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Total Synthesis of Paralemnolide A

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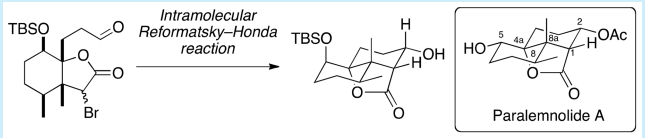
Supporting Information

ABSTRACT: The first total synthesis of tricyclic bisnorsesquiterpene paralemnolide A, isolated from the soft coral *Paralemnalia thyrsoides*, was achieved. This synthesis features the lactonization of the cyclohexene derivative having a *tert*-butyl ester via stereoselective epoxidation followed by treatment with a Brønsted acid and construction of the novel tricyclic skeleton by an intramolecular Reformatsky−Honda reaction.



Members of the soft coral genus *Paralemnalia* are rich sources of biologically active natural products.[1] In 2012, Duh and co-workers reported the isolation of bisnorsesquiterpene paralemnolide A **1**, from the soft coral *Paralemnalia thyrsoides*.[1b] The unique tricyclic structure of **1**, including its peculiar ring system, was assigned using 2D NMR as shown in Figure 1. In addition, the absolute configuration of **1** was

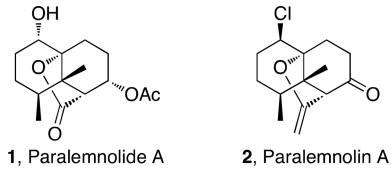


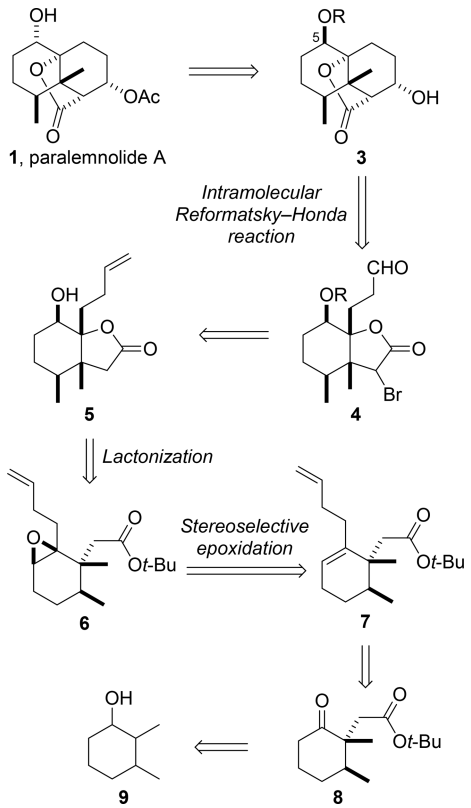
Figure 1. Structures of paralemnolide A, **1**, and paralemnolin A, **2**.

determined as 1*R*, 2*S*, 4a*R*, 5*S*, 8*S*, and 8a*S* using a modified Mosher method involving the hydroxyl group at the C5 position. The biological activity of paralemnolide A **1** reported moderate cytotoxicity (ED_{50} = 3.8 μg/mL) against the P-388 cell line, but no cytotoxic activity against the A549 and HT-29 cell lines, and antiviral activity against human cytomegalovirus. Norsesquiterpene paralemnolin A **2** containing a chlorine atom was isolated from the same soft coral in 2005 by Sheu and co-workers.[1h] The unusual tricyclic structure of **2** was assigned using 2D NMR spectroscopic analysis and X-ray crystallographic analysis as depicted in Figure 1. Its absolute stereochemistry was established using the Flack parameter for the X-ray diffraction analysis. Although these small and complex molecules are challenging targets for total synthesis, no studies of their total synthesis have been reported.

Interest in the structural features of these novel tricyclic natural products prompted a synthetic study based on the intramolecuar Reformatsky−Honda reaction. The present report describes the stereoselective total synthesis of paralemnolide A in 14 steps starting from 2,3-dimethylcyclohexanol.

The strategy for the total synthesis of paralemnolide A **1** is outlined in Scheme 1. The target natural compound would be synthesized from tricyclic compound **3** via transformations that

Scheme 1. Synthetic Scheme for Paralemnolide A, 1



included stereochemistry inversion of the hydroxyl group at the C5 position. Tricyclic lactone **3** containing the principal framework of **1** would be constructed through intramolecular Reformatsky−Honda reaction of the α-bromolactone **4** tethering aldehyde group. Precursor **4** would be derived from lactone **5** by α-bromination of the carbonyl group and oxidative

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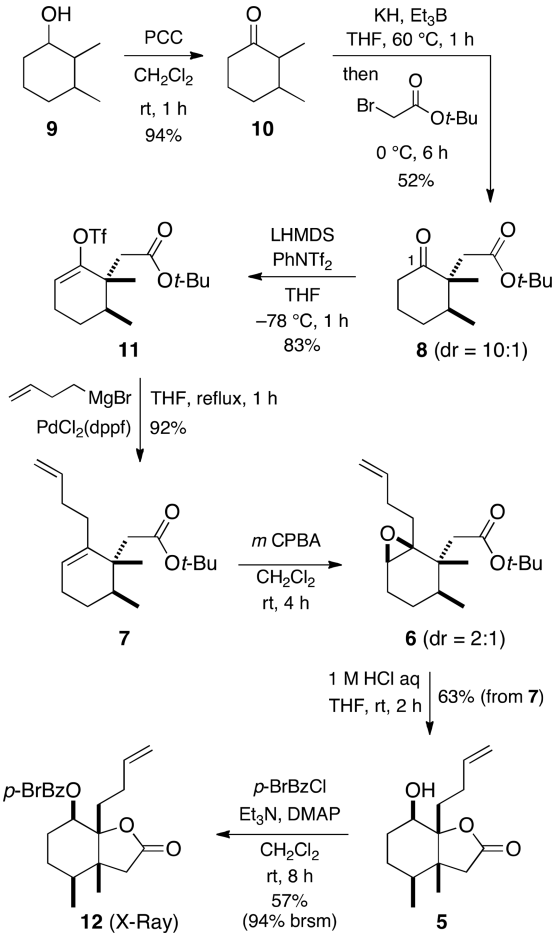
cleavage of the carbon−carbon double bond. The bicyclic lactone **5** would be obtained through stereoselective epoxidation of cyclohexene derivative **7** followed by treatment of epoxide **6** with a Brønsted acid. The cyclohexene derivative **7** would be synthesized from 2,2,3-trisubstituted cyclohexanone **8** via introduction of an alkenyl side chain through Kumada coupling. The cyclohexene derivative **8** would be easily prepared from commercially available 2,3-dimethylcyclohexanol (**9**) as the starting material.

This synthetic study began with the preparation of cyclohexene derivative **7**, the precursor for epoxidation, from 2,3-dimethylcyclohexanol, as shown in Scheme 2. Oxidation of

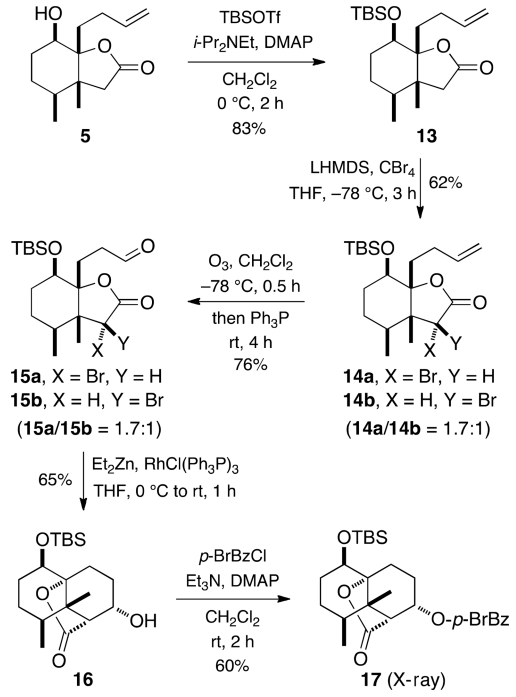
Scheme 2. Stereoselective Synthesis of Bicyclic Lactone 5



2,3-dimethylcyclohexanol (**9**) with PCC gave 2,3-dimethylcylcohexanone (**10**) in high yield.[2] After treatment of 2,3-dimethylcyclohexanone (**10**) with potassium hydride and triethylborane in THF at 60 °C according to a procedure by Negishi,[3] alkylation of the thermodynamically more stable boron enolate with *tert*-butyl bromoacetate afforded the desired product **8** in 52% yield (dr = 10:1). Introduction of a butenyl side chain at the C1 position of **8** was realized by a metal-catalyzed Kumada coupling reaction[4] of vinyl triflate **11** prepared from ketone **8**, with butenylmagnesium bromide. Enolization of ketone **8** with LHMDS, followed by trapping of the enolate anion with *N*-phenylbis(trifluoromethanesulfone)-amide yielded the corresponding vinyl triflate **11**. After the screening of metal catalysts for the Kumada coupling reaction, $PdCl_2$(dppf)[5] was found suitable for this reaction. Thus, Kumada coupling of vinyl triflate **11** with butenylmagnesium bromide in the presence of $PdCl_2$(dppf) in THF under reflux for 1 h furnished the coupling product **7** in 92% yield. Stereoselective epoxidation of cyclohexene derivative **7** with *m*-chloroperbenzoic acid (*m*CPBA) gave an inseparable mixture of epoxide **6** and its diastereomer in a 2:1 ratio as a crude product. This crude product was treated immediately with a Brønsted acid, 1 M hydrochloric acid, to afford the bicyclic lactone **5** in 63% yield in two steps. Related configurations of bicyclic lactone **5** were confirmed using X-ray crystallography of the *p*-bromobenzoate **12**,[6] derived from **5** by esterification with *p*-bromobenzoyl chloride. The stereochemical configuration of all substituted groups of the bicyclic lactone, two types of methyl groups, the butenyl side chain, and the hydroxyl group was *syn*, which indicates that epoxidation of cyclohexene derivative **7** with *m*CPBA proceeded from the opposite side of the *tert*-butoxycarbonylmethyl group, which is the most bulky group of **7**, and that lactonization of epoxide **6** under acidic conditions involved 5-*exo*-cyclization of the ester carbonyl group with the more cationic carbon of the epoxide portion that was activated by protonation.

After synthesis of bicyclic lactone **5**, the tricyclic skeleton of the target molecule was constructed, as shown in Scheme 3.

Scheme 3. Stereoselective Synthesis of Tricyclic Compound 16



Upon protection of the hydroxyl group of **5** with TBS, many different reaction conditions for α-bromination of **13** were investigated, including different bases (LDA and LHMDS) and brominating agents (NBS, CBr_4, and *N*-phenyltrimethyl-ammonium tribromide). The combination of LHMDS and CBr_4 in THF at −78 °C gave the best results to afford **14a** and **14b** in 62% yield in a 1.7:1 ratio.[7] The stereochemistry of the bromolactone **14b** was confirmed by X-ray crystallographic analysis.[8] Ozonolysis of the mixture of bromides **14a** and **14b** produced a mixture of aldehydes **15a** and **15b** (Reformatsky−Honda reaction precursors) in 76% yield. To construct the rigid tricyclic framework,[9] which was the key feature of this project,

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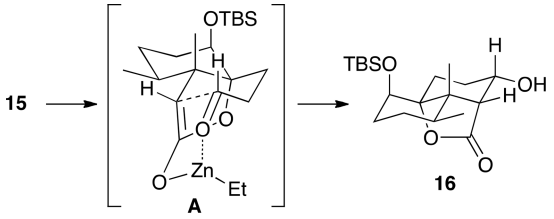
an intramolecular Reformatsky−Honda reaction[10] using Wilkinson's catalyst and diethylzinc of the mixture of α-bromolactones **15a** and **15b** produced the cyclized product **16** in moderate yield as the sole product. The relative configuration of the tricyclic compound **16** was confirmed from X-ray crystallographic analysis of its *p*-bromobenzoate derivative **17**[11] obtained by esterification of **16**.

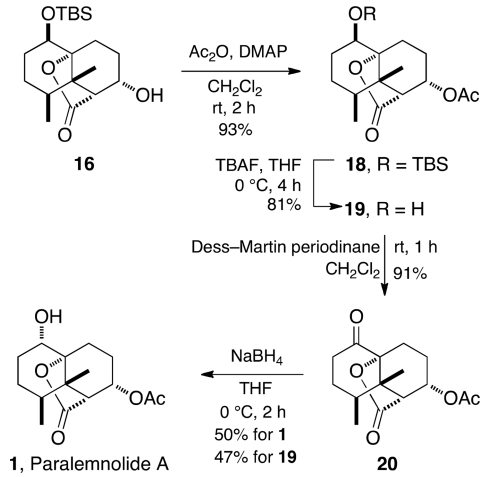
The intramolecular Reformatsky−Honda reaction of **15** proceeded via the six-membered ring transition state of zinc enolate **A**[10a] as shown in Scheme 4 to afford the α-hydroxyl cyclized product **16** as a single isomer.

Scheme 4. Possible Mechanism of the Reformatsky−Honda Reaction of 15



Upon obtaining tricyclic compound **16**, the final stage of the synthesis was performed. After attaching an acetyl group to the hydroxyl group of **16**, cleavage of the TBS group of the resulting **18** with TBAF gave alcohol **19** in 81% yield (Scheme 5). Inversion of the stereochemical configuration at the C1

Scheme 5. Total Synthesis of 1



position of **19** was the final step. First, Mitsunobu reaction using benzoic acids, phosphines, and diazo compounds were attempted. However, no desired products were detected under Mitsunobu reaction conditions. These results led to development of a two-step operation, oxidation followed by reduction with a hydride reagent. After oxidation of **19** with Dess−Martin periodinane, hydride reduction of the resulting ketone **20** with hydride reagents was conducted. Although many reduction conditions for ketone **20** resulted in decomposition of the acetoxy portion and/or lactone of **20**, use of sodium borohydride afforded the target molecule **1** and **19** as a separable mixture in 97% yield. Unfortunately, stereoselective reduction of **20** was not achieved, with a 1:1 ratio of target compound to its diastereomer **19**. The alcohol **19** was recyclable to the ketone **20** by Dess−Martin oxidation. The spectral data for synthetic sample **1** were completely identical with those for natural product **1**.

In conclusion, the first total synthesis of tricyclic bisnorsesquiterpene paralemnolide A was accomplished. This synthesis features the formation of a lactone ring via epoxidation followed by acid treatment of the resulting epoxide tether *tert*-butyl ester portion, and construction of the novel tricyclic skeleton by intramolecuar Reformatsky−Honda reaction. This methodology can be extended to the synthesis of the related natural product, paralemnolin A. Related investigations are now underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03038.

Experimental procedures, spectral data (PDF)
Crystallographic data for compound **12** (CIF)
Crystallographic data for compound **14b** (CIF)
Crystallographic data for compound **17** (CIF)

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Notes

The authors declare no competing financial interest.

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(6) CCDC 1574422 contains the supplemental crystallographic data of **12** for this paper.
(7) The reaction conditions, except for the combination of LHMDS and CBr_4, gave the complex mixture including trace amounts of **14a** and **14b**.
(8) CCDC 1574427 contains the supplemental crystallographic data of **14b** for this paper.
(9) Although many aldol-type cyclizations of aldehyde, which were obtained by ozonolysis of **13** to build the tricyclic skeleton, were attempted at first, all examinations of intramolecular aldol-type reaction failed.
(10) (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549. (b) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307.
(11) CCDC 1574428 contains the supplemental crystallographic data of **17** for this paper.

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