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Studies on the total synthesis of methyl sartortuoate construction of the 2,3,3,6-tetrasubstituted D-ring segment

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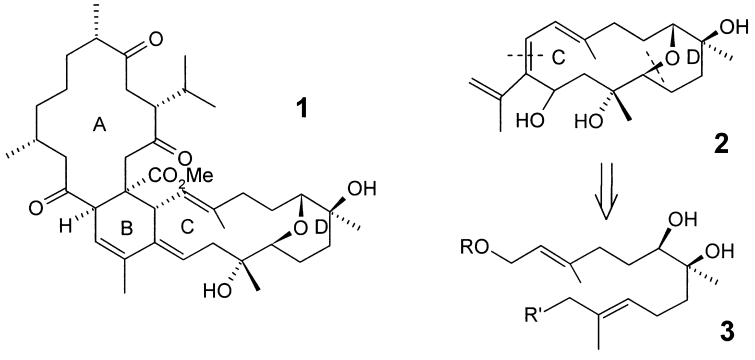
Abstract

An asymmetric synthesis of the 2,3,3,6-tetrasubstituted D-ring segment of methyl sartortuoate including four stereogenic centers is described.

Keywords: methyl sartortuoate; cembrenoids; Diels–Alder reaction.

Methyl sartortuoate (**1**) is a tetracyclic tetraterpenoid isolated from the sarcophyton tortuosum tixier-durivault by Su et al.[1] The novelty and challenge of its structure as well as the potential bioactivity attracted our attention and led us towards the total synthesis. Bisected from the B-ring, the molecule could be regarded as a Diels–Alder combination of two cembrenoids, i.e. the dienophilic A ring unit and the diene C, D ring unit (Scheme 1). As part of our synthetic studies on the 14-membered diene unit (**2**), we wish to describe herein the preparation of the 2,3,3,6-tetrasubstituted D-ring segment (**14**).



Scheme 1.

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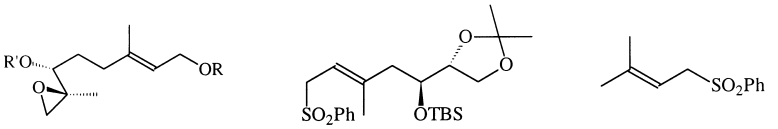
Based on a retrosynthesis, it was thought that compound **3**, as a precursor of the D-ring, could be prepared by the coupling of an epoxy alcohol with a sulfone-stabilized allylic anion as developed by Marshall et al.[2] Therefore, different epoxides and sulfones were prepared to evaluate this approach. As shown in Scheme 2, compound **4** was obtained from geraniol in four steps, **5** from D-mannitol in eight steps and **6** from 3-methyl-2-buten-1-ol in one step.[3]



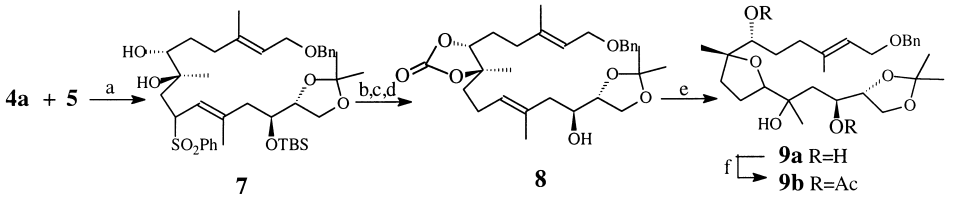
4a R=Bn, R'=H
4b R=TBDPS, R'=H
4c R=TBDPS, R'=TES

5

6

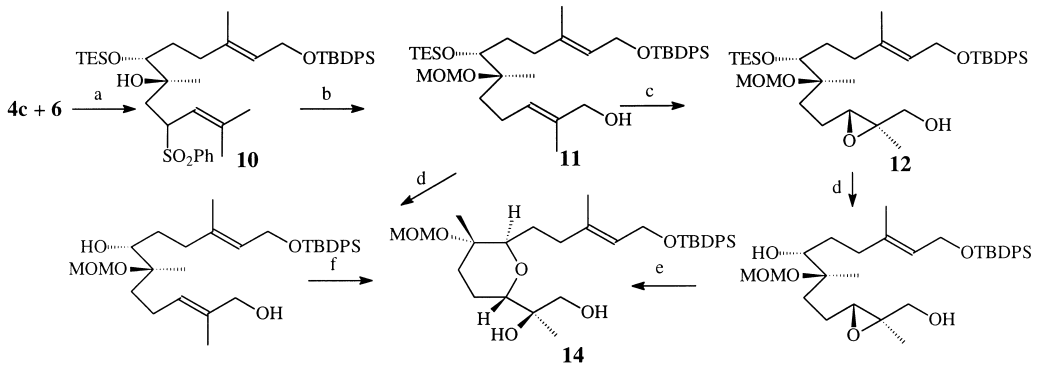
Scheme 2.

The coupling of **4a** with **5** was carried out following Marshall's procedure.[2] Compound **4a** was treated with 1 equiv. EtMgBr prior to the addition of the lithium derivative of **5**,[4] and the desired diol **7** was produced in 46% yield with 34% of the recovered starting materials. After **7** was converted into **8**, epoxidation of **8** using $VO(acac)_2$/TBHP and treatment of the resultant epoxide with anhydrous K_2CO_3 in MeOH gave a single product **9a**. ^1H NMR did not distinguish possible five- and six-membered ring structures, but exposure of **9a** to Ac_2O/Py at rt yielded a diacetyl product **9b**, which suggested that 5-exo epoxide-opening had taken place using the tertiary hydroxyl group to give the undesired tetrahydrofuran containing product (Scheme 3).



Scheme 3. Reagents and conditions: (a) 1 equiv. EtMgBr, THF/HMPA, –78°C, 15 min, then 1 equiv. BuLi, –78°C, 6 h, 46%; (b) 6% Na/Hg, Na_2HPO_4, THF/MeOH, –78°C–rt, 80%; (c) triphosgene, NEt_3, CH_2Cl_2, 95%; (d) TBAF, rt, 90%; (e) (1) cat. $VO(acac)_2$, 1 equiv. TBHP, CH_2Cl_2, 0°C, 1 h; (2) K_2CO_3, MeOH, rt, 18 h, 41% for two steps; (f) Ac_2O, pyridine, rt overnight, 87%

It is well known that nucleophilic epoxide-opening reactions can be accelerated by Lewis-acid catalysis. In order to raise the coupling efficiency, we attempted to find an approach which could change Marshall's intramolecular catalysis into an intermolecular process. After examination of various reagents, triethylsilyl was chosen to protect the hydroxyl group of **4b**, and the coupling of **4c** and **6** was executed by using *n*-BuLi as the base and BF_3Et_2O as the Lewis acid at –78°C. The desired product **10** was obtained in 91% yield without recovery of the starting materials. After desulfonylation and protection of the tertiary hydroxyl group, selective allylic oxidation[5] with SeO_2/TBHP afforded the allylic alcohol **11**. Sharpless AE of **11** smoothly produced the required epoxy alcohol **12** in 92% yield, then selective desilylation and treatment with $Ti(OPr^i)_4$ in refluxing benzene gave the desired tetrasubstituted D-ring segment **14** in 85% yield.[6] Alternatively, the TES ether was removed first, then Sharpless AE afforded the same compound **14** in 82% yield[7] (Scheme 4).



Scheme 4. Reagents and conditions: (a) 1 equiv. BuLi, 1 equiv. BF_3Et_2O, THF, –78°C, 2 h, 92%; (b) (1) 6% Na/Hg, Na_2HPO_4, THF/MeOH, –78°C–rt; (2) MOMCl, DIPEA, CH_2Cl_2, 0°C–rt, overnight; (3) 0.5 equiv. SeO_2, 3 equiv. TBHP, CH_2Cl_2, 10°C, 3 h, 25% for three steps; (c) cat. D-(–)-DIPT, $Ti(O^iPr)_4$, CH_2Cl_2, 1 equiv. TBHP, –25°C, 92%; (d) PPTS, $MeOH/H_2O$, overnight, 95%; (e) $Ti(O^iPr)_4$, benzene, reflux, 1 h, 89%; (f) 1.2 equiv. D-(–)-DIPT, 1.1 equiv. $Ti(O^iPr)_4$, CH_2Cl_2, 1.2 equiv. TBHP, –25°C, overnight, 82%

In conclusion, we have successfully constructed the 2,3,3,6-tetrasubstituted D-ring segment **14** of methyl sartortuoate and established four stereogenic centers. Further work towards the 14-membered diene unit **2** is underway in this laboratory.

Acknowledgements

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