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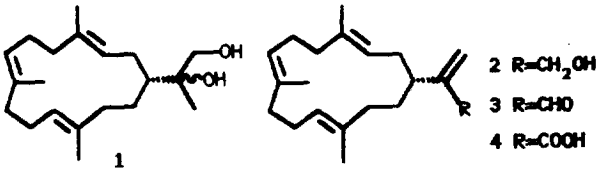
Studies on Macrocyclic Diterpenoids (X IX) -Total Synthesis of (*RR/SS*)-Sinulariol-B

Xiangjun Yue and Yulin Li*

State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Abstract The first total synthesis of (*RR/SS*)-sinulariol-B(**1**) was achieved in ten steps and ~ 10% overall yield from *E*- geraniol (**8**). The key step was the macrocyclization of precursor **5** by thioether- stabilized carbanionic alkylations.

Cembranoids, a 14-membered cyclic diterpene family, have become of interest to synthetic chemists and biologists because of their unusual structures and wide range of biological activities[1,2]. Four marine cembranoids, namely sinulariol-B(**1**)[3], sinulariol-D(**2**), sinulariol-A(**3**) and sinularic acid-A(**4**)[4], were isolated in 1987 and 1988 from the southern Japan soft coral *Sinularia maxi*. The geometrical structures and configurations were confirmed to be 3*E*,7*E*,11*E*,and 1*R*,respectively. As an approach to the asymmetric syntheses of **1** — **4**, it is desirable to study the total synthesis of (*RR/SS*)-sinulariol-B(**1**). In this communication we wish to report the first total synthesis of (*RR/SS*)-sinulariol-B(**1**).



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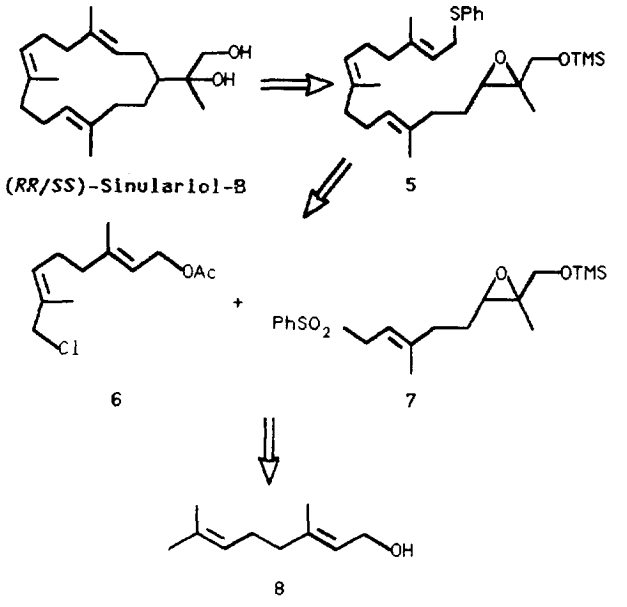
Our strategy is outlined in Scheme 1, and there are two key steps: (1) the coupling of sulfone **7** with allylic chloride **6** by sulfone-stabilized carbanionic alkylation, and (2) the macrocyclization of precursor **5** by

intramolecular thioether-stabilized carbanionic alkylation.

Scheme 1



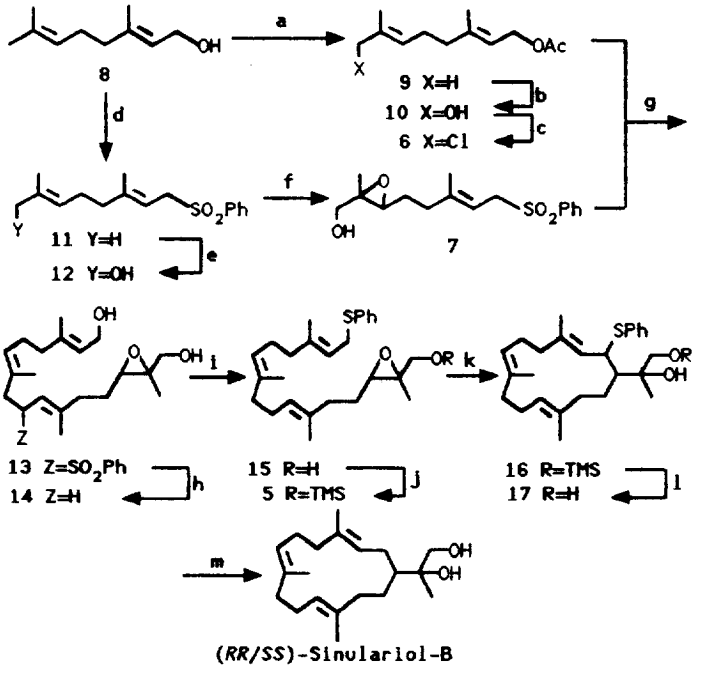
The synthesis begins with *E*-geraniol (Scheme 2). Acetylation of *E*-geraniol (**8**) with Ac_2O in pyridine gave acetate **9**[5] in 98% yield, which was then converted into alcohol **10** in 73% yield by selective oxidation of the terminal *E* methyl group with SeO_2/*t*-BuOOH according to the Sharpless procedure[6]. Reaction of alcohol **10** with the suspension of NCS and Ph_3P in dry THF[7] yielded allylic chloride **6**. Sulfone **11** was prepared in 75% yield from *E*-geraniol (**8**) using the Grieco procedure[8], which was then transformed into sulfonyl alcohol **12** in 78% yield by selective oxidation with SeO_2/*t*-BuOOH. Epoxidation[9] of the sulfonyl alcohol **12** with *t*-BuOOH in the presence of $VO(acac)_2$ gave epoxide **7** in 96% yield.

Alkylation of the anion of sulfone **7** with allylic chloride **6** took place smoothly in dry THF at −78℃ and the acetyl group was removed from the product without damage to the rest of the molecule by treatment with anhydrous K_2CO_3 in dry MeOH at room temperature to give sulfonyl diol **13** in 88% yield. The sulfonyl group was reductively removed from sulfonyl diol **13** by reaction with Li-$EtNH_2$[10] at −78℃ to yield diol **14** in 78% yield. Thioether **15** was prepared in 64% yield from **14** by reaction with NCS-Ph_3P complex and PhSLi in dry THF at room temperature in one pot, which was protected with TMSCl[11] to yield cyclization precursor **5** quantitatively.

With cyclization precursor **5** available, we next turned to the key step in the projected synthesis-an intramolecular S_N2 reaction of thioether-stabilized carbanion. Slow addition of **5** in dry THF over a 30-h period to a cooled (−78℃), well-stirred solution of LDA and Dabco[12] in dry THF gave intermediate **16** in 48% yield. After deprotection of **16** in the usual way the (phenylthio)diol was obtained in ~100% yield, which then underwent reduction with Li-$EtNH_2$ at −78℃ to produce the synthetic (*RR*/*SS*)-sinulariol-B(**1**) in 67% yield.

The spectral data of the synthetic (*RR/SS*)-simulariol-B(1) thus obtained showed good agreement with those of the natural sinulariol-B. So, we succeeded in obtaining (*RR/SS*)-sinulariol-B in ten steps and ~ 10% overall yield from *E*-geraniol. We believe that our strategy for synthesis of (*RR/SS*)-sinulariol-B makes possible the asymmetric synthesis[13] of sinulariol-B, sinulariol-D, sinularial-A and sinularic acid-A by means of Sharpless asymmetric epoxidation[14].

Scheme 2



a) Ac_2O, Py, rt, 98%; b) SeO_2, *t*-BuOOH, CH_2Cl_2, rt, 73%; c) Ph_3P, NCS, THF, rt, 85%; d) PBr_3, Et_2O then $PhSO_2Na$, DMF, rt, 75%; e) SeO_2, *t*-BuOOH, CH_2Cl_2, rt, 78%; f) VO(acac)$_2$, *t*-BuOOH, PhH, reflux, 96%; g) LDA, −78℃ then K_2CO_3-MeOH, rt, 88%; h) Li-$EtNH_2$, −78℃, 78%; i) Ph_3P, NCS, THF, rt. then PhSLi, 64%; j) TMSCl, imi, DMF, 50℃, 98%; k) LDA, −78℃, Dabco, 48%; l) n-$Bu_4N^+F^-$, ~100%; m) Li-$EtNH_2$, −78℃, 67%.

Acknowledgement

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References and Notes

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5. All compounds we prepared were confirmed by spectra data of ^{1}HNMR, IR and MS, among which compounds **5**,**16** and **17** were first synthesized.

5 ν_{max}/cm^{-1} (film): 1650, 1458, 1401, 1150, 720, 690; δ_H(80MHz,$CDCl_3$): 0.02(s, 9H, $3CH_3$), 1.30(s, 3H, CH_3), 1.60(s, 3H, CH_3), 1.66(s, 6H, $2CH_3$), 1.40—2.40(m, 12H, $6CH_2$), 3.01(t, 1H, J=6.1Hz, epoxy H), 3.51(d, 2H, J=7.6Hz, CH_2S), 3.68 and 3.82(each 1H, d, J=12.8Hz, OCH_2), 4.90—5.40(m, 3H, 3CH=), 7.20—7.50(m, 5H, ArH); *m/z*: 486(M^+, 2%), 471(1), 456(2), 377(3), 161(20), 135(21), 93(100), 55(38); Anal. Calcd for $C_{29}H_{46}O_2SSi$: C, 71.55; H, 9.51. Found: C, 71.89; H, 9.41.

17 mp. 90.5—92℃; ν_{max}/cm^{-1}(KBr): 3360—3100(br), 1665, 1385, 890, 840, 690, 660; δ_H(400MHz,$CDCl_3$): 1.07(s, 3H, CH_3), 1.30(s, 3H, CH_3), 1.52(s, 3H, CH_3), 1.54(s, 3H, CH_3), 1.40—2.10 (m, 13H, CH, $6CH_2$), 3.54(d, 1H, J=11.8Hz), 3.65(d, 1H, J=11.8Hz, 3.81(dd, 1H, J=8.6 and 10.8 Hz, CHSPh), 4.70—5.30(m, 3H, 3CH=), 7.20—7.50(m, 5H, ArH); *m/z*: 414(M^+, 2%), 305(8), 304(4), 287(5), 153(20), 93(48), 81(100), 71(74); Anal. Calcd for $C_{26}H_{38}O_2S$: C, 75.31; H, 9.24. Found: C, 75.45; H, 9.12.

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