Pergamon

Tetrahedron Letters 41 (2000) 4641–4644

TETRAHEDRON LETTERS

Studies towards the total synthesis of methyl isosartortuoate: enantioselective synthesis of a precursor of the macrocycle

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Received 19 January 2000; accepted 10 April 2000

Abstract

A concise synthesis of a precursor of dienyl cembranoids starting from geraniol is reported. All of the four chiral centers in the dienyl unit were established by Sharpless kinetic resolution, asymmetric epoxidation and dihydroxylation.

Methyl isosartortuoate **1** is the first tetraterpenoid of this structural type isolated by Chinese scientists from *Sarcophton Tortuosum Tixier–Durivanlt* collected in the South China Sea.[1] A plausible biogenesis would involve generation of the cyclohexene ring by a Diels–Alder reaction of two cembrenes[2] (the dienophile **2** and diene **3** shown in Scheme 1), even though these cembrenes have not been isolated. This interesting possibility as well as the unusual architectural features of methyl isosartortuoate prompted us to initiate a research project aimed at its total synthesis.

Our retrosynthesis is shown in Scheme 1. Although carbocyclization has been successfully employed in several total syntheses,[3] we chose to employ a [2,3] Wittig ring contraction of the 17-membered cyclic propargyl allylic ether **5** which should lead to the 14-membered carbocyclic nucleus **4**. Herein, we describe a stereoselective synthesis of the precursor **6**, in which all of the chiral centers in the diene unit have been established.

The synthetic work first focused on the construction of the chiral THF ring by two Sharpless AE reactions followed by an intramolecular epoxide-opening process (Scheme 2). The commercially available geraniol was first converted into the secondary allylic alcohol **7**,[4] then Sharpless kinetic resolution[5] of **7** provided an optically active terminal epoxyalcohol **8** in 40% yield and 94% ee. After protection of the hydroxyl group of **8** with ethyl vinyl ether, subsequent opening of the terminal epoxide with the lithium salt of propargyl-*O*-THP[6] ether in the presence of $BF_3{\cdot}Et_2O$ at –78°C gave **10** in 60% yield. Protection of the resulting hydroxyl group with MOM ether, deprotection of the primary alcohol with accompanying a hydrolysis of the EE group and an

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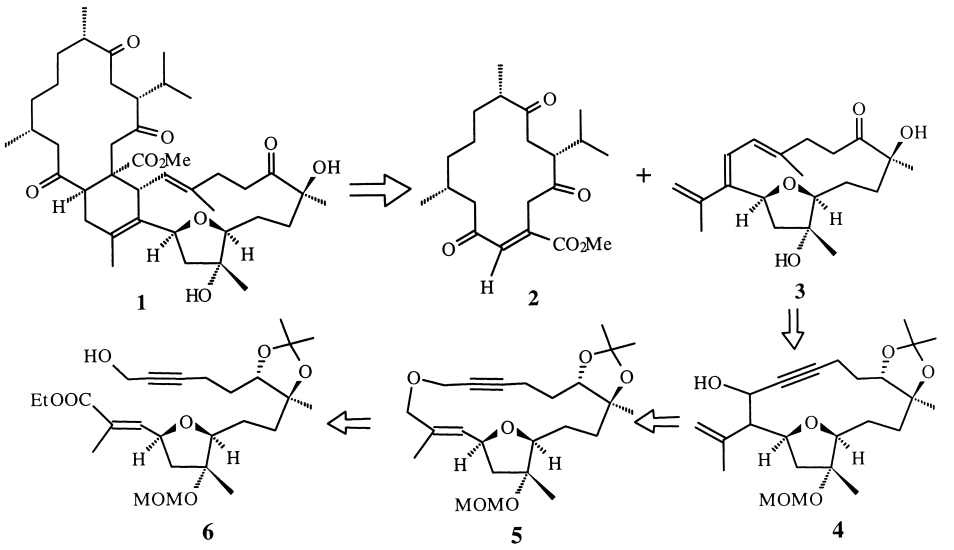
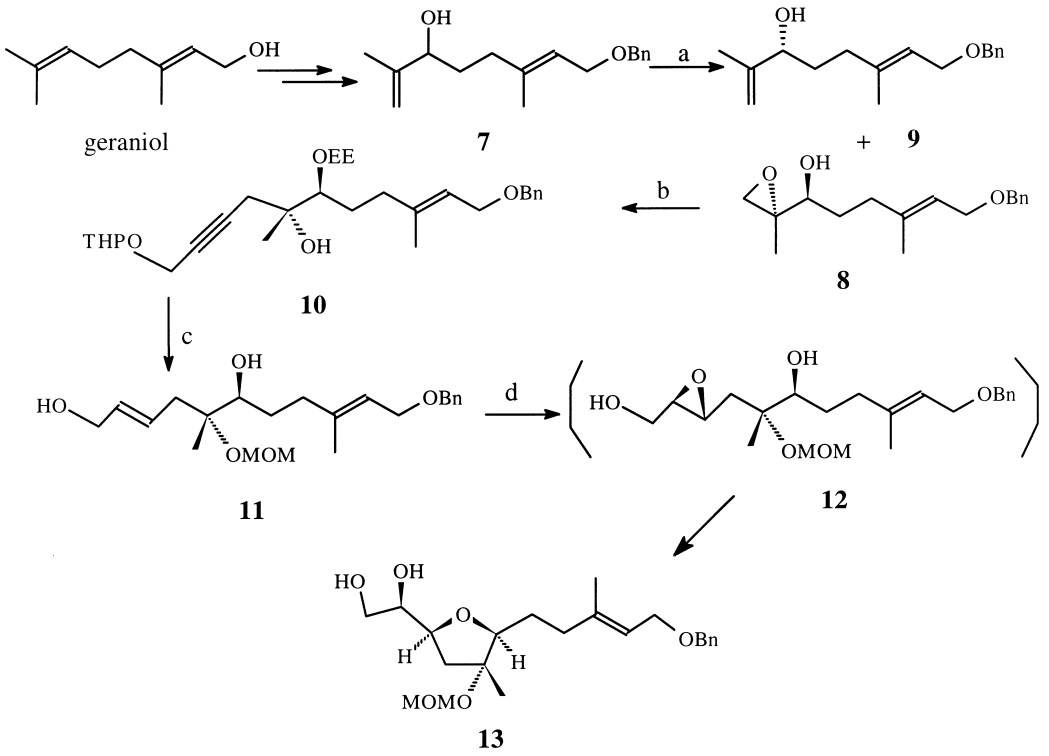
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00607-9



Scheme 1.

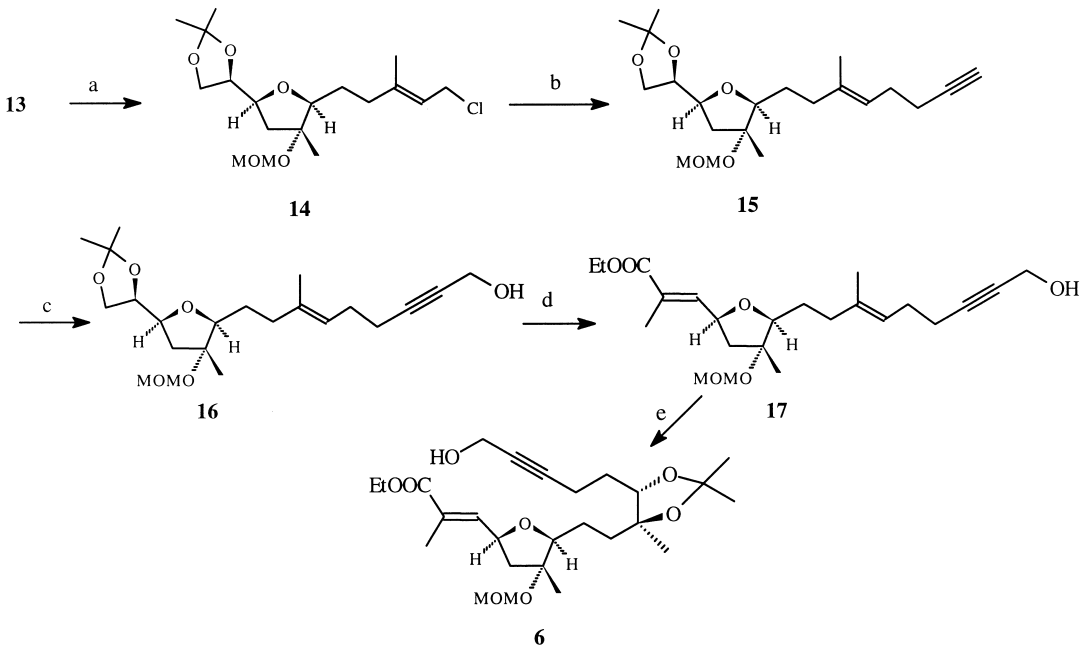


Scheme 2. Reagents: (a) *L*-(+)-DIPT, 4 Å MS, Ti(*i*-PrO)$_4$, TBHP, –20°C(56%); (b) i, PPTS, ethyl vinyl ether; ii, BuLi, –78°C, THP-O-CH_2CCH, $BF_3{\cdot}Et_2O$(62%); (c) i, MOMCl, *i*-Pr_2NEt; ii, PTS, CH_3OH; iii, $LiAlH_4$ in ether, reflux(68%); (d) *D*-(–)-DIPT, Ti(*i*-PrO)$_4$, TBHP, –20°C (99%)

E-selective reduction of the alkyne afforded the desired allylic alcohol **11**. Sharpless asymmetric epoxidation[5] of **11** gave the epoxide **12** which rapidly underwent a Lewis acid catalyzed ring-opening[7] in situ to furnish the necessary 2,5-disubstituted THF compound **13** in 99% yield. However, our results showed that the diastereoselectivity was not good in the second AE reaction based on HPLC (2,5-configuration of the tetrahydrofuran ring ~1.35:1, *trans:cis*). When the secondary hydroxyl was protected as the ethyl vinyl ether, the diastereoselectivity increased to 95%.

With tetrahydrofuran **13** in hand, the chain extension in both directions was explored (Scheme 3). Protection of the vicinal diol gave the corresponding acetonide,[13] on the right hand side, the benzyl group was then removed with lithium naphthalenide.[8] Treatment of the allylic alcohol with 2 equiv. of triphosgene[9] afforded the chloride **14** in 80% yield. This chloride was again homologated to the acetylene **15** in 70% yield via coupling with TIPS-protected propargylmagnesium bromide[10] in the presence of CuI followed by fluoride cleavage of the silyl protecting group. Treatment of the acetylene **15** with *n*-BuLi at –78°C, followed by addition of paraformaldehyde yielded the alcohol **16**. The acetonide was removed smoothly with HOAc:H_2O (4:1). Oxidative cleavage of the resulting diol using silica gel-supported metaperiodate[11] produced an aldehyde which, without purification, underwent olefination with carbethoxyethylidenetriphenylphosphorane to give the unsaturated ester **17** (*E*:*Z* = 1.3:1).

Sharpless asymmetric dihydroxylation[12] of the ester **17** and protection of the resultant diol gave the acetonide **6**[14] in 78% yield for two steps, with 80% diastereoselectivity. The macrocyclization of **6** and further synthetic studies directed towards the cembranoid diene **3** are now undergoing in our laboratory.



Scheme 3. Reagents and conditions: (a) i, PPTS, dimethoxypropane; ii, lithium naphthalenide, –20°C; iii, triphosgene, Et_3N, –78°C(75%); (b) i, TIPS–$CH_2CCMgBr$, CuI, –20°C; ii, Bu_4NF, THF (70%); (c) *n*-BuLi, CH_2O(88%); (d) i, HOAc/H_2O(4:1); ii, $NaIO_4$; iii, toluene, $Ph_3P{=}C(CH_3)CO_2Et$(63%); (e) i, K_2CO_3, $K_3Fe(CN)_6$, $NaHCO_3$, $K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, 0°C, H_2O/*t*-BuOH = 1:1; ii, PPTS, dimethoxypropane(78%)

Acknowledgements

We are grateful to the Academy of Sciences and National Natural Science Foundation of China for their financial support (No. 29572079).

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12. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem Rev.* **1994**, *94*, 2483.
13. The corresponding acetonide **13′**: Data for **13′:** $[\alpha]_D^{25} = -15.9$ (c 1.3, $CHCl_3$) ^{1}H NMR δ (300 MHz, $CDCl_3$), 7.31 (m, 5H), 5.41 (t, $J = 7$Hz, 1H), 4.74 (d, $J = 7.51$Hz, 2H), 4.50 (s, 2H), 4.03 (m, 5H), 3.77 (m, 2H), 3.37 (s, 3H), 2.22 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H), 1.70 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H).
14. Data for **6**: ^{1}H NMR δ (300 MHz, $CDCl_3$), 6.75 (d, $J = 8$Hz, 1H), 4.77 (m, 2H), 4.70 (m, 1H), 4.24 (s, 2H), 4.19 (q, 2H), 3.95 (m, 1H), 3.82 (m,1H), 3.39 (s, 3H), 2.42 (m, 2H), 2.17 (m, 1H), 2.05 (m, 1H), 1.85 (s, 3H), 1.42 (s, 3H), 1.29 (m, 16H), 1.09 (s, 3H).