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Enantioselective total synthesis of natural 11,12-epoxycembrene-C

Yulin Li,[a,*] Zuosheng Liu,[a] Jiong Lan,[a] Jing Li,[a] Lizeng Peng,[a] Weidong Z. Li,[a] Ying Li[a] and Albert S. C. Chan[b]

[a]*National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*

[b]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, PR China*

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Abstract

The first enantioselective total synthesis of (+)-11,12-epoxycembrene-C (**1**), a novel naturally occurring cembranoxide isolated from tropical marine soft coral, was achieved via a general approach by employing an intramolecular McMurry coupling and Sharpless asymmetric epoxidation as key steps from readily available starting materials.

Keywords: cembrane diterpenoid; McMurry coupling; Sharpless epoxidation; 11,12-epoxycembrene-C; total synthesis.

Cembranoids, a family of 14-membered cyclic diterpenoid natural products existing in terrestrial and especially in marine organisms,[1] are of great interest to synthetic organic chemists and biologists because of their unique structure and wide range of biological activities.[2] Naturally occurring cembranoid epoxides (cembranoxides) have been found as chemical components of various tropical marine soft corals and represent a class of oxidative metabolites of cembrane diterpenes. (+)-11,12-Epoxycembrene-C (**1**), a novel cembrane epoxide, was first isolated in 1978 by Bowden and co-workers[3] from the Australian soft coral *Sinularia grayi*, which has subsequently been found in various marine soft corals, i.e. *Nephthea* sp.,[4] *Lobophytum* sp.,[5,6] *Eunicea* sp.,[7] and *Sinularia* sp.[8] Its chemical structure was determined by means of extensive spectroscopic techniques and chemical degradation.[3] The absolute stereochemistry of the epoxide function of **1** was deduced as (11*S*,12*S*) indirectly by Horeau's method.[5]

* Corresponding author.

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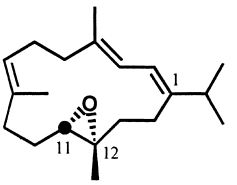
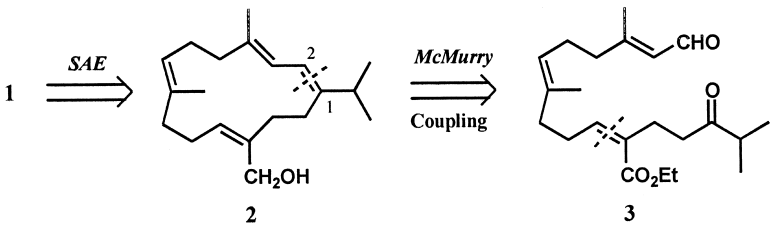


(+)-11, 12-Epoxycembrene-C (1)

Stereoselective and enantioselective construction of the epoxide functionality in the macrocyclic cembrane skeleton comprises a challenging task for total synthesis. A general, facile and highly stereoselective synthetic method for the synthesis of cembranoxides such as **1** is highly desirable as well as the assignments of the absolute stereochemistry of the epoxide function unambiguously. In continuation of our on-going program on the asymmetric synthetic studies of cembranoids, we report the first total synthesis of **1** in this paper.

The low-valent titanium-induced intramolecular dicarbonyl olefination coupling (McMurry reaction)[9] is proven to be a valuable and versatile protocol for the construction of carbocyclic skeleton and has been illustrated in a great number of natural product syntheses as well as highly strained non-natural compounds. The strong reducing conditions and extended reaction times normally used make the process incompatible with the easily reducible functional groups elsewhere in the substrate. Less reactive ester or lactone carbonyl in the substrate might survive under the usual conditions for the reductive olefination of the keto aldehyde precursors mediated by low-valent titanium and be left intact although very few examples under these circumstances have been reported in the literature.[10,11]

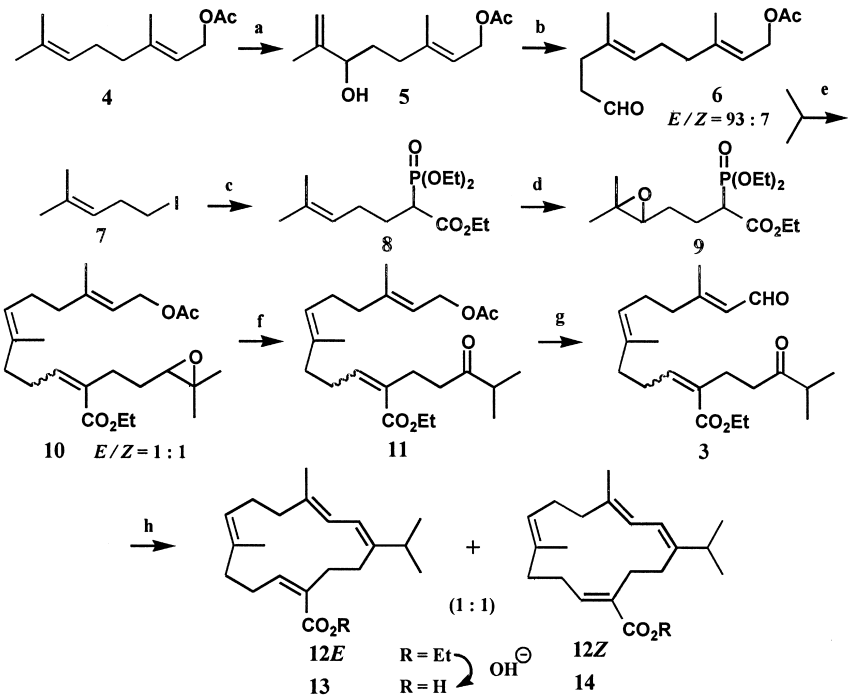
The general strategic plan is depicted in Scheme 1. The epoxide group of **1** would be introduced enantioselectively by Sharpless asymmetric epoxidation (SAE)[12] of the corresponding trisubstituted carbocyclic allylic alcohol **2**. Accordingly, the cembrane ring would be closed by means of the well-developed intramolecular McMurry coupling of the keto aldehyde **3**, which bears an α,β-unsaturated ester carbonyl moiety inert under the reaction conditions. In turn, substrate **3** could be obtained by assembly of two pieces via Wadsworth–Horner–Emmons olefination.



Scheme 1.

The total synthesis of 11,12-epoxycembrene-C (**1**) is detailed in Scheme 2. Allylic alcohol **5**, readily available[13] from geranyl acetate (**4**) in four steps, was converted into the corresponding vinyl ether by a known procedure[14] catalyzed by $Hg(OAc)_2$, which was then subjected to the thermal Claisen rearrangement[15] in a sealed tube at 110°C providing predominantly the desired *trans* aldehyde **6**[16] in a ratio of 93:7 as determined by GC. Homoprenyl iodide **7**[17] was

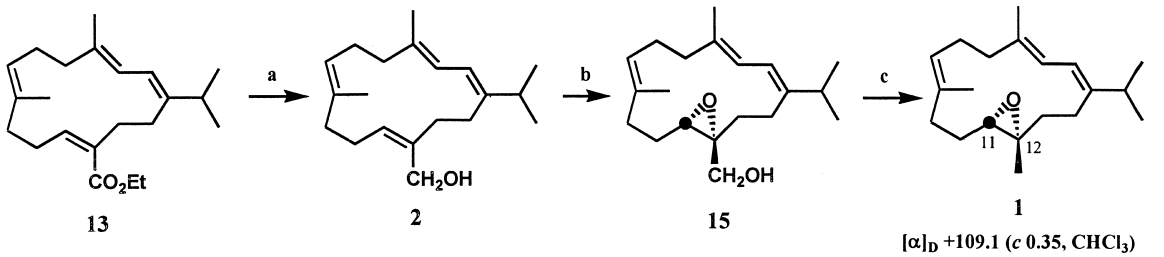
transformed to phosphono-ester **8** in 88% yield by a standard method,[17] which was then exposed to *m*-CPBA in CH_2Cl_2 to give the epoxide **9** in 93% yield. The Wadsworth–Horner–Emmons coupling[18] of phosphono-ester **9** with aldehyde **6** mediated by LDA led to ester **10** in 73% yield as a mixture of an equal amount of geometric isomers as determined by ^{1}H NMR. Ketone **11** was obtained by the rearrangement[19] of the epoxide **10** (*E*+*Z*) catalyzed by $LiClO_4$. Saponification of **11** and subsequent MnO_2 oxidation (72%, two steps) gave the keto aldehyde **3**, which was added slowly via a syringe pump to a slurry of low-valent titanium reagent (prepared by the in situ reduction of $TiCl_4$ with zinc power[9]) in THF under reflux for 6 h to afford the desired carbocyclic ester **12** as the readily separable *E* and *Z* isomers (1:1) by silica gel column chromatography in a combined yield of 48%. Basic hydrolysis of the esters **12***E* and **12***Z* gave acids **13** (R = H) and **14** (R = H), respectively, corresponding to crotocembraneic acid and neocrotocembraneic acid, respectively,[20] two novel cembranoids isolated from the stem bark of the Thai traditional medicinal plant *Croton oblongifolius*, based on the spectroscopic comparison with the natural products.



Scheme 2. *Reagents and conditions*: (a) Ref. 13; (b) 1. $Hg(OAc)_2$, ethyl vinyl ether, reflux, 83%; 2. sealed tube, 110°C, 90%; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMF, 60°C, 88%; (d) *m*-CPBA, CH_2Cl_2, 0°C, 93%; (e) LDA, THF, −78°C, 30 min then aldehyde **6**, −78°C to 23°C, 73%; (f) $LiClO_4$, C_6H_6, reflux, 81%; (g) 1. K_2CO_3, MeOH, 23°C; 2. MnO_2, *n*-hexane, 23°C, 72%; (h) $TiCl_4$, Zn, THF, reflux, 48%

Reduction of ester **13** with $LiAlH_4$ in ether gave allylic alcohol **2** in 92% yield, which was epoxidized under Sharpless asymmetric epoxidation[12] conditions with D-(−)-DET to afford epoxy alcohol **15** in 85% yield and 95% *ee* as determined by high resolution (400 MHz) ^{1}H

NMR analysis of the corresponding Mosher's ester[21] (Scheme 3). Standard iodination[22] of **15** (Ph_3P, imidazole, Py, I_2) and subsequent reductive dehalogenation[23] of the corresponding intermediary iodide with $NaBH_3CN$ in HMPA furnished the title compound **1**, which showed identical spectroscopic properties (^1H, ^{13}C NMR) with those of natural product as well as the specific rotation of the synthetic **1** {$[\alpha]_D^{18}$ +109.1 (*c* 0.75, $CHCl_3$)} and that of natural product reported {$[\alpha]_D$ +117 (*c* 0.09, $CHCl_3$)}.[3]



Scheme 3. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O, rt, 92%; (b) $Ti(O^iPr)_4$, D-(−)-DET, *t*-BuOOH, CH_2Cl_2, −20°C, 85%; (c) 1. Ph_3P, I_2, imidazole, Py, Et_2O–CH_3CN (3:1), 0°C, 90%; 2. $NaBH_3CN$, HMPA, THF, 60°C, 90%

In summary, the first enantioselective total synthesis of (+)-11,12-epoxycembrene-C (**1**) has been accomplished via a macro-olefination strategy by using titanium-mediated McMurry coupling as the key step and the Sharpless asymmetric epoxidation for the introduction of chiral epoxide function. Based on the enantioselective Sharpless epoxidation, we assume that the configuration of natural (+)-11,12-epoxycembrene-C (**1**) might be (11*S*,12*S*).

Acknowledgements

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