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Enantioselective Total Synthesis of Macrolide Antitumor Agent (–)-Lasonolide A

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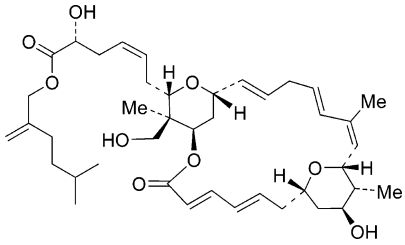
ABSTRACT



Lasonolide A (1)

An enantioselective total synthesis of (–)-lasonolide A is described. The upper tetrahydropyran ring was constructed stereoselectively by an intramolecular 1,3-dipolar cycloaddition reaction. The bicyclic isooxazoline led to the tetrahydropyran ring as well as the quaternary stereocenter present in the molecule. The lower tetrahydropyran ring was assembled by a catalytic asymmetric hetero-Diels–Alder reaction as the key step. Three stereocenters were enantioselectively installed in this single step reaction.

Marine natural products continue to provide structurally diverse molecules with intriguing biological properties. Many such molecules exhibit potent antitumor activity; however, the scarcity of natural abundance often limits their subsequent biological studies.[1] Lasonolide A (**1**), a 20-membered macrolide, was isolated from the Caribbean marine sponge, *Forcepia* sp., by McConnell and co-workers in 1994.[2] Since then, a series of other lasonolides with potent antitumor properties were isolated. Lasonolide A remains to be the most potent of the series with IC_{50} values of 8.6 and 89 nM against A-549 human lung carcinoma and Panc-1 human pancreatic carcinoma, respectively.[2] The initial structural and stereochemical assignment of lasonolide A was established by extensive NMR studies. Its structure and absolute stereochemistry were later revised through total synthesis[3a] and subsequent biological studies by Lee and co-workers.[3b] Lasonolide A's structural features as well as its potent antitumor activities attracted considerable synthetic interest. Thus far, three total syntheses[3−5] and a number of synthetic studies on both tetrahydropyran rings[6] have been reported. Herein we report an enantioselective total synthesis of (−)-lasonolide A (**1**).

The retrosynthetic analysis is outlined in Figure 1. Lasonolide A (**1**) can be disconnected at C25−C26 into side chain fragment phosphonium salt **2** and the 20-membered

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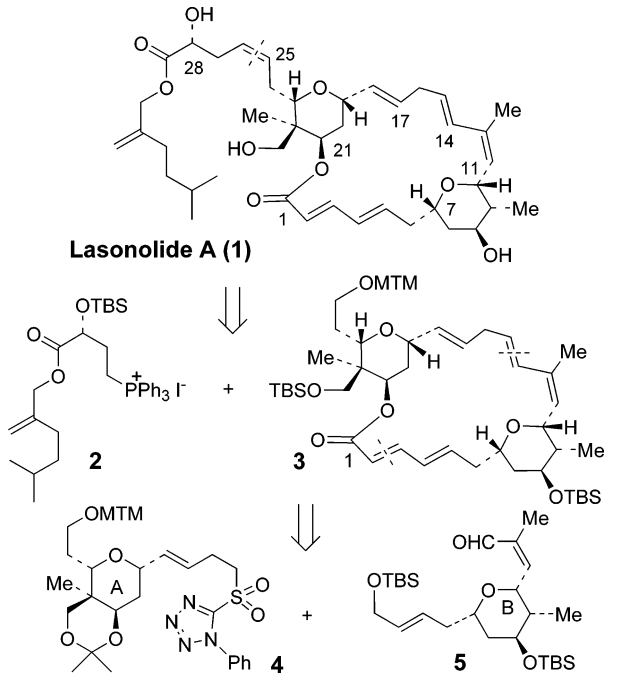


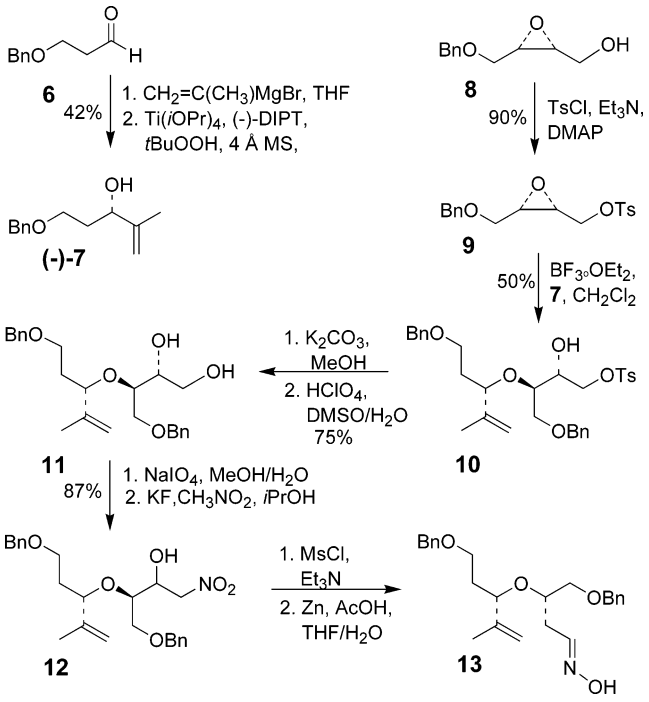
Figure 1. Retrosynthetic analysis of lasonolide A.

macrolide core **3** containing tetrahydropyrans A and B. Further disconnection of macrolactone **3** would lead to sulfone **4** and aldehyde **5**. Assembly of the macrocycle would proceed through Julia−Kocienski coupling[7] between **4** and **5** at the C14−C15 and subsequent intramolecular Horner−Wadsworth−Emmons reaction at C2−C3. Fragment containing ring A (**4**) would be built through an intramolecular [3+2] nitrile oxide cycloaddition. Construction of ring B (**5**) containing fragment could be efficiently achieved from the asymmetric chromium-catalyzed hetero-Diels−Alder reaction.[8]

The synthesis of ring A started with the known aldehyde **6**[9] as shown in Scheme 1. Isopropenyl magnesium bromide was added to aldehyde to form racemic allylic alcohol *rac*-**7** in 94% yield. Kinetic resolution utilizing Sharpless asymmetric epoxidation[10] provided the desired optically pure alcohol (−)-(*S*)-**7** in 45% yield and 98% ee. The known epoxide **8**[10] was converted to its corresponding tosylate **9**.

Regioselective epoxide opening of **9** with alcohol **7** in the presence of catalytic BF_3•OEt_2 provided ether **10** according to the Hoffmann protocol.[11] Treatment of alcohol tosylate **10** with K_2CO_3 afforded the corresondong epoxide, which was converted to diol **11** by treatment with aqueous $HClO_4$. Oxidative cleavage of diol **11** followed by condensation of the corresponding aldehyde with nitromethane afforded nitro alcohol **12** as a diastereomeric mixture. The newly generated stereocenter was eliminated by converting **12** into the corresponding nitroalkene with MsCl and Et_3N. Reduction of the resulting nitroalkene using Zn and AcOH provided oxime **13**.

Scheme 1. Enantioselective Synthesis of Oxime **13**



Exposure of **13** to sodium hypochlorite led to facile intramolecular 1,3-dipolar cycloaddition via the nitrile oxide to afford isoxazoline **14** as a single diastereomer (Scheme 2).[12] The quaternary stereocenter at C22 was constructed efficiently at the same time as forming the tetrahydropyran ring. Raney-nickel catalyzed hydrogenolysis of isooxazoline **14** provided β-hydroxy ketone **15**.[13] L-Selectride reduction of the ketone provided the corresponding axial alcohol. The resulting diol was protected as acetonide **16** in 87% yield in two steps. Both benzyl groups of **16** were removed by catalytic hydrogenation to provide diol. The diol was then protected as bis-TBS-ether **17**. Exposure of **17** to TBAF provided desired alcohol **18** in 40% yield along with recovered **17** (32%) and the corresponding diol (24%), which was converted to **17**. Alcohol **18** was obtained in 62% yield after one recycle. Dess−Martin oxidation[14] of **18** followed by Wittig reaction afforded olefin, which was treated with TBAF to give alcohol **19**. Cross metathesis between olefin **19** and sulfone **20**[15] in the presence of second generation Grubbs' catalyst[16] provided olefin **21** in 81% yield.[17] Alcohol

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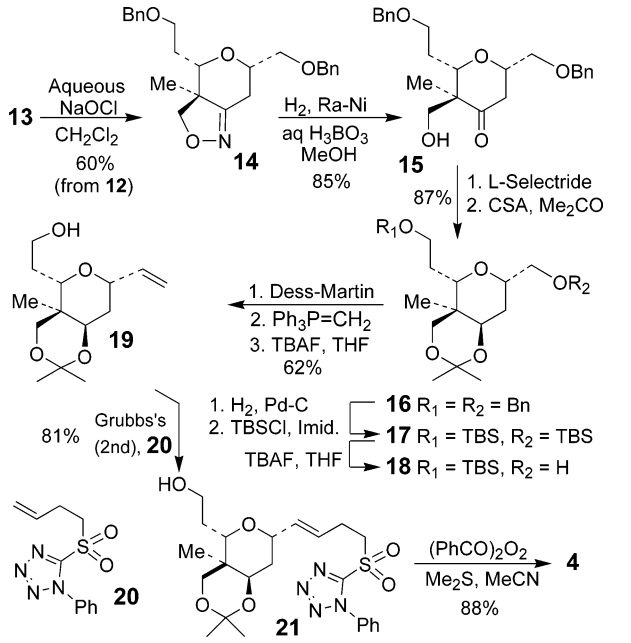
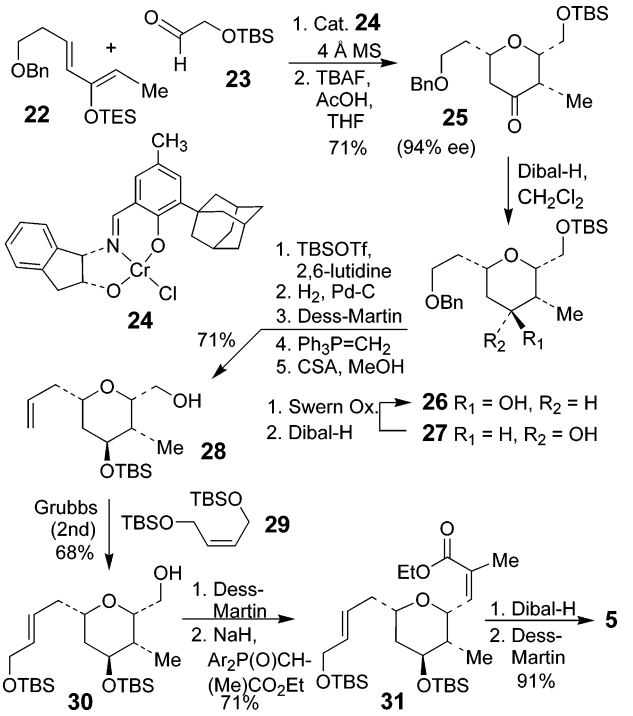
21 was protected with benzoyl peroxide and Me_2S to provide MTM ether **4** in 88% yield.[18]

Scheme 2. Stereoselective Synthesis of **4**



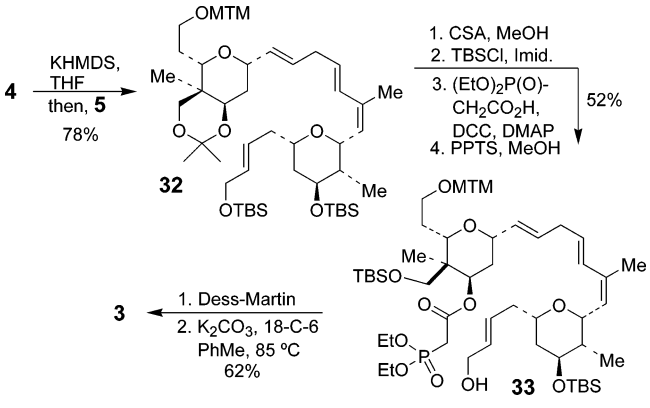
The synthesis of the lower tetrahydropyran ring B of lasonolide A is shown in Scheme 3. The chiral tridentate Schiff base chromium(III) complex (1*S*,2*R*)-**24** developed by Jacobsen[8] was used as catalyst (10 mol %) in the asymmetric hetero-Diels−Alder reaction between diene **22**[19] and aldehyde **23**.[20] The resulting dihydropyran silyl enol ether was treated with TBAF/AcOH in the same pot to remove the TES group and give the corresponding ketone **25** in 71% yield and 94% ee.[21] Reduction of the ketone with Dibal-H gave axial alcohol **26** and equatorial alcohol **27** as a 1:2 separable mixture in 96% combined yield. Among all the other reducing agents we tried, including L-Selectride, $NaBH_4$, DIBAL, Red-Al, $LiEt_3BH$, SmI_2, and BH_3, the undesired equatorial hydroxy pyran **27** was always the predominant product. Therefore, we recycled **27** back to **26** using Swern oxidation followed by reduction. Protection of the secondary alcohol with TBSOTf, debenzylation under Pd/H_2, Dess−Martin oxidation of the corresponding alcohol and following Wittig reaction furnished the olefin, of which the primary TBS group was selectively removed with CSA to afford alcohol **28** in 71% yield over 5 steps. Cross metathesis between olefin **28** and bis-TBS-butene **29** in the presence of second generation Grubbs' catalyst provided olefin **30** in 68% yield. Alcohol **30** was oxidized to the corresponding aldehyde under Dess−Martin conditions. Horner−Wadsworth−Emmons olefination of the above aldehyde with ethyl 2-[di(*o*-isopropylphenyl)phosphono] propionate under Ando's conditions[22] provided the trisubstituted *Z*-olefin **31** in 71% yield for 2 steps. DIBAL reduction of ester **31** followed by Dess−Martin oxidation gave aldehyde **5** in 91% yield for 2 steps.

Scheme 3. Stereoselective Synthesis of Fragment **5**



The final stages for assembly of lasonolide A are illustrated in Scheme 4. Sulfone **4** and aldehyde **5** were coupled under

Scheme 4. Synthesis of Macrolide **2**



Julia−Kocienski conditions[7] to provide tetraene **32** in 78% yield. Acetonide and primary TBS groups were removed by

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(21) The ee was determined by ^{19}F NMR of the Mosher ester of **27**.

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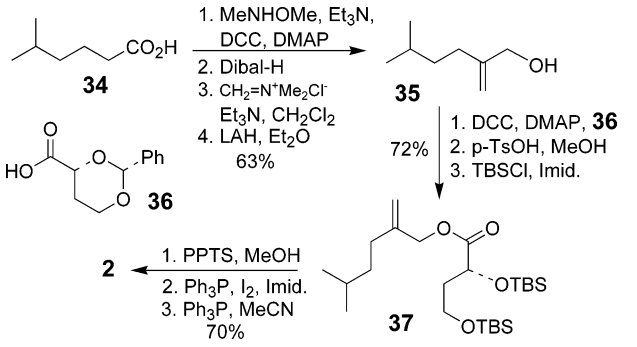
CSA to give triol. The two primary hydroxy groups were then protected with TBSCl. The secondary alcohol was converted to phosphonoacetate by using DCC and DMAP. The less hindered allylic primary TBS group was removed by PPTS to provide the hydroxy phosphonoacetate **33**. Dess−Martin oxidation of alcohol **33** followed by intramolecular Horner−Wadsworth−Emmons olefination furnished macrolactone **3** in 62% yield for 2 steps.

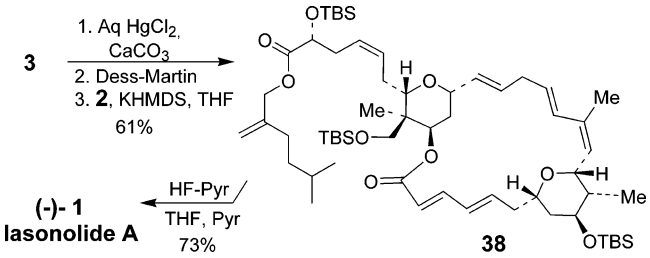
Preparation of phosphonium salt **2** was carried out as shown in Scheme 5. Commercially available acid **34** was converted to the corresponding Weinreb amide. DIBAL reduction of the amide provided aldehyde. Methylenation of the resulting aldehyde with Eschenmoser's salt,[23] followed by reduction of the resulting aldehyde with LAH provided allylic alcohol **35** in 63% yield for 4 steps. Esterification of known acid **36**[24] with alcohol **35** gave the corresponding ester, which was converted to bis-TBS-ether **37** by deprotection of the benzylidene group followed by protection of the resulting diol as TBS-ethers. Phosphonium salt **2** was prepared from **37** as described previously.[3]

Scheme 5. Synthesis of Phosphonium Salt **2**



Synthesis of lasonolide A was carried out from macrolactone **3** as shown in Scheme 6. Removal of the MTM group was achieved by exposure to $HgCl_2$[25] in the presence of $CaCO_3$ in aqueous acetonitrile. Dess−Martin oxidation of the resulting alcohol provided the corresponding aldehyde. Wittig olefination with **2**-derived phosphorane afforded the TBS-protected lasonolide A **38**. Final global TBS-deprotection with HF·Py in the presence of excess pyridine furnished (−)-lasonolide A (**1**, $[\alpha]^{23}_D$ −24 (*c* 0.37, $CDCl_3$)). The spectroscopic data of synthetic lasonolide A (**1**) are identical with those of the natural product.[2]

Scheme 6. Synthesis of (−)-Lasonolide A



In summary, we have reported an asymmetric total synthesis of (−)-lasonolide A. The two key highly substituted tetrahydropyran fragments of lasonolide A were synthesized in enantiomerically pure form. The upper tetrahydropyran ring was constructed by an intramolecular 1,3-dipolar cycloaddition via nitrile oxide to bicyclic isoxazoline with stereoselective building of the quaternary center. The lower tetrahydropyran ring was assembled by a catalytic asymmetric hetero-Diels−Alder reaction while setting three stereocenters enantioselectively at the same time. The synthesis also features Lewis acid-catalyzed opening of epoxide to stereoselectively form substituted ether, efficient cross metathesis of functionalized olefins, and the intramolecular Horner−Emmons reaction. Eight of the nine chiral centers were derived through asymmetric synthesis. The present synthesis will provide access to a variety of structural analogues of lasonolide A for biological studies.

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Supporting Information Available: Experimental procedures, spectral data for compounds, and ^{1}H NMR and ^{13}C NMR spectra for **1**, **3**−**5**, **10**−**12**, **14**, **15**, **19**, **21**, **25**, **26**, and **30**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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