Studies toward the synthesis of dienophile unit of methyl sartotuoate

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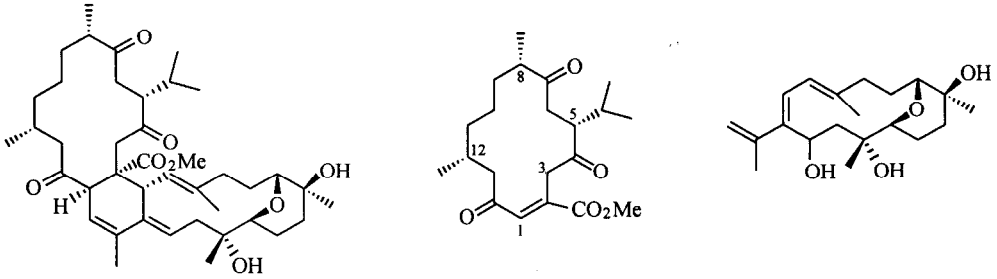
The preparation of C3-C14 fragment of the dienophile unit of methyl sartotuoate is described. The key steps included Roush reaction and CuI catalyzed epoxy-opening reaction of *i*-PrMgBr.

Keywords Methyl sartotuoate, Roush reaction, Sharpless AE reaction, synthesis

Methyl sartotuoate (**1**) is one of the member of the biscembranoids (tetraterpenoids) isolated from soft coral *Sarcophyton tortuosum* Tixier-Durivault collected in South China Sea by Su and co-workers.[1] It was hypothesized that **1** originated from dienophile unit **2** and diene unit **3** (Fig. 1) although **2** and **3** have not been isolated yet.[1] Because dienophile **2** is also a key structural moiety of methyl isosartotuoate,[2] the preparation of **2** was first studied.

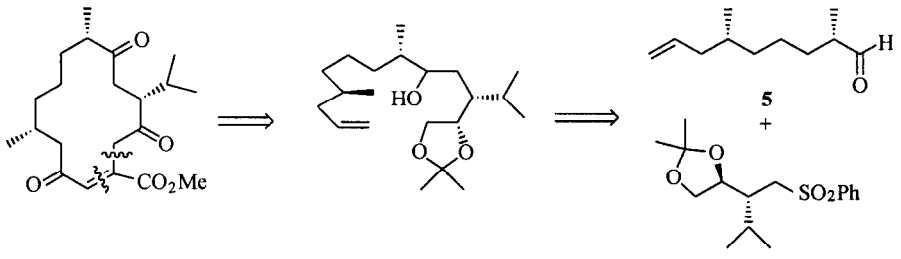


methyl sartotuoate **1** dienophile unit **2** diene unit **3**

Fig. 1 Structures of **1** and related units.

According to the intramolecular Wittig-Horner macrocyclization strategy, a retrosynthetic analysis of **2** led to the key fragment **4**, in which three stereogenic centers have been involved. Continuing the analysis, 1,5-chiral dimethyl section **5** and isopropyl section **6** with sulfone could be the proper intermediates. Here we wish to communicate our results (Scheme 1).

Scheme 1



2 **4** **6**

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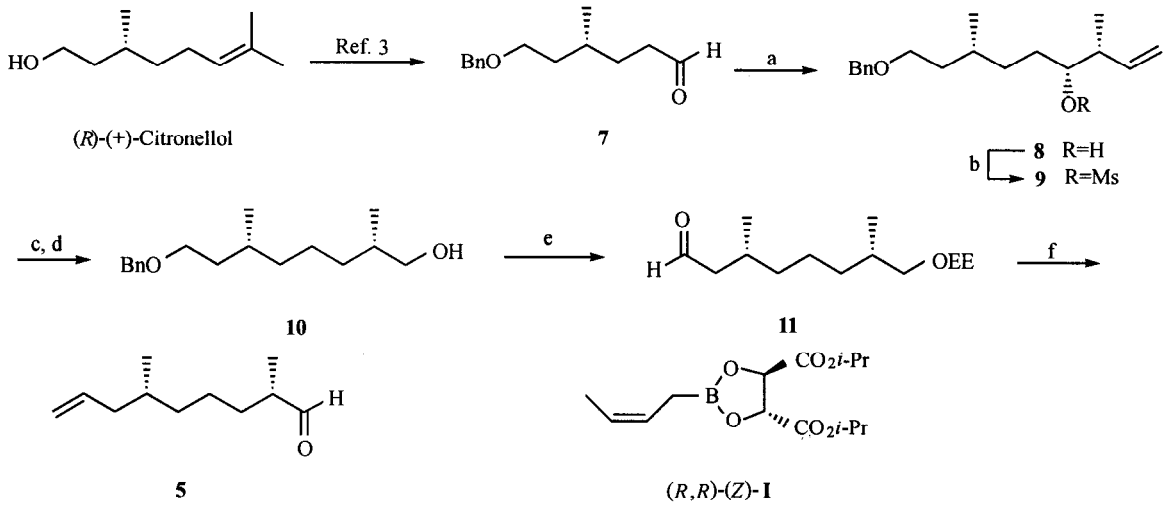
The synthesis of **5** started from (*R*)-(+)-citronellol (>95% *ee*) (Scheme 2), which was transformed to aldehyde **7** according to the reported procedure.[3] Then **7** reacted with Roush reagent [(+)-diisopropyl tartrated modified (*Z*)-crotylboronate][4] to introduce the chiral methyl group. The *d.e.* value of **8** was determined to be 90% by analysis of the MTPA esters.[5] In order to remove the secondary hydroxyl group, **8** was sulfonated to give **9** in 85% yield. Exposure of **9** to ozone and reduction with $NaBH_4$ and $LiAlH_4$ afforded alcohol **10** in 74% yield. The spectroscopic data of **10** were in agreement with the reported data.[6] Finally, protection, deprotection and functional transformation of **10** gave the 1,5-chiral dimethyl section **5**[7] in 60% overall yield from **10**.

Scheme 2



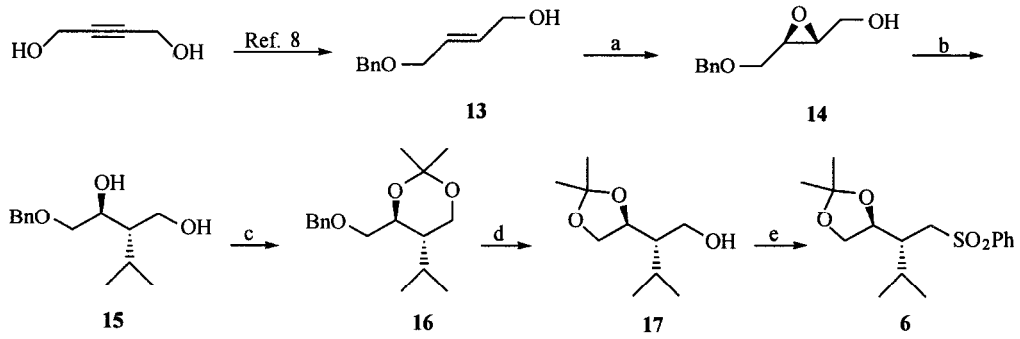
Reagents and conditions: a) (*R*, *R*)-(*Z*)-**I**, 4Å MS, toluene, −78℃, 13 h, 83%; b) MsCl, Py, CH_2Cl_2, −5℃→0℃, overnight, 85%; c) i. O_3, CH_2Cl_2, −78℃; ii. $NaBH_4$, CH_3OH, −78℃→rt., overnight, 86%; d) $LiAlH_4$, THF, reflux, 5 h, 86%; e) i. CH_2=CHOEt, PPTS, CH_2Cl_2, rt., 93%; ii. 10%Pd-C, EtOAc, 70℃, 95%; iii. Dess-Martin periodinane, CH_2Cl_2, 0℃, 15 min, 95%; f) i. Ph_3PCH_3I, *t*-BuOK, toluene, r.t., 4 h, then **11**, overnight, 86%; ii. CH_3OH, PPTS, rt., 94%; iii. Dess-Martin Periodinane, CH_2Cl_2, 0℃, 90%.

Synthesis of **6** was shown in Scheme 3. 2-Butyne-1,4-diol was first converted to **13**.[8] Sharpless epoxidation[9] of **13** was catalyzed with (−)-diisopropyl tartrate to give **14**. Because of the symmetry of **14**, the regiochemical preference for epoxy-opening was inconsequential. Copper(I) catalyzed reaction of isopropylmagnesium bromide with epoxide **14** was regio- and stereo-selective, and gave 1,3-diol **15** as the only product. Neither the corresponding 1,2-diol nor the product resulting from a Payne rearrangement of the hydroxyl epoxide was detected. **15** was converted into the acetonide **16**, and its ^1H NMR spectrum[10] indicated the epoxide opening with the inversion of configuration at C-2. Reductive cleavage of benzyl group in **16**, and then transketalization of the resultant product in acetone provided the five-membered ring acetonide **17** as a 10∶1 equilibrium mixture with six-membered ring acetonide.[11] Finally, compound **17** was converted into sulfone **6** via bromide (Scheme 3).[12]

With fragments **5** and **6** in hand, our attention was focused on the connection of the fragments. The connection was achieved by treatment of **6** with 1 eq. *n*-BuLi in THF at −40℃ follwed by adding **5** at −78℃. The product **18** was obtained as a mixture of diastereoisomers in 85% yield. Reductive removals of the sulfonyl group in **18** with Li/NH_3 and aluminum amalgam were impracticable due to the low yield. At last, **18** was oxidized to ketosulfone **19**, and then removal of sulfonyl group with SmI_2/CH_3OH in THF at −78℃[13] followed by reducing the ketone with $NaBH_4$ gave **4**[14] in 85% yield (Scheme 4).

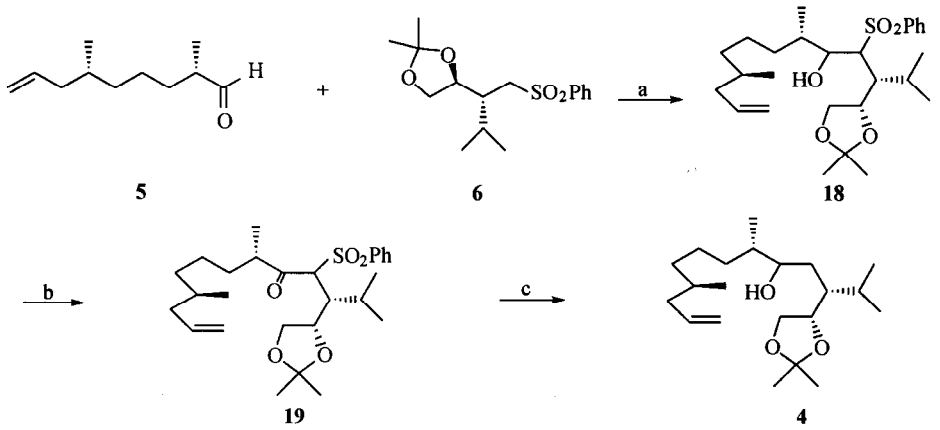
In summary, a key intermediate of the dienophile unit of methyl sartotuoate (**1**) was prepared in an efficient way. The total synthesis of methyl sartotuoate is in progress in our laboratory.

Scheme 3



Reagents and conditions: a) 10% (−)-DIPT, 12% $Ti(OiPr)_4$, 4Å MS, CH_2Cl_2, −30℃, overnight, 78%; b) 0.1 eq. CuI, 4 eq. ^iPrMgBr, THF, −40℃→−30℃, 8 h, 70%; c) 2,2-dimethoxylpropane, acetone, PTS, rt., overnight, 94%; d) i. Na/NH_3, −78℃, 92%; ii. acetone, PTS, rt., overnight, 90%; e) i. CBr_4, Ph_3P, CH_2Cl_2, 0℃, 3 h, 79%; ii. $PhSO_2Na$, DMF, 50℃, 4.5 h, 70%.

Scheme 4



Reagents and conditions: a) i. 1.1 eq. **5**, THF, −40℃, then 1.0 eq. *n*-BuLi, 30 min; ii. 1 eq. 6, −78℃, 1 h, 85%; b) Dess-Martin Periodinane, CH_2Cl_2, 0℃, 85%; c) i. SmI_2/CH_3OH, THF, −78℃, 10 min; ii. $NaBH_4$, CH_3OH, −78℃→0℃, 85%.

References and notes

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7. Data of **5**: $[\alpha]_D^{20} = 9.61°$ (*c* 0.95, $CHCl_3$). δ_H(300 MHz, $CDCl_3$): 0.90(d, J = 6.5 Hz, 3H), 1.13(d, J = 7.0 Hz, 3H), 1.23—1.55(m, 7H), 1.90—2.15(m, 2H), 2.20—2.53(m, 1H), 4.92, 5.08(2bs, 2H), 5.59—6.03(m, 1H), 9.64(bs, 1H). EIMS *m/z*: 167(M^+ − 1), 153, 141, 139, 125, 55.
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10. Data of **16**: δ_H(300 MHz, $CDCl_3$): 0.70 (d, J = 4.6 Hz, 3H), 0.72(d, J = 4.6 Hz, 3H), 1.34(s, 3H), 1.52(s, 3H), 1.62—1.70(m, 1H), 1.73—1.83(m, 1H), 3.49 (dd, J = 10.6, 3.4 Hz, 1H), 3.54(dd, J = 10.6, 4.5 Hz, 1H), 3.62(dd, J = 11.6, 9.3 Hz, 1H), 3.74(dd,

J = 11.6, 5.3 Hz, 1H), 3.94(ddd, J = 10.3, 4.3, 3.6 Hz, 1H), 4.47(d, J = 12.3 Hz, 1H), 4.42(d, J = 12.3 Hz, 1H), 7.06—7.33(m, 5H).

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b) Data of Compound **6**: $[\alpha]_D^{20}$ = 5.5° (c 3.4, $CHCl_3$). δ_H(300 MHz, C_6D_6): 0.93(d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.28(s, 6H), 1.93—1.95(m, 1H), 2.04—2.08(m, 1H), 3.07(dd, J = 15.0, 6.7 Hz, 1H), 3.34(dd, J = 15.0, 3.0 Hz, 1H), 3.59(dd, J = 8.5, 7.4 Hz, 1H), 3.99(dd, J = 8.5, 6.6 Hz, 1H), 4.14—4.19(m, 1H), 7.55—7.66(m, 3H), 7.92—7.95(m, 2H). EIMS m/z: 313(M^+ + 1), 297, 255, 171, 143, 101, 95, 77; HRMS Calcd. For $C_{16}H_{24}O_4S$: 312.1395, Found. 312.1424.

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14. Data of **4**: $[\delta]_D^{20}$ = 8.05° (c 2.34, $CHCl_3$). δ_H(300 MHz, $CDCl_3$): 0.75—1.60(m, 30H), 1.87—1.90(m, 1H), 2.04—2.06(m, H), 2.25—2.45(m, 1H), 3.38—3.45 (m, 1H), 3.50—3.62(m, 1H), 3.85—3.92 (m, 2H), 5.01—5.07(m, 2H), 5.76(m, 1H). EIMS m/z: 325 ($M^+ - CH_3$), 323, 157, 143, 101, 97. Anal. $C_{21}H_{40}O_3$. Calcd.: C, 74.07; H, 11.84, Found: C, 73.71; H, 11.87.

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