Bridgehead Substitution of 1-Methoxybicyclo[2.2.2]oct-5-en-2-one Derivatives: Towards the Synthesis of (±)-*allo*-Cedrol [Khusiol][1]

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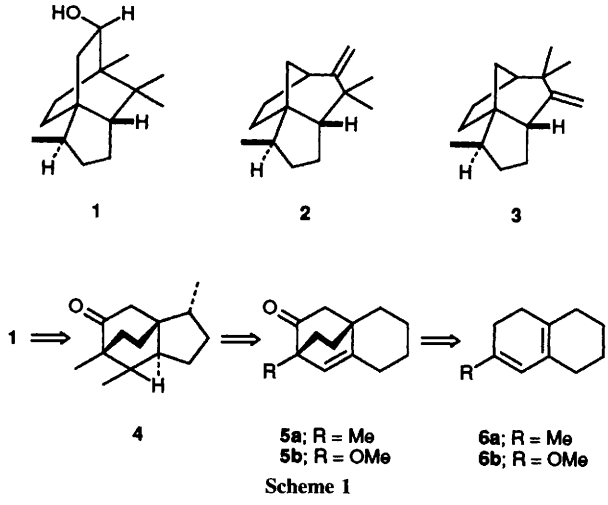
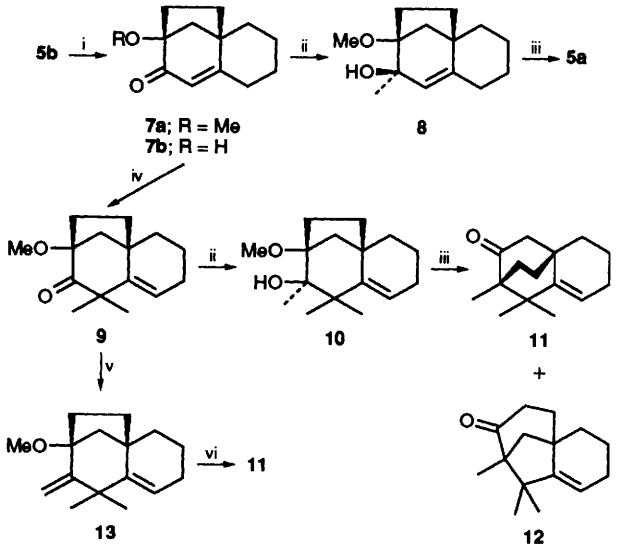
Preparation of the key intermediates, **11** and **21**, required for the synthesis of (±)-*allo*-cedrol (khusiol) is reported by a novel methodology involving the substitution at the bridgehead position of 1-methoxybicyclo[2.2.2]oct-5-en-2-one derivatives.

The tricyclic sesquiterpene alcohol, (+)-*allo*-cedrol **1**, isolated[2] from *Juniperous rigida* Sieb. *et* Zucc., was considered to be the biogenetic precursor of prezizaene **2** and zizaene **3** and possesses the unique bicyclo[2.2.2]octane framework fused to a five-membered ring with a bridged methyl group. Its optical antipode, (−)-khusiol was isolated[3] from *Vetiveria zizanioides* Linn. Because of their novel structure and in continuation of our synthetic studies[4,5] towards tricyclic sesquiterpenes from bridged polycyclic compounds, we contemplated the intermediates **4** and **5a** as possible synthons for (±)-*allo*-cedrol (khusiol), as outlined in Scheme 1. Synthetic routes to **5a** involved cycloaddition of the diene **6a** with a ketene equivalent. However, preparation of **6a** involves cumbersome procedures.[6] We report a new strategy for the synthesis of the intermediates **11** and **21** through the bridgehead substitution of the tricyclic compounds **5b** and **14**. The compounds **11** and **21** can be considered as potential intermediates for the synthesis of (±)-*allo*-cedrol **1**.



Scheme 1



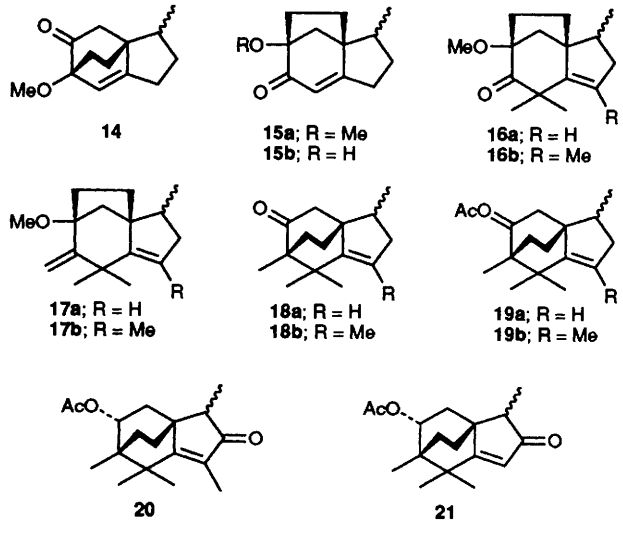
Scheme 2 *Reagents and conditions*: i, PTS, C_6H_6, reflux; ii, MeLi in Et_2O; iii, cat. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 15 min; iv, KOBu^t, Bu^{t}OH, MeI, C_6H_6; v, Ph_3PMeI, potassium *tert*-pentoxide, C_6H_6, reflux; vi, $BF_3{\cdot}OEt_2$ (2 equiv.), CH_2Cl_2, room temp., 24 h; PTS = toluene-*p*-sulfonic acid

Compound **5b**[7] was prepared by hydrolysis of the readily available Diels–Alder adduct between 2-chloroacrylonitrile and 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene. Reaction of **5b** with PTS in refluxing benzene afforded a 3 : 1 mixture of 1-methoxytricyclo[7.2.1.$0^{4,9}$]dodeca-3-en-2-one **7a** and the hydroxy compound **7b** in 80% yield which was easily separated by chromatography. Similar conversion of 1-methoxybicyclo[2.2.2]oct-5-en-2-ones into a mixture of 1-methoxy- and 1-hydroxybicyclo[3.2.1]oct-3-en-2-ones has been reported.[8,9] Addition of methyllithium to **7a** yielded the alcohol **8** which on treatment with a catalytic amount of $BF_3{\cdot}OEt_2$ afforded **5a** in good yields.

Alkylation of **7a** with MeI–KOBu^t–Bu^{t}OH afforded the ketone **9** which gave the alcohol **10**, on reaction with methyllithium. The alcohol **10** was smoothly rearranged to a mixture of **11** and **12** in 80% yield. Although this mixture could not be separated, its ^{1}H NMR spectrum showed distinct signals for the olefinic proton integrating in the ratio of 2 : 1 for the compounds **11** and **12** respectively. Wittig reaction of **9** with methyltriphenylphosphonium iodide gave the olefin **13** which was rearranged exclusively to the ketone **11** with $BF_3{\cdot}OEt_2$ (2 equiv.).

In an alternative approach, the adduct **14**[4] was converted into a mixture of the unsaturated ketones **15a** and **15b** with PTS in refluxing benzene. Methylation of **15a** with MeI–KOBu^t–Bu^{t}OH afforded unexpectedly a mixture (1 : 1) of the ketones **16a** and **16b**. This mixture could not be separated and hence was used directly for further transformations.

The mixture **16a** and **16b** was subjected to the Wittig olefination with Ph_3PMeI, yielding a mixture of **17a** and **17b** which was rearranged to the ketones **18a** and **18b** with $BF_3{\cdot}OEt_2$. Reduction of **18a** and **18b** with $NaBH_4$ followed by acetylation yielded a mixture of the *endo*-acetates **19a** and **19b** which was oxidised with pyridinium dichromate–Bu^{t}OOH resulting in the unsaturated ketones **20** and **21**.† The ketones



20 and **21** could be easily separated by column chromatography.

Although the mixtures **16**, **17**, **18** and **19** could not be separated, their ^{1}H NMR spectra were consistent with the proposed structure having a vinyl methyl signal. It is interesting that during the alkylation of the ketone **15a** methylation also occurred at the γ-position.

Catalytic hydrogenation of **21**, followed by Wolff–Kishner reduction and oxidation yielded the ketone **4** as a mixture of diastereoisomers at C–2 and C–5.‡ The spectral data of **4** were comparable to those of an authentic sample, kindly provided by Prof. G. K. Trivedi.

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Footnotes

† All new compounds gave satisfactory analytical and spectral data. Spectral data for compound **20**, ^{1}H NMR (270 MHz, $CDCl_3$), δ 0.91 (3H, s, CH_3), 1.01 (3H, d, *J* 7.5 Hz, Me), 1.1–2.2 (6H, m), 1.24 (3H, s, Me), 1.38 (3H, s, Me), 1.83 (3H, s, Me), 2.03 (3H, s, OAc), 2.56 (1H, dd, *J* 13.6 and 10.5 Hz), 4.8 (1H, dd, *J* 10 and 5 Hz, C*H*OAc). For compound **21**, ^{1}H NMR (270 MHz, $CDCl_3$), δ 0.91 and 0.92 (3H, s, Me), 1.03 (3H, d, *J* 7.5 Hz, Me), 1.1–2.1 (m, 6H), 1.16 and 1.19 (3H, s, Me), 1.32 (3H, s, Me), 2.04 and 2.05 (3H, s, OAc), 2.44 and 2.59 (1H dd, *J* 13.8 and 10.2 Hz), 4.7–4.94 (1H, m, C*H*OAc), 5.86 (1H, s, =CH).

‡ Further separation of these diastereoisomers and their transformation into khusiol is under progress.

References

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