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First enantioselective total synthesis of (−)-13-hydroxyneocembrene

Zuosheng Liu, Tao Zhang and Yulin Li*

National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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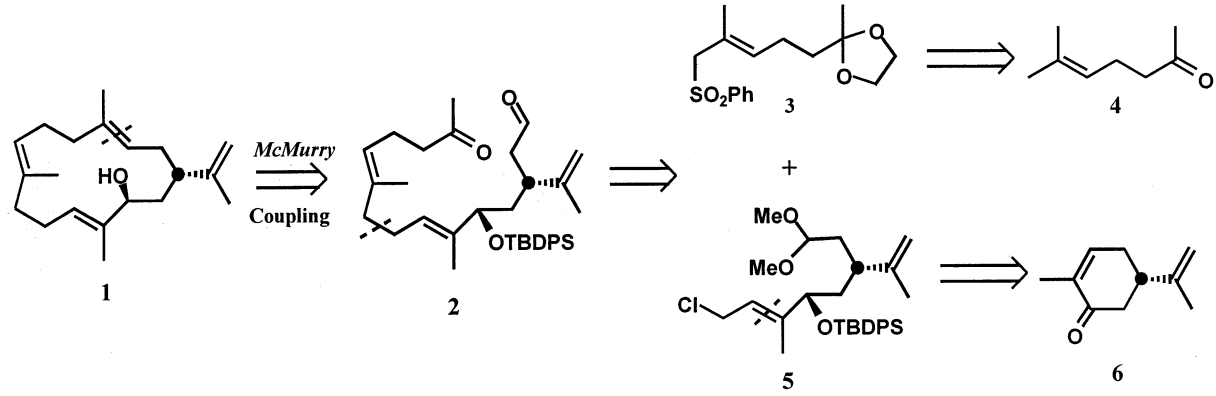
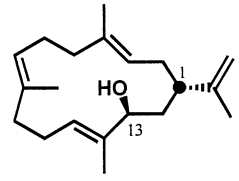
Abstract—The first enantioselective total synthesis of (−)-13-hydroxyneocembrene (**1**), a naturally occurring cembranoids isolated from soft coral *Sarcophyton trocheliophorum*, was achieved via a general approach by employing intramolecular McMurry coupling as a key step from (*S*)-(+)-carvone.

Cembranoids, a family of 14-membered cyclic diterpenoid natural products existing in terrestrial and especially in marine organism,[1] are of great interest to synthetic organic chemists and biologists because of their unique structure and wide range of biological activities.[2] (−)-13-Hydroxyneocembrene (**1**), a cembranoid which was isolated in 1988 by Suleimenova et al. from the soft coral *Sarcophyton trocheliophorum*,[3] has been shown to be an effective inductor of the release of labeled glucose from the lecithincholesterol liposomes and has cytostatic activities.[4] Its chemical structure was characterized spectroscopically and the absolute configuration of **1** has been defined to be (1*S*,13*S*) by X-ray structural analysis of its *p*-nitrobenzoate.[3] The total synthesis of (±)-**1** has been accomplished by our group.[5] In continuation of our on-going program on



Scheme 1.



(−)-13-Hydroxyneocembrene (1)

Keywords: cembrene diterpenoid; McMurry coupling; 13-hydroxyneocembrene; total synthesis.

* Corresponding author. Tel.: +86-9318912595; fax: +86-931-8912283; e-mail: liyl@lzu.edu.cn

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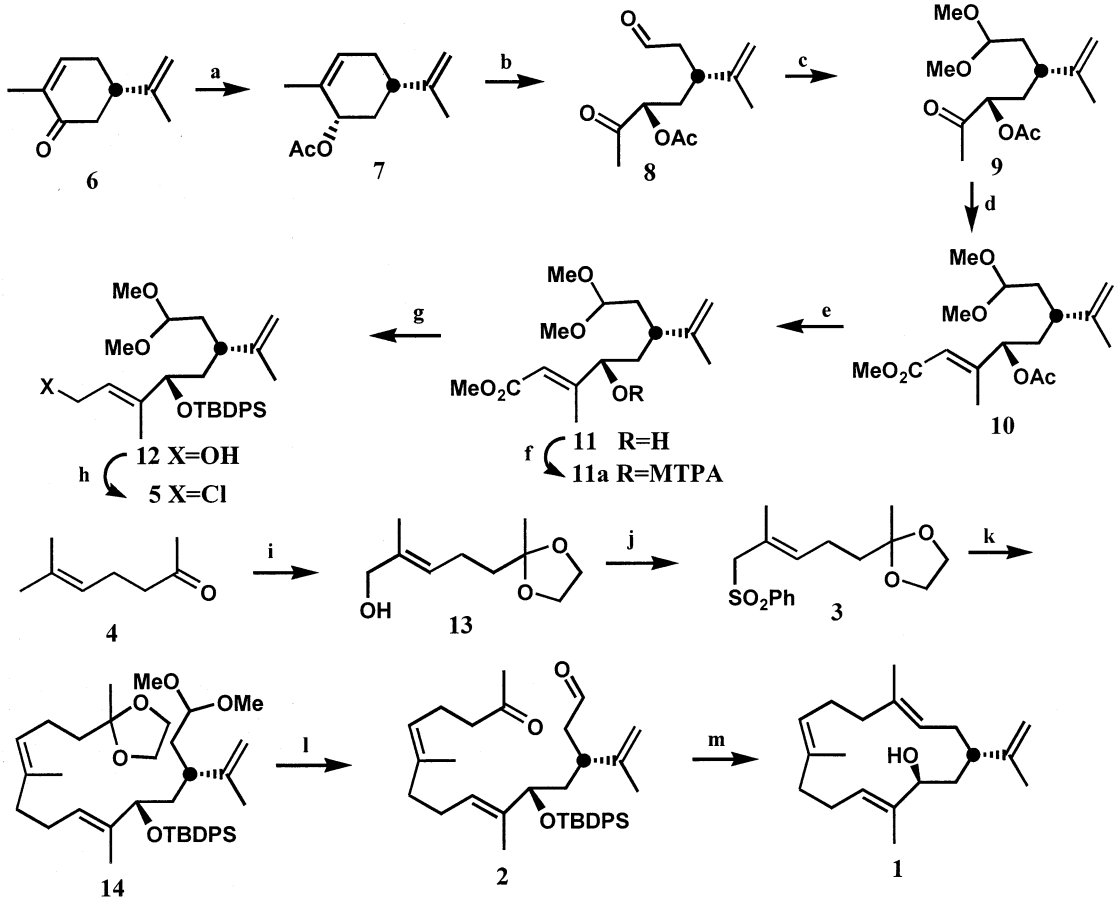
the asymmetric synthetic studies of cembranoids, we report the first total synthesis of (−)-**1** in this letter.

The strategic plan was depicted in Scheme 1. The cembrane ring would be constructed by means of the well-developed intramolecular McMurry coupling[6] of the keto aldehyde precursor **2**. Preparation of the macrocylization precursor **2** involves a convergent coupling of allylic phenyl sulphone **3** derived from 6-methyl-5-hepten-2-one (**4**) with allylic chloride **5** derived from (*S*)-(+)-carvone (**6**).

The total synthesis of (−)-13-hydroxyneocembrene (**1**) is detailed in Scheme 2. Stereoselective reduction of (*S*)-(+)-carvone with $LiAlH_4$ in ether[7] gave the *cis*-(−)-carveol, which was protected with Ac_2O in pyridine to afford carvyl acetate **7** in 98.9% yield. Ozonolysis followed by reduction with dimethyl sulfide[8] gave the keto aldehyde **8** in 62.4% yield. Treatment of keto aldehyde **8** with a catalytic mount of NH_4Cl in MeOH gave the acetal **9** in 88.0% yield. Reaction of α-acetoxy ketone **9** with carboethoxymethylene-triphenylphosphorane in the presence of a catalytic amount of benzoic acid in refluxing toluene[9] for 72 h generated only (*E*)-alkene adduct **10** in 82.0% yield. Saponification of **10** gave the alcohol **11**. The e.e. value of the alcohol **11**, determined by high resolution (400 MHz) ^1H NMR analysis of the corresponding Mosher's ester **11a**,[10] was 95%. The alcohol **11** was protected with TBDPSCl[11] and followed by reduction with Dibal-H in CH_2Cl_2 at −78°C afforded the allylic alcohol **12**. Chlorination of **12** with NCS-Ph_3P in THF[12] gave the chloride **5**.

Oxidation of 6-methyl-5-hepten-2-one (**4**) by SeO_2 (0.2 equiv.) in the presence of 70% *tert*-butylhydroperoxide in CH_2Cl_2[13] and protection of the ketone group with a large excess of ethylene glycol using oxalic acid as a catalyst in refluxing benzene gave the ethylene acetal **13**. Chlorination of **13** with NCS-Ph_3P and treatment of the corresponding chloride with anhydrous $PhSO_2Na$ in DMF[14] gave the benzene sulfonyl derivative **3**. The addition of catalytic amount of $NaHCO_3$ prevented hydrolysis of the acetal protection group.



Scheme 2. Reagents and conditions: (a) 1. $LiAlH_4$, Et_2O, −78°C, 2 h; 2. Ac_2O, Py, DMAP, 23°C, 98.9%. (b) 1. O_3, CH_2Cl_2–MeOH (3:2), −78°C; 2. Me_2S, −78°C ~ 23°C, 24 h, 62.4%. (c) NH_4Cl, MeOH, 50°C, 6 h, 88.0%. (d) $Ph_3P{=}CHCO_2Me$, $PhCO_2H$, toluene, reflux, 72 h, 82.0%. (e) K_2CO_3, MeOH, 23°C, 1 h, 93.1%. (f) $C_6H_5C(OMe)(CF_3)CO_2H$, DCC, DMAP, CH_2Cl_2, 23°C, 6 h, 94.0%. (g) 1. TBDPSCl, imidazole, DMF, 23°C, 2 h, 90.9%; 2. Dibal-H, CH_2Cl_2, −78°C, 2 h, 86.9%. (h) NCS, Ph_3P, THF, 23°C, 12 h, 92.0%. (i) 1. SeO_2, *t*-BuOOH, CH_2Cl_2, 23°C, 3 h, 50.3%; 2. Oxalic acid, $HOCH_2CH_2OH$, C_6H_6, reflux, 6 h, 92.0%. (j) 1. NCS, Ph_3P, THF, 23°C, 12 h, 80%; 2. $PhSO_2Na$, DMF, $NaHCO_3$, 23°C, 24 h, 74%. (k) 1. *n*-BuLi, −78°C, 30 min then added **5**, −78°C ~ 23°C, 2 h, 92.4%; 2. Na(Hg), Na_2HPO_4, MeOH,, 23°C, 6 h, 90.6%. (l) *p*-TsOH, acetone, 40°C; 4 h, 89.0%. (m) 1. $TiCl_4$, Zn, Py, DME, reflux, 10 h, 81.2%; 2. *n*-Bu_4NF, THF, 60°C, 24 h, 85.0%.

Coupling reaction of chloride **5** with the lithium salt of **3** (formed by treatment with *n*-BuLi in THF at −78°C) in THF at −78°C proceeded smoothly to afford coupling adduct, which gave the reduced product **14** by treatment with Na(Hg) in MeOH.[15] Treatment of **14** with a catalytic amount of *p*-TsOH in acetone gave the keto aldehyde **2**. The cyclization precursor **2** was added slowly via a syringe pump to a suspension of low-valent titanium reagent (preformed by in situ reduction of $TiCl_4$ with zinc in the presence of a trace amount of pyridine[16]) in DME under reflux over 10 h to afford the desired cyclized ethers consisting of (−)-3*E*, 7*E*, 11*E*-13-(*tert*-butyldiphenylsiloxy)-neocembrene and its 3*Z* isomer in a ratio of approximately 2.5:1 (by 400 MHz ^{1}HNMR).[8] Desilylation of cyclized ether with tetra-*n*-butylammonium fluoride (TBAF) in THF[17] at 60°C for 24 h gave (−)-13-hydroxyneocembrene (**1**), which has showed identical spectral data with those of natural product **1** reported.[3] The optical property of synthetic **1** $\{[\alpha]_D^{25}$ −122 (*c* 0.5, MeOH)} is comparable with that of natural product $\{[\alpha]_D^{20}$ −150 (*c* 0.2, MeOH)}. Accordingly, the absolute stereochemistry of the C-1 and C-13 of natural product **1** is concluded as (1*S*,13*S*).

In summary, first enantioselective total synthesis of (−)-13-hydroxyneocembrene (**1**) has been accomplished via a macro-olefination strategy by using titanium-mediated McMurry coupling as the key step.

Acknowledgements

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