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The First Total Synthesis of (±)-Eremopetasidione

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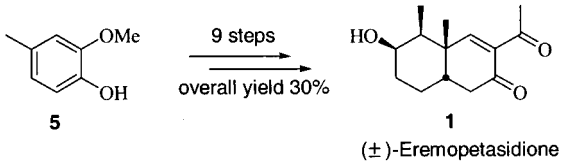
ABSTRACT



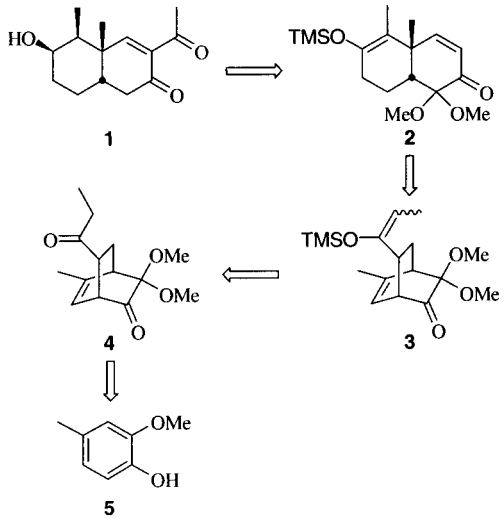
5 1 (±)-Eremopetasidione

The total synthesis of racemic eremopetasidione, a norsesquiterpenoid, has been achieved in nine steps and 30% overall yield starting from creosol (5). Diels–Alder reaction of masked *o*-benzoquinone 6 and ethyl vinyl ketone and Cope rearrangement of 2-silyloxy-1,5-dienone 3 are the key steps.

A large variety of natural products of biological importance possess the decalin skeleton as an integral part of their structure. Functionalized decalins with suitable stereochemistry are possible intermediates for several terpenoids and related natural products.[1] Recently, we have demonstrated that masked *o*-benzoquinones (MOBs)[2,3] and masked *p*-benzoquinones (MPBs)[4] are efficient intermediates for the stereoselective syntheses of highly functionalized *cis*-decalins. A four-step stereocontrolled synthesis of *cis*-decalins involving Diels−Alder reaction and Cope rearrangement is among them.[3] In this Letter we report the first total synthesis of racemic eremopetasidione (**1**) using this methodology.

(−)-Eremopetasidione, a norsesquiterpenoid, has been isolated[5] recently from rhizomes of *Petasites japonicus* MAXIM., which have been used in the treatment of tonsillitis, contusion, and poisonous snake bites in Chinese medicine.[6] Eremopetasidione possesses four stereogenic centers, two methyl groups and a hydroxyl group on the *cis*-decalin skeleton. Retrosynthetically, we envisaged C-acetylation of *cis*-decalin **2** to be a means potentially well suited to access of **1** (Scheme 1). The intermediate **2** would be generated by the Cope rearrangement of 2-silyloxy-1,5-dienone **3** followed by double bond isomerization,[3] and **3** could be obtained from bicyclo[2.2.2]octenone derivative **4**.

Scheme 1



1 2 3 4 5

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(2) (a) Rao, P. D.; Chen, C.-H.; Liao, C.-C. *Chem. Commun.* **1998**, 155. (b) Hsiu, P.-Y.; Liao, C.-C. *Chem. Commun.* **1997**, 1085. (c) Lee, T.-H.; Liao, C.-C.; Liu, W.-C. *Tetrahedron Lett.* **1996**, *37*, 5897.

(3) Hsu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *Tetrahedron Lett.* **1998**, *39*, 659.

(4) Tsai, Y.-F.; Peddinti, R. K.; Liao, C.-C. *Chem. Commun.* **2000**, 475.

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(6) *Dictionary of Chinese Materia Medica*; Shanghai Scientific Technological Publishers and Shougakukan:, Shougakukan, Tokyo, 1985; p 2386.

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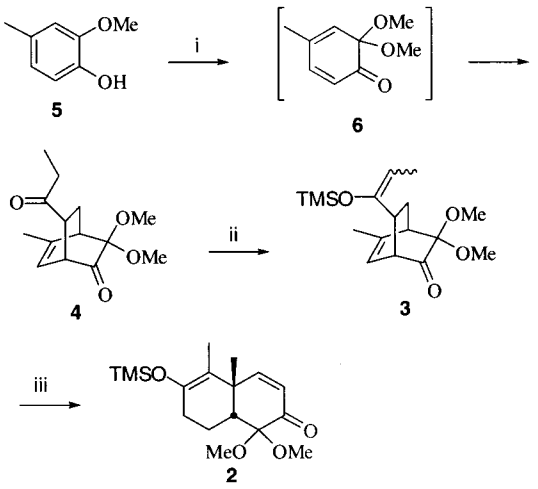
Access to this cycloadduct was to be gained from creosol (**5**) and ethyl vinyl ketone (EVK) via Diels−Alder cycloaddition of in situ generated MOB **6**. In this synthetic plan, another key issue which must be addressed is the generation of four contiguous stereogenic centers on decalin skeleton.

The *cis*-decalin **2** was synthesized according to our earlier report;[3] however, the yield was improved in the present study. The regio- and stereocontrolled intermolecular Diels−Alder reaction[7] of EVK and MOB **6**, which was prepared in situ by the oxidation of **5** with diacetoxyiodobenzene (DAIB) in MeOH, afforded cycloadduct **4** as a single isomer in excellent yield (Scheme 2). Transformation of **4** into silyl enol ether[8]

Scheme 2

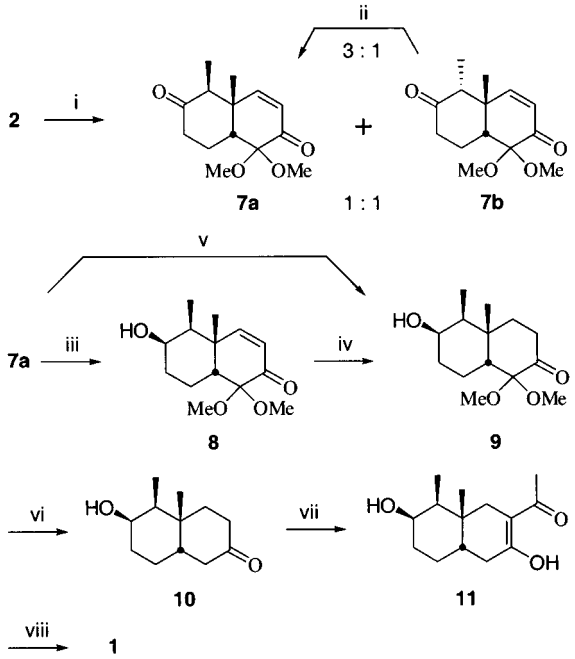


[a]Reagents and conditions: (i) DAIB, MeOH, EVK, rt (96%) (ii) NEt_3, TMSOTf, C_6H_6, rt (96%); (iii) $HC(OMe)_3$, mesitylene, 220 °C (70%).

3 followed by Cope rearrangement furnished the desired decalin **2**. To the best of our knowledge, we are the first to employ bicyclo[2.2.2]octenone with 2-silyloxy-1,5-diene as a substrate for the Cope rearrangement.[3]

Having achieved construction of *cis*-decalin core **2** from **5** in good yield, we then proceeded to install the remaining two stereogenic centers (Scheme 3). Exposure of **2** to 1% oxalic acid gave a mixture of epimers **7a**,**b** which can be separated by silica gel column chromatography in excellent yield,[9] however, in 1:1 ratio. The ratio of **7a** and **7b** was determined by the ^{1}H NMR (400 MHz) analysis of their mixture. Treatment of **7b** with DBU resulted in the formation of **7a** and **7b** in a 3:1 ratio, respectively. Selective reduction

Scheme 3



[a]Reagents and conditions: (i) 1% $(CO_2H)_2$, ether, rt (95%); (ii) DBU, CH_2Cl_2, rt (89%); (iii) 1 equiv. L-selectride, THF, -78 °C (90%); (iv) H_2, Pd/C, EtOAc, rt (95%); (v) 2 equiv. L-selectride, THF, -78 °C (92%); (vi) SmI_2, MeOH/THF, rt (89%); (vii) 1) LHMDS, CH_3COCN, THF, -78 °C; 2) 2N NaOH, rt (85%); (viii) DDQ, 1,4-dioxan, rt (84%).

of **7a** took place with 1 equiv of L-Selectride to furnish alcohol **8** bearing the required four contiguous stereogenic centers. The stereochemical outcome of intermediate **8** was confirmed by ^{1}H NMR nuclear Overhauser enhancement difference (NOED) experiments. The structure of **8** was further confirmed by X-ray diffraction studies (Figure 1).

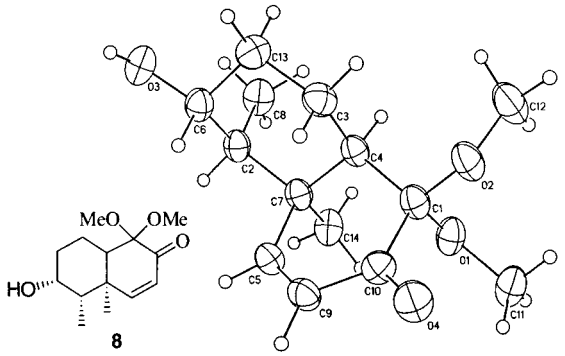


Figure 1. ORTEP plot of the crystal structure of **8** (numbering is arbitrary).

Hydrogenation of enone **8** in the presence of Pd/C produced ketone **9**. Alternatively, the conversion of **7a** to **9** was realized in excellent yield in a single step when **7a** was reduced with 2 equiv of L-Selectride.

(7) For recent examples of Diels−Alder reactions of MOBs, see: (a) Chen, C.-H.; Rao, P. D.; Liao C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254. (b) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko. S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102. (c) Hsieh, M.-F.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, 1441. (d) Gao, S.-Y.; Lin, Y.-L.; Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421. (e) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909.

(8) Corey, E. J.; Cho, H.; Ruecker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(9) All new compounds were satisfactorily characterized by IR, ^{1}H (400 MHz), ^{13}C (100 MHz) NMR, DEPT, and low- and high-resolution MS analyses.

With the advanced intermediate **9** in hand, the stage was set for completion of the total synthesis. Demethoxylation[10] of **9** with samarium iodide in THF in the presence of MeOH as proton source afforded **10** (Scheme 3). C-Acetylation[11] of the enolate derived from **10** with pyruvonitrile, and subsequent treatment with NaOH, produced **11**. Finally, dehydrogenation[12] of enol **11** was effected with DDQ to accomplish the total synthesis of (±)-eremopetasidione (**1**). The structure of **1** was elucidated by ^{1}H−^{1}H and ^{1}H−^{13}C COSY and NOED (Figure 2) studies. Furthermore, ^{1}H and

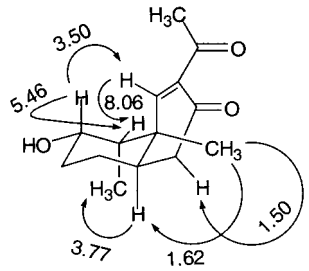


Figure 2. ^{1}H NMR studies of NOE (%) for **1**.

^{13}C NMR spectral data of natural (−)-**1**[5] and our synthetic **1** are identical.[13−15]

(10) Hwang, J.-T.; Liao, C.-C. *Tetrahedron Lett*. **1991**, *32*, 6583.

In conclusion, we have accomplished the first total synthesis of racemic eremopetasidione in nine synthetic operations in 30% overall yield. The Diels−Alder reaction of a masked *o*-benzoquinone and the Cope rearrangement of a 2-silyloxy-1,5-dienone are the key steps in our strategy.

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Supporting Information Available: ^{1}H and ^{13}C NMR and DEPT spectra for compounds **1**−**4** and **7**−**11**, X-ray crystallographic data for compound **8**, and ^{1}H−^{1}H and ^{1}H−^{13}C COSY spectra for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Tang, Q.; Sen, S. E. *Tetrahedron Lett*. **1998**, *39*, 2249.

(12) Edwards, J. A.; Calzada, M. C.; Ibánez, L. C.; Rivera, M. E. C.; Urquiza, R.; Cardona, L.; Orr, J. C.; Bowers, A. *J. Org. Chem*. **1964**, *29*, 3481.

(13) In the ^{1}H NMR spectrum of **1**, a multiplet was observed at δ 1.53−1.62, which was also observed for (−)-**1** (ref 14). In the ^{13}C NMR spectra of (−)-**1**,[5] the signal at δ 38.9 was due to an impurity, and the signal at δ 44.1, which was observed in our spectrum for **1**, was also noticed for (−)-**1** as a weak signal (ref 14).

(14) Kikuchi, M. Personal communication.

(15) We are grateful to Professor Kikuchi for providing spectral data (IR, ^{1}H and ^{13}C NMR, difference NOE spectra and MS) of (−)-**1**.