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Synthetic studies on the dienophile unit of methyl isosartortuoate. Part 1: Assembly of the acyclic precursor

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Abstract—A strategically functionalized compound, as the acyclic precursor of the dienophile unit of methyl isosartortuoate has been synthesized, and its stereochemistry was also assigned.

Methyl isosartortuoate **1** is the first tetracyclic tetraterpenoid exhibiting a novel molecular architecture, isolated from the marine *Sarcophyton tortuosum tixierdurivanlt* by Su et al.[1a] A preliminary bioassay proved that compounds of this type displayed inhibitory effects against mice S_{180}[1c] and cytotoxic activity towards KB cells,[2a] but the scarcity of the material made further studies difficult. It has been hypothesized[1,2] that a plausible biogenesis would involve the generation of the cyclohexene ring by a Diels–Alder reaction of two cembrenoids (e.g. **3** and **4**, Fig. 1). The structural novelties and the potential bioactivities as well as the interesting biogenetic possibility prompted us to initiate a synthetic project[3] towards methyl isosartortuoate **1** and methyl sartortuoate **2**.[1a,c] In this and the following letter[4] we wish to report our results of the research on the synthesis of dienophile **5**, which is the common dienophile unit of compounds **1** and **2**.

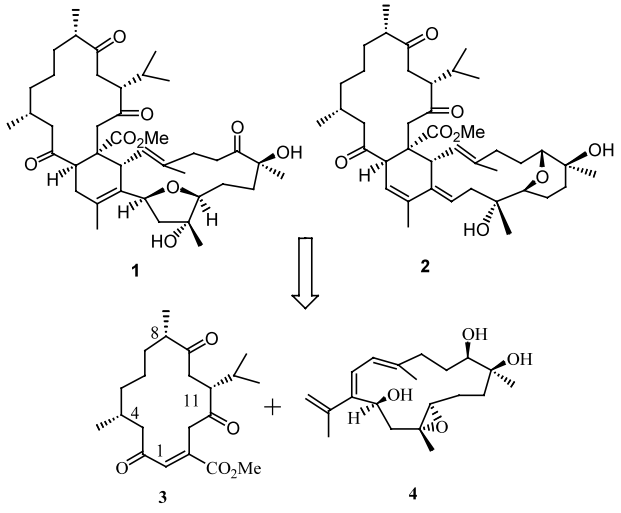

Figure 1. Structures of methyl isosartortuoate **1**, methyl sartortuoate **2** and their biogenetic precursors **3** and **4**.

Our initial attempts for the elaboration of **5** were based on an intramolecular Wittig–Horner macrocyclization strategy, which has been successfully employed in the syntheses of 14-membered carbocycles.[5] However, such a cyclization of **6** proved unsuccessful.[3a] Thus, we changed the plan and temporarily removed the carbonyl of ketone **5** from the ring. The resultant simplified compound **7** was expected to provide higher feasibility and more tactical flexibility in the macrocyclization. Further retrosynthesis is shown in Figure 2.

According to the new synthetic strategy, we prepared the sulfone segment **9** as shown in Scheme 1. Optically active epoxide **12**[6] was derived from **11** by Sharpless asymmetric epoxidation with 95% ee. Initial attempts at the nucleophilic epoxy opening reaction of **12** with isopropylmagnesium bromide catalyzed by CuI gave complicated mixtures. To the best of our knowledge, no direct opening of hydroxy epoxides with isopropylmagnesium bromide has been reported,[7] so various reaction conditions were tried. We found that, to ensure an acceptable selectivity and yield, it was crucial to control the temperature of forming the CuI catalyzed Grignard reagent. When it was formed in advance at around −50°C, and the whole reaction was also conducted at low temperature (−78°C), C-2 to C-3 selectivity was improved to 2.5:1 and the diol **13** was obtained in 65%

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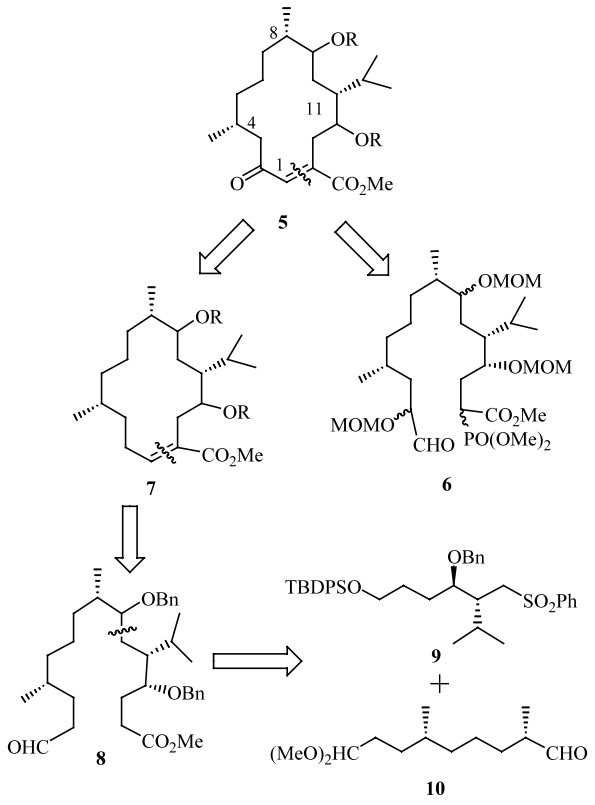
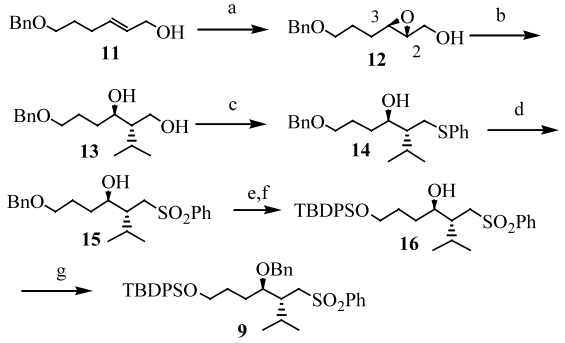


Figure 2. Retrosynthesis of dienophile **5**.

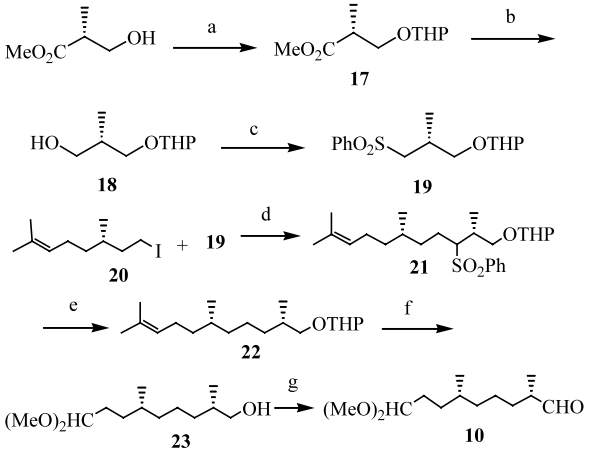


Scheme 1. *Reagents and conditions*: (a) D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, −20°C, 90%, 95% ee; (b) ^{i}PrMgBr, 0.1 equiv. CuI, THF, −50°C, 1.5 h, then epoxide **11**, −78°C 1 h, 65%; (c) $(PhS)_2$, Bu_3P, Py, 80%; (d) MCPBA, CH_2Cl_2, 75%; (e) Pd/C, MeOH, 97%; (f) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 92%; (g) BnBr, THF, Bu_4NI, NaH, 85%.

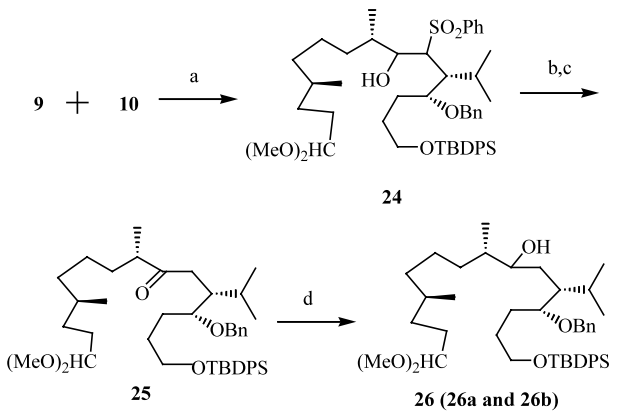
yield. Next, the primary hydroxyl group of **13** was converted selectively to the sulfone group by treatment with $(PhS)_2$-PBu_3[8] followed by oxidation with *m*CPBA. For the protection of the secondary hydroxy group, the benzyl ether was considered to be the most suitable for subsequent transformations after a preliminary screening. So **15** was converted to **16** through debenzylation and silylation. However, benzylation of compound **16** proceeded only after some difficulty. It is noteworthy that this reaction depended on the solvent used. Protection with NaH/BnBr/DMF gave a very complicated mixture. When NaH/BnBr/THF/Bu_4NI was used, the reaction proceeded smoothly and fast (it was essentially complete after 1 h at rt), and the desired benzyl ether **9** was obtained in 85% yield. It seems that complex factors caused by deprotonation of the sulfone[9] and deprotection of the TBDPS ether[10] were suppressed under the latter reaction conditions.

The synthesis of the other segment, the (2*S*,6*R*)-dimethyl substituted aldehyde **10**, could be accomplished by coupling sulfone **19** with iodide **20** prepared from (*S*)-(+)-citronellol[11] (Scheme 2). Fragment **19** was obtained from methyl (*R*)-(−)-3-hydroxyisobutyrate in four steps in 80% overall yield. Coupling of the sulfone **19** with iodide **20** proceeded smoothly to afford **21**, which was desulfonated to give compound **22**. Previous exploration suggested that the conversion of the double bond of **22** in advance into an acetal group would be beneficial for subsequent transformations, for example, the formation and α-bromination of the ester (see the next letter).[4] The exposure of compound **22** to ozone followed by a workup with Me_2S/*p*-TsOH/$CH(OMe)_3$ gave acetal **23** in one pot in 80% yield. Oxidation of **23** afforded the required aldehyde **10**.

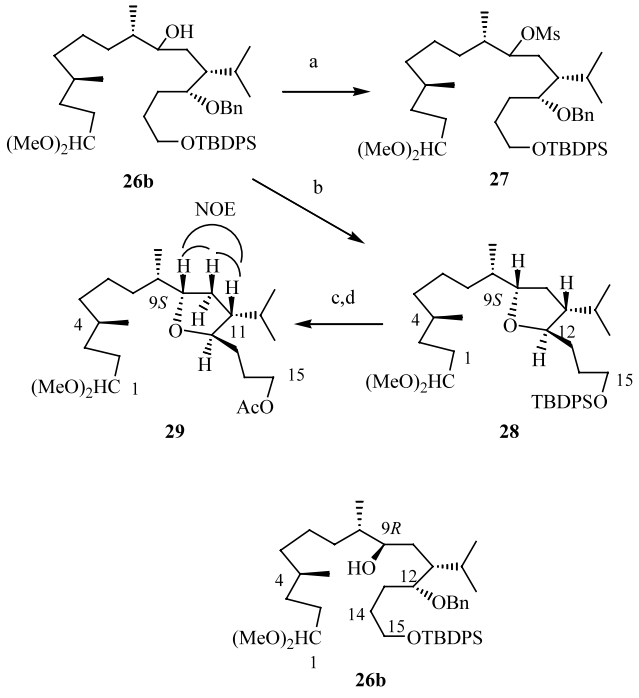
With segments **9** and **10** in hand, their coupling was carried out by treatment of the sulfone anion of **9** with aldehyde **10** in THF at −78°C (Scheme 3). Unfortunately, the yield was only 40%, and no improvement was achieved by addition of a Lewis acid.[12] It is assumed that the coupling process was sluggish because of steric hindrance, and the aldehyde was being lost by enolization. Based on this idea, the assumed side reaction was minimized when a pre-cooled and highly diluted solution of aldehyde **10** (0.07 M in THF) was added slowly to the sulfone anion solution, and indeed compound **24** was obtained in up to 88% yield. After oxidation, desulfonation and reduction, the separable hydroxy epimers **26a** and **26b**[13] were obtained in a ratio of 1:1.



Scheme 2. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2; (b) $LiAlH_4$, Et_2O, 95% for two steps; (c) (i) $(PhS)_2$, Bu_3P, THF, 93%; (ii) MCPBA, CH_2Cl_2, $NaHCO_3$, 83%; (d) BuLi, THF, 90%; (e) Na(Hg), CH_3OH, THF, 84%; (f) O_3, MeOH, CH_2Cl_2, −78°C; then Me_2S, PTSA, $CH(OMe)_3$, 80%; (g) Swern oxid., 90%.

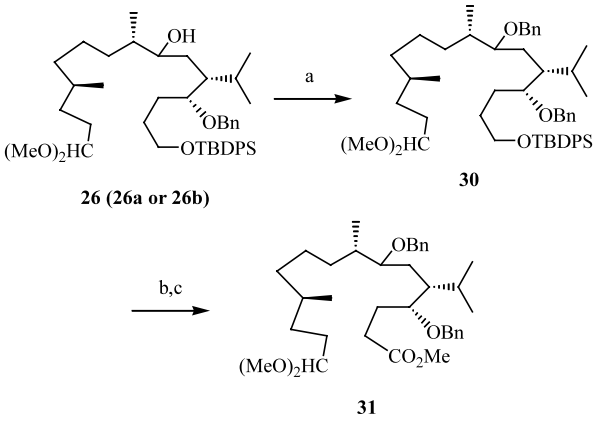


Scheme 3. *Reagents and conditions*: (a) **9**, BuLi, THF, −78°C, then aldehyde **10**, 88%; (b) Dess–Martin periodinane, pyridine, CH_2Cl_2; (c) lithium naphthanilide, THF, −78°C, 69% for two steps; (d) $LiAlH_4$, ether, 98%.



Scheme 4. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, rt 30 min, 80%; (b) MsCl, Et_3N, CH_2Cl_2, rt 2 days, 85%; (c) Bu_4NF, THF; (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt.

In theory both epimers **26a** and **26b** could be used as intermediates, but they exhibited quite different reaction properties in the following transformations (see the next letter[4]). So the C-9 configuration was determined as shown in Scheme 4. Treatment of compound **26b** with $NEt_3/MsCl/CH_2Cl_2$ at rt for 30 min afforded the mesylate **27** in 80% yield. However, with the reaction time increased, a THF-ring containing product **28** was formed as a byproduct.[14] Further increasing the reaction time to 2 days at rt led to an improved 85% yield of **28**. In order to distinguish proton signals in its NMR, the TBDPS ether of **28** was converted into the acetate **29**.[15] The 2D NOESY spectra of **29** showed no



Scheme 5. *Reagents and conditions*: (a) NaH, BnBr, Bu_4NI, THF, DMF, 50°C, 80%; (b) Bu_4NF, THF, 92%; (c) (i) Swern oxid.; (ii) I_2, KOH, MeOH, 0°C, 85% for two steps.

NOE correlation between 9-H and 12-H, suggesting that the THF ring was *trans*. This assignment was also confirmed by the presence of strong NOE correlations between 9-H and 10-H (β), 9-H and 11-H, and between 10-H (β) and 11-H. The stereochemistry of compounds **29** and **26b** were finally assigned shown in Scheme 4.

When the secondary hydroxyl group of **26** (**26a** or **26b**) was protected as its benzyl ether (Scheme 5), an interesting solvent effect was again noticed. The reaction of **26** with NaH/BnBr/DMF was still very complex. On treating **26** with $NaH/BnBr/Bu_4NI/THF$, no reaction took place even after refluxing for 10 h. Interestingly, we found that the addition of DMF played a role in controlling both the yield and the rate of the reaction. The combination of $NaH/BnBr/Bu_4NI/THF$ and a small amount of DMF increased the yield of **30** to 80%.

Finally a three-step procedure involving desilylation, Swern oxidation, and oxidation with $I_2/KOH/MeOH$[16] afforded directly the desired ester **31**[17] (Scheme 5).

In summary, a strategically chiral precursor **31** for carbocyclization to the dienophile unit of methyl isosartortuoate **1** has been prepared. Further manipulation of **31** to **5** is reported in the following letter.[4]

Acknowledgements

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13. Physical and spectroscopic data. For **26a**: $[\alpha]_D^{20}=-32.1$ (*c* 0.85, $CHCl_3$); IR (film) 3460, 2956, 1464, 1429, 1112, 1067 cm^{-1}; ESI-MS (*m*/*z*, %) 741.6 ($M+Na^+$, 100.0); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.30∼7.40 (m, 11H), 4.63, 4.43 (AB system, 2H, $J=12.0$ Hz, CH_2Ph), 4.36 (t, 1H, $J=6.3$ Hz, acetal H), 3.71 (m, 3H, CHO, $CH_2OTBDPS$), 3.34 (s, 6H, $2CH_3O$), 3.34 (m, 1H, CHO), 1.86 (m, 2H), 1.55∼1.70 (m, 8H), 1.45∼1.08 (m, 10H), 1.08 (s, 9H, $3CH_3$), 0.89 (m, 9H, $3CH_3$), 0.75 (d, 3H, 6.3 Hz, CH_3). Anal. calcd for $C_{45}H_{70}O_5Si$: C, 75.16; H, 9.81. Found: C, 75.50; H, 9.61%. For **26b**: $[\alpha]_D^{20}=-9.7$ (*c* 1.20, $CHCl_3$); IR (film) 3453, 2955, 2932, 1112, 1067 cm^{-1}; ESI-MS (*m*/*z*, %) 741.6 ($M+Na^+$, 40.0); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H, ArH), 7.42 (m, 6H, ArH), 7.34 (m, 5H, ArH), 4.63, 4.40 (AB system, 2H, $J=11.1$ Hz, CH_2Ph), 4.33 (t, 1H, $J=6.0$ Hz, acetal H), 3.68 (t, 2H, $J=6.3$ Hz, $CH_2OTBDPS$), 3.52 (m, 3H, 2CHO, OH), 3.31 (s, 6H, $2CH_3O$), 1.92 (m, 1H), 1.78 (m, 2H), 1.10∼1.60 (m, 19H), 1.06 (s, 9H, $3CH_3$), 0.86 (m, 12H, $4CH_3$). Anal. calcd for $C_{45}H_{70}O_5Si$: C, 75.16; H, 9.81. Found: C, 74.95; H, 9.60%.
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15. By combination of 2D NOESY (600 MHz) and 2D COESY (400 MHz), the chemical shifts (δ = ppm) of compound **28** was assigned as following: 15-H (4.10, 2H), 14-H (1.82), 14-H (1.70), 12-H (3.65), 11-H (1.57), 10-H (β) (1.95), 10-H (α) (1.25), 9-H (3.57).
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17. Physical and spectroscopic data for **31**: $[\alpha]_D^{20}=+48.3$ (*c* 0.50, $CHCl_3$); IR (film) 2955, 1740, 1455, 1368, 1069, 698 cm^{-1}; ESI-MS (*m*/*z*, %) 616.6 ($M+NH_4^+$, 100.0), 621.6 ($M+Na^+$, 55.0); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H, ArH), 4.58, 4.38 (AB system, 2H, $J=12$ Hz, CH_2Ph), 4.36 (m, 3H, CH_2Ph, acetal H), 3.60 (s, 3H, OCH_3), 3.37 (m, 2H), 3.31 (s, 6H, $2CH_3O$), 2.32 (m, 2H, CH_2CO_2Me), 1.87 (m, 4H), 1.73 (m, 1H), 1.60–1.05 (m, 13H), 0.95 (d, 3H, $J=7.0$ Hz, CH_3), 0.90 (m, 9H, $3CH_3$). Anal. calcd for $C_{37}H_{58}O_6$: C, 74.21; H, 9.76. Found C, 74.24; H, 9.64%.