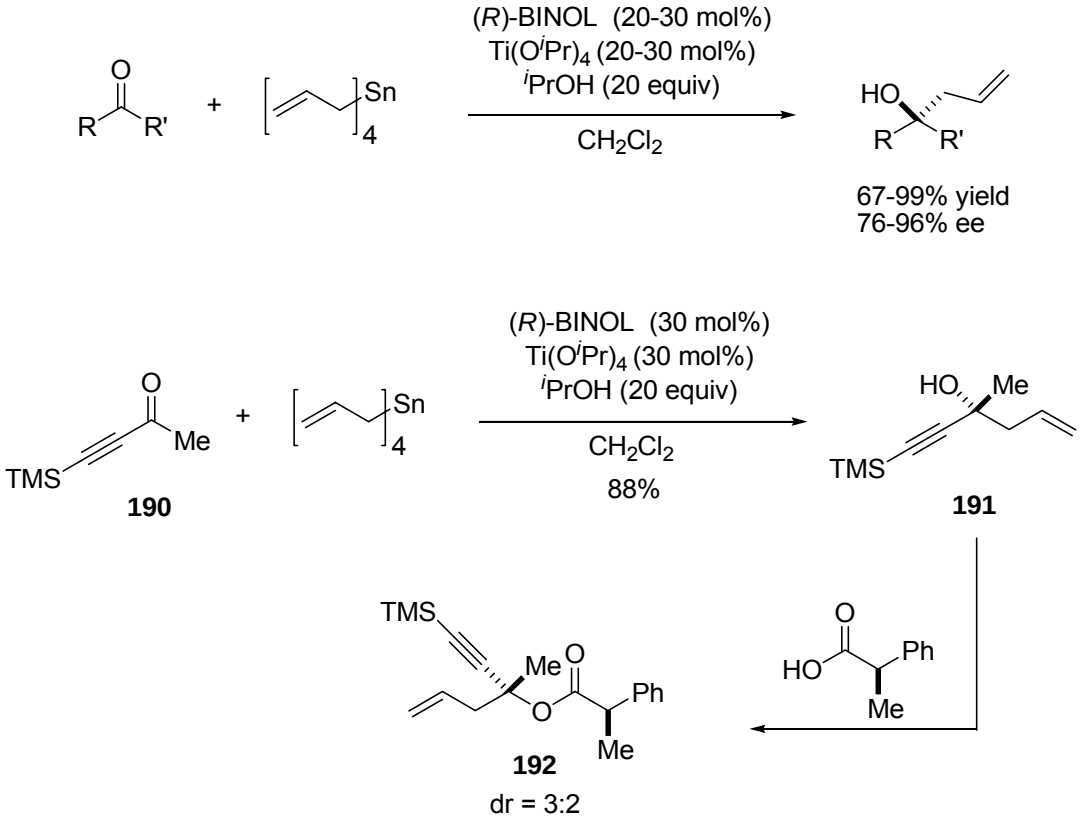
Scheme 27. Attempted C_{16} Tertiary Carbinol Installation via Asymmetric Tagliavini Ti(IV)-BINOL Allylation



The recent investigations by Walsh lead to a major breakthrough in the catalytic, asymmetric allylation of ketones. Through a more detailed examination of the catalyst system utilized by Tagliavini, it was discovered that the major titanium-containing component was BINOL-Ti(O^iPr)$_2$. When BINOL-Ti(O^iPr)$_2$ was prepared independently from BINOL and Ti(O^iPr)$_4$ with subsequent removal of ^{i}PrOH and employed in allylation reactions,

enantioselectivities comparable to those obtained by Tagliavini were obtained. However, when the catalyst preparation was not followed by removal of ^{i}PrOH, a marked increase in enantioselectivity of the tertiary alcohol product of the allylation reaction was realized. Optimized reaction conditions entailed treating a solution of BINOL (20-30 mol%) and Ti($O^{i}Pr$)$_4$ (20-30 mol%) in CH_2Cl_2 with ^{i}PrOH (20 equiv) followed by the ketone substrate and tetraallylstannane (1.5 equiv). Encouraged by the high levels of enantioselectivity obtained by Walsh et al., we prepared alcohol **191** in 88% yield according to the published procedure (Scheme 28). However, conversion of the resulting tertiary alcohol product to its corresponding (*R*)-methoxyphenyl acetate ester once again revealed synthetically unacceptable levels of diastereoselection (3:2).

Scheme 28. Attempted C_{16} Tertiary Carbinol Installation via Walsh Protocol



Given the unsatisfactory results obtained in the previously described allylation reactions, we turned our attention to a reagent system successfully employed by Mukaiyama and coworkers for the asymmetric allylation of aldehydes and activated ketones (Figure 28).[81] Mukaiyama's protocol incorporates chiral diisopropyltartrate ligands (5.0 equiv) into Sn(II)-catecholate **193** (2.0 equiv)[82] to afford the corresponding stannate complex **194** which is speculated to undergo oxidative addition with allyl bromide (2.0 equiv) in the presence of catalytic amounts of CuI (10 mol%) to produce the chiral Sn(IV)-allylating agent **195**. Reaction of **195** with various aromatic aldehyde and pyruvate electrophiles in CH_2Cl_2 at –78 °C afforded the corresponding homoallylic alcohols in high yield with excellent levels of enantioselectivity.

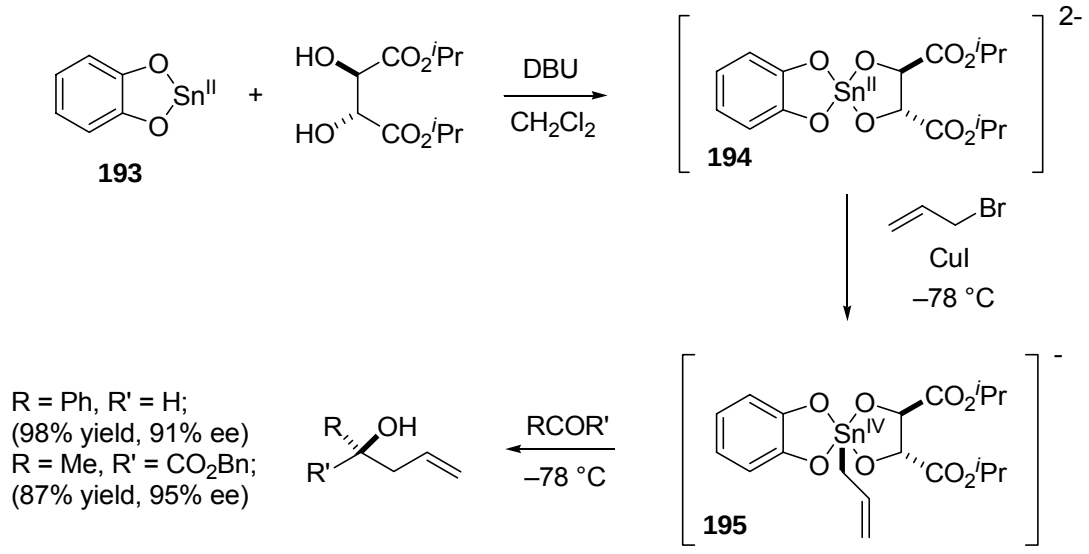


Figure 28. Mukaiyama's Asymmetric Allylation of Carbonyl Compounds

Intrigued by the high enantioselectivities observed by Mukaiyama, and confident in our ability to transform the activating benzyl ester moiety into the requisite TMS-alkyne in subunit **187**, we

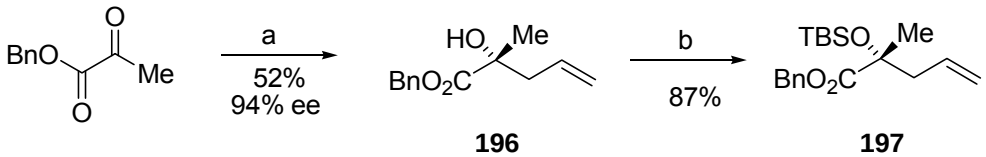
[81] (a) Nishida, M.; Tozawa, T.; Yamada, K.; Mukaiyama, T. *Chem. Lett*. **1996**, 1125. (b)Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 2301.
[82] Honnick, W. D.; Zuckerman, J. J. *Inorg. Chem*. **1978**, *17*, 501.

elected to explore the possibility of initiating our synthesis of fragment **172** with the asymmetric allylation of benzyl pyruvate.

2.4.3 Synthesis of the C_{14}–C_{21} Subunit

The synthesis of the C_{14}–C_{21} β-ketophosphonate subunit **187** commenced with the asymmetric allylation of benzyl pyruvate with the chiral Sn(IV) allylating agent **195** according to the published procedure described by Mukaiyama et al.[75] Initially, there was some concern as to the reproducibility of this literature procedure as the high enantioselectivities were representative of very small-scale reactions. In Mukaiyama's examples, reactions typically employed 0.2 mmol (~35 mg) of the benzyl pyruvate substrate. Incorporating this allylation protocol into our synthetic scheme for the preparation of **187** would obviously require performing the reaction on significantly larger scale, and we were concerned whether we would observe the same excellent enantioselectivity in a large scale reaction. Gratifyingly, performing the reaction on 3.0 g of benzyl pyruvate afforded tertiary alcohol **196** in 52% yield with 94% ee (Scheme 29). Silyl protection of the chiral tertiary alcohol with TBSOTf and 2,6-lutidine then delivered silyl ether **197** in 87% yield.

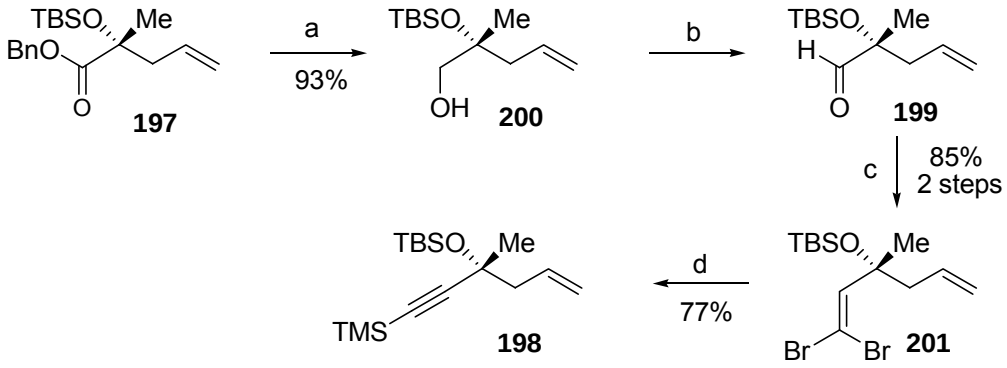
Scheme 29. Mukaiyama Asymmetric Sn(IV)-Allylation of Benzyl Pyruvate[a]



[a]Conditions: (a) (–)-DIPT, Sn(II)-catecholate, DBU, CuI, CH_2CHCH_2Br, CH_2Cl_2, –85 °C. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

While the benzyl ester was essential for the activation of the allylation substrate, it now required further elaboration to an alkyne. This was envisioned to occur by half-reduction to the corresponding aldehyde with subsequent Corey-Fuchs homologation to provide the protected alkyne **198** (Scheme 30). However, attempted half-reduction of **197** to the corresponding aldehyde **199** with 1.0 equivalent of DIBAL-H at –90 °C consistently resulted in mixtures of the desired aldehyde product **199**, starting ester, and overreduction to alcohol **200**. Given this inability to control the half-reduction, benzyl ester **197** was treated with an excess of DIBAL-H to cleanly afford the corresponding alcohol **200** which was then cleanly oxidized to the desired aldehyde under Parikh-Doering conditions.[83] Corey-Fuchs homologation[84] of aldehyde **199** with CBr_4 and PPh_3 in CH_2Cl_2 furnished the vinyl dibromide **201** in 85 % yield from alcohol **200**. After treating **201** with ^{n}BuLi and TMSCl, we arrived at the trimethylsilyl-protected alkyne **198**.

Scheme 30. Conversion of Benzyl Ester **197** to Alkyne **198**[a]



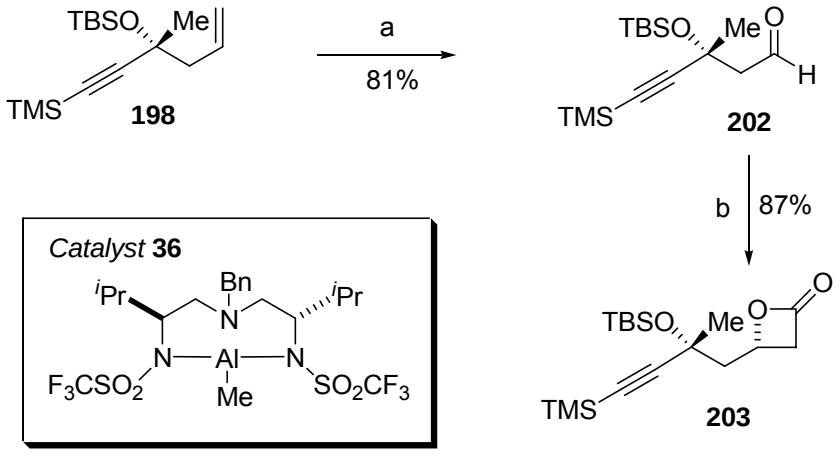
[a]Conditions: (a) DIBAL-H, CH_2Cl_2, –78 °C. (b) SO_3•py, DMSO, Et_3N, CH_2Cl_2, 0 °C. (c) PPh_3, CBr_4, CH_2Cl_2. (d) i. ^{n}BuLi, THF, –78 °C. ii. TMSCl, –78 °C to 0 °C.

With alkyne **198** in hand, we attempted to apply the asymmetric AAC reaction to form the C_{18}–C_{19} bond and concomitantly establish the requisite C_{18} hydroxyl-bearing stereocenter of

[83] Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc*. **1967**, *89*, 5505.
[84] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *36*, 3769.

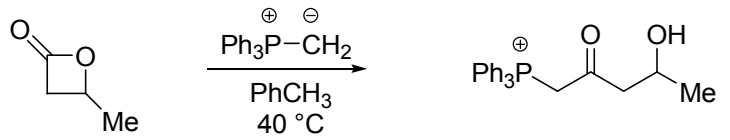
amphidinolide B_1 (Scheme 31). Selective ozonolysis of the monosubstituted olefin over the TMS-protected alkyne proceeded rapidly at –78 °C in CH_2Cl_2/MeOH/py (5:5:1) to afford the desired aldehyde coupling partner for the AAC reaction. There was some concern regarding the protected tertiary alcohol stereocenter in aldehyde **202**. In all previous examples of diastereoselective AAC reactions to achieve 1,3-stereochemical relationships, the aldehyde component of the AAC contained a protected secondary alcohol stereocenter where the small hydrogen atom could be oriented toward the approaching ketene nucleophile. In the present reaction, the C_{16} methyl group would be aligned with the incoming nucleophile, and the manner in which this more sterically demanding substituent would affect the observed diastereoselectivity of the reaction was uncertain. We were pleased to discover that subjecting aldehyde **202** to standard AAC conditions (10 mol% of (*S*, *S*)-catalyst **36**) resulted in the complete conversion of **202** to the corresponding β-lactone **203** in 87% isolated yield with high levels of diastereoselectivity (*dr* = 30:1) induced by the chiral aluminum triamine catalyst.

Scheme 31. AAC-Based Installation the C_{18} Hydroxyl-Bearing Stereocenter[a]

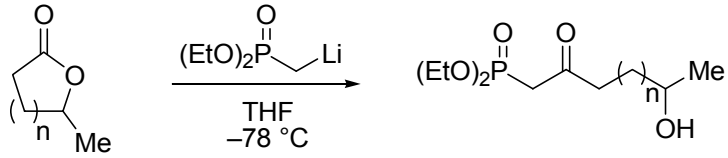


aConditions: (a) O_3, PPh_3, CH_2Cl_2/MeOH/py, –78 °C. (b) 10 mol% *Catalyst* **36**, DIPEA, AcBr, CH_2Cl_2, –50 °C.

According to our previously described retrosynthetic strategy, completion of the C_{14}–C_{21} β-ketophosphonate subunit **187** was predicated on the regioselective ring opening of lactone **203** with a lithium phosphonate anion. This transformation is greatly underrepresented in the literature, most likely due to the low availability of enantiomerically enriched β-lactones; however, a few related examples exist that encouraged our pursuit of this bond construction. It has been demonstrated that, when treated with alkylidenetriphenylphosphoranes, β-propiolactone undergoes ring opening at the carbonyl carbon to afford δ-hydroxy-β-ketophosphoranes in modest yield (Eq 14).[85] Also, γ- and δ-lactones have been shown to react with lithiumalkylphosphonates arriving at the corresponding β-ketophosphonate (Eq 15).[86] Based on this precedent, we anticipated the successful nucleophilic addition/elimination reaction between β-lactones and lithium alkylphosphonates.



(14)



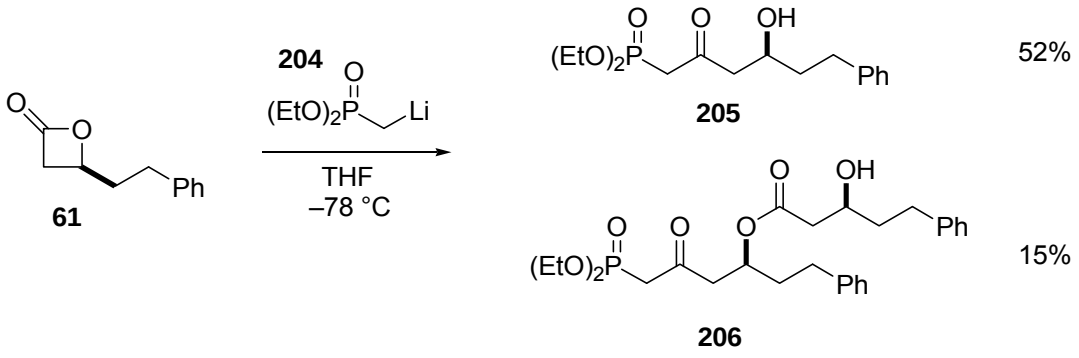
(15)

To explore the reactivity of enantiomerically enriched β-lactones toward lithium alkylphosphonates, hydrocinnamaldehyde derived lactone **61** was selected as a test substrate (Scheme 32). We were pleased to learn that treating a –78 °C solution of the lithium anion of

[85] Le Roux, J.; Le Corre, M. *J. Chem. Soc., Chem. Commun*. **1989**, 1464.
[86] Altenbach, H.-J.; Holzapfel, W.; Smerat, G.; Finkler, S. H. *Tetrahedron Lett*. **1985**, *26*, 6329.

diethylmethylphosphonate **204** (1.5 equiv) in THF with lactone **61** resulted in the formation of the desired β-ketophosphonate **205** in 52% isolated yield; however, it was accompanied by a significant amount (15%) of a by-product **206** that apparently resulted from the acylation of the newly generated lithium alkoxide product of β-lactone ring opening based on ^{1}H NMR and MS analysis.

Scheme 32. Lithium Phosphonate Anion Ring Opening of b-Lactone **61**



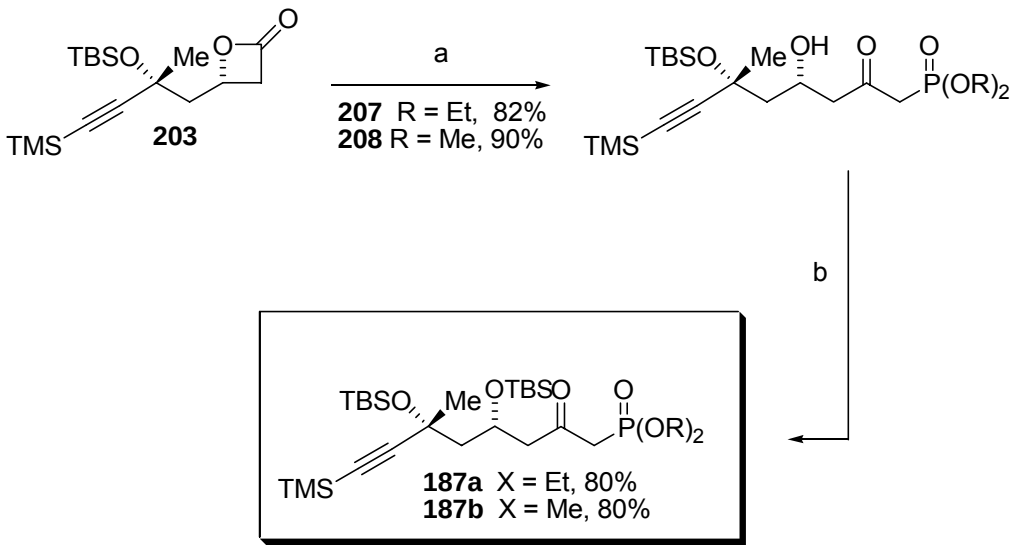
The formation of self-acylated product **206** would suggest a competition for the β-lactone electrophile existing between the intended lithium diethylphosphonate nucleophile and the newly generated lithium alkoxide arising from ring opening of **61**. Presumably, a marked increase in the concentration of the phosphonate anion should work to suppress the competitive nucleophilic addition by the lithium alkoxide. Indeed, doubling the concentration of lithium diethyl phosphonate (3.0 equiv) effectively eliminated the self-acylation product[87] and furnished the desired β-ketophosphonate **205** in 83% yield.

Having successfully demonstrated the synthesis of β-ketophosphonates from enantiomerically enriched β-lactones, we could then apply this new strategy to complete the β-

[87] No detectable amount of self-acylation product **206** was observed upon ^{1}H NMR analysis of crude product mixtures.

ketophosphonate subunit **187** (Scheme 33). Lithiation of 3.0 equiv of diethylmethylphosphonate at –78 °C in THF, followed by treatment with β-lactone electrophile **203** resulted in regioselective lactone ring opening to β-ketophosphonate **207** in 82% yield. Employing the lithium anion of dimethylmethyl phosphonate cleanly afforded the corresponding β-ketophosphonate **208** in slightly higher yields (88-90%). The resulting secondary alcohol was then protected as its *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMF) thus completing the synthesis of the C_{14}–C_{21} subunit.

Scheme 33. Completion of the C_{14}–C_{21} Subunit **187**[a]



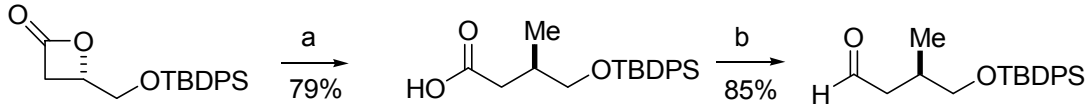
(a) $(RO)_2(P{=}O)CH_2Li$, THF, –78 °C. (b) TBSCl, imidazole, DMF.

2.4.4 Synthesis of the C_{22}–C_{26} Subunit

We had originally envisioned a potential route to the C_{22}–C_{26} α-chiral aldehyde fragment of **147** commencing with the enantiomerically enriched β-lactone **105** (Scheme 34). Treatment of **105**

with excess dimethylmagnesiocuprate resulted in S_N2 ring opening to establish the requisite C_{23} methyl-bearing stereocenter and delivered carboxylic acid **209** in 79% yield. Acid **209** was then efficiently converted to the corresponding aldehyde **210** (85%) according to Brown's one-pot reduction/oxidation sequence previously employed in the total synthesis of (–)-laulimalide.

Scheme 34. Synthesis of Aldehyde **210**[a]

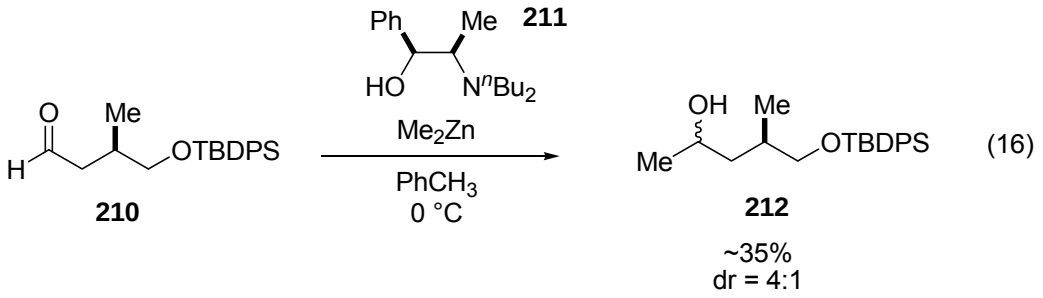


105 **209** **210**

[a] Conditions: (a) CuBr, MeMgBr, TMSCl, THF/DMS, –50 °C to rt. (b) i. $BH_3{\cdot}SMe_2$, Et_2O; ii. PCC, CH_2Cl_2.

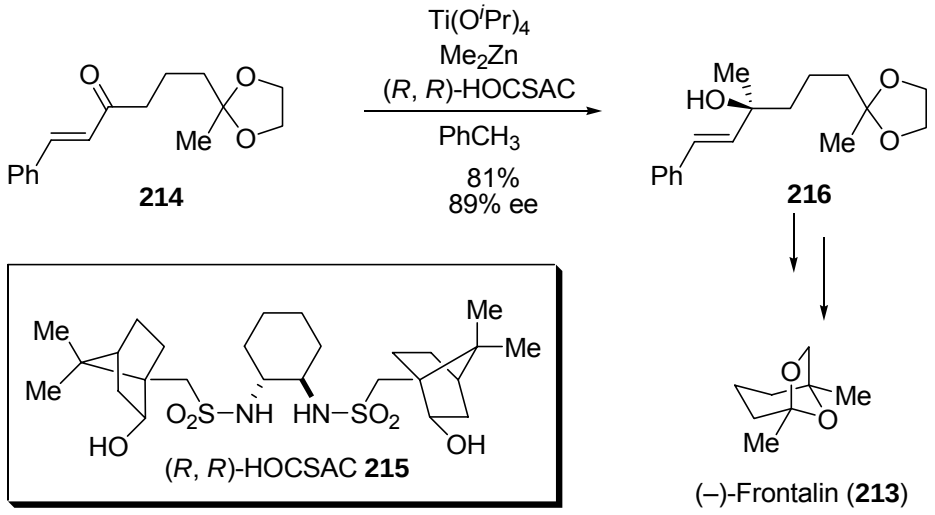
Installation of the requisite C_{25} hydroxyl-bearing stereocenter was to be accomplished via a diastereoselective dimethylzinc addition to aldehyde **210**. While the asymmetric addition of diethylzinc to aromatic and aliphatic aldehydes has been well established, the corresponding dimethylzinc additions are lesser known.[88] Initial attempts to arrive at suitable reaction conditions to promote the desired dimethylzinc addition employed Soia's *N*,*N*-di-*n*-butylnorephedrine amino alcohol catalyst **211** (Eq 16). However, subjecting aldehyde **210** to a 0 °C solution of **211** (10 mol%) and Me_2Zn (2.2 equiv) in toluene for 24 h resulted in a sluggish reaction that afforded the secondary alcohol product **212** as a 4:1 inseparable mixture of diastereomers (500 MHz ^{1}H NMR) in rather modest yield (~35%). The ineffectiveness of this protocol prompted the investigation of other means of promoting this transformation.

[88] Pu, L.; Yu, H.-B. *Chem. Rev*. **2001**, *101*, 757 and references therein.



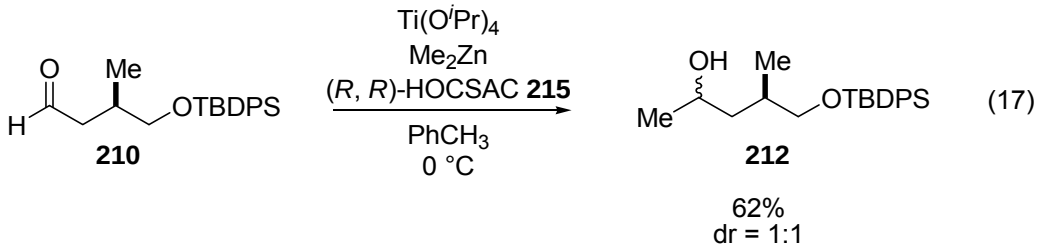
Another intriguing possibility for achieving the desired diastereoselective dimethylzinc addition to aldehyde **210** was described by Yus et al. in the total synthesis of the pine beetle pheromone, (–)-frontalin (**213**).[89] The key step in the synthesis of **213** involved the enantioselective addition of dimethylzinc to an α,β-unsaturated ketone **214** at 0 °C in the presence of Ti(O^{i}Pr)$_4$ and a substoichiometric amount of the chiral sulfonamide ligand (1*R*, 2*R*)-bis(hydroxycamphorsulfonamido)cyclohexane (HOCSAC) **215**[90] to afford the chiral tertiary alcohol **216** in 81% yield with an enantiomeric excess of 89% (Scheme 35).

Scheme 35. Asymmetric Dimethylzinc Addition to Ketones: Total Synthesis of (–)-Frontalin (**213**)



[89] Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem*. **2003**, *15*, 2745.
[90] Ligand **215** and ***ent*-215** were prepared according to the literature procedure: Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc*. **2000**, *122*, 3250.

Given the success with the sterically and electronically more demanding ketone substrate, we anticipated similar results with aldehyde **210**. Exposure of **210** to these reaction conditions did result in an increased isolated yield of alcohol **212** (62%); however, no selectivity was achieved based on 500 MHz ^{1}H NMR analysis of the crude reaction mixture (dr = 1:1) (Eq 17). Attributing the lack of selectivity to a possible mismatched substrate/catalyst pairing, the reaction was repeated with the enantiomeric (1*S*, 2*S*)-sulfonamide ligand ***ent*-215**. Disappointingly, no selectivity was observed possibly owing to unfavorable steric interactions caused by the preexistent β-stereocenter in **210**.



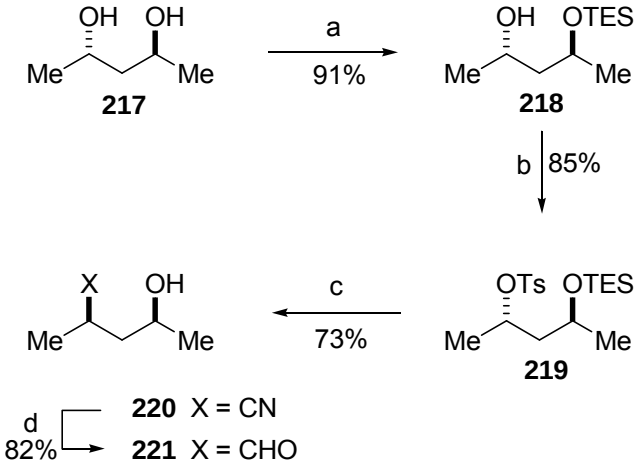
(17)

A rapid alternative synthesis of the C_{22}–C_{26} fragment amphidinolide B_1 from (2*S*, 4*S*)-(+)-pentanediol was disclosed in Shioiri's total synthesis of geodiamolide A.[73] This method has also been applied in several other syntheses of the upper fragment of **133** and was viewed as a convenient option (Scheme 36). Selective monosilylation of **217** with sodium hydride and triethylsilyl chloride at ambient temperature yielded the monoprotected diol **218** in 91% yield.[91] We elected to mono-protect the diol as the triethylsilyl ether in an attempt to build orthogonality into our protecting group strategy as the late stage macrolactonization to close the 26-membered ring will require selective removal of the C_{25} protecting group to ensure a higher degree of success. Tosylation of the remaining secondary alcohol was performed with *p*-toluenesulfonyl

[91] McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Am. Chem. Soc*. **1986**, *51*, 3388.

chloride in pyridine solvent to obtain the secondary tosylate **219** in 53% yield accompanied by an unidentifed by-product after 4 days at 4 °C. A far more efficient reagent system for the tosylation of secondary alcohol **218** was realized by substituting 1,4-diazabicyclo[2.2.2]octane (DABCO) for pyridine.[92] Tosylate **219** could now be obtained in 85% yield after 1.5 h at 0 °C without any undesired elimination products. Cyanide displacement of the secondary tosylate (NaCN, DMSO, 50 °C) arrived at nitrile **220** and subsequent DIBAL-H reduction provided the C_{22}–C_{26} α-chiral aldehyde subunit **221** which was used without further purification.

Scheme 36. Synthesis of the C_{22}–C_{26} Subunit **221**[a]



[a] Conditions: (a) NaH, TESCl, THF. (b) DABCO, TsCl, CH_2Cl_2. (c) NaCN, DMSO, 50 °C. (d) DIBAL-H, CH_2Cl_2, –78 °C

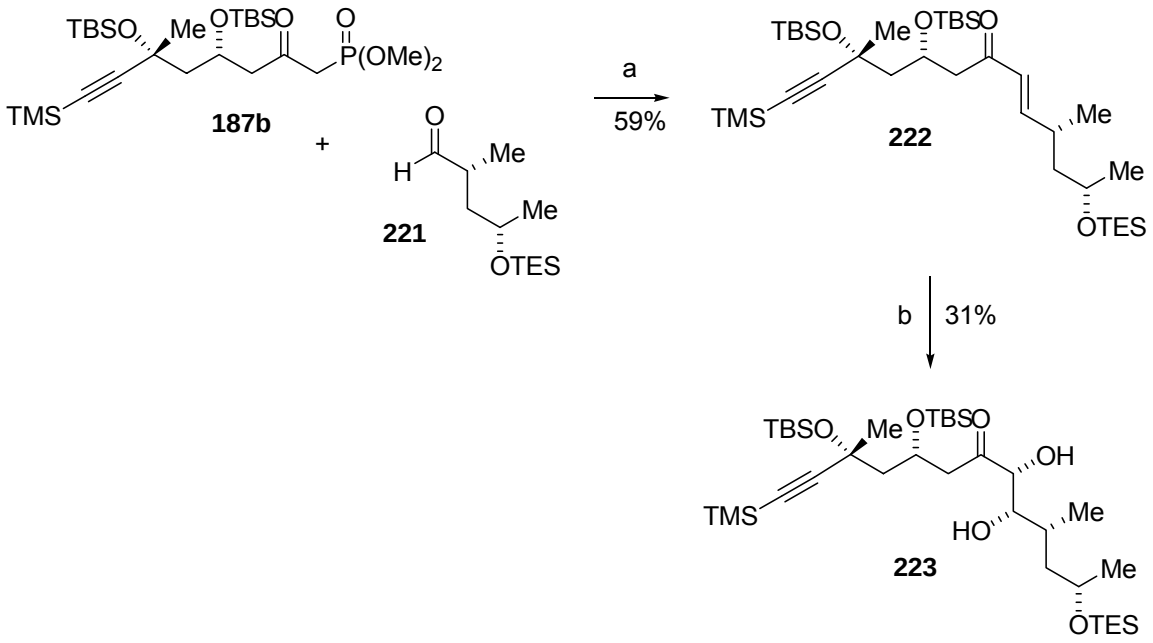
2.4.5 Subunit Coupling and Functionalization for Fragment Union

Assembly of the two subunits **187b** and **221** was achieved under Roush-Masamune olefination conditions (LiCl, DIPEA, CH_3CN) to deliver the desired (*E*)-olefin **222** as a single regioisomer

[92] Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, *12*, 1433.

in moderate yield (Scheme 37).[93] Installation of the *syn*-diol moiety was then performed according to the reaction conditions described in Myles' synthesis of the C_{14}–C_{26} fragment of amphidinolide B_1.[76f] Exposure of enone **222** to a 0 °C suspension of AD-mix α (2.1 g/mmol), K_2OsO_4•$2H_2O$ (10 mol%), and $(DHQ)_2PHAL$ (10 mol%) in 1:1 $^tBuOH/H_2O$ resulted in the sluggish dihydroxylation of the electron-deficient (*E*)-olefin affording the desired diol diastereomer **223** in 31% isolated yield along with a second diol diastereomer and unreacted starting material after 24 h at 0 °C.

Scheme 37. Fragment Union and Diol Installation

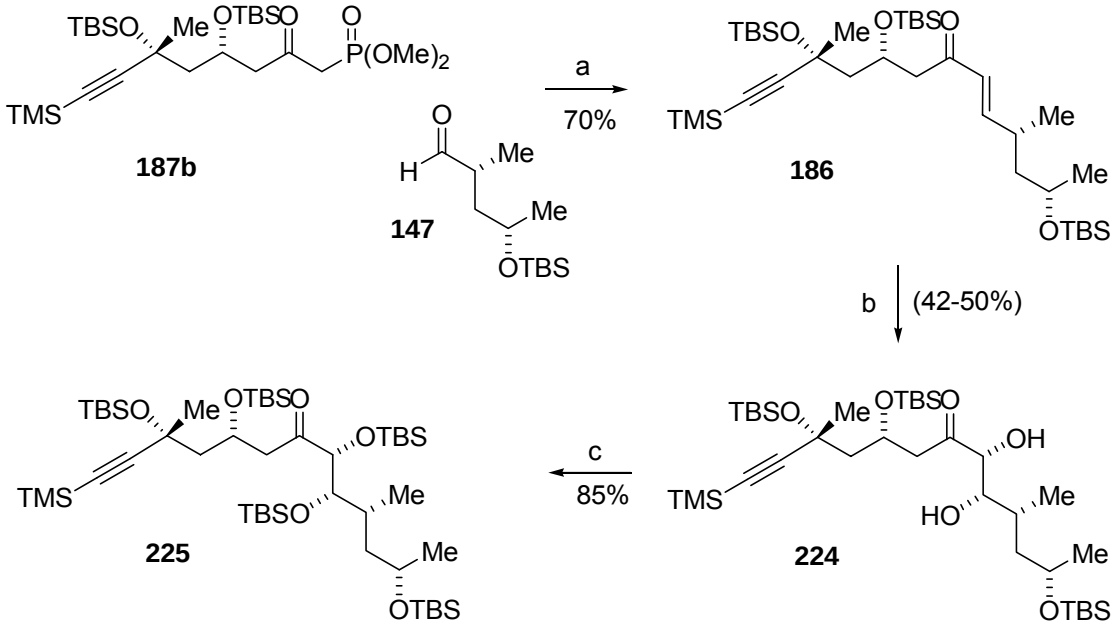


aConditions: (a) LiCl, DIPEA, CH_3CN. (b) AD-mix α, 10 mol% K_2OsO_4•$2H_2O$, 10 mol% $(DHQ)_2PHAL$, $NaHCO_3$ $^tBuOH/H_2O$

[93] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183.

Poor reproducibility of the yields in the synthesis of TES–protected aldehyde **221** led us to prepare the more commonly employed TBS–protected aldehyde **147**.[72] Aldehyde **147** was generated according to the literature procedure (Scheme 36) with the only modification being the incorporation of the DABCO-mediated tosylation protocol. Roush-Masamune olefination of phosphonate **187b** and aldehyde **147** (LiCl, DIPEA, CH_3CN) afforded the desired (*E*)-olefin **186** in slightly higher yield (70%). Enone **186** was then subjected to the previously described Sharpless reagent system (AD-mix α (2.1 g/mmol), $K_2OsO_4 \bullet 2H_2O$ (10 mol%), and $(DHQ)_2PHAL$ (10 mol%) in 1:1 $^tBuOH/H_2O$). Methanesulfonamide (1.0 equiv) was also added to the reaction in an attempt to accelerate osmate ester hydrolysis. The added methanesulfonamide served its purpose as near complete consumption of the starting enone was observed by TLC after 8 h at 0 °C. Although yields of the *syn* diol **224** were improved from earlier trials (42-50%), they were still variable and not synthetically acceptable for such a late stage reaction. Additional attempts at enhancing the isolated yield of **224** by increasing the osmium and chiral amine loading from 10 to 20 mol% proved to be ineffective. Protection of the diol was then achieved using excess TBSOTf (3.0 equiv) and 2,6-lutidine (5.0 equiv) to furnish the fully protected C_{14}–C_{26} fragment **225** (Scheme 38).

Scheme 38. Fragment Coupling and Diol Installation



[a]Conditions: (a) LiCl, DIPEA, CH_3CN. (b) AD-mix α, 10 mol% $K_2OsO_4 \bullet 2H_2O$, 10 mol% $(DHQ)_2PHAL$, $NaHCO_3$, $MeSO_2NH_2$, $^tBuOH/H_2O$. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2.

2.5 FUTURE WORK

Given the inefficient introduction of the C_{21},C_{22} *syn*-diol via the Sharpless asymmetric dihydroxylation of olefin **186**, an alternative route involving a diastereoselective glycolate aldol reaction will be investigated (Figure 29). Such a strategy would require the regioselective generation of (Z)-enolate **226** from lactone **203** derived ketone **227** which would serve to selectively add to the previously synthesized C_{22}–C_{26} aldehyde **147** to generate the required *syn* diol relationship.

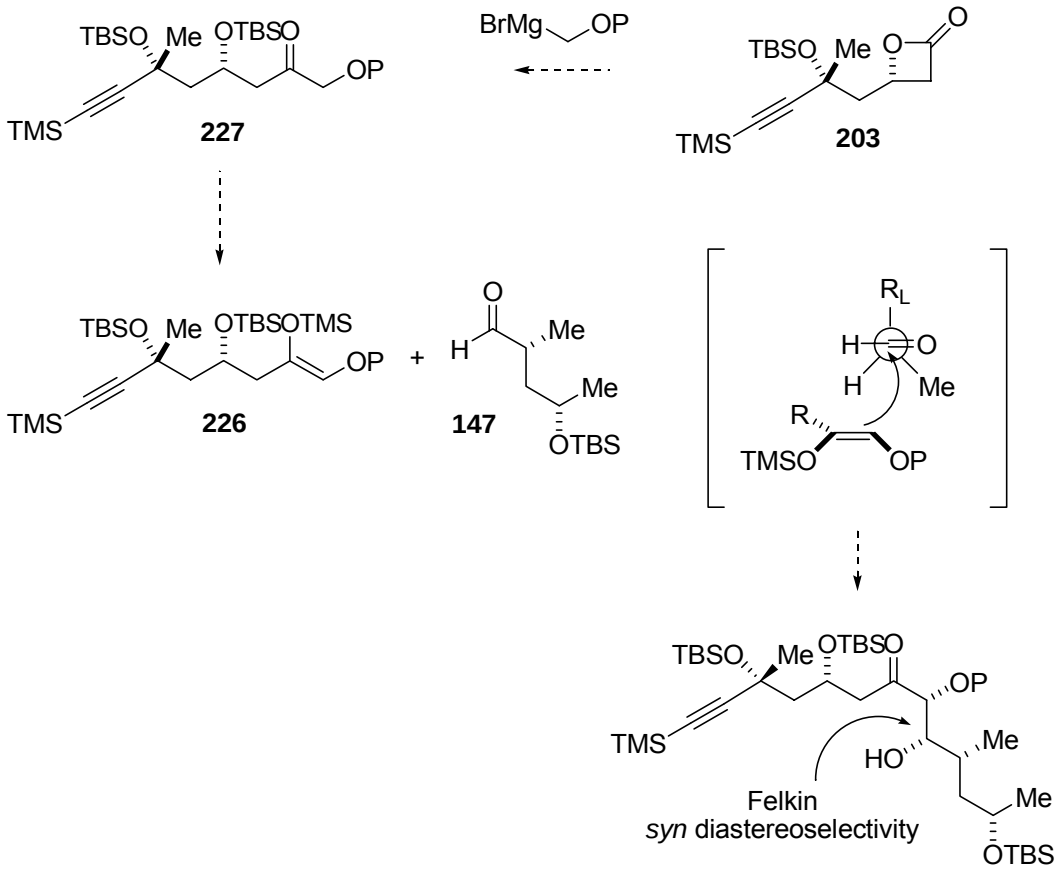


Figure 29. Diastereoselective Glycolate Aldol Reaction in the Formation of the C_{21},C_{22} *syn*-diol Relationship of Amphidinolide B_1

Completion of the total synthesis of amphidinolide B_1 will be predicated on the union of the major fragments **172**, **173**, and **174** (Figure 30). The C_{14}–C_{26} fragment **172** will be functionalized for fragment coupling through the deprotection and subsequent carbostannylation of the C_{14}–C_{15} alkyne to furnish the requisite trisubstituted olefin **228**. Julia olefination of epoxyaldehyde **174** and sulfone **173** will then assemble the intact C_1–C_{13} fragment **171**. Suzuki coupling between vinyl iodide **172,** dervied from lithium halogen exchange of **228**, and the pinacol boronate ester moiety in **171** will be employed to unite the major fragments, forming the *s-cis* diene moiety. Silyl deprotection and Yamaguchi macrolactonization of seco acid **229** will then complete the total synthesis of amphidinolide B_1 (**133**).

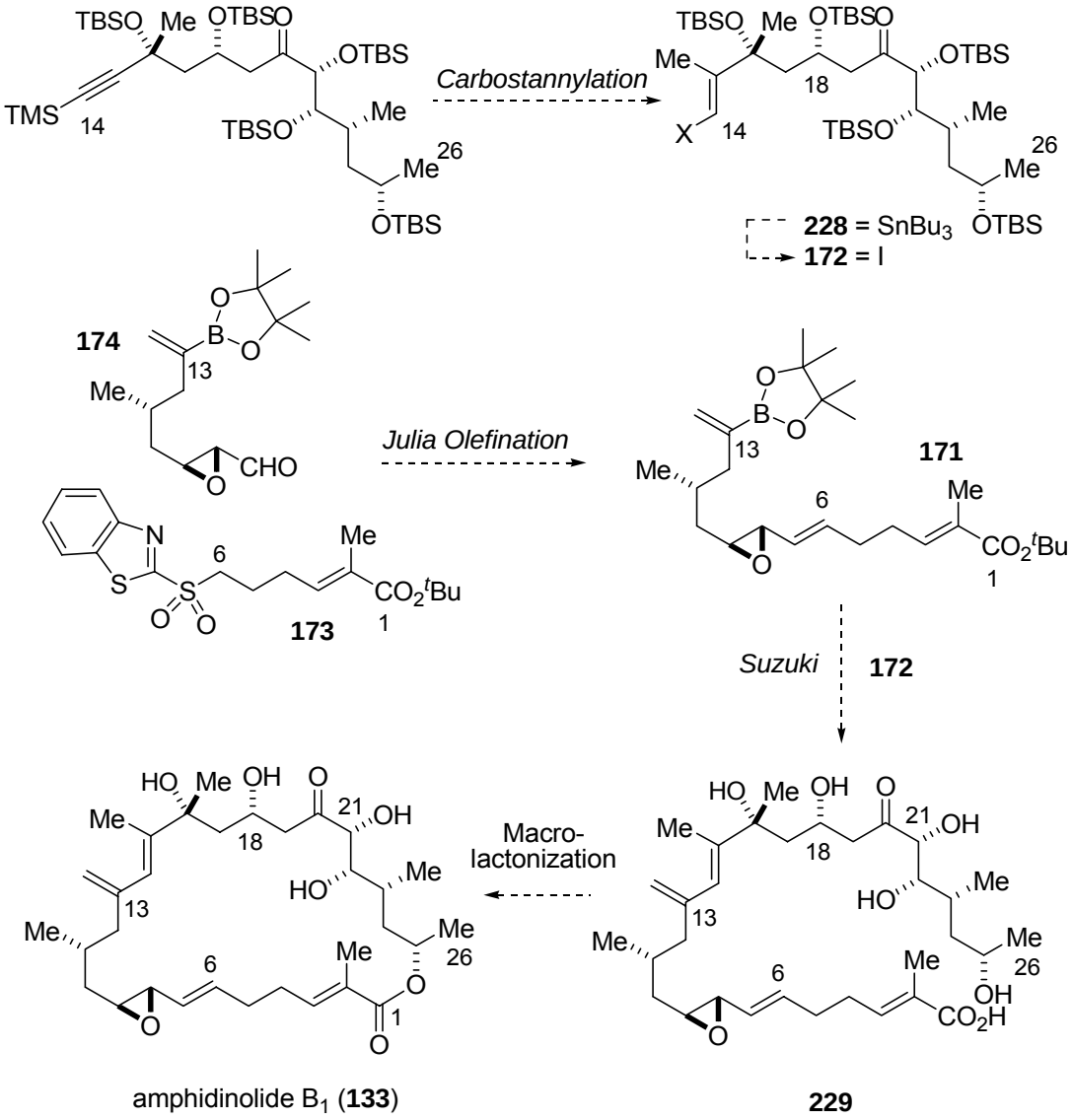


Figure 30. Completion of the Total Synthesis of Amphidinolide B_1

2.6 CONCLUSIONS

Asymmetric AAC reactions have been instrumental in our recent studies toward the total synthesis of the cytotoxic marine natural product, amphidinolide B_1 (**133**). By exploiting the synthetic utility of AAC reaction technology, key stereochemical relationships present in major fragments **172** and **174** were established. A highly enantioselective installation of the C_{16} tertiary carbinol stereocenter was acheived through the large-scale application of Mukaiyama's Sn(IV)-allylation protocol, and a rapid synthesis of sulfone subunit **173** was realized from commercially available γ-butyrolactone. Also, for the first time, the regioselective ring opening of β-lactones by phosphonate anions has been documented.

2.7 EXPERIMENTAL SECTION

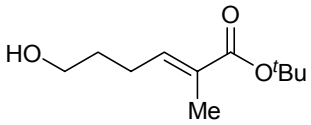
General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100mL, solvent) with units of degree•g•cm^{-3}. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker DPX 301 and DPX 302 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (C**H**Cl$_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on Bruker DPX 301 and DPX 302 spectrometers (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[94] Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralpak™ AS-H column (250 × 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Tetrahydrofuran (THF) was either distilled from potassium benzophenone ketyl or passed

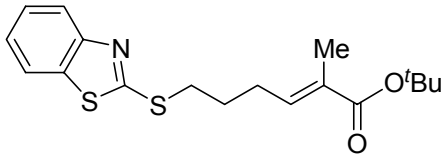
[94] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

through two columns of alumina, and diethyl ether (Et_2O) was distilled from sodium benzophone ketyl. Dichloromethane (CH_2Cl_2), dimethylsulfide (DMS), *N*,*N*-diisopropylethylamine (DIPEA), and triethylamine (Et_3N) were distilled from CaH_2 under N_2.

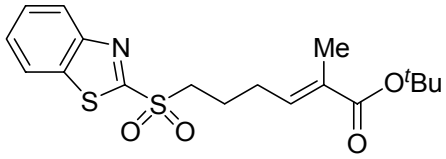


(2*E*)-*tert*-Butyl-6-hydroxy-2-methylhex-2-enoate (178): To a –78 °C solution of 1.9 g of γ-butyrolactone (22.0 mmol) in 35 mL of CH_2Cl_2 was added a 24 mL of a 1.0 M solution of DIBAL-H in hexanes dropwise via syringe. The resulting clear, colorless solution was maintained at –78 °C for 1 h, then quenched with MeOH (2 mL) and saturated Rochelle's salt (2 mL). The mixture was warmed to ambient temperature and maintained for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil that was used immediately in the next reaction without further purification.

To a 0 °C solution of 9.0 g of phosphorane **177** (23.0 mmol) in 50 mL of THF was added a solution of lactol **176** in 10 mL of THF dropwise via syringe. The reaction was allowed to warm to ambient temperature overnight, at which point 20 mL of H_2O was added. The mixture was extracted with Et_2O, and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (30% Et_2O/pentane) provided 3.11 g (70%) of the title compound as a clear, colorless oil: IR (thin film): 3427, 2977, 2933, 2872, 1705, 1648, 1456, 1168, 851, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.61 (dt, *J* = 1.3, 7.5 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.37 (brs, 1H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.75 (s, 3H), 1.66 (tt, *J* = 6.5 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 140.3, 129.5, 79.9, 62.0, 31.4, 28.0, 24.9, 12.2; LRMS (EI, 70eV): *m/z* 144 $[M-^tBu]^+$; HRMS calcd for $C_7H_{12}O_3$: 144.0786, found 144.0792.

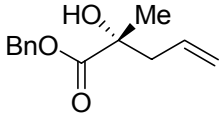


***tert*-Butyl-6-(benzothiazol-2-ylsulfanyl)-2-methylhex-2-enoate:** To a 0 °C solution of 0.334 g of 2-mercaptobenzothiazole (2.0 mmol) and 0.393 g of PPh_3 (1.5 mmol) in 10 mL of THF was added 0.200 g of alcohol **178** (1.0 mmol) in 2 mL of THF. The resulting yellow solution was then treated with 0.285 mL of diethylazodicarboxylate (1.8 mmol) slowly dropwise via syringe. After maintaining for 45 min at ambient temperature, the resulting suspension was diluted with Et_2O (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Hexanes were added and the resulting white precipitate was removed by filtering through Celite. Purification of the crude product by flash chromatography on silica gel (2% EtOAc/hexanes) afforded 0.260 g (74%) of the title compound as a pale yellow oil. IR (thin film): 3062, 2976, 2930, 1704, 1650, 1456, 1427, 1291, 1254, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 3.38 (t, J = 7.1 Hz, 2H), 2.36 (q, J = 7.4 Hz, 2H), 1.82 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 166.5, 153.1, 139.0, 135.1, 130.3, 125.9, 124.1, 121.4, 120.8, 80.0, 32.9, 28.2, 28.0 (3C), 27.5, 12.4; HRMS calcd for $C_{18}H_{23}NO_2S_2$: 349.1170, found 349.1171.



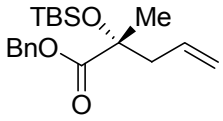
***tert*-Butyl-6-(benzothiazol-2-ylsulfonyl)-2-methylhex-2-enoate (173):** To a solution of 0.200 g of thioether (0.573 mmol) and 5 mg of $MnSO_4$•H_2O (0.029 mmol) at ambient temperature was added an aqueous mixture of 0.300 mL of 30% H_2O_2 dropwise via syringe. The resulting pale orange mixture was maintained at ambient temperature for 5 h at which point saturated aqueous NaCl was added (20 mL). The reaction mixture was extracted with Et_2O (3

× 20 mL). The combined organics were then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification the crude product by flash chromatography on silica gel (10% Et_2O/hexanes) afforded 0.150 g (69%) of the title compound as a colorless, viscous oil: IR (thin film): 3065, 2976, 2930, 1701, 1649, 1555, 1473, 1330, 1150, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.65–7.54 (m, 2H), 6.52 (br t, *J* = 7.4 Hz, 1H), 3.51 (br t, *J* = 7.6 Hz, 2H), 2.31 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.02 (tt, *J* = 7.4, 7.4 Hz, 2H), 1.74 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 165.5, 152.5, 137.4, 136.6, 131.1, 128.0, 127.6, 125.3, 122.2, 80.2, 54.0, 27.9 (3C), 26.9, 21.5, 12.4; HRMS calcd for $C_{18}H_{23}NO_4S_2$: 381.1068, found 381.1053.

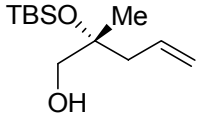


(2*R*)-Benzyl-2-hydroxy-2-methylpent-4-enoate (196):[42] To a white suspension of 6.00 g of tin (II) catecholate (26.4 mmol), 0.251 g of CuI (1.32 mmol), and 14.0 mL of (–)-diisopropyltartrate (66.0 mmol) in 40 mL of CH_2Cl_2 at ambient temperature was added a solution of 9.90 mL of DBU (66.0 mmol) in 40 mL of CH_2Cl_2 via syringe. The resulting clear, pale pink solution was maintained at ambient temperature for 1 h, cooled to –85 °C, then treated with a solution of 2.35 g of benzyl pyruvate (13.2 mmol) in 40 mL of CH_2Cl_2 dropwise via syringe pump over the course of 1 h. A solution of 2.30 mL of allyl bromide (26.4 mmol) in 40 mL of CH_2Cl_2 was added slowly via syringe pump (over 2.5 h) and the reaction mixture was maintained overnight at –80 °C. The reaction was quenched with 1 M HCl (200 mL) and hexanes (80 mL), then extracted with 2:1 hexanes/CH_2Cl_2 (3 × 150 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on an ISCO CombiFlash Companion™ (330 g column, 8-20% Et_2O/pentane) to obtain 1.50 g (52%) of a pale yellow liquid: Separation

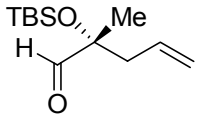
of enantiomers by chiral HPLC [Daicel Chiralpak AS-H column, 0.9 % ^{i}PrOH/hexanes, 0.7 mL/min, T_r 18.7 min (*S*) and 19.2 min (*R*)] determined the enantiomeric excess to be 94%; $[\alpha]_D$ = +6.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.42 (m, 5H), 5.73 (dddd, *J* = 7.3, 7.3, 10, 18 Hz, 1H), 5.20 (s, 3H), 5.05–5.12 (m, 2H), 3.13 (s, 1H), 2.53 (dd, *J* = 7.3, 14 Hz, 1H), 2.40 (dd, *J* = 7.3, 14 Hz, 1H), 1.45 (s, 3H).



(2*R*)-Benzyl-2-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-enoate (197): To a 0 °C solution of 1.0 g of alcohol **196** (4.54 mmol) in 7 mL of CH_2Cl_2 was added 1.60 mL of 2, 6-lutidine (13.6 mmol) followed by 1.67 mL of *tert*-butyldimethylsilyltrifluoromethanesulfonate (7.27 mmol). The reaction was warmed to ambient temperature and maintained for 2 h. Saturated aqueous $NaHCO_3$ was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (1% EtOAc/hexanes) yielded 1.32 g (87%) of the title compound as a clear, colorless liquid: $[\alpha]_D$ = +3.3 (*c* 2.4, $CHCl_3$); IR (thin film): 3077, 3035, 2955, 2929, 2894, 2856, 1749, 1641, 1498, 1457, 1376, 1253, 1004, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.30 (m, 5H), 5.80 (dddd, *J* = 7.2, 7.2, 10, 17 Hz, 1H), 5.15 (d, *J* = 12 Hz, 1H), 5.10 (d, *J* = 12 Hz, 1H), 4.95-5.07 (m, 2H), 2.50 (dd, *J* = 7.3, 14 Hz, 1H), 2.40 (dd, *J* = 7.0, 14 Hz, 1H), 1.44 (s, 3H), 0.87 (s, 9H), 0.077 (s, 3H), 0.065 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 135.8, 133.2, 128.5, 128.4, 128.2, 118.0, 66.6, 46.5, 25.9, 25.8, 18.3, –2.69, –3.11; LRMS (EI, 70eV): *m/z* 293 (M+ - CH_2CHCH_2); HRMS calcd for $C_{16}H_{25}O_3Si$: 293.1573, found 293.1570.

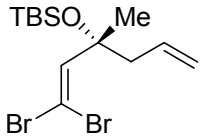


(2*R*)-2-(*tert*-butyldimethylsilyloxy)-2-methyl-pent-4-en-1-ol (200): To a –70 °C solution of 1.85 g of ester **197** (5.54 mmol) in 55 mL of CH_2Cl_2 was added a 1.0 M solution of diisobutylaluminum hydride (DIBAL-H) in hexanes dropwise via syringe. The resulting clear, colorless solution was allowed to warm to –30 °C over 2 h whereupon 0.900 mL of MeOH (22.1 mmol) was slowly added. The reaction mixture was then warmed to ambient temperature, treated with saturated aqueous Rochelle's salt (125 mL), and maintained for 2.5 h. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics were washed with brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (4% Et_2O/pentane) afforded 1.17 g (92%) of the title compound as a clear, colorless liquid: $[\alpha]_D$ = –0.5 (*c* 1.9, $CHCl_3$); IR (thin film): 3444, 3077, 2955, 2931, 2889, 2858, 1641, 1468, 1374, 1254, 1048, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (dddd, *J* = 7.4, 7.4, 11, 16 Hz, 1H), 5.06–5.11 (m, 2H), 3.40 (d, *J* = 11 Hz, 1H), 3.33 (d, *J* = 11 Hz, 1H), 2.35 (dd, *J* = 7.5, 14 Hz, 1H), 2.28 (dd, *J* = 7.4, 14 Hz, 1H), 1.20 (s, 3H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 117.8, 76.1, 69.9, 44.2, 25.8 (3C), 23.9, –2.1; LRMS (EI, 70eV): *m/z* 229 $[M-H]^+$; HRMS calcd for $C_{12}H_{25}O_2Si$: 229.1624, found 229.1623.

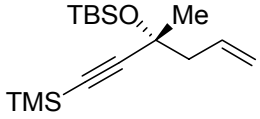


(2*R*)-2-(*tert*-butyldimethylsilyloxy)-2-methyl-pent-4-enal (199): To a 0 °C solution of 1.1 g of alcohol **200** (4.78 mmol) in 20 mL of CH_2Cl_2 was added 3.33 mL of Et_3N (23.9 mmol), 13 mL of DMSO (mmol), and 2.28 g of SO_3•py. The reaction mixture was maintained for 3 h at 0 °C, and then treated with a pH 7 buffer solution (15 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product mixture was purified by flash chromatography on silica gel

(1% Et_2O/pentane) to obtain 1.09 g (100%) of aldehyde **199** as a clear, colorless liquid: $[\alpha]_D$ = +25 (*c* 2.2 , $CHCl_3$); IR (thin film): 3080, 2965, 2931, 2897, 2858, 2798, 2706, 1739, 1642, 1254, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 5.79 (dddd, 7.2, 7.2, 10, 17 Hz, 1H), 5.00–5.20 (m, 2H), 1.28 (s, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 132.2, 118.8, 43.5, 25.8 (3C), 22.5, –2.31, –2.41; LRMS (EI, 70eV): *m/z* 213 $[M\text{-}CH_3]^+$; HRMS calcd for $C_{11}H_{21}O_2Si$: 213.1311, found 213.1312.

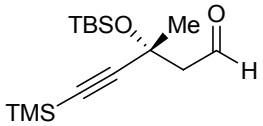


(3*R*)-*tert*-Butyl-[1-(2, 2-dibromovinyl)-1-methyl-but-3-enyloxy]-dimethylsilane (201): To a 0 °C solution of 5.01 g of PPh_3 (19.1 mmol) in 19 mL of CH_2Cl_2 was added a solution of 3.17 g of CBr_4 (9.56 mmol) in 19 mL dropwise via syringe. The resultant orange-yellow solution was maintained at 0 °C for 20 min, whereupon 1.09 g of aldehyde **199** in 19 mL of CH_2Cl_2 was added. After 1h, the reaction mixture was diluted with 10% EtOAc/hexanes (150 mL) and filtered through silica gel. Purification by flash chromatography (hexanes) provided 1.60 g (87%) of the title compound as a clear, colorless liquid: $[\alpha]_D$ = +13 (*c* 2.1, $CHCl_3$); IR (thin film): 3078, 2955, 2931, 2893, 2857, 1641, 1606, 1470, 1373, 1255, 1154, 1076, 1003, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.69 (s, 1H), 5.83 (dddd, *J* = 7.1, 7.1, 9.3, 15 Hz, 1H), 2.54 (dd, *J* = 7.3, 14 Hz, 1H), 2.42 (dd, *J* = 7.0, 14 Hz, 1H), 1.49 (s, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 133.6, 118.0, 86.2, 46.7, 27.1, 25.9 (3C), –2.1, –2.4; LRMS (EI, 70eV): *m/z* 369 $[M\text{-}CH_3]^+$; HRMS calcd for $C_{12}H_{21}OSiBr$: 366.9728, found 366.9744.



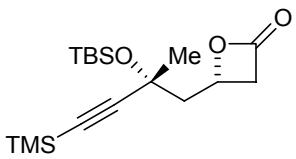
(4*R*)-4-*tert*-Butyldimethylsilyloxy)-4-methyl-6-trimethylsilyl-hex-1-en-5-yne (198): To a –78 °C solution of 1.55 g of vinyl bromide **201**

(4.04 mmol) in 20 mL of THF was added 7.60 mL of a 1.6 M solution of ^{n}BuLi in hexanes dropwise via syringe. The resulting pale yellow solution was maintained for 1 h at –78 °C, then warmed to 0 °C for an additional 1 h. After cooling to –78 °C, the reaction mixture was treated with 1.52 mL of freshly distilled TMSCl (12.1 mmol). The reaction was allowed to warm slowly to 0 °C over 3 h. Saturated aqueous NH_4Cl was added (40 mL), and the mixture was extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 0.920 g (77%) of the title compound **198** as a clear, colorless liquid: $[\alpha]_D$ = +0.64 (*c* 2.2, $CHCl_3$); IR (thin film): 3079, 2958, 2932, 2899, 2858, 2169, 1643, 1252, 839, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (ddt, *J* = 7.2, 11, 18 Hz, 1H), 5.10- 5.01 (m, 2H), 2.38 (d, *J* = 7.1 Hz, 2H), 1.39 (s, 3H), 0.87 (s, 9H), 0.18 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 117.6, 110.1, 88.3, 68.8, 49.6, 30.4, 25.7, 18.1, –0.2, –2.9, –3.0; LRMS (EI, 70eV): *m/z* 281 [M-CH_3] $^+$; HRMS calcd for $C_{15}H_{29}OSi_2$: 281.1757 found 281.1744.

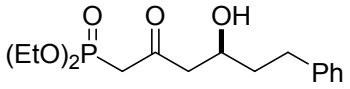


(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-trimethylsilyl-pent-4-ynal (202): A –78 °C solution of 0.415 g of olefin **198** (1.40 mmol) in 3.3 mL of CH_2Cl_2, 3.3 mL of MeOH, and 0.7 mL of pyridine was treated with O_3 until a pink color was observed. The reaction was quenched with 0.384 g of PPh_3 (1.40 mmol) and allowed to warm to ambient temperature. The crude product mixture was concentrated and purified by flash chromatography (10% CH_2Cl_2/hexanes) to obtain 0.360 g (86%) of a clear, colorless liquid: $[\alpha]_D$ = +36 (*c* 1.4, $CHCl_3$); IR (thin film): 2959, 2931, 2898, 2858, 2739, 2170, 1731, 1252, 1115, 1041, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.88 (t, *J* = 2.9 Hz, 1H), 2.58 (brd, *J* = 2.9 Hz, 2H), 1.54 (s, 3H), 0.86 (s, 9H), 0.21 (s, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9,

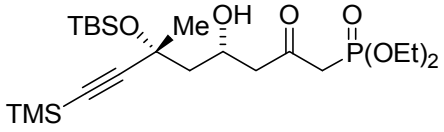
107.9, 90.4, 66.6, 56.9, 31.3, 25.5, 17.9, –0.4, –2.9, –3.3; LRMS (EI, 70eV): *m/z* 283 $[M\text{-}CH_3]^+$; HRMS calcd for $C_{14}H_{27}O_2Si_2$: 283.1549, found 283.1556.



(4*S*, 2′*R*)-4-[2-*tert*-Butyldimethylsilyloxy)-2-methyl-4-trimethylsilyl-but-3-ynyl]-oxetan-2-one (203): To a solution of 0.127 g of triamine ligand **36** (0.235 mmol) in 1.0 mL of CH_2Cl_2 at ambient temperature was added 0.130 mL of a 2.0 M solution of trimethylaluminum in hexanes dropwise via syringe. The clear, colorless catalyst solution was maintained for 2.5 h at ambient temperature, then diluted with CH_2Cl_2 (7 mL). After cooling to –50 °C, 0.695 mL of DIPEA (3.99 mmol) was added followed by 0.330 mL of acetyl bromide (4.46 mmol). The resulting pale yellow solution was stirred at –50 °C whereupon 0.700 g of aldehyde **202** (2.35 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise via syringe. The reaction was maintained for 3 h at –50 °C, and was quenched by pouring into cold hexanes (50 mL). The resulting mixture was filtered through silica gel (Et_2O) and concentrated. The crude product was then purified by flash chromatography (1% EtOAc/hexanes) to afford 0.720 g (87%) of the title compound as a pale yellow oil: $[\alpha]_D$ = +30 (*c* 2.3, $CHCl_3$); IR (thin film): 2957, 2930, 2857, 2169, 1835, 1251, 1165, 1125, 1077, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.83 (dddd, *J* = 4.2, 4.2, 5.7, 8.8 Hz, 1H), 3.57 (dd, *J* = 5.7, 17 Hz, 1H), 3.29 (dd, *J* = 4.2, 17 Hz, 1H), 2.32 (dd, *J* = 4.2, 14 Hz, 1H), 2.03 (dd, *J* = 9.0, 14 Hz, 1H), 1.50 (s, 3H), 0.86 (s, 9H), 0.22 (s, 3H), 0.19 (s, 9H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 107.9, 90.3, 69.1, 67.8, 48.9, 44.6, 31.6, 31.5, 25.6 (3C), 17.9, –0.34 (3C), –3.0, –3.1; LRMS (EI, 70eV): *m/z* 325 $[M\text{-}CH_3]^+$; HRMS calcd for $C_{16}H_{29}O_3Si_2$: 325.1655, found 325.1647.

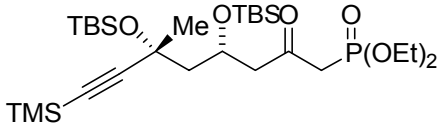


(*4S*)-Diethyl 4-hydroxy-2-oxo-6-phenylhexylphosphonate (205): To a –78 °C solution of 0.165 mL of diethylmethylphosphonate (1.13 mmol) in 3.0 mL of THF was added 0.640 mL of a 1.6 M solution of ^{n}BuLi in hexanes dropwise via syringe. The resulting cloudy, white suspension was maintained for 30 min, then treated with 0.066 g of lactone **61** (0.375 mmol) in THF (0.75 mL). The reaction was maintained at –78 °C for 45 min. Saturated aqueous NH_4Cl (3 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (80% EtOAc/hexanes) provided 0.102 g (83%) of the title compound as a pale yellow oil: $[\alpha]_D$ = +18 (*c* 4.0, $CHCl_3$); IR (thin film): 3400, 3061, 3026, 2984, 2930, 1713, 1246, 1024, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.19 (m, 2H), 7.19–7.10 (m, 3H), 4.20–3.95 (m, 5H), 3.55 (brd, *J* = 3.5 Hz, 1H), 3.12 (s, 1H), 3.05 (s, 1H), 2.85–2.55 (m, 4H), 1.85–1.60 (m, 2H) 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 141.6, 128.2 (2C), 128.1 (2C), 125.6, 66.7, 62.5, 62.4, 50.9, 43.7, 38.1, 31.5, 16.1, 16.0; LRMS (EI, 70eV): *m/z* 328; HRMS calcd for $C_{16}H_{25}O_5P$: 328.1440, found 328.1452.



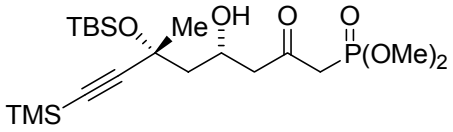
(4*S*,6*R*)-Diethyl-[6-(*tert*-butyldimethyl-silyloxy)-4-hydroxy-6-methyl-2-oxo-8-trimethylsilyl-oct-7-ynyl]-phosphonate (207): To a –78 °C solution of 0.360 mL of diethylmethylphosphonate (2.47 mmol) in 6.0 mL of THF was added 1.40 mL of a 1.6 M solution of ^{n}BuLi in hexanes dropwise via syringe. The resulting cloudy, white suspension was maintained for 30 min, then treated with 0.233 g of lactone **203** in THF (1.2 mL). The reaction was maintained at –78 °C for 1 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with EtOAc (3

× 30 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (50% EtOAc/hexanes) provided 0.281 g (83%) of β-ketophosphonate **207** as a pale yellow oil: $[\alpha]_D$ = +22 (*c* 2.4, $CHCl_3$); IR (thin film): 3405, 2957, 2930, 2857, 2167, 1716, 1252, 1028, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.44 (dddd, *J* = 2.4, 5.4, 9.3, 12.0 Hz, 1H), 4.10 m, 4H), 3.73 (brs, 1H), 3.11 (dd, *J* = 13.6, 17.5 Hz, 1H), 3.07 (dd, *J* = 13.6, 17.5 Hz, 1H), 2.77 (dd, *J* = 7.3, 16.2 Hz, 1H), 2.68 (dd, *J* = 5.2, 16.2, Hz, 1H), 1.87 (dd, *J* = 9.2, 14 Hz, 1H), 1.72 (dd, *J* = 2.4, 14 Hz, 1H), 1.48 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 6H), 0.82 (s, 9H), 0.17 (s, 6H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0 (d, *J* = 25 Hz), 109.5, 89.6, 69.0, 65.1, 51.3, 50.3, 43.9, 42.2, 30.2, 25.6 (3C), 17.8, 16.2, 16.1, –0.47 (3C), –2.9, –3.2; LRMS (EI, 70eV): *m/z* 477 $[M\text{-}CH_3]^+$; HRMS calcd for $C_{21}H_{42}O_6Si_2P$: 477.2258, found 477.2257.



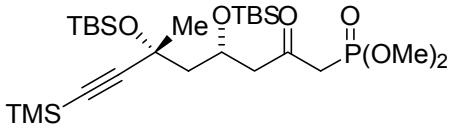
(4*S*, 6*R*)-Diethyl-[4, 6-bis-(*tert*-butyldimethyl-silyloxy)-6-methyl-2-oxo-8-trimethylsilyl-oct-7-ynyl]-phosphonate (187a): To a 0 °C solution of 0.280 g of alcohol **207** in 1.2 mL of DMF was added 0.078 g of imidazole (1.14 mmol) and 0.172 g of *tert*-butyldimethylchlorosilane (1.14 mmol). The reaction mixture was then warmed to ambient temperature and maintained for 48 h. A mixture of saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL) was added, and the crude reaction was extracted with EtOAc (3 × 30 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was then purified by flash chromatography (20% EtOAc/hexanes) to afford 0.276 g (80%) of the title compound as a viscous, pale yellow oil: $[\alpha]_D$ = +28 (*c* 1.4, $CHCl_3$); IR (thin film): 2957, 2930, 2898, 2857, 2166, 1717, 1472, 1252, 1027, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.52–4.42 (m, 1H), 4.09

(p, *J* = 7.1 Hz, 4H), 3.15–2.90 (m, 3H), 2.79 (dd, *J* = 8.6, 15.8 Hz, 1H), 1.84 (dd, *J* = 9.3, 13.9 Hz, 1H), 1.68 (dd, *J* = 2.3, 13.9 Hz, 1H), 1.39 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 6H), 0.80 (s, 18H), 0.16 (s, 3H), 0.13 (s, 9H), 0.097 (s, 3H), 0.063 (s, 3H), 0.012 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6 (d, *J* = 26 Hz), 109.1, 89.5, 68.3, 67.4, 62.2, 52.6, 51.8, 44.7, 43.0, 32.4, 25.8 (3C), 25.7 (3C), 17.9, 17.8, 16.2, 16.1, –0.37 (3C), –3.0, –3.2, –4.3, –4.8; LRMS (ESI): *m/z* 629; HRMS calcd for $[C_{28}H_{59}O_6Si_3PNa]^+$: 629.3255, found 629.3273.

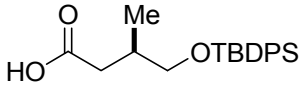


(4*S*, 6*R*)-Dimethyl-[6-(*tert*-butyldimethyl-silyloxy)-4-hydroxy-6-methyl-2-oxo-8-trimethylsilyl-oct-7-ynyl]-phosphonate (208): To a –78 °C solution of 0.335 mL of dimethylmethylphosphonate (3.13 mmol) in 7.5 mL of THF was added 1.80 mL of a 1.6 M solution of ^{n}BuLi in hexanes dropwise via syringe. The resulting cloudy, white suspension was maintained for 30 min, then treated with 0.355 g of lactone **203** in THF (2.5 mL). The reaction was maintained at –78 °C for 1 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (50% EtOAc/hexanes) provided 0.438 g (90%) of β-ketophosphonate **208** as a pale yellow oil: $[\alpha]_D$ = +25 (*c* 2.5, $CHCl_3$); IR (thin film): 3408, 2957, 2857, 2167, 1718, 1473, 1253, 1183, 1116, 1043, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45 (dddd, *J* = 2.5, 5.0, 7.5, 9.7 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.77 (dd, *J* = 7.5, 16 Hz, 1H), 2.67 (dd, *J* = 5.0, 16 Hz, 1H), 1.88 (dd, *J* = 9.2, 14 Hz, 1H), 1.73 (dd, *J* = 2.5, 14 Hz, 1H), 1.49 (s, 3H), 0.83 (s, 9H), 0.20-0.17 (m, 6H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9 (d, *J* = 26 Hz), 109.5, 89.7, 69.0, 65.1, 52.9, 51.3,

50.2, 42.8, 41.1, 30.2, 25.6 (3C), 17.8, –0.46 (3C), –2.9, –3.2; LRMS (EI, 70eV): *m/z* 449 [M-CH_3]$^+$; HRMS calcd for $C_{19}H_{38}O_6Si_2P$: 449.1945, found 449.1927.

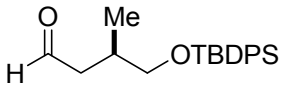


(4*S*, 6*R*)-Dimethyl-[4, 6-bis-(*tert*-butyldimethylsilyloxy)-6-methyl-2-oxo-8-trimethylsilyl-oct-7-ynyl]-phosphonate (187b): To a 0 °C solution of 0.430 g of alcohol **208** (0.927 mmol) in 1.2 mL of DMF was added 0.126 g of imidazole (1.85 mmol) and 0.280 g of *tert*-butyldimethylchlorosilane (1.85 mmol). The reaction mixture was then warmed to ambient temperature and maintained for 16 h. A mixture of saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL) was added, and the crude reaction was extracted with EtOAc (3 × 25 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was then purified by flash chromatography (EtOAc/hexanes) to afford 0.430 g (80%) of the title compound as a viscous, pale yellow oil: $[\alpha]_D$ = +29 (*c* 1.3, $CHCl_3$); IR (thin film): 2956, 2930, 2897, 2857, 2166, 1719, 1473, 1253, 1187, 1035, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 (dddd, *J* = 9.0, 9.0 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.96-3.16 (m, 3H), 2.79 (dd, *J* = 8.8, 16Hz, 1H), 1.86 (dd, *J* = 9.5, 14 Hz, 1H), 1.71 (dd, *J* = 2.4, 14 Hz, 1H), 1.41 (s, 3H), 0.82 (s, 18 H), 0.18 (s, 3H), 0.16 (s, 9H), 0.12 (s, 3H), 0.085 (s, 3H), 0.035 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5, 109.0, 89.6, 68.3, 67.4, 52.3, 52.7, 51.8, 43.6, 41.9, 32.4, 25.8 (3C), 25.7 (3C), 17.9, 17.8, –0.34, –2.9, –3.2, –4.2, –4.8; LRMS (EI, 70eV): *m/z* 563 [M-CH_3]$^+$; HRMS calcd for $C_{25}H_{52}O_6Si_3P$: 563.2809, found 563.2801.



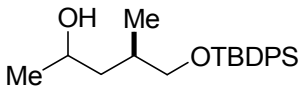
(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutyric acid (209): To a –50 °C solution of 2.69 g of CuBr (18.8 mmol) in 185 mL of THF and 20 mL of dimethylsulfide was added 12.5 mL of a 3.0 M ethereal solution of

methylmagnesium bromide (37.5 mmol) slowly dropwise. The resulting clear, faint green solution was stirred at –50 °C for 30 min then warmed to –30 °C for 30 min. The reaction was then cooled to –50 °C and 4.6 g of 7 (12.5 mmol) in 15 mL of THF was added via cannula. After maintaining the reaction at –50 °C for 45 min, 2.4 mL of TMSCl (18.8 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. A mixture of saturated NH_4Cl (500 mL) and 1 M HCl (200 mL) was added and the mixture was extracted with Et_2O (4 × 150 mL). The combined organics were washed with saturated NH_4Cl and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford 3.85 g (79%) of the title compound **209** as a pale yellow viscous oil: $[\alpha]_D$ = +6.3 (*c* 1.1, $CHCl_3$); IR (thin film): 3071, 3049, 2960, 2931, 2858, 1709, 1589, 1428, 1112, 702; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75–7.65 (m, 4H), 7.50–7.35 (m, 6H), 3.59 (dd, *J* = 4.9, 9.9 Hz, 1H), 3.46 (6.6, 9.9 Hz, 1H), 2.75–2.60 (m, 1H), 2.35–2.15 m, 2H), 1.06 (s, 9H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 135.6 (4C), 133.6 (2C), 129.6 (2C), 127.5, 68.1, 38.2, 32.8, 26.8 (3C), 19.2, 16.8; LRMS (EI, 70eV): *m/z* 299 [M-^{t}Bu]$^+$; HRMS calcd for $C_{17}H_{19}O_3Si$: 299.1103, found 299.1111.



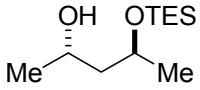
(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutyraldehyde (210): To a solution of 1.15 g of carboxylic acid **209** (3.23 mmol) in 30 mL of Et_2O at ambient temperature was added 2.4 mL of a 2.0 M THF solution of $H_3B{\bullet}SMe_2$ (4.84 mmol) slowly dropwise. The resulting clear, colorless solution was heated to reflux and maintained for 45 min. After cooling to ambient temperature, the solvent was removed, and the remaining viscous residue was dissolved in 30 mL of CH_2Cl_2. To this colorless solution was added 1.75 g of pyridinium chlorochromate (8.08 mmol), and the resulting brown suspension

was heated to reflux and maintained for 1 h. The reaction was then cooled to ambient temperature, diluted with Et_2O, filtered through Celite, and concentrated. Purification of the crude product by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 0.950 g (85%) of the title compound as a viscous, colorless oil: $[\alpha]_D$ = +2.9 (*c* 1.6, $CHCl_3$); IR (thin film): 3134, 3071, 3050, 2959, 2717, 1726, 1589, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.80 (t, *J* = 2.2 Hz, 1H), 7.70–7.60 (m, 4H), 7.45–7.35 (m, 6H), 3.59 (dd, J = 5.0, 9.9 Hz, 1H), 3.44 (dd, *J* = 7.0, 9.9 Hz, 1H), 2.70–2.55 (m, 1H), 2.40–2.20 (m, 2H), 1.06 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 135.6 (4C), 133.5, 129.7 (3C), 127.7 (4C), 68.4, 48.1, 31.3, 26.8 (3C), 19.2, 16.7; LRMS (EI, 70eV): *m/z* 283 $[M\text{-}^tBu]^+$; HRMS calcd for $C_{17}H_{19}O_2Si$: 283.1154, found 283.1153.

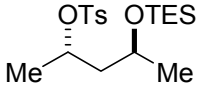


(4*R*)-5-(*tert*-Butyldiphenylsiloxy)-4-methylpentan-2-ol (212): To a 0 °C solution of 0.018 g of (*R*,*R*)-HOCSAC ligand **X** (0.032 mmol) in 1.0 mL of toluene was added 0.125 mL of $Ti(O^iPr)_4$ (0.417 mmol) followed by 0.385 mL of a 2.0 M solution of Me_2Zn in toluene (0.769 mmol). The resulting pale green solution was then cooled to –25 °C and 0.109 g of aldehyde **210** (0.320 mmol) in 0.5 mL of toluene was added dropwise via syringe. The reaction was maintained for 24 h at –25 °C before being quenched by MeOH (1 mL) and saturated aqueous NH_4Cl (3 mL). The mixture was extracted with Et_2O (3 × 10 mL) and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (10% EtOAc/hexanes) provided 0.071 g (62% combined yield of a 1:1 mixture of diastereomers) of title compound **212** as a clear, colorless oil: IR (thin film): 3364, 3071, 3050, 2961, 2930, 2857, 1472, 1428, 1112, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.68 (m, 8H), 7.50–7.38 (m, 12H), 4.03–3.88 (m,

2H), 3.55 (t, *J* = 5.9 Hz, 4H), 2.66 (brs, 1H), 2.30 (brs, 1H), 1.98–1.80 (m, 2H), 1.60–1.30 (m, 4H), 1.22 (t, *J* = 5.7 Hz, 6H), 1.09 (s, 18H), 0.94 (d, *J* = 7.4 Hz, 3H), 0.91 (d , *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.5, 129.6, 127.6, 69.8, 69.0, 66.4, 65.6, 44.7, 43.9, 33.7, 32.5, 26.8 (6C), 24.2, 23.5, 19.2, 17.5; HRMS calcd for $[C_{22}H_{32}O_2SiNa]^+$: 379.2069, found 379.2064.

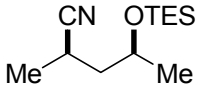


(2*S*, 4*S*)-4-Triethylsilyloxypentan-2-ol (218): To a 0 °C solution of 0.494 g of (2*S*, 4*S*)-(+)-pentanediol (4.74 mmol) in 9.5 mL of THF was added 0.228 g of a 60% dispersion of NaH in mineral oil (5.69 mmol) portionwise. Gas evolution and a white precipitate were observed. The resulting cloudy, white suspension was warmed to ambient temperature and maintained for 2 h. The resulting orange mixture was then treated with 0.955 mL of triethylchlorosilane (5.69 mmol) and maintained for 2 h. The reaction mixture was then diluted with Et_2O then washed with brine. The ether layer was then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) provided g of title compound **218** as a clear, colorless liquid: $[\alpha]_D$ = +21 (*c* 2.6, $CHCl_3$); IR (thin film): 3432, 2960, 2878, 1458, 1415, 1375, 1239, 1124, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12-4.26 (m, 2H), 3.48 (brs, 1H), 1.67 (ddd, *J* = 3.9, 9.6, 14.0 Hz, 1H), 1.50 (ddd, *J* = 2.3, 4.9, 14.0 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.5, 64.4, 45.8, 23.7, 22.8, 6.7, 4.8; LRMS (EI, 70eV): *m/z* 217 $[M-H]^+$, 189 $[M-CH_3CH_2]^+$; HRMS calcd for $C_9H_{21}O_2Si$: 189.1311, found 189.1309.



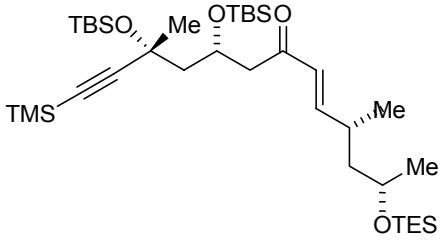
(2*S*, 4*S*)-4-Triethylsilyloxy-2-pentyl-4-methylphenylsulfonate (219): To a

0 °C solution of 3.10 g of alcohol **218** (14.2 mmol) and 3.19 g of DABCO (28.4 mmol) in 20 mL of CH_2Cl_2 was added 4.07 g of TsCl (21.3 mmol) portionwise. The resulting white suspension was maintained at 0 °C for 30 min then at ambient temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and filtered through silica gel (CH_2Cl_2). The filtrate was then concentrated to afford 5.0 g (94%) of a clear, colorless oil: $[\alpha]_D$ = +21 (*c* 1.9, $CHCl_3$); IR (thin film): 2956, 2913, 2877, 1599, 1458, 1365, 1240, 1008, 904, 816, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.81 (m, 1H), 3.87 (m, 1H), 2.43 (s, 3H), 1.75 (ddd, *J* = 3.9, 7.8, 14 Hz, 1H), 1.59 (ddd, *J* = 4.4, 8.3, 14 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.58 (q, *J* = 8.0 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2, 135.1, 129.6 (2C), 127.4 (2C), 78.6, 65.1, 47.2, 24.3, 21.6, 21.5, 6.8 (3C), 5.1 (3C).



(2*R*, 4*S*)-2-Methyl-4-triethylsilyloxypentanenitrile (220): To a solution of 0.286 g of tosylate **219** (0.769 mmol) in 0.9 mL of DMSO was added 0.151 g of NaCN (3.08 mmol) at ambient temperature. The reaction mixture was heated to 50 °C and maintained for 24 h. After cooling to ambient temperature, the crude, orange reaction mixture was purified by flash chromatography on silica gel (5% Et_2O/pentane) to provide 0.127 g (73%) of the title compound as a clear, colorless liquid: $[\alpha]_D$ = +3.1 (*c* 1.4, $CHCl_3$); IR (thin film): 2956, 2913, 2878, 2239, 1459, 1378, 1239, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.01–3.90 (m, 1H), 2.75 (ddq J = 7.3, 1.88 (ddd, *J* = 7.1, 7.1, 13.9 Hz, 1H), 1.58 (ddd, *J* = 5.4, 7.3, 13.1 Hz, 1H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H). 0.97 (t, *J* = 7.8 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.3, 65.4, 43.5, 23.5, 21.5, 17.9, 6.8 (3C), 5.0

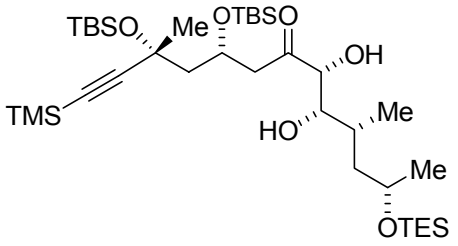
(3C); LRMS (EI, 70 eV): *m/z* 198 $[M\text{-}CH_3CH_2]^+$; HRMS calcd for $C_{10}H_{20}NOSi$: 198.1314, found 198.1313.



(8*E*)-(3*R*, 5*S*, 10*R*, 12*S*)-3, 5-Bis-(*tert*-butyldimethylsilyloxy)-3, 10-dimethyl-12-triethylsilyloxy-1-trimethylsilyltridec-8-en-1-yn-7-one (222): To a –78 °C solution of 0.125 g of nitrile **220** (0.550 mmol) in 1.2 mL of CH_2Cl_2 was added 0.580 mL of a 1.0 M solution of DIBAL-H in hexanes dropwise via syringe. The resulting colorless solution was maintained at –78 °C for 1 h, then quenched with 1 M $KHSO_4$ (5 mL). The reaction mixture was warmed to ambient temperature and extracted with Et_2O (3 × 20 mL). After washing with 1M $KHSO_4$ and brine, the combined organics were dried over Na_2SO_4, filtered, and concentrated to afford 0.103 g (82%) of aldehyde **221** as a clear, colorless liquid that was used immediately in the next reaction without further purification.

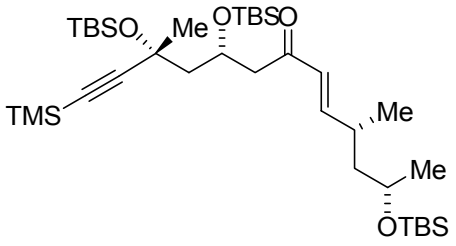
To a mixture of 0.045 g of LiCl (0.522 mmol) in 2.0 mL of CH_3CN at ambient temperature was added 0.302 g of β-ketophosphonate **187b** (0.522 mmol) in 1.2 mL of CH_3CN. The reaction mixture was stirred for 5 min then treated with 0.076 mL of DIPEA (0.435 mmol) dropwise via syringe. The resulting white suspension was maintained for 15 min whereupon 0.100 g of aldehyde **221** (0.435 mmol) in 1.2 mL of CH_3CN was added. The suspension dissipated, and the resulting pale yellow solution was maintained for 60 h at ambient temperature. Saturated aqueous NH_4Cl was added (10 mL) and the mixture was extracted with EtOAc (3 × 25 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (1% EtOAc/hexanes)

provided 0.175 g (59%) of the title compound as a viscous, pale yellow oil: $[\alpha]_D$ = +12 (*c* 2.0, $CHCl_3$); IR (thin film): 2957, 2857, 2167, 1696, 1678, 1626, 1462, 1365, 1251, 991, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.72 (dd, *J* = 7.6, 16 Hz, 1H), 6.07 (dd, *J* = 1.1, 16 Hz, 1H), 4.60 (dddd, *J* = 2.6, 2.6, 9.1, 9.1 Hz, 1H), 3.88–3.78 (m, 1H), 2.98 (dd, *J* = 2.5, 15 Hz, 1H), 2.75 (dd, *J* = 9.1, 15 Hz, 1H), 2.46 (m, 1H), 1.91 (dd, *J* = 9.2, 14 Hz, 1H), 1.78 (dd, *J* = 2.6, 14 Hz, 1H), 1.62 (ddd, *J* = 7.3, 7.3, 14 Hz, 1H), 1.46 (s, 3H), 1.33 (ddd, *J* = 5.6, 7.7, 14 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.55-0.63 (m, 6H), 0.21 (s, 3H), 0.19 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 152.1, 129.2, 109.3, 89.5, 68.4, 67.6, 66.0, 52.4, 49.4, 46.1, 33.1, 32.5, 25.9 (3C), 25.8 (3C), 24.0, 19.2, 18.0, 17.9, 6.9 (3C), 5.1 (3C), –0.25, –2.8, –3.1, –4.2, –4.6; HRESIMS calcd for $[C_{36}H_{74}O_4Si_4Na]^+$: 705.4562, found 705.4567.



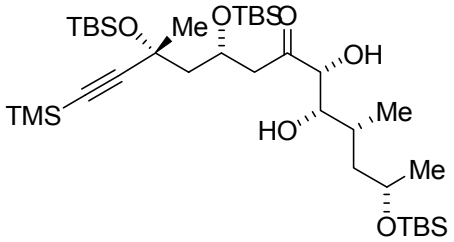
(3*R*, 5*S*, 8*R*, 9*S*, 10*R*, 12*S*)-3, 5-Bis-(*tert*-butyldimethylsilyloxy)-3, 10-dimethyl-12-triethylsilyloxy-1-trimethylsilyltridec-8-en-1-yn-7-one (223): To a suspension of 0.200 g of AD-mix α in 0.8 mL of $^tBuOH/H_2O$ (1:1) was added 3.5 mg of $K_2OsO_4•2H_2O$ (9.53 μmol), 7.5 mg of $(DHQ)_2PHAL$ (9.53 μmol), and 24 mg of $NaHCO_3$ (286 μmol). The resulting yellow-orange suspension was maintained for 10 min, cooled to 0 °C, then treated with 0.065 g of enone **222** (95.3 mmol) in 0.3 mL of $^tBuOH/H_2O$ (1:1) dropwise via syringe. The reaction mixture was maintained for 20 h at 0 °C at which point 0.038 g of Na_2SO_3 was added. After warming to ambient temperature, the resulting brown mixture was maintained for 1 h and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2

× 15 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by flash chromatography on silica gel (3% EtOAc/hexanes) to provide 0.021 g (31%) of the title compound as a clear, colorless oil: $[\alpha]_D$ = +10 (*c* 1.8, $CHCl_3$); IR (thin film): 3452, 2957, 2930, 2857, 2167, 1715, 1463, 1373, 1252, 1118, 1074, 9990, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.67–4.57 (m, 1H), 4.12 (dd, *J* = 1.7, 4.2 Hz, 1H), 3.77 (d, *J* = 4.2 Hz, 1H), 3.03 (dd, *J* = 2.8, 16 Hz, 1H), 2.86 (dd, *J* = 8.4, 16 Hz, 1H), 2.14 (d, *J* = 9.0 Hz, 1H), 2.05–1.88 (m, 2H), 1.79 (dd, *J* = 2.7, 14 Hz, 1H), 1.66 (ddd, *J* = 3.4, 9.3, 13 Hz, 1H), 1.46 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.84 (s, 18H), 0.66–0.56 (m, 6H), 0.21 (s, 3H), 0.19 (s, 9H), 0.13 (s, 3H), 0.128 (s, 3H), 0.076 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 109.1, 89.8, 74.6, 68.4, 67.0, 66.3, 51.8, 47.0, 43.5, 34.0, 32.5, 29.7, 25.9 (3C), 25.7 (3C), 24.8, 18.0, 17.9, 15.4, 6.9 (3C), 5.2 (3C), –0.27, –2.8, –3.1, –4.2, –4.6; HRESI-MS calcd for $C_{36}H_{76}O_6Si_4Na$: 739.4617, found 739.4636.



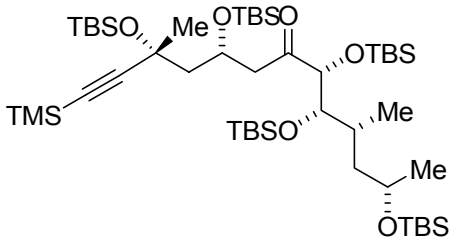
(8*E*)(3*R*, 5*S*, 10*R*, 12*S*)-3, 5, 12-Tris-(*tert*-butyldimethylsilyloxy)-3, 10-dimethyl-1-trimethylsilyltridec-8-en-1-yn-7-one (186): To a mixture of 0.073 g of LiCl (1.73 mmol) in 4 mL of CH_3CN at ambient temperature was added 1.0 g of β-ketophosphonate **187b** (1.73 mmol) in 4 mL of CH_3CN. The reaction mixture was stirred for 5 min then treated with 0.250 mL of DIPEA (1.49 mmol) dropwise via syringe. The resulting white suspension was maintained for 15 min whereupon 0.285 g of aldehyde **147** (0.435 mmol) in 4 mL of CH_3CN was added. The suspension dissipated, and the resulting pale yellow solution was maintained for 60 h at ambient temperature. Saturated aqueous NH_4Cl was added (20 mL) and the mixture was extracted with

EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (1% EtOAc/hexanes) provided 0.590 g (70%) of the title compound as a viscous, pale yellow oil: $[\alpha]_D$ = +16 (*c* 1.1, $CHCl_3$); IR (thin film): 2957, 2929, 2896, 2857, 2167, 1701, 1677, 1626, 1472, 1463, 1361, 1252, 990, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.71 (dd, *J* = 7.5, 15.9 Hz, 1H), 6.06 (d, *J* = 15.9 Hz, 1H), 4.65–4.53 (m, 1H), 3.89–3.76 (m, 1H), 2.97 (dd, *J* = 2.2, 15.2 Hz, 1H), 2.73 (dd, *J* = 9.1, 15.2 Hz, 1H), 2.45 (m, 1H), 1.89 (dd, *J* = 9.3, 13.9 Hz, 1H), 1.76 (dd, *J* = 2.5, 13.9 Hz, 1H), 1.59 (ddd, *J* = 7.3, 7.3, 14 Hz, 1H), 1.44 (s, 3H), 1.29 (ddd, *J* = 5.6, 7.7, 14 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.81 (s, 9H), 0.20 (s, 3H), 0.18 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H), 0.05–0.02 (m, 6H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 152.2, 129.1, 109.3, 89.5, 68.4, 67.6, 66.0, 52.4, 49.4, 46.0, 33.0, 32.5, 25.9 (3C), 25.8 (3C), 25.7 (3C), 24.0, 19.0, 18.0, 18.0, 17.9, –0.24, –2.8, –3.1, –4.1, –4.2, –4.6, –4.8; HRESIMS calcd for $[C_{36}H_{74}O_4Si_4Na]^+$: 705.4562, found 705.4595.



(3*R*, 5*S*, 8*R*, 9*S*, 10*R*, 12*S*)-3, 5, 12-Tris-(*tert*-butyldimethylsilyloxy)-3, 10-dimethyl-1-trimethylsilyl-tridec-8-en-1-yn-7-one (224): To a suspension of 0.422 g of AD-mix α in 1.6 mL of $^tBuOH/H_2O$ (1:1) was added 0.015 g of $K_2OsO_4•2H_2O$ (40.2 μmol), 0.031 mg of $(DHQ)_2PHAL$ (40.2 μmol), 0.051 g of $NaHCO_3$ (0.602 mmol), and 0.038 g of methanesulfonamide (0.402 mmol). The resulting yellow-orange suspension was maintained for 10 min, cooled to 0 °C, then treated with 0.137 g of enone **186** (0.200 mmol) in 0.8 mL of $^tBuOH/H_2O$ (1:1) dropwise via syringe. The reaction mixture was maintained for 8 h at 0 °C at which point 0.076 g of Na_2SO_3 was added. After

warming to ambient temperature, the resulting brown mixture was maintained for 1 h and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by flash chromatography on silica gel (3% EtOAc/hexanes) to provide 0.061 g (42%) of the title compound as a clear, colorless oil: $[\alpha]_D$ = +13 (*c* 5.3, $CHCl_3$); IR (thin film): 3456, 2957, 2929, 2897, 2857, 2167, 1717, 1472, 1463, 1361, 1252, 1118, 1073, 990, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.67–4.57 (m, 1H), 4.12 (dd, *J* = 1.7, 4.2 Hz, 1H), 3.98–3.86 (m, 1H), 3.77 (d, *J* = 4.2 Hz, 1H), 3.03 (dd, *J* = 2.8, 16 Hz, 1H), 2.86 (dd, *J* = 8.4, 16 Hz, 1H), 2.14 (d, *J* = 9.0 Hz, 1H), 2.05–1.88 (m, 2H), 1.79 (dd, *J* = 2.7, 14 Hz, 1H), 1.66 (ddd, *J* = 3.4, 9.3, 13 Hz, 1H), 1.46 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.84 (s, 18H), 0.66–0.56 (m, 6H), 0.21 (s, 3H), 0.19 (s, 9H), 0.131 (s, 3H), 0.128 (s, 3H), 0.076 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 109.1, 89.8, 74.6, 68.4, 67.0, 66.3, 51.8, 47.0, 43.5, 34.0, 32.5, 29.7, 25.9 (3C), 25.7 (3C), 24.8, 18.0, 17.9, 15.4, 6.9 (3C), 5.2 (3C), –0.27, –2.8, –3.1, –4.2, –4.6; HRESI-MS calcd for $C_{36}H_{76}O_6Si_4Na$: 739.4617, found 739.4647.



(3*R*, 5*S*, 8*R*, 9*S*, 10*R*, 12*S*)-3, 5, 8, 9, 12-Pentakis-(*tert*-butyldimethylsilyloxy)-3, 10-dimethyl-1-trimethylsilyl-tridec-1-yn-7-one (225): To a 0 °C solution of 0.015 g of diol **224** (20.9 μmol) in 0.4 mL of CH_2Cl_2 was added 12 μL of 2, 6-lutidine (110 μmol) followed by 14 μL of *tert*-butyldimethyltrifloromethane sulfonate (62.8 μmol) dropwise via syringe. The reaction was warmed to ambient temperature and maintained for 2 h at which point saturated aqueous $NaHCO_3$ (3 mL) was added. The mixture

was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with brine. After being dried over Na_2SO_4, filtered, and concentrated, the resulting oil was purified by flash chromatography on neutral silica gel (Iatrobeads–1% EtOAc/hexanes) to afford 0.015 g of the title compound as a pale yellow oil: $[\alpha]_D$ = +25 (*c* 1.8, $CHCl_3$); IR (thin film): 2930, 2896, 2858, 2167, 1722, 1473, 1463, 1254, 1069, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.60–4.50 (m, 1H), 4.06 (d, *J* = 4.6 Hz, 1H), 3.95-3.76 (m, 1H), 3.75–3.63 (m, 1H), 2.95 (dd, *J* = 6.5, 17.7 Hz, 1H), 2.81 (dd, *J* = 5.4, 17.7 Hz, 1H), 2.10–1.95 (m, 1H), 1.84 (dd, *J* = 6.2, 13.7 Hz, 1H), 1.72 (dd, *J* = 5.2, 13.7 Hz, 1H), 1.45 (s, 3H), 1.12 (d, *J* = 5.9 Hz, 3H), 0.95 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (s, 18 H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.19 (s, 9H), 0.15 (s, 3H), 0.13 (s, 6H), 0.10 (s, 6H), 0.08 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.0, 109.6, 89.4, 81.1, 79.2, 68.8, 66.2, 66.1, 52.2, 49.8, 45.6, 32.4, 30.3, 26.1 (3C), 26.0 (3C), 25.9 (6C), 25.8 (3C), 25.7, 24.6, 18.4, 18.3, 18.1, 18.0, 18.0, 17.9, –0.20 (3C), –2.8, –2.9 (2C), –3.8, –4.1, –4.2, –4.3, –4.5, –4.6, –4.9; HRESI-MS calcd for $C_{48}H_{104}O_6Si_6Na$: 967.6346, found 967.6359.

CHAPTER 3. DIASTEREOSELECTIVE β-LACTONE ENOLATE ALKYLATION IN THE CONSTRUCTION OF QUATERNARY CARBON STEREOCENTERS

3.1 BACKGROUND

Asymmetric quaternary carbon formation represents an important and challenging area in organic synthesis.[95] Enolate alkylation has emerged as the most common method for achieving the stereoselective installation of quaternary carbons. This traditional enolate alkylation strategy can potentially be limited by poor control over the *E*/*Z* geometry in the reacting α,α-disubstituted enolate which ultimately compromises reaction diastereoselection. Such issues have been resolved through the use of metal chelates or cyclic enolate moities which are often times incorporated within the structure of a chiral auxiliary.[96] While these methods have been quite successful in the construction of quaternary carbon stereocenters, a disadvantage arises in the necessity of added synthetic manipulations to install and remove the auxiliary from the desired material. An interesting alternative to chiral auxiliary mediated asymmetric quaternary carbon formation can be realized through the alkylation of β-lactone enolates.

[95] For recent reviews on the asymmetric synthesis of quaternary carbon stereocenters see: a) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037. b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed*. **1998**, *37*, 388.

[96] (a) Boeckman, R. K., Jr.; Boehmler, D. Musselman, R. A. *Org. Lett*. **2001**, *3*, 3777. (b) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (c) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem. Int. Ed*. **2002**, *41*, 2338. (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.

The earliest examples of β-lactone enolate alkylation to form asymmetric quaternary centers were reported by Mulzer et al.[97] Treating α-substituted β-lactones **230** derived from the corresponding 3-hydroxycarboxylic acids with lithium diisopropylamide (LDA) in THF at –78 °C cleanly generated the corresponding lithium enolate **231** which was subsequently trapped with a variety of electrophiles to afford α,α-disubstituted β-lactones in good yield and with excellent diastereoselectivity (>98:2). The origin of the observed *trans*-selectivity in the formation of the quaternary carbon center was attributed to the conformational rigidity of the lactone enolate system whereby incoming electrophiles would approach opposite the bulky C_4 substituent in order to minimize nonbonded interactions (Figure 28).

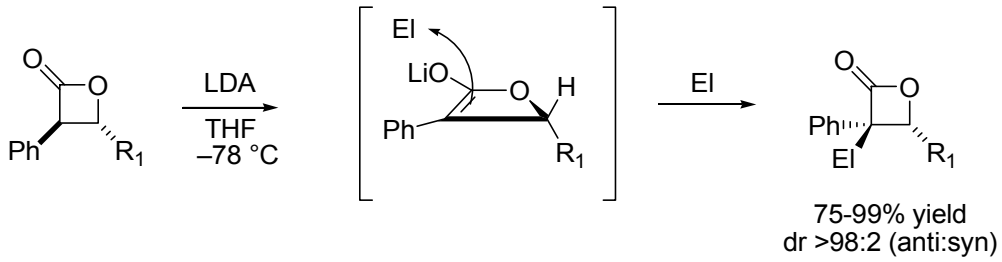
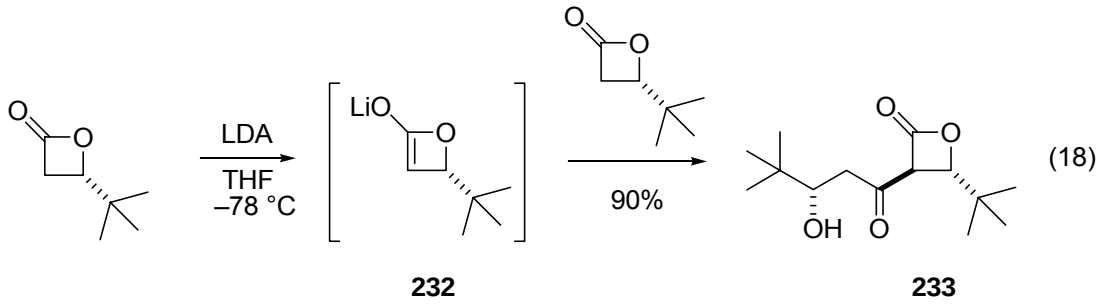


Figure 31. Rationale for the observed diastereoselectivity in the alkylation of β-lactone enolates

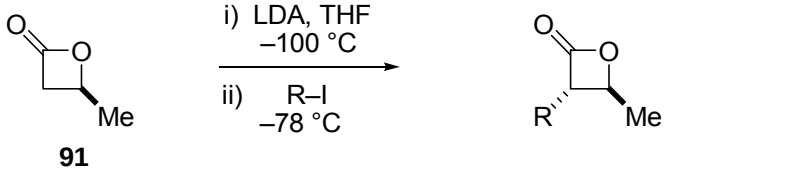
These preliminary investigations, while successful in demonstrating the utility β-lactone enolates for the diastereoselective formation of quaternary carbon stereocenters, were limited to the use of α-phenyl substituted lactones with bulky C_4 substituents (^{i}Pr, ^{t}Bu). In the case of lactone enolates unsubstituted at C_3, the rapid dimerization of enolate **232** and another lactone molecule occurs to form the Claisen self-condensation product **233** in high yield (Eq 18).

[97] (a) Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620. (b) Mulzer, J.; Kerkmann, T. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 465. (c) Mulzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 777. (d) Mulzer, J.; Chucholowski, A.; Lammer, O.; Jibril, I.; Huttner, G. *J. Chem. Soc., Chem. Commun.* **1983**, 869.



232 **233** (18)

Following the initial reports by Mulzer, further investigation into the enolization and subsequent alkylation of C_3 unsubstituted β-lactones was undertaken. In 1987, Seebach et al. disclosed the first successful example of the alkylation of a C_3 unsubstituted β-lactone enolate employing (*S*)-β-butyrolactone (**91**).[98] Seebach's enolization method required slowly treating a solution of LDA with lactone **91** at very low temperatures (–100 °C). Subsequent addition of either methyl or ethyl iodide (2.0 equiv) at –78 °C resulted in the generation of *trans*-3,4-disubstituted lactones **234** and **235** in modest yield with good levels of diastereoselection.

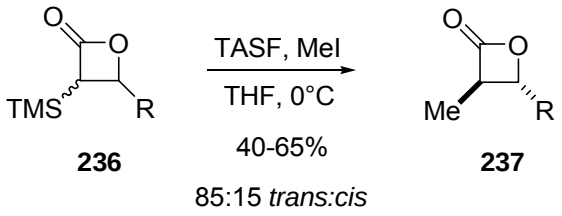


91 (19)

234 R = Me; 31% (dr 8:1)
235 R = Et; 37% (dr 9:1)

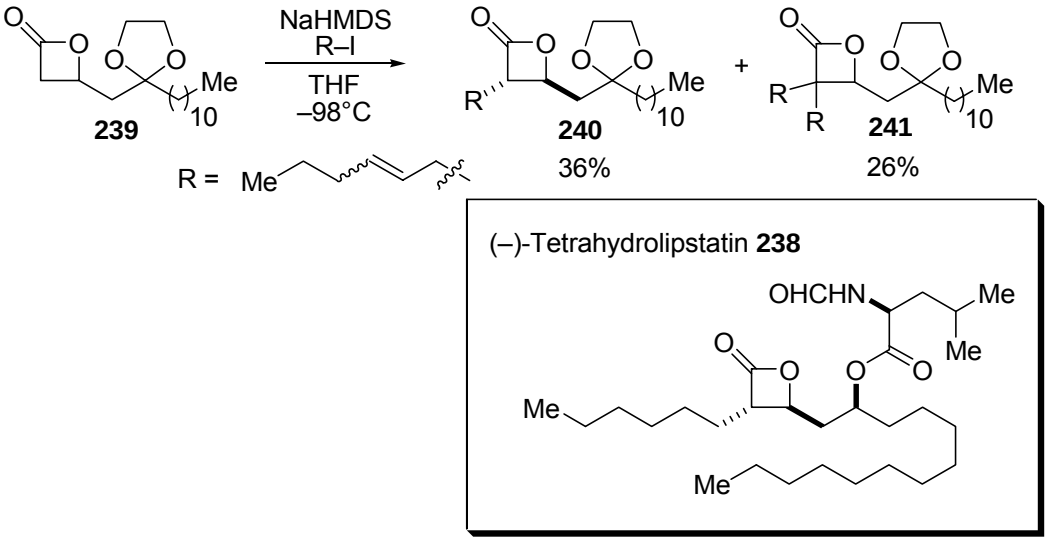
Another interesting approach to achieve the formal enolization and alkylation of C_3-unsubstituted β-lactones was later reported by Mead and Yang (Eq 20).[99] The strategy involved the disilylative alkylation of a 3-trimethylsilyl-2-oxetanone **236** in the presence of tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TASF) and MeI. The lactone products **237** were obtained in variable yields with modest *trans*-diastereoselection.

[98] Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1320.
[99] Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829.



(20)

The most recent example involving the alkylation of C_3-unsubstituted β-lactone enolates was described by Parsons et al. in the total synthesis of the potent pancreatic lipase inhibitor (–)-tetrahydrolipstatin **238** (Eq 21).[100] The requisite hexyl side chain of the natural product was to be introduced via the enolization and subsequent alkylation of lactone **239**. Extensive optimization identified the combination of NaHMDS as base and the presence of an in situ electrophile (1-iodohex-2-ene) as the most effective reaction conditions for achieving β-lactone enolate alkylation. The desired monoalkylated product **240** was obtained in 36% isolated yield (52% based on recovered starting material) along with 26% of the dialkylated β-lactone **241**.



(21)

[100] Parsons, P. J.; Cowell, J. K. *Synlett* **2000**, *1*, 107.

3.2 ENOLATE ALKYLATION OF AAC-DERIVED β-LACTONES

We envisaged that the enantiomerically enriched β-lactone products of asymmetric acyl halide-aldehyde cyclocondensation (AAC) reaction technology would offer an efficient means for establishing equivalent bond constructions. Enolization and subsequent alkylation of β-lactones of type **242** should afford *trans*-3,4-disubstituted lactones which could then be resubjected to the reaction conditions in the presence of a different electrophile to result in the production of β-lactones possessing asymmetric quaternary stereocenters.

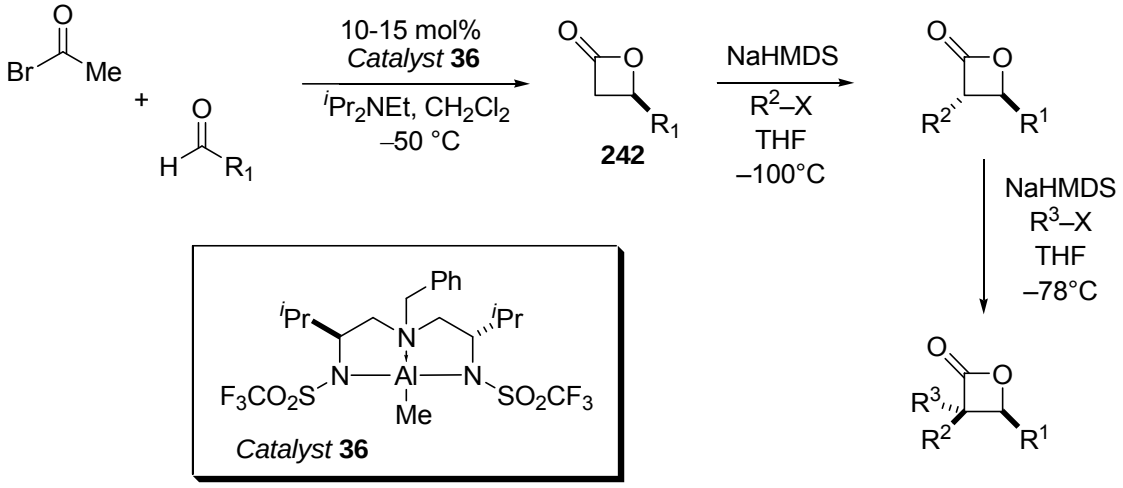
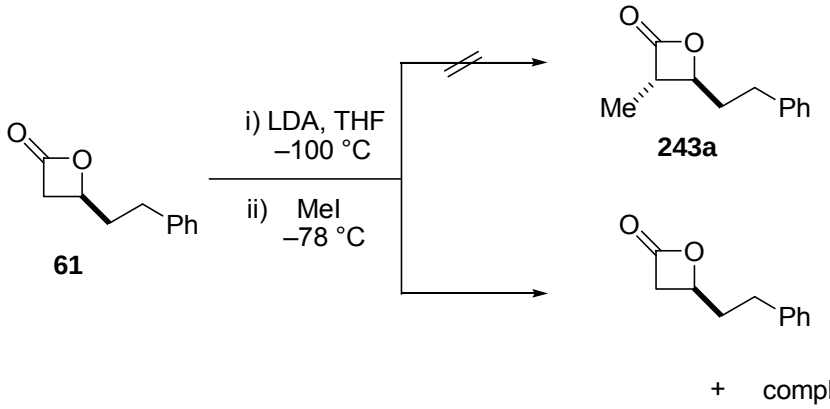


Figure 32. AAC-Derived β-Lactones in Asymmetric Quaternary Carbon Formation

Although prior literature precedent suggested that the enolization and subsequent alkylation of C_3-unsubstituted β-lactones was a nontrivial endeavor, we desired a set of reaction conditions that would efficiently generate β-lactone enolates for subsequent iterative functionalization with alkylating agents to afford asymmetric quaternary carbon stereocenters. Initially, we examined the very low temperature reaction conditions for β-lactone enolate formation reported by Seebach.[74] Following Seebach's protocol, a –100 °C solution of LDA in

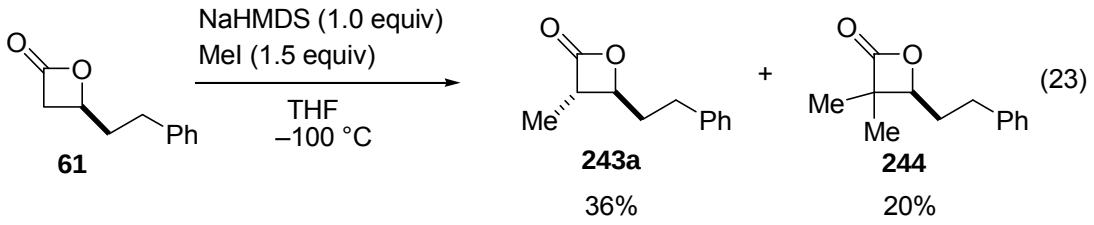
THF was slowly treated with a THF solution of (4*S*)-4-phenethyloxetan-2-one **61** via syringe pump (Eq 22). This solution was then warmed to –78 °C and MeI was added. Unfortunately, these conditions yielded a complex mixture of products, presumably owing to the competing Claisen self-condensation pathway described by Mulzer, along with unreacted starting material by TLC and ^{1}H NMR analysis. None of the desired *trans*-3,4-disubstituted lactone **243a** was observed.



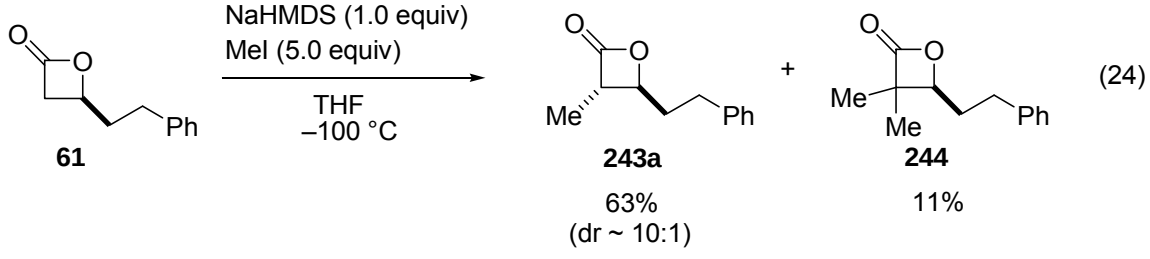
(22)

Turning to Parsons' previously described total synthesis of (–)-tetrahydrolipstatin, we next sought to improve upon these earlier results that incorporated an in situ electrophile to intercept the reactive β-lactone enolate. In an attempt to repeat the result obtained by Parsons, a –100 °C solution of NaHMDS (1.0 equiv) and MeI (1.5 equiv) in THF was slowly treated with a THF solution of lactone **61** via syringe pump (Eq 23). After work-up and chromatographic separation, we were pleased to obtain *trans*-3,4-disubstituted lactone **243** in 36% isolated yield as a 10:1 mixture of *anti*/*syn* diastereomers along with 20% of the 3,3-dimethylated product **244** and 17% of unreacted starting material in accordance with that observed by Parsons. The

observed coupling constant in the ^{1}H NMR spectrum of lactone **243** ($J_{3,4}$ = 4.0 Hz) was indicative of the formation of the *trans*-disubstituted lactone.[101]



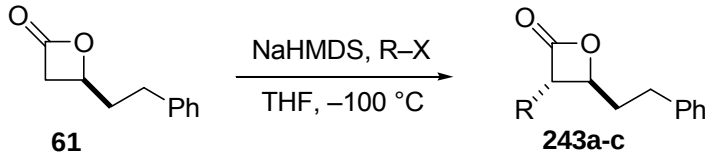
Attempts at optimizing this alkylation reaction first entailed a reverse addition of base to the lactone and electrophile at low temperature (Eq 24). Syringe pump addition of NaHMDS (1.0 equiv) to a –100 °C solution of lactone **61** and MeI (1.5 equiv) in THF resulted complete consumption of the starting lactone and an increased yield of the desired *trans*-disubstituted product **241** to 47%. An additional 11% of the disubstituted by-product was also obtained. The isolated yield of lactone **241** was eventually maximized by employing the previously described reverse addition of base to the starting lactone and a large excess of the MeI electrophile (5.0 equiv) at –100 °C. Lactone **241** was obtained in 63% isolated yield (dr ~ 10:1) along with an additional 11% of dialkylated material representing the highest isolated yield for the alkylation of a C_3-unsubstituted β-lactone enolate to date.



[101] Mulzer, J.; Pointner, A.; Chucholowski, A.; Bruntrup, G. *J. Chem. Soc., Chem. Commun*. **1979**, 52.

These optimized conditions were then used in conjunction with a variety of electrophiles in order to examine the scope of the alkylation reaction. While MeI delivered lactone **243a** in 63% yield, the less active ethyl iodide electrophile (entry b) afforded none of the desired *trans*-disubstituted lactone. More highly activated allyl and benzyl bromides provided the expected *trans*-lactone products **243b-c**, however, only in modest yields (entries c and e) potentially owing to competitive self-condensation. In an attempt to suppress the nonproductive self-condensation reaction pathway, a more highly activated alkylating agent, allyl iodide, was employed (entry d). Gratifyingly, allyl iodide proved to be substantially more reactive than allyl bromide allowing enolate alkylation to effectively compete with the nonproductive self-condensation pathway affording (3*S*, 4*S*)-3-allyl-4-phenethyl-oxetan-2-one **243b** in 68% isolated yield along with minor amounts of the corresponding diallylated material.

Table 5. Enolization and Alkylation of α-Unsubstituted β-Lactones



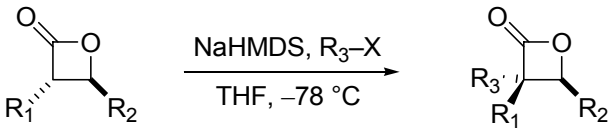
61 **243a-c**

entry	R–X	Yield[a] (%)
a	CH_3I	63 (**243a**)
b	CH_3CH_2I	---
c	CH_2CHCH_2Br	38 (**243b**)
d	CH_2CHCH_2I	68 (**243b**)
e	$PhCH_2Br$	38 (**243c**)

[a]Isolated yields of purified products.

While the efficient preparation of 3,4-*trans*-alkylated products were limited to substitution patterns derived from very reactive electrophiles, i.e. MeI and allyl iodide, these initial experiments generated quantities of several β-lactone substrates for further investigation into the stereoselective installation of quaternary carbon centers. Employing similar reaction conditions as described in the initial alkylation step (NaHMDS, in situ R–X, THF, –78 °C) lactones **243a-c** were successfully enolized and trapped in situ with various electrophiles (Table 5). Activated electrophiles such as allyl and benzyl bromide (entries a, b, f, and h) cleanly afforded the corresponding α,α-disubstituted β-lactones in excellent yield with high levels of diastereoselectivity. Similarly, substanitially poorer primary alkyl iodide electrophiles (EtI and ^{n}BuI) were also effective alkylating agents toward β-lactone enolates (entries c and d). However, increased steric bulk in the structure of the electrophile (entry e) was not tolerated when the β-branched isobutyl iodide was employed resulting in a significantly lower yield of the corresponding α,α-disubstituted β-lactone **245e**. These alkylation experiments successfully demonstrated the synthetic utility of the enantiomerically enriched β-lactone products of the AAC reaction toward asymmetric quaternary carbon construction; however, our inability to efficiently prepare *trans*-disubstituted β-lactones with C_3 substituents other than methyl or allyl severely limited the generality of the method.

Table 6. Alkylation of 3,4-*trans*-Disubstituted β-Lactones



243a-c **245a-h**

entry	R_1	R_2	R_3–X	Yield (%)[a]	*anti*:*syn*[b,c]
a	Me	CH_2CH_2Ph	CH_2CHCH_2Br	93 (**245a**)	97:3
b	Me	CH_2CH_2Ph	BnBr	94 (**245b**)	93:7
c	Me	CH_2CH_2Ph	EtI	94 (**245c**)	>98:2
d	Me	CH_2CH_2Ph	$CH_3(CH_2)_2CH_2I$	88 (**245d**)	95:5
e	Me	CH_2CH_2Ph	$(CH_3)_2CHCH_2I$	10 (**245e**)	–
f	Me	CH_2OBn	CH_2CHCH_2Br	93 (**245f**)	>98:2
g	Allyl	CH_2CH_2Ph	MeI	91 (**245g**)	14:86
h	Bn	CH_2CH_2Ph	CH_2CHCH_2Br	89 (**245h**)	5:95

[a]Isolated yields of purified products. [b]Diastereomer ratios were determined by ^{1}H NMR analysis of crude product mixtures. [c]Stereochemistry of major diastereomer was assigned based on literature precedent. See ref. 74d.

In an attempt to circumvent the initial problematic enolization and alkylation of α-unsubstituted β-lactones, we eagerly turned to a newly developed AAC reaction employing the second generation unsymmetrical aluminum(III) triamine catalyst **180**. This second generation AAC reaction employs substoichiometric amounts of catalylst **180** (10-20 mol %) and enables the effective preparation of 3,4-*cis*-disubstituted β-lactones (**246**) from a variety of aldehydes and alkyl-substituted ketenes (Figure 32).[102] The resulting lactones were obtained in good yield with good to excellent enantio- and diastereoselectivities.

[102] Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14.

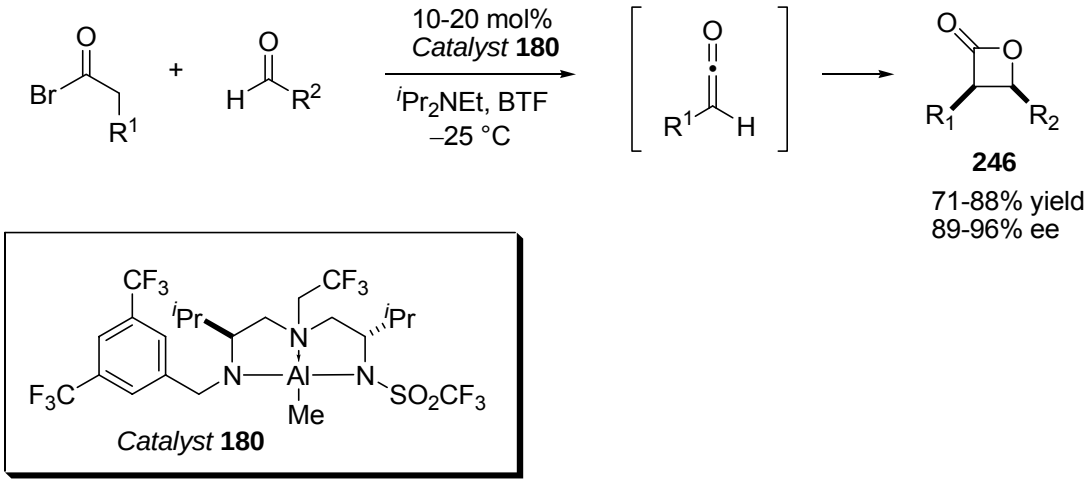
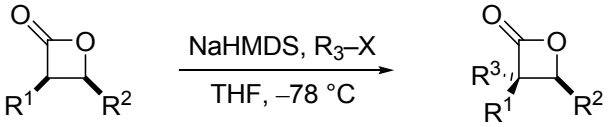


Figure 33. Second generation asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions of substituted ketenes

Merging the newly acquired 3,4-*cis*-disubstituted β-lactone products from the second generation AAC reaction with the previously described alkylation protocol resulted in the successful installation of quaternary carbon stereocenters in a variety of α-substituted β-lactones that had formerly been inaccessible through traditional AAC reaction technology (Table 6). Lactones containing either ethyl or *n*-propyl substituents at the α-position (entries a, b, and c) were readily enolized and alkylated in good yield with high levels of diastereoselectivity (*anti*/*syn* >98:2). Bulky α-substituents (entry d) were also tolerated affording the corresponding α,α-substituted β-lactone **247d** as a single diastereomer in 94% yield.

Table 7. Alkylation of 3,4-*cis*-Disubstituted β-Lactones



246a-f **247a-i**

entry	R_1	R_2	R_3–X	Yield (%)[a]	*anti*:*syn*[b,c]
a	Et	CH_2CH_2Ph	CH_2CHCH_2Br	92 (**247a**)	>98:2
b	^{n}Pr	CH_2CH_2OBn	CH_2CHCH_2Br	83 (**247b**)	>98:2
c	^{n}Pr	CH_2CH_2Ph	BnBr	86 (**247c**)	>98:2
d	^{i}Pr	Ph	BnBr	94 (**247d**)	>98:2
e	Me	C_6H_{11}	CH_2CHCH_2Br	52 (**247e**)	95:5
f	Me	CH_2CH_2Ph	BnBr	48 (**247f**)	>98:2
g	Me	CH_2CH_2Ph	EtI	21 (**247g**)	>98:2
h	Me	CH_2CH_2Ph	^{n}BuI	12 (**247h**)	>98:2
i	Me	CH_2CH_2Ph	MeI	69 (**247i**)	–

[a]Isolated yields of purified products. [b]Diastereomer ratios were determined by ^{1}H NMR analysis of crude product mixtures. [c]Stereochemistry of major diastereomer was assigned based on literature precedent. See ref. 74d.

Limitations to the method were observed, however, when a methyl group was incorporated at the C_3 position of the β-lactone substrates (entries e-h). While the observed diastereoselectivity in the alkylation event remained constant (≥ 95:5), isolated yields of the β-lactone products were significantly attenuated. These low isolated yields can potentially be attributed to the competitive Claisen self-condensation reaction pathway reported by Mulzer and Seebach. As depicted in Figure 33, nucleophilic attack of a lactone enolate on the starting *cis*-3,4-disubstituted β-lactone can proceed along a relatively unhindered trajectory reminiscent of a C_3-unsubstituted substrate resulting in substantial enolate acylation and further lactone

consumption via oligomerization. As previously observed in the case of C_3 unsubstituted β-lactone enolates, the nature of the alkylating agent appears to play a major role in the degree of competition between alkylation and self-condensation as more reactive electrophiles (entries e, f, and i) afforded the corresponding α,α-disubstituted β-lactones in higher yields than less reactive primary alkyl iodides (entries g and h). Although poor yields were obtained when using 3,4-*cis*-disubstituted β-lactones containing an α-methyl group, we have previously demonstrated the success of 3,4-*trans*-disubstituted lactones possessing an α-methyl group in the diastereoselective β-lactone enolate alkylation in the construction of quaternary carbon stereocenters. This difference in reactivity between the two diastereomeric lactones can be rationalized by a hindered trajectory of a lactone enolate approaching a *trans* lactone from either face. As a result, the two approaches are complementary.

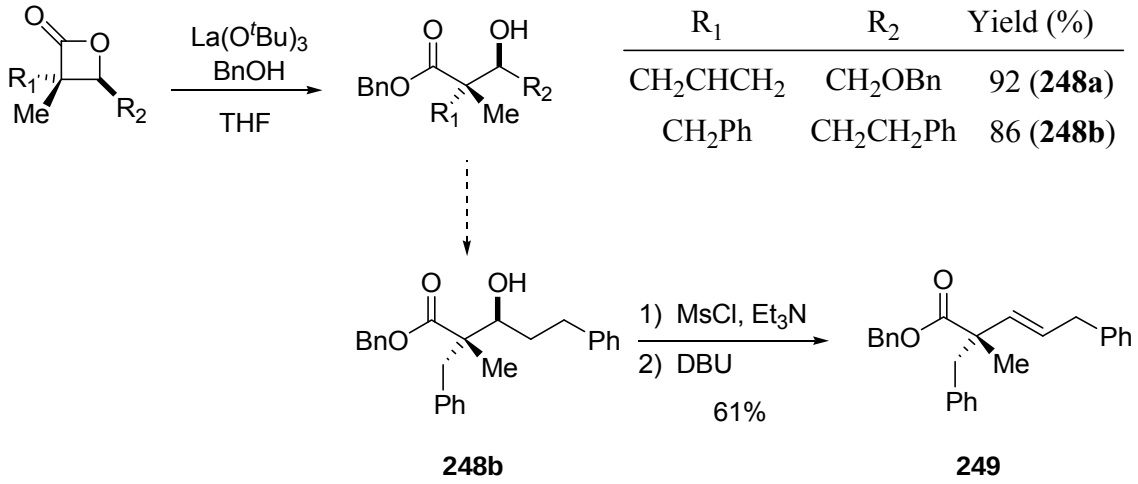
Figure 34. Rationalization for low yields of alkylation with 3-methyl-3,4-cis-disubstituted β-lactones

3.3 SYNTHETIC APPLICATION OF α,α-DISUBSTITUTED β-LACTONES

Having prepared a variety of α,α-disubstituted β-lactones, a series of investigations were conducted to determine whether the increased steric bulk of the newly installed quaternary carbon stereocenter would impact the differential electrophilic reactivity patterns typically

displayed by less substitiuted β-lactones. To our delight, treatment of lactones **245f** and **245b** with La(O^{t}Bu)$_3$ and BnOH resulted in based-mediated alcoholysis cleanly affording the ring opened ester aldol adducts **248a** and **248b**. Further elaboration of β-hydroxyester **c** by mesylation and subsequent elimination then provided the α, α-disubstituted β, γ-unsaturated carboxylate ester **249** in 61% yield (Scheme 39).

Scheme 39. La(O^{t}Bu)$_3$ Mediated Ring Opening of α,α-Disubstituted β-Lactones



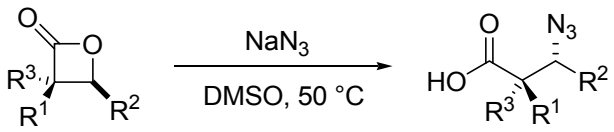
R_1	R_2	Yield (%)
CH_2CHCH_2	CH_2OBn	92 (**248a**)
CH_2Ph	CH_2CH_2Ph	86 (**248b**)

Similarly, geminal α-substitution appears to have little effect on the azide-mediated S_N2 ring opening of β-lactones (Table 8). When lactones **245b-d** were subjected to NaN_3 (2.0 equiv) in DMSO at 50 °C,[103] the corresponding β-azido acids were obtained in near quantitative yield. However, when the steric environment around the electrophilic C_4 stereocenter was dramatically increased (entry d), the S_N2 pathway became less accessible resulting in a 5:1 mixture of starting lactone and the desired β-azido acid after 3 days at 50 °C. Despite the low reactivity observed with especially hindered substrates, azide-mediated ring opening of α, α-disubstituted β-lactones

[103] Nelson, S. G.; Spencer, K. L. *Angew. Chem. Int. Ed*. **2000**, *39*, 1323.

has proven to be an efficient strategy leading to synthetically useful α, α-disubstituted β-amino acids.

Table 8. Azide-Mediated S_N2 Ring Opening of α,α-Disubstituted β-Lactones



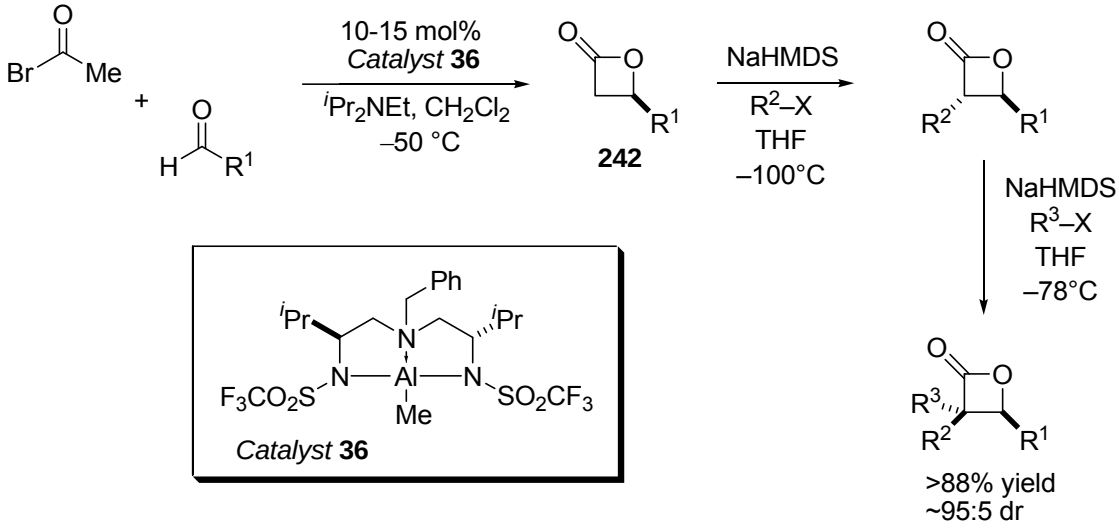
245b-d, 247d **250a-d**

entry	R_1	R_2	R_3	Yield[a] (%)
a	Me	Et	CH_2CH_2Ph	98 (**250a**)
b	Me	CH_2Ph	CH_2CH_2Ph	95 (**250b**)
c	Me	^{n}Bu	CH_2CH_2Ph	97 (**250c**)
d	^{i}Pr	CH_2Ph	Ph	14 (**250d**)

[a]Isolated yields of purified products.

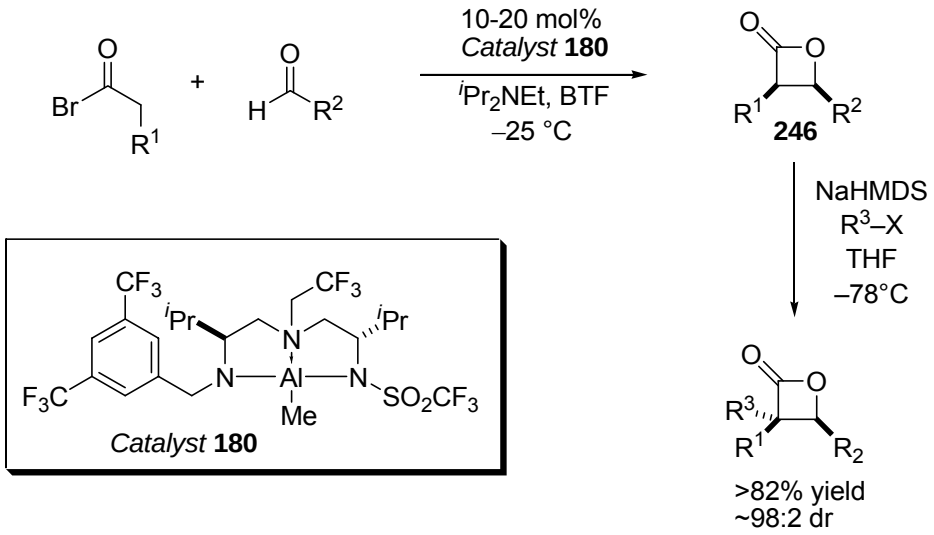
3.4 CONCLUSIONS

The enantiomerically enriched β-lactone products of catalytic, asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions have been successfully employed in the stereoselective construction of quaternary carbon stereocenters. Treatment of β-lactones of type **242** with NaHMDS at low temperature resulted in enolization and subsequent alkylation with in situ electrophiles to afford *trans*-3,4-disubstituted lactones in moderate to good yield with good levels of diastereoselectivity. Resubjecting the monoalkylated products to the reaction conditions and employing a different electrophile resulted in the efficient production of α,α-disubstituted-β-lactones in high yield with high *trans*-diastereoselectivity.

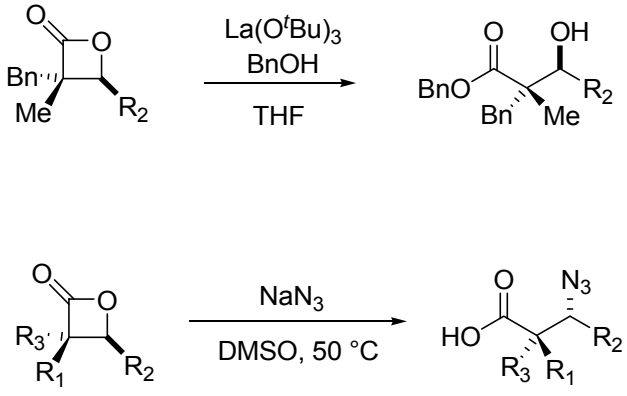


A more efficient route to α,α-disubstituted β-lactones was realized by employing the recently developed second generation AAC reaction. This approach avoided the initial problematic enolization and alkylation of α-unsubstituted β-lactones by installing the enolate stabilizing α-stereocenter via the reaction of aldehydes with alkyl substituted ketenes in the

presence of substoichiometric amounts of catalyst **180**. Asymmetric quaternary carbon formation could now be accomplished in two steps affording the desired α,α-disubstituted-β-lactones in high yield with excellent diastereoselectivity.

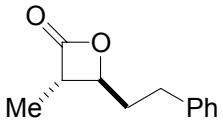


Once synthesized, the quaternary center containing lactones were subjected to traditional β-lactone ring opening reaction conditions to furnish the corresponding α,α-disubstituted ester aldol adducts and β-azido acids in excellent yield.

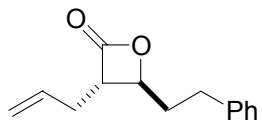


3.5 EXPERIMENTAL SECTION

General Procedure for the Enolization and Alkylation of α-Unsubstituted β-Lactones: To a –100 °C solution of 0.209 g of lactone **61** (1.19 mmol) and 0.370 mL of MeI (5.93 mmol) in 60 mL THF was added 1.20 mL of a 1.0 M solution of NaHMDS in THF slowly via syringe pump over 1 h. The reaction was maintained for an additional 1 h at –100 °C, then quenched with saturated aqueous NH_4Cl. After warming to ambient temperature, the reaction mixture was extracted with EtOAc and the combined organics were washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (4% EtOAc/hexanes) provided 0.142 g (63%) of lactone **243a** as a clear, colorless oil.

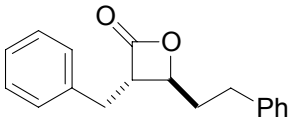


(3*S*, 4*S*)-3-Methyl-4-phenethyl-oxetan-2-one (243a): $[\alpha]_D$ = –82 (c 1.7, $CHCl_3$); IR (thin film): 3063, 3028, 2936, 2876, 1824, 1603, 1496, 1455, 1385, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 4.18 (ddd, *J* = 4.0, 5.9, 7.5 Hz, 1H), 3.21 (dq, *J* = 4.0, 7.5 Hz, 1H), 2.84 (ddd, *J* = 5.8, 8.8, 14.3 Hz, 1H), 2.76–2.65 (m, 1H), 2.27–2.03 (m, 2H), 1.33 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 140.0, 128.5, 128.2, 126.2, 78.5, 50.7, 35.6, 31.1, 12.2; LRMS (EI, 70eV): *m/z* 190; HRMS calcd for $C_{12}H_{14}O_2$: 190.0994, found 190.0993.

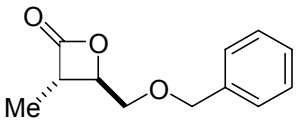


(3*S*, 4*S*)-3-Allyl-4-phenethyl-oxetan-2-one (243b): Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded 0.155 g (68%) of a clear, colorless oil: $[\alpha]_D$ = –61 (c 2.3, $CHCl_3$); IR (thin film): 3083, 3064, 3027, 2931, 2861, 1820, 1642, 1603, 1497, 1454, 1384, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–

7.19 (m, 5H), 5.85–5.69 (m, 1H), 5.16 (brs, 1H), 5.12 (dd, *J* = 1.4, 5.7 Hz, 1H), 4.28 (ddd, *J* = 4.0, 5.5, 7.7 Hz, 1H), 3.30 (ddd, *J* = 4.0, 6.1, 8.3 Hz, 1H), 2.88–2.64 (m, 2H), 2.58–2.39 (m, 2H), 2.26–2.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.4, 140.0, 132.9, 128.5, 128.2, 126.3, 118.2, 76.3, 55.3, 35.8, 31.4, 31.2; LRMS (EI, 70eV): *m/z* 216; HRMS calcd for $C_{14}H_{16}O_2$: 216.1150, found 216.1149.



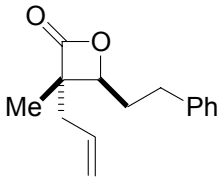
(3*S*, 4*S*)-3-Benzyl-4-phenethyl-oxetan-2-one (243c): Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded 0.110 g (38%) of a pale yellow oil: $[\alpha]_D$ = –19 (c 1.8, $CHCl_3$); IR (thin film): 3086, 3062, 3028, 2926, 2860, 1820, 1603, 1497, 1454, 1384, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.27 (m, 6H), 7.25–7.11 (m, 4H), 4.33 (ddd, *J* = 4.2, 6.1, 7.2 Hz, 1H), 3.52 (ddd, *J* = 4.2, 6.0, 9.1 Hz, 1H), 3.13 (dd, *J* = 6.0, 14.3 Hz, 1H), 2.99 (dd, *J* = 9.0, 14.3 Hz, 1H), 2.66 (ddd, *J* = 5.7, 9.4, 14.6 Hz, 1H), 2.56–2.49 (m, 1H), 2.25–2.11 (m, 1H), 2.03–1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 140.0, 137.0, 128.8, 128.6, 128.5, 128.1, 127.0, 126.2, 76.4, 57.1, 35.5, 33.4, 29.6; LRMS (EI, 70eV): *m/z* 266; HRMS calcd for $C_{18}H_{18}O_2$: 266.1307, found 266.1298.



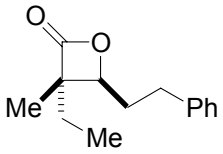
(3*S*, 4*R*)- 4-Benzyloxymethyl-3-methyl-oxetan-2-one (243d): Purification by flash chromatography on silica gel (10% EtOAc/hexanes) afforded 0.188 g (35%) of a pale yellow oil: $[\alpha]_D$ = –48 (c 2.3, $CHCl_3$); IR (thin film): 3063, 3031, 2867, 1821, 1496, 1454, 1362, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 4.60 (s, 2H), 4.34 (ddd, *J* = 4.3, 4.3, 4.3 Hz, 1H), 3.80 (dd, *J* = 3.2, 11.7 Hz, 1H), 3.72 (dd, *J* = 4.6, 11.7 Hz. 1H), 3.59 (dq, *J* = 4.1, 7.6 Hz, 1H), 1.39 (d, *J* = 7.6 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 137.4, 128.3, 127.7, 127.5, 77.2, 73.5, 69.0, 47.2, 12.0; LRMS (EI, 70eV): *m/z* 178; HRMS calcd for $C_{11}H_{14}O_2$: 178.0994, found 178.0996.

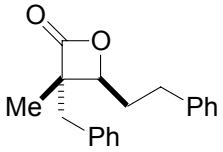
General Procedure for the Enolization and Alkylation of α-Substituted β-Lactones: To a –78 °C solution of 0.092 g of lactone **243a** (0.484 mmol) and 0.210 mL of allyl bromide (2.42 mmol) in 6 mL of THF was added 0.580 mL of a 1.0 M solution of NaHMDS in THF slowly via syringe pump over 45 min. The reaction was maintained at –78 °C for 1 h. Saturated aqueous NH_4Cl was added and the mixture was warmed to ambient temperature. The reaction mixture was extracted with EtOAc and the combined organics were washed with brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (3% EtOAc/hexanes) afforded 0.096 g (86%) of a pale yellow oil.



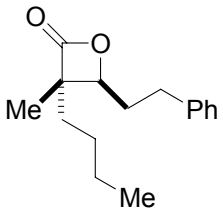
(3*S*, 4*S*)-3-Allyl-3-methyl-4-phenethyl-oxetan-2-one (245a): $[\alpha]_D$ = –44 (c 2.2, $CHCl_3$); IR (thin film): 3083, 3022, 2975, 2935, 2863, 1818, 1644, 1598, 1496, 1455, 1378, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2H), 7.26–7.20 (m, 3H), 5.76 (dddd, *J* = 7.3, 7.3, 10.2, 17.2 Hz, 1H), 5.22–5.13 (m, 2H), 4.36 (dd, *J* = 4.5, 9.3 Hz, 1H), 2.85 (ddd, *J* = 5.4, 9.8, 14.1 Hz, 1H), 2.69 (ddd, *J* = 6.9, 11, 13.8 Hz, 1H), 2.49 (dd, *J* = 7.0, 14 Hz, 1 H), 2.39 (dd, *J* = 7.6, 14 Hz, 1H), 2.08 (dddd, *J* = 5.4, 9.3, 9.3, 14 Hz, 1H), 1.95 (dddd, *J* = 4.5, 6.8, 11, 14 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 140.4, 131.6, 128.6, 128.3, 126.3, 119.8, 79.8, 56.7, 40.0, 32.4, 31.6, 14.4; LRMS (EI, 70eV): *m/z* 230; HRMS calcd for $C_{15}H_{18}O_2$: 230.1307, found 230.1307.



(3*S*, 4*S*)-3-Ethyl-3-methyl-4-phenethyl-oxetan-2-one (245c): Isolated as a pale yellow oil (94%, single diastereomer): $[\alpha]_D$ = –47 (c 1.0, $CHCl_3$); IR (thin film): 3027, 2971, 2937, 2880, 1818, 1496, 1455, 1384, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.17 (m, 5H), 4.28 (dd, *J* = 4.3, 9.3 Hz, 1H), 2.86 (ddd, *J* = 5.4, 9.7, 14 Hz, 1H), 2.70 (ddd, *J* = 7.1, 9.2, 14 Hz, 1H), 2.12 (dddd, *J* = 4.1, 9.3, 9.3, 14 Hz, 1H), 1.96 (dddd, *J* = 4.4, 6.3, 11, 14 Hz, 1H), 1.75 (bq, *J* = 7.3 Hz, 2H), 1.26 (s, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 140.5, 128.6, 128.4, 126.3, 80.1, 57.8, 32.6, 31.7, 28.7, 13.9, 8.56; LRMS (EI, 70eV): *m/z* 218; HRMS calcd for 218.1307: found, 218.1305.

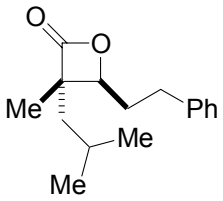


(3*S*, 4*S*)-3-Benzyl-3-methyl-4-phenethyl-oxetan-2-one (245b): $[\alpha]_D$ = –25 (c 2.0, $CHCl_3$); IR (thin film): 3062, 3027, 2931, 1820, 1603, 1496, 1454, 1382, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.24 (m, 6H), 7.17-7.08 (m, 4H), 4.42 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.09 (d, *J* = 14 Hz, 1H), 2.84 (d, *J* = 14 Hz, 1H), 2.78 (ddd, *J* = 5.3, 9.6, 14 Hz, 1H), 2.57 (ddd, *J* = 7.3, 12, 14 Hz, 1H), 2.06 (dddd, *J* = 5.3, 9.3, 9.3, 14 Hz, 1H), 1.86 (dddd, *J* = 4.4, 7.2, 12, 14 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 140.3, 135.4, 129.8, 128.6, 128.5, 128.4, 127.2, 126.3, 79.3, 57.9, 41.5, 32.1, 31.7, 15.1; LRMS (EI, 70eV): *m/z* 280; HRMS calcd for $C_{19}H_{20}O_2$: 280.1463, found 280.1470.

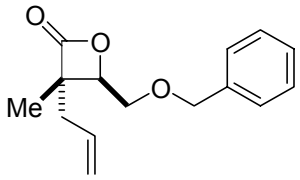


(3*S*, 4*S*)-3-Butyl-3-methyl-4-phenethyl-oxetan-2-one (245d): Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded the title compound as a pale yellow oil (88%): $[\alpha]_D$ = –49 (c 2.4, $CHCl_3$); IR (thin film): 3063, 3027, 2957, 2934, 2862, 1822, 1496, 1455, 1382, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.27–7.21 (m, 3H), 4.31 (dd, *J* = 4.3, 9.4 Hz, 1H), 2.87 (ddd, *J* =

5.3, 10, 14 Hz, 1H), 2.70 (ddd, *J* = 6.9, 9.4, 14 Hz, 1H), 2.09 (dddd, *J* = 5.4, 9.4, 9.4, 14 Hz, 1H), 1.96 (dddd, *J* = 4.3, 6.9, 11, 14 Hz, 1H), 1.70 (dd, *J* = 7.2, 9.0 Hz, 2H), 1.50–1.39 (m, 1H), 1.38–1.31 (m, 2H), 1.29–1.20 (s+m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 140.4, 128.5, 128.3, 126.3, 80.5, 57.2, 35.5, 32.5, 31.7, 26.2, 22.8, 14.3, 13.8; LRMS (EI, 70eV): *m/z* 246; HRMS calcd for $C_{16}H_{22}O_2$: 246.1619, found 246.1613.

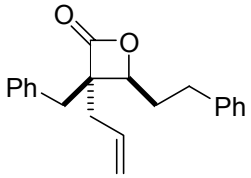


(3*S*, 4*S*)-3-Isobutyl-3-methyl-4-phenethyl-oxetan-2-one (245e): Purification by flash chromatography on silica gel (2% EtOAc/hexanes) afforded lactone **245e** as a pale yellow oil (10%): $[\alpha]_D$ = –53 (*c* 0.2, $CHCl_3$); IR (thin film): 3027, 2958, 2871, 1820, 1455, 1383, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.29 (m, 2H), 7.27–7.20 (m, 3H), 4.33 (dd, *J* = 3.7, 9.6 Hz, 1H), 2.91 (ddd, *J* = 5.3, 9.3, 14 Hz, 1H), 2.69 (ddd, *J* = 7.7, 8.5, 14 Hz, 1H), 2.14–1.93 (m, 2H), 1.81–1.73 (m, 2H), 1.56 (dd, *J* = 6.0, 10 Hz, 1H), 1.25 (s, 3H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 140.5, 128.6, 128.4, 126.3, 81.7, 56.7, 44.5, 32.4, 31.8, 24.4, 23.9, 22.4, 14.1; LRMS (EI, 70eV): *m/z* 246; HRMS calcd for $C_{16}H_{22}O_2$: 246.1619, found 246.1616.

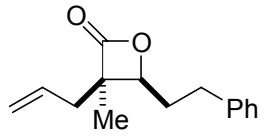


(3*S*, 4*R*)- 3-Allyl-4-benzyloxymethyl-3-methyl-oxetan-2-one (245f): Isolated as a pale yellow oil (93%, single diastereomer): $[\alpha]_D$ = –9.1 (*c* 2.8, $CHCl_3$); IR (thin film): 3066, 3031, 2976, 2865, 1824, 1642, 1496, 1455, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 5.78 (dddd, *J* = 6.9, 7.7, 11, 18 Hz, 1H), 5.24–5.23 (m, 1H), 5.21–5.17 (m, 1H), 4.63 (d, *J* = 12 Hz, 1H), 4.56 (d, *J* = 12 Hz, 1H), 4.51 (dd, *J* = 5.2, 6.4 Hz, 1H), 3.78 (dd, *J* = 6.4, 11 Hz, 1H), 3.73 (dd, *J* = 5.2, 11 Hz, 1H), 2.52 (ddt, *J* = 1.2, 6.8, 14 Hz, 1H), 2.42 (ddt, *J* = 1.0, 7.7, 14 Hz, 1H), 1.29 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 173.7, 137.3, 131.4, 128.4, 127.8, 127.6, 120.0, 77.6, 73.6, 68.4, 57.1, 40.0, 14.2; LRMS (EI, 70eV): *m/z* 247 (M+H); HRMS calcd for $C_{15}H_{18}O_3$: 246.1256, found 246.1246.

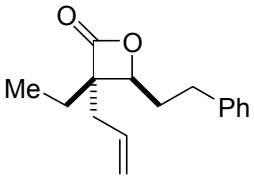


(3*R*, 4*S*)-3-Allyl-3-benzyl-4-phenethyl-oxetan-2-one (245h): Purification by flash chromatography on silica gel (3% EtOAc/hexanes) afforded the title compound as a pale yellow oil: (84%): $[\alpha]_D$ = –51 (*c* 3.0, $CHCl_3$); IR (thin film): 3063, 3028, 2926, 2859, 1816, 1640, 1603, 1496, 1454, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 10H), 5.73 (dddd, *J* = 6.5, 8.0, 14, 17 Hz, 1H), 5.22 (br d, *J* = 10 Hz, 1H), 5.12 (dq, *J* = 1.3, 17 Hz, 1H), 4.50 (dd, *J* = 3.8, 9.9 Hz, 1H), 3.31 (d, *J* = 14 Hz, 1H), 2.96 (ddd, *J* = 5.1, 9.8, 14 Hz, 1H), 2.80 (d, *J* = 14 Hz, 1H), 2.77 (ddd, *J* = 7.1, 9.2, 14 Hz, 1H), 2.40 (brdd, *J* = 6.4, 14 Hz, 1H), 2.31–2.17 (m, 2H), 2.10 (dddd, *J* = 3.8, 7.1, 9.9, 11 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 140.4, 135.2, 131.6, 130.2, 128.6, 128.4, 127.0, 126.3, 120.2, 79.0, 60.2, 36.4, 34.7, 32.3, 31.8; LRMS (EI, 70eV): *m/z* 306; HRMS calcd for $C_{21}H_{22}O_2$: 306.1620, found 306.1609.

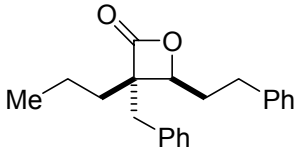


(3*R*, 4*S*)-3-Allyl-3-methyl-4-phenethyl-oxetan-2-one (245g): Isolated as a pale yellow oil (94%, 6:1 mixture of diastereomers): IR (thin film): 3064, 3027, 2958, 2930, 2863, 1822, 1641, 1603, 1496, 1455, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.27–7.20 (m, 3H), 5.80 (dddd, *J* = 6.6, 7.8, 10, 14 Hz, 1H), 5.20–5.05 (m, 2H), 4.25 (dd, *J* = 4.0, 9.8 Hz, 1H), 2.90 (ddd, *J* = 5.3, 9.3, 14 Hz, 1H), 2.68 (ddd, *J* = 7.7, 7.7, 14 Hz, 1H), 2.54 (ddt, *J* = 1.4, 6.6, 14 Hz, 1H), 2.34 (ddt, *J* = 1.0, 7.8, 14 Hz, 1H), 2.20–1.94 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 140.4, 131.9,

128.6, 128.4, 126.3, 119.3, 82.6, 56.0, 34.8, 32.2, 31.7, 19.8; LRMS (EI, 70eV): *m/z* 230; HRMS calcd for $C_{15}H_{18}O_2$: 230.1307, found 230.1312.

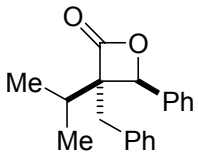


(3*S*, 4*S*)-3-Allyl-3-ethyl-4-phenethyl-oxetan-2-one (247a): Isolated as a pale yellow oil (92%, single diastereomer): $[\alpha]_D$ = –41 (*c* 2.1, $CHCl_3$); IR (thin film): 3083, 3063, 3027, 2973, 2882, 1817, 1732, 1642, 1604, 1496, 1455, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.27–7.20 (m, 3H), 5.74 (dddd, *J* = 7.5, 7.5, 10, 17 Hz, 1H), 5.22–5.15 (m, 2H), 4.36 (dd, *J* = 3.9, 9.9 Hz, 1H), 2.87 (ddd, *J* = 5.1, 10, 14 Hz, 1H), 2.69 (ddd, *J* = 6.9, 9.5, 14 Hz, 1H), 2.55–2.42 (m, 2H), 2.12 (dddd, *J* = 5.2, 9.7, 9.7, 14 Hz, 1H), 1.96 (dddd, *J* = 3.9, 6.9, 10, 14 Hz, 1H), 1.90 (dddd, *J* = 7.5, 7.5, 7.5, 15 Hz, 1H), 1.66 (dddd, *J* = 7.5, 7.5, 7.5, 15 Hz, 1H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 140.5, 131.6, 128.6, 128.4, 126.3, 119.7, 79.9, 60.4, 36.0, 32.0, 31.8, 21.1, 8.4; LRMS (EI, 70eV): *m/z* 244; HRMS calcd for $C_{16}H_{20}O_2$, 244.1463, found 244.1472.

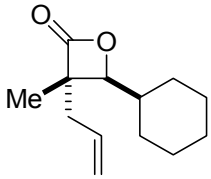


(3*S*, 4*S*)-3-Benzyl-4-phenethyl-3-propyl-oxetan-2-one (247c): Isolated as a pale yellow oil (86%, single diastereomer): $[\alpha]_D$ = –32 (*c* 2.1, $CHCl_3$); IR (thin film): 3086, 3062, 2960, 2873, 1815, 1603, 1496, 1455, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 6H), 4.40 (dd, *J* = 3.7, 9.9 Hz, 1H), 3.15 (d, *J* = 14 Hz, 1H), 2.88 (d, *J* = 14 Hz, 1H), 2.80 (ddd, *J* = 5.1, 9.7, 14 Hz, 1H), 2.58 (ddd, *J* = 7.5, 8.9, 14 Hz, 1H), 2.10 (dddd, *J* = 5.0, 9.3, 14 Hz, 1H), 1.89 (dddd, *J* = 3.7, 7.4, 9.6, 14 Hz, 1H), 1.80–1.62 (m, 2H), 1.60–1.46 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 140.4, 135.5, 129.7, 128.6, 128.5, 128.4, 127.1, 126.3, 79.0, 61.4, 38.1,

31.6, 31.2, 17.6, 14.5; LRMS (EI, 70eV): *m/z* 308; HRMS calcd for $C_{21}H_{24}O_2$: 308.1776, found 308.1781.

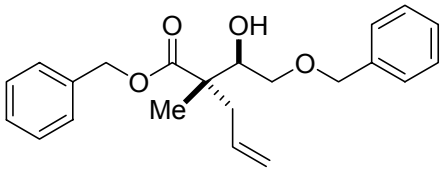


(3*R*, 4*S*)-3-Benzyl-3-isopropyl-4-phenyl-oxetan-2-one (247d): Isolated as a white solid (94%, single diastereomer): $[\alpha]_D$ = –78 (*c* 1.6, $CHCl_3$); IR (thin film): 3063, 3027, 2958, 2930, 1811, 1495, 1454, 1373, 1268, 1140, 921, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.30 (m, 10H), 5.27 (s, 1H), 3.25 (d, *J* = 14 Hz, 1H), 2.86 (d, *J* = 14 Hz, 1H), 2.20 (septet, *J* = 6.8 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.52 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 135.7, 134.8, 130.5 (2C), 128.9 (2C), 128.6, 128.3 (2C), 127.3, 126.7 (2C), 78.2, 68.5, 32.8, 28.3, 17.6, 16.2; LRMS (EI, 70eV): *m/z* 236 $[M\text{-}CO_2]^+$; HRMS calcd for $C_{18}H_{20}$: 236.1565 , found 236.1566.

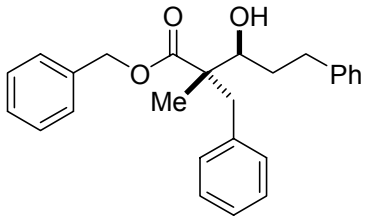


(3*S*, 4*S*)-3-Allyl-4-cyclohexyl-3-methyloxetan-2-one (247e): Isolated as a pale yellow oil (52%, 19:1 mixture of diastereomers): $[\alpha]_D$ = +3.0 (*c* 2.0, $CHCl_3$); IR (thin film): 3080, 2932, 2854, 1823, 1642, 1452, 1382, 1137, 985, 925, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (dddd, *J* = 7.4, 7.4, 10, 18 Hz, 1H), 5.23–5.20 (m, 1H), 5.18–5.13 (m, 1H), 3.96 (d, *J* = 11 Hz, 1H), 2.48 (dd, *J* = 7.0, 14 Hz, 1H), 2.38 (dd, *J* = 7.6, 14 Hz, 1H), 2.01–1.89 (m, 1H), 1.85–1.61 (m, 4H), 1.56–1.47 (m, 1H), 1.31 (s, 3H), 1.29–1.12 (m, 2H), 1.10–0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 132.0, 119.7, 84.4, 56.4, 40.4, 38.2, 29.1, 28.3, 26.1, 25.1, 25.0, 14.5; LRMS (EI, 70eV): *m/z* 208; HRMS calcd for $C_{13}H_{20}O_2$, 208.1463, found 208.1470.

General procedure for the La(O^{t}Bu)$_3$-Mediated Ring Opening of α, α-Disubstituted β-Lactones:[25a] To a solution of La(O^{t}Bu)$_3$ in THF was added benzyl alcohol at ambient temperature. The reaction mixture was maintained until complete consumption of the starting material was observed by TLC. The reaction was then purified by column chromatography.

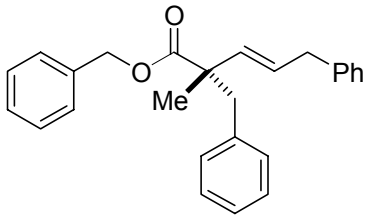


(1′*R*, 2*S*)- Benzyl-2-(2-benzyloxy-1′-hydroxyethyl)-2-methylpent-4-enoate (248a): Purification by flash chromatography (5% EtOAc/hexanes) afforded 0.022 g (92%) of hyroxyester **248a** as a clear, colorless oil: $[\alpha]_D = -8.6$ (*c* 2.7, $CHCl_3$); IR (thin film): 3467, 3065, 3032, 2979, 2919, 1731, 1640, 1454, 1214, 1086, 739, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.25 (m, 10H), 5.76–5.60 (m, 1H), 5.08–4.98 (m, 2H), 4.49 (s, 2H), 3.85 (ddd, *J* = 2.8, 5.9, 7.0 Hz, 1H), 3.62 (dd, *J* = 2.8, 9.8 Hz, 1H), 3.54 (dd, *J* = 5.9, 9.8 Hz, 1H), 3.22 (d, *J* = 7.0 Hz, 1H), 2.58 (dd, *J* = 7.2, 13.6 Hz, 1H), 2.28 (dd, *J* = 7.7, 13.6 Hz, 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 137.9, 135.9, 133.1, 128.5, 128.4, 128.1, 127.8, 127.7, 75.0, 73.6, 71.0, 66.5, 48.9, 40.7, 17.7; LRMS (EI, 70eV): *m/z* 263 $[M-C_7H_7]^+$; HRMS calcd for $C_{15}H_{19}O_4$: 263.1283, found 263.1274.



(2*S*, 3*S*)-2-Benzyl-3-hydroxy-2-methyl-5-phenyl-pentanoic acid benzyl ester (248b): Purification by flash chromatography (5% EtOAc/hexanes) afforded 0.073 g (86%) of hyroxyester **248b** as a clear, colorless oil: $[\alpha]_D = -35$ (*c* 1.8, $CHCl_3$); IR (thin film): 3506, 3085, 3062, 3028, 2948, 2858, 1720, 1603, 1496, 1454, 1273, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.18 (m, 12H), 7.10–7.05 (m, 2H), 5.10 (s, 2H), 3.61 (ddd, *J* = 1.8, 8.9, 11 Hz, 1H), 3.11 (d, *J* = 13 Hz, 1H), 2.97 (ddd, *J* = 4.8, 10, 14 Hz, 1H), 2.86 (d, *J* = 13 Hz, 1H),

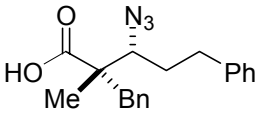
2.80 (d, J = 8.8 Hz, 1H), 2.64 (ddd, J = 6.7, 9.9, 14 Hz, 1H), 1.89 (dddd, J = 1.8, 6.7, 10, 14 Hz, 1H), 1.56 (dddd, J = 4.8, 10, 11, 14 Hz, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 142.1, 136.8, 135.5, 130.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 126.6, 125.8, 75.1, 66.5, 52.3, 42.5, 34.1, 32.8, 17.6; LRMS (EI, 70eV): *m/z* 388, 370 (M-H_2O); HRMS calcd for $C_{26}H_{28}O_3$: 388.2038, found 388.2036.



(2*S*)-2-Benzyl-2-methyl-5-phenylpent-3-enoic acid benzyl ester (249): To a 0°C solution of 0.036 g of hydroxyester **248b** (0.093 mmol) and 26 μL of Et_3N (0.186 mmol) in 0.9 mL of CH_2Cl_2 was added 11 μL of methanesulfonyl chloride (0.139 mmol). The reaction was maintained at 0°C for 30 min, and then diluted with ether (10 mL). The resulting cloudy white mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organics were dried over Na_2SO_4, filtered, and concentrated. The crude mesylate was then dissolved in benzene, treated with DBU, and heated at reflux for 18 h. Upon cooling to ambient temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ followed by brine. The organic layer was again dried over Na_2SO_4, filtered, and concentated. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 0.021 g (61%) of the title compound **249** as a clear, colorless oil: $[\alpha]_D$ = +13 (*c* 1.3, $CHCl_3$); IR (thin film): 3085, 3062, 3029, 2979, 2935, 1731, 1603, 1495, 1454, 1100, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.21 (m, 10H), 7.15–7.08 (m, 4H), 5.83 (dt, J = 1.3, 16 Hz, 1H), 5.62 (dt, J = 6.7, 16 Hz, 1H), 5.15 (s, 2H), 3.39 (d, J = 6.7 Hz, 2H), 3.11 (d, J = 13 Hz, 1H), 2.91 (d, J = 13 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 140.2, 137.1, 136.0, 134.6, 130.4, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0,

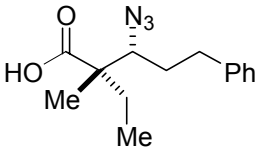
127.9, 126.4, 126.0, 66.4, 49.2, 45.6, 39.0, 20.6; LRMS (EI, 70eV): *m/z* 370; HRMS calcd for $C_{26}H_{26}O_2$: 370.1933, found 370.1942.

General Procedure for the Azide-Mediated Ring Opening of α, α-Disubstituted β-Lactones:[104] To a 50 °C solution of 0.015 mg of NaN_3 (0.229 mmol) in 0.3 mL of DMSO was added 0.032 g of lactone **245b** in 0.3 mL of DMSO followed by a 0.1 mL rinse. The resulting clear, colorless solution was maintained for 3 h at 50 °C, then cooled to ambient temperature. After acidification with 1 M HCl (2 mL), the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 × 10 mL). The combined organics were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to afford 0.035 g of β-azido acid **250b**.

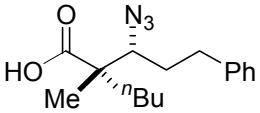


(2*S*, 3*R*)-3-Azido-2-benzyl-2-methyl-5-phenylpentanoic acid (250b): Isolated as a pale yellow oil (95%): $[\alpha]_D = -35$ (*c* 1.9, $CHCl_3$); IR (thin film): 3063, 3028, 2929, 2099, 1705, 1603, 1545, 1496, 1454, 1275, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.19 (m, 10H), 3.70 (brd, *J* = 9.4 Hz, 1H), 3.09–3.00 (m, 1H), 2.98 (d, *J* = 13 Hz, 1H), 2.79 (ddd, *J* = 7.9, 7.9, 16 Hz, 1H), 2.15-1.75 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1, 140.7, 136.7, 130.1, 128.5, 128.4, 128.1, 126.7, 126.2, 67.9, 53.2, 43.6, 33.5, 33.1, 16.0; LRMS (EI, 70eV): *m/z* 295 (M-N_2); HRMS calcd for $C_{19}H_{21}NO_2$ (M-N_2): 295.1572, found 295.1575.

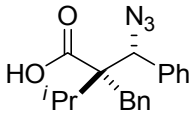
[104] A modified work-up procedure was performed for the isolation of the azido acid products compared to the original procedure described in ref. 81.



(2*S*, 3*R*)-3-Azido-2-ethyl-2-methyl-5-phenylpentanoic acid (250a): Isolated as a pale yellow oil (98%): $[\alpha]_D$ = –39 (*c* 0.2, $CHCl_3$); IR (thin film): 3028, 2931, 2099, 1702, 1456, 1386, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.28 (m, 2H), 7.24–7.19 (m, 3H), 3.60 (dd, *J* = 2.3, 11 Hz, 1H), 2.94 (ddd, *J* = 5.0, 9.7, 14 Hz, 1H), 2.69 (ddd, *J* = 7.3, 9.3, 14 Hz, 1H), 1.93–1.62 (m, 4H), 1.12 (s, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 140.7, 128.5, 128.4, 126.2, 67.9, 51.9, 33.5, 33.1, 30.6, 15.4, 8.8; LRMS (EI, 70eV): *m/z* 232 (M-N_2); HRMS calcd for $C_{14}H_{18}NO_2$ (M-N_2): 232.1338, found 232.1335.



(2*S*, 3*R*)-2-(1-Azido-3-phenyl-propyl)-2-methylhexanoic acid (250c): Isolated as a pale yellow oil (97%): $[\alpha]_D$ = –16 (*c* 1.0, $CHCl_3$); IR (thin film): 3064, 3027, 2956, 2863, 2099, 1702, 1496, 1455, 1383, 1254, 1219, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.27 (m, 2H), 7.24–7.19 (m, 3H), 3.59 (dd, *J* = 2.3, 11 Hz, 1H), 2.94 (ddd, *J* = 4.8, 9.6, 14 Hz, 1H), 2.69 (ddd, *J* = 7.3, 9.2, 14 Hz, 1H), 1.13 (s, 3H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 140.7, 128.5, 128.4, 126.2, 68.0, 51.7, 37.5, 33.5, 33.0, 26.5, 23.1, 16.2, 13.8; LRMS (EI, 70eV): *m/z* 260 (M-N_2); HRMS calcd for $C_{16}H_{22}NO_2$ (M-N_2): 260.1651, found 260.1650.



(2*R*, 3*R*)-3-Azido-2-benzyl-2-isopropyl-3-phenylpentanoic acid (250d): Isolated as a pale yellow residue (14%): $[\alpha]_D$ = –97 (*c* 0.4, $CHCl_3$); IR (thin film): 3031**,** 2922, 2850, 2104, 1700, 1454, 1255, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2H), 7.39–7.31 (m, 3H), 7.31–7.20 (m, 5H), 4.92 (s, 1H), 3.05 (d, *J* = 14 Hz, 1H), 2.99 (d, *J* = 14 Hz, 1H), 2.38 (septet, *J* = 6.9 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* =

6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 137.3, 136.4, 130.3 (2C), 129.3 (2C), 128.4. 128.3 (2C), 128.2 (2C), 126.7, 67.9, 58.2, 39.2, 30.5, 29.7, 19.7, 18.5; LRMS (EI, 70eV): *m/z* 295 $[M-N_2]^+$; HRMS calcd for $C_{19}H_{21}NO_2$: 295.1572, found 295.1569.