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# TOTAL SYNTHESES OF (+)-THYRSIFEROL AND (+)-VENUSTATRIOL

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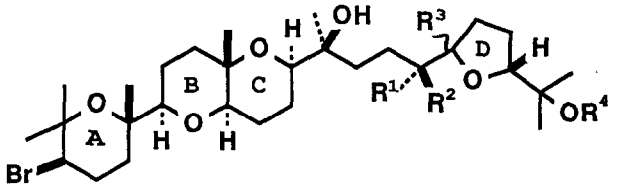
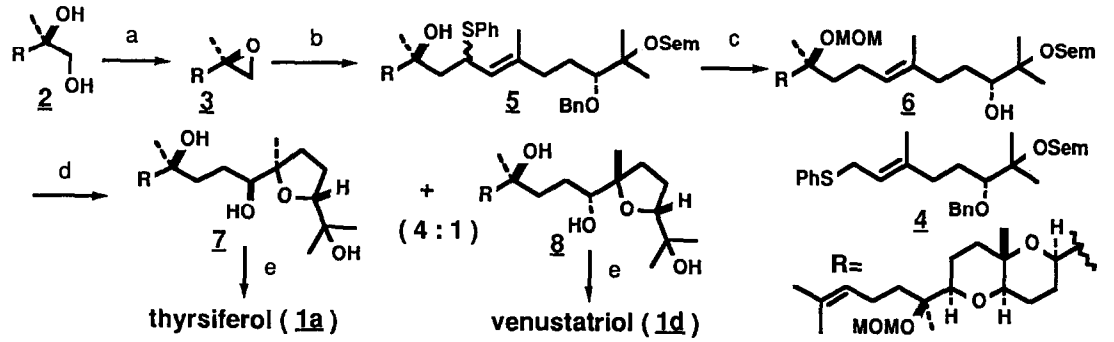
Triterpenoid polyethers (+)-thyrsiferol (1a) and (+)-venustatriol (1d) were totally synthesized from trivial compounds.

Tetracyclic polyethers biogenetically derived from squalene such as thyrsiferol (1a),[1] its acetates (1b, 1c)[2] and venustatriol (1d),[3] isolated from red algae, have been shown to have strong cytotoxicity (1b, 1c) or significant anti-viral activity (1d). Their structures were determined by X-ray analysis[1,3] of 1b and 1d which were revealed to have a strained tetrahydropyran ring (C-ring) as a distorted boat form. We were interested in their remarkable bioactivities and unique shapes of these molecules and started studying the syntheses of these polyethers.[4] We report here total syntheses of (+)-thyrsiferol (1a) and (+)-venustatriol (1d).



**1a** $R^1$=H, $R^2$=OH, $R^3$=α-$CH_3$, $R^4$=H
**1b** $R^1$=H, $R^2$=OAc, $R^3$=α-$CH_3$, $R^4$=H
**1c** $R^1$=H, $R^2$=OH, $R^3$=α-$CH_3$, $R^4$=Ac
**1d** $R^1$=OH, $R^2$=H, $R^3$=β-$CH_3$, $R^4$=H

The compound 2, which was lately synthesized by us,[4] was converted to epoxide 3 ($[\alpha]_D^{24}$-12.3°, c=1.0, $CHCl_3$). The epoxide 3 was coupled with 4,[5,6] a properly protected fragment corresponding to the D-ring, to give $C_{30}$-ether 5 in 99% yield. A newly formed hydroxyl group was protected as MOM ether and then its phenylthio and benzyl groups were removed to afford 6[5] in 76%




**conditions** **a**: (i) TsCl, Py., $CH_2Cl_2$, r.t.,(quant.) (ii) $K_2CO_3$, MeOH, r.t, (91%); **b**: 4eq. of, 1.5 eq of 4 n-BuLi, TMEDA, THF, -20°C, (99%); **c**: (i) MOMCl, $^iPr_2NEt$, $CH_2Cl_2$, r.t., (95%), (ii) Li, $^iPrOH$, $NH_3$, THF, -78°C, (76%); **d**: (i) VO(acac)$_2$, TBHP, $CH_2Cl_2$, r.t., 2hr. (58% as a mixture of diastereomers), (ii) HCl, MeOH, r.t., **e**: TBCO, $CH_3NO_2$

yield. Bishomoallyl alcohol 6 was subjected to a metal catalyzed oxidation[7] to yield a mixture of diastereomers in 58% yield. After removal of protective groups, 7[5] and 8[5] (4:1) were separated by HPLC (RP-18, 40% $H_2O/CH_3CN$). The tetraol 7 was treated with TBCO[8] to achieve bromonium ion induced cyclization of the A-ring and thyrsiferol (1a) was obtained in 20% yield.

The synthetic compound was completely identical with the natural product in all respects (400MHz NMR, IR, MS spectra and HPLC retention time) (synthetic: $[\alpha]_{400}^{23}$25°, $[\alpha]_{300}^{23}$50°, $[\alpha]_{220}^{23}$200°, (c=0.20, MeOH), natural[9]: $[\alpha]_{400}^{23}$25°, $[\alpha]_{300}^{23}$60°, $[\alpha]_{220}^{23}$220°, (c=0.20, MeOH)).

Another tetraol 8 was also converted to venustatriol (1d) through the same sequence of reactions ($[\alpha]_D^{24}$10.5°,c=0.2, $CHCl_3$, lit.[3] $[\alpha]_D^{20}$9.4°, c=3.2, $CHCl_3$). The NMR spectral data of synthetic 1d were perfectly coincident with those of (+)-venustatriol.

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**References and Notes**

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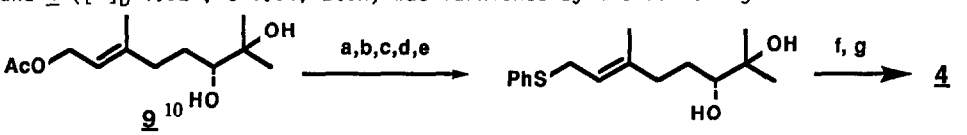
3) S.Sakemi, T.Higa, C.W.Jefford, G.Bernardinelli, Tetrahedron Lett., **27**, 4287 (1986).
4) Synthesis of A-B-C-ring segment of thyrsiferol; M.Hashimoto, T.Kan, M.Yanagiya, H.Shirahama and T.Matsumoto, Tetrahedron Lett. in press (1987).
5) $^1$NMR data 4: ($CDCl_3$) δ0.05(9H,s), 0.95(2H,t,8Hz), 1.23, 1.30 and 1.59(each 3H,s), 3.17(1H, bdd,3,8), 3.4-3.8(4H), 4.50(1H,d,12), 4.70(1H,d,12), 4.78(2H,bs), 5.30(1H,bt,7) and 7.1-7.4 (10H). 6: ($C_6D_6$) 0.07(9H,s), 1.03(2H,t,8), 1.26, 1.31, 1.34, 1.36, 1.38, 1.65, 1.72, and 1.79(each 3H,s), 3.2-3.8(11H), 4.05(1H,dd,4,13), 4.7-4.9(6H), 5.41 and 5.62(each 1H,bt,7). 7: ($CDCl_3$) 1.10, 1.12, 1.15, 1.16, 1.21, 1.22, 1.61 and 1.69(each 3H,s), 3.26(1H,dd,2.4, 10.3), 3.45(1H,dd,1.9,9.8), 3.64(1H,dd,7.3,11.2), 3.72(1H,dd,2.9,12.6), 3.76(1H,dd,6.0,9.0) and 5.11(1H,bt,7.3). 8: ($CDCl_3$) 1.10, 1.14, 1.15, 1.18, 1.20, 1.27, 1.62 and 1.69(eac,3H, s), 3.25(1H,dd,2.4,10.3), 3.60(1H,dd,2.0,10.7), 3.63(1H,dd,7.3,11.2), 3.72(1H,dd,3.0,12.7), 3.83(1H,t,7.3) and 5.11(1H,bt,6.8).
6) Compound 4 ($[\alpha]_D^{23}$1.92°, c=1.04, EtOH) was furnished by the following scheme.




**a**: TsOH,An; **b**: $K_2CO_3$, MeOH (96% through 2 steps); **c**: $PPh_3$, $CCl_4$; **d**: NaSPh; **e**: TsOH, MeOH (68% through 3 steps); **f**: NaH, BnCl; **g**: SemCl,$^i$Pr$_2$NEt (83% through 2 steps)

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9) Thyrsiferol was obtained by hydrolysis ($K_2CO_3$/MeOH) of its acetate isolated from Laurencia obtusa.
10)T.Katsuki, K.B.Sharpless, J. Am. Chem. Soc., **102**, 5974 (1980); W.Eschenmoser, P.Uebelhalt, C.H.Eugster, Helv. Chim. Acta, **66**, 82 (1983); S.Yamada, N,Oh-hashi, K,Achiwa, Tetrahedron Lett., 2257, 2561 (1976).

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