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Total Synthesis of (−)-Exiguolide

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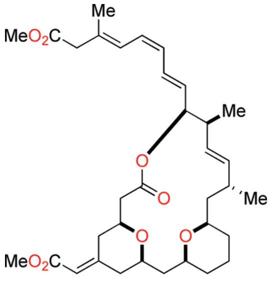
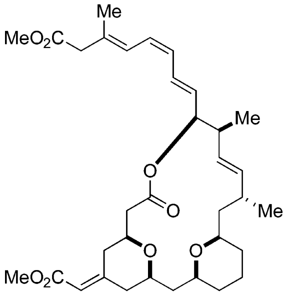
ABSTRACT



(–)-exiguolide

Total synthesis of (−)-exiguolide, the natural enantiomer, has been accomplished for the first time. The bis(tetrahydropyran) subunit was efficiently synthesized via consecutive olefin cross-metathesis/intramolecular oxa-conjugate addition/reductive etherification. Construction of the 20-membered macrocycle was achieved by Yamaguchi macrolactonization. Stereoselective introduction of the (*E*,*Z*,*E*)-triene side chain via Suzuki−Miyaura coupling completed the total synthesis.

(−)-Exiguolide (**1**, Figure 1) was isolated from the methanol extract of the marine sponge *Geodia exigua* Thiele (order Astrophorida, family Geodiidae) by Ohta, Ikegami, and coworkers.[1] The gross structure including relative stereochemistry was determined by the combination of extensive 2D NMR analysis, conformational analysis based on NOESY correlations, and $^3J_{\mathrm{H,H}}$ values and the *J*-based configuration analysis.[2] Subsequently, Lee et al. reported a total synthesis of the unnatural enantiomer of **1**, which established the absolute configuration of this natural product.[3] It is reported that (−)-**1** specifically inhibits fertilization of sea urchin (*Hemicentrotus pulcherrimus*) gametes but not embryogenesis of the fertilized egg. The complex 20-membered macrolactone core embedded with the methylene bis-THP (THP = tetrahydropyran) subunit, a common structural motif that can be found in marine antineoplastic agents bryostatins,[4] is not only synthetically challenging but also biologically intriguing as (−)-**1** might represent a structurally simplified, naturally occurring bryostatin analogue.[5] We describe herein our total synthesis of (−)-exiguolide, the natural enantiomer.



(–)-exiguolide (**1**)

Figure 1. Structure of (−)-exiguolide (**1**).

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[1] Ohta, S.; Uy, M. M.; Yanai, M.; Ohta, E.; Hirata, T.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 1957.

[2] Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866.

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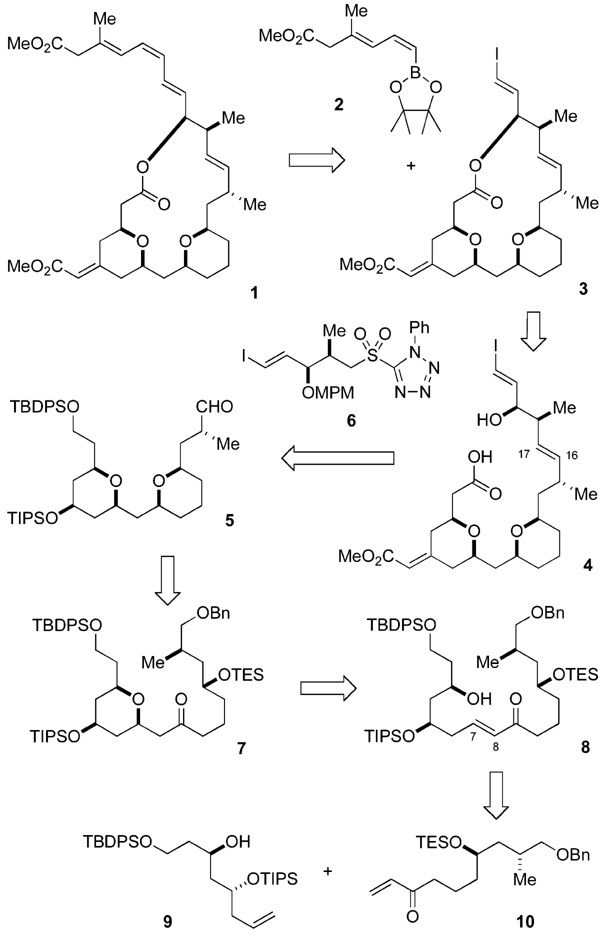
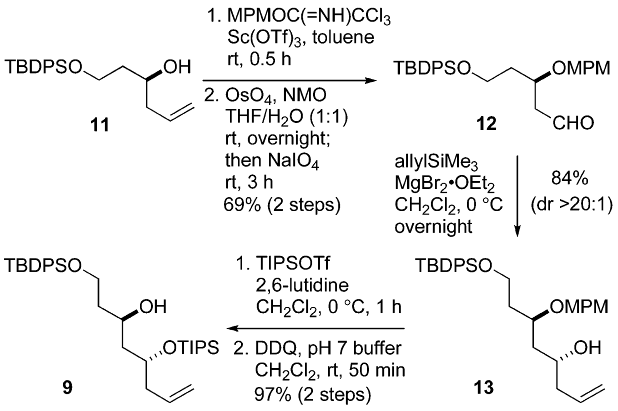
10.1021/ol902778y

Scheme 1. Synthesis Plan toward (−)-Exiguolide (**1**)



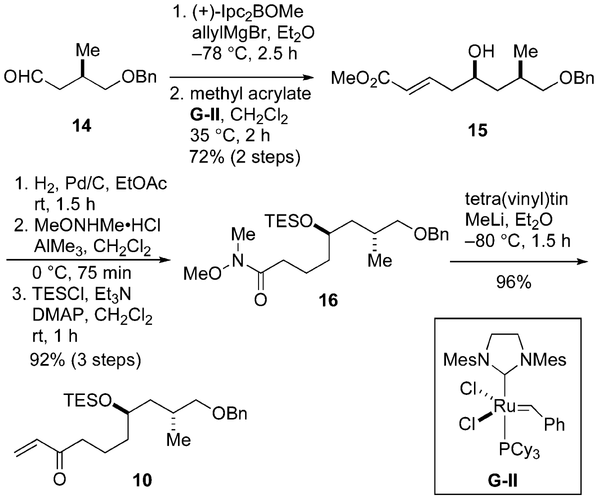
Our synthetic plan toward **1** is summarized in Scheme 1. Stereoselective construction of the (*E*,*Z*,*E*)-triene side chain would be viable by Suzuki−Miyaura coupling[6] of (*Z*)-vinyl boronate **2** and (*E*)-vinyl iodide **3**. The 20-membered macrolactone core of **3** would be accessible through macrolactonization of hydroxy acid **4**. The C16−C17[7] double bond of **4** was envisaged to be formed by Julia−Kocienski coupling[8] of aldehyde **5** and sulfone **6**. Lee et al. have synthesized the methylene bis-THP subunit of (+)-**1** in a linear manner via intramolecular Prins and radical cyclizations.[3] In contrast, we planned an efficient and convergent entry to **5** from the readily available acyclic fragments **9** and **10** via the intermediacy of silyloxy ketone **7** and enone **8**. Thus, bicyclic ether **5** could be delivered from silyloxy ketone **7** via reductive etherification,[9] and the latter could originate from enone **8** by intramolecular oxa-conjugate addition.[10] Enone **8** was expected to be prepared from **9** and **10** via olefin cross-metathesis (CM).[11] Notably, our strategy takes advantage of the high chemoselectivity of CM and the inherent reactivity of the functional groups present in **9** and **10**.

Scheme 2. Synthesis of Alcohol **9**



The synthesis of alcohol **9** is illustrated in Scheme 2. Protection of **11** (>95% ee by Mosher ester analysis)[12] as its MPM ether followed by oxidative cleavage of the double bond delivered aldehyde **12** in 69% yield (two steps). Chelation-controlled allylation of **12** afforded homoallylic alcohol **13** in 84% yield as a single diastereomer (dr > 20:1). Silylation of **13** was followed by deprotection of the MPM group to give alcohol **9** in 97% yield (two steps).

Scheme 3. Synthesis of Enone **10**



The synthesis of enone **10** commenced with Brown asymmetric allylation[13] of the known aldehyde **14**[14] (Scheme 3).

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(5) For a review, see: Cossy, J. C. R. *Chimie* **2008**, *11*, 1477.

(6) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *Chem. Commun.* **2005**, 4759.

(7) The carbon numbering in this paper corresponds to that of the natural product.

(8) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (c) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831.

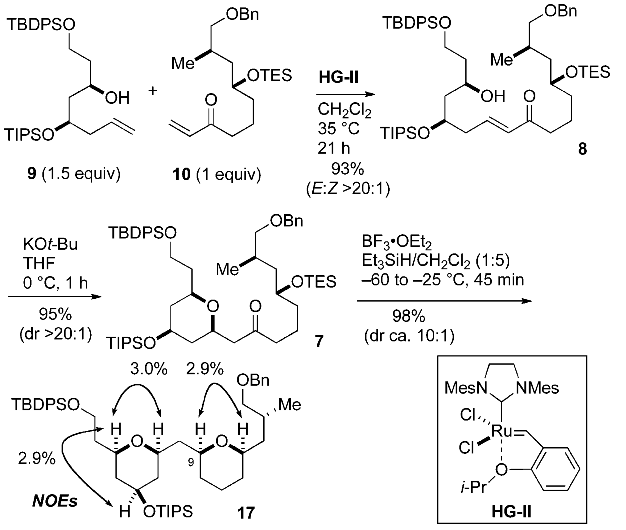
(9) Lewis, D. L.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(10) For a recent review, see: Larrosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683.

(11) For a recent review, see: Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.

Subsequent olefin cross-metathesis with methyl acrylate using Grubbs second-generation catalyst (**G-II**)[15] led to enoate **15** in 72% yield (two steps). After hydrogenation of the double bond, the resulting ester was transformed to the corresponding Weinreb amide. The remaining hydroxy group was masked as its TES ether to give **16** in 92% yield (three steps). Exposure of **16** to vinyllithium generated in situ from tetra(vinyl)tin and MeLi furnished enone **10** in 96% yield.

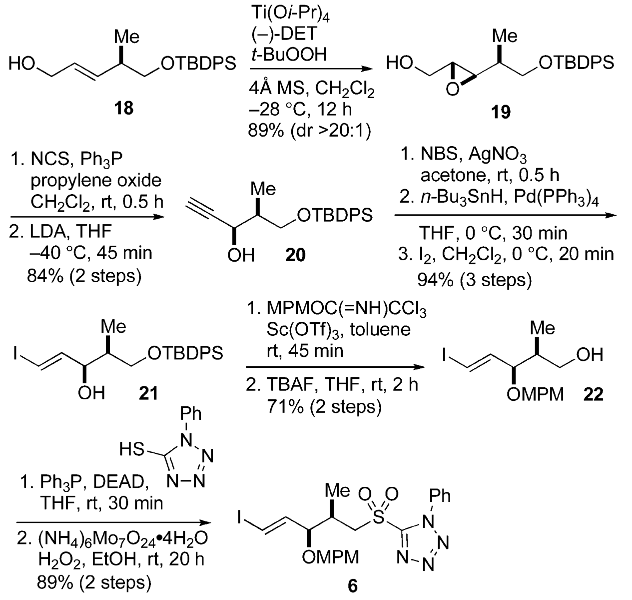
Scheme 4. Construction of the bis-THP Subunit **5**



With the requisite fragments in hand, we proceeded to build up the methylene bis-THP subunit of **1** (Scheme 4). First, assembly of the fragments **9** and **10** was accomplished via CM using 10 mol % of Hoveyda−Grubbs second-generation catalyst (**HG-II**)[16] in CH_2Cl_2 at 35 °C, leading to (*E*)-enone **8** in 93% yield as a single stereoisomer (*E*:*Z* > 20:1). Exposure of **8** to 20 mol % of KO*t*-Bu in THF at 0 °C smoothly effected intramolecular oxa-conjugate addition to afford silyloxy ketone **7** in 95% yield as a single stereoisomer (dr >20:1). The resultant silyloxy ketone **7** was directly treated with $BF_3{\cdot}OEt_2$ in 1:5 Et_3SiH/CH_2Cl_2 (−60 to −25 °C) to furnish the methylene bis-THP **17** in 98% yield with an approximately 10:1 diastereoselectivity at the C9 stereogenic center. At this stage, the newly generated stereogenic centers were established by NOE experiments as shown. Thus, the methylene bis-THP subunit of **1** was successfully constructed in a highly stereocontrolled manner in only three steps from acyclic fragments **9** and **10**.

The synthesis of sulfone **6** (Scheme 5) started with Sharpless asymmetric epoxidation of the known allylic alcohol **18**,[17] available in four steps from (*S*)-Roche ester, giving epoxy alcohol **19** in 89% yield (dr > 20:1). Chlorination of **19**[18] followed by exposure of the resultant chloroepoxide to LDA[19] gave propargylic alcohol **20** in 84% yield (two steps). After conversion of **20** to the corresponding bromoalkyne, palladium-catalyzed hydrostannylation[20] and subsequent iododestannylation delivered (*E*)-vinyl iodide **21** in 94% yield (three steps). Protection of **21** as the MPM ether was followed by desilylation to give alcohol **22** in 71% yield (two steps). Mitsunobu coupling of **22** with 1-phenyl-1*H*-tetrazole-5-thiol and ensuing peroxide treatment afforded sulfone **6** in 89% yield (two steps).

Scheme 5. Synthesis of Sulfone **6**



Completion of the total synthesis of (−)-**1** is illustrated in Scheme 6. Cleavage of the benzyl ether of **17** by hydrogenolysis gave alcohol **23** in 90% yield after removal of the minor C9 epimer by flash chromatography on silica gel. Oxidation of **23** with Dess−Martin periodinane gave aldehyde **5** in 97% yield. Julia−Kocienski coupling of an anion derived in situ from sulfone **6** and aldehyde **5** was examined under several conditions. This coupling reaction initially suffered from poor conversion under the standard conditions (e.g., KHMDS, DME, −55 °C to rt, 18% yield, 35% yield based on recovered **5**, *E*:*Z* > 20:1). However, we eventually found that treatment of sulfone **6** (2.2 equiv) with LHMDS

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(12) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 4275.

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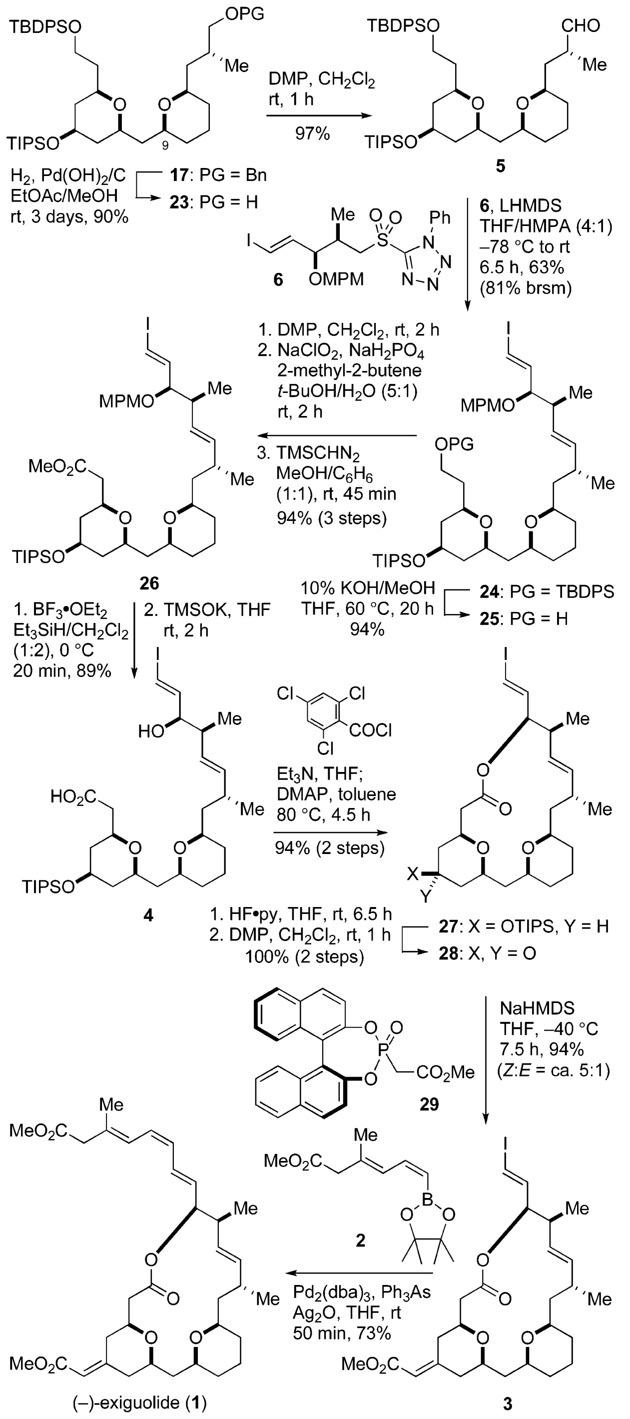
(22) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(23) (a) Tanaka, K.; Ohta, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 4071. (b) Evans, D. A.; Csarter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (c) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.

Scheme 6. Completion of the Total Synthesis of (−)-Exiguolide



(2.2 equiv) in THF/HMPA (4:1) at −78 °C followed by addition of aldehyde **5** and warming the reaction mixture to room temperature afforded the desired (*E*)-olefin **24** in 63% yield (81% yield based on recovered **5**, *E*:*Z* > 20:1). The unreacted **5** and excess **6** could be recovered and recycled efficiently. Selective deprotection of the TBDPS group under basic conditions afforded alcohol **25** in 94% yield. A two-stage oxidation followed by esterification gave methyl ester **26** in 94% yield for the three steps. Cleavage of the MPM group and subsequent saponification of the methyl ester[21] afforded hydroxy acid **4**, which underwent smooth macrocyclization under Yamaguchi conditions[22] to furnish the 20-membered lactone **27** in 84% yield (three steps). Deprotection of the TIPS group of **27** was followed by oxidation of the resultant alcohol to give ketone **28** in 100% yield (two steps). The exocyclic enoate functionality was introduced to **28** by Horner−Wadsworth−Emmons reaction using chiral phosphonate **29** developed by Fuji et al.,[23] giving a separable 5:1 mixture of stereoisomers favoring the desired (*Z*)-isomer **3**. Finally, stereoselective incorporation of the triene side chain was realized through Suzuki−Miyaura coupling of **3** with (*Z*)-vinyl boronate **2**[24] under exceptionally mild conditions ($Pd_2(dba)_3$, Ph_3As, Ag_2O, THF, room temperature),[25] leading to (−)-exiguolide (**1**) in 73% yield. The spectroscopic data of synthetic **1** (^1H and ^{13}C NMR, HRMS, and $[\alpha]_D$) were in full accordance with those reported.[1,3]

In conclusion, the total synthesis of (−)-exiguolide (**1**), the naturally occurring enantiomer, was accomplished for the first time. Our strategy for the construction of the methylene bis-THP subunit of **1** harnessed the high chemoselectivity of olefin metathesis reactions that allowed for direct utilization of the pre-existing functionalities of **9** and **10** in subsequent ring-forming events, thereby maximizing the overall efficiency of the strategy. The sterically encumbered C16−C17 double bond was constructed in a stereoselective manner via Julia−Kocienski coupling under the modified conditions. The 20-membered macrocycle was efficiently assembled based on Yamaguchi macrolactonization. Finally, the stereoselective construction of the (*E*,*Z*,*E*)-triene side chain via Suzuki−Miyaura coupling under exceptionally mild conditions successfully completed the total synthesis.

Acknowledgment. We thank Professor Shinji Ohta (Nagahama Institute of Bio-Science and Technology) for kindly providing us with copies of ^1H and ^{13}C NMR spectra of natural exiguolide. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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