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Efficient Synthesis of the Optically Active Cyclopentane Derivative, A Versatile Intermediate Toward the *Euphorbia* Diterpenes

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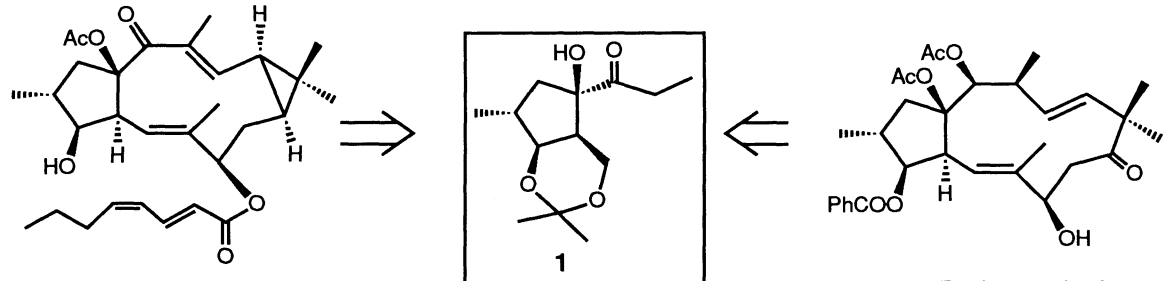
A practical synthesis of the cyclopentane derivative shared by the diterpenes isolated from the plant *Euphorbia helioscopia* L. has successfully been accomplished starting from the optically active cyclopenten-diol derivative.

Euphorbiaceae is well-known to supply a number of cyclopentane-contained diterpenes exhibiting antitumor or cancer promoting activities. Adolf and Hecker proposed their biosynthetic correlation that stepwise transannular cyclization and/or ring-opening of lathyrane derived from casbene afforded jatrophane, jatropholone, tigliane daphnane and ingenane skeletons.[1] Based on their hypothesis, such toxic diterpenes as euphoscopins, euphornins (jatrophane), and euphohelioscopins (lathyrane) isolated from *Euphorbia helioscopia* L. by one of the authors[2] would be precursors of phorbols (tigliane) and ingenol (ingenane) in biomimetic synthetic methodology. In this context we independently initiated an extensive investigation on syntheses of the *Euphorbia* diterpenes and their biomimetic conversion,[3] although many synthetic research have been published for intriguing structures and biological activities of these diterpene family.[4] To accomplish our project, we required practical amounts of the highly functionalized cyclopentane derivative **1** which is shared by majority of the diterpenes. We disclose herein an effective synthesis of the optically active cyclopentane derivative **1**.

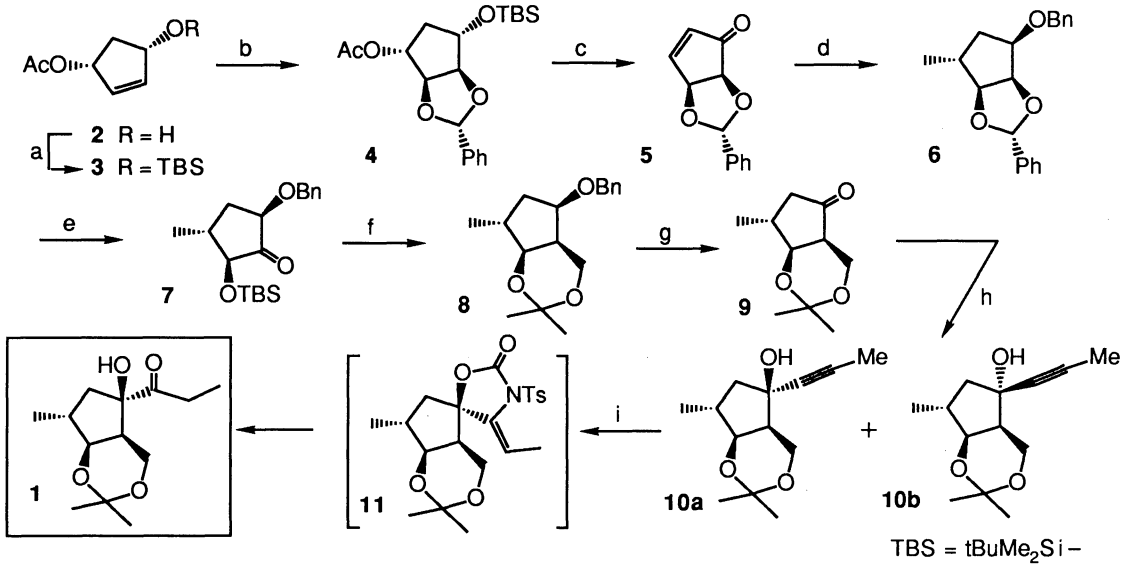


Euphohelioscopin A Euphoscopin A

The readily accessible alcohol **2**[5] was converted to the silyl ether **3**, which was oxidized with OsO_4, followed by protection of the diol as the benzylidene acetal to give **4**. After transformation of the acetyl group in **4** into a mesyl group, the silyl group was removed with nBu_4NF, and the product was submitted to the Swern oxidation to afford the enone **5** in good yield. Introduction of a methyl group into **5** was achieved by the reaction with $MeCu \cdot BF_3$,[6] and the desired 1,4-adduct was submitted to reduction and benzylation to provide **6**. Introduction of a C_1 unit to **6** was undertaken as follows: removal of the acetal followed by selective silylation and oxidation furnished the corresponding ketone **7**, which was then submitted to the Petasis methylenation[7]

and hydroboration to yield a diol characterized as the acetal **8**. Conversion of **8** into the ketone **9** was effected in two steps. 1,2-Addition of 1-propynyl magnesium bromide to the ketone **9** furnished the desired 1-propynyl adducts (**10a** and **10b**). Treatment of **10a** with TsNCO effected introduction of an ethyl ketone group through the cyclic carbamate **11** to give the desired **1**.[8] Since each reaction step could be effectively operated as above mentioned, this process could furnish the key synthetic intermediate **1** on a gram order scale.

Further investigation related to this project is in progress.



a. TBSCl, Imd (97%). b. i) OsO_4, NMO (94%); ii) $PhCH(OMe)_2$, TsOH (96%). c. i) K_2CO_3 / MeOH (81%); ii) MsCl, Et_3N (97%); iii) nBu_4NF (87%); iv) Swern oxid (74%). d. i) MeLi, CuI, BF_3•OEt_2 (79%); ii) L-Selectride (96%); iii) BnCl, NaI, NaH (87%). e. i) TsOH / MeOH (69%); ii) TBSCl, Imd (92%), iii) Swern oxid (87%). f. i) Cp_2TiCl_2 / PhMe (77%); ii) BH_3•THF, then aq.NaOH, H_2O_2 (77%); iii) TsOH / MeOH (92%); iv) CH_2=C(Me)OMe, CSA (99%). g. i) Li, liqNH_3, EtOH (95%); ii) Swern oxid (90%).h. MeCCMgBr, $CeCl_3$ (**10a**: 74%, **10b**: 16%). i. i) TsNCO, CuI, Et_3N; ii) aqNaOH (50% in two steps).

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8) **1**: m/z 227.1317 ($C_{12}H_{19}O_4$, M-Me); $[\alpha]_D^{19}$ +26.2° (*c* 0.98, $CHCl_3$); IR (film) 3550 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3H, d, J= 7.3 Hz), 1.05 (3H, t, J= 7.3 Hz), 1.36 (3H, s), 1.47 (3H, s), 1.57 (1H, dd, J= 5.4, 13.5 Hz), 2.21 (1H, dd, J= 8.3, 13.5 Hz), 2.29 (1H, m), 2.39 (1H, m), 2.71 (1H, dq, J= 18.6, 7.3 Hz), 2.80 (1H, dq, J= 18.6, 7.3 Hz), 3.86 (1H, dd, J= 1.5, 12.5 Hz), 3.95 (1H, s), 4.09 (1H, d, J= 4.4 Hz), and 4.10 (1H, dd, J= 4.4, 12.5 Hz); ^{13}C NMR ($CDCl_3$) δ 8.3 (q), 18.7 (q), 19.3 (q), 29.9 (q), 31.7 (t), 39.4 (d), 42.3 (d), 48.1 (t), 59.3 (t), 79.8 (d), 89.8 (s), 98.4 (s), and 214.1 (s).

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