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Toward the total synthesis of methyl isosartortuoate: construction of the backbone of the diene unit

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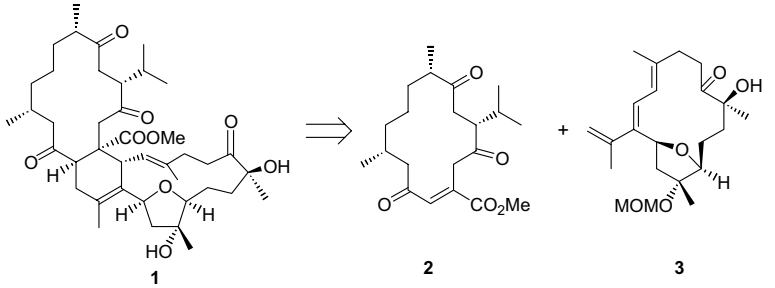
Abstract—The backbone of diene precursor in the proposed biogenesis of methyl isosartortuoate through a Diels–Alder reaction has been constructed via dehydration to establish the conjugated system; and double cyclization by using Horner–Wittig–Emmons reaction and the chiral epoxy ring opening.

Methyl isosartortuoate with a novel tetracyclic tetraterpenoid architecture was first isolated by Su et al. in 1986 from the marine *Sarcophyton tortuosum Tixier-Durivault*.[1] It has been hypothesized that a plausible biogenesis would involve generation of the cyclohexane ring by a Diels–Alder reaction of two cembrenes (the dienophile **2** and diene **3**, shown in Scheme 1).[2] Even though these cembrenes have not been isolated, the structural complexity, in conjunction with the interesting biogenic possibility, captured our attention.[3] Herein, we describe the synthesis of the immediate precursor to the diene unit **3**.

As shown in Scheme 2, the synthesis of the diene unit **3** of methyl isosartortuoate could be strategically transformed into compound **4**, which could be prepared by dehydration of **5**. The chiral THF ring **5** would be constructed via an asymmetric epoxidation followed by intramolecular epoxy ring opening. A plausible route to **6** would involve the macrocyclization of aldehydophosphonoacetate **8** by an HWE reaction, which was accessible from **9** by a sequence of transformations as shown in Scheme 3.

According to this synthetic plan, alcohol **9** was prepared from geraniol and efficiently converted into the aldehydophosphonoacetate **8** as outlined in Scheme 3. In order to prepare the optically active alcohol **10**, several methods were explored.[4] The conversion was successfully accomplished by Sharpless asymmetric epoxidation[5] and subsequent reductive rearrangement of the 2,3-epoxyl alcohols using PPh_3, I_2, and pyridine.[6] Next asymmetric epoxidation of **10** and protection of the secondary hydroxyl group by ethyl vinyl ether afforded **12**.



Scheme 1.

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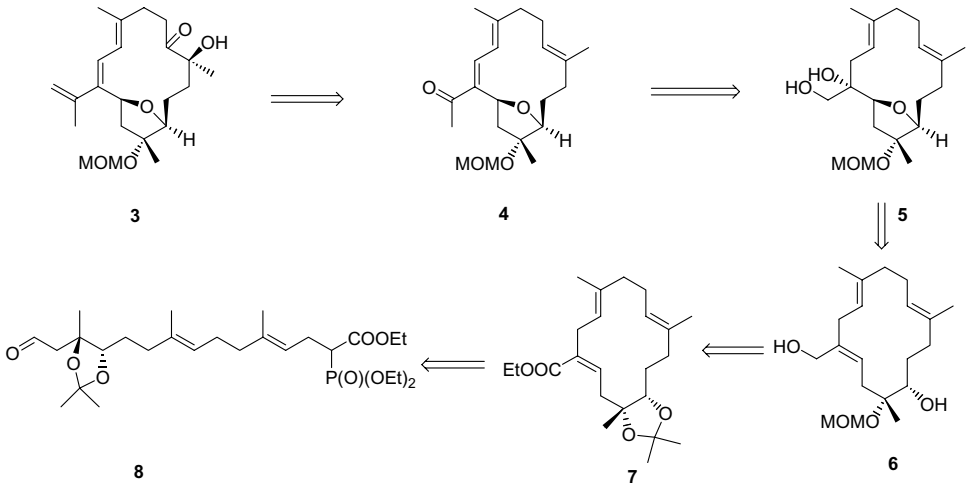
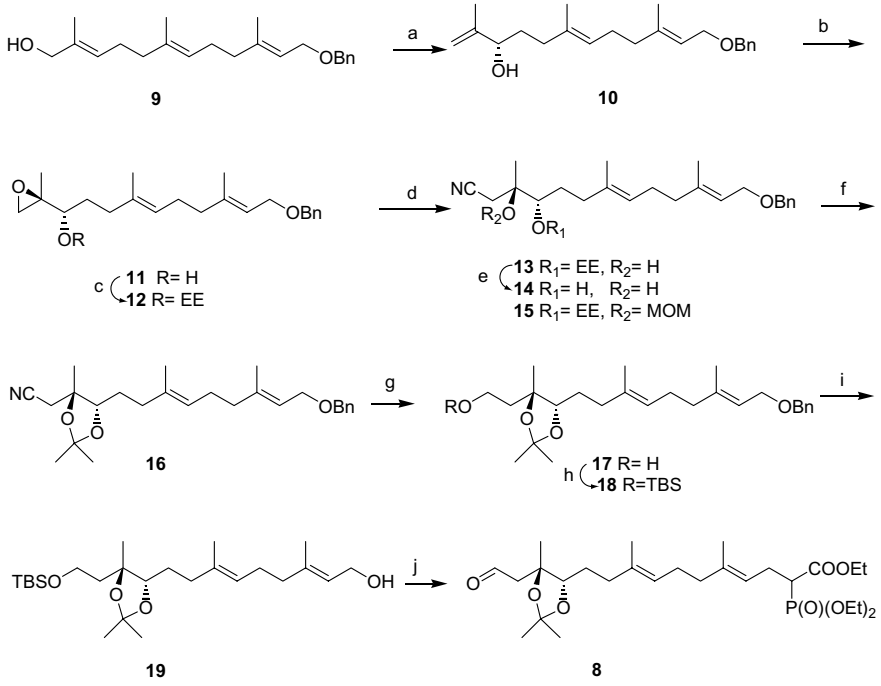


Scheme 2.

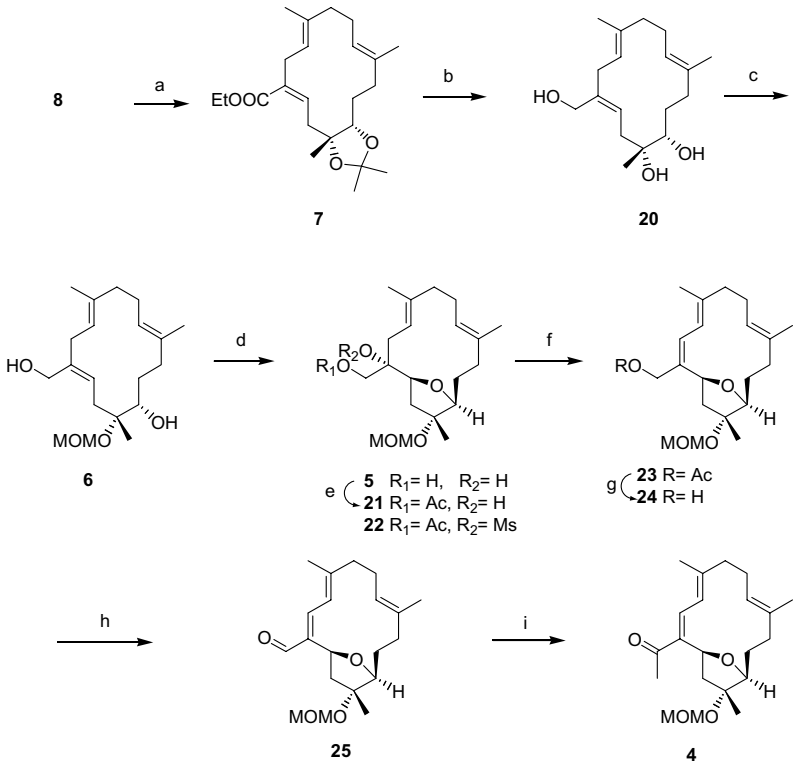


Scheme 3. Reagents and conditions: (a) 4 Å MS, L-(+)DIPT, $Ti(OPr^i)_4$, TBHP, CH_2Cl_2, 92.1%; PPh_3, I_2, pyridine, H_2O, CH_3CN–Et_2O (3:5), 87.3%. (b) 4 Å MS, L-(+)DIPT, $Ti(OPr^i)_4$ TBHP, CH_2Cl_2. (c) Ethyl vinyl ether, PPTS, CH_2Cl_2, 97.5%. (d) NaCN, $LiClO_4$, CH_3CN, 92.1%. (e) PTS, CH_3OH, 95.6%. (f) Dimethoxylpropane, PPTS, CH_2Cl_2, 97.3%. (g) DIBAL-H, Toluene, −78 °C; $NaBH_4$, CH_3OH, 87.9% for two steps. (h) TBSCl, DMAP, Et_3N, CH_2Cl_2, 96.1%. (i) Li-naphthalenide, 0 °C, 98.3%. (j) Triphosgene, Et_3N, 0 °C; $(EtO)_2P(O)CH_2COOEt$, ^{t}BuOH, DMSO, rt, 83.4% for two steps; NH_4F, CH_3OH, 87.2%; Dess–Martin peroidinane, CH_2Cl_2, 93.6%.

Treatment of **12** with $NaCN/LiClO_4$ in CH_3CN provided the β-hydroxynitrile **13**.[7] However, reduction[8] of **15** ($R_1 = EE$, $R_2 = MOM$) with DIBAL-H followed by acid hydrolysis of the imine and its reduction with $NaBH_4$ just afforded the desired product in 33–65% yield because of β-elimination. On the contrary, reduction of **16** was readily realized with DIBAL-H in toluene at −78 °C followed by acid hydrolysis with silica gel in $CHCl_3$ for 1 min and reduction of the resulting product to give **17** in 87.9% yield. After protecting the primary hydroxy group with TBS and removing the Bn group,[9] the resulting allylic alcohol was converted into the allylic chloride.[3b]

The phosphonoacetates moiety was introduced via S_N2 displacement of the allylic chloride by ethyl (diethoxyphosphoryl) acetate carbanion in DMSO (83.4% for two steps).[10] Removal of the TBS protecting group and oxidation of the resulting primary alcohol with Dess–Martin peroidinane gave the precursor **8** for macrocyclization.

The intramolecular HWE reaction has been used successfully in various size of c-rings,[11] however, there were few examples for macrocylization of β-alkoxyl aldehydophonoacetate. Due to the possible β-elimination, a variety of reaction conditions for macrocyclization were screened. It was found that only the β-elimination



Scheme 4. Reagents and conditions: (a) NaH, 18-Crown-6, DME, 10–16 °C, 68.7%. (b) DIBAL-H, CH_2Cl_2, −78 °C, 98%; PTS, MeOH, reflux, 74.9%. (c) Ac_2O, pyridine, rt, 99%; MOMCl, DIPEA, DMAP, Et_3N, CH_2Cl_2, 91.7%; DIBAL-H, CH_2Cl_2, −78 °C, 90%. (d) 4 Å MS, L-(+)DIPT, $Ti(OPr^i)_4$ TBHP, CH_2Cl_2, 95.5%. (e) Ac_2O, pyridine, rt, 85.3%. (f) $SOCl_2$, pyridine, DMAP, CH_2Cl_2, 62.8%. (g) K_2CO_3, CH_3OH, rt, 96.7%. (h) Dess–Martin peroidinane, CH_2Cl_2, 72.4%. (i) CH_3Li, THF, −78 °C; Dess–Martin peroidinane, CH_2Cl_2, 69.5% for two steps.

product was obtained under the condition of DBU/LiCl in CH_3CN. Interestingly, the slow addition of **8** via a syringe pump to a slurry of NaH (3 equiv) and 18-Crown-6 (3 equiv) in DME at 10–16 °C was found to afford the desired carbocyclic ester in 68.7% yield ($Z:E = 7:1$) and the β-elimination product in 18.4% yield (Scheme 4).

Having prepared the carbocyclic ester **7**, we used asymmetric epoxidation again to construct the chiral disubstituted-tetrahydrofuran ring. Reduction of the ester function and hydrolysis of isopropylidene ketal in **7** afforded the separable *Z*-triol and *E*-triol. After selective protection of tertiary hydroxyl group by MOMCl via a sequence of transformations, the epoxidation of **6** followed by a Lewis acid-catalyzed ring opening furnished **5**[12] in 95.5% yield.

After selective acetylation of the primary hydroxyl group of **5** to afford monoacetate **21**, we set out to find a suitable dehydration protocol. Several literature methods[13] such as MsCl, pyridine,[13a,b] and phosphorus oxychloride ($POCl_3$)[13c] were studied. However, the former gave the mesylated **21** while the latter did not react. Gratifyingly, it was found that the traditional method of reacting alcohol **21** with thionyl chloride/pyridine at room temperature furnished alkene **23** in 62.8% yield.[14] Removal of acetyl group with K_2CO_3 in CH_3OH gave the allylic alcohol **24**. Oxidation of **24** with Dess–Martin peroidinane and subsequent treatment of the aldehyde product **25** with CH_3Li in THF at −78 °C followed by oxidation of the resulting alcohol afforded the unsaturated ketone **4**.[15]

In summary, an efficient asymmetric synthesis of 14-membered backbone **4**, required for the preparation of the diene unit of methyl isosartortuoate, has been accomplished by double cyclization. The synthesis is highlightened by a successful HWE macrocyclization for β-alkoxyl aldehydophonoacetate **8** to construct the 14-membered carbocylic unsaturated ester **7** and dehydration of the Sharpless AE product **5** to prepare the unsaturated ketone **4**. Further studies toward the total synthesis of methyl isosartortuoate are still ongoing in our laboratory.

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12. Compound **5**: $[\alpha]_D^{20}$ −75.0 (*c* 0.5, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz): 5.17 (t, $J = 7.6$ Hz, 1H), 5.02 (br, 1H), 4.71 (AB, $J = 7.5$ Hz, 2H), 3.91 (dd, $J = 6.5$, 10.3 Hz, 1H), 3.58–3.57 (m, 3H), 3.37 (s, 3H), 2.43–2.37 (m, 2H), 2.30–2.02 (m, 9H), 1.7–1.52 (m, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 135.1, 134.3, 125.4, 119.4, 91.8, 88.5, 84.4, 81.3, 74.7, 64.5, 55.2, 40.9, 38.6, 38.1, 36.7, 27.1, 25.1, 16.7, 16.0. IR (neat): 3351, 2984, 2951, 2929, 2883, 2839, 1744, 1439, 1378, 1145, 1131, 1105, 1092, 1071, 1035, 924. MS (ESI): 355 [M+H$^+$] (100%), 377 [M+Na$^+$] (50%). HRMS (ESI) calcd for [M+Na]$^+$ ($C_{20}H_{34}O_5$): 377.2298; Found: 377.2293.
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15. Compound **4**: ^1H NMR ($CDCl_3$, 300 MHz): 7.30–6.82 (AB, $J = 10.8$ Hz, 2H), 5.16 (br, 1H), 4.93 (dd, $J = 5.6$, 10.2 Hz, 1H), 4.81–4.73 (AB, $J = 7.5$ Hz, 2H), 3.77 (dd, $J = 2.2$, 11.3 Hz, 1H), 3.42 (s, 3H), 2.66 (dd, $J = 5.2$, 13.2 Hz, 1H), 2.46–2.13 (m, 5H), 2.34 (s, 3H), 2.07–1.93 (m, 2H), 1.88 (s, 3H), 1.82–1.70 (m, 1H), 1.59 (s, 3H), 1.53–1.41 (m, 1H), 1.26 (s, 3H). MS (ESI): 349 [M+H$^+$] (26%), 371 [M+Na$^+$] (18%). HRMS (ESI) calcd for [M+Na$^+$] ($C_{21}H_{32}O_4$): 371.2193; Found: 371.2195.