A Novel Route to Usefully Functionalised Spiro[*n*.4] Systems; Application to a Formal Synthesis of (±)-α-Cedrene

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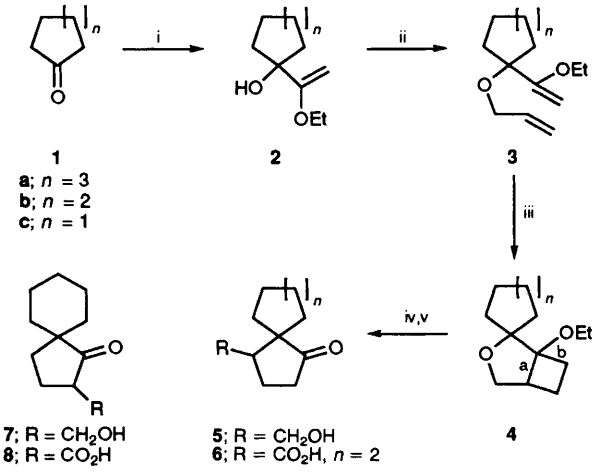
A facile route for the construction of functionalised spiro[*n*.4] systems through pinacol type rearrangement of appropriately designed cyclobutane derivatives with an application to a synthesis of (±)-α-cedrene is described.

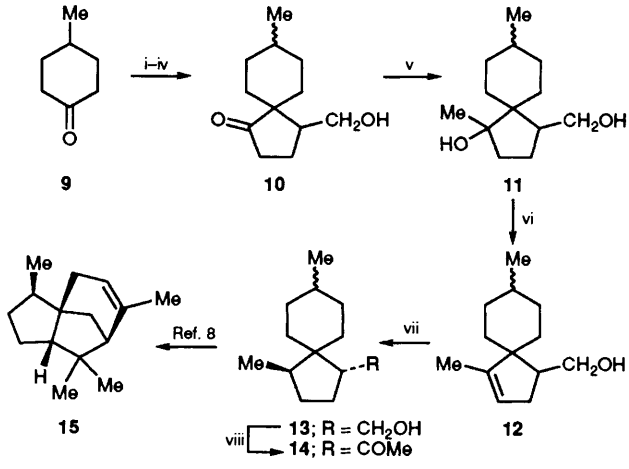
Development of new methods for the construction of usefully functionalised spiro systems continues[1] to be the focus of intense interest. 1,4-Bifunctionalised spiro cyclopentanes are particularly useful in providing an entry into a wide variety[2] of natural products in addition to the spiranes. Despite the large number of syntheses[1,3] of spiro natural products, a direct method for constructing spiro subunits at the carbonyl carbon of cyclic ketones remains elusive. Herein we report a facile route for the construction of functionalised spiro[*n*.4]systems *via* a pinacol type rearrangement of alkoxycyclobutane derivatives prepared by intramolecular alkene–enol ether photocycloaddition.

In a representative sequence (Scheme 1), reaction[4] of cycloheptanone **1a** with ethoxyvinyllithium in tetrahydrofuran (THF) at −70 °C afforded in 81% yield the alcohol **2a**, b.p. 130–135 °C (5 mm Hg). The alcohol **2a** was transformed to the allyl ether derivative **3a**, b.p. 160–165 °C (0.5 mmHg) in 83% yield on treatment with NaH and allyl bromide in refluxing THF–hexamethylphosphoramide (HMPA) (5:1). The diallyl ether derivative **3a** in diethyl ether solution, on irradiation through a quartz immersion well in the presence of CF_3SO_2Cu as catalyst, underwent smooth cycloaddition[5] to afford after chromatographic purification the oxabicyclo[3.2.0] heptane **4a**† in 54% yield. The rearrangement of the four-membered ring in **4a** could be accomplished efficiently by use of trifluoromethanesulfonic acid (TFSA) in dichloromethane at room temperature to afford exclusively the spiro cyclopentanone **5a** in 76% yield. That the rearrangement of **4a** had taken place to produce a hydroxy-cyclopentanone derivative was indicated by its IR absorptions at 1725 (C=O) and 3420 cm^{-1} (OH) and the disappearance of OCH_2CH_3 signals in the ^1H NMR spectrum of the product. Similarly cyclohexanone **1b** and cyclopentanone **1c** afforded the spiro ketones **5b** and **5c** respectively in good yields.

That the structure of the rearrangement product is **5** as predicted to arise by exclusive migration of the internal bond '*a*' having maximum continuous orbital overlap[6] with the p-orbital at the cationic centre was established as follows. The product obtained by rearrangement of **4b** was oxidised to afford in 86% yield the keto-acid **6**, m.p. 103 °C. The failure of the keto-acid thus obtained to undergo decarboxylation excluded the β-keto acid structure **8** which would arise if rearrangement of **4b** had involved migration of the peripheral bond '*b*' to produce **7**. Thus, through a four-step sequence, cyclic ketones can be converted very efficiently to spiro[*n*.4] systems with the carbonyl and the hydroxymethylene groups on the five-membered ring disposed in a manner so as to lead entry into a variety of natural products.



Scheme 1 *Reagents and conditions*: i, Bu^{t}Li, ethyl vinyl ether, THF, −70 °C to room temp., 81–90%; ii, NaH–THF, allyl bromide, HMPA, reflux, 81–86%; iii, *hν*, Et_2O, CF_3SO_2Cu, 54–60%; iv, TFSA, CH_2Cl_2, −78 °C to room temp., 2 h, 50–78%; v, CrO_3, H_2SO_4, H_2O, acetone, 0 °C to room temp., 1 h



Scheme 2 *Reagents and conditions*: i, Bu^{t}Li, ethyl vinyl ether, THF, −70 °C, 81%; ii, NaH–THF, allyl bromide, HMPA, reflux, 89%; iii, *hν*, Et_2O, CF_3SO_2Cu, 58%; iv, TFSA, CH_2Cl_2, room temp., 76%; v, dihydropyran, pyridinium toluene-*p*-sulfonate (PPTS), CH_2Cl_2, then MeLi, THF, reflux, then PPTS, MeOH, 67% overall; vi, Me_2SO, 165 °C, 73%; vii, H_2, PtO_2, EtOH, 99%; viii, Me_2SO, $(COCl)_2$, NEt_3, CH_2Cl_2, −65 °C, then MeLi, Et_2O, then Jones reagent, acetone, 55% overall

† Compounds **4**, **5**, **10**, **12** and **13** gave satisfactory microanalytical data. Satisfactory spectral data were obtained for all new compounds. ^1H NMR ($CDCl_3$) data for selected compounds: **2a**, δ (200 MHz) 1.29 (3H, t, *J* 7 Hz), 1.43–2.06 (13H, m), 3.72 (2H, q, *J* 6.9 Hz), 3.87 (1 H, d, *J* 2.4 Hz) and 4.18 (1H, d, *J* 2.6 Hz). **3a**, δ (200 MHz), 1.28 (3H, t, *J* 7 Hz), 1.40–1.80 (8H, m), 1.88 (4H, m), 3.74 (2H, q, *J* 7 Hz), 3.82 (2H, m), 4.03 (1H, d, *J* 2.4 Hz), 4.19 (1H, d, *J* 2.4 Hz), 5.06–5.38 (2H, m) and 5.84–6.10 (1H, m). **4a**, δ (200 MHz) 1.18 (3H, t, *J* 7 Hz), 1.36–1.90 (12H, m), 2.02–2.38 (4H, m), 2.70–2.98 (1H, m), 3.46–3.64 (3H, m) and 3.84 (1H, ABq, *J* 10 Hz). **5a**, δ (100 MHz), 1.32–2.44 (18H, m), 3.56 (1H, q, A of ABX, J_{AB} 10 Hz, J_{AX} 3 Hz) and 3.89 (1H, q, B of ABX, J_{AB} 10 Hz, J_{BX} 3 Hz). **6** (as methyl ester), δ (200 MHz), 1.20–1.82 (11H, m), 2.08–2.70 (3H, m), 3.10 (1H, m) and 3.68 (3H, s). **10**, δ (100 MHz) 0.92 (3H, br s), 1.12–2.84 (15H, m) and 3.36–3.96 (2H, m). **12**, δ (100 MHz) 0.96 (3H, d, *J* 6.4 Hz), 1.12–2.72 (16H, m, with d, *J* 1.7 Hz at δ 1.73 for the vinylic Me), 3.32–3.96 (2H, m) and 5.3 (1H, br s). **14**, δ (100 MHz) 0.68–2.48 (20H, m), 2.14, 2.20 and 2.24 (3H, all s COMe) and 2.52–3.16 (1H, m). The component with a COMe peak at δ 2.24 comprising *ca.* 15–20% in this mixture was completely equilibrated with NaOMe–MeOH to produce a 3:1 mixture of the components having COMe peaks at δ 2.14 and 2.20 indicating the less stable *syn*-orientation of the Me and the COMe groups in this component (*cf.* ref. 8).

The synthetic potential of this novel strategy is demonstrated by a formal synthesis of (±)-α-cedrene as delineated in Scheme 2. Following the above sequence spiroannelation on 4-methylcyclohexanone **9** afforded the spiro cyclopentanone **10**. Protection of the hydroxy group in **10** as the tetrahydropyranyl ether followed by MeLi addition and deprotection afforded the diol **11** in overall 67% yield. Selective dehydration[7] of the tertiary hydroxy group in **11** was achieved by heating in dimethyl sulfoxide to afford the spiro cyclopentene **12**. Hydrogenation of **12** over Adam's catalyst afforded mainly **13**. Transformation of **13** to the known[8] methyl ketones **14**‡ through three consecutive steps involving Swern oxidation, MeLi addition and Jones oxidation, dictated that hydrogenation proceeded stereoselectively. The ketones **14** have already been transformed[8] in three steps to α-cedrene **15**.[9] Thus with the synthesis of **14**, a formal synthesis of α-cedrene **15** is achieved.

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‡ The ketones **14** displayed IR, ^{1}H NMR and mass spectra comparable with those reported (ref. 8).

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