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# Novel Approach for the Stereocontrolled Construction of Eudesmane Skeleton: A Concise Synthesis of (±)-Balanitol

**Zhe Zhang, Wei-Dong Z. Li,* and Yulin Li***

*National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China*

*liwd@lzu.edu.cn*

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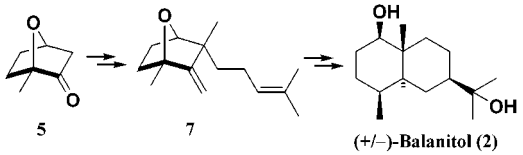
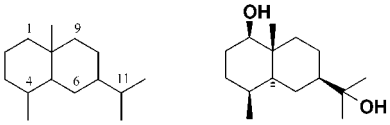
## ABSTRACT



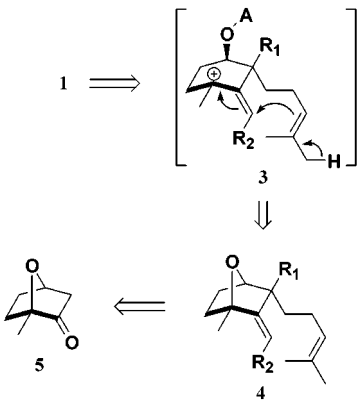

**A novel method for the stereocontrolled construction of the eudesmane ring system based on a cationic cyclization is presented, and the approach is exemplified in a short and efficient total synthesis of (±)-balanitol (2).**

Although considerable efforts have been devoted to the total synthesis of eudesmane sesquiterpenoids over the past decades, the stereocontrolled construction of the decalin skeleton **1** possessing multiple hydroxyl functions still represents a significant synthetic challenge.[1] A novel general and diversified strategy for the stereocontrolled total synthesis of eudesmane sesquiterpenes is highly desirable.




In connection with our ongoing studies[2] on the total synthesis of bioactive sesquiterpenoids, we intended to explore a new strategy for the stereoselective assembly of the decalin ring system bearing an oxygenated functional group at the C-1 and/or C-6 position(s). We envisioned that the C-1 oxygenated decalin of eudesmane **1** would be generated through an intramolecular electrophilic olefin cyclization[3] of the cationic species **3** (see Scheme 1), which could be formed selectively through an acid-mediated ring opening of tetrahydrofuran diene **4**.

**Scheme 1**




(1) For earlier comprehensive reviews on sesquiterpene syntheses, see: (a) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiely and Sons: New York, 1973; Vol 2, pp 197−558. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiely and Sons: New York, 1983; Vol 5. For recent examples, see: (c) White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404. (d) Spivey, A. C.; Woodhead, S. J.; Weston, M.; Andrews, B. I. *Angew. Chem., Int. Ed.* . **2001**, *40*, 769 and references therein.

(2) For recent works from our laboratory, see: (a) Zhou, G.; Gao, X.; Li, W.-Z.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 3101. (b) Li, W.-D. Z.; Zhou, G.; Gao, X.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 4649 and references therein.

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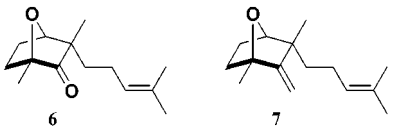
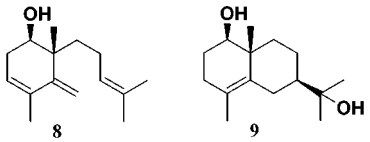
Tetrahydrofuran diene **4**, in which $R_1$ represents a methyl or a hydroxylated methyl group and $R_2$ a hydrogen or a cation-stablizing heteroatom substituent, is accessible from 1-methyl-7-oxabicyclo[2,2,1]heptan-2-one (**5**). A preliminary demonstration of this strategy was exemplified in the total synthesis of (±)-balanitol (**2**), a naturally occurring 1$\beta$-hydroxy-4,5-dihydroeudesmol.

The synthesis (see Supporting Information for experimental procedures) commenced from the known bicyclic ketone **5**.[4] We noticed that good regioselectivity (up to 7:1) of ketone **5** could be achieved when a small amount of water was present in the reaction mixture. Successive alkylation of ketone **5** with homoprenyl iodide (LHMDS, THF, −78 °C to rt, 65%) and methyl iodide (LDA, THF, −78 °C to rt, 75%) gave stereoselectively the desired *exo*-methyl tetrahydrofuran ketone **6** in 49% yield from **5**. Standard methylenation of **6** ($Ph_3P{=}CH_2$, THF, 22 °C, 24 h) furnished the bicyclic diene **7** in 84% yield.




To effect the proposed electrophilic olefin cyclization of tetrahydrofuran diene **7**, a variety of Lewis acids were examined under a variety of reaction conditions. Treatment of **7** with $TiCl_4$, $SnCl_4$, $ZnCl_2$, $EtAlCl_2$, $MgBr_2$, or $BF_3{\cdot}OEt_2$ (either stoichiometric or catalytic amount) by using $CH_2Cl_2$ or $CH_3CN$ as solvent respectively at various temperatures gave rise, unfortunately, to diene **8**[5] as the major isolable product from the reaction mixture in low yield, which presumably resulted from the hypothetical cationic species **3**. Acetic acid did not promote the desired cyclization, while the use of trifluoroacetic acid led to ring opening of the tetrahydrofuran function to form diene **8** and many other unidentified products.




To our delight, formoylsis[6] of **7** in 88% formic acid at 20 °C for 1.5 h proceeded[7] smoothly to give the corresponding C-1 formate **10** of decalinic diol **9**, after chromatographic purification on silica gel, in 32% isolated yield as *the sole separable product* along with a mixture of unidentifiable nonpolar materials. Despite the relatively low chemical yield, the key cyclization is highly stereoselective and operationally simple. Deformylation (NaOH, *t*-BuOH−$H_2O$, 20 °C) of formate **10** afforded crystalline diol **9** (mp 152−154 °C, 95%). The stereochemical assignment for the newly generated C-7 center of cyclization product was based[8] on the characteristic chemical shift of C(7) (49.8 ppm) in the $^{13}C$ NMR spectrum of diol **9** (see Supporting Information for spectral data). The optically active diol (+)-**9** was first isolated[9] from Japanese cedar *Cryptomeria japonica* in 1995. Synthetic (±)-**9** showed spectroscopic properties identical to those of natural **9**, which further confirmed the stereochemistry of the cyclization product **9**. The corresponding C-1 mesylate[10] and tosylate[11] of eudesmene diol **9** have been employed as key intermediates in the conversion to (+)-hedycaryol, a germacrane sesquiterpenol. The synthesis of diol **9** described herein is short, efficient, and highly stereoselective.

Catalytic hydrogenation (10% Pd−C, EtOH, rt, 95%) of **9** proceeded rapidly and gave the desired title compound **2** along with its *cis*-decalin isomer in a ratio of 3:1 as determined by $^1H$ NMR and GC analysis. The highly face selective hydrogenation of **9** was finally achieved over Adams' catalyst ($PtO_2$)[12] in acetic acid to afford crystalline **2** (mp 133−135 °C) quantitatively, which exhibited spectral data ($^1H$, $^{13}C$ NMR, MS and IR) identical to those of natural **2**. Natural **2** was first isolated in 1978 by Polonsky and coworkers[13] from the bark of the Indian tree *Balanites roxburghii*, and its structure was elucidated by chemical correlation and extensive spectroscopic analysis. The interesting fact is that (±)-**2** had been synthesized[14] previously by Heathcock and Ratcliffe as an advanced intermediate in the total synthesis of α-bulnesene and bulnesol, via a lengthy *trans*-decalinic route in 1977 before **2** was revealed as a natural product. The first total synthesis of (+)-**2** was reported[15] by Pinder et al. in 1987 starting from (+)-isopiperitenone through an interesting [2 + 2] photocycloaddition method.

In summary, a concise and highly stereoselective total synthesis of (±)-balanitol (**2**) was achieved in five steps from known oxabicyclic ketone **5** in an overall yield of 13% through a novel approach for the construction of the characteristic eudesmane decalin ring system on the basis

(3) For relevant cases, see: (a) Schwartz, M. A.; Crowell, J. D.; Musser, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 4361. (b) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193. (c) Schwartz, M. A.; Willbrand, A. M. *J. Org. Chem.* **1985**, *50*, 1359. (d) Vite, G. D.; Spencer, T. A. *J. Org. Chem.* **1988**, *53*, 2555.

(4) (a) DiFazio, M. P.; Wallace, W. A.; Sneden, A. T. *Heterocycles* **1989**, *29*, 2391. (b) DiFazio, M. P.; Sneden, A. T. *J. Nat. Prod.* **1990**, *53*, 1357.

(5) Structure was characterized by $^1H$ NMR and IR spectra.

(6) For examples, see: (a) Johnson, W. S.; Jensen, N. P.; Hooz, J.; Leopold, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 5872. (b) Dastur, K. P. *J. Am. Chem. Soc.* **1974**, *96*, 2605. (c) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761.

(7) The cyclization of **7** in neat formic acid (>99%) proceeded much faster but gave a poor yield of the desired product.

(8) (a) Raharivelomanana, P.; Bianchinl, J. P.; Ramanoelina, A. R. P.; Rasoarahona, J. R. E.; Faure, R.; Cambon, A. *Phytochemistry* **1998**, *47*, 1085. (b) Uchiyama, T.; Miyase, T.; Ueno, A.; Usmanghani, K. *Phytochemistry* **1991**, *30*, 655. (c) Yahara, S.; Higashi, T.; Iwaki, K.; Nohara, T.; Marubayashi, N.; Ueda, I.; Kohda, H.; Goto, K.; Izumi, H.; Nuno, M.; Katsuki, S.; Isoda, S.; Satake, M. *Chem. Pharm. Bull.* **1989**, *37*, 2995.

(9) Su, W.-C.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *39*, 603.

(10) Minnaard, A. J.; Wijnberg, J. B. P. A.; De Groot, A. *Tetrahedron* **1994**, *50*, 4755.

(11) Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34.

(12) (a) McQuillin, F. J.; Parrack, J. D. *J. Chem. Soc.* **1956**, 2973. (b) Lee, E.; Lee, D. S.; Choi, Y. W.; Lee, K. H. *Tetrahedron Lett.* **1992**, *33*, 6673.

(13) Cordano, G.; Merrien, M. A.; Polonsky, J.; Rabanal, R. M.; Varenne, P. *J. Indian Chem. Soc.* **1978**, *55*, 1148.

(14) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.

(15) Anglea, T. A.; Pinder, A. R. *Tetrahedron* **1987**, *43*, 5537.

of an intramolecular electrophilic cation−olefin cyclization. The strategy is of great potential for the divergent synthesis of complex polyhydroxylated eudesmane sesquiterpenoids through the structurally divergent precursor **4** (such as varying $R_1$, $R_2$).

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**Supporting Information Available:** Spectral data and experimental procedures for compounds **6**, **7**, **9**, **10**, and **2**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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