A Radical Cyclisation Approach to the 2-Oxabicyclo[2.2.1]heptane Ring System

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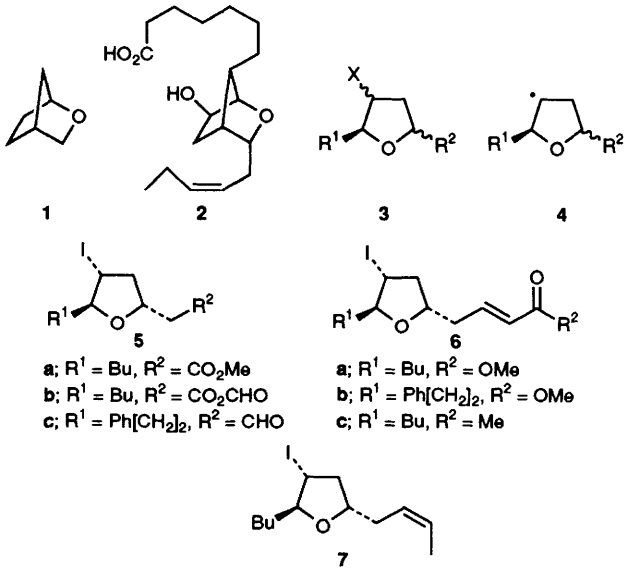
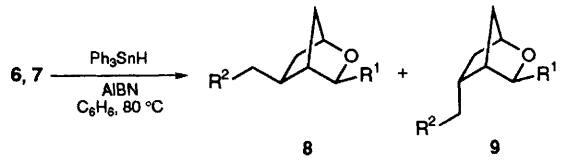
Intramolecular cyclisations of radicals generated from the β-substituted tetrahydrofurans **6**, **7** and **14c** onto suitably positioned alkene functions attached to the α′-position of the heterocycle give good to excellent yields of the 2-oxabicyclo[2.2.1]heptanes **8**, **9** and **16**.

The 2-oxabicyclo[2.2.1]heptane ring system **1** is relatively uncommon but has recently been brought to prominence by the isolation of the Cymathere ethers (*e.g.* **2**) from the brown algae *Cymathere triplicata*.[1] Previous approaches to this ring system include examples of intramolecular Williamson ether synthesis, which have been used in the preparation of analogues of the prostaglandin endoperoxides PGG_2 and PGH_2,[2] related intramolecular cyclisations of 1-hydroxymethyl-3,4-epoxycyclopentanes,[3] electrophile-induced 5-*exo*-trig cyclisations of a monoterpene, plinol C,[4] and an isolated example of a radical addition–rearrangement process, starting from a 7-oxabicyclo[2.2.1]hept-4-en-1-one.[5] The corresponding lactones, available for example by Baeyer–Villiger oxidations of bicyclo[2.1.1]hexan-5-ones, are represented by the more familiar camphanic acids which have been employed as homochiral derivatizing agents,[6] while the related lactols can be prepared both from *cis*-3-hydroxycyclopentane-1-carbaldehydes[7] and from carbanion-mediated intramolecular cyclisations of epoxy-nitriles derived from 2-methoxytetrahydrofurans.[8] Herein, we report a new approach to the oxabicyclo[2.2.1]heptane ring system based upon intramolecular cyclisations of radicals derived from β-functionalised tetrahydrofurans. We have recently reported flexible and highly stereoselective approaches to both 2,5-*cis*- and 2,5-*trans*-β-substituted tetrahydrofurans (**3**; X = I or OH) by iodoetherifications of homoallylic alcohols.[9] In seeking ways to elaborate further these initial products, we reasoned that anion formation at the β-position would probably not be viable owing to elimination of the ring oxygen, although reactions which suggest that this is not always the case are known, for example when X = $PhSO_2$.[10] In contrast, the corresponding radicals **4** should be kinetically stable and not undergo similar ring opening. Given a suitably positioned radical acceptor in one of the side chains, access to a variety of bicyclic systems should be possible using such intermediates.

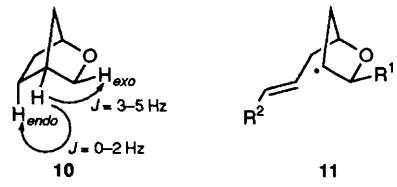
Model substrates having a 2,5-*trans* substitution pattern were derived from the iodotetrahydrofuran **5a**,[9]† reduction of which using diisobutylaluminium hydride (Dibal-H) in hexanes at −78 °C led smoothly to the corresponding aldehyde **5b** in >80% isolated yield, and from the aldehyde **5c**, derived from the corresponding dithiane derivative. Subsequent Wittig homologations, using the stabilized phosphoranes derived from methyl haloacetate or haloacetone and dichloromethane as solvent (20 °C; 16 h), provided excellent yields of the (*E*)-alkenes **6**, while condensation with ethylidenetriphenylphosphorane in tetrahydrofuran (THF; −78 to 0 °C) led, after column chromatography, to the (*Z*)-alkene **7**. After some experimentation, we were pleased to find that the central cyclisation could be effected under relatively dilute conditions by slow addition of Ph_3SnH–AIBN to a hot solution of the alkene in benzene.[11] Thus, addition during 2 h of a 20 mmol l^{-1} solution of triphenyltin hydride (1.5 equiv.) in benzene containing AIBN (6 mmol l^{-1}; 0.3 equiv.) to a gently refluxing 8.5 mmol l^{-1} solution of the alkenoate **6a** in dry benzene gave, after a further 2 h reflux, washing with aqueous potassium fluoride and column chromatography, a 3:1 mixture of the oxabicyclo[2.2.1]heptanes **8a** and **9a** in 77% isolated yield.[12] The stereochemical assignments were based on the established differences between the coupling constants in bicyclo[2.2.1]heptanes, as shown in formula **10**,[3,13] and are consistent with the intermediacy of a radical **11** in which the butyl substituent is positioned exclusively in an *exo* position and the ester side chain is positioned such that the radical adds predominantly to that face of the alkene which leads mainly to the less sterically encumbered di-*exo* isomer **8**. In the same manner, treatment of the 5-phenethyl-iodotetrahydrofuran **6b** with Ph_3SnH–AIBN led to the same ratio of products **8b** and **9b**. Similar treatment of the enone **6c** led, in 90% isolated yield, to a 4:1 ratio of products, **8c** and **9c** corresponding to the foregoing di-*exo* and 3-*exo*-5-*endo* acetates **8a**,**b** and **9a**,**b**. Cyclisation of the (*Z*)-alkene **7** was somewhat less efficient and led to a combined 59% isolated yield of the two isomers **8d** and **9d** in a ratio of 7:2. This latter result presumably reflects the lower reactivity of the alkene function as a radical acceptor.

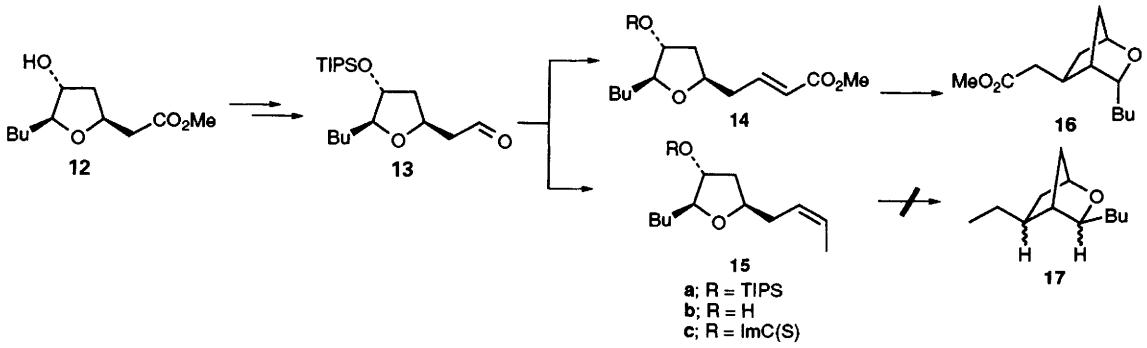
The prospects for effecting related cyclisations starting with a 2,5-*cis* substitution pattern in the initial substrate were examined using the hydroxy-tetrahydrofuran **12**.[9] Sequential





a; R^1 = Bu, R^2 = CO_2Me [**8**/**9** = 3:1; 77%]
b; R^1 = Ph[CH_2]$_2$, R^2 = CO_2Me [**8**/**9** = 3:1; 70%]
c; R^1 = Bu, R^2 = COMe [**8**/**9** = 4:1; 90%]
d; R^1 = Bu, R^2 = Me [**8**/**9** = 7:2; 59%]





TIPS = triisopropylsilyl; Im = Imidazol-1-yl

protection (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h; 70%) and partial reduction (Dibal-H, hexanes, −78 °C, 3 h; 85%) gave the aldehyde **13**. Subsequent Wittig homologations using both Ph_3PCHCO_2Me and $MeCHPPh_3$, as outlined above, gave the alkenes **14a** and **15a** respectively, which were deprotected (Bu_4NF, THF, 20 °C, 40 h) to give the required alkenyl tetrahydrofurans **14b** and **15b**. Each of these was heated in tetrahydrofuran with 1,1′-thiocarbonyldiimidazole (16 h) to give the corresponding thionoimidazole esters **14c** and **15c** in essentially quantitative yields. We were pleased to find that slow addition of a solution of tributyltin hydride in toluene during 8 hours to a refluxing solution of the thionoester **14c** in the same solvent (30 ml $mmol^{-1}$)[11,14] gave, after chromatography, a 77% isolated yield of a single 2-oxabicyclo[2.2.1]heptane, identified as the 3-*endo*-5-*exo* diastereoisomer **16**, based on the foregoing NMR data.[13] Possibly, the origins of this excellent level of stereoselection lie in the initial conformation of the thionoester in which the smaller butyl substituent occupies a more crowded 'axial' position, translated into an *endo* position by a radical cyclisation; presumably, the *endo* position of the butyl group precludes radical addition to the alternative face of the alkenoate function which would lead to the 3-*endo*-5-*endo* isomer. Unfortunately, a similar reaction of the ethylidene derivative **15** gave none of the expected products **17**, but rather only deoxygenated material, reflecting the poorer radical acceptor ability of the alkene function in this compound.

In conclusion, the radical cyclisations described herein represent a simple, relatively efficient and in some cases highly stereoselective approach to the 2-oxabicyclo[2.2.1]heptane system. In addition, as the precursors (**5**, **12**) may be readily obtained in homochiral form,[9] the method will be applicable to the asymmetric synthesis of examples of this ring system. A similar radical cyclisation approach to homologous 2-oxabicyclo[2.2.2]octanes has recently been reported;[15] the success of these methods suggests that many related ring systems could be accessed in a similar fashion.

We thank Rhône-Poulenc-Rorer Ltd and the SERC for financial support through the CASE scheme.

Received, 12th August 1994; Com. 4/04963B

Footnote

† The iodo-tetrahydrofuran **5** was derived from (±)-(*E*)-methyl 3-hydroxy-5-decenoate as previously described;[9] all compounds mentioned in this paper are racemates.

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