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A Novel Synthesis of Tricyclo[5.3.1.$0^{1,5}$]undecanes: Total Syntheses of 2-norCedrene and a Funebrene Analogue

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Abstract: *A new rearrangement method has been developed for the construction of the tricyclo[5.3.1.$0^{1,5}$]undecane and tricyclo[6.3.1.$0^{1,6}$]dodecane frame works. The key features include the efficient preparations of the alcohols* ***5****,* ***15*** *and* ***19*** *and their rearrangement to the tricyclic skeleton which led to the synthesis of 2-norcedrene* ***3*** *and an analogue of funebrene* ***13****.*
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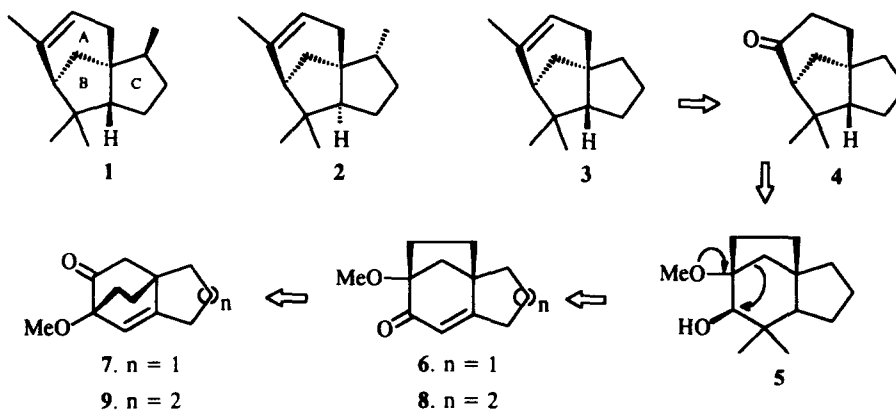
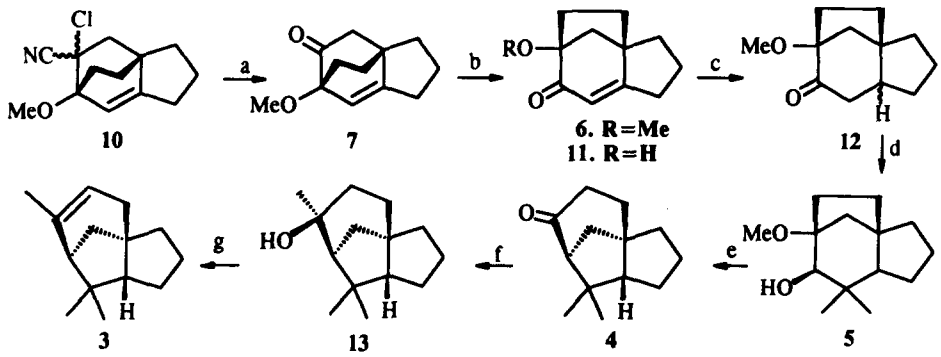
The sesquiterpenes α-cedrene **1**, isolated[1] from *Juniperus rigida* and α-funebrene **2**, isolated[2] from *Cupressus funebris* possess a relatively rare tricyclo[5.3.1.$0^{1,5}$] undecane skeleton. A number of strategies for the synthesis of α-cedrene have been reported.[4] Although the structure of α-funebrene has been deduced from spectral data[2b] and biogenetic considerations,[3] this has not been confirmed by synthesis so far. We now describe a facile method for the construction of the tricyclo[5.3.1.$0^{1,5}$]undecane skeleton which culminated in the total synthesis of 2-norcedrene **3** and an analogue of funebrene **17**.



Our retrosynthetic analysis is outlined above. The tricyclic ketone **4** can be obtained by an *anti* migration of the methanobridge upon acid treatment of the secondary alcohol **5**. The alcohol **5** can be

Scheme 1



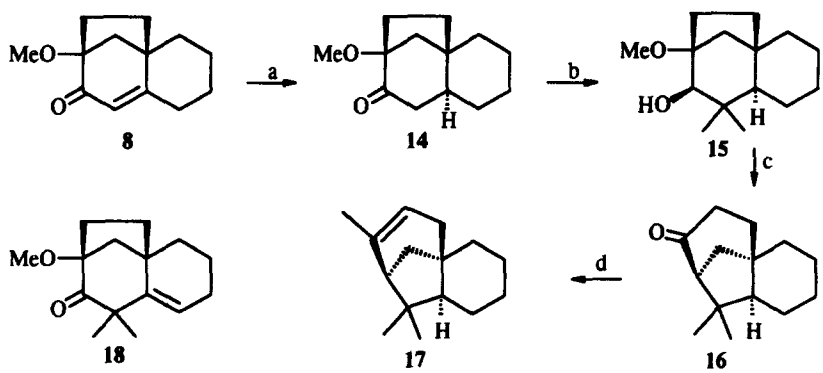
Reagents & Conditions:a) KOH, DMSO, H_2O, 55°C, 48h, 82%; b) BF_3.MeOH, CH_2Cl_2, R.T., 12h, 95%; c) Pd-C, limonene, Δ, 6h, 98%; d) (i) NaH, MeI, DME, 60°C, 4h, (ii) $NaBH_4$, MeOH, 0°C, 2h, 92% for two steps; e) $BF_3.OEt_2$, benzene, reflux, 24h, 87%; f) MeLi, ether, 0°C-reflux, 3h, 91%; g) (i) $POCl_3$, pyridine, 0°C, 1h, (ii) HI, benzene, R.T., 24h, 88% for two steps.

prepared from the enone **6**. Acid treatment of **7** would furnish the enone **6** since a similar ketone **9** was transformed into the enone **8** during the total synthesis of *allo*-cedrol earlier in our laboratory.[5]

Thus, the chloro-cyano compound[6] **10** was hydrolysed (Scheme 1) to the ketone **7** which upon treatment with BF_3.MeOH furnished a separable mixture of the enones **6** & **11** in a 9:1 ratio. Catalytic transfer hydrogenation[7] of the enone **6** provided the ketone **12** (with 89:11 of *cis:trans* ring junction) which was converted to the alcohol **5**[9] through *gem*-dimethylation (NaH/MeI) followed by reduction with sodium borohydride.

Treatment of **5** with $BF_3.OEt_2$ afforded the ketone **4**[9] which involved a synchronous migration of

Scheme 2



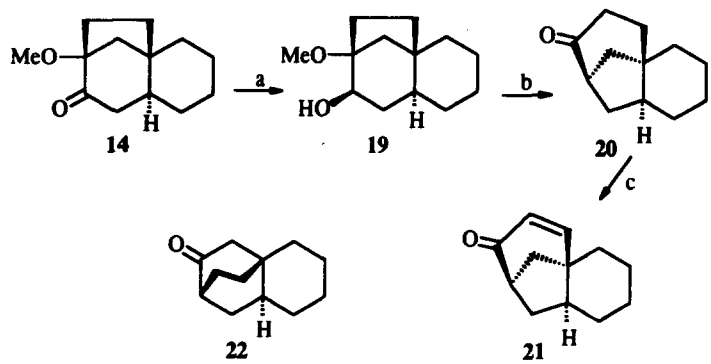
Reagents & Conditions: a) Pd-C, H_2, EtOAc, R.T., 16h, quant.; b) (i) NaH, MeI, DME, 60°C, 4h, (ii) $NaBH_4$, MeOH, 0°C, 2h, 94% for two steps; c) $BF_3.OEt_2$, benzene, reflux, 40h, 90%; d) (i) MeLi, ether, 0°C, 2h, then reflux, 50h, (ii) $POCl_3$, pyridine, 0°C, 2h, (iii) HI, benzene, R.T., 24h, 81%[8].

the *anti*-bond leading to the tricyclo[5.3.1.$0^{1,5}$]undecane skeleton. Stereoselective addition[1c] of methyllithium gave norcedrol **13**[9] which upon dehydration[4] furnished 2-norcedrene **3**.[8,9] The spectral data of **13** and **3** are comparable with that of the natural cedrol and α-cedrene respectively except for the secondary methyl group on the ring C.

Similarly, the known enone **5**[4] upon catalytic hydrogenation furnished exclusively the ketone **14**, which was converted (Scheme 2) to the alcohol **15**. Treatment of the alcohol **15** with $BF_3.OEt_2$ under refluxing condition produced the ketone **16**. Addition of MeLi on **16** followed by dehydration led to an analogue of funebrene **17**.[9] By adopting the methodology developed earlier in our laboratory for the conversion of a six membered ring into a five membered ring having a methyl group, the compound **18**[5] can be converted into funebrene using the above sequence of reactions.

The evidence for the migration of the methanobridge rather than the ethanobridge during the acid catalysed rearrangement of the compounds **5** and **15** is obtained as follows (Scheme 3). Rearrangement of the alcohol **19**, obtained by the reduction of **14**, afforded the ketone **20** which furnished the enone **21** through a sequence of reactions involving phenylselenation, oxidation followed by elimination. The structure of the product **21**[9] is unequivocally deduced from its spectral data which showed the presence of an α,β-unsaturated ketone thus confirms that the methanobridge is migrated during the acid catalysed rearrangement. However migration of the ethanobridge during the rearrangement would have resulted in the tricyclic ketone **22** in which introduction of a double bond conjugated to the ketone leading to an α,β-unsaturated ketone structure would be difficult.

Scheme 3



Reagents & Conditions: a) $NaBH_4$, MeOH, 0°C, 2h, 97%; b) $BF_3.OEt_2$, benzene, reflux, 42h, 92%; c) LDA, PhSeCl, -78°C; H_2O_2, R.T., 1h, 78%.

Thus a new rearrangement has been developed for the construction of the tricyclo-[5.3.1.$0^{1,5}$]undecane skeleton which was utilized for the synthesis of 2-norcedrene **3**. The rearrangement also provides a general method for the construction of tricyclo[6.3.1.$0^{1,6}$]dodecane frame work with strained *trans*-hydrindane subunit which culminated in the funebrene analogue **17**.

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8. The yield is for three steps based on 50% of the unreacted ketone **16** which was recycled to give a combined yield of 81%.
9. All the new compounds exhibited satisfactory spectral and analytical data. Data of some selected compounds is given below:

   5:IR (neat): ν_{max} 3500(br), 1450, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07(3H, s, Me), 1.09(3H, s, Me), 1.33-2.06(13H, m), 2.41(1H, brs, OH), 3.25(3H, s, OMe) & 3.62(1H, d, $J_{W(7,9\alpha)}$=1.8Hz, C*H*OH); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 19.88(t), 24.44(t), 25.22(q), 27.43(t), 29.38(q), 31.85(t), 35.94(s,t), 38.67(t), 49.79(q), 50.05(s), 57.14(d), 78.05(d) & 85.29(s).

   4: IR (neat): ν_{max} 1700, 1450, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99(3H, s, Me), 1.01(3H, s, Me), 1.32-2.5(14H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.39(q), 26.42(q), 27.57(t), 27.76(t), 36.59(t), 36.97(t), 37.18(t), 39.66(t), 43.2(s), 53.21(s), 56.23(d), 66.53(d), 214.01(s).

   13: IR (neat): ν_{max} 3400(br), 1450 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): δ 0.92(3H, s, Me), 1.2(3H, s, Me), 1.25(3H, s, Me), 1.1-1.8 (14H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 27.44(t), 27.71(q), 27.83(t), 28.72(q), 30.34(q), 35.91(t), 36.77(t), 37.03(t), 40.42(t), 43.51(s), 53.11(s), 56.03(d), 60.77(d), 74.93(s).

   3: IR (neat): ν_{max} 1640, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.97(3H, s, Me), 1.03(3H, s, Me), 1.1-1.8(10H, m), 1.67(3H, d, J=1.8Hz, =C-Me), 2.34(2H, m, =CHC*H*$_2$), 5.23(1H, m, olefinic).

   17: IR (neat): ν_{max} 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.8(3H, s, Me), 1.01(3H, s, Me), 0.9-1.7 (12H, m), 1.62(3H, d, =CCH_3), 2.32(2H, m, =CHC*H*$_2$), 5.12(1H, m, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.88, 21.11, 21.22, 24.51, 27.4, 33.41, 33.79, 40.85, 42.29, 42.56, 43.04, 52.35, 59.32, 119.04, 141.58

   21: IR (neat): ν_{max} 1670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 1.1-2.6(14H, m), 5.9(1H, d, J=10.8 Hz, =C*H*CO), 7.02(1H, d, J=10.8 Hz, C*H*=CHCO).

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