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Synthetic studies on the dienophile unit of methyl isosartortuoate. Part 2: SmI_2-mediated 14-membered carbocyclization

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Abstract—The dienophile unit of methyl isosartortuoate has been synthesized. The 14-membered carbocycle was constructed by a SmI_2-mediated intramolecular Reformatsky reaction. The introduction of the oxo group at the γ-position of the α,β-unsaturated ester was achieved by rearrangement of an β,γ-epoxy ester. © 2002 Elsevier Science Ltd. All rights reserved.

In our previous letter,[1] we outlined our synthetic strategy and described the synthesis of the acyclic precursor **2** of the dienophile unit **1** of methyl isosartortuoate (Fig. 1). Herein we would like to report the construction of the 14-membered carbocycle and the elaboration of the dienophile **1**.

A number of methods have been developed for macrocarbocyclization,[2] among which the SmI_2-promoted intramolecular Reformatsky reaction reported by Inanaga in 1991[3] is particularly attractive. It was thought that the distinct properties of samarium such as its large ionic radius, flexible coordination, and high oxophilicity would play an important role in facilitating the cyclisation. Thus, we chose to investigate its efficiency in the carbocyclization of the acyclic precursor **2**. α-Bromoester-ω-aldehyde **4** was initially prepared as outlined in Scheme 1.

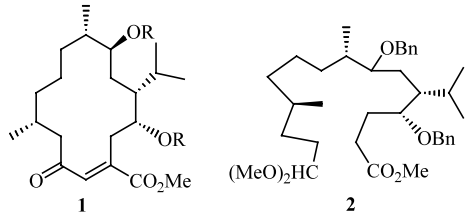
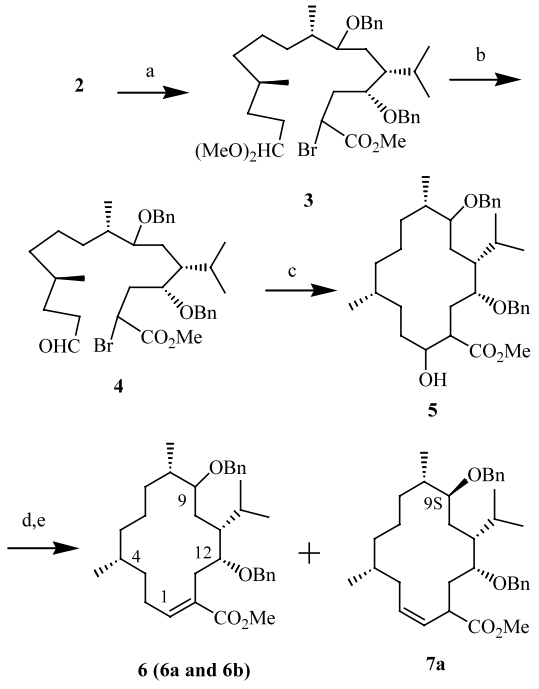


Figure 1.



Scheme 1. *Reagents and conditions*: (a) LDA, THF, TMSCl, Et_3N, −78°C; then NBS, rt, 90%; (b) Amberlyst 15, acetone, H_2O, 90%; (c) SmI_2, THF, 0°C, 1 mmol/2 h; (d) MsCl, Et_3N, CH_2Cl_2, rt; (e) DBU, toluene, reflux, 10 h, 60% for three steps.

Treatment of ester **2** with LDA/TMSCl/Et_3N followed by bromination with NBS gave the α-bromoester **3** in 90% yield. Hydrolysis of the acetal group[4] afforded the

Keywords: methyl isosartortuoate; dienophile unit; β,γ-epoxy ester rearrangement; SmI_2-mediated; carbocyclization.

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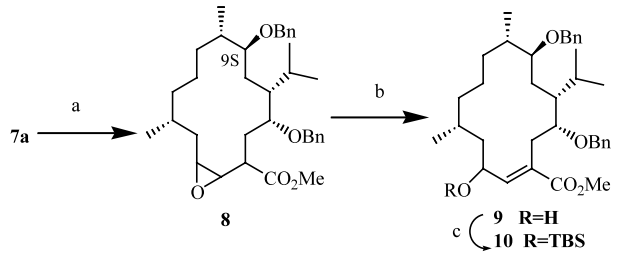
required α-bromoester-ω-aldehyde **4**. In the presence of an excess of SmI_2, the cyclization of **4** proceeded smoothly at 0°C to yield a multi-product isomeric mixture, which was mesylated and treated with DBU to give three chromatographically separable products (~1:2:1) in 60% overall yield. The two less polar products were characterized as the α,β-unsaturated esters **6a** and **6b**[5] possessing a *cis*-cycloalkene differing in configuration at the C-9 protected hydroxyl group. The structure of the more polar component, **7a**, was determined to be a rearranged product of **6a** (see also Scheme 3).

After the successful macrocyclization, we focused our attention on the introduction of the oxo-substitutent at the γ-position of the α,β-unsaturated ester **6**. Direct allylic oxidation using CrO_3[6] or SeO_2,[7] or allylic bromination[8] of compound **6** proved to be unsuccessful. As an alternative, the rearrangement under basic conditions of an β,γ-epoxy ester offered a different approach.[9] Compound **7a** was thus treated with MCPBA at rt to yield the β,γ-epoxy ester **8** in 70% yield (Scheme 2). Under basic conditions, compound **8** smoothly rearranged to the γ-hydroxy-α,β-unsaturated ester **9**. An improved result was obtained when the CH_3OH/CH_3ONa system was applied and **9** was obtained in 70% yield. The oxo group at the γ-position of the α,β-unsaturated ester had now been successfully introduced.

Based on the above results, and to take advantage of the isomers **6**, it was important to isomerize the double bond of the α,β-unsaturated esters **6** to give the corresponding β,γ-isomers. In general, this transformation can be achieved by treating α,β-unsaturated esters with bases. When epimers **6a** and **6b** were treated with DBU in toluene at reflux (Scheme 3), epimer **6a** afforded the desired β,γ-unsaturated ester **7a** in a ratio of 2.5:3 (**7a**:**6a**). However this isomerization failed for **6b**.[10] This phenomenon reflects a subtle relationship between reaction properties and the conformations of large rings. For this reason, the C-9 configuration was determined in the acyclic precursor (the details have been presented in the previous letter[1]), as *S* in **6a** and **7a**.

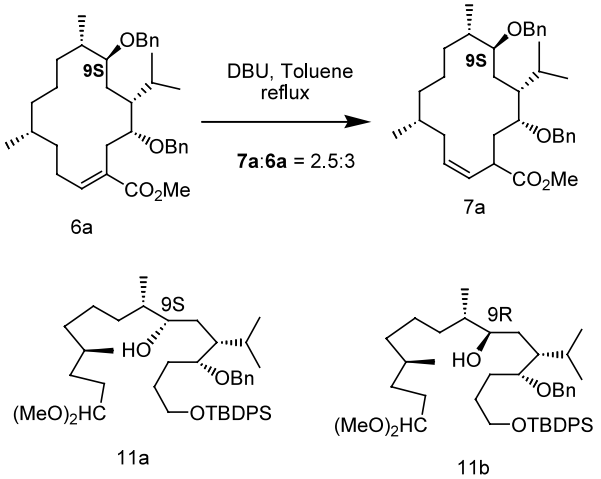
With respect to **6b**, the corresponding acyclic precursor **11b** was selected for inversion of the configuration (Scheme 3). Although Mitsunobu conditions or direct S_N2 substitution of the mesylate derivative[11] of **11b** failed to realize this conversion, it was converted into the useful compound **11a** by repeated oxidation and reduction cycles.[12]



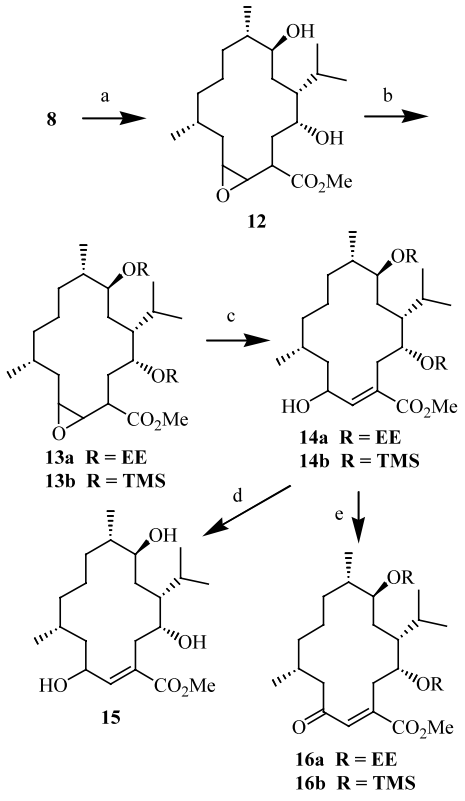
Scheme 2. *Reagents and conditions*: (a) *m*CPBA, CH_2Cl_2, 25°C, 70%; (b) CH_3OH, CH_3ONa, 70%; (c) TBSCl, DMAP, CH_2Cl_2, Et_3N, rt, 90%.

The final task was to form the dienophile structural unit. Obviously, it was necessary to remove or change the benzyl groups. Hydrogenation of compound **10** which possesses a bulky TBS group gave the corresponding saturated product. However, to our delight, hydrogenation of **8** with $Pd(OH)_2/MeOH/EtOAc$ at rt afforded the desired compound **12** (Scheme 4). Experiments showed that **12** was unstable due to the presence of the epoxide and free hydroxy groups, and was also unable to undergo the basic rearrangement. Hence, the two free hydroxy groups needed to be reprotected. After several protecting groups had been exhausted, the ethoxyethyl ether (EE) and the trimethylsilyl (TMS) groups proved to be the protecting groups of choice, and compounds **13a** and **13b** were obtained in 75% and 70% yield respectively. The EE-protected compound **13a** could be smoothly rearranged to **14a** with CH_3ONa/CH_3OH and was further oxidized with Dess–Martin periodinane[13] to give ketone **16a**. But deprotection of **14a** or **16a** under acidic conditions gave a complicated mixture. For the TMS-protected compound **13b**, since the TMS group was labile to the original rearrangement conditions (CH_3OH/CH_3ONa), milder basic conditions were examined. Fortunately, the rearrangement could be realized by treating **13b** with DBU in refluxing toluene and the desired compound **14b** was obtained in 90% yield. Deprotection of **14b** with $NH_4F/MeOH$[14] gave the triol **15** quantitatively. To our disappointment, **15** could not be oxidized directly to the corresponding trione. However, after Dess–Martin periodinane oxidation of **14b**, we obtained the desired compound **16b**[15] which is the bis-TMS-protected form of dienophile unit **1**.

In summary, a SmI_2-promoted 14-membered carbocyclization has been accomplished and the bis-TMS-protected compound **16b** has been synthesized, which is a dienophile for a total synthesis of methyl isosartortuoate. The synthesis of the natural product is still on going in this laboratory.



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) $Pd(OH)_2$, CH_3OH, EtOAc, H_2, 70%; (b) for **13a**, ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 30 min, 75%; for **13b**, TMSCl, Et_3N, DMAP, CH_2Cl_2;, rt, 1 h, 70%; (c) for **14a**, CH_3ONa, CH_3OH, rt, 4 h, 70%; for **14b**, DBU, toluene, reflux, 10 h, 90%; (d) NH_4F, CH_3OH, 25°C, 9 h, quantitatively; (e) Dess–Martin periodinane, Py, CH_2Cl_2, 80%.

Acknowledgements

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References

1. Hong, Z.-Y; Chen, X.-C.; Xu, X.-X. *Tetrahedron Lett*. **2003**, *44*, 485.
2. Tius, M. A. *Chem. Rev*. **1988**, *88*, 719.
3. (a) Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett*. **1991**, *32*, 6371; (b) This cyclization method has been applied in the total synthesis of taxol. See: Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J*. **1999**, *5*, 121.
4. Coppola, G. M. *Synthesis* **1984**, *12*, 1021.
5. Physical and spectroscopic data. For **5a**: $[\alpha]_D^{20}=-1.6$ (*c* 1.25, $CHCl_3$); EI-MS (*m*/*z*, %) 535 (M^++1, 0.2), 427 (2.4), 91 (100.0); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H, ArH), 6.88 (dd, 1H, $J=9.6$ Hz, 6.6 Hz, vinyl H), 4.51 (m, 4H), 3.77 (m, 1H, OCH), 3.74 (s, 3H, OCH_3), 3.54 (m, 1H, OCH), 2.87, 2.39 (ABX System, 2H, $J=13.6$ Hz, 8.7 Hz, 4.5 Hz, allylic H), 2.25 (m, 1H), 1.99 (m, 3H), 1.74 (m, 2H), 1.48 (m, 4H), 1.32 (m, 4H), 1.13 (m, 2H), 0.90 (m, 12H, 4 CH_3); ^{13}C NMR ($CDCl_3$): δ 168.6, 144.5, 139.6, 139.3, 130.3, 128.1 (2), 128.0 (2), 127.7, 127.6, 127.4 (2), 127.1, 127.0, 80.9, 72.5, 71.0 (2), 51.5, 44.5, 34.2, 33.5, 33.3, 32.0, 31.8, 30.9, 30.7, 27.0, 23.5, 22.7, 20.7, 20.6, 20.5, 17.2; HRMS (EI) calcd for $C_{35}H_{50}O_4$ $[M]^+$: 534.3709; found: 534.3706.
For **5b**: IR (film) 2954, 2871, 1718, 1455, 1068 cm^{-1}; ESI-MS (*m*/*z*, %) 535.5 ($M+H^+$, 60.0); ^1H NMR (300 Hz, $CDCl_3$): δ 7.30 (m, 10H, ArH), 6.90 (m, 1H, vinyl H), 4.64 (m, 1H, CH_2Ph), 4.34 (m, 3H, CH_2Ph), 3.67 (s, 3H, OCH_3), 3.60 (m, 2H, OCH), 2.77 (m, 1H, allylic H), 2.25 (m, 1H, allylic H), 2.10 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40–1.10 (m, 10H), 0.88 (m, 12H, 4 CH_3).
6. Mehta, G.; Reoldy, D. S. *Synlett* **1997**, 612.
7. Bestmann, H. J.; Schober, R. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 791.
8. Beccalli, E. M.; Majon, L.; Marchesini, A. *J. Org. Chem*. **1981**, *46*, 222.
9. (a) Larcheveque, M. *Synthesis* **1983**, 297; (b) Cory, R. M.; Ritchie, B. M.; Shrier, A. M. *Tetrahedron Lett*. **1990**, *31*, 6789.
10. Other deconjugation methods such as LDA/TMSCl/HCl or photo rearrangement were tried, but did not isomerize the double bond of **6**. See: (a) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc*. **1987**, *109*, 8117; (b) Hanessian, S.; Dube, D.; Hodges, P. J. *J. Am. Chem. Soc*. **1987**, *109*, 7063; (c) Mortezaei, R.; Awandi, D.; Henin, F.; Muzart, J.; Pete, J. P. *J. Am. Chem. Soc*. **1988**, *110*, 4824.
11. (a) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y. *Tetrahedron Lett*. **1975**, *37*, 3183; (b) Yankee, E. W.; Cooper, E. L. *J. Am. Chem. Soc*. **1974**, *96*, 5876.
12. Selective reduction of the ketone with $NaBH_4$–$CeCl_3$, $LiAlH(OR)_3$, DIBALH, or other reagents failed to improve the ratio of **11a**.
13. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277; (b) Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899.
14. Robins, M. J.; Zhang, W. *Tetrahedron Lett*. **1992**, *33*, 1177.
15. Physical and spectroscopic data for **16b**: IR (film) 2958, 1726, 1691, 1437, 1251, 1078, 840 cm^{-1}; ESI-MS (*m*/*z*, %) 513.5 ($M+H^+$, 5.0), 535.5 ($M+Na^+$, 22.0); ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (s, 1H, vinyl H), 4.08 (m, 1H), 3.78 (s, 3H, OCH_3), 3.67 (m, 1H), 3.27 (m, 1H), 2.66 (m, 1H), 2.50 (m, 2H), 2.24 (m, 1H), 1.71 (m, 2H), 1.55 (m, 1H), 1.21–1.39 (m, 7H), 1.18 (m, 1H), 1.00 (d, 3H, $J=6.9$ Hz, CH_3), 0.87 (d, 3H, $J=6.9$ Hz, CH_3), 0.82 (d, 3H, $J=6.9$ Hz, CH_3), 0.76 (d, 3H, $J=7.2$ Hz, CH_3), 0.12 (s, 9H, 3 CH_3), 0.09 (s, 9H, 3 CH_3); HRMS (EI) calcd for $C_{27}H_{52}O_5Si_2$: 512.3354; found: 512.3343.