Total Synthesis of the Novel Sesquiterpenes of *Eremophila georgei* Diels[1]

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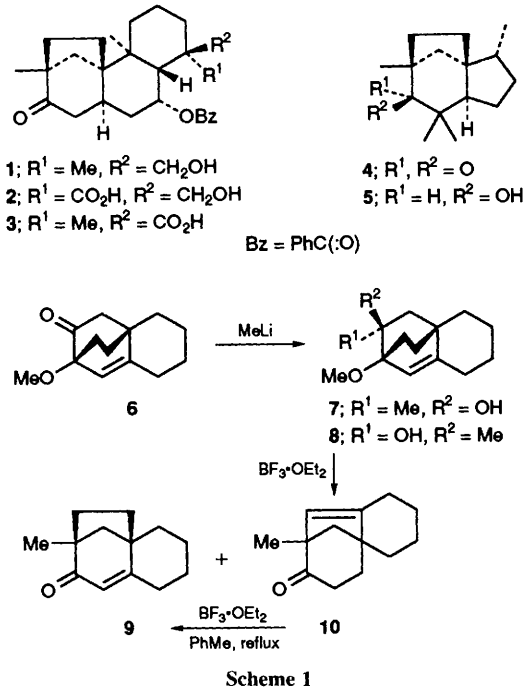
The first stereoselective total synthesis of the natural sesquiterpenes **4** and **5**, having the tricyclo[6.2.1.$0^{1,5}$]undecane skeleton with a bridgehead methyl group, is reported *via* the intermediate **9**, which was obtained by the acid catalysed rearrangement of the alcohols **7** and **8**.

Several natural products have been isolated containing the bicyclo[3.2.1]octane framework with a bridgehead methyl group. These are represented by the tetracyclic diterpenes scopadulciol **1**, scopadulcic acids A **2** and B **3**, from *Scoparia dulcis* L.[2] and the tricyclic sesquiterpenes **4** and **5** from *E. georgei* Diels.[3] The structural complexity of these natural products is illustrated by their unique tricyclic system with a *trans*-hydrindan nucleus having a methyl group at the bridgehead position which make these sesquiterpenes a synthetically challenging targets. In continuation of our interest in the synthesis of bridged ring systems,[1] we describe herein the first total synthesis of the sesquiterpenes **4** and **5**, from the readily available alcohols **7** and **8**.

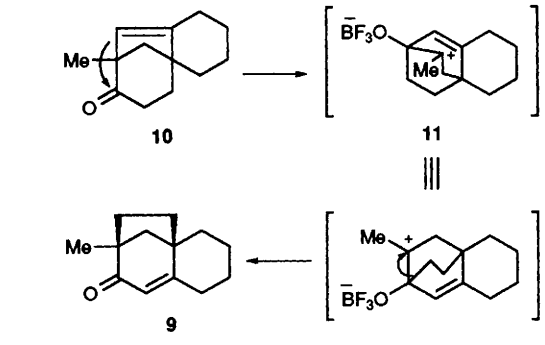
The intermediate **9** was prepared from the known[4] tricyclic ketone **6** as outlined in Scheme 1. Treatment of **6** with MeLi afforded a 1 : 1 mixture of the *exo* and *endo* alcohols, **7** and **8**, which are separable by column chromatography. The *exo* alcohol **7** on exposure to $BF_3{\cdot}Et_2O$ in benzene afforded a mixture of the enone **9** and an isomeric ketone **10** in 1 : 4 ratio, while the *endo* alcohol **8** rearranged to the products **9** and **10** in the ratio of 4 : 1, under identical conditions.† Since the *endo* alcohol **8** rearranged predominantly to the unsaturated ketone **9**, which is required for the synthesis, several experiments[5] were initiated to obtain the alcohol **8** exclusively.‡ In all the cases only mixtures of **7** and **8** were obtained with the *exo* alcohol **7** predominating.

Since our target was to obtain the unsaturated ketone **9** in good yield and the exclusive formation of the *endo* alcohol **8** from the ketone **6** appeared to be a remote possibility, the acid catalysed rearrangement was investigated in detail, during which time we observed a novel rearrangement of the ketone **10** to the enone **9**. Treatment of **10** with $BF_3{\cdot}Et_2O$ in refluxing benzene for 10 h afforded a 1 : 9 mixture of the enone **9** and the ketone **10**, while prolonged reflux for 68 h resulted in **9** and **10** in the ratio of 94 : 6. However, in refluxing toluene, rearrangement of **10** was complete in 7 h giving a 96 : 4 ratio of the compounds **9** and **10** (92%). The transformation of **10** into **9** could be attributed to the formation of the carbocation **11** at the bridgehead position as depicted in Scheme 2. The results clearly establish the equilibrium favouring the formation of the enone **9** and it is of interest that, during the rearrangement of **10** to **9**, a bicyclo[3.2.1]octane framework is converted to a new isomeric bicyclo[3.2.1]octene skeleton, *via* the bicyclo[2.2.2]octane derivative **11**.

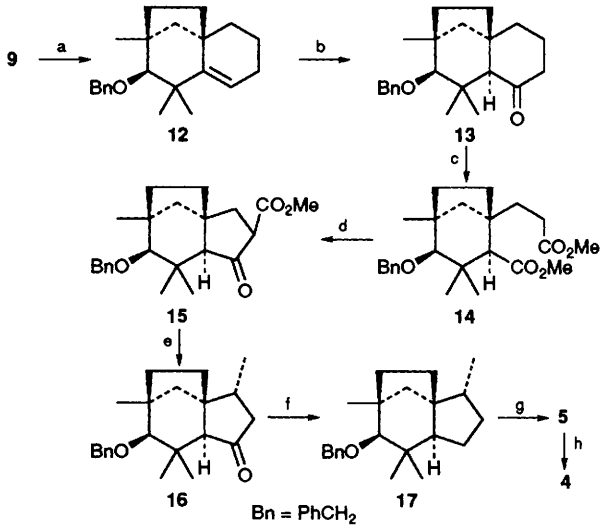
Having obtained the intermediate **9** in excellent yield, the synthesis of the sesquiterpenes **4** and **5** was achieved through the sequence of reactions[4] illustrated in Scheme 3. The dialkylation of the enone **9** followed by reduction of the



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions*: (a), i, KOBu^t (3 equiv.), MeI; ii, Bu^i_2AlH, THF, −78 °C to room temp.; iii, NaH, $PhCH_2Br$, 1,2-dimethoxyethane, tetrabutylammonium iodide, reflux, 72%; (b), i, BH_3·THF, aq. NaOH, H_2O_2; ii, PCC, CH_2Cl_2, 77%; (c), i, NaOH, furfural; ii, O_3, EtOAc, −78 °C, AcOH, H_2O_2; iii, CH_2N_2, 68%; (d), i, KOBu^t (1.2 equiv.), C_6H_6, reflux, 78%; (e), i, NaH, PhSeCl, H_2O_2; ii, Me_2CuLi, −100 °C; iii, 1,4-diazabicyclo[2.2.2]octane (DABCO), *o*-xylene, 85 °C, 6 h, 65%; (f), i, Bu^i_2AlH, THF, −78 °C to room temp.; ii, NaH, CS_2, MeI, THF, reflux; iii, tributyltin hydride, azoisobutyronitrile, toluene, reflux 85%; (g), H_2, Pd/C, EtOH, 2 h, 100%; (h), PDC, CH_2Cl_2, 100%

carbonyl group and protection of the resultant alcohol afforded the benzyl ether **12** in good yield. Hydroboration–oxidation of **12** followed by oxidation with pyridinium chlorochromate (PCC) yielded the tricyclic ketone **13** as a single diastereoisomer since the BH_3 addition is expected to take place from the less hindered α-face of the molecule. The contraction of the six-membered ring was achieved by the ozonolysis of the furfurylidene derivative of **13**, followed by an oxidative work up to the diacid and Dieckmann condensation of the diester **14** to the β-ketoester **15**. The compound **15** was transformed into the tricyclic ketone **16**, which undergoes a stereoselective conjugate addition at −100 °C with Me_2CuLi. Deoxygenation of **16** was achieved without perturbing the stereochemistry at the ring junction through the corresponding alcohol using Barton's protocol[6] to yield the benzyl ether **17** in good yield. Hydrogenolysis of **17** afforded the sesquiterpene **5** which was oxidized with pyridinium dichromate (PDC) to the sesquiterpene **4** in high yield.§

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Footnotes

† *Selected spectral data*: **9**: IR ν/cm^{-1} 1677 and 1614; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.36–1.96 (m, 12 H), 2.4 (br, 2 H), 5.64 (br s, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 19.32 (q), 22.32 (t), 24.27 (t), 30.38 (t), 34.54 (t, 2 × C), 35.97 (t), 47.16 (s), 50.93 (s), 52.62 (t), 122.20 (d), 169.41 (s), 203.49 (s).

10: IR, ν/cm^{-1} 1700; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.20–2.64 (m, 14 H), 5.2 (d, *J* 2 Hz, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 17.30 (q), 22.37 (t), 26.01 (t), 26.66 (t), 29.26 (t), 34.86 (t), 36.81 (t), 46.43 (s), 55.79 (t), 56.58 (s), 127.59 (d), 149.96 (s), 211.60 (s).

16: IR, ν/cm^{-1} 3440; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.96 (d, *J* 7.2 Hz, 3 H), 1.10 (s, 6 H), 1.24 (s, 3 H), 1.28–2.60 (m, 10 H), 2.92 (s, 1 H), 4.60 (s, 2 H), 7.26 (br s, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.57, 139.06, 128.04 and 126.98 (5 × ArC), 93.81, 76.54, 61.03, 52.13, 47.59 (2 × C), 46.40, 38.22, 35.88, 35.18, 33.41, 30.67, 25.07, 17.57, 16.26.

5: IR, ν/cm^{-1} 1735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, *J* 7.1 Hz, 3 H), 0.91 (s, 3 H), 1.03 (s, 3 H), 1.06 (s, 3 H), 1.11–1.92 (m, 13 H), 3.18 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.41, 54.14, 53.71, 47.79, 46.25, 40.43, 37.85, 34.74, 33.59, 32.22, 29.29, 24.98, 23.31, 19.82, 16.22.

‡ The ketone **6** was treated with reagents such as MeLi–$LiClO_4$, Me_2CuLi and Me_3CuLi_2.

§ The spectral data of **4** and **5** were identical with the authentic spectra kindly provided by Professor Ghisalberti.

References

1 For Part 12 of the series Synthesis based on Cyclohexadienes, see P. S. Shanker and G. S. R. Subba Rao, *J. Chem. Soc., Chem. Commun.*, 1994, 621.

2 T. Hayashi, M. Kishi, M. Kawasaki, M. Arisawa, M. Shimuzu, S. Suzuki, M. Yoshizaki, N. Morita, Y. Tezuka, T. Kikuchi, L. H. Berganza, E. Ferro and I. Bassualdo, *Tetrahedron Lett.*, 1987, **28**, 3693.

3 P. J. Carrol, E. L. Ghisalberti and D. E. Ralph, *Phytochemistry*, 1976, **15**, 777; E. L. Ghisalberti, A. H. White and A. C. Willis, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1300.

4 N. Selvakumar and G. S. R. Subba Rao, *Tetrahedron Lett.*, 1993, **34**, 7789.

5 E. C. Ashby and S. A. Noding, *J. Org. Chem.*, 1979, **44**, 4371; O. Arzona, R. F. Pradilla, C. Manzano, S. Perez and J. Plumet, *Tetrahedron Lett.*, 1987, **28**, 5547; T. L. Macdonald and W. C. Still, *J. Am. Chem. Soc.*, 1975, **97**, 5280.

6 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.