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Total Synthesis of (±)-Clavubicyclone

Hisanaka Ito,* Shunta Takeguchi, Takahiro Kawagishi, and Kazuo Iguchi*

School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

itohisa@ls.toyaku.ac.jp; onocerin@ls.toyaku.ac.jp

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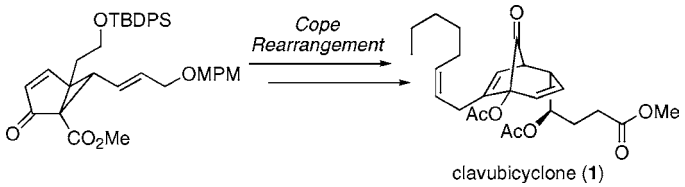
ABSTRACT



The total synthesis of racemic clavubicyclone (1), which was isolated from Okinawan soft coral by our group, is described. The bicyclo[3.2.1]-octane skeleton was prepared by Cope rearrangement of a divinylcyclopropane derivative. Three functional groups on the skeleton were constructed by Barton decarboxylation, Wittig reaction, and alkylation.

Clavubicyclone (**1**) and tricycloclavulone were recently isolated from Okinawan soft coral, *Clavularia viridis*, by our group as novel prostanoid-related compounds which have a bicyclo[3.2.1]octane skeleton (clavubicyclone) and a tricyclo[5.3.0.0^{1,4}]decane skeleton (tricycloclavulone) (Figure 1).[1] Although the planar structures and relative stereochemistries of the chiral centers on the cyclic cores were determined by spectroscopic analysis, the stereochemistry of the carbon bearing the acetoxyl group on the side chain as well as the absolute stereochemistry had not yet been examined. We recently achieved an enantioselective total synthesis of tricycloclavulone, and the determination of the relative and absolute stereochemistries[2] was attained. Clavubicyclone (**1**), having a bicyclo[3.2.1]octane skeleton, two side chains, and an acetoxyl group on the bridgehead position, is a quite attractive synthetic target for organic chemists. Therefore, effective construction of the bicyclic core of **1** was examined, and we report herein the total synthesis of (±)-clavubicyclone (**1**).

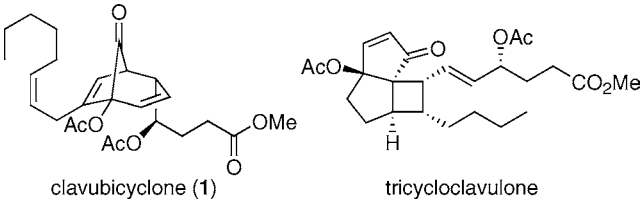


Figure 1. The structures of marine prostanoid-related compounds, clavubicyclone (**1**) and tricycloclavulone.

Our strategy for the total synthesis of clavubicyclone (**1**) focused on the use of Cope rearrangement of **4** to construct the bicyclo[3.2.1]octane skeleton[3,4] and Barton decarboxylation to create the bridgehead acetoxyl group (Scheme 1). For the preparation of compound **4**, aldol reaction of **6** with dienolate and the following intramolecular cyclopropanation using a Rh catalyst were employed. Conversion of the methoxycarbonyl group of **3** to an acetoxyl group would be achieved through Barton decarboxylation and the following oxidation of the resulting radical intermediate by oxygen. The construction of both side chains would achieve the total synthesis of clavubicyclone (**1**).

(1) Iwashima, M.; Terada, I.; Okamoto, K.; Iguchi, K. *J. Org. Chem.* **2002**, *67*, 2977−2981.

(2) (a) Ito, H.; Kobayashi, T.; Hasegawa, M.; Iguchi, K. *Tetrahedron Lett.* **2003**, *44*, 1259−1261. (b) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 4520−4521.

(3) (a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C. *Chem. Rev.* **1989**, *89*, 165−198. (b) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715−737. (c) Arai, M.; Crawford, R. J. *Can. J. Chem.* **1972**, *50*, 2158−2162. (d) Baldwin, J. E.; Gilbert, K. E. *J. Am. Chem. Soc.* **1976**, *98*, 8283−8284.

(4) For an example of a synthesis of natural product through Cope rearrangement of divinylcyclopropane, see: Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427.

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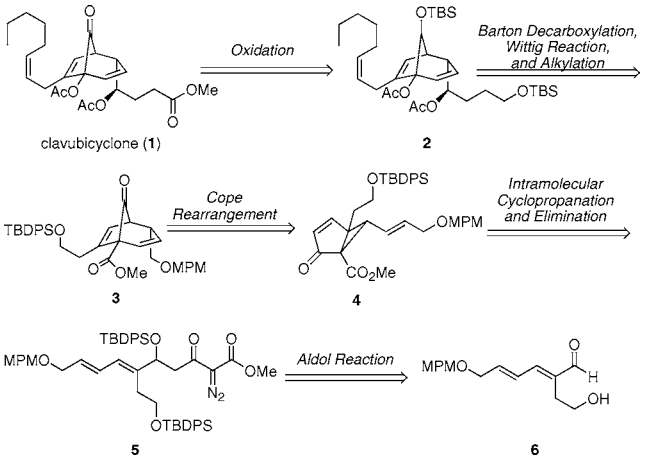
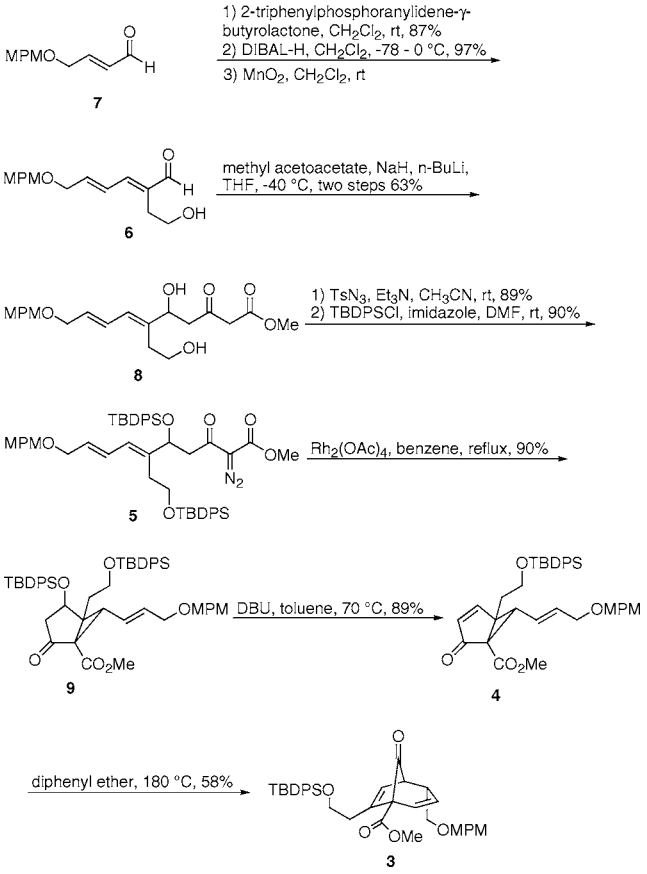
Scheme 1. Retrosynthetic Analysis of Clavubicyclone



The synthesis of the bicyclo[3.2.1]octane skeleton is shown in Scheme 2. Compound **7** was prepared according to the reported procedure in two steps from *cis*-2-butene-1,4-diol.[5] Wittig reaction of **7** with 2-triphenylphosphoranylidene-γ-butyrolactone,[6] reduction of the lactone moiety to diol, and selective oxidation of the allylic alcohol moiety with MnO_2 gave aldehyde **6**. Reaction of the dianion of methyl acetoacetate with **6** gave compound **8**, which could be converted to **5**, a precursor for intramolecular cyclopropanation in two steps. Intramolecular cyclopropanation of **5** proceeded under the presence of a catalytic amount of rhodium acetate dimer, and compound **9** was obtained in 90% yield as a diastereomeric mixture (3:1). Elimination of the alkoxyl group on the cyclopentanone ring of the diastereomeric mixture of **9** proceeded by treating it with DBU to afford compound **4** (single isomer) as a precursor of Cope rearrangement.

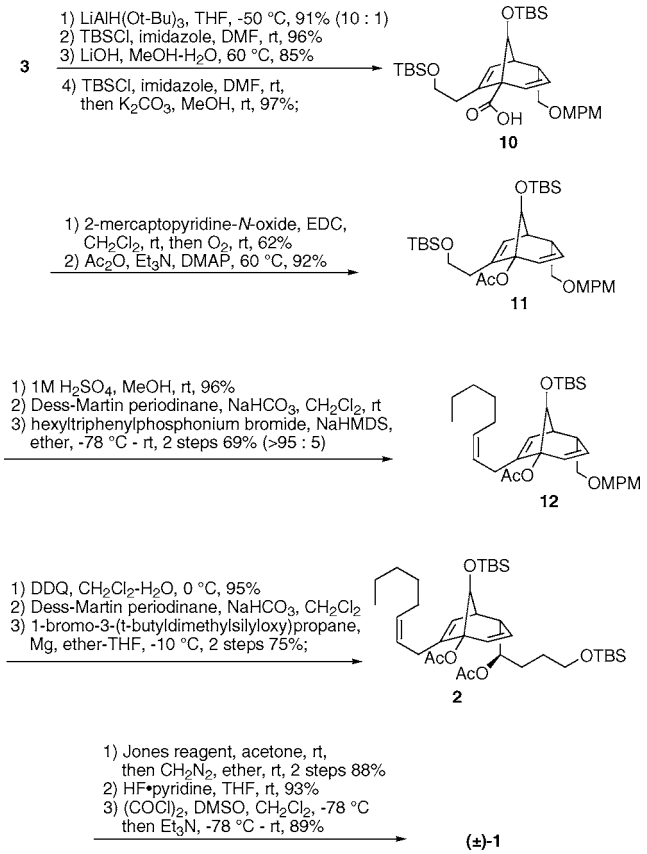
Scheme 2. Construction of Bicyclo[3.2.1]octane Skeleton



Cope rearrangement of **4** was examined under several conditions. In toluene, the reaction was carried out at 110 °C for 72 h, and the product **3** was obtained in 34% yield along with undetectable byproducts. When the reaction was carried out at 140 °C in xylene, compound **4** disappeared after 18 h; however, the yield was almost the same (36%) as that in the case of toluene. In the case of diphenyl ether, the reaction proceeded at 180 °C within 0.5 h, and the yield significantly increased and compound **3** was obtained in 58% yield.

The effort for the total synthesis of clavubicyclone (**1**) is shown in Scheme 3. Prior to the conversion of three functional groups on the bicyclo[3.2.1]octane skeleton, protection of the ketone group was examined. The reaction for the formation of a ketal group, however, did not proceed. Therefore, the ketone was reduced to a hydroxyl group in a

Scheme 3. Total Synthesis of Clavubicyclone



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(6) Lyga, J. W.; Secrist, J. A., III. *J. Org. Chem.* **1983**, *48*, 1982−1988.

diastereoselective manner (10:1), and the resulting hydroxyl group was protected with a TBS group. The stereochemistry of the newly formed chiral center was not determined. Hydrolysis of the methoxycarbonyl group was carried out in the presence of LiOH, but the TBDPS group was also cleaved. Therefore, the primary hydroxyl group was protected by a TBS group again to give compound **10**. Conversion of compound **10** to **11** was achieved by Barton decarboxylation.[7,8] Thus, after the Barton ester formation under dark condition, oxygen gas was introduced to the reaction mixture, and the decarboxylation reaction and subsequent oxidation of the Barton ester were carried out under fluorescent light, and the following acetylation gave compound **11** in 57% (two steps). Selective cleavage of the TBS groups of **11** to obtain primary alcohol proceeded under acid hydrolysis conditions. Oxidation of the hydroxyl group and Wittig reaction of the resulting aldehyde with the ylide, which was prepared from hexyltriphenylphosphonium bromide with NaHMDS in ether, proceeded to give **12** in a highly *Z*-selective manner (>95:5). If the reaction was carried out in THF, migration of the carbon−carbon double bond to form an α,β-unsaturated aldehyde occurred and the product was not obtained. With the use of *n*-BuLi as a base for the preparation of the ylide, a *Z*:*E* mixture (3:1) of **12** was obtained.

Deprotection of the MPM group of **12** and subsequent oxidation of the resulting hydroxyl group gave the aldehyde. Introduction of a three-carbon unit was performed by alkylation of the aldehyde with 3-(*tert*-butyldimethylsilyloxy)propylmagnesium bromide (diastereomeric ratio was 1:1). Although the diastereoselectivity of the introduction of the three-carbon unit was not observed, it would be resolved by the use of an asymmetric allylation in the case of the synthesis of an enantiomerically pure compound. After the separation of the diastereomers, acetylation of the hydroxyl group of the one diastereomer gave compound **2**.[9] Selective deprotection of the primary silyl ether of **2** and the following oxidation of the resulting hydroxyl group to a hydroxycarbonyl group was achieved by treating **2** with Jones reagent for 15 min. If longer reaction time (more than 30 min) was employed for the deprotection and subsequent oxidation of the secondary silyl ether, decomposition was observed. The following methyl esterification of the resulting hydroxycarbonyl group by treating it with diazomethane gave a methyl ester in 88% yield (two steps). Deprotection of the secondary silyl ether and the following oxidation of the resulting hydroxyl group by Swern oxidation achieved the total synthesis of (±)-clavubicyclone (**1**). The spectral data (^{1}H, ^{13}C, and MS) of synthetic clavubicyclone (**1**) were identical with those of natural **1**.[1]

In conclusion, the total synthesis of (±)-clavubicyclone was achieved through Cope rearrangement for the construction of a bicyclo[3.2.1]octane skeleton. Work for the synthesis of **1** as an enantiomerically pure form and the determination of the absolute stereochemistry is now underway.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) We also examined the use of another diastereomer for the total synthesis. The final compound derived from another diastereomer was not identical to clavubicyclone (**1**).