Tandem 5-*exo-trig* allyl and 3-*exo-trig* radical cyclisation and rearrangement to copa and ylanga type sesquiterpene skeleton

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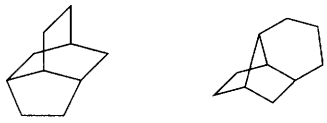
A novel tandem 5-*exo-trig* allyl and 3-*exo-trig* radical cyclisation and rearrangement to copa and ylanga type sesquiterpene skeleton is reported.

The use of radicals in organic synthesis has been given increased attention during the last two decades.[1] Although allyl radicals have been known for almost a decade,[2] they have rarely been used in organic synthesis[3,4] as they are less reactive and more stable when compared to their saturated and vinylic counterparts. In continuation of our interest in the synthesis of sesquiterpenes using radical cyclisation,[5] herein we describe the 5-*exo-trig* allyl radical cyclisation route to isotwistane **1**, which underwent further cyclisation and rearrangement to a copa and ylanga sesquiterpene skeleton **2**.

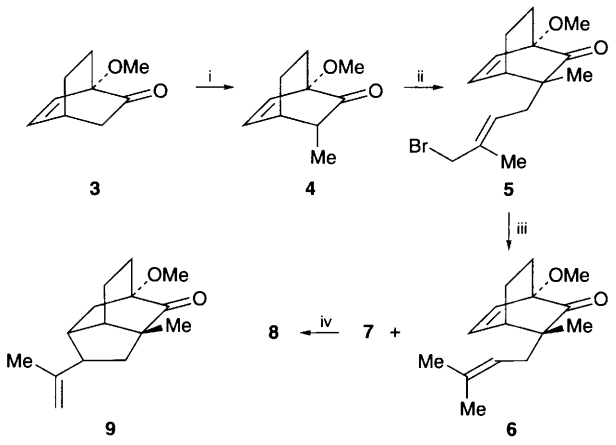


1 **2**

Our synthetic sequence, starting from the known[6] bicyclooctenone **3** having a bridgehead methoxy group, is depicted in Scheme 1. Although Grignard addition to the bicyclooctenone is not selective, it is known[7] that alkylation of the bicyclooctenone proceeds at low temperature stereoselectively to afford the *endo* alkylated product. Thus, alkylation of the lithium enolate of **3** with methyl iodide gave the ketone **4** in 95% yield having the methyl group in the *endo* position. Further alkylation of the lithium enolate generated from **4** at −78 °C with 1,4-dibromo-2-methylbut-2-ene[8] proceeded stereoselectively and regioselectively to give the *endo* bromide **5**.†

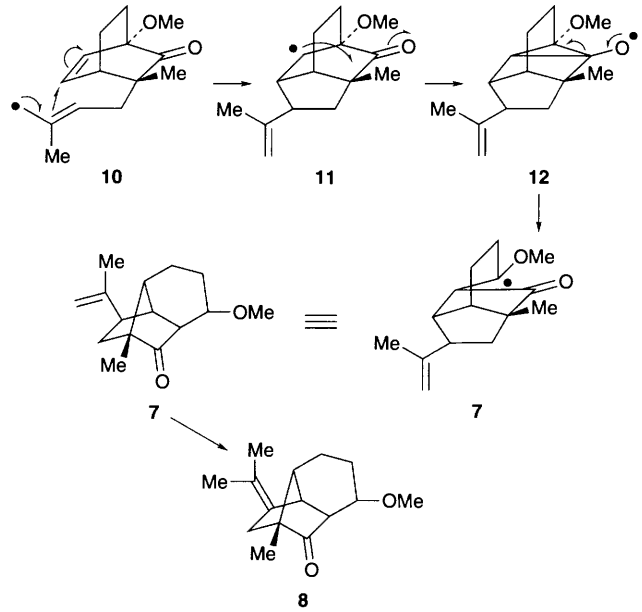
Radical cyclisation of **5** under standard conditions[2] [0.005 M benzene solution of **5** with 1.1 equiv. of tributyltin hydride (TBTH) and 0.1 equiv. of AIBN, reflux, 1–2 h] afforded a mixture containing the reduced product **6**† (5%) and a new compound **7** (71%), whose IR spectrum showed an absorption band at 1740 cm^{-1}. The ^{13}C NMR spectrum of **7** showed a methine carbon at δ 78.2 indicating that **7** is different from the 5-*exo-trig* allyl radical cyclised product **9**. On treatment with toluene-*p*-sulfonic acid (PTSA), compound **7** was quantitatively converted into a new isomer **8**,† whose IR spectrum showed the presence of a carbonyl absorption at 1740 cm^{-1}. The off-resonance ^{13}C NMR spectrum of **8** showed the presence of four singlets, four doublets, three triplets and four quartets. A doublet at δ 78.53 clearly showed that the OMe group is attached to a carbon atom bearing a hydrogen. This data clearly established the structure of the cyclised and isomerised products as **7** and **8**, and that the isopropenyl substituent present in **7** is isomerised to the isopropylidene group under acidic conditions to give **8**.

A probable mechanism for the formation of the compounds **7** and **8** is indicated in Scheme 2. As expected, the initial 5-*exo-trig* allyl radical cyclisation gave the radical **11** which underwent a 3-*exo-trig* radical cyclisation onto the carbonyl group resulting in the cyclopropyloxyl radical **12** which



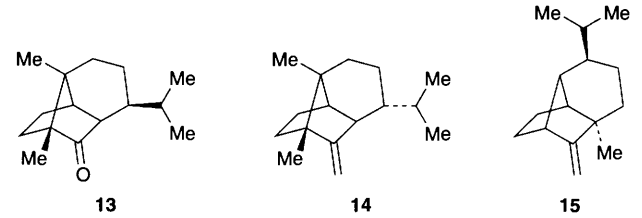
3 **4** **5** **9** **6**

Scheme 1 *Reagents and conditions*: i, LDA, THF, MeI, −78 °C; ii, LDA, THF, HMPA, 1,4-dibromo-2-methylbut-2-ene, −78 °C; iii, AIBN, TBTH, benzene, reflux, 1–2 h; iv, PTSA, benzene, reflux, 0.5 h



10 **11** **12** **7** **7** **8**

Scheme 2



13 **14** **15**

rearranged to give **7**. Formation of a radical adjacent to the methoxy group appears to be the driving force for this rearrangement.‡

A number of natural products possess this skeleton, *e.g.* copacamphor **13**,[9] sinularene **14**[10] and sativene **15**,[11] and the above strategy might be contemplated for their total synthesis.

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Footnotes

† All the compounds exhibited spectral data consistent with their structures. *Selected spectral data* for **5**: ν_{max}/cm^{-1} 3020, 2920, 1716; δ_H (90 MHz, $CDCl_3$) 6.51 (1 H, m), 6.21 (1 H, dd, *J* 6.4, 1.8 Hz), 5.73 (1 H, t, *J* 6.8 Hz), 3.99 (2 H, s), 3.52 (3 H, s), 2.62 (1 H, m), 1.2–2.36 (6 H, m), 1.73 (3 H, s), 1.11 (3 H, s); δ_C (22.5 MHz, $CDCl_3$) 212.4(s), 136.47(d), 134.4(s), 127.6(d), 125.5(d), 84.1(s), 52.1(q), 46.9(s), 40.8(t), 39.9(d), 36.8(t), 26.4(q), 21.8(t), 21.7(t), 14.6(q). For **8**: ν_{max}/cm^{-1} 3010, 2920, 1740; δ_H (200 MHz, $CDCl_3$) 3.42 (1 H, m), 3.35 (3 H, s), 2.68 (1 H, d, *J* 1.6 Hz), 2.42 (1 H, br s), 1.2–2.22 (7 H, m), 1.66 (3 H, s), 1.50 (3 H, s), 1.09 (3 H, s); δ_C (22.5 MHz, $CDCl_3$) 218.1(s), 130.7(s), 121.7(s), 78.5(s), 55.4(q), 55.0(s), 53.2(d), 49.5(d), 48.0(d), 41.2(t), 25.2(t), 20.9(t), 19.7(q), 19.7(q), 10.48(q). For **6** ν_{max}/cm^{-1} 3010, 2915, 1720; δ_H (90 MHz, $CDCl_3$) 6.45 (1 H, m), 6.17 (1 H, dd, *J* 6.7, 1.7 Hz), 5.12 (1 H, t, *J* 7 Hz), 3.52 (3 H, s), 2.61 (1 H, m), 1.25–2.18 (6 H, m), 1.73 (3 H, s), 1.59 (3 H, s), 1.08 (3 H, s); δ_C (22.5 MHz, $CDCl_3$) 213.1(s), 136.5(d), 134(s), 127.4(d), 118.7.(d), 84.2(s), 52.7(q), 47.8(s), 39.5(d), 36.5(t), 26.2(t), 25.7(t), 21.1(q), 21.0(q), 17.6(q).

‡ A bicyclooctenone analogous to **5** having a bridgehead methyl group underwent a smooth 5-*exo-trig* allyl radical cyclisation exclusively to give a compound analogous to **9**.

References

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