

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

Duncan E. Shaw,^a Garry Fenton^b and David W. Knight*^a

^a Department of Chemistry, Nottingham University, University Park, Nottingham, UK NG7 2RD

^b Rhône-Poulenc-Rorer, Central Research, Rainham Road South, Dagenham, Essex, UK RM10 7XS

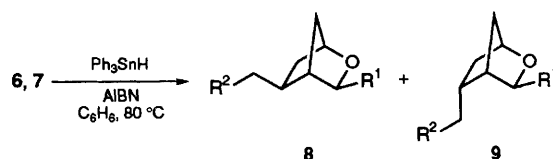
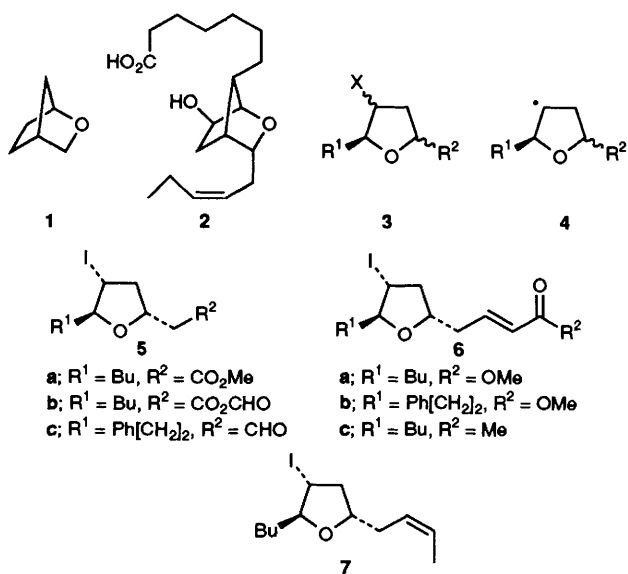
Intramolecular cyclisations of radicals generated from the β -substituted tetrahydrofurans **6**, **7** and **14c** onto suitably positioned alkene functions attached to the α' -position of the heterocycle give good to excellent yields of the 2-oxabicyclo[2.2.1]heptanes **8**, **9** and **16**.

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 PGG₂ and PGH₂,² related intramolecular cyclisations of 1-hydroxy-methyl-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-carbaldehydes⁷ 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 = PhSO₂.¹⁰ 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.

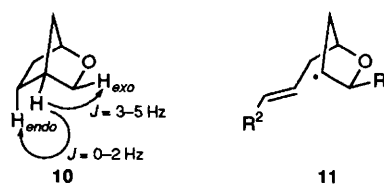
Model substrates having a 2,5-*trans* substitution pattern were derived from the iodotetrahydrofuran **5a**,^{9†} reduction of

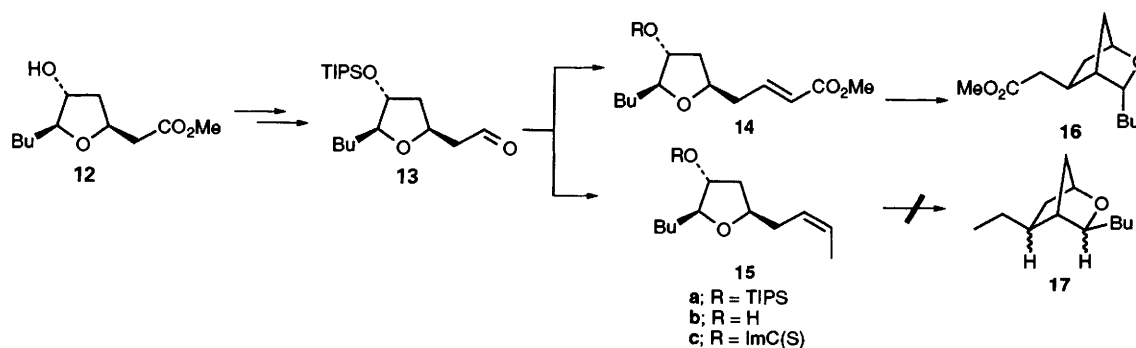
which using diisobutylaluminium hydride (Dibal-H) in hexanes at -78°C led smoothly to the corresponding aldehyde **5b** in $>80\%$ isolated yield, and from the aldehyde **5c**, derived from the corresponding dithiane derivative. Subsequent Wittig homologations, using the stabilized phosphoranes derived from methyl haloacetate or haloacetone and dichloromethane as solvent (20°C ; 16 h), provided excellent yields of the (*E*)-alkenes **6**, while condensation with ethylenetriphenylphosphorane 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 Ph₃SnH–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-iodo-tetrahydrofuran **6b** with Ph₃SnH–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**; R¹ = Bu, R² = CO₂Me [8/9 = 3:1; 77%]
b; R¹ = Ph[CH₂]₂, R² = CO₂Me [8/9 = 3:1; 70%]
c; R¹ = Bu, R² = COMe [8/9 = 4:1; 90%]
d; R¹ = Bu, R² = 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 $\text{Ph}_3\text{PCHCO}_2\text{Me}$ 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.

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Footnote

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

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