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Total Synthesis of (+)-Eurylene

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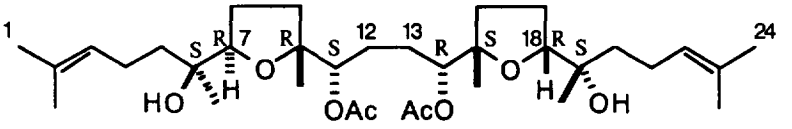
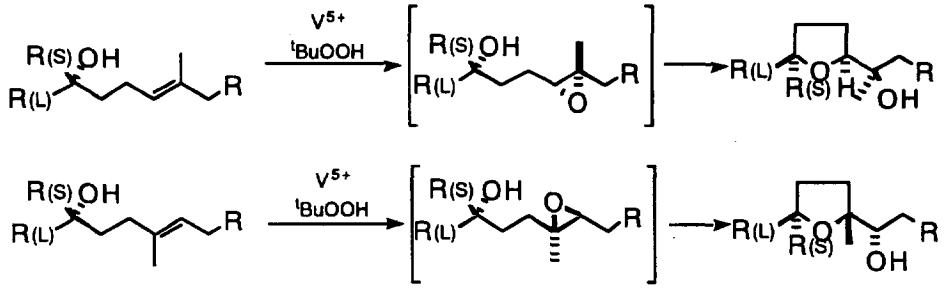
Summary: Eurylene **1**, a cytotoxic bicyclic squalenoid isolated from *Eurycoma longifola*, has been synthesized utilizing the double vanadium(V)-catalyzed oxidation reaction of different bishomoallyl alcohol systems.

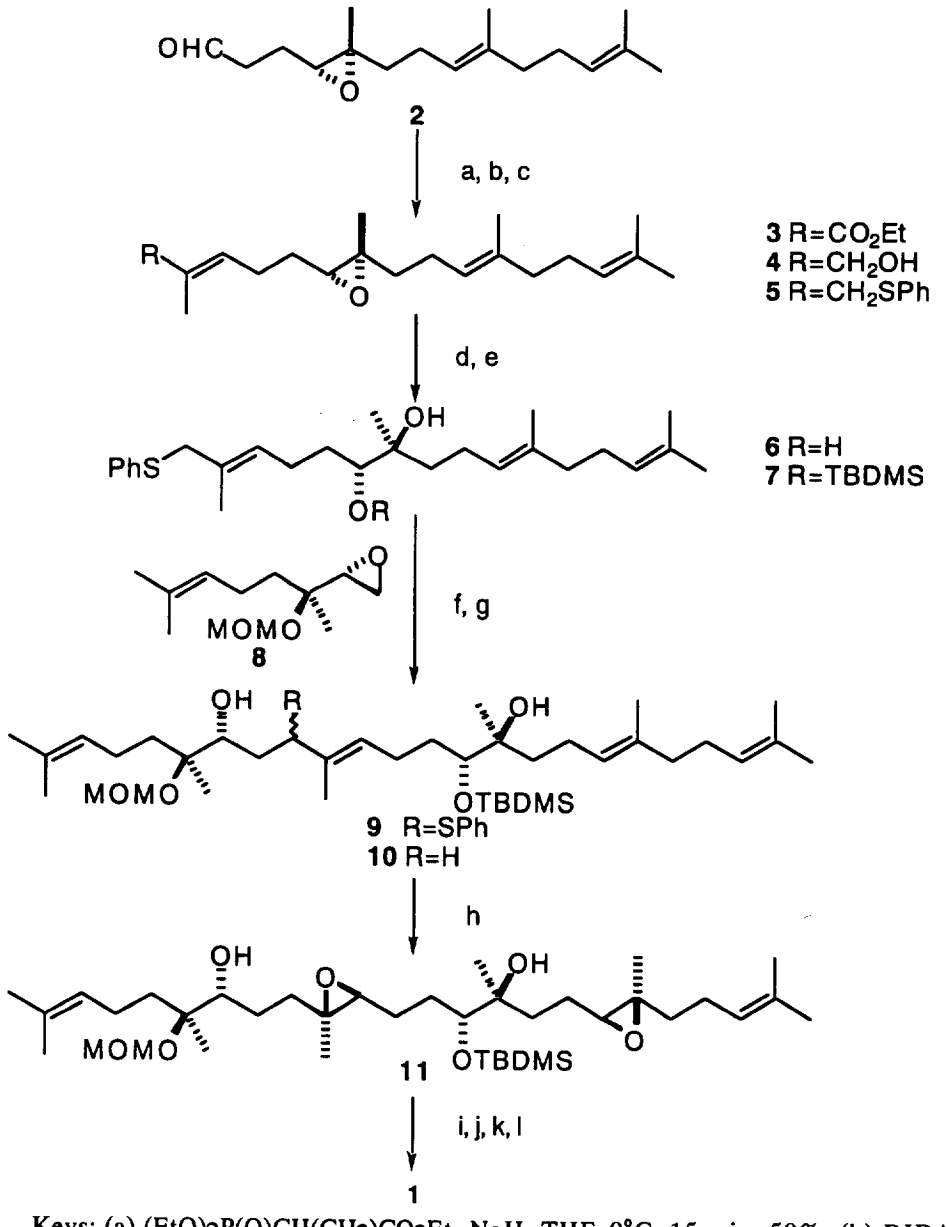
Eurylene **1** is a cytotoxic bicyclic squalenoid isolated from *Eurycoma longifola* (simaroubaceae).[1] This cytotoxic squalenoid has two stereochemically different tetrahydrofuran rings. The one in the left hand (C_1-C_{12}) segment has a 2,5-*trans*-tetrahydrofuran, and the one in the right hand (C_{13}-C_{24}) segment has a 2,5-*cis*-tetrahydrofuran.



Eurylene 1

In the course of the studies on the total syntheses of thyrsiferols[2] and teurilene,[3] we developed a rule for the vanadium(V)-catalyzed oxidation-cyclization of the bishomoallyl alcohol system, i.e., a 5-substituted 4-alken-1-ol gave a *cis*-2,5-disubstituted tetrahydrofuran via the *syn*-epoxide,[4] while a 4-substituted 4-alken-1-ol gave a *trans*-2,5-disubstituted tetrahydrofuran via the *anti*-epoxide.[3,5] By utilizing these rules, the two stereochemically different tetrahydrofurans of eurylene can be constructed at once. We report the total synthesis of eurylene using this method.





Keys: (a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, THF, 0°C, 15 min, 59%; (b) DIBAL, toluene, -78°C, 15 min, 96%; (c) PhSSPh, $^nBu_3P$, CH_2Cl_2, rt, 30 min, 100%; (d) cat. $HClO_4$, 6 : 1 THF-H_2O, reflux, 1 h, 61%; (e) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -20°C, 20 min, 95%; (f) **8**, ^{n}BuLi, TMEDA, HMPA, THF, -20°C, 30 min, 58%; (g) Li, 1 : 1 NH_3-EtOH, -78°C, 4h, 88%; (h) TBHP, cat. $VO(acac)_2$, MS 3A, benzene, rt, 3h; Me_2S, rt, 30 min; (i) cat. CSA, rt, 2h; (j) TBAF, THF, reflux, 2h; (k) cat. HCl, 10 : 1 THF-H_2O, reflux, 15 min, 28% in 4 steps from **10**; (l) Ac_2O, pyridine, rt, 50 h, 83%.

The Horner-Emmons olefination of the optically active aldehyde **2**[6] with sodium triethyl 2-phosphonopropionate in tetrahydrofuran (THF) at 0°C gave the ethyl ester **3**, which was reduced to alcohol **4** by 2.6 equiv. of diisobutylaluminium hydride (DIBAL) in toluene at -78°C. The alcohol **4** was converted to the sulfide **5** by dipheny disulfide with tributylphosphine in dichloromethane.[7] Epoxide cleavage of the sulfide **5** using catalytic perchloric acid in 6:1 THF-H_2O at reflux for 1h gave the diol **6**, whose secondary hydroxyl group was protected by 1.5 equiv. of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) with 2,6-lutidine in dichloromethane at -20°C for 20 min to give the silyl ether **7**.[8]

The bishomoallyl alcohol **10**[9] was assembled from the silyl ether **7** and the oxirane **8**[3,11] by treatment with 3 equiv. of butyllithium (^nBuLi) in *N,N,N',N'*-tetramethylethylenediamine (TMEDA) / hexamethylphosphoramide (HMPA) / THF at -20°C[12] and then desulfurization under Birch condition (lithium in liquid ammonia with ethanol). Treatment of the bishomoallyl alcohol **10** with 0.05 equiv. of vanadyl acetylacetonate ($VO(acac)_2$) and 4 equiv. of *tert*-butyl hydroperoxide (TBHP) in benzene over activated molecular sieves 3A (MS 3A) at room temperature for 30 min gave the unstable bisepoxide **11**,[13] which was converted to deacetyleurylene in the three-step sequence (1) acid catalyzed cyclization of the left hand's epoxide (treatment with methyl sulfide then catalytic camphorsulfonic acid (CSA) *in situ*);[14] (2) deprotection of the silyl group (tetrabutylammonium fluoride (TBAF) in THF at reflux); and (3) acid catalyzed cyclization of the right hand's epoxide with deprotection of methoxymethyl (MOM) group (catalytic hydrochloric acid in THF aq. at reflux). Finally, acetylation of the secondary hydroxyl groups gave eurylene (+)-**1**. The sepctroscopic data (400 MHz ^1H NMR, IR) of the synthetic eurylene were identical to those reported in the literature[1b]. (mp 141-144°C, $[\alpha]^{16}_D = +4°$ (c = 0.7, $CHCl_3$); lit. mp 146-148°C, $[\alpha]_D = +4°$ (c = 0.14, $CHCl_3$))

References and notes

1. (a) Itokawa, H.; Kishi, E.; Takeya, K.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1803. (b) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765. For synthetic studies, see: (c) Gurjar, M. K. *Tetrahedron Lett.* **1993**, *34*, 1833. (d) Yoshio, S; Minami, H.; Mori, H.; Oshita, Y.; Tabata, T.; Fukuyama, Y.; Kodama, M.; Takayanagi, H.; Morinaka, Y.; Fukazawa, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1993**, *35*, 471. (e) Molander, G. A.; Swallow, S. *J. Org. Chem.* **1994**, *59*, 7148.
2. (a) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5665. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143. (c) Kan, T.;

Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417. (d) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088.

3. (a) Hashimoto, M.; Yanagiya, M.; Shirahama, H.; *Chem. Lett.* **1988**, 645. (b) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron. Lett.* **1988**, *29*, 5947. (c) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299.
4. Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2741.
5. (a) Nozaki, K.; Shirahama, H. *Chem. Lett.* **1988**, 1847. (b) Hanessian, S; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.
6. Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1982**, *23*, 5413.
7. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *17*, 1409.
8. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (1.5H, s), 0.08 (1.5H, s), 0.11 (1.5H, s), 0.12 (1.5H, s), 0.89 (4.5H, s), 0.91 (4.5H, s), 1.08 (1.5H, s), 1.19 (1.5H, s), 1.60 (6H, s), 1.68 (3H,s), 1.73 (1.5H,s), 1.76 (1.5H, s), 3.21-3.25 (0.5H, m), 3.40 (0.5H, dd, J = 6.6 Hz, 3.3 Hz), 3.48 (1H, s), 3.50 (1H, s), 5.07-5.24 (3H, m), 7.12-7.34 (5H, m).[10]
9. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.10 (2.1H, s), 0.11 (2.1H, s), 0.12 (0.9H, s), 0.13 (0.9H, s), 0.89 (2.7H, s), 0.92 (6.3H, s), 1.12 (2.1H, s), 1.21 (3H, s), 1.23 (0.9H, s), 1.32-1.80 (8H, m), 1.58 (3H, s), 1.61 (9H, s), 1.68 (6H, s), 1.91-2.40 (12H, m), 3.00 (1H, d, J = 5.0 Hz), 3.41 (3H, s), 3.47 (1H, dd, J = 6.9 Hz, 3.7 Hz), 4.69 (1H, d, J = 7.3 Hz), 4.75 (1H, d, J = 7.3 Hz), 5.05-5.24 (4H, m).[10]
10. These spectrum were observed as the mixture of the conformers.
11. Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.*, **1986**, *51*, 1922.
12. Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910.
13. The diastereoselectivity was not determined because of the complexity of the reaction due to cleavage of the protective groups and/or oxidation of the olefinic bonds at the end of the molecule. But it should be fairly good considering the yield of **1** (28 % overall yield for 4 steps containing this step).
14. The right hand's epoxide was not cyclized under this condition.

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