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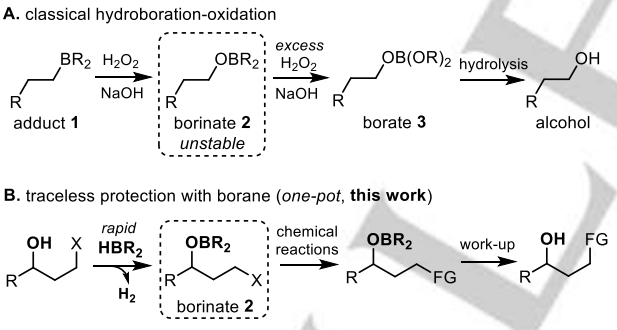
COMMUNICATION

Enantioconvergent and Concise Synthesis of Lasonolide A

Lin Yang, Zuming Lin, Shunjie Shao, Qian Zhao, and Ran Hong*

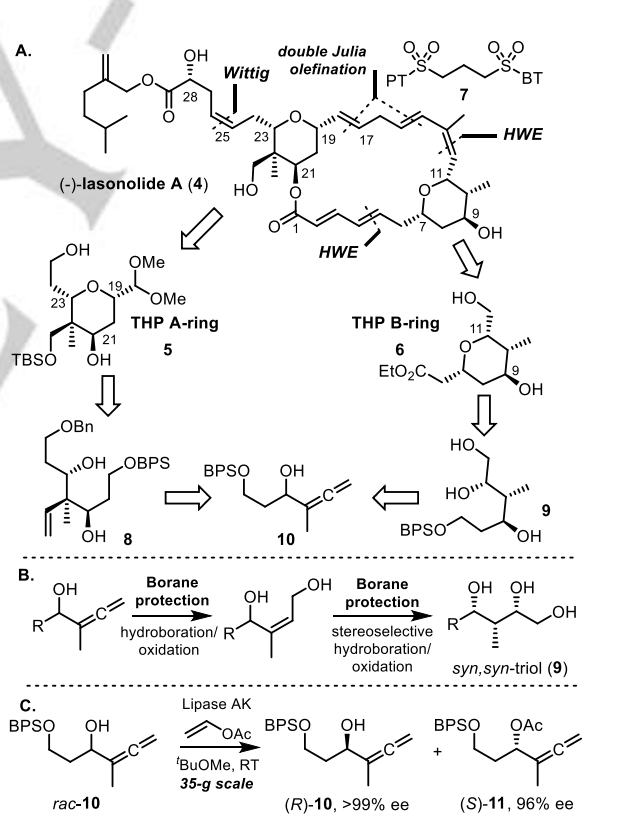
Abstract: Efficient access to medicinally significant natural product is an essential basis for the development of pharmaceuticals. The limited availability of marine natural products impedes broad biological evaluation. Despite several elegant syntheses of (-)-lasonolide A having been reported, a practical synthesis of this potent anticancer polyketide remains elusive. Based on application of borane as a traceless protection and development of an unprecedented bissulfone reagent for double Julia olefination, (-)-lasonolide A was assembled in an enantioconvergent manner by an array of stereoselective hydroboration, allylation, oxidation, and oxa-Michael cyclization. This concise route may provide a realistic solution for accessing derivatives and analogs.

Hydroboration of alkene and subsequent oxidation are widely adopted protocols in organic synthesis since the generalization six decades ago.[1] The oxidation step-derived borinate **2** was generally unstable and thus difficult for isolation (Scheme 1A).[2,3] However, the diagonal element silicon-derived various silane reagents are popularized as protecting groups for alcohol in organic synthesis.[4] We envisioned that the lability of borinate **2** can be adopted as a tentative protection due to a rapid reaction of borane with alcohol without interfering other functional groups and feasible removal of boryl group during the work-up stage (Scheme 1B). Given the stress of economics in organic synthesis,[5] such protection strategy would diminish additional reagents, waste disposal, and purification steps.[6] The additional challenge for the boryl group as protection is that the mutual compatibility of borinate **2** with chemical transformations. As a proof of the concept, we devised an efficient synthesis of antitumor marine polyketide lasonolide A (**4**) with the capacity of alkylborane as traceless protecting group.



Scheme 1. (A) Hydroboration/oxidation process; (B) Logic of protection design with borane. FG = functional group.

Lasonolide A (**4**) was identified by McConnell and co-workers from a Caribbean orange-red marine sponge, *Frocepia* sp. (Scheme 2A).[7] The complex macrolide exhibited promising activities for the treatment of pancreatic cancer with a distinct mode of action (MOA) from most other cancer drugs, which highlights its potential as a valuable drug in the treatment of multi-drug resistance cancer cell lines.[8] The biological profile as well as its unique chemical structure render the polyene macrolide an intriguing target for the synthetic community.[9] Despite many complex marine natural products are identified as promising drug leads,[10] harvesting from vulnerable marine resources becomes unsustainable.[11] Development of scalable synthetic route with feasible operations remains a high demand.



Scheme 2. (A) Synthetic design of lasonolide A (**4**); (B) Construction of the triol moiety in the B-ring via iterative hydroboration-oxidation process; (C) Enzymatic resolution of allenic alcohol (**10**). THP = tetrahydropyran, BPS = tert-butyldiphenylsilyl, PT = phenyl tetrazolyl, BT = benzothiazolyl, TBS = tert-butyldimethylsilyl.

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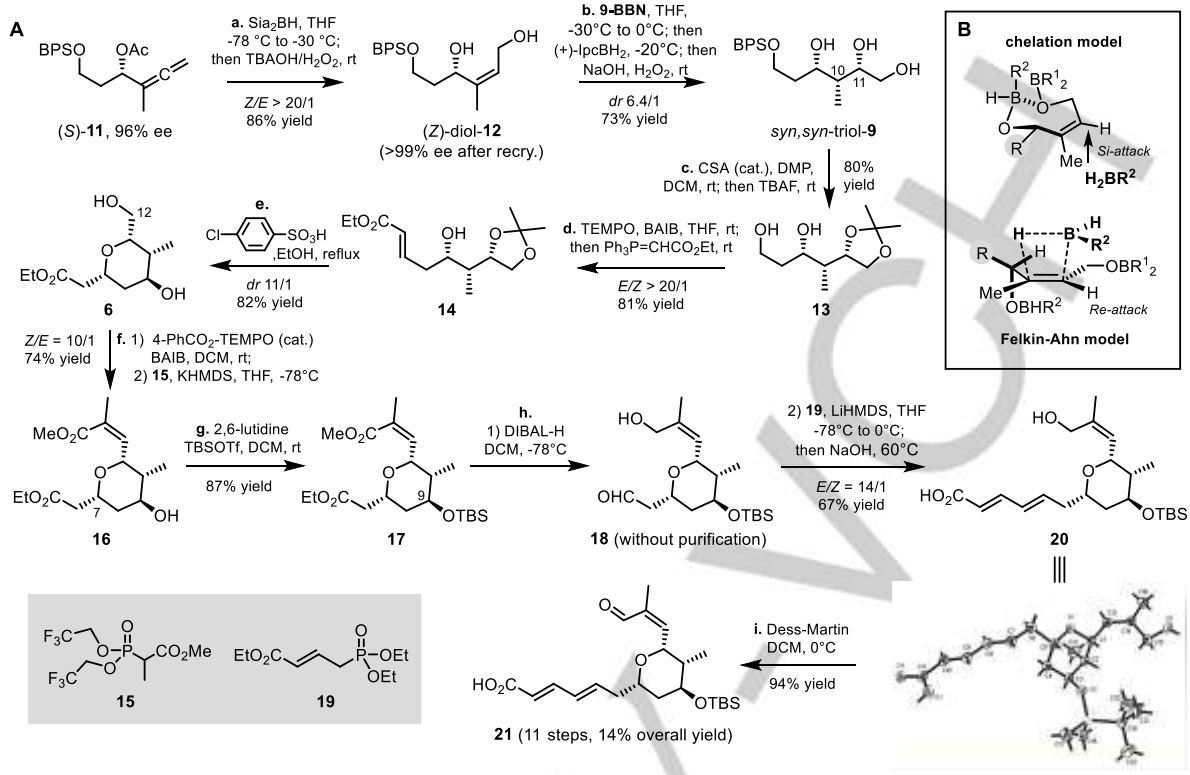

Scheme 3. (A) Synthetic route toward acid **21**; (B) A possible stereochemical control for the hydroboration of borinate derived from **12**. TBAOH = Tetrabutylammonium hydroxide, CSA = camphorsulfonic acid, DMP = 2,2-dimethoxypropane, BAIB = bis(acetoxy)-iodobenzene, TEMPO = 2,2,6,6-tetramethylpiperidine oxide, DIBAL-H = diisobutylaluminium hydride, Dess-Martin = Dess-Martin periodinane.

The logic of our modular approach is outlined in Scheme 2A, involving a connection of two key tetrahydropyran fragments **5** and **6** through a double Julia olefination with bissulfone **7** and an end-game macrolactonization. The remaining double bonds can be installed by operationally feasible Wittig-type olefinations. For tetrahydropyrans A and B, an enantio-divergent approach was developed based on the hydroboration-allylation[12] and an unprecedented iterative hydroboration-oxidation (Scheme 2B). In this approach, two enantiomers derived from the enzymatic kinetic resolution (KR) of racemic α-allenic alcohol[13] (Scheme 2C) are converted into the two individual fragments that are then merged into the advanced intermediate at a later stage in the synthesis.[14]

The key element to introduce a hydroxy group at C11 in the B-ring relies on the stereoselective hydroboration of the tri-substituted alkene, which was derived from the first hydroboration of the allene. α-Acetoxyl allene derivative (*S*)-**11** was documented as a poor substrate[15] for hydroboration due to the complicated pathways to form various compounds, such as a diene, a 1,2-diol, an *E*-1,4-diol, and a homoallylic alcohol (Figure S3 and Table S1).[16] The dominant side product diene implicated competition between 1,4-elimination and alkyl migration on to the boron. It was found that a solution of tetrabutylammonium hydroxide (TBAOH) and hydroperoxide was effective to directly deliver *Z*-alkene diol **12**, indicating a preferable alkyl migration on to boron as well as its dual role of hydrolyzing the acyl group. The enantiomeric excess of the diol was further enriched up to >99% ee after recrystallization (Scheme 3A). To install the secondary alcohol at C11, our initial attempt at the hydroboration/oxidation afforded a complex mixture including *Z*-to-*E* isomers of the alkene and a 1,4-diol with uncertain stereochemistry at C10-Me due to the reversibility of the hydroboration (Figure S5).[16,17] We envisioned that a possible rigid conformation derived from the chelation of alkylborane with the diol substrate might block the subsequent stereoselective hydroboration due to the bulky group on the boron. Alternative transition state via the Felkin-Ahn model proposed in the reaction of the substrate with borane would favor the requisite facial selectivity (Scheme 3B). After experimentation (Table S2), 9-BBN was first added to react with the primary alcohol of **12** (^{11}B NMR for the corresponding borinate at 56.4 ppm)[16] then an excess of $IpcBH_2$ was introduced to promote the hydroboration-oxidation to generate *syn*,*syn*-triol **9** in good diastereoselectivity (*ds* 6.4/1) and 70% isolated yield on a 2-gram scale.

With the triol **9** in hand, subsequent protection and removal of the silyl group was operated in "one-pot" to yield compound **13**, in which the primary alcohol was selectively oxidized and subsequent Wittig reaction[18] gave the conjugated ester **14**. Upon treatment of *para*-chlorobenzenesulfonic acid (CBSA), the cascade process including removal of ketal and oxa-Michael cyclization[19] (6-*exo*) was realized to deliver *cis*-tetrahydropyran **6** in 82% yield. The following chain elongation at C12 was proposed to adopt one-pot protocol of oxidation-olefination. However, it was found that epimerization at C11 occurred during the oxidation of the C12 primary alcohol with bis(acetoxy)iodobenzene (BAIB) and TEMPO. Therefore, a series of TEMPO derivatives were screened (Table S3) and 4-$PhCO_2$-TEMPO[20] with BAIB provided

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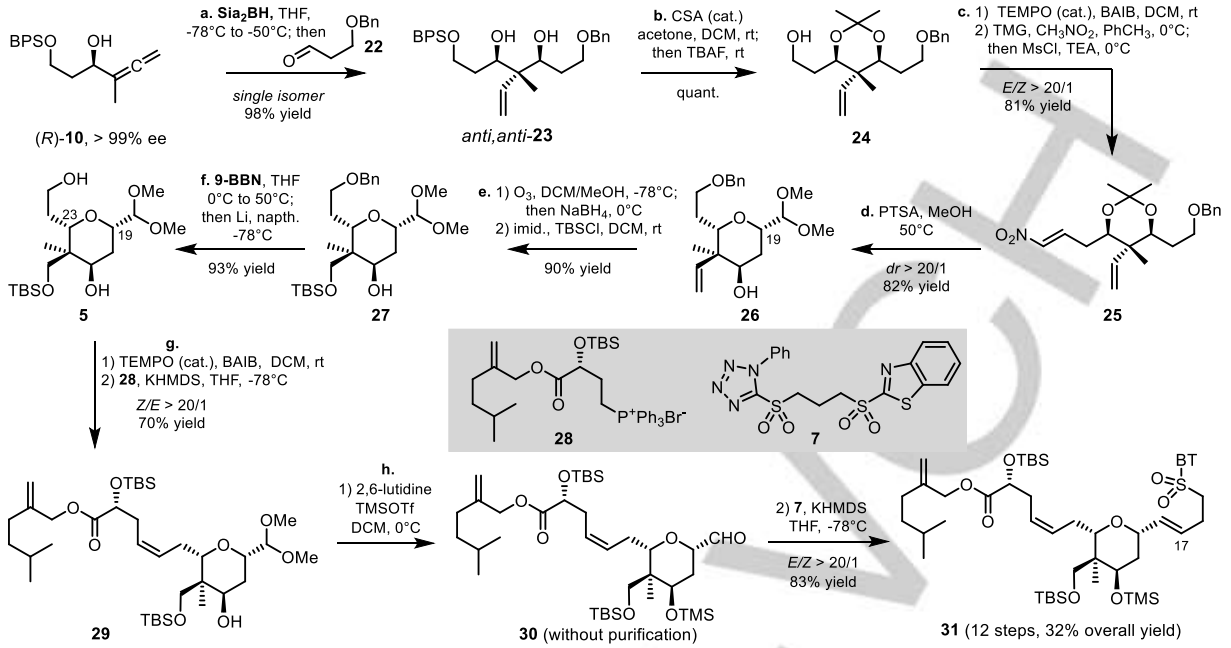


Scheme 4. Synthetic route toward sulfone **31**. TBA F= tetrabutylammonium fluoride, TMG = tetramethylguanidine, PTSA = *para*-toluenesulfonic acid, TEA = triethylamine, TMS = trimethylsilyl.

the best isolated yield without considerable epimerization. The subsequent reaction with Still-Gennari phosphonate **15** [21] furnished the trisubstituted *cis*-conjugated ester **16** in good yield (*Z*/*E* 10/1). After silylation of C9-OH, chemoselective control of the DIBAL-H reduction of the two esters could afford aldehyde **18** in excellent yield (96%). Encouragingly, without further purification, aldehyde **18** was suitable for the following Horner–Wadsworth–Emmons (HWE) reaction with phosphate **19**[22] to generate acid **20** after hydrolytic work-up (67% yield from **17**). X-ray analysis[23] further confirmed the requisite stereochemistry of the three carbon-carbon double bonds, while the coupling pattern of the vinylic protons in the NMR spectra of **20** were not conclusive. Dess-Martin periodinane[24] readily promoted the oxidation of the allylic alcohol to form *Z*-enone acid **21** in 94% yield.

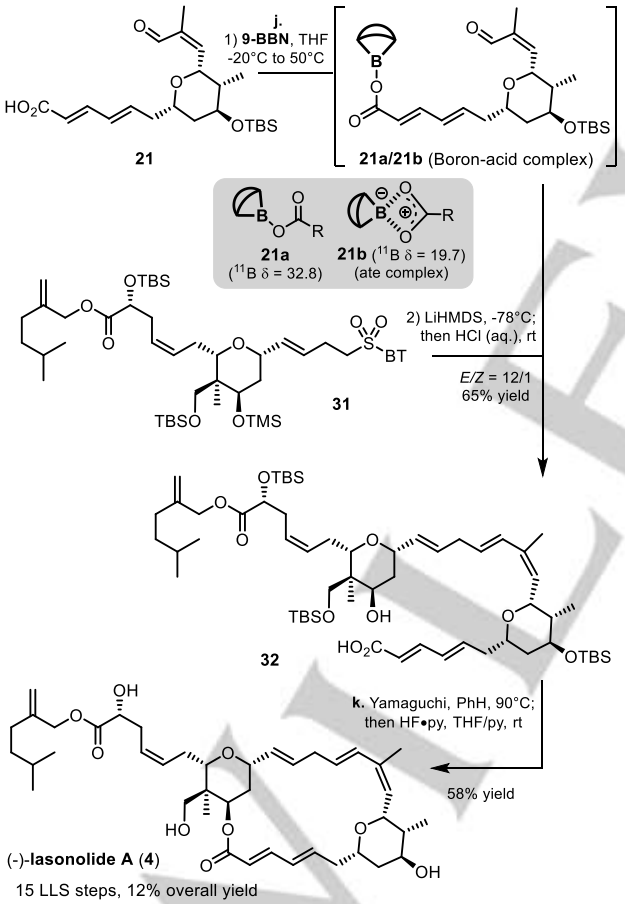
Although a similar synthetic sequence was established in our previous investigation,[12[the A ring formation was planned through another Michael addition. In contrast to the difficulty of hydroboration previously encountered with the allene bearing a free adjacent alcohol,[15,25] direct hydroboration of (*R*)-**10** with disiamylborane (Sia_2BH) (^{11}B: 53.7 ppm)[16] and subsequent allylation of aldehyde **22** delivered *anti*,*anti*-diol **23** in 98% yield as a single isomer (Scheme 4). This traceless protection strategy for hydroboration of allenic alcohol circumvented the silyl protection as shown in our previous study (*ds* 15/1).[12] Ketalization of the diol in the presence of CSA followed by desilylation using TBAF delivered compound **24** in quantitative yield. The following oxidation, Henry reaction, and elimination were conducted in one-pot to afford nitroalkene **25** in excellent yield. Although the oxa-Michael cyclization was well precedented,[26] applications of this reaction to nitro alkenes remains rare.[27] It is particularly noteworthy that, upon treatment of *para*-methylbenzenesulfonic acid (PTSA) to compound **25** in refluxing methanol, a tandem process including deketalization, oxa-Michael addition, Nef reaction, and acetalization occurred. The impressive high yield, regioselectivity, and stereoselectivity in resultant **26** as well as the complexity established in a tandem manner provide an efficient solution for accessing such multi-centered tetrahydropyran (A ring), which is superior to the reported sequences.[9]

After cleavage of the vinyl group by ozonolysis, subsequent reduction and protection afforded silyl ether **27**. The next step would be removal of the benzyl group for the introduction of the side chain. Although hydrogenolysis with 10% Pd/C was convenient and gave a high yield of diol **5**, we managed to devise transition-metal-free conditions for the debenzylation. A lithium-naphthalene system[28] was effective when the secondary alcohol at C21 was protected by 9-BBN (^{11}B: 56.7 ppm).[16] Without the borane pretreatment, the silyl group was migrated to the C21-OH to result in the reduced yield. The structure of the silyl-migrated product **5a** was further elucidated by X-ray analysis,[23] which also confirmed the requisite stereochemistry of C19-C23 in the A-ring. A gram-scale and chemoselective oxidation of the primary alcohol and subsequent Wittig olefination with **28**[9e] proceeded smoothly to deliver advanced intermediate **29** in 70% yield with excellent Z-selectivity (*Z*/*E* = >20/1). With trimethylsilyl triflate (TMSOTf) and 2,6-lutidine,[29] deacetalization readily occurred to release aldehyde **30**, and the C21-OH was protected in situ by the trimethylsilyl group. The crude aldehyde was suitable for the subsequent Julia olefination without further purification.[30] Inspired by Kang's iterative protocol by Julia reaction[9b] to merge two aldehyde fragments, bissulfone **7** was designed to integrate two highly functionalized aldehyde motifs and to avoid the oxidation step of converting the second thioether to sulfone after the first Julia olefination. After meticulous evaluation of the reactivity of several sulfones (Figure S6 and Table S4), **7** was treated with KHMDS to deprotonate the phenyl tetrazolyl (PT) sulfone [31] preferentially. The generated anion was reacted with

10.1002/anie.201811093

aldehyde **30** to install the C17/C18 alkene while the benzothiazolyl (BT) sulfone remained intact. The corresponding sulfone **31** was then achieved in 83% isolated yield with an excellent stereoselectivity (*Z*/*E* > 20/1).

A direct application of the free dienyl acid **21** (Scheme 5) to Julia reaction was unsuccessful, suggesting protection of the acid group to be necessary. Primary mechanistic studies revealed that the complexation of the acid **21** with 9-BBN was complete after 30 min at 50 °C and two new signals (**21a** and **21b**) were shown in the ^{11}B NMR spectra (32.8 and 19.7 ppm).[16,32] The ate-complex was stable enough at room temperature and no appreciable reduction of aldehyde was observed (Figure S7). To this borane ate-complex solution, sulfone **31** and LiHMDS were added at -75 °C for the requisite Julia olefination. After acidic work-up, the *E*-isomer of seco acid **32** was isolated in 65% yield.[33] Finally, Yamaguchi macrolactonization[34] and subsequent global desilylation were adopted to deliver the target molecule, (-)-lasonolide A (**4**) (58% yield, 35.8 mg). The spectroscopic data of the synthetic sample were identical to the original data [7] as well as those reported in other synthetic studies.[9]



Scheme 5. Completion of lasonolide A. py = pyridine.

In summary, a modular strategy for the concise synthesis of lasonolide A was achieved. The salient feature is the development of an enantioconvergent approach for accessing the two chiral tetrahydropyran motifs bearing multiple stereocenters from one pair of enantiomers, which were readily derived from the decagram scale kinetic resolution of racemic α-allenic alcohol (15 longest linear steps from readily available *rac*-**10**, 12% overall yield). The unprecedented iterative hydroboration/oxidation converted the allene into the stereotriad of the B-ring. A cascade process to construct the A-ring was superb and offers a platform for derivatization. Moreover, for the first time, metastable borinate and borane-ate complex were designed as traceless protection to facilitate the crucial stereoselective hydroboration of allene and alkene, debenzylation, and Julia olefination, which save additional protection and deprotection operations. It is also noteworthy that the reactivity-oriented design of bissulfone provided a C3-homologation linker to react with two distinct aldehydes through a sequential manner. The overall synthesis sequence also circumvents additional transition metal removal steps.[35] By implementing our previous tactics for the construction of tetrahydropyran stereoisomers,[12] more macrolide analogs can be assembled for future medicinal development.

Acknowledgments

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Keywords: borane • hydroboration • macrolactonization • olefination • oxa-Michael

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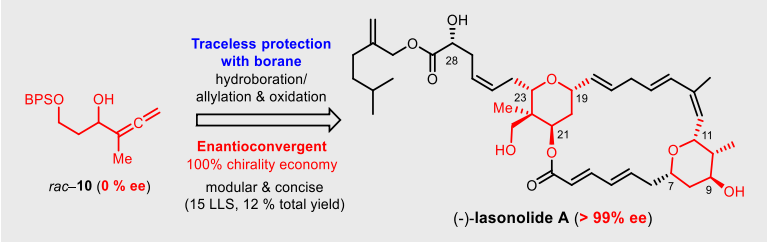

The "gifted" borane! Stemming from classical hydroboration chemistry, a novel traceless protection strategy for alcohol was designed and implemented in a concise and modular synthesis of potent antitumor marine polyketide lasonolide A. The given strategy paves a way to readily access derivatives for future medicinal investigation.

*Lin Yang, Zuming Lin, Shunjie Shao, Qian Zhao, and Ran Hong**

Page No. – Page No.

Enantioconvergent and Concise Synthesis of Lasonolide A