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Synthesis of Constanolactone E

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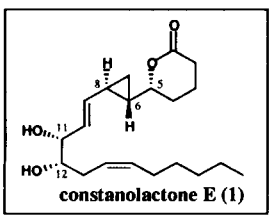
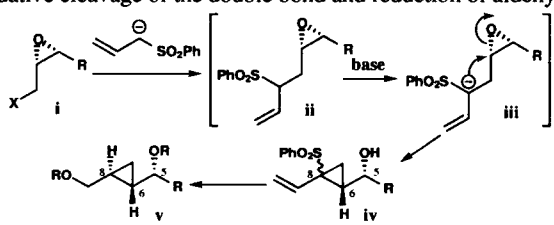
Abstract: Synthesis of marine eicosanoid constanolactone E was achieved through the one-pot formation of chiral cyclopropane derivative **4** using the anion of allyl phenyl sulfone and chiral epoxymesylate **3**. Copyright © 1996 Elsevier Science Ltd

Constanolactone E, isolated from the marine red alga *Constantinea simplex*, is a cyclopropane-containing eicosanoid.[1,2] The absolute configurations of C-11 and -12 positions were determined based on the CD spectrum of the corresponding di-*p*-bromobenzoate derivative. The absolute configurations of C-5, -6 and -8 positions remain to be clarified. The synthesis of the chiral cyclopentane derivative was previously reported, using the anion of allyl phenyl sulfone and chiral diepoxide[3] and the stereocontrolled synthesis of antibiotic brefeldin A using this reaction was achieved.[4] To explore potential applications of the cycloalkane formation, a new method for the synthesis of chiral cyclopropane derivative was developed and the synthesis of constanolactone E using this new method was achieved. The cyclopropane formation is carried out in a one-pot process involving the following sequences: 1) an anion of allyl phenyl sulfone reacts with chiral epoxide **i** to give epoxysulfone **ii**, 2) a deprotonation of **ii** *in situ* generates an anion of epoxysulfone **iii** and 3) intramolecular cyclization gives chiral cyclopropane derivative **iv**, having requisite chiral centers at C-5 and -6.[5] The cyclopropane derivative **iv** was converted to **v**, corresponding to the C-1~9 segment of constanolactone E, by removal of the phenylsulfoyl group, oxidative cleavage of the double bond and reduction of aldehyde.



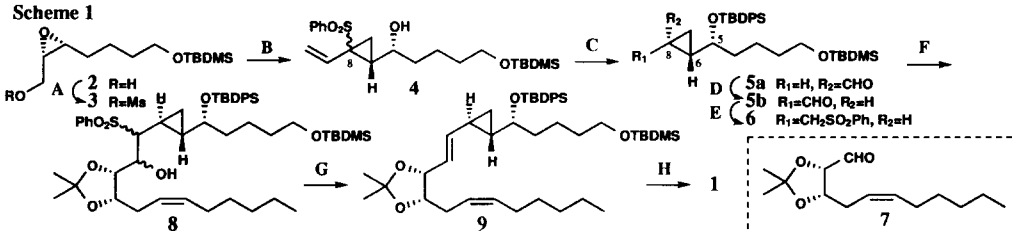


Reaction of the lithio derivative of allyl phenyl sulfone (2.4 equiv.) with chiral epoxymesylate **3** (1.0 equiv.), prepared from epoxyalcohol **2**,[6] in THF at -78°C to room temperature over 12 h, gave chiral cyclopropane **4** as a diastereomeric mixture at C-8 in a ratio of 8:1 in 83% yield (Scheme 1).[7] Without separation of the diastereomers, the hydroxyl group in **4** was protected as TBDPS ether, the phenylsulfonyl group was removed by treatment with SmI_2 in the presence of HMPA and the terminal olefin was oxidized by

ozone to give a mixture of aldehydes **5a** and **5b** (**5a** : **5b** = 8 : 1). Epimerization of the C-8 position in **5a** was carried out by treatment with K_2CO_3 in MeOH at 55°C to afford aldehyde **5b** predominantly (**5a** : **5b** = 1 : 15), bearing the requisite chiral centers at C-5, C-6, and C-8 corresponding to the C-1~9 segment. Aldehyde **5b** was converted to sulfone **6** in the following three steps: 1) $NaBH_4$ reduction to alcohol, 2) thioetherification and 3) mCPBA oxidation of phenylthio ether.

Coupling reaction of sulfone **6** with aldehyde **7**,[8] corresponding to the C-10~20 segment, afforded *E*-olefin **9**, *via* alcohol **8**, by the Julia's method.[9] Following the selective deprotection of TBDMS ether in **9**, hydroxymethyl group was converted to the methoxycarbonyl group. Deprotections of acetonide and TBDPS ether, and then lactonization completed the synthesis of constanolactone E (**1**), $[\alpha]_D$ +34° (*c* 0.18, MeOH). The spectral data of **1** and the reported data of natural constanolactone E, $[\alpha]_D$ +33° (*c* 0.22, MeOH),[1a] were identical including the sign of optical rotation. This synthesis confirmed the absolute configuration of constanolactone E to be 5*R*, 6*S*, 8*R*, 11*R*, and 12*S*.

Scheme 1



Reagents and conditions : **A**. MsCl, DMAP, CH_2Cl_2, r.t., 97%; **B**. allyl phenyl sulfone, BuLi, THF, -78°C ~ r.t., 83%; **C**. i) TBDPSCl, imidazole, DMF, r.t., 81%, ii) SmI_2, HMPA, THF, r.t., 92%, iii) O_3, CH_2Cl_2-MeOH, -78°C, Me_2S, r.t., 80%; **D**. K_2CO_3, MeOH, 55°C, 99%; **E**. i) $NaBH_4$, MeOH, 0°C, 98%, ii) PhSSPh, Bu_3P, Py, r.t., 99%, iii) mCPBA, Na_2HPO_4, CH_2Cl_2, r.t., 99%; **F**. BuLi, THF, -78°C, then **7**, 80%; **G**. i) Ac_2O, Py, DMAP, r.t., 70%, ii) Na-Hg, MeOH-THF, 0°C, 56%; **H**. i) AcOH-H_2O-THF, r.t., 85%, ii) PDC, 4ÅMS, CH_2Cl_2, r.t., iii) $NaClO_2$, ^{t}BuOH-H_2O, 0°C, iv) CH_2N_2, Et_2O, 0°C, 85% (3 steps); v) AcOH-H_2O (4:1), r.t., 77%, vi) Bu_4NF, DMF, 45°C, then 1*N* HCl, 60%.

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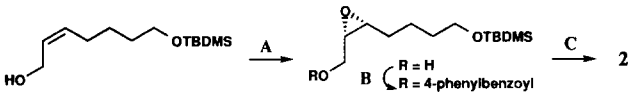
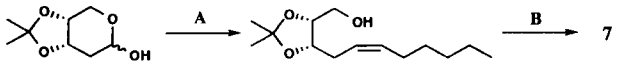
References and Notes

1. a) Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.*, **1994**, *59*, 7227-7237. b) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.*, **1990**, *31*, 2995-2998.
2. Synthesis of constanolactones A and B: White, J. D.; Jennies, M. S. *J. Am. Chem. Soc.*, **1995**, *117*, 6224-6233. Synthesis of relative eicosanoid: a) White, J. D.; Jennies, M. S. *J. Am. Chem. Soc.*, **1993**, *115*, 2970-2971. b) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31-39.
3. Miyaoka, H.; Kajiwara, M. *Chem. Pharm. Bull.*, **1992**, *40*, 1659-1661.
4. Miyaoka, H.; Kajiwara, M. *J. Chem. Soc., Chem. Commun.*, **1994**, 483-484.
5. Numbering of compounds is in accordance with that for constanolactone E.
6. Enantiomerically pure epoxyalcohol **2** was prepared from (*Z*)-7-[(*tert*-butyldimethylsilyl)oxy]-2-hepten-1-ol[10] in the following.



Reagents and conditions : **A**. TBHP, L-(+)-DET, $Ti(O^iPr)_4$, 4ÅMS, CH_2Cl_2, -20°C, 89%, ~80%ee; **B**. 4-phenylbenzoic acid, DCC, DMAP, CH_2ClCH_2Cl, r.t., 98%; **C**. i) Bu_4NF, THF, r.t., 95%, ii) recrystalization from $CHCl_3$-hexane, 68%, ~100%ee, iii) TBDMSCl, $^iPr_2NEt$, CH_2ClCH_2Cl, r.t., 90%, iv) K_2CO_3, MeOH, r.t., 98%.

7. The ratio of the diastereomers was determined by ^{1}H-NMR analysis.
8. Aldehyde **7** was synthesized from 2-deoxy-D-ribose-3,4-acetonide[11] in the following.



Reagents and conditions : **A**. $Ph_3P{=}CH(CH_2)_4CH_3$, HMPA, THF, -78°C ~ 0°C, 90%; **B**. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, quant.

9. Julia, M.; Paris, J.-M. *Tetrahedron Lett.*, **1973**, 4833-4836.
10. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.*, **1989**, *111*, 5335-5340.
11. Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.*, **1980**, *102*, 7984-7985.

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