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SYNTHESIS OF A-B-C-RING SEGMENT OF THYRSIFEROL CONSTRUCTION OF A STRAINED TETRAHYDROPYRAN RING EXISTENT AS A BOAT FORM

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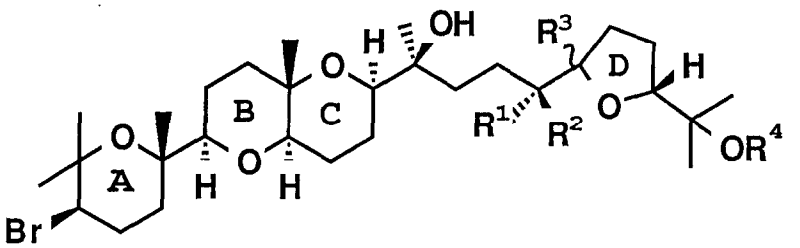
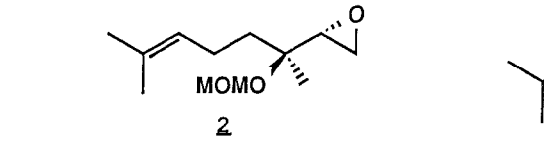
Tricyclic bromoether 17, which contained twenty of thirty carbons of thyrsiferol (1d), was synthesized in optically active form starting from trivial compounds 2 and 3.

Recently several squalene-derived tetracyclic ethers such as thyrsiferol (1a)[1], its acetates (1b, 1c)[2] and venustatriol (1d)[3] were isolated from red algae of the genus Laurencia. Some of them exhibited strong cytotoxicity against P388 (e.g. 1b, 1c)[2] or significant anti-viral activity (e.g. 1d).[3] Their structures were determined on the bases of X-ray analysis[1,3] of 1b and 1d which were shown to have a strained tetrahydropyran ring (C-ring) as a distorted boat form. The remarkable bioactivity and unique shape of this molecule prompted us to study a synthesis of thyrsiferols (1a-d). In this paper we wish to describe a synthesis of an A-B-C-ring segment of thyrsiferol.



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

The optically active epoxide 2[4] ($[\alpha]_D^4$ -3.65° (c=4, $CHCl_3$)) was coupled to the sulfide 3[5] by n-BuLi and DABCO in THF at -78°C for 3 h to afford 4 in 78% yield. Phenylthio group of 4 was removed by reduction[6] (Na/i-PrOH/THF/reflux, 3 h) to give 5 (77%). Regioselective oxidation of the bishomoallylalcohol system in 5 was effected by metal catalyzed conditions[7] ($VO(acac)_2$/t-BuOOH/CH_2Cl_2/r.t., 7 h) and the tetrahydrofuran 6 was obtained (72%). Ring expansion of the tetrahydrofuran to a tetrahydropyran was carried out by Kishi's procedure.[8] Treatment of 6 with MsCl/Et_3N/CH_2Cl_2 (r.t., 12 h) then Ag_2CO_3 in aq. acetone at 50°C furnished 7 (42%) which was converted to allylalcohol 11



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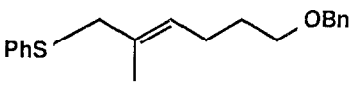

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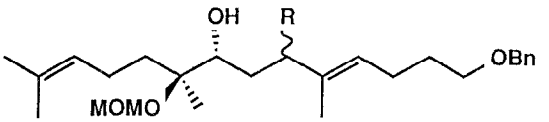
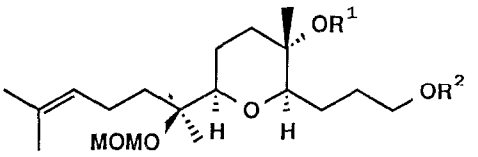
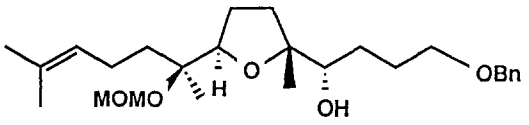


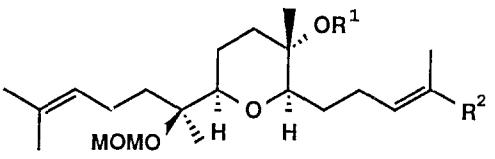
4 R=SPh
5 R=H



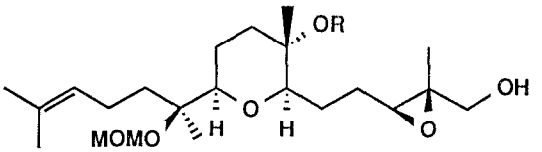
7 R^1=H, R^2=Bn
8 R^1=TMS, R^2=Bn
9 R^1=TMS, R^2=H



6



10 R^1=TMS, R^2=CO_2Et
11 R^1=TMS, R^2=CH_2OH

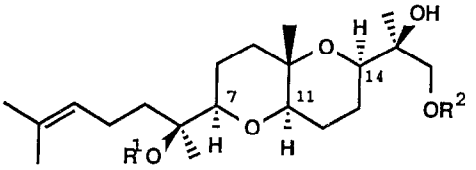


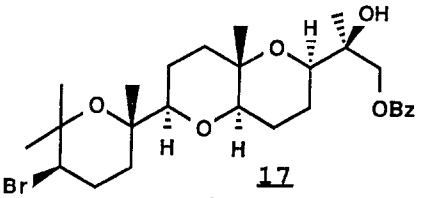
12 R=TMS
13 R=H

by the following sequential reactions, i) TMSCl/Et_3N/DMAP/CH_2Cl_2/0°C, 30 min, (→ 8, 85%), ii) Li/NH_3/THF/-78°C, 1 h, (→ 9, 82%), iii) a) PDC/NaOAc/CH_2Cl_2/ r.t., 30 min, b) $CH_3C(PPh_3)CO_2Et$/CH_2Cl_2/reflux, 3 h, (→ 10, 97%), iv) DIBAH/ hexane/-78°C, 10 min, (→ 11, 92%). The allylalcohol 11 was stereoselectively oxidized to the β-epoxyalcohol 12 with a chiral reagent (t-BuOOH/ $Ti(Oi\text{-}Pr)_4$/ L-(+)-DIPT/CH_2Cl_2/-20°C, 4 h), and without further purification, 12 was desilylated (n-Bu_4NF/THF/r.t., 1.5 h) to yield β-epoxydiol 13 (82%). The tetrahydropyran ring of 13 was corresponding to the B-ring of thyrsiferol.

Construction of C-ring was next attempted.[9] Treatment of 13 with $Ti(Oi\text{-}Pr)_4$ in toluene (reflux, 12 h) brought the compound 14 in 49% yield and 14 was converted to its benzoate ester 15 (BzCl/Et_3N/CH_2Cl_2, 79%). Stereochemistry of 15 was established by NMR employing difference NOE technique. Irradiation of the signal due to 11α-H (δ 3.57 ppm, dd, J= 3.9, 11.2 Hz) induced NOE at the peaks due to 7α-H (δ 3.45 ppm, dd, J= 2, 11 Hz) and 14α-H (δ 3.91 ppm, dd, J= 2.9, 12.7 Hz) to reveal that the side chain at C-14 had β-equatorial orientation and newly formed C-ring took a boat form.

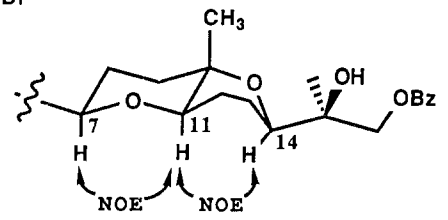
The A-ring was constructed by bromonium ion induced cyclization. The alcohol 15 was demasked (→ 16, cat.HCl/MeOH/r.t., 82%) and 16 was treated with





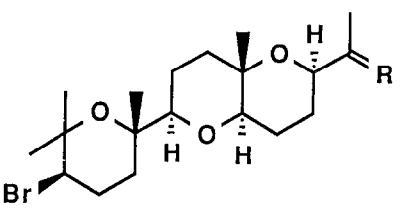
17

14 R^1=MOM, R^2=H
15 R^1=MOM, R^2=Bz
16 R^1=H, R^2=Bz



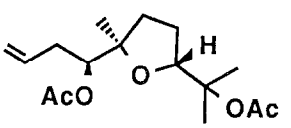
TBCO[10] in CH_3NO_2 to give rise to the tricyclic compound **17** in 36% yield. The tricyclic ether **17** thus obtained had seven of ten chiral centers of thyrsiferol.

For confirmation of the stereochemistry, **17** was converted to methyl ketone **18** ($\Delta\varepsilon_{305}$ +0.11 (MeOH, c=1.86×10^{-3} M), $(MH)^+$=403.1464, $C_{19}H_{32}O_4Br$) by saponification (K_2CO_3/MeOH/r.t., 3 h, 95%) and successive oxidation ($NaIO_4$/MeOH/r.t., 1 h, quant.). On the other hand, natural 15-anhydrothyrsiferyl diacetate (**19**)[11] was converted to **18** ($\Delta\varepsilon_{305}$ +0.12 (MeOH, c=2.20×10^{-3} M), $(MH)^+$= 403.1140, $C_{19}H_{32}O_4Br$) by the following sequential treatment (i. OsO_4/Py/Et_2O/r.t., 2 h then H_2S, ii. $NaIO_4$/MeOH/r.t., 1 hr). Both compounds **18** originated from natural and synthetic source were completely identical by comparison with their IR, NMR, CD and MS spectra and chromatographic behavior.



18 R=O

19 R=



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5) The sulfide (3) was prepared from 1,4-butanediol by the following series of reactions, i) NaH(0.8eq.)/BnCl(0.8eq.)/DMF/r.t.,(70 %); ii) PCC/ CH_2Cl_2/r.t., then $CH_3CH(PO(OEt)_3)CO_2Et$/NaH/THF/0 °C,(73 %); iii) Red-Al/ benzene/reflux,(73 %); iv) CCl_4/PPh_3/benzene/reflux,(76 %); v) NaSPh/ DMF/0°C,(93 %).

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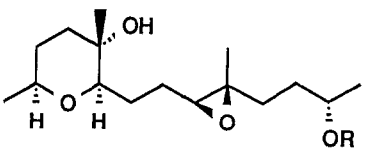
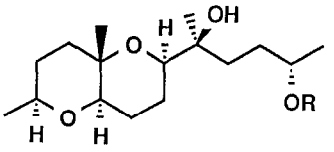
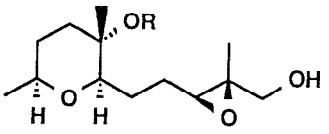
9) Among many ring forming reactions available we focused on a ring closure attributed to intramolecular attack of an alcohol at an epoxide group. In order to find out suitable conditions for closing the strained ring, model studies were performed using compounds 20 and 22. Extensive examination of acidic or basic conditions disclosed two procedures usable and especially one of them hopeful. Treatment of 20a with PPTS in benzene[i] (reflux, 5 h) gave 21 though it was low yield, and treatment of 22 with $Ti(Oi\text{-}Pr)_4$ in benzene[ii] (reflux, 12 h) gave 23 in 56% yield with 15 % recovery of 20. i. K. Tsuzuki, Y. Nakajima, T. Watanabe, M. Yanagiya, T. Matsumoto, Tetrahedron Lett., 989 (1978), ii. M. Caron, K. B. Sharpless, J. Org. Chem., **50**, 1557 (1985).



20a R=Bz
20b R=TBDMS



21 R=Bz



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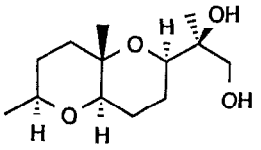

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