ORGANIC LETTERS

2003
Vol. 5, No. 24
4741−4743

Total Syntheses of Sesterpenic Acids: Refuted (±)-Bilosespenes A and B

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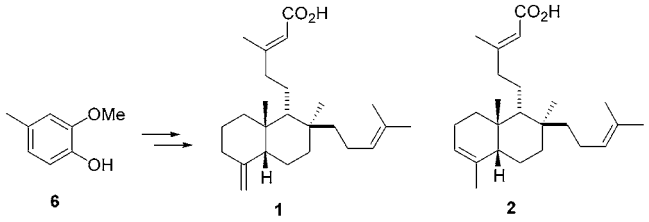
Received October 5, 2003

ABSTRACT



6 1 2

The total syntheses of racemic sesterpenic acids 1 and 2 have been accomplished from creosol (6) in 12 and 13 steps, respectively. Intramolecular Diels–Alder reaction of masked *o*-benzoquinone 7 generated from 6 and allyl alcohol, stereoselective addition of alkenylcerium(III) chloride 8 to ketone 5, and anionic oxy-Cope rearrangement of dienol 4 are the key steps.

Owing to their widespread occurrence in a large variety of natural products of biological importance, decalins remain a focus of attention for synthetic organic chemists.[1] Functionalized decalins with suitable stereochemistry are possible intermediates for several terpenoids and related natural products possessing biological activity. Most recently, we have shown that masked *o*-benzoquinones (MOBs)[2] and masked *p*-benzoquinones (MPBs)[3] are efficient intermediates for the stereoselective syntheses of highly functionalized *cis*-decalins. A four-step stereocontrolled synthesis of *cis*-decalins involving intermolecular Diels−Alder reaction and anionic oxy-Cope rearrangement is one of the strategies.[4] In this Letter we report a stereoseletive synthesis of bilosespenes A and B (**1** and **2**) based on the construction of a *cis*-decalin core generated by intramolecular Diels−Alder reaction and anionic oxy-Cope rearrangement.

Bilosespenes A and B (**1** and **2**) have been isolated[5] recently from the Red Sea sponge *Dysidea cinerea* as an unstable and inseparable mixture. This mixture has been found to have cytotoxicity against several cancer cells: P-388 Mouse lymphoma, A-549 Human lung carcinoma, HT-29 Human colon carcinoma, and MEL-28 Human melanoma in a concentration of 2.5 μg/mL (IC_{50}). Bilosespene possesses four stereogenic centers and an α,β-unsaturated acid. Retrosynthetically, we envisaged C-alkylation of tricyclic compound **3** to be a means potentially well-suited to access **1** and **2** (Scheme 1). The intermediate **3** would be generated by the anionic oxy-Cope rearrangement of **4**, which could be obtained from cycloadduct **5**. Access to tricyclic compound **5** was to be gained from creosol (**6**) and allyl alcohol via the Diels−Alder cycloaddition of in situ generated MOB **7**. In this synthetic plan, another key step is stereoselective addition to ketone **5** to generate anionic oxy-Cope rearrangement precusor **4**.

The tricyclic β,γ-enone **5** was obtained[6] via intramolecular Diels−Alder reaction of MOB **7**, produced in situ from oxidation of creosol (**6**) with diacetoxyiodobenzene (DAIB) in the presence of allyl alcohol (Scheme 2). Treatment of **5** with cerium reagent **8** produced single stereoisomer product **4**.[7] Reaction of **4** with potassium hydride and 18-crown-6 in refluxing THF gave *cis*-decalin **3** via anionic oxy-Cope

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(4) (a) Lee, T.-H.; Liao, C.-C. *Tetrahedron Lett.* **1996**, *37*, 6869. (b) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912.

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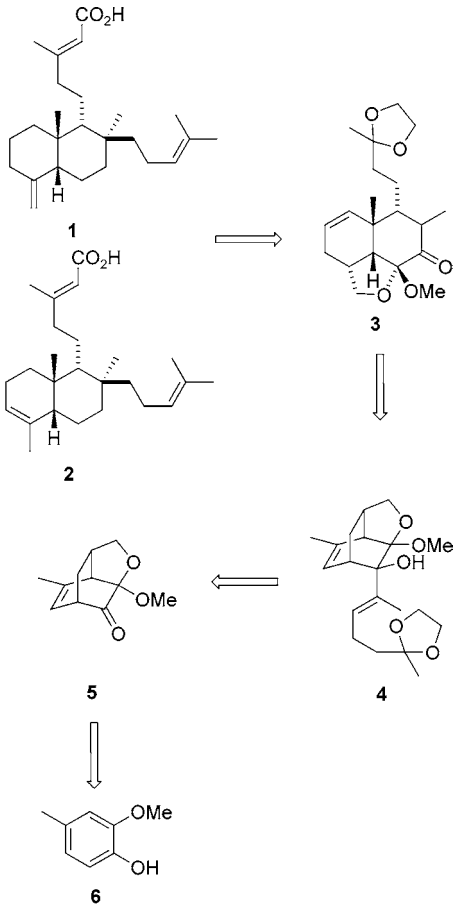
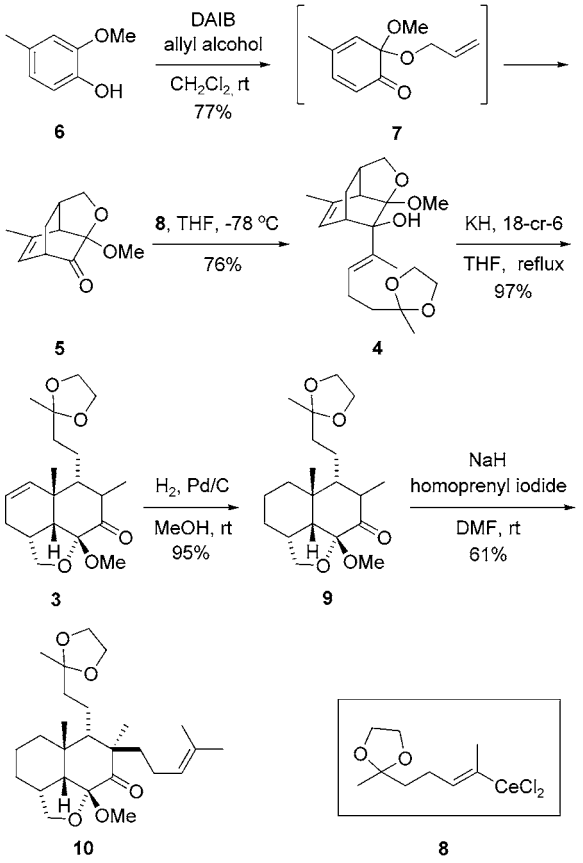
10.1021/ol035944i CCC: $25.00
Published on Web 10/29/2003

Scheme 1



Scheme 2



rearrangement. Hydrogenation of **3** in the presence of Pd/C produced compound **9**. Alkylation of the sodium enolate derived from **9** with homoprenyl iodide[8] in DMF[9] afforded tricyclic compound **10** in 61% yield. The structure of **10** was confirmed by X-ray diffraction studies (Figure 1).

With *cis*-decalin **10** secured, the stage was set for the introduction of the exocyclic double bond. Ketone **10** was reduced with samarium diiodide in THF in the presence of MeOH as proton source, and this was followed by Huang−Minlon reduction[10] to afford alcohol **12** (Scheme 3). Conversion of the alcohol **12** into selenide **13** was performed using Grieco's method.[11] Compound **13** was then transformed into **15** in excellent yield by hydrolysis of the ketal moiety and sodium periodate mediated oxidative-elimination.[12]

Having successfully installed the requisite *exo*-methylene group, all that remained to complete the synthesis of the target molecule was to convert the carbonyl function into α,*β*-unsaturated acid moiety.

Toward that objective, Horner−Emmons reaction[13] of ketone **15** was performed in refluxing THF to give (*E*)-α,*β*-unsaturated ester **16** exclusively (Scheme 4). Finally, treat-

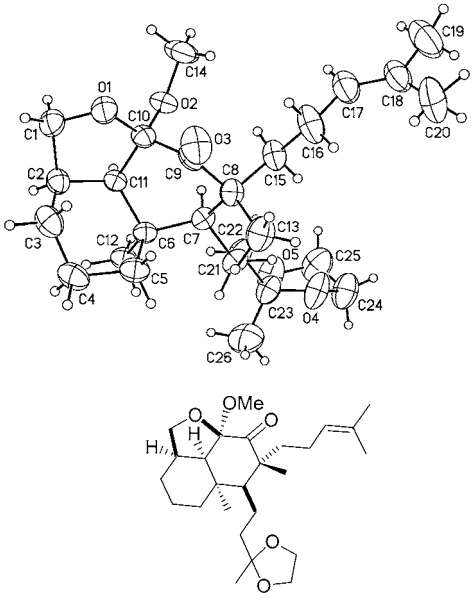


Figure 1. ORTEP plot of the crystal structure of **10** (numbering is arbitrary).

(7) 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.

(8) (a) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37. (b) Vidari, G.; Lanfranchi, G.; Masciaga, F.; Moriggi, J. D. *Tetrahedron: Asymmetry* **1996**, *7*, 3009.

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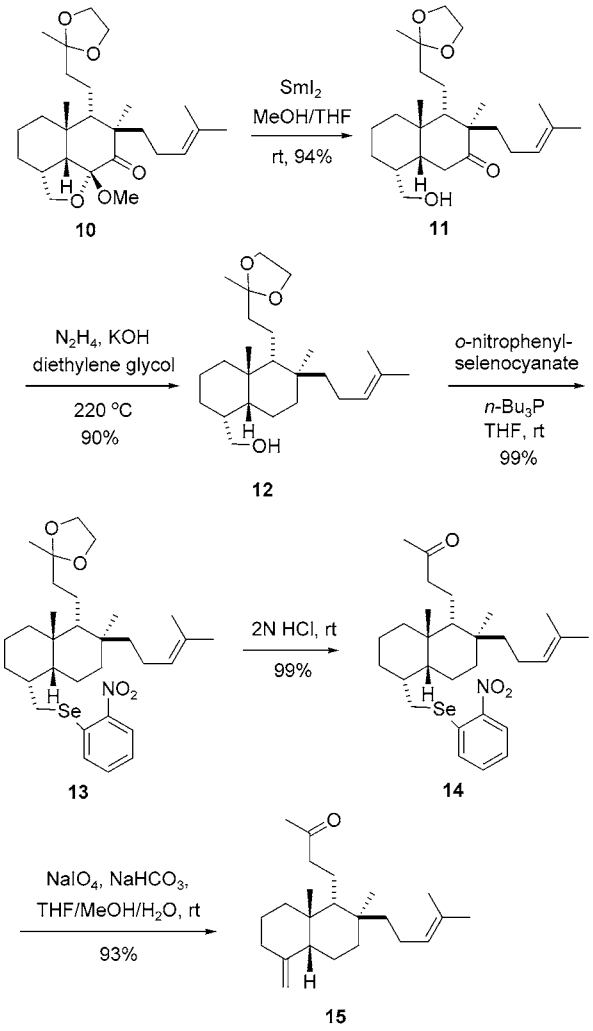
(10) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487.

(11) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

Scheme 3



ment of **16** with potassium hydroxide accomplished the total synthesis of sesterpenoid acid **1**.

Sesterpenic acid **1** is quite stable when stored at room temperature for a long time and neither decomposed nor converted into acid **2**. Furthermore, the exocyclic double bond of **1** could be isomerized into the *endo*-double bond of **2** by treating with *p*-toluenesulfonic acid[14] in CH_2Cl_2. The structures of acids **1** and **2** were elucidated by $^1H-^{13}C$ COSY and ^1H NMR nuclear Overhauser enhancement difference (NOED) experiments (Figure 2). However, the ^1H and ^{13}C

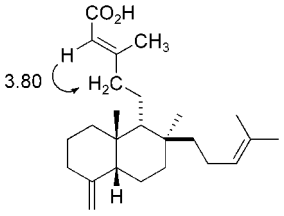
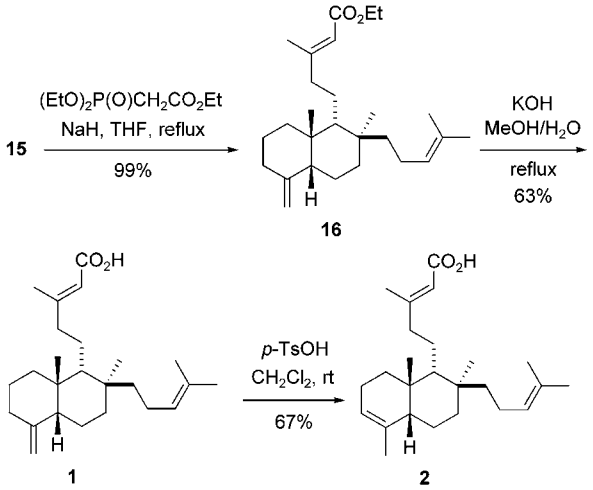


Figure 2. ^1H NMR study of NOE (%) for **1**.

Scheme 4



NMR spectra[15] of **1** and **2** were quite different from those reported for the natural products.[5]

In conclusion, we have accomplished total syntheses of the alleged structures of sesterpenic acids **1** and **2** in 12 and 13 synthetic steps, respectively. An intramolecular Diels–Alder reaction of masked *o*-benzoquinone **7**, a stereoselective addition to ketone **5**, and an anionic oxy-Cope rearrangement with dienol **4** were all key steps in our strategy.

Acknowledgment. Financial support from National Science Council of the Republic of China is sincerely acknowledged. We thank Dr. R. K. Peddinti for helpful discussions.

Supporting Information Available: Spectral data of all new compounds and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035944I

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(14) Piers, E.; Breau, M. L.; Han, Y.; Plourde, G. L.; Yeh, W. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 963.
(15) Compound **1**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, J = 3.6, 3.6 Hz, 1H), 0.90 (s, 3H), 0.94 (s, 3H), 1.04–1.12 (m, 1H), 1.22–2.00 (m, 14H), 1.61 (s, 3H), 1.69 (s, 3H), 2.06–2.23 (m, 4H), 2.19 (s, 3H), 4.62–4.63 (m, 1H), 4.64–4.65 (m, 1H), 5.05–5.09 (m, 1H), 5.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.4 (CH_3), 19.8 (CH_3), 21.7 (CH_2), 23.0 (CH_2), 24.4 (CH_2), 25.3 (CH_2), 25.7 (CH_3), 26.5 (CH_3), 27.0 (CH_2), 31.1 (CH_2), 37.5 (CH_2), 37.6 (C), 39.7 (C), 44.8 (CH_2), 45.0 (CH_2), 54.5 (CH), 56.5 (CH), 108.3 (CH_2), 114.3 (CH), 125.0 (CH), 131.1 (C), 152.2 (C), 164.0 (C), 171.5 (C). Compound **2**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.89 (s, 3H), 0.94 (dd, J = 3.6, 3.6 Hz, 1H), 1.02–1.11 (m, 1H), 1.17–1.42 (m, 5H), 1.45–1.55 (m, 2H), 1.61 (s, 3H), 1.63–1.71 (m, 2H), 1.67 (s, 3H), 1.69 (s, 3H), 1.76–1.80 (m, 1H), 1.86–2.00 (m, 4H), 2.18–2.27 (m, 2H), 2.20 (s, 3H), 5.06–5.09 (m, 1H), 5.27 (br s, 1H), 5.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 21.7 (CH_2), 22.7 (CH_3), 23.4 (CH_2), 23.5 (CH_2), 24.5 (CH_2), 24.9 (CH_3), 25.5 (CH_2), 25.7 (CH_3), 37.4 (C), 37.6 (CH_2), 37.9 (C), 44.6 (CH_2), 45.0 (CH_2), 49.7 (CH), 56.1 (CH), 114.5 (CH), 119.6 (CH), 125.1 (CH), 131.1 (C), 137.1 (C), 164.0 (C), 172.0 (C).