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Total Synthesis of (−)-Exiguolide

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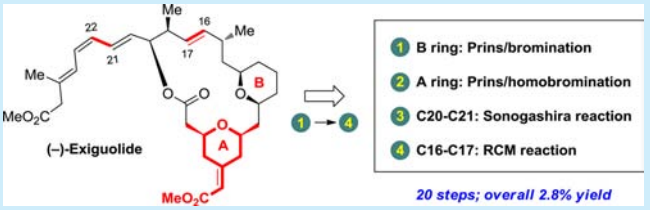
Supporting Information

ABSTRACT: A concise total synthesis of (−)-exiguolide has been completed in an overall 2.8% yield over 20 steps in the longest linear path. The key strategies involve (1) Prins cyclization/homobromination of dienyl alcohol with the B ring-substituted aldehyde, prepared by Prins cyclization/bromination, to construct the A ring with excellent *cis*-*Z* stereochemical control and (2) an unusual side chain installation/macrocyclization strategy featuring Sonogashira cross-coupling followed by a ring-closing metathesis reaction to deliver the target.



(−)-Exiguolide is a unique 20-membered macrolide, which was isolated from the marine sponge *Geodia exigua* Thiele by Ohta and co-workers in 2006 (Figure 1, right).[1] Biological studies

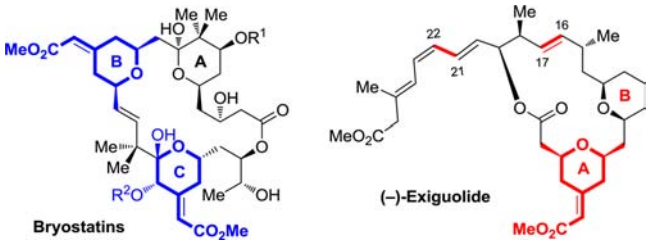
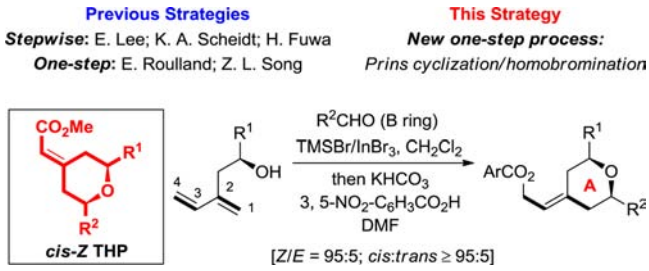


Figure 1. (−)-Exiguolide, a structurally simpler analogue of bryostatins.

suggested that this molecule might have anticancer activities.[2] This assumption was further verified by recent investigations, in which (−)-exiguolide was found to inhibit proliferation of a series of cancer cell lines.[3] (−)-Exiguolide is attractive also because of its structural similarity to bryostatins (Figure 1, left). An interesting biogenetic hypothesis has been accordingly provided by Cossy[4] that (−)-exiguolide may be a structurally simpler analogue of bryostatins.[5] As one of the most important marine natural products in the past three decades, bryostatins exhibit remarkable activities against a range of cancers and other noncancer diseases such as Alzheimer's that led to their extensive usage in clinical trials.[6] Thus, one would expect that studies on (−)-exiguolide might provide an entry to finding new and simpler alternatives to structurally complex bryostatins. Due to the low natural abundance, however, research on the structure−activity relationship (SAR) of (−)-exiguolide has been largely limited. Therefore, it is of importance to develop an efficient chemical synthesis of (−)-exiguolide. To date, five total syntheses of this popular target have been completed previously by Lee, Fuwa, Roulland, Scheidt, and our group.[7]

(−)-Exiguolide contains a methylene bis-*cis*-tetrahydropyran motif embedded in the macrocycle. Different from common THPs such as the B ring, the A ring possesses a configurationally defined exocyclic methyl enoate. A similar ring structure can be also found as the B and C rings in bryostatins. Good configuration control is essential to ensure the desired biological activity, since only *Z*-(−)-exiguolide inhibits the growth of cancer cells.[3a] Previous construction of the A ring mainly relied on a stepwise strategy as shown in Lee,[7a] Fuwa,[7b] and Scheidt's[3a] independent synthesis (Scheme 1). The *cis*-

Scheme 1. Comparison of Previous and Our Strategies To Construct the A Ring of Exiguolide



pyranone was generated first, followed by Fuji's asymmetric Horner−Wadsworth−Emmons reaction[8] to give moderate *Z*/*E* selectivity. Roulland[7c] constructed the A ring using a ruthenium-catalyzed ene−yne cross-coupling/Michael addition process developed by Trost.[9] Very recently, we reported our method featuring a geminal bis(silyl) Prins cyclization.[10] In both of these two one-step strategies, the exocyclic vinylsilane was generated first and was next transformed into enoate by iodination and carbonylation. In this work, we employ a new one-step approach to synthesize the A ring. The process

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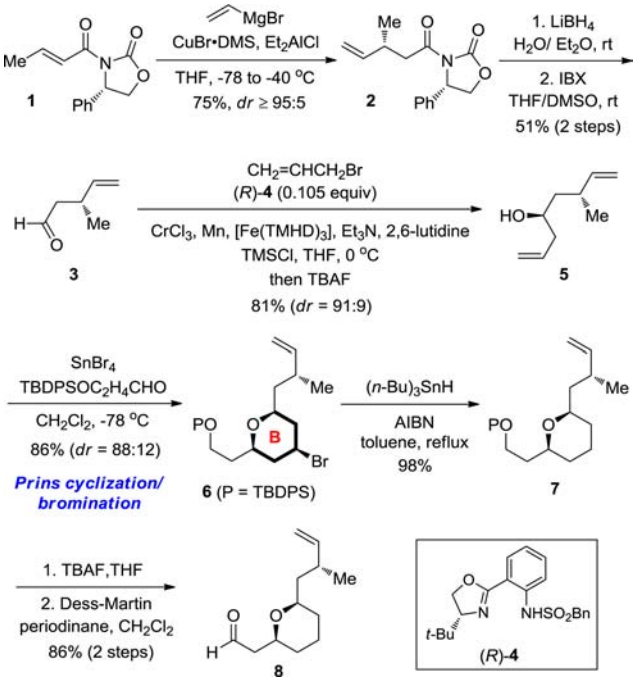
features a TMSBr/$InBr_3$-promoted Prins cyclization[11]/homobromination of dienyl alcohol with aldehyde, which contains the B ring prepared by Prins cyclization/bromination (Scheme 1). In addition, previous syntheses of the side-chain-attached macrocycle skeleton all followed a traditional manner of macrocyclization/side chain installation. In this work, we adopt a reverse synthetic logic: Sonogashira cross-coupling to install the side chain, followed by a ring-closing metathesis (RCM) reaction to form the macrocycle skeleton. Here we reported the details of our total synthesis of (−)-exiguolide.

The synthesis commenced with the preparation of the known chiral aldehyde **3**, which was previously synthesized by seven steps in an overall 26% yield.[12] Our modified three-step synthesis started from an Et_2AlCl-promoted asymmetric Michael addition of vinylcopper species to Evans' auxiliary-derived crotonoyl imide **1** (Scheme 2).[13] The adduct **2** was

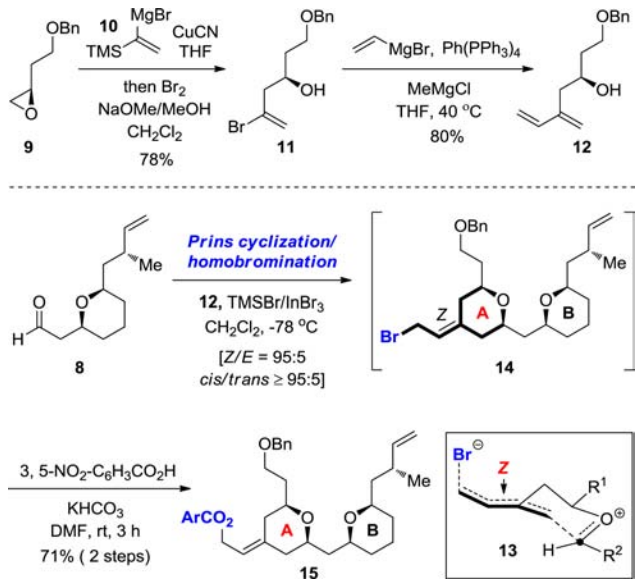
Scheme 2. Prins Cyclization/Bromination To Construct the B Ring



obtained in 75% yield with ≥95:5 *dr*. Reduction of the imide with $LiBH_4$ to a primary alcohol and oxidation with IBX provided aldehyde **3** in 51% yield. Kishi's Fe/Cr-mediated asymmetric allylation was subsequently employed using sulfonamide (*R*)-**4** as a chiral ligand to give homoallylic alcohol **5** in 81% yield with 91:9 *dr*.[14] Rychnovsky's nonracemic protocol[15] with $SnBr_4$ as a Lewis acid and bromine source was launched for Prins cyclization/bromination of **5** with $TBDPSOC_2H_4CHO$. THP **6** containing the desired B ring was delivered in 86% yield as an 88:12 mixture of two bromo-isomers. Removal of the bromide with $(n\text{-}Bu)_3SnH$/AIBN generated **7**, which underwent deprotection of the silyl group and oxidation of the resulting primary alcohol with Dess−Martin periodinane[16] to provide aldehyde **8** as a single *cis*-isomer in an overall 85% yield.

The dienyl alcohol **12**, which is requisite for the construction of the A ring by Prins cyclization/homobromination with aldehyde **8**, was prepared from the known chiral epoxide **9**[17] over the following three steps (Scheme 3, top). Epoxide ring

Scheme 3. Prins Cyclization/Homobromination To Construct the A Ring



opening by the Grignard reagent **10** and subsequent bromination gave the vinyl bromide **11** in 78% yield.[18] **11** was in turn transformed into **12** in 80% yield by a $Pd(PPh_3)_4$-catalyzed Kumada coupling[19] with vinyl magnesium bromide. Prins cyclization/homobromination of **12** with aldehyde **8** was then performed using Loh's protocol[20] with 1.2 equiv of TMSBr as the bromine source and 0.2 equiv of $InBr_3$ as the Lewis acid in CH_2Cl_2 at −78 °C (Scheme 3, bottom). The reaction proceeded readily by the proposed transition state **13** to construct the A ring.[21] However, purification of the bromo-substituted **14** by silica gel column chromatography led to partial decomposition. The problem was finally solved through a mild allylic substitution protocol using 3,5-NO_2-$C_6H_3CO_2H$ and $KHCO_3$ in DMF at room temperature for 3 h. The ester-substituted **15** was delivered in 71% yield with a *cis*/*trans* ratio of ≥95:5 and a *Z*/*E* ratio of 95:5.

The synthesis continued from **15**, which was converted into diol **16** in 69% yield by reducing the ester group with DIBAL-H and removing the benzyl group with Li/naphthalene (Scheme 4). The allylic hydroxyl group in **16** was then selectively oxidized with MnO_2 to give the corresponding enal. The subsequent Pinnick oxidation[22] and methylation of the formed acid with $TMSCHN_2$ generated enoate **17** in an overall 68% yield over three steps. **17** contains the same AB ring skeleton as (−)-exiguolide. Sequential Dess-Martin oxidation and Pinnick oxidation of **17** gave rise to the acidic intermediate **18** in 86% yield.

The C16−C21 fragment **22** was prepared from chiral oxazolidinone **19**, which underwent Evans' asymmetric aldol[23] reaction to give **21** in 81% yield with ≥95:5 *dr* (Scheme 5, top). Reduction of the imide to an alcohol, TEMPO oxidation to aldehyde, and the subsequent Wittig olefination and iodination with NIS generated **22** in an overall 43% yield. Esterification of acid **18** with alcohol **22** provided **23** in 80% yield, which was used for our original plan: RCM reaction[24] to form a macrocycle via C16−C17 double bond formation (Scheme 5, bottom). Unfortunately, extensive examination using various catalysts such as Grubbs' catalyst, Hoveyda−Grubbs' catalyst, and Zhan's catalyst only led to an ∼30% yield with poor

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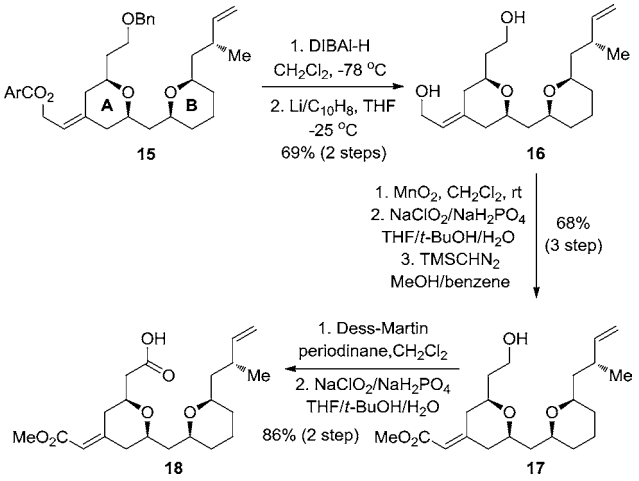
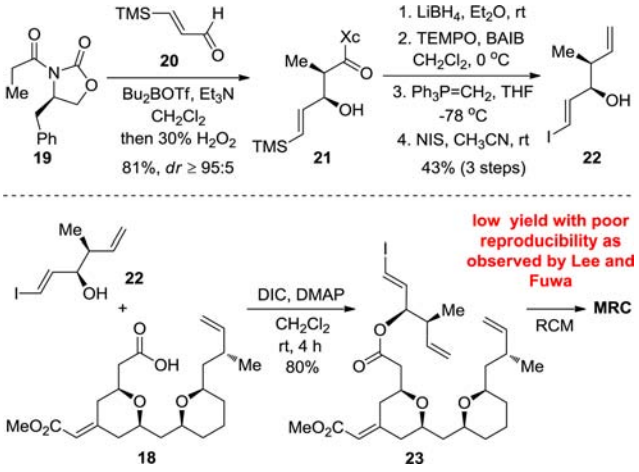
Scheme 4. Synthesis of 18 Containing the Same AB Ring Skeleton as (−)-Exiguolide



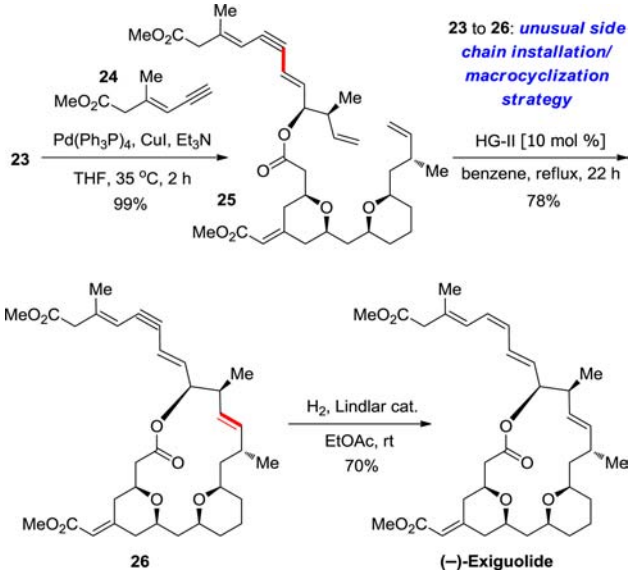
Scheme 5. Synthesis of RCM Precursor 23



reproducibility. Moreover, a nearly stoichiometric amount of catalyst was required to achieve this yield. In fact, the low RCM efficiency was also observed by Lee[7a] and Fuwa[7b] independently in their total synthesis of (−)-exiguolide. The vinyl iodide moiety, which was believed to be incompatible with the catalyst, might interfere severely with the RCM reaction to form the macrocycle.

The above obstacle led us to envision that the RCM reaction might become workable if the impact of vinyl iodide could be avoided by coupling with the side chain first. The idea appeared to be unusual synthetic logic, as previous syntheses all followed a traditional manner of macrocyclization/side chain installation. On the other hand, this strategy presents obvious risks involving competing alkene and enyne metathesis side reactions. Using this plan, Sonogashira cross-coupling[25] of **23** with the known alkyne **24**[7a,c] was first carried out to install the side chain, giving **25** in 99% yield (Scheme 6). To our delight, subsequent macrocyclization catalyzed by 10 mol % Hoveyda−Grubbs' second catalyst[26] occurred regioselectively between two terminal alkenes. The macrocycle **26** was generated as a single *E*-C16−C17 isomer in 78% yield. The internal C20−C21 and C24−C25 double bonds, which should be less reactive than the terminal alkene, were unaffected during the process. Finally, partial hydrogenation of alkyne in **26** to *Z*-C22−C23 alkene with the Lindlar catalyst afforded (−)-exiguolide in 70%

Scheme 6. Sequential Sonogashira Cross-Coupling/RCM Reaction To Form the Macrocycle Skeleton



yield. The spectroscopic data for synthetic (−)-exiguolide were in full accordance with those reported for the naturally occurring compound ($[\alpha]^{D}_{20}$ = −83.4 [*c* 0.08 in $CHCl_3$], ref 1 $[\alpha]^{D}_{20}$ = −92.5 [*c* 0.069 in $CHCl_3$]).

In summary, we have completed a concise total synthesis of (−)-exiguolide from the known crotonoyl imide **1** in 2.8% yield over 20 steps in the longest linear path. The key strategies involve (1) Prins cyclization/homobromination of dienyl alcohol with B ring-substituted aldehyde to construct the A ring with excellent *cis-Z* stereochemical control and (2) an unusual side chain installation/macrocyclization strategy featuring Sonogashira cross-coupling followed by an RCM reaction to deliver the target. Further studies including synthesis and biological evaluations of (−)-exiguolide analogues are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02162.

Experimental procedures and spectral data for products (PDF)

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Author Contributions

§Z.Z. and H.X. contributed equally.

Notes

The authors declare no competing financial interest.

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