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Total Synthesis of Potent Antitumor Agent (−)-Lasonolide A: A Cycloaddition-Based Strategy

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Abstract: A detailed account of the enantioselective total synthesis of (−)-lasonolide A is described. Our initial synthetic route to the top tetrahydropyran ring involved Evans asymmetric alkylation as the key step. Initially, we relied on the diastereoselective alkylation of an α-alkoxyacetimide derivative containing an α′ stereogenic center and investigated such an asymmetric alkylation reaction. Although alkylation proceeded in good yield, the lack of diastereoselectivity prompted us to explore alternative routes. Our subsequent successful synthetic strategies involved highly diastereoselective cycloaddition routes to both tetrahydropyran rings of lasonolide A. The top tetrahydropyran ring was constructed stereoselectively by an intramolecular 1,3-dipolar cycloaddition reaction. The overall process constructed a bicyclic isoxazoline, which was later unravelled to a functionalized tetrahydropyran ring as well as a quaternary stereocenter present in the molecule. The lower tetrahydropyran ring was assembled by a Jacobsen catalytic asymmetric hetero-Diels–Alder reaction as the key step. The synthesis also features a Lewis acid catalyzed epoxide opening to form a substituted ether stereoselectively.

Keywords: antitumor agents · cycloaddition · lasonolide A · macrocycles · total synthesis

Introduction

Lasonolide A (**1**), a structurally unique 20-membered macrolide, was isolated from the Caribbean marine sponge *Forcepia* sp. by McConnell and co-workers in 1994.[1] Lasonolide A exhibits potent cytotoxic activity against the proliferation of A549 human lung carcinoma and P388 murine leukemia cells. It showed cell adhesion in the EL-4.IL-2 cell line, which detects signal-transduction agents.[1] Thus far, the biological mechanism of action of lasonolide A is unknown owing to its low natural abundance. The proposed structure of lasonolide A was initially determined through extensive NMR spectroscopic studies by McConnell and co-workers.[1] During total-synthesis and biological studies of lasonolide A, Lee and co-workers revised the geometry of two of the double bonds and the absolute stereochemistry of lasonolide A.[2] The most prominent structural features of lasonolide A are a 20-membered macrolactone, which contains two highly substituted tetrahydropyran units bearing a total of eight stereogenic centers, and five disubstituted and trisubstituted double bonds as part of the macrolide backbone.

The novel structural features and promising antitumor activities of lasonolide A prompted significant interest in synthesis and biological studies. Since the first total synthesis by Lee and co-workers,[2] several other total syntheses[3–5] and synthetic studies on both tetrahydropyran rings[6] have been reported in the literature. A number of diverse strategies and methodologies have been developed toward the synthesis of lasonolide A, especially for building the two highly substituted tetrahydropyran rings. Recently, we reported a convergent and enantioselective synthesis of (−)-lasonolide A.[5] Herein, we report the details of our synthetic efforts that led to the convergent total synthesis of (−)-lasonolide A. The synthesis involves a Lewis acid catalyzed hetero-Diels–Alder reaction to construct the lower tetrahydropyran ring and an intramolecular 1,3-dipolar cycloaddition reaction to assemble the upper tetrahydropyran ring. Other key reactions include a Lewis acid catalyzed epoxide opening to form a substituted ether stereoselectively, an efficient cross-metathesis reaction to construct the functionalized olefins,

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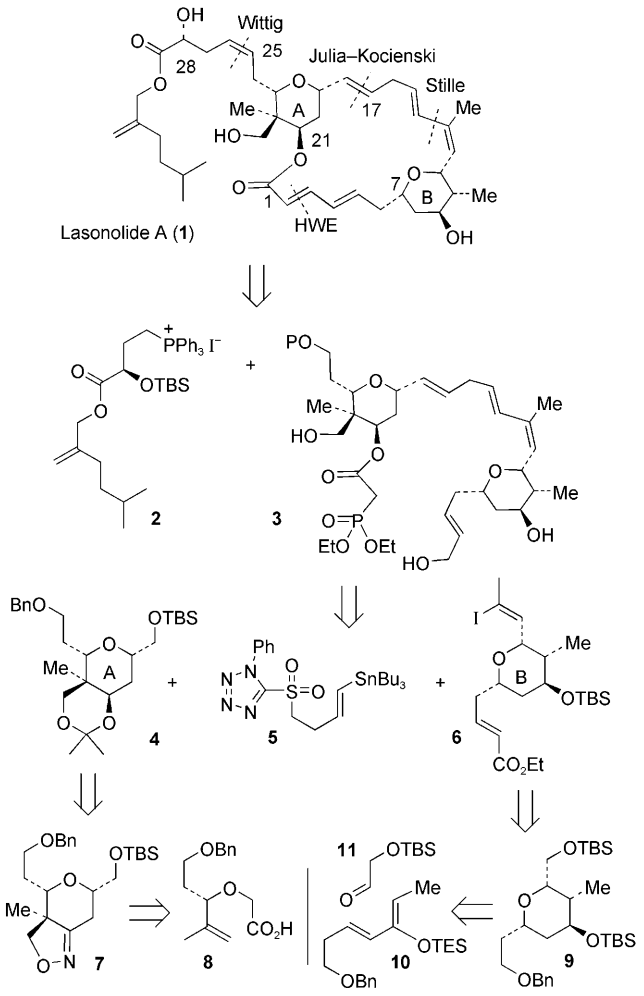
and an intramolecular Horner–Wadsworth–Emmons reaction to form the macrolactone.

Results and Discussion

Preliminary Strategy for the Two Core Tetrahydropyran Rings

Our initial retrosynthetic analysis of lasonolide A is outlined in Scheme 1. Strategic disconnection of lasonolide at C25–C26 would result in phosphonium salt **2** and Horner–Wadsworth–Emmons substrate **3** for the 20-membered macrolide

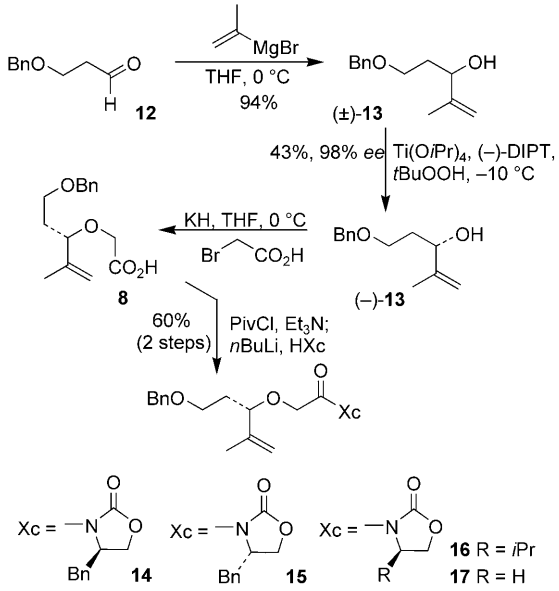


Scheme 1. Initial retrosynthetic analysis of lasonolide A (**1**). Bn = benzyl, HWE = Horner–Wadsworth–Emmons, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

core of lasonolide A. Further disconnection of phosphonoacetate **3** would provide functionalized tetrahydropyran rings **4** and **6** and tin derivative **5**. We planned to carry out Stille coupling of **5** and **6** followed by Julia–Kocienski olefination to construct the Horner–Emmons precursor **3**. Functionalized tetrahydropyran ring **4** was planned to be derived from the reduction of isoxazoline **7**. This isoxazoline derivative would be derived from acid **8** through an intramolecular [3+2] nitrile oxide cycloaddition reaction. Both double bonds in tetrahydropyran ring **6** would be installed from precursor **9** by the Wittig reaction. The tetrahydropyran ring in **9** could be constructed by a Lewis acid catalyzed hetero-Diels–Alder reaction of silyloxy diene **10** and an appropriately protected aldehyde **11**.

Initial Synthetic Route to the Top Tetrahydropyran Ring A

The synthesis of ring A began with the addition of isopropenylmagnesium bromide to aldehyde **12** to form racemic allylic alcohol *rac*-**13** in 94% yield (Scheme 2). Optically active alcohol (−)-**13** was prepared from the kinetic resolu-



Scheme 2. Preparation of oxazolidinones **14**–**17**. DIPT = diisopropyl tartrate, Piv = pivaloyl.

tion of racemic mixture *rac*-**13** by means of Sharpless asymmetric epoxidation.[7] Alkylation of alcohol (−)-**13** with bromoacetic acid and NaH provided acid **8** in poor yield. However, the use of KH as a base gave an excellent yield of **8**. Carboxylic acid **8** was converted into its mixed pivalic anhydride, and the resulting anhydride was treated with different lithio oxazolidinones to give the corresponding *N*-acyl oxazolidinones (**14**–**17**) in 60% yield (2 steps).

We planned to use the auxiliaries in **14**–**17** to introduce an α stereocenter by the diastereoselective alkylation reaction developed by Evans et al.[8] After extensive investigation, we chose *tert*-butyl iodoacetate as the alkylating agent. Sodium bis(trimethylsilyl)amide turned out to be superior to its lithium or potassium counterparts as the base. Although the asymmetric alkylation proceeded in good to excellent yields, the observed diastereoselectivity was far from satisfactory for our synthesis. The influence of substrate structure on selectivity is shown in Table 1. In entry 1, alkylation of acyl (*R*)-benzyloxazolidinone **14** provided the expected

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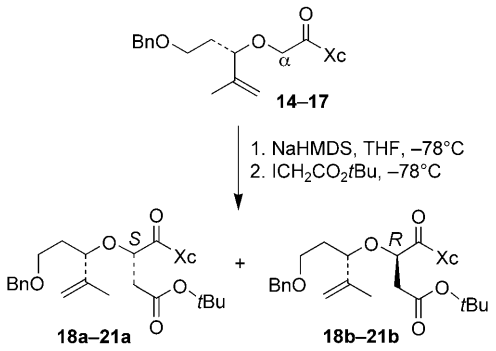
Table 1. Alkylation of acyl oxazolidinones.[a]

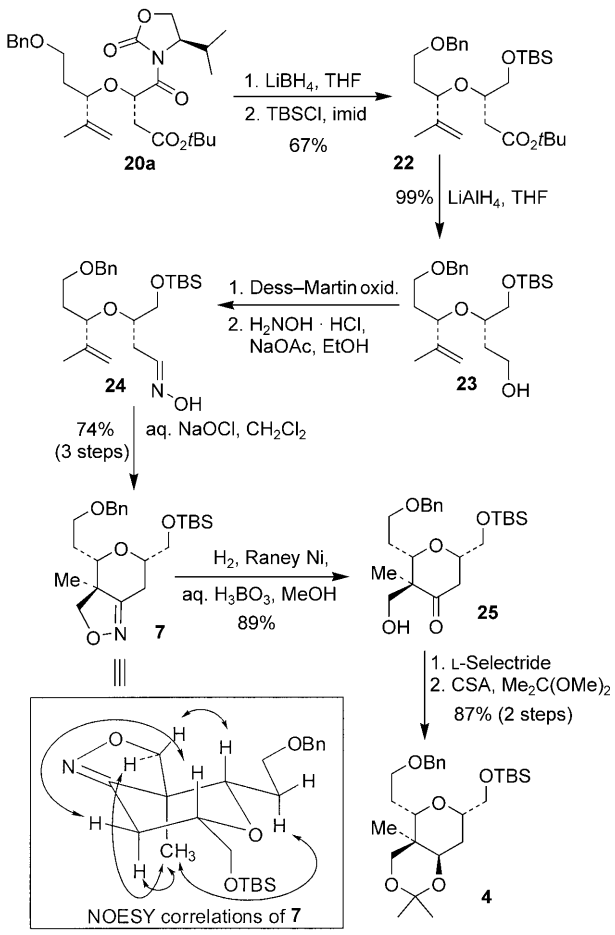


Entry	Starting material	Desired product (yield [%])	Undesired product (yield [%])	a/b
1	**14**	**18a** (20)	**18b** (44)	1:2.2
2	**15**	**19a** (24)	**19b** (40)	1:1.6
3	**16**	**20a** (40)	**20b** (44)	1:1.1
4	**17**	**21a** (18)	**21b** (57)	1:3.1

[a] HMDS = 1,1,1,3,3,3-hexamethyldisilazide.

diastereomer **18a** as the minor product in 20% yield. The undesired **18b** was the major product in 44% yield. The *S* configuration of the newly generated α stereocenter in **18a** was determined by conversion of **18a** into isoxazoline **7** by following similar reactions as shown in Scheme 3. The presence of an α-alkoxy group as well as the α′ stereogenic center may be responsible for the poor observed diastereoselectivity in this asymmetric alkylation reaction.[9] We hoped that a change in the configuration of the auxiliary from *R* to *S* may provide the desired alkylation product as the major product. Unfortunately, alkylation of **15** gave a similar result to **14**. As shown in Table 1, entry 2, asymmetric alkylation of **15** afforded desired isomer **19a** in 24% yield and undesired isomer **19b** in 40% yield. By replacing the *R*-benzyl group with an *R*-isopropyl group in the auxiliary (Table 1, entry 3), the product ratio in the alkylation of **16** was improved to 1:1.1 (**20a**/**20b**). For comparison, we carried out the alkylation with achiral oxazolidinone **17** (Table 1, entry 4). The alkylation was selective (**21a**/**21b** = 1:3.1); however, the minor isomer **21a** was the desired one. The stereochemistry of compounds **19a/b**–**21a/b** was confirmed after reductive removal of oxazolidinone with $LiBH_4$ followed by comparison with the reduction of **18a/b**. A change in protecting group from benzyl to triisopropylsilyl (TIPS) did not improve the selectivity. Treatment of **16** with NaHMDS at −78°C followed by addition of *tert*-butyl iodoacetate at the same temperature afforded the desired product **20a** in 40% yield along with its diastereomer **20b** in 44% yield (Table 1, entry 3). The diastereomers were separated, and we elected to carry out the subsequent steps with **20a** at this point.

As outlined in Scheme 3, selective reduction of *N*-acyl oxazolidinone **20a** with $LiBH_4$ afforded the hydroxy ester, which was protected with TBSCl and imidazole to provide TBS ether **22**. The *tert*-butyl ester was reduced to the corresponding alcohol **23** by $LiAlH_4$ in near-quantitative yield.

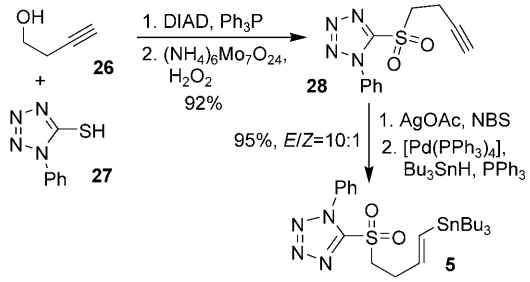


Scheme 3. Preparation of top tetrahydropyran ring **4**. CSA = camphor sulfonic acid, imid = imidazole.

Oxidation of **23** with Dess–Martin periodinane[10] followed by treatment of the resulting aldehyde with hydroxylamine and sodium acetate in ethanol furnished oxime **24**. Exposure of **24** to sodium hypochlorite led to facile intramolecular 1,3-dipolar cycloaddition via the nitrile oxide to afford isoxazoline **7** as a single diastereomer.[11] The tetrahydropyran ring as well as the quaternary stereocenter at C22 were constructed efficiently in the cycloaddition process. Raney nickel catalyzed hydrogenolysis of isoxazoline **7** provided β-hydroxy ketone **25** in 89% yield.[12] L-Selectride reduction of the ketone gave the corresponding alcohol with excellent diastereoselectivity (9:1 d.r., axial/equatorial). The resulting diol was protected as acetonide **4** in the following step. The stereochemical outcome of the key cycloaddition process was confirmed by the NOESY correlations of **7** (Scheme 3).

Initial Approach to the Bottom Tetrahydropyran Ring B

We initially planned to construct the *Z*,*E*-conjugated double bonds at C12–C15 by palladium-mediated Stille coupling[13] between *E*-vinylstannane **5** and *Z*-trisubstituted alkenyl iodide **6**. The preparation of fragment **5** is shown in Scheme 4. Because direct hydrostannation of the terminal

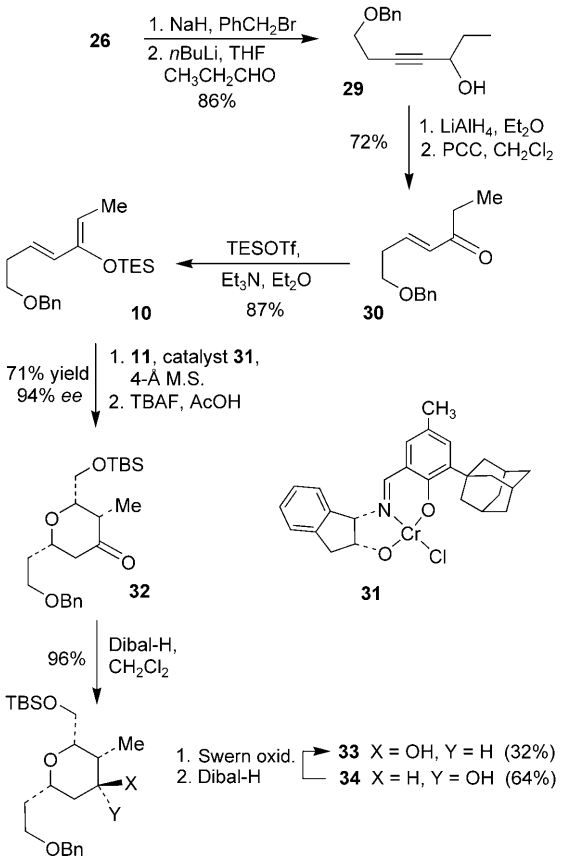


Scheme 4. Preparation of vinyl stannane **5**. DIAD = diisopropyl azodicarboxylate, NBS = *N*-bromosuccinimide.

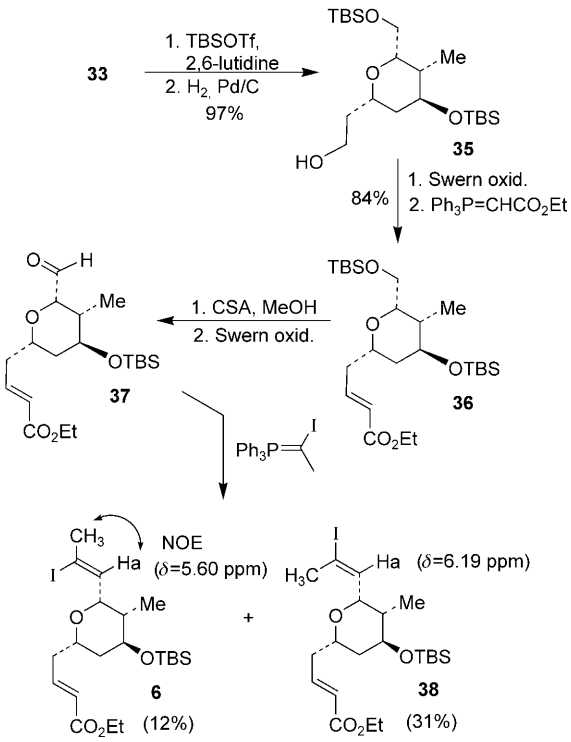
alkyne **26** exhibited low regioselectivity, we used catalytic hydrostannation of 1-bromo-1-alkyne to obtain the regio- and stereodefined *E*-vinylstannane.[14] Thus, 3-butyn-1-ol (**26**) was converted into acetylenic sulfone **28** by Mitsunobu substitution[15] and selective molybdate oxidation.[16] Bromination of **28** with NBS in the presence of silver acetate provided the acetylenic bromide,[17] which was converted into vinylstannane **5** as an *E*/*Z* mixture (10:1) by treatment with tributyltin hydride and catalytic amounts of $[Pd(PPh_3)_4]$ and PPh_3.

The synthesis of the bottom tetrahydropyran ring started from the preparation of nucleophilic diene **10** (Scheme 5). Protection of alcohol **26** with BnBr and NaH gave the benzyl ether in quantitative yield. Deprotonation of the alkyne with *n*BuLi followed by addition of propionaldehyde afforded propargylic alcohol **29** in 86% yield. Reduction of the triple bond with $LiAlH_4$ in THF provided the *E*-allylic alcohol in 93% yield. PCC oxidation produced the α,β-unsaturated ketone **30**. The enone was converted into the Diels–Alder precursor dienol silyl ether **10** by treatment with Et_3N and TESOTf. The chiral tridentate Schiff base chromium(III) complex (1*S*,2*R*)-**31** developed by Jacobsen and co-workers[18] was used as the catalyst (10 mol%) in the asymmetric hetero-Diels–Alder reaction between diene **10** and (*tert*-butyldimethylsilyloxy)acetaldehyde (**11**). The resulting dihydropyran silyl enol ether was treated with TBAF/AcOH in the same reaction flask to remove the TES group and to give the corresponding ketone **32** in 71% yield and with 94% *ee*. Reduction of the ketone with Dibal-H gave axial alcohol **33** and equatorial alcohol **34** as a 1:2 separable mixture in 96% combined yield. The other reducing agents tried, including L-selectride, $NaBH_4$, $LiAlH_4$, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), $LiEt_3BH$, SmI_2, and BH_3, afforded the undesired equatorial hydroxy pyran **34** as the predominant product. Therefore, we recycled **34** back to **33** using Swern oxidation followed by reduction, and the overall conversion yield from **32** into **33** was 53% after one cycle.

As depicted in Scheme 6, protection of secondary alcohol **33** with TBSOTf and subsequent debenzylation with H_2/Pd gave primary alcohol **35** in 97% yield. The spectral data of alcohol **35** is identical to that of the same intermediate in the synthesis of Lee and co-workers.[2] This confirmed the stereochemical outcome of our asymmetric hetero-Diels–



Scheme 5. Preparation of bottom tetrahydropyran ring **33**. Dibal-H = diisobutylaluminum hydride, M.S. = molecular sieves, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, PCC = pyridinium chlorochromate.



Scheme 6. Preparation of vinyl iodide **6**.

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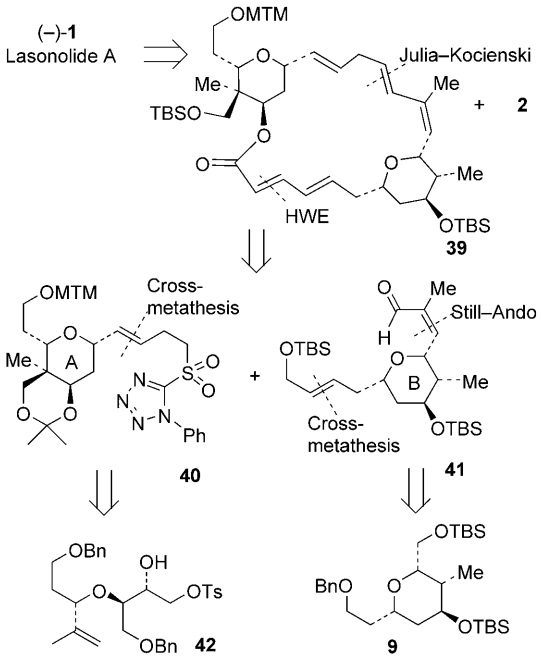
Alder reaction. Alcohol **35** was oxidized to the corresponding aldehyde under Swern conditions and then treated with (carbethoxymethylene)triphenylphosphorane to furnish the *E*-unsaturated ester **36** in 84% yield over 2 steps. Selective removal of the primary TBS protecting group in **36** with CSA in MeOH gave the corresponding primary alcohol, which was subsequently oxidized to its corresponding aldehyde **37**. Stork–Zhao–Wittig reaction[19] converted the aldehyde into the trisubstituted vinyl iodide by condensation with α-iodoethylidene triphenylphosphorane. This protocol typically provides the *Z*-vinyl iodide as the major product and has been utilized in a number of total syntheses.[20] However, in our case, the Wittig reaction between aldehyde **37** and α-iodoethylidene triphenylphosphorane produced a mixture of *Z* (**6**) and *E* (**38**) isomers in a 1:2.6 ratio. The desired *Z*-vinyl iodide **6** was obtained as a minor isomer in 12% yield. The *Z*/*E* stereochemistry in **6** and **38** was determined by comparison of the NMR chemical shifts of the vinyl proton. The shift of Ha in **6** and **38** was 5.60 and 6.19 ppm, respectively. Because the signal of the vinyl hydrogen atom *cis* to iodine should appear at a higher frequency than that *trans* to iodine,[21] we concluded that **6** is the *Z* isomer and **38** is the *E* isomer. The stereochemistry was also confirmed by NOESY correlation analysis of the two isomers. There was interaction between the protons on the methyl group and the vinyl proton Ha in **6**, and this proved their *cis* relationship. On the contrary, no such correlation was found in **38**.

Although fragments **4** and **6** could be obtained in optically pure form, the yield and selectivity for the crucial auxiliary-directed alkylation in fragment **4** and the installation of the *Z*-vinyl iodide in fragment **6** were far from satisfactory for our total synthesis. Our attempts to convert the undesired isomer into the desired one were fruitless. It appeared necessary to modify our synthetic strategy to improve selectivity and efficiency for both tetrahydropyran rings of lasonolide A.

New Strategy for the Two Core Tetrahydropyran Rings

The second-generation retrosynthetic analysis is illustrated in Scheme 7. Disconnection of lasonolide A (**1**) at C25–C26 would give side-chain fragment phosphonium salt **2** and the 20-membered macrolide core **39**, which contains the tetrahydropyran rings A and B. Further disassembly of macrolactone **39** would lead to sulfone **40** and aldehyde **41**. Construction of the macrocycle could be achieved by Julia–Kocienski[22] coupling between **40** and **41** at C14–C15 and subsequent intramolecular HWE reaction[23] at C2–C3. The *E* double bond in fragment **40** was planned to be installed by a cross-metathesis process,[24] and the pyran ring A would be prepared through an intramolecular [3+2] 1,3-dipolar cycloaddition from ether **42**. The *E* olefin in fragment **41** could also be connected by cross-metathesis, and the *Z* double bond would be set up through an HWE reaction with the Ando modification[25] from the same precursor **9** used in our previous approach.

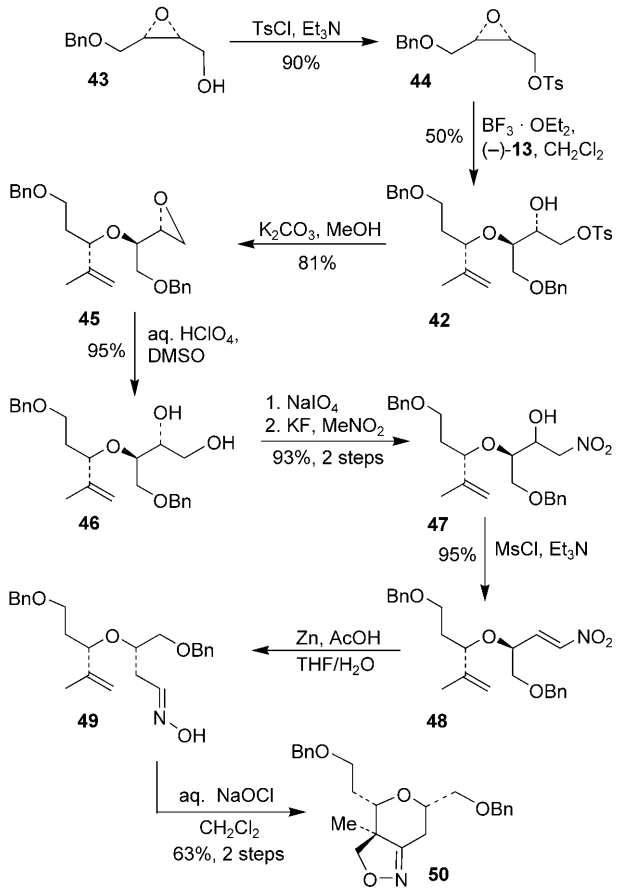


Scheme 7. Modified retrosynthetic analysis of lasonolide A (**1**). MTM = methylthiomethyl, Ts = *p*-toluenesulfonyl.

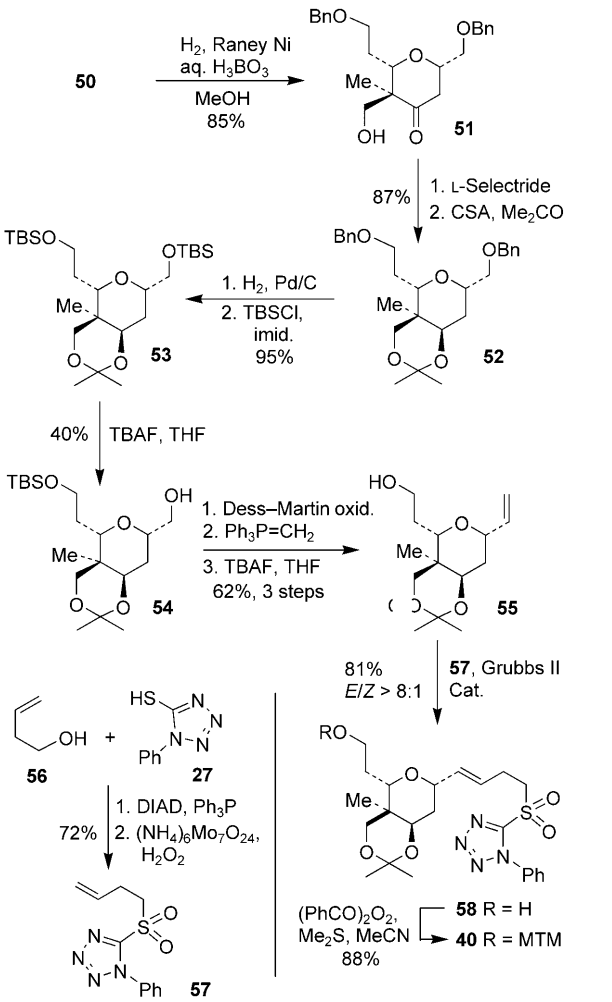
Second-Generation Synthesis of Top Tetrahydropyran Ring A

Construction of top ring A started from the known epoxide **43**[7] (Scheme 8). Tosylation of alcohol **43** gave tosylate **44**. The epoxide was regioselectively opened by alcohol (−)-**13** in the presence of catalytic $BF_3{\cdot}OEt_2$ to provide ether **42** according to the Hoffmann protocol.[26] Epoxidation of hydroxy tosylate **42** with K_2CO_3 afforded epoxide **45**, which was heated with aqueous $HClO_4$ in DMSO to give diol **46**. Oxidative cleavage of diol **46** by $NaIO_4$ followed by condensation of the corresponding aldehyde with nitromethane and KF afforded nitro alcohol **47** as a diastereomeric mixture. The mixture was converted into nitroalkene **48** with MsCl and Et_3N. The resulting nitroalkene was reduced to oxime **49** by using Zn and AcOH. Intramolecular [3+2] cycloaddition of **49** as described in Scheme 3 afforded isoxazoline **50** as a single diastereomer.

Raney nickel catalyzed hydrogenolysis of isoxazoline **50** provided β-hydroxy ketone **51** (Scheme 9). L-Selectride reduction of the ketone gave the corresponding axial alcohol as a single diastereomer. The resulting diol was protected as acetonide **52** in 87% yield over 2 steps. Differentiation of the two primary benzyl groups in **52** by palladium-catalyzed hydrogenolysis or hydrogen transfer was unsuccessful. Lipase-catalyzed selective esterification was also fruitless. Thus, both benzyl groups were removed to provide the corresponding diol, which was then protected as bis-TBS ether **53**. Treatment of **53** with 1.2 equivalents of TBAF provided the desired alcohol **54** in 40% yield along with recovered **53** (32%) and the corresponding diol (24%), which could be converted back into **53**. Alcohol **54** was obtained in 62%



Scheme 8. Preparation of isoxazoline **50** by [3+2] cycloaddition. DMSO = dimethyl sulfoxide.

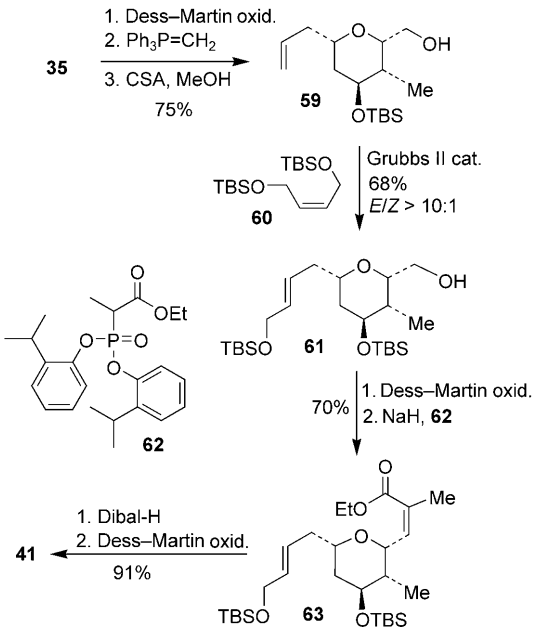


Scheme 9. Preparation of sulfone **40** by cross-metathesis; imid. = imidazole.

yield after one recycle. Dess–Martin oxidation of **54** followed by Wittig reaction afforded the terminal olefin, which was treated with TBAF to give alcohol **55**. Cross metathesis between olefin **55** and sulfone **57** in the presence of Grubbs II catalyst[27] provided *trans* olefin **58** in 81% yield (E/Z > 8:1). Owing to the poor solubility of the homo dimer of **57** in CH_2Cl_2, the cross-metathesis required a dilute reaction solution (0.02 M) and high catalyst loading (35% mol). The concentrated solution only gave incomplete reaction. Protection of alcohol **58** with benzoyl peroxide and Me_2S provided MTM ether **40** in 88% yield.[28] Sulfone **57** was obtained from alcohol **56** by Mitsunobu substitution and selective molybdate oxidation.

Synthesis of Bottom Tetrahydropyran Ring B

Tetrahydropyran **35** obtained from the hetero-Diels–Alder reaction was now employed for the synthesis of **41** (Scheme 10). Dess–Martin oxidation of alcohol **35** and subsequent Wittig reaction furnished the olefin, of which the primary TBS group was selectively removed with CSA to afford alcohol **59** in 75% yield over 3 steps. Cross-metathesis between olefin **59** and bis-TBSO butene **60** in the presence of Grubbs II catalyst provided olefin **61** in 68% yield



Scheme 10. Preparation of aldehyde **41**.

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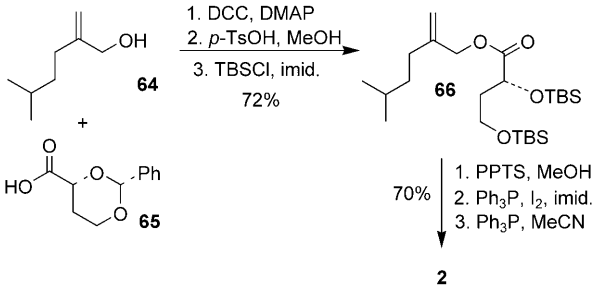
($E/Z > 10{:}1$). It was crucial to control the reaction time and amount of catalyst. Prolonged reaction time (>12 h) or high catalyst loading (>10 mol%) could cause poor yield and isomerization of the allylic double bond. Alcohol **61** was oxidized to the corresponding aldehyde under Dess–Martin conditions. HWE olefination of the above aldehyde according to Ando conditions[25] with ethyl 2-[di(*o*-isopropylphenyl)phosphono]propionate **62** provided the trisubstituted *Z* olefin **63** in 70% yield over 2 steps. Ester **63** was reduced by Dibal-H to the corresponding alcohol. Subsequent Dess–Martin oxidation gave aldehyde **41** in 91% yield over 2 steps.

Synthesis of Phosphonium Salt 2

The preparation of phosphonium salt **2** for the lasonolide A side chain is shown in Scheme 11. Phosphonium salt **2** was prepared from esterification of alcohol **64**[5] with known acid

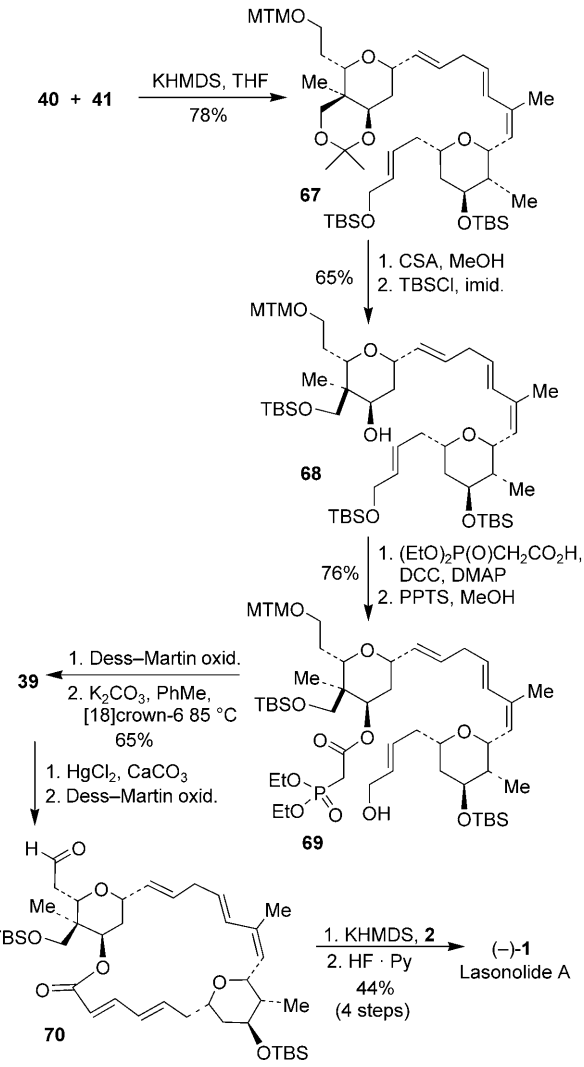


Scheme 11. Preparation of phosphonium salt **2**. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate.

65.[29] The resulting ester was converted into bis-TBS ether **66** by removal of the benzylidene group followed by protection of the resulting diol as TBS ethers. Phosphonium salt **2** was obtained from **66** as described previously.[2]

Synthesis of (−)-Lasonolide A: Fragment Coupling and Macrocyclization

With both sulfone **40** and aldehyde **41** in hand, coupling between the two fragments was carried out under Julia–Kocienski conditions[22] with KHMDS as the base (Scheme 12). The resulting tetraene **67** was treated with CSA in MeOH to remove the acetonide and primary TBS groups. The two primary hydroxy groups of the resulting triol were then selectively protected with TBSCl to give tris-TBS ether **68**. The free secondary alcohol was treated with phosphonoacetic acid, DCC, and DMAP to provide the corresponding ester. Removal of the less hindered allylic primary TBS group by PPTS in MeOH afforded hydroxy phosphonoacetate **69**. Dess–Martin oxidation of alcohol **69** followed by intramolecular HWE olefination[23] furnished macrolactone **39** in 65% yield over 2 steps. Deprotection of the MTM ether with $HgCl_2$ in the presence of $CaCO_3$ in aqueous acetonitrile[30] led to the corresponding alcohol, which was oxidized by Dess–Martin periodinane to provide aldehyde **70**. Subsequent Wittig olefination with **2**-derived phosphorane afforded TBS-protected lasonolide A with a *Z* olefin. Finally, global TBS removal with HF·Py in the presence of excess pyridine furnished (−)-lasonolide A (**1**; $[\alpha]_D^{23}$ −24 (*c* 0.37, $CDCl_3$)). The spectroscopic (^1H and ^{13}C NMR, IR, and optical rotation) and HRMS data of synthetic lasonolide A (**1**) are in agreement with those of the natural product.[1,2]



Scheme 12. Synthesis of lasonolide A (**1**). Py = pyridine.

Conclusions

In summary, we have reported an asymmetric total synthesis of (−)-lasonolide A (**1**), a potent anticancer agent, in 0.12% overall yield and with 32 steps in the longest linear sequence. Our initial approach to the synthesis of the highly substituted tetrahydropyran fragments of lasonolide involved an asymmetric alkylation as the key step. However, asymmetric alkylation of α-alkoxy acetimide derivatives

bearing an α′ chiral center proceeded with poor stereoselectivity under a variety of reaction conditions. We then devised alternative routes involving a 1,3-dipolar cycloaddition and an asymmetric hetero-Diels–Alder reaction for the construction of the highly functionalized tetrahydropyran rings of lasonolide A. The top tetrahydropyran ring was synthesized by intramolecular 1,3-dipolar nitrile oxide cycloaddition to a bicyclic isoxazoline with the stereoselective construction of the quaternary center. The bottom tetrahydropyran ring was assembled by a highly effective Jacobsen catalytic asymmetric hetero-Diels–Alder reaction as the key step. The hetero-Diels–Alder reaction set three stereocenters in a highly diastereoselective manner. Other key reactions featured in the synthesis include a Lewis acid catalyzed epoxide opening to form a substituted ether stereoselectively, an efficient cross-metathesis of functionalized olefins with Grubbs II catalyst, and an intramolecular Horner–Emmons reaction to form the 20-membered macrolide. Eight of the nine chiral centers of (−)-lasonolide A were stereoselectively constructed by asymmetric synthesis. The current synthesis will now pave the way for studies into structure–activity relationships and the synthesis of less complex lasonolide derivatives as anticancer agents.

Experimental Section

General Methods

All moisture-sensitive reactions were carried out under nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether, and benzene: distilled from sodium and benzophenone; dichloromethane, pyridine, triethylamine, and diisopropylethylamine: distilled from CaH_2. All other solvents were of HPLC grade. Column chromatography was performed with 240–400-mesh silica gel under low pressure of 5–10 psi. TLC was carried out with silica gel 60-F-254 plates visualized under UV light and stained with either phosphomolybdic acid or acidic *p*-anisaldehyde. ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz with chemical shifts (δ) reported in ppm. ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz with chemical shifts reported in ppm. Infrared spectra were recorded as thin films on NaCl plates on a Fourier transform spectrometer. Optical rotations were measured with a sodium (589, D-line) lamp polarimeter.

Syntheses

13: 3-Buten-1-ol (10 g, 138 mmol) was added to a suspension of NaH (60 wt% in mineral oil, 6.12 g, 153 mmol) in THF (200 mL) at 0 °C. After 30 min, benzyl bromide (18.3 mL, 153 mmol) was added. The mixture was allowed to warm to room temperature overnight, and the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (pure hexanes→5% EtOAc/hexanes) afforded the benzyl ether (21.4 g, 95%) as a clear oil. A solution of the above olefin (20.0 g, 124 mmol) in CH_2Cl_2 (240 mL) was cooled to −78 °C. O_3 was bubbled through the solution until the blue color persisted for 5 min. O_2 and N_2 were successively bubbled through the solution for 10 min each to purge the remaining ozone. Ph_3P (35.6 g, 136 mmol) was added portionwise at −78 °C, and the mixture was allowed to warm to room temperature overnight. Evaporation of the solvent and purification of the residue by column chromatography (CH_2Cl_2) afforded 3-benzyloxypropanal (**12**; 17.0 g, 85%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.78 (s, 1H), 7.26–7.36 (m, 5H), 4.53 (s, 2H), 3.81 (t, J = 6.0 Hz, 2H), 2.68 ppm (t, J = 6.0 Hz, 2H). A solution of **12** (12.0 g, 73 mmol) in THF (50 mL) was added to isopropenylmagnesium bromide (220 mL, 110 mmol, 0.5 M solution in THF) by cannula at 0 °C. The mixture was stirred for 5 min, and the reaction was quenched with saturated aqueous NH_4Cl followed by 2 N HCl at 0 °C. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) provided racemic allylic alcohol **13** (14.1 g, 94%) as a colorless oil. Ti(O*i*Pr)$_4$ (5.18 mL, 17.7 mmol) was added to a solution of **13** (14.1 g, 68.4 mmol) and (−)-diisopropyl tartrate (6.13 g, 26.2 mmol) in CH_2Cl_2 (220 mL) with 4-Å molecular sieves (3.6 g) at −20 °C. The mixture was stirred for 30 min at −20 °C, treated with a solution of *tert*-butyl hydroperoxide in decane (16.7 mL, 91.7 mmol, 5.5 M), and stirred at −20 °C for 60 h. The reaction was quenched with an aqueous solution of $FeSO_4$ and citric acid at −20 °C, and the mixture was vigorously stirred at 23 °C for 30 min. The above mixture was filtered through celite, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were concentrated and stirred for 1 h with Et_2O and 30% NaOH in brine to hydrolyze the DIPT. After phase separation and extraction, the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (15% EtOAc/hexanes) provided (−)-**13** (6.34 g, 45%, 98% *ee*) as a colorless oil. The *ee* value was determined by ^{19}F NMR spectroscopy of the (−)-MTPA (2-methoxy-2-trifluoromethyl-2-phenylacetic acid) ester of (−)-**13**. $[\alpha]_D^{23}$ = −5.54 (c = 3.05, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3429, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5H), 5.01 (s, 1H), 4.85 (s, 1H), 4.51 (s, 2H), 4.24 (dd, J = 7.0, 5.0 Hz, 1H), 3.67 (ddd, J = 9.5, 6.0, 6.0 Hz, 1H), 3.60 (ddd, J = 9.5, 7.0, 5.5 Hz, 1H), 3.33 (s, 1H, OH), 1.85–1.88 (m, 2H), 1.74 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.2, 138.1, 128.5, 127.7, 110.7, 74.1, 73.3, 68.4, 34.8, 18.1 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Na$: 229.1205 $[M+Na]^+$; found: 229.1206.

8: A solution of (−)-**13** (1.38 g, 6.7 mmol) in THF (20 mL) was added to a suspension of potassium hydride (2.68 g, 20.1 mmol, 30% dispersion in mineral oil) in THF (20 mL) at 0 °C. The mixture was stirred at 23 °C for 10 min and cooled to 0 °C, and a solution of bromoacetic acid (1.02 g, 7.27 mmol) in THF (5 mL) was added dropwise. The mixture was warmed to 23 °C overnight, and the reaction was quenched with H_2O (50 mL). The mixture was diluted with 2 N NaOH and Et_2O and separated. The aqueous layer was acidified to pH 2 with concentrated HCl and extracted four times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc/hexanes) to provide acid **8** (1.59 g, 90%) as a yellow oil. $[\alpha]_D^{23}$ = −25 (c = 7.0, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3031, 1730, 1115 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.57 (s, 1H, CO_2H), 7.26–7.36 (m, 5H), 4.98 (s, 1H), 4.96 (s, 1H), 4.53 (s, 2H), 4.38–4.64 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 79.5 Hz, 2H), 3.95 (dd, J = 8.5, 4.5 Hz, 1H), 3.67 (ddd, J = 9.5, 7.0, 5.5 Hz, 1H), 3.58 (ddd, J = 9.5, 6.0, 6.0 Hz, 1H), 1.99–2.05 (m, 1H), 1.77–1.83 (m, 1H), 1.67 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 143.0, 137.9, 128.6, 128.4, 128.1, 128.0, 127.8, 114.9, 82.4, 73.1, 67.1, 65.1, 33.6, 16.5 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{20}O_4Na$: 287.1260 $[M+Na]^+$; found: 287.1258.

General procedure for the preparation of acyl oxazolidinones **14**–**17**: *i*Pr$_2$NEt (1.3 mL, 7.5 mmol) was added to a solution of **8** (1.30 g, 5.0 mmol) in THF (10 mL) followed by PivCl (0.8 mL, 6.5 mmol) at −78 °C. The mixture was warmed to 23 °C and stirred for 3 h. In a separate flask, a solution of (4*R*)-4-isopropyloxazolidin-2-one (900 mg, 7.0 mmol) in THF (15 mL) was cooled to −78 °C and treated with *n*BuLi (4.4 mL, 7.0 mmol, 1.6 M in hexane). The solution of lithiated oxazolidinone was added to the mixed anhydride, precooled at −78 °C, by cannula. The mixture was warmed to 23 °C for 2 h, the reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give **16** (1.38 g, 74%). $[\alpha]_D^{23}$ = −76 (c = 1.8, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1781, 1719, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.34 (m, 5H), 4.93–4.95 (m, 2H), 4.55 (AB, J_{AB} = 18.0 Hz, $\Delta\nu_{AB}$ = 66.5 Hz, 2H), 4.51 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 16.0 Hz, 2H), 4.42 (dt, J = 8.5, 3.5 Hz, 1H), 4.32 (dd, J = 8.5, 8.5 Hz, 1H), 4.25 (dd, J = 8.5, 3.5 Hz, 1H), 3.96 (dd, J = 8.0, 5.5 Hz, 1H), 3.66 (ddd, J = 9.5, 6.5, 6.5 Hz, 1H), 3.57 (ddd, J = 9.5, 6.5, 6.5 Hz, 1H), 2.38–2.46 (m, 1H), 2.01–

2.09 (m, 1H), 1.80–1.88 (m, 1H), 1.68 (s, 3H), 0.91 (d, J=7.0 Hz, 3H), 0.86 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.3, 154.0, 143.5, 138.7, 128.3, 127.7, 127.5, 114.8, 81.9, 73.0, 67.7, 67.0, 64.3, 58.2, 33.9, 28.2, 17.9, 16.7, 14.6 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{29}NO_5Na$: 398.1943 $[M+Na]^+$; found: 398.1949.

14: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.18–7.36 (m, 10H), 4.99 (s, 2H), 4.66 and 4.51 (AB, J_{AB}=18.0 Hz, $\Delta\nu_{AB}$=71.0 Hz, 2H), 4.62–4.66 (m, 1H), 4.53 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=19.0 Hz, 2H), 4.16–4.24 (m, 2H), 4.04 (dd, J=8.0, 5.0 Hz, 1H), 3.69–3.75 (m, 1H), 3.58–3.64 (m, 1H), 3.28 and 2.80 (ABX, J_{AB}=13.5 Hz, J_{AX}=9.5 Hz, J_{BX}=3.0 Hz, $\Delta\nu_{AB}$=241.5 Hz, 2H), 2.06–2.14 (m, 1H), 1.85–1.92 (m, 1H), 1.73 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.4, 153.4, 143.6, 138.7, 135.1, 129.5, 129.1, 129.0, 128.4, 127.8, 127.5, 127.4, 114.8, 81.8, 73.0, 67.8, 67.3, 67.0, 54.8, 37.7, 34.0, 16.7 ppm.

15: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.19–7.30 (m, 10H), 5.00 (s, 2H), 4.62–4.69 (m, 1H), 4.64 and 4.53 (AB, J_{AB}=18.0 Hz, $\Delta\nu_{AB}$=45.0 Hz, 2H), 4.53 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=18.5 Hz, 2H), 4.38–4.46 (m, 2H), 4.07 (dd, J=8.0, 5.5 Hz, 1H), 3.68–3.74 (m, 1H), 3.58–3.64 (m, 1H), 3.28 and 2.82 (ABX, J_{AB}=13.5 Hz, J_{AX}=9.5 Hz, J_{BX}=3.0 Hz, $\Delta\nu_{AB}$=231.5 Hz, 2H), 2.06–2.12 (m, 1H), 1.85–1.91 (m, 1H), 1.72 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.3, 153.4, 143.5, 138.7, 135.1, 129.5, 129.0, 128.6, 128.4, 128.1, 127.7, 127.5, 114.9, 81.6, 73.0, 67.7, 67.2, 67.0, 54.8, 37.7, 33.9, 16.7 ppm.

17: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.33 (m, 5H), 4.94 (s, 2H), 4.40–4.63 (m, 6H), 3.94–4.04 (m, 3H), 3.72–3.78 (m, 1H), 3.54–3.60 (m, 1H), 2.02–2.08 (m, 1H), 1.80–1.86 (m, 1H), 1.67 ppm (s, 3H).

General procedure of alkylation for the preparation of α-alkylated acyl oxazolidinones **18a**–**21a** and **18b**–**21b**: NaHMDS (4.3 mL, 4.3 mmol, 1 M in THF) was added to a solution of **16** (1.34 g, 3.57 mmol) in THF at −78 °C. After the mixture was stirred for 1 h at −78 °C, *tert*-butyl iodoacetate (1.57 g, 6.5 mmol) was added. After 30 min, the reaction was quenched by the addition of saturated NH_4Cl, and the mixture was warmed to 23 °C. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by column chromatography (15–25% EtOAc/hexanes) provided **20a** (698 mg, 40%) along with its diastereomer **20b** (767 mg, 44%).

20a: $[\alpha]_D^{23}$=−57 (c=3.7, $CHCl_3$); IR (neat): 1781, 1715, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26–7.34 (m, 5H), 5.36 (dd, J=7.1, 5.2 Hz, 1H), 4.93 (s, 1H), 4.88 (s, 1H), 4.47 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=25.9 Hz, 2H), 4.38 (dt, J=5.8, 4.0 Hz, 1H), 4.16 (d, J=5.8 Hz, 2H), 3.88 (dd, J=8.2, 5.3 Hz, 1H), 3.62 (ddd, J=9.3, 6.8, 6.8 Hz, 1H), 3.55 (ddd, J=9.4, 6.3, 6.3 Hz, 1H), 2.69 (ABX, J_{AB}=15.6 Hz, J_{AX}=7.1 Hz, J_{BX}=5.2 Hz, $\Delta\nu_{AB}$=57.3 Hz, 2H), 2.31–2.39 (m, 1H), 1.94–2.02 (m, 1H), 1.71–1.79 (m, 1H), 1.68 (s, 3H), 1.42 (s, 9H), 0.88 (d, J=7.0 Hz, 3H), 0.85 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.6, 168.8, 153.5, 143.9, 138.8, 128.3, 127.5, 127.4, 114.6, 80.9, 80.5, 72.7, 71.5, 67.1, 63.8, 58.4, 39.2, 33.9, 28.1, 28.0, 17.9, 16.5, 14.7 ppm; HRMS (ESI): m/z calcd for $C_{27}H_{39}NO_7Na$: 512.2625 $[M+Na]^+$; found: 512.2644.

20b: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26–7.34 (m, 5H), 5.44 (dd, J=8.5, 5.0 Hz, 1H), 4.96 (s, 1H), 4.78 (s, 1H), 4.42 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=18.5 Hz, 2H), 4.33 (dt, J=8.0, 3.0 Hz, 1H), 4.20 (t, J=9.0 Hz, 1H), 4.14 (dd, J=9.0, 3.0 Hz, 1H), 4.04 (dd, J=8.0, 4.5 Hz, 1H), 3.22–3.50 (m, 2H), 2.55 (ABX, J_{AB}=16.0 Hz, J_{AX}=8.0 Hz, J_{BX}=5.0 Hz, $\Delta\nu_{AB}$=40.5 Hz, 2H), 2.24–2.32 (m, 1H), 1.94–2.02 (m, 1H), 1.69–1.77 (m, 1H), 1.61 (s, 3H), 1.39 (s, 9H), 0.86 (d, J=7.0 Hz, 3H), 0.81 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.1, 168.9, 153.8, 144.6, 138.5, 128.3, 127.7, 127.5, 115.3, 83.8, 81.0, 73.2, 72.9, 67.0, 63.5, 58.5, 39.2, 33.6, 28.2, 28.0, 18.0, 16.5, 14.5 ppm; HRMS (ESI): m/z calcd for $C_{27}H_{39}NO_7Na$: 512.2625 $[M+Na]^+$; found: 512.2636.

18a: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.19–7.32 (m, 10H), 5.37 (t, J=6.5 Hz, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 4.59–4.65 (m, 1H), 4.52 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=16.5 Hz, 2H), 4.12 (dd, J=9.5, 3.0 Hz, 1H), 4.07 (t, J=8.0 Hz, 1H), 3.94 (dd, J=8.0, 5.5 Hz, 1H), 3.65 (m, 1H), 3.53–3.59 (m, 1H), 3.32 (dd, J=13.0, 3.0 Hz, 1H), 2.66–2.81 (m, 3H), 1.94–2.02 (m, 1H), 1.74–1.82 (m, 1H), 1.69 (s, 3H), 1.44 ppm (s, 9H).

18b: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.22–7.32 (m, 10H), 5.49 (dd, J=7.5, 5.5 Hz, 1H), 5.06 (s, 1H), 4.87 (s, 1H), 4.60–4.66 (m, 1H), 4.49 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=16.5 Hz, 2H), 4.01–4.17 (m, 3H), 3.54–3.60 (m, 1H), 3.48–3.54 (m, 1H), 3.35 (dd, J=13.5, 3.5 Hz, 1H), 2.69 (dd, J=16.0, 5.5 Hz, 1H), 2.58–2.65 (m, 2H), 1.98–2.06 (m, 1H), 1.74–1.82 (m, 1H), 1.70 (s, 3H), 1.44 ppm (s, 9H).

19a: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.17–7.31 (m, 10H), 5.42 (t, J=6.5 Hz, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 4.65–4.71 (m, 1H), 4.51 (AB, J_{AB}=11.5 Hz, $\Delta\nu_{AB}$=30.5 Hz, 2H), 4.13–4.22 (m, 2H), 4.06 (dd, J=8.0, 5.5 Hz, 1H), 3.62–3.68 (m, 1H), 3.53–3.58 (m, 1H), 3.32 (dd, J=13.0, 3.0 Hz, 1H), 2.62–2.80 (m, 3H), 1.96–2.04 (m, 1H), 1.74–1.83 (m, 1H), 1.72 (s, 3H), 1.43 ppm (s, 9H).

19b: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.20–7.33 (m, 10H), 5.42 (dd, J=7.5, 5.0 Hz, 1H), 4.95 (s, 1H), 4.82 (s, 1H), 4.60–4.66 (m, 1H), 4.48 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=16.5 Hz, 2H), 4.17 (d, J=5.5 Hz, 2H), 4.07 (dd, J=8.0, 5.5 Hz, 1H), 3.52–3.56 (m, 1H), 3.48–3.52 (m, 1H), 3.29 (dd, J=13.5, 3.0 Hz, 1H), 2.70–2.77 (m, 2H), 2.65 (dd, J=16.0, 7.5 Hz, 1H), 1.96–2.04 (m, 1H), 1.73–1.81 (m, 1H), 1.68 (s, 3H), 1.46 ppm (s, 9H).

21a: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25–7.33 (m, 5H), 5.38 (t, J=6.5 Hz, 1H), 4.94 (s, 1H), 4.93 (s, 1H), 4.49 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=23.0 Hz, 2H), 4.34–4.40 (m, 1H), 4.24–4.30 (m, 1H), 3.92–3.96 (m, 3H), 3.60–3.65 (m, 1H), 3.51–3.57 (m, 1H), 2.78 and 2.66 (ABX, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{BX}=6.0 Hz, $\Delta\nu_{AB}$=60.0 Hz, 2H), 1.90–1.98 (m, 1H), 1.73–1.81 (m, 1H), 1.69 (s, 3H), 1.41 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.0, 169.1, 143.9, 138.8, 128.3, 127.5, 127.4, 114.5, 81.1, 80.5, 72.7, 71.0, 67.0, 62.4, 42.6, 39.1, 34.0, 28.0, 16.7 ppm.

21b: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25–7.33 (m, 5H), 5.44 (dd, J=7.5, 6.0 Hz, 1H), 4.94 (s, 1H), 4.83 (s, 1H), 4.47 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=15.5 Hz, 2H), 4.37–4.43 (m, 1H), 4.06 (dd, J=8.5, 5.5 Hz, 1H), 3.94–4.00 (m, 2H), 3.51–3.57 (m, 1H), 3.44–3.50 (m, 1H), 2.72 and 2.61 (ABX, J_{AB}=16.0 Hz, J_{AX}=7.5 Hz, J_{BX}=5.5 Hz, $\Delta\nu_{AB}$=56.0 Hz, 2H), 1.93–2.01 (m, 1H), 1.72–1.80 (m, 1H), 1.64 (s, 3H), 1.43 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=172.3, 168.9, 153.1, 145.0, 138.5, 128.4, 127.7, 127.5, 114.4, 83.1, 81.1, 73.0, 72.5, 66.9, 62.4, 42.5, 39.0, 33.8, 28.1, 16.7 ppm.

22: MeOH (70 μL) was added to a solution of **20a** (517 mg, 1.06 mmol) in THF (4 mL) followed by lithium borohydride (2.11 mL, 2.11 mmol, 1 M in THF) at 0 °C. The mixture was stirred at 0 °C for 3 h, and the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted twice with EtOAc. The organic layers were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (25% EtOAc/hexanes) to give the alcohol (308 mg, 80%) as a clear oil. $[\alpha]_D^{23}$=−30 (c=1.9, $CHCl_3$); IR (neat): $\tilde{\nu}$=3454, 1727, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29–7.35 (m, 5H), 4.94 (s, 1H), 4.89 (s, 1H), 4.52 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=18.5 Hz, 2H), 4.08 (dd, J=9.5, 4.5 Hz, 1H), 3.74–3.85 (m, 1H), 3.69–3.75 (m, 2H), 3.45–3.51 (m, 2H), 2.45 (ABX, J_{AB}=15.0 Hz, J_{AX}=7.5 Hz, J_{BX}=6.0 Hz, $\Delta\nu_{AB}$=45.7 Hz, 2H), 1.80–1.87 (m, 1H), 1.70–1.79 (m, 1H), 1.67 (s, 3H), 1.43 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.7, 144.7, 137.9, 128.5, 127.9, 127.8, 113.5, 80.6, 79.4, 74.0, 73.0, 66.9, 63.3, 38.7, 33.7, 28.1, 16.8 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{32}O_5Na$: 387.2148 $[M+Na]^+$; found: 387.2137. Imidazole (140 mg, 2.06 mmol) was added to a solution of the above alcohol (300 mg, 0.82 mmol) in *N*,*N*-dimethylformamide (DMF; 4 mL) followed by *tert*-butyldimethylsilyl chloride (186 mg, 1.24 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) provided TBS ether **22** (326 mg, 86%). $[\alpha]_D^{23}$=−39 (c=1.0, $CHCl_3$); IR (neat): $\tilde{\nu}$=1729, 1112, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.33 (m, 5H), 4.91 (s, 2H), 4.48 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=15.0 Hz, 2H), 4.05 (dd, J=7.8, 5.1 Hz, 1H), 3.74–3.83 (m, 1H), 3.65 (dd, J=10.8, 4.5 Hz, 1H), 3.44–3.57 (m, 3H), 2.43 (ABX, J_{AB}=15.5 Hz, J_{AX}=6.9 Hz, J_{BX}=5.4 Hz, $\Delta\nu_{AB}$=53.5 Hz, 2H), 1.84–1.93 (m, 1H), 1.70–1.79 (m, 1H), 1.66 (s, 3H), 1.43 (s, 9H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.0, 144.6, 138.6, 128.3, 127.5, 127.4, 113.6, 80.1, 79.1, 73.7, 72.9, 67.1, 63.6, 38.9, 34.1, 28.1, 25.9, 18.3,

16.6, −5.4 ppm; HRMS (ESI): *m/z* calcd for $C_{27}H_{46}O_5SiNa$: 501.3012 $[M+Na]^+$; found: 501.3022.

23: A solution of **22** (300 mg, 0.62 mmol) in Et_2O (25 mL) was added dropwise to a suspension of $LiAlH_4$ (45 mg, 1.18 mmol) in Et_2O (1 mL) at 0 °C. After 2 h at 0 °C, aqueous potassium sodium tartrate was added, and the mixture was vigorously stirred for 2 h at room temperature until two clear phases appeared. The aqueous phase was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave alcohol **21** (254 mg, 99%). $[\alpha]_D^{23}=-51$ ($c=1.7$, $CHCl_3$); IR (neat): $\tilde{\nu}=3436$, 1089, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.26$–7.34 (m, 5H), 4.95 (s, 1H), 4.94 (s, 1H), 4.48 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=17.5$ Hz, 2H), 4.11 (dd, $J=8.5$, 5.5 Hz, 1H), 3.69–3.74 (m, 3H), 3.51–3.56 (m, 3H), 3.47 (dt, $J=9.0$, 6.0 Hz, 1H), 1.81–1.87 (m, 2H), 1.72–1.77 (m, 2H), 1.70 (s, 3H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=144.3$, 138.5, 128.3, 127.6, 127.5, 114.5, 79.1, 75.7, 73.0, 66.9, 64.1, 60.3, 35.1, 34.1, 25.9, 18.2, 16.5, −5.4 ppm; LRMS (ESI): $m/z=431.4$ $[M+Na]^+$.

24: Dess–Martin periodinane (413 mg, 0.97 mmol) was added to a solution of **21** (267 mg, 0.65 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was warmed to room temperature for 6 h, and the reaction was quenched with aqueous Na_2SO_3 and $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave the aldehyde (240 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$): $\delta=9.73$ (s, 1H), 7.29–7.37 (m, 5H), 4.93 (s, 2H), 4.48 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=16.0$ Hz, 2H), 4.06 (dd, $J=7.5$, 5.0 Hz, 1H), 3.84–3.92 (m, 1H), 3.73 (dd, $J=10.0$, 4.0 Hz, 1H), 3.49–3.57 (m, 2H), 3.47 (dt, $J=9.0$, 6.0 Hz, 1H), 2.56 (ABMX, $J_{AB}=16.0$ Hz, $J_{AX}=7.0$ Hz, $J_{BX}=6.0$ Hz, $J_{AM}=3.0$ Hz, $J_{BM}=2.0$ Hz, $\Delta\nu_{AB}=47.5$ Hz, 2H), 1.84–1.90 (m, 1H), 1.72–1.77 (m, 1H), 1.64 (s, 3H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=201.7$, 144.2, 138.5, 128.4, 127.6, 127.5, 114.4, 79.5, 73.0, 72.4, 66.8, 63.8, 47.0, 34.0, 25.9, 18.2, 16.5, −5.4 ppm. The above aldehyde (240 mg, 0.59 mmol) and NaOAc (194 mg, 2.36 mmol) were dissolved in EtOH (4 mL). Hydroxylamine hydrochloride (123 mg, 1.77 mmol) was added to the solution at room temperature. The mixture was stirred for 1 h and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to provide oxime **24** (265 mg, crude, used without further characterization).

7: A solution of crude **24** in CH_2Cl_2 (6 mL) was treated with bleach (3 mL, 4% aqueous sodium hypochlorite) at room temperature for 4 h. The reaction was quenched with aqueous Na_2SO_3 and $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) gave isoxazoline **7** (230 mg, 82% over 2 steps) as a clear oil. $[\alpha]_D^{23}=-23$ ($c=1.9$, $CHCl_3$); IR (neat): $\tilde{\nu}=3060$, 1462, 1100, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.28$–7.35 (m, 5H), 4.48 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=25.0$ Hz, 2H), 4.06–3.86 (AX, $J_{AX}=8.0$ Hz, $\Delta\nu_{AX}=102.0$ Hz, 2H), 3.68 (ABX, $J_{AB}=11.0$ Hz, $J_{AX}=5.0$ Hz, $J_{BX}=5.0$ Hz, $\Delta\nu_{AB}=37.0$ Hz, 2H), 3.52–3.58 (m, 3H), 3.38–3.42 (m, 1H), 2.63 (dd, $J=14.5$, 3.0 Hz, 1H), 2.27 (dd, $J=14.5$, 11.5 Hz, 1H), 1.80–1.88 (m, 1H), 1.53–1.59 (m, 1H), 1.18 (s, 3H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=161.6$, 138.2, 128.4, 127.7, 80.9, 77.7, 76.7, 73.1, 66.3, 65.5, 53.6, 31.7, 25.8, 25.7, 18.3, 15.8, −5.3 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{37}NO_4Na$: 442.2390 $[M+Na]^+$; found: 442.2397.

25: Boric acid (120 mg, 1.93 mmol) and a spatula tip (estimated 10–20 mg) of an aqueous suspension of W-2 Raney nickel were added to a solution of **7** (202 mg, 0.48 mmol) in methanol/water (5 mL/1 mL). The mixture was placed under hydrogen by repeated (>5×) evacuation and flushing with H_2 gas by means of a balloon attached to a three-way stopcock. The mixture was stirred vigorously for 4 h and then filtered through celite into a separating funnel containing saturated aqueous $NaHCO_3$ and CH_2C1_2. After separation, the aqueous layer was extracted two more times with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (25% EtOAc/hexanes) gave hydroxy ketone **25** (180 mg, 89%) as a clear oil. $[\alpha]_D^{23}=-68$ ($c=1.4$, $CHCl_3$); IR (neat): $\tilde{\nu}=3459$, 1710, 1113, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.26$–7.35 (m, 5H), 4.50 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=38.5$ Hz, 2H), 3.80–3.86 (m, 2H), 3.62–3.66 (m, 5H), 3.44 (dd, $J=12.0$, 6.0 Hz, 1H), 2.65–2.72 (m, 1H), 2.57 (br s, 1H), 2.26 (dd, $J=14.5$, 2.5 Hz, 1H), 1.77–1.83 (m, 2H), 1.04 (s, 3H), 0.89 (s, 9H), 0.05 ppm (d, $J=3.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=214.0$, 138.4, 128.4, 127.7, 127.6, 77.4, 76.5, 67.2, 65.5, 64.2, 54.1, 41.3, 29.4, 25.8, 18.3, 14.7, −5.2, −5.3 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{38}O_5SiNa$: 445.2387 $[M+Na]^+$; found: 445.2391.

4: L-Selectride (0.24 mL, 0.24 mmol, 1 M in THF) was added to a solution of **25** (34 mg, 0.08 mmol) in THF (2 mL) at −78 °C. After 1 h, the reaction was quenched with H_2O. Upon warming to room temperature, 1 N NaOH and 30% H_2O_2 were added, and the mixture was stirred for 1 h at room temperature. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (35% EtOAc/hexanes) gave the diol (28 mg, 82%) along with its diastereomer (3 mg, 9%). $[\alpha]_D^{23}=-48$ ($c=3.3$, $CHCl_3$); IR (neat): $\tilde{\nu}=3391$, 1105, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.26$–7.37 (m, 5H), 4.52 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=16.0$ Hz, 2H), 4.09 (dd, $J=9.0$, 2.0 Hz, 1H), 3.97 (br s, 1H), 3.88–3.92 (m, 1H), 3.80–3.86 (m, 1H), 3.51–3.66 (m, 7H), 1.79–1.85 (m, 1H), 1.65–1.71 (m, 1H), 1.56–1.62 (m, 1H), 1.49–1.55 (m, 1H), 0.89 (s, 9H), 0.73 (s, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=137.9$, 128.5, 127.9, 127.8, 75.0, 73.4, 72.9, 71.9, 69.9, 68.7, 66.4, 40.2, 32.3, 30.0, 25.9, 18.4, 15.0, −5.2 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{40}NO_5Na$: 447.2543 $[M+Na]^+$; found: 447.2567. 2,2-Dimethoxypropane (10 μL, 0.1 mmol) and camphor sulfonic acid (0.6 mg, 0.0025 mmol) were added to a solution of the above diol (27 mg, 0.05 mmol) in acetone (2 mL) at room temperature. After the mixture was stirred for 3 h, it was neutralized with triethylamine (0.1 mL) and concentrated. Purification by column chromatography (10% EtOAc/hexanes) afforded acetonide **4** (28 mg, 95%). $[\alpha]_D^{23}=-40$ ($c=1.4$, $CHCl_3$); IR (neat): $\tilde{\nu}=1102$, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.26$–7.37 (m, 5H), 4.51 (AB, $J_{AB}=12.0$ Hz, $\Delta\nu_{AB}=33.0$ Hz, 2H), 4.19 (dd, $J=10.5$, 1.5 Hz, 1H), 3.88 (t, $J=3.0$ Hz, 1H), 3.68–3.77 (m, 2H), 3.51–3.64 (m, 5H), 1.78–1.83 (m, 1H), 1.71–1.77 (m, 1H), 1.59–1.68 (m, 1H), 1.42–1.48 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 0.89 (s, 9H), 0.74 (s, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=138.8$, 128.3, 127.7, 127.4, 98.4, 73.0, 72.8, 72.0, 71.9, 68.4, 66.4, 66.2, 34.6, 29.9, 29.5, 26.0, 18.8, 18.4, 14.8, −5.2 ppm; HRMS (ESI): *m/z* calcd for $C_{26}H_{44}O_5SiNa$: 487.2856 $[M+Na]^+$; found: 487.2848.

28: 1-Phenyl-1*H*-tetrazole-5-thiol (1.17 g, 6.6 mmol) was added to a solution of 3-butyn-1-ol (385 mg, 5.5 mmol) in THF (15 mL) followed by triphenylphosphine (1.73 g, 6.6 mmol) and DIAD (1.27 mL, 6.6 mmol) at 0 °C. The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc/hexanes) to provide the sulfide (1.21 g, 97%) as a clear oil. $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (2.35 g, 1.9 mmol) was added to a solution of above sulfide (219 mg, 0.95 mmol) in EtOH (6 mL) and H_2O_2 (6 mL, 30%) at 0 °C. The mixture was stirred at room temperature overnight, and the reaction was quenched with aqueous Na_2SO_3. The mixtutre was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (25% EtOAc/hexanes) afforded sulfone **28** (238 mg, 95%). IR (neat): $\tilde{\nu}=3292$, 1351, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.58$–7.64 (m, 5H), 3.91 (t, $J=7.0$ Hz, 2H), 2.88 (dt, $J=7.0$, 2.7 Hz, 2H), 2.06 ppm (t, $J=2.7$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=153.1$, 132.9, 131.6, 129.8, 125.2, 78.1, 71.6, 54.5, 13.4 ppm.

5: AgOAc (25 mg, 0.15 mmol) was added to a solution of **28** (131 mg, 0.5 mmol) in acetone (2 mL) followed by NBS (134 mg, 0.75 mmol). The mixture was stirred at room temperature overnight in the dark, and the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (25% EtOAc/hexanes) to provide the bromoalkyne (173 mg, 100%). A solution of Bu_3SnH (0.31 mL, 1.15 mmol) in THF (2 mL) was added to a solution of above bromoalkyne (173 mg, 0.5 mmol), Ph_3P (14 mg,

0.05 mmol), and [Pd(PPh$_3$)$_4$] (29 mg, 0.025 mmol) in THF (4 mL) at −78 °C by syringe pump over 30 min. After the mixture was stirred at room temperature for 1 h, it was concentrated in vacuo and purified by column chromatography (10% EtOAc/hexanes) to provide vinyl stannane **5** (264 mg, 95%) as an *E*/*Z* (10:1) mixture. IR (neat): $\tilde{\nu}$ = 1597, 1349, 1152 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.58–7.62 (m, 5H), 6.14 (d, *J* = 19.0 Hz, 2H), 5.93 (dt, *J* = 19.0, 6.0 Hz, 2H), 3.90–3.98 (m, 2H), 2.73–2.82 (m, 2H), 1.44–1.52 (m, 6H), 1.28–1.36 (m, 6H), 0.82–0.94 ppm (m, 15H); HRMS (EI): *m*/*z* calcd for $C_{19}H_{29}SN_4O_2Sn$: 497.1033 [*M*−Bu]$^+$; found: 497.1032.

29: Compound **26** (1.88 g, 26.8 mmol) was added to a suspension of NaH (60 wt% in mineral oil, 2.14 g, 53.3 mmol) in THF (60 mL) at 0 °C. After 30 min, tetrabutylammonium iodide (500 mg, 1.35 mmol) and benzyl bromide (3.5 mL, 29.2 mmol) were added. The mixture was allowed to warm to room temperature overnight, and the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (pure hexanes→5% EtOAc/hexanes) afforded the benzyl ether (4.17 g, 97%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.31–7.37 (m, 5H), 4.57 (s, 2H), 3.61 (t, *J* = 6.9 Hz, 2H), 2.52 (dt, *J* = 6.9, 2.4 Hz, 2H), 2.01 ppm (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.0, 128.4, 127.7, 81.3, 73.0, 69.4, 68.1, 19.9 ppm. *n*BuLi (1.6 M in hexane, 16.3 mL, 26.1 mmol) was added to a solution of above alkyne (4.17 g, 26.1 mmol) in THF (80 mL) at −78 °C. After 30 min, propionaldehyde was added. The mixture was stirred at −78 °C for 1 h, and the reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) afforded propargyl alcohol **29** (4.87 g, 86%) as a clear oil. IR (neat): $\tilde{\nu}$ = 3400, 1454, 1099 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.26–7.34 (m, 5H), 4.53 (s, 2H), 4.25 (dt, *J* = 6.3, 1.8 Hz, 1H), 3.56 (t, *J* = 6.9 Hz, 2H), 3.08 (br s, 1H), 2.51 (dt, *J* = 6.9, 1.8 Hz, 2H), 1.63–1.70 (m, 2H), 0.98 ppm (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 137.9, 128.4, 127.7, 82.5, 81.6, 72.8, 68.3, 63.5, 30.9, 20.0, 9.5 ppm.

30: A solution of **29** (4.87 g, 22.3 mmol) in THF (20 mL) was added to a suspension of $LiAlH_4$ (1.69 g, 44.6 mmol) in THF (60 mL) by cannula at 0 °C. The mixture was stirred at room temperature for 24 h, and the reaction was quenched with H_2O (2 mL) at 0 °C. Next, 2 N HCl was added, and the mixture was stirred for 2 h at room temperature until two clear phases appeared. The aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) afforded the allylic alcohol (4.56 g, 93%) as a clear oil. IR (neat): $\tilde{\nu}$ = 3400, 1454, 1098 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.26–7.34 (m, 5H), 5.62 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.51 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.49 (s, 2H), 3.91 (dt, *J* = 6.5, 6.5 Hz, 1H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.84 (br s, 1H), 2.35 (dt, *J* = 6.5, 6.5 Hz, 2H), 1.43–1.60 (m, 2H), 0.89 ppm (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 138.4, 135.1, 128.4, 127.8, 127.7, 127.6, 74.1, 72.8, 69.8, 32.7, 30.0, 9.9 ppm. PCC (8.95 g, 41.4 mmol) was added to a solution of the above alcohol (4.56 g, 20.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was stirred at room temperature for 3 h and filtered though celite while being eluted with Et_2O, and the filtrate was concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) afforded enone **30** (3.47 g, 77%) as a clear oil. IR (neat): $\tilde{\nu}$ = 1673, 1632, 1101 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.26–7.31 (m, 5H), 6.84 (dt, *J* = 16.0, 7.0 Hz, 1H), 6.15 (d, *J* = 16.0 Hz, 1H), 4.51 (s, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.56 (q, *J* = 7.5, 2H), 2.51(dt, *J*=6.5, 6.5 Hz, 2H), 1.09 ppm (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 200.9, 143.4, 138.1, 131.5, 128.4, 127.7, 73.1, 68.3, 33.2, 32.9, 8.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}O_2Na$: 241.1205 [*M*+Na]$^+$; found: 241.1206.

10: Et_3N (4.18 mL, 29.8 mmol) and triethylsilyl triflate (4.04 mL, 17.9 mmol) were added to a solution of **30** (3.25 g, 14.9 mmol) in Et_2O (40 mL) at −78 °C. The mixture was stirred at 0 °C for 3 h and poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted twice with hexanes. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) afforded silyl enolate **10** (4.40 g, 90%) as a clear oil. IR (neat): $\tilde{\nu}$ = 1698, 1628, 1117 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.29–7.36 (m, 5H), 5.95 (d, *J* = 15.5 Hz, 1H), 5.80 (dt, *J* = 15.0, 7.5 Hz, 1H), 4.76 (q, *J* = 7.0 Hz, 1H), 4.53 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.43 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.73 ppm (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 149.5, 138.5, 130.6, 128.4, 127.7, 127.6, 124.3, 107.9, 73.0, 70.2, 32.8, 11.4, 6.9, 5.5 ppm.

32: Catalyst (1*S*,2*R*)-**31** (300 mg, 0.66 mmol) was added to a mixture of **10** (2.26 g, 6.6 mmol), **11** (1.73 g, 9.9 mmol), and powdered 4-Å molecular sieves (1.2 g) under argon. The reaction mixture was stirred for 40 h at room temperature and then filtered through a short pad of silica gel, eluting with 25% EtOAc/hexanes. The filtrate was concentrated, and the residue was dissolved in THF (15 mL). At 0 °C, acetic acid (0.75 mL, 13 mmol) and TBAF (1 M in THF, 9.8 mL, 9.9 mmol) were added, and the mixture was allowed to stir for 30 min. The mixture was diluted with EtOAc and washed with $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (10% EtOAc/hexanes) provided pyranone **32** (1.84 g, 71%) as a yellow oil. $[\alpha]_D^{23}$ 20 (*c* 2.0, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1717, 1119, 839 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.28–7.36 (m, 5H), 4.49 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 14.0 Hz, 2H), 3.78–3.84 (m, 1H), 3.68–3.74 (m, 2H), 3.56–3.64 (m, 3H), 2.52–2.57 (m, 1H), 2.45 (dd, *J* = 14.5, 12.5 Hz, 1H), 2.26 (d, *J* = 14.5 Hz, 1H), 1.89–1.96 (m, 1H), 1.79–1.87 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 211.3, 138.3, 128.4, 127.7, 78.7, 74.3, 73.1, 66.1, 62.0, 46.3, 44.6, 36.5, 25.8, 18.2, 10.6, −5.3, −5.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{36}OSiNa$: 415.2281 [*M*+Na]$^+$; found: 415.2299.

Reduction of **32**: Dibal-H (5.6 mL, 5.58 mmol, 1 M in CH_2Cl_2) was added to a solution of **32** (1.84 g, 4.69 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate, and the mixture was stirred for 2 h at room temperature. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (25% EtOAc/hexanes) gave alcohol **33** (592 mg, 32%) along with *cis* alcohol **34** (1.18 g, 64%).

33: $[\alpha]_D^{23}$ = −12 (*c* = 1.1, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3434, 1094, 837 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.28–7.36 (m, 5H), 4.50 (s, 2H), 3.95 (dt, *J* = 6.5, 2.5 Hz, 1H), 3.86–3.93 (m, 1H), 3.81–3.84 (m, 1H), 3.64 and 3.48 (ABX, J_{AB} = 10.0, J_{AX} = 6.5, J_{BX} = 6.5 Hz, $\Delta\nu_{AB}$ = 80.0, 2H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.36 (br s, 1H), 1.77–1.82 (m, 1H), 1.68–1.77 (m, 2H), 1.57–1.63 (m, 1H), 1.45–1.50 (m, 1H), 0.91 (s, 9H), 0.86 (d, *J* = 5.5 Hz, 3H) 0.07 ppm (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 138.5, 128.4, 127.7, 127.7, 74.4, 73.0, 70.5, 69.5, 67.0, 63.6, 36.3, 35.8, 34.5, 25.9, 18.3, 10.8, −5.1, −5.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{39}OSi$: 375.2618 [*M*+H]$^+$; found: 375.2635.

34: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.30–7.38 (m, 5H), 4.53 (s, 2H), 3.92 (d, *J* = 11.7 Hz, 1H), 3.66–3.72 (m, 1H), 3.58–3.65 (m, 2H), 3.54–3.60 (m, 2H), 3.44–3.48 (m, 1H), 2.03–2.10 (m, 1H), 1.83–1.90 (m, 1H), 1.78–1.83 (m, 1H), 1.72–1.77 (m, 1H), 1.62–1.68 (m, 1H), 1.40–1.44 (m, 1H), 0.93 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H) 0.09 ppm (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 138.5, 128.3, 127.6, 127.5, 78.8, 73.2, 73.0, 70.9, 66.7, 63.1, 36.0, 35.5, 35.3, 25.8, 18.2, 4.6, −5.3, −5.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{39}OSi$: 375.2618 [*M*+H]$^+$; found: 375.2610.

35: 2,6-Lutidine (0.35 mL, 3.0 mmol) was added to a solution of **33** (592 mg, 1.50 mmol) in CH_2Cl_2 (8 mL) followed by *tert*-butyldimethylsilyl triflate (0.41 mL, 1.8 mmol). The mixture was stirred at room temperature for 2 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) provided the TBS ether (755 mg, 99%) as a clear oil. $[\alpha]_D^{23}$ = −1.3 (*c* = 1.3, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1099, 837 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.26–7.34 (m, 5H), 4.50 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 14.5 Hz, 2H), 3.96 (dt, *J* = 7.0, 2.0 Hz, 1H), 3.88–3.96 (m, 1H), 3.78–3.86 (m, 1H), 3.61 and 3.46 (ABX, J_{AB} = 10.0, J_{AX} = 7.5, J_{BX} = 6.5 Hz, $\Delta\nu_{AB}$ = 75.0, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 1.76–1.82 (m, 1H), 1.67–1.73 (m, 2H), 1.56–1.60 (m, 1H),

1.36–1.40 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.85 (d, J=7.5 Hz, 3H), 0.05 (s, 6H), 0.04 ppm (d, J=4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.7, 128.3, 127.6, 127.4, 74.2, 73.0, 71.0, 69.7, 67.2, 63.4, 36.4, 36.0, 35.2, 25.8, 18.2, 18.1, 10.7, −4.8, −5.1, −5.4 ppm; LRMS (ESI): m/z= 531.9 $[M+Na]^+$. Pd/C (78 mg, 0.074 mmol, 10 wt.%) was added to a solution of the above benzyl ether (755 mg, 1.48 mmol) in MeOH (15 mL), and the mixture was stirred under a H_2 balloon at room temperature for 20 h. The reaction suspension was filtered through celite and concentrated. Purification by column chromatography (15% EtOAc/hexanes) provided alcohol **35** (600 mg, 97%) as a clear oil. $[\alpha]_D^{23}$=+14 (c=1.5, $CHCl_3$); IR (neat): $\tilde{\nu}$=3436, 1097, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.98–4.04 (m, 2H), 3.75–3.85 (m, 3H), 3.60 and 3.45 (ABX, J_{AB}= 10.5 Hz, J_{AX}=7.0 Hz, J_{BX}=6.5 Hz, $\Delta\nu_{AB}$=78.0 Hz, 2H), 1.70–1.76 (m, 1H), 1.63–1.69 (m, 2H), 1.56–1.62 (m, 1H), 1.30–1.34 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.05 (s, 6H), 0.04 ppm (d, J= 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=74.6, 74.1, 70.7, 63.5, 62.3, 37.4, 36.1, 35.0, 25.8, 25.8, 18.2, 18.0, 10.8, −4.9, −5.3, −5.5 ppm; LRMS (ESI): m/z=419.5 $[M+H]^+$.

36: Oxalyl chloride (75 μL, 0.86 mmol) was added to a solution of DMSO (122 μL, 1.73 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After 20 min, **7** (61 mg, 0.14 mmol) was added. The mixture was stirred at −78 °C for 1 h, and the reaction was quenched with Et_3N (0.4 mL, 2.88 mmol). After the mixture was stirred at −78 °C for 30 min, it was warmed to room temperature and stirred for another 1 h. The mixture was poured into 0.2 N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Filtration and concentration in vacuo gave the crude aldehyde, which was used directly in next step without further purification. A solution of the above crude aldehyde and (carbethoxymethylene)triphenylphosphorane (200 mg, 0.57 mmol) in CH_2Cl_2 (5 mL) was heated under reflux for 20 h. The resulting mixture was cooled to room temperature and filtered through a short silica-gel pad eluted with 25% EtOAc/hexanes. The filtrate was concentrated, and the residue was purified by column chromatography (5% EtOAc/hexanes) to provide ester **36** (57 mg, 84% over 2 steps) as a clear oil. $[\alpha]_D^{23}$=+7.6 (c=1.1, $CHCl_3$); IR (neat): $\tilde{\nu}$=1723, 1072, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.96 (dt, J=15.5, 7.0 Hz, 1H), 5.85 (d, J=15.5 Hz, 1H), 4.16 (q, J=7.0 Hz, 2H), 3.96 (dt, J=7.0, 2.5 Hz, 1H), 3.84–3.90 (m, 1H), 3.78–3.82 (m, 1H), 3.62 and 3.45 (ABX, J_{AB}= 10.0 Hz, J_{AX}=7.0 Hz, J_{BX}=6.5 Hz, $\Delta\nu_{AB}$=84.5 Hz, 2H), 2.32–2.39 (m, 1H), 2.23–2.29 (m, 1H), 1.64–1.70 (m, 1H), 1.52–1.58 (m, 1H), 1.31–1.35 (m, 1H), 1.26 (t, J=7.0 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.82 (d, J= 7.0 Hz, 3H), 0.03 (d, J=1.0 Hz, 6H), 0.02 ppm (d, J=3.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.5, 145.6, 123.0, 74.4, 71.0, 70.9, 63.4, 60.1, 38.7, 35.9, 34.7, 25.8, 25.8, 18.2, 18.0, 14.3, 10.6, −4.9, −5.2, −5.4 ppm; HRMS (ESI): m/z calcd for $C_{25}H_{50}O_5Si_2Na$: 509.3095 $[M+Na]^+$; found: 509.3112.

37: camphor sulfonic acid (12.4 mg, 0.054 mmol) was added to a solution of **36** (135 mg, 0.28 mmol) in MeOH (3 mL) at room temperature. After the mixture was stirred for 30 min, it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (20% EtOAc/hexanes) afforded the alcohol (100 mg, 97%) as a clear oil. $[\alpha]_D^{23}$=+20 (c=1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.95 (dt, J=15.5, 7.0 Hz, 1H), 5.85 (d, J=15.5 Hz, 1H), 4.16 (q, J=7.0 Hz, 2H), 4.01 (dt, J=9.0, 2.5 Hz, 1H), 3.87–3.93 (m, 1H), 3.73–3.79 (m, 1H), 3.63 and 3.41 (ABX, J_{AB}=11.5 Hz, J_{AX}=9.0 Hz, J_{BX}=3.5 Hz, $\Delta\nu_{AB}$=111.7 Hz, 2H), 2.35–2.41 (m, 1H), 2.29–2.34 (m, 1H), 2.07 (br s, 1H), 1.52–1.58 (m, 2H), 1.33–1.37 (m, 1H), 1.26 (t, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.82 (d, J= 7.0 Hz, 3H), 0.01 ppm (d, J=1.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.4, 145.2, 123.3, 75.1, 70.9, 70.8, 64.4, 60.2, 38.7, 36.8, 34.5, 25.8, 18.0, 14.3, 11.4, −4.9 ppm. Oxalyl chloride (0.12 mL, 1.35 mmol) was added to a solution of DMSO (0.2 mL, 2.7 mmol) in CH_2Cl_2 (4 mL) at −78 °C. After 20 min, the above alcohol (100 mg, 0.27 mmol) was added. The mixture was stirred at −78 °C for 1 h, and the reaction was quenched with Et_3N (0.56 mL, 4.05 mmol). After the mixture was stirred at −78 °C for 30 min, it was warmed to room temperature and stirred for another 1 h. The mixture was poured into 1 N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Filtration and concentration in vacuo gave crude aldehyde **37** (100 mg, 100%), which was used directly in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.63 (s, 1H), 6.99 (dt, J=15.5, 7.0 Hz, 1H), 5.89 (d, J=16.0 Hz, 1H), 4.35 (d, J= 3.0 Hz, 1H), 4.17 (q, J=7.0 Hz, 2H), 3.92–3.98 (m, 1H), 3.81–3.86 (m, 1H), 2.45–2.51 (m, 1H), 2.35–2.41 (m, 1H), 1.98–2.03 (m, 1H), 1.62–1.67 (m, 1H), 1.37–1.41 (m, 1H), 1.27 (t, J=7.0 Hz, 3H), 0.85–0.89 (m, 12H), 0.04 ppm (d, J=3.0 Hz, 6H).

Preparation of vinyl iodides **38** and **6**: nBuLi (0.25 mL, 0.4 mmol, 1.6 M in hexane) was added to a suspension of ethyl triphenylphosphonium iodide (167 mg, 0.4 mmol) in THF (3 mL) at 23 °C. After 5 min, the above homogeneous solution was transferred into a solution of iodine (101 mg, 0.4 mmol) in THF (4 mL) at −78 °C. The resulting suspension was vigorously stirred for 5 min and warmed to −20 °C. NaHMDS (0.4 mL, 0.4 mmol, 1 M in THF) was added at −20 °C to produce a red solution, followed by stirring for 5 min and addition of a solution of **37** (73 mg, 0.197 mmol) in THF (1 mL). After 10 min at −20 °C, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) afforded E-vinyl iodide **38** (28 mg, 31%) and Z-vinyl iodide **6** (11 mg, 12%).

(E)-**38**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.96 (dt, J=16.0, 7.0 Hz, 1H), 6.19 (dd, J=7.5, 1.5 Hz, 1H), 5.86 (d, J=16.0 Hz, 1H), 4.64 (dd, J=8.0, 2.0 Hz, 1H), 4.18 (q, J=7.0 Hz, 2H), 3.88–3.94 (m, 1H), 3.79–3.85 (m, 1H), 2.42 (s, 3H), 2.35–2.40 (m, 1H), 2.28–2.34 (m, 1H), 1.53–1.60 (m, 2H), 1.30–1.34 (m, 1H), 1.28 (t, J=7.0 Hz, 3H), 0.92 (d, J=7.5 Hz, 3H), 0.89 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.5, 145.2, 140.8, 123.3, 96.1, 72.9, 71.3, 70.6, 60.2, 39.6, 38.7, 33.8, 28.6, 25.8, 18.0, 14.3, 11.3, −4.8, −4.9 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{37}O_4ISiNa$: 531.1404 $[M+Na]^+$; found: 531.1416.

(Z)-**6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.98 (dt, J=16.0, 7.0 Hz, 1H), 5.87 (d, J=16.0 Hz, 1H), 5.60 (dd, J=7.0, 1.5 Hz, 1H), 4.55 (dd, J=7.0, 2.5 Hz, 1H), 4.18 (q, J=7.0 Hz, 2H), 3.93–3.99 (m, 1H), 3.79–3.84 (m, 1H), 2.51 (s, 3H), 2.35–2.40 (m, 1H), 2.29–2.34 (m, 1H), 1.75–1.80 (m, 1H), 1.55–1.61 (m, 1H), 1.30–1.34 (m, 1H), 1.28 (t, J=7.0 Hz, 3H), 0.92 (s, 9H), 0.91 (d, J=7.5 Hz, 3H), 0.06 ppm (d, J=16.5 Hz, 6H); HRMS (ESI): m/z calcd for $C_{21}H_{37}O_4ISiNa$: 531.1404 $[M+Na]^+$; found: 531.1406.

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