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Total Synthesis of (±)-*allo*-Cedrol [Khusiol][1]

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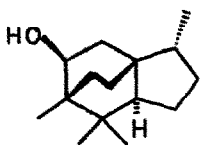
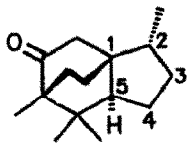
Abstract: The first total synthesis of (±)-allo cedrol **1** is described from the ketone **11** which involves the Lewis acid catalysed rearrangement of the prezizaene analogue **8** as the key step.

The sesquiterpene (+)-*allo*-cedrol **1**, isolated[2] from *Juniperus rigida* Sieb. et Zucc. is enatiomeric with (-)-khusiol, isolated[3] from *Vetiveria zizanioides* Linn. and possesses the unique tricyclo[5.2.2.$0^{1,5}$]undecane skeleton. The presence of three quaternary centres and a methyl group at the bridge head position makes this molecule synthetically challenging. Earlier we have reported[4] the synthesis of the ketone **2** from the enone **3** as an isomeric mixture at the C-2 and C-5 positions. The tedious separation of these diastereoisomers prompted us to investigate an alternative strategy where in the stereochemistry at the C-2 and C-5 positions is controlled.



1



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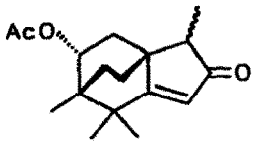
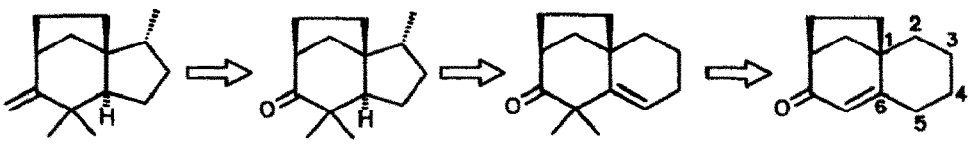


3

Recently we reported[5] a stereospecific synthesis of prezizaene **4** from the tricyclic-enone **7** (Scheme 1) in which the ethano bridge had regulated the stereochemistry at the C-2 and C-6 positions in the subsequent steps.

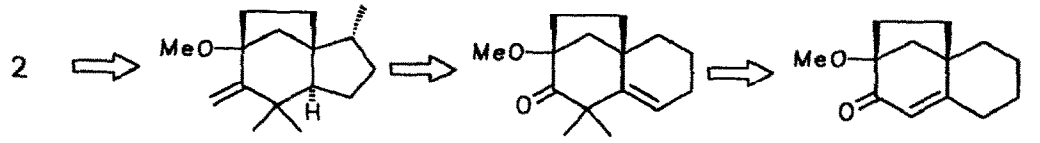
Scheme 1



4 5 6 7

Our earlier results[4] showed that the ketone **2** can be derived from the olefin **8** (Scheme 2), which is an analogue of prezizaene **4** having a methoxyl group at C-8. Since **4** is synthesized from the unsaturated ketone **7**, the compound **8** should in principle be prepared from the enone **10**. Here in, we describe the first stereospecific total synthesis of (±)-*allo*-cedrol.

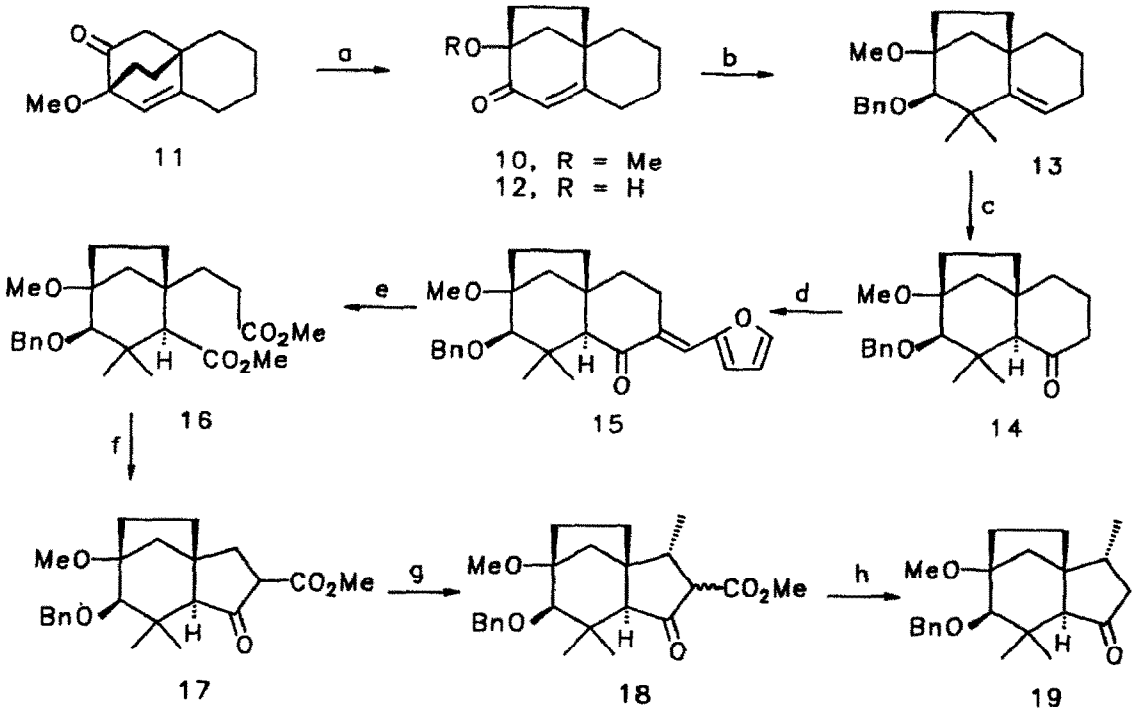
Scheme 2



8 9 10

Thus when the ketone **11**[6] was refluxed with anhydrous para toluene sulphonic acid in benzene a mixture (3:1) of the enones **10**[7] and **12** were obtained in 80% yield[8]. This mixture was separated and the compound **10** was exhaustively methylated to afford the ketone **9** which was subjected to the sequence of reactions indicated in the Scheme 3.

Scheme 3



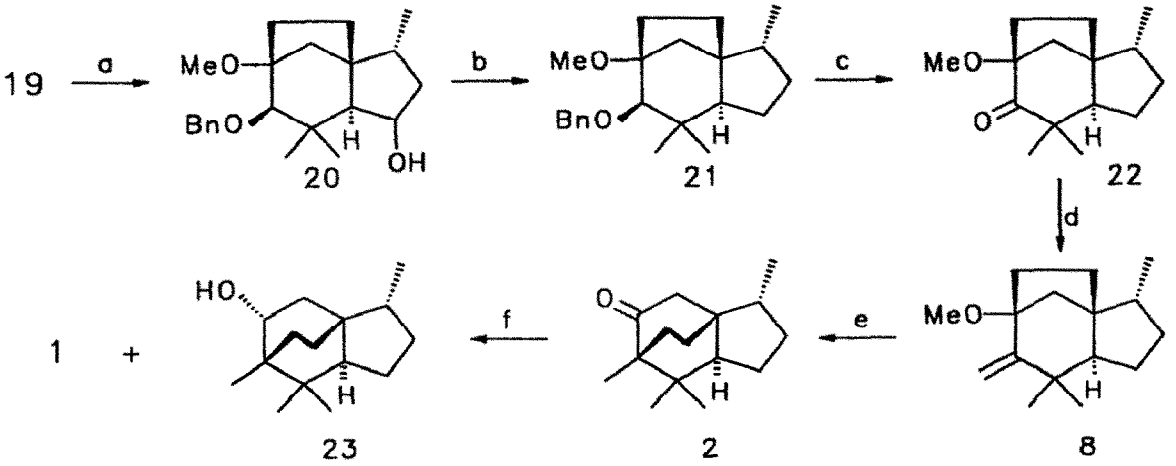
Reagents & conditions: a) PTS,PhH,Δ,80%; b) [i] ^{t}BuOK,^{t}BuOH,MeI,68%; [ii] $NaBH_4$,MeOH,95%; [iii] NaH,BnBr,THF,TBAI,70°C,88%; c) [i] BH_3,THF,NaOH,H_2O_2; [ii] PCC,86%; d) NaOH,furfural,EtOH; e) [i] O_3,EtOAc,-78°C; [ii] H_2O_2,AcOH; [iii] CH_2N_2,74%; f) NaH,THF,80%; g) [i] NaH, PhSeCl, H_2O_2,85%; [ii] Me_2CuLi, Et_2O,77%; h) DABCO,toluene,95°C,87%.

Reduction of **9** with $NaBH_4$ followed by benzylation yielded the benzyl ether **13** which was converted to the ketone **14**[7] through hydroboration and oxidation. The furfurylidene derivative **15** of **14** was prepared and subjected to ozonolysis followed by an oxidative work-up resulting in the dicarboxylic acid which gave the dimethylester **16** with ethereal diazomethane. Dieckmann cyclization of **16** gave the compound **17** which was converted into the keto-ester **18** through dehydrogenation followed by conjugate addition with dimethyl copper lithium. Decarboxylation of **18** with DABCO afforded the ketone **19**[7] in an overall yield of **16.5%** from the unsaturated ketone **10**.

Having obtained the ketone **19** in good quantities, we next turned our attention to the completion of the synthesis of *allo*-cedrol (Scheme 4). Since Wolff-Kishner reduction of **19** resulted in the epimerisation at C-5, the deoxygenation at C-4 was attempted under Barton's conditions[9].

Thus the alcohol **20** obtained by reduction of the ketone **19** with $LiBH_4$, afforded the xanthate with $BuLi/CS_2/MeI$ in THF which was hydrogenolysed with hypophosphorous acid. Metal-ammonia reduction

Scheme 4



Reagents and conditions : a) $LiBH_4$,THF,90%; b) [i] BuLi,CS_2,MeI,THF,94%; [ii] H_3PO_2, Et_3N, dioxane,120°C,79%; c) [i] Li,liq NH_3; [ii] PCC,78%; d) Ph_3PCH_3I,^{t}AmOK,toluene,120°C,80%; e)$BF_3.OEt_2$,62%; f) ref. 3

of **21**[7] followed by PCC oxidation yielded the ketone **22** which was subjected to Wittig olefination with methyl triphenyl phosphonium iodide to give the compound **8**[7]. Treatment of **8** with $BF_3.OEt_2$ in methylene chloride afforded (±)-khusione **2**[7], identical with the spectra of the authentic sample.

Since (-)-khusione has been converted[3] into (-)-khusiol, a formal synthesis of (±)-khusiol is thus completed.

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7. All the new compounds reported here gave the expected analytical and spectral data. Data of some selected compounds is given below:

   10 : m.p. 72°C (hexane); IR (neat): 1670,1600,1450 cm^{-1}; ^1H NMR (90MHz,$CDCl_3$):δ 3.42 (s,3H,OMe),5.74(s,1H,olefinic); ^{13}C NMR (22.5MHz,$CDCl_3$):δ 22.0,24.6,30.7,32.9,34.6,35.5,47.7, 48.6,53.7,88.6,123.7,170.8,200.7.

   14 : m.p. 75.3°C (hexane);IR (neat): 1695,1450,1355,1100 cm^{-1}; ^1H NMR (90MHz,$CDCl_3$):δ 1.25(s, 3H),1.37(s,3H),3.28(brs,1H,C*H*OBn),3.35(s,3H,OMe),4.59 and 5.03(ABq,2H,J=11Hz,benzylic CH_2), 7.16-7.48(m,5H,ArH); ^{13}C NMR (100MHz,$CDCl_3$):δ 16.3,21.8,26.9,31.2,33.2,39.1,40.3,42.9,47.1, 49.2,51.4,64.8,76.3,85.2,90.3,127.2(3C),128.2(2C),139.9,209.3.

   19 : m.p. 71°C; IR (neat): 1730,1115 cm^{-1}; ^1H NMR (90MHz,$CDCl_3$):δ 1.05(d,3H,J=7.2Hz),1.19(s, 3H),1.29(s,3H),3.39(s,4H,OMe and C*H*OBn),4.60 and 5.02(ABq,2H,J=11Hz,benzylic CH_2), 7.2-7.52(m,5H,ArH); ^{13}C NMR (22.5MHz,$CDCl_3$):δ 16.4,17.5,26.1,33.0,36.4,37.4,42.0,46.1,50.4,51.0, 60.7,76.1,86.9,89.5,127(3C),128.1(2C),139.5,215.6.

   21 :IR (neat): 1450,1350,1100,735,695 cm^{-1}; ^1H NMR (300MHz,$CDCl_3$):δ 0.9(d,3H,J=7Hz),1.04(s, 3H),1.05(s,3H),3.36(s,3H,OMe),3.42(brs,1H,C*H*OBn),4.6and5.04(ABq,2H,J=11Hz,benzylicCH_2), 7.16-7.43(m,5H,ArH); ^{13}C NMR (75MHz,$CDCl_3$): δ 17.4,19.6,22.7,25.9,32.0,32.6,33.8,38.0,40.5, 42.0,50.9,51.9,53.7,75.8,87.2,89.6,126.8,127.1(2C),127.9(2C),140.0.

   8 :IR (neat): 1630,1110,910 cm^{-1}; ^1H NMR (90MHz,$CDCl_3$):δ 0.88(d,3H,J=7.2Hz),1.12(s,3H),1.18 (s,3H),3.34(s,3H,OMe),4.94(bs,1H),5.1(bs,1H); ^{13}C NMR (100MHz,$CDCl_3$):δ 19.8,23.0,27.6,31.1, 31.8,33.2,35.2,37.2,41.2,43.7,52.5,52.7,54.5,87.3,104.4,159.8.

   2 :IR (neat): 1710,1450 cm^{-1}; ^1H NMR (200MHz,$CDCl_3$) δ 0.8(s,3H),0.84(d,3H,J=7.2Hz),0.88(s, 3H),0.94(s,3H)^{13}CNMR(75MHz,$CDCl_3$):δ13.9,18.1,19.7,24.2,27.8,28.6,29.3,33.9,34.4,39.0,44.0, 46.8,50.1,54.1,218.7.
8. For similar rearrangement see (a) Alfaro,I; Ashton,W.; Rabone,K.L.; Rogers,N.A.J. *Tetrahedron*, **1974**, *30*, 559. (b) Uyehara,T.; Osanai,K.; Sugimoto,M.; Suzuki,I.; Yamamoto,Y. *J.Am.Chem.Soc.* **1989**, *111*, 7264.
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