A study of the stereochemical features of 5-*endo-trig* iodocyclisations of 2-alkenylcycloalkan-1-ols

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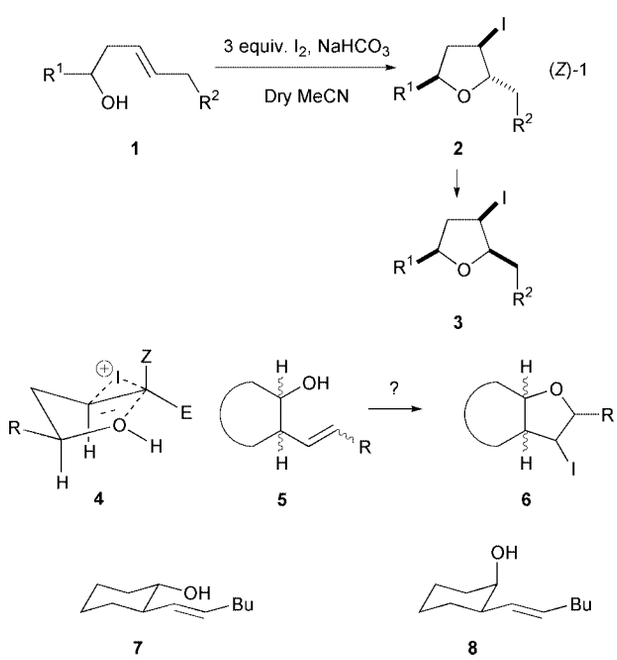
Overall 5-*endo-trig* iodocyclisations of all isomers of the 2-alkenylcyclopentan-1-ols and -cyclohexan-1-ols **11**, **12**, **14** and **16** have been examined. Only in the cases of the *trans*-alkenylcyclopentanols **11a** and **12a** are the reactions either unsuccessful or low yielding, by reason of formation of a relatively strained *trans*-fused 5/5 ring system. In contrast, iodocyclisations of *cis*-alkenylcyclopentanols work well but only show useful stereoselection in the case of the *cis*-(*Z*)-alkenylcyclopentanol **16a**. All examples involving the cyclohexanols **14** and **16** are high yielding and generally lead to single isomers of perhydro-3-iodobenzofurans **18**, **20**, **23** and **26**. Transition state conformations are proposed which account for these observations and which should be useful in applying this type of cyclisation to related substrates.

During the past few years, overall 5-*endo-trig* cyclisations have become established as synthetically useful and often highly stereoselective processes for the elaboration of saturated five-membered heterocycles.[1–3] In the case of the (*E*)-homoallylic alcohols **1**, such cyclisations can be effected by treatment with three equivalents each of iodine and sodium hydrogen carbonate in dry acetonitrile and lead, highly selectively, to the tetrahydrofuran diastereoisomers **2**. These conditions are based on those originally developed by Bartlett and co-workers[4] during their studies of iodolactonization reactions. In the present examples, the use of anhydrous conditions appears to be essential: if water is present, the major products are the iodohydrins derived from the homoallylic alcohols **1**. In contrast to the generally rapid cyclisations of the (*E*)-isomers **1**, similar reactions of the corresponding (*Z*)-isomers are much slower and give poorer yields of the all-*cis* trisubstituted tetrahydrofurans **3**, but again as single diastereoisomers. These observations are consistent with the intermediacy of the chair conformation **4**, controlled by the equatorial position of the substituent R; the poorer cyclisations of the (*Z*)-isomers of alcohols **1** are thus explained by the necessarily axial positioning of the alkene substituent Z. We were intrigued by the prospect that this type of cyclisation could be extended to the formation of ring-fused tetrahydrofurans **6** from stereoisomers of the 2-alkenylcycloalkanols **5**.[5] However, at the outset, extrapolation of the transition state model **4** to the more constrained analogues **5** gave unclear indications regarding the prospects for success; while the 1,2-*trans*-isomers appeared to be very well set up for cyclisation *via* conformation **7**, it was far from clear whether the related *cis* isomers would undergo cyclisation at all, as the two reacting centres appeared rather distant in the anticipated initial reacting conformation **8**. In the event, most of the cyclisations were very successful; herein, we report full details of these findings.[6]



Results and discussion

The necessary starting materials **11**, **12**, **14** and **16** were readily prepared from epoxycyclopentane and epoxycyclohexane respectively [**9**; $n = 1, 2$] (Scheme 1). Yamaguchi–Hirao alkylation[7] of lithiohexyne using these electrophiles with boron trifluoride–diethyl ether as the activating species led to good isolated yields of the *trans*-2-alkynylcycloalkanols **10**. Direct reduction using lithium aluminium hydride in refluxing tetrahydrofuran–toluene[8] then gave the first pair of precursors, the *trans*-(*E*)-isomers **11**. Lindlar reduction gave the corresponding *trans*-(*Z*)-isomers **12**, both in excellent yields. The related *cis*-isomers, **14** and **16**, were accessed by a smooth Mitsunobu inversion[9] of the initial alkynols **10** using *p*-nitrobenzoic acid as the nucleophile.[10] Treatment of the

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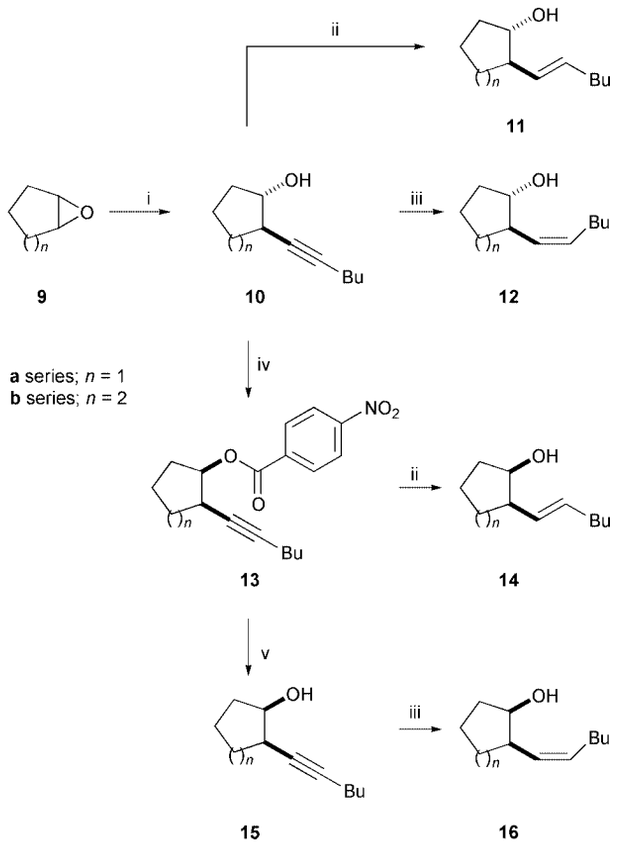
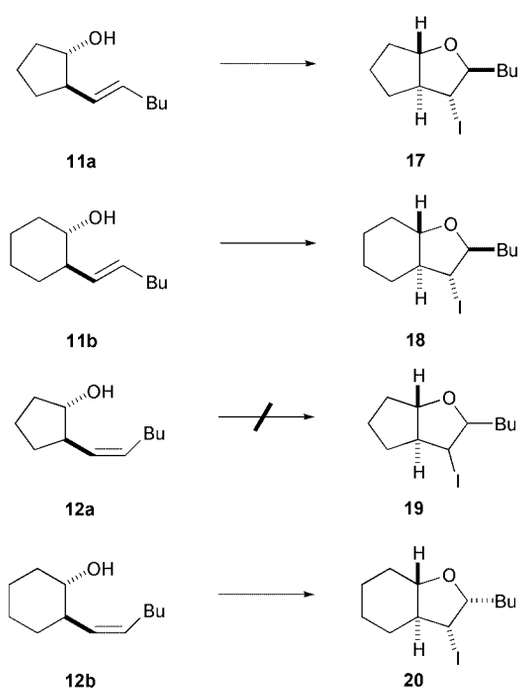


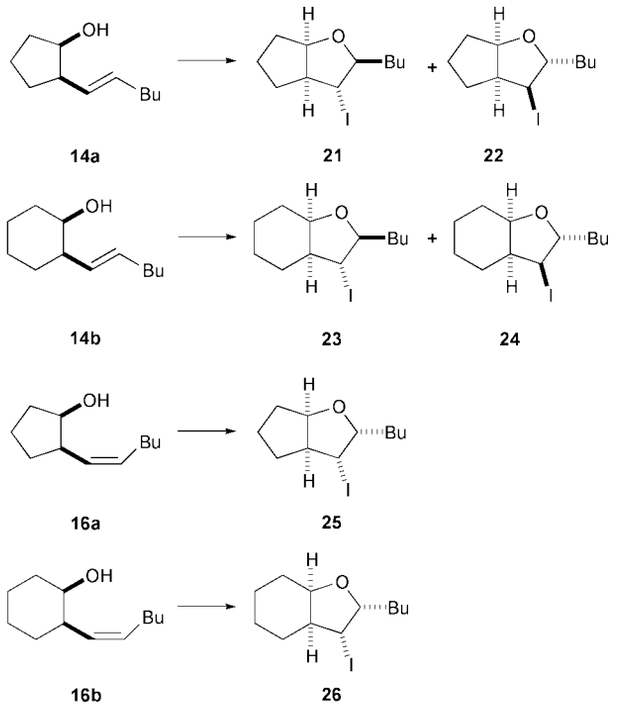
Scheme 1 *Reagents and conditions*: i, BuCCLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; ii, $LiAlH_4$, THF–toluene, reflux; iii, H_2, 5% Pd-C, quinoline, EtOAc, 20 °C; iv, *p*-$NO_2C_6H_4CO_2H$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 20 °C; v, NaOH, MeOH, 20 °C.

resulting esters **13** with lithium aluminium hydride, by the foregoing method, both removed the ester group and reduced the alkyne to give the required *cis*-(*E*)-alkenylcycloalkanols **14**, while saponification of esters **13** followed by Lindlar reduction of the resulting alkynols **15** gave the final members of the series, the *cis*-(*Z*)-isomers **16**.

The central cyclisations were performed under a standard set of conditions,[1,4] consisting of exposure of the substrates **11**, **12**, **14** and **16** to three equivalents of iodine in dry acetonitrile containing three equivalents of sodium hydrogen carbonate at 0 °C. The *trans*-(*E*)-alkenylcyclopentanol **11a** underwent rather slow cyclisation and it was only after approximately 48 hours that the starting material has all reacted according to TLC analysis, which indicated the formation of an ominous number of products. A simple aqueous work-up followed by chromatographic separation delivered a single hexahydrocyclopenta-[*b*]furan **17** in 29% isolated yield, the structure of which was deduced as outlined below. Other products appeared to be the corresponding iodohydrins, presumably formed as water was generated during the cyclisation leading to the bicycle **17**, although the addition of drying agents such as molecular sieves or magnesium sulfate failed to improve the yield. On reflection, we realised that this could be regarded as a remarkable result, in that the relatively strained *trans*-fused 5/5 ring system in **17** had been formed at all. Further, the relative stereochemistry was consistent with a reacting conformation based on that anticipated (**7**) from initial studies.[1] This was borne out when the corresponding cyclohexane derivative **11b** was similarly exposed to iodine: in this case, cyclisation occurred to give a single perhydrobenzofuran **18** in essentially quantitative yield in about one hour at 0 °C. This was consistent with the formation of a much less strained *trans*-fused 6/5 ring system during cyclisation, again *via* a transition state related to conformation **7**. Despite the excellent yield obtained from this cyclisation, we examined a few alternative conditions using substrate **11b**. We found that powdered sodium hydroxide could be used as the base, in place of sodium hydrogen carbonate, without reducing the yield. The cyclisation also worked, but slightly less efficiently (~ 80% isolated yield), in the absence of base; hence, in such favourable examples, competing iodohydrin formation is not especially deleterious although clearly in examples containing more sensitive functionality, exposure to the hydrogen iodide generated during the cyclisation could be a significant drawback. *N*-Iodosuccinimide was also effective as an iodonium source, but cyclisation was some five times slower. Perhaps surprisingly, when either triethylamine or *N*,*N*-diisopropylethylamine (Hünig's base) was used as the base in place of sodium hydrogen carbonate, no cyclisation was observed even after prolonged exposure to three equivalents of iodine. The requirement of three equivalents of iodine suggests that more complex species than simply iodonium ions are necessary for these and related cyclisations[1,3,4] and that these are not present when tertiary amines are used as base; in all cases, use of less than three equivalents resulted in incomplete conversion, as had been noted previously.[1,3] Returning to the original substrates, it was next found that the *trans*-(*Z*)-cyclopentanol **12a** failed to cyclise to give isomers of the *trans*-fused system **19**, whereas the corresponding cyclohexanol **12b** underwent smooth but slow cyclisation, relative to the related *trans*-(*E*)-isomer **11b**, to give the perhydrobenzofuran diastereoisomer **20**. Our model work[1] had revealed that (*Z*)-homoallylic alcohols in general are relatively poor substrates for this type of cyclisation (see above and structure **4**). It seems likely therefore that a similar effect applies in these two cases which involve the (*Z*)-isomer of conformation **7**. In the case of the cyclopentanol **12a**, a combination of this and the additional requirement of formation of a *trans*-fused 5/5 bicyclic system **19** proved just too much to permit the cyclisation to proceed. That the less strained *trans*-5/6 bicycle **20** was formed in good yield but at a much slower rate, relative to cyclisation of the corresponding *trans*-(*E*)-isomer **11b**, is probably just a reflection of a higher energy transition state brought about by the pseudoaxial positioning of the butyl side-chain.



We then turned to the corresponding *cis*-alkenylcycloalkanols **14** and **16**, not certain if these would undergo cyclisation at all, in view of the likely initial conformation **8**. In the event, cyclisations of the *cis*-(*E*)-cycloalkanols **14a** and **14b**



turned out to be somewhat too facile, being both relatively rapid and giving mixtures of products. The *cis*-fused hexahydrocyclopenta[*b*]furans **21** and **22** were obtained in a 1.25 : 1 ratio, slightly improved by performing the cyclisations at −78 °C. At this lower temperature, the cyclisations took up to five hours to go to completion and the addition of dichloromethane was used to prevent the reaction mixture from freezing. Similarly, the two *cis*-fused perhydrobenzofuran isomers **23** and **24** were obtained from the *cis*-(*E*)-cyclohexanol **14b** but in a more useful ratio of 5 : 1 at 0 °C, improved to *ca.* 10 : 1 at −78 °C. Hence, such cyclisations are indeed viable and, assuming an initial major conformation **8** for these substrates, suggest that a late transition state is involved based on the conformation **27** (Fig. 1). The minor isomer **24** could then arise *via* the less favourable conformation **28** which would lead to the iodonium ions **29** and **30** and thence to the observed minor product. The much poorer stereoselection obtained from the cyclopentanol **14a** is presumably a reflection of the lower energy differences between related conformations in a five-ring system. By contrast, the final series, the *cis*-(*Z*)-cycloalkanols **16**, appeared to have just the right balance between favourable (formation of a *cis*-fused ring system) and unfavourable (cyclisation onto a (*Z*)-alkene) factors. Cyclisations were relatively slow but very clean and gave > 90% isolated yields of the single diastereoisomers **25** and **26**, consistent with conformation **31** (Fig. 1). The more sterically demanding (*Z*)-alkene function presumably renders the alternative conformation **32**, in which the C–OH and alkenyl substituent bonds are aligned in parallel fashion, inaccessible, at least at the present reaction temperature.

We also briefly examined the related bromocyclisation reaction and found that the *trans*-(*E*)-cyclohexanol **11b** could be transformed into the bromoperhydrobenzofuran **33** with the same excellent level of stereoselectivity but required reaction in refluxing carbon tetrachloride when *N*-bromosuccinimide was the bromonium ion source. The detailed structure of this bromo analogue **33** was deduced by comparison between its spectral data and those of the corresponding iodo derivative **18** (see below). Finally, partly to extend the synthetic utility of these cyclisations and also to provide additional structural proof of the initial products, we examined methods for the displacement of the iodine by other heteroatoms. Firstly, treatment of the perhydroiodofurans **20** and **18** with silver tetrafluoroborate in hot DMF[11] gave reasonable isolated yields,

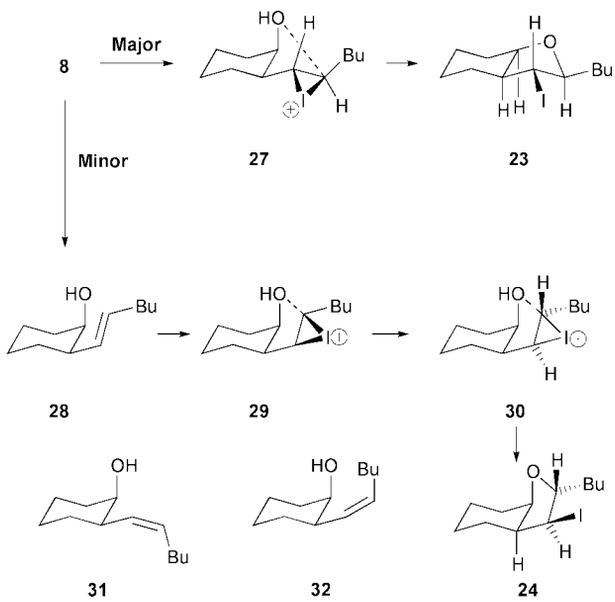


Fig. 1

64 and 77% respectively, of the formyloxy derivatives **34** and **35**. In both cases, the reactions proceeded with complete inversion. This is in direct contrast to the observation made by Bartlett and Ting[11] that a similar reaction of the annulated iodotetrahydropyran **36** led to the corresponding formyloxy derivative **37** but with retention of configuration. This latter result can be explained by assuming anchiomeric assistance from the ring oxygen and hence the intermediacy of the oxonium species **38** and a double inversion process. Presumably, in the present cases, a similar intermediate **39** is not involved as it is just too strained and hence formation of the observed products **34** and **35** proceeds by a straightforward S_N2 process. The 2,3-*trans* stereochemistry in the substrate **18** did not appear to hinder the displacement and formation of the 2,3-*cis* product **35** was equally facile, at least to a first approximation. This mechanism is also involved in the formation of the azide **40** and the sulfide **41** from perhydroiodofuran **18**; again, the unoptimised yields were acceptable and formation of the more hindered 2,3-*cis* isomers did not seem to inhibit the displacement significantly. Clearly, these transformations provide an additional set of options for using the initial iodocyclisation products in synthesis.

In all the foregoing cases, once the basic molecular formulae had been established from the usual analytical and spectroscopic data, the detailed structures and stereochemistries were ascertained using extensive NMR experiments. Firstly, it was vital to prove that the products were in fact ring-fused iodotetrahydrofurans rather than the isomeric oxetanes **43**, which could arise from 4-*exo* cyclisations of the precursors **42**. Initially, this was done by assigning a high field methine resonance in the ^{13}C NMR spectrum, positioned around 30 ppm due to a heavy atom effect,[12] to the CHI group. By a combination of ^{1}H–^{1}H and ^{1}H–^{13}C correlation spectra, this was clearly shown to be positioned between two other methines, one between 75 and 90 ppm and the other at around 30 ppm, assigned to the 2-CHO and 3a-CH groups, clearly precluding the oxetane structures **43**. The remaining methine resonance in the ^{13}C spectra was then correlated with the other ring junction CHO methine carbon. The remaining features of the spectra, together with coupling constant correlations then confirmed the assigned structures as annulated tetrahydrofurans. Finally, difference nuclear Overhauser enhancement spectra were used to assign the respective stereochemistries, some examples of which are shown in Fig. 2 in which only the positive differences of >2% are shown. Other compounds in the series gave much the same results, as detailed in the Experimental section,

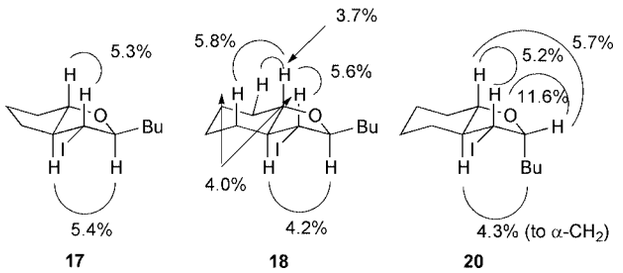
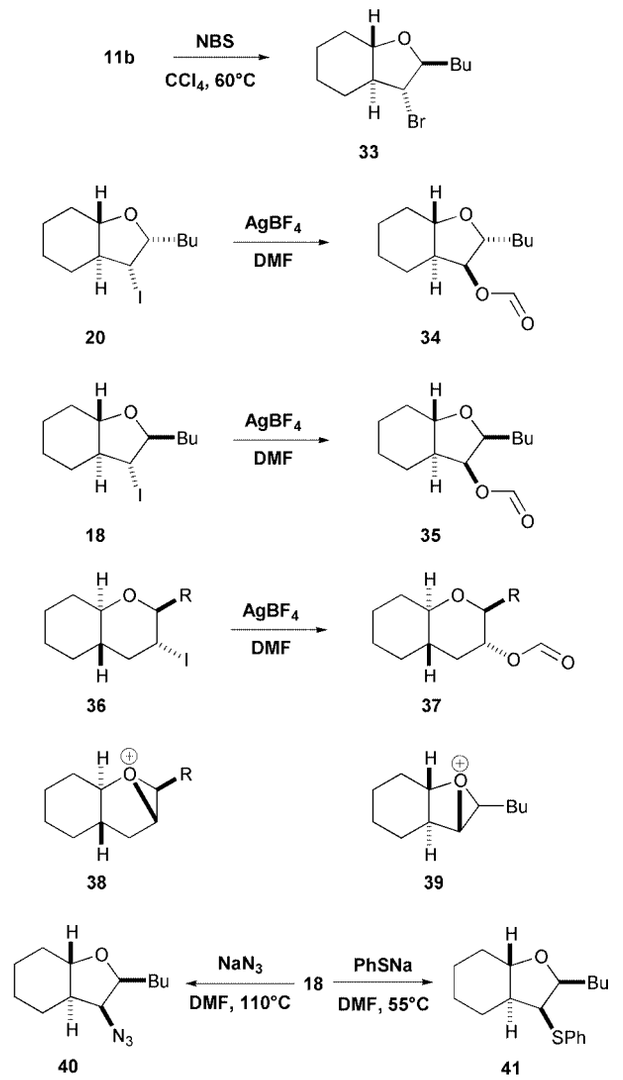
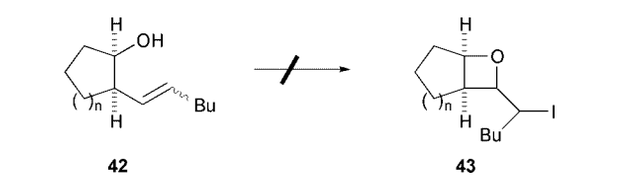


Fig. 2



thus putting the structural assignments on a firm footing. Similar tactics, especially comparative coupling constant data and difference NOE measurements, were used to deduce the stereochemistries of the derived 3-substituted analogues **33**–**35**, **40** and **41**.



In conclusion, these studies indicate that such overall 5-*endo-trig* cyclisations represent a generally useful approach to most of the isomers possible for this type of bicyclic system. Although there will clearly be some limitations, the mild conditions suggest that many substituents could be incorporated into the precursors without a deleterious effect upon the cyclisation, as could additional heteroatoms, especially at various positions in the initial ring.

Experimental

Infrared spectra were recorded using a Perkin-Elmer 1720 FTIR instrument for thin films between NaCl plates. ^{1}H NMR spectra were recorded using a Bruker WM 250 PFT (250), a JEOL EX270 PFT (270) or a Bruker AM 400 PFT (400) spectrometer. Coupling constants are quoted in hertz. ^{13}C spectra were recorded using the same instruments operating at 62.5, 67.5 and 100 MHz respectively. All spectra were recorded using dilute solutions in deuteriochloroform with tetramethylsilane as an internal standard. Molecular weights and mass spectra were determined using either a VG 7070E or an AEI MS 902 spectrometer, operating in the electron impact mode, unless otherwise stated. All reactions were performed under an atmosphere of dry nitrogen unless otherwise stated and, where appropriate, in oven-dried glassware. All solvents were purified and dried using standard methods.[13] Petrol refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether. CC indicates column chromatography using SORBSIL^R (40–60 μm) silica gel. All solutions from work ups were dried by brief exposure to dried magnesium sulfate followed by filtration.

trans-2-(Hex-1-ynyl)cyclopentanol 10a

Butyllithium (21.0 ml of a 1.6 M solution in hexanes, 33.6 mmol) was added dropwise during 0.25 h to a stirred solution of hex-1-yne (3.86 ml, 33.6 mmol) in dry tetrahydrofuran (50 ml), cooled in a solid carbon dioxide–acetone bath. After an additional 20 min at −78 °C, boron trifluoride–diethyl ether (2.75 ml, 22.4 mmol) was added dropwise during 5 min and the resulting solution stirred for a further 10 min, before the addition of a solution of cyclopentene oxide **9a** (1.95 ml, 22.4 mmol) in dry tetrahydrofuran (5 ml) during 2 min. The resulting mixture was stirred for 1.3 h at −78 °C then quenched by the addition of saturated aqueous ammonium chloride (50 ml). The resulting mixture was separated and the aqueous layer extracted with ethyl acetate (3 × 50 ml). The combined organic solutions were dried and evaporated. CC (25% ether–petrol) of the residue gave the *hydroxyacetylene* **10a** (2.30 g, 62%) as a pale yellow oil, ν_{max}/cm^{-1} 3425, 2959, 2873 and 2204; δ_H (250 MHz) 0.90 (3H, t, *J* 6.5, CH_3), 1.90 (1H, br s, OH), 1.26–2.22 (12H, m), 2.54 (1H, m, 2-H) and 4.11 (1H, m, 1-H); δ_C (67.5 MHz) 13.6 (CH_3), 18.4, 21.8, 22.1, 31.1, 31.3, 33.2 (all CH_2), 38.8 (2-CH), 79.6 (1′(2′)-C), 81.3 (2′(1′)-C) and 81.9 (1-CH): *m*/*z* 166 (M^+, 1%), 148 (6), 123 (14), 106 (51), 91 (58), 80 (100), 79 (71) and 67 (68) [Found: M^+, 166.1379. $C_{11}H_{18}O$ requires *M*, 166.1358].

trans-2-(Hex-1-ynyl)cyclohexanol 10b

The foregoing method, when applied to cyclohexene oxide **9b** (4.00 ml, 39.5 mmol) with all other quantities appropriately scaled, gave the *hydroxyacetylene* **10b** (4.43 g, 62%) as a colourless oil, ν_{max}/cm^{-1} 3406, 2932, 2859 and 2234; δ_H (270 MHz) 0.90 (3H, t, *J* 7.1, CH_3), 1.08–2.19 (15H, m), 2.67 (1H, br s, OH) and 3.37 (1H, ddd, *J* 9.4, 9.4 and 3.9, 1-H); δ_C (100 MHz) 13.7 (CH_3), 18.5, 22.0, 24.4, 25.0, 31.2, 31.5, 33.0 (all CH_2), 39.2 (2-CH), 74.0 (1-CH), 81.2 (1′(2′)-C) and 82.9 (2′(1′)-C); m/z 180 (M^+, 2%), 162 (5), 137 (27), 120 (44), 105 (35), 95 (54), 91 (72), 84 (59), 79 (81) and 67 (100) [Found: M^+, 180.1549. $C_{12}H_{20}O$ requires *M*, 180.1514].

(1α,2β,*E*)-2-(Hex-1-enyl)cyclopentanol 11a

Lithium aluminium hydride–bis(tetrahydrofuran) complex (7.67 ml of a 1.0 M solution in toluene, 7.67 mmol) was added dropwise during 2 min to a stirred solution of the hydroxy-

acetylene **10a** (0.49 g, 2.95 mmol) in dry tetrahydrofuran (20 ml) and dry toluene (20 ml) at ambient temperature and the resulting mixture stirred at reflux for 48 h. The cooled, stirred mixture was treated cautiously with ethyl acetate (20 ml) and water (20 ml). After 10 min, the two layers were separated and the aqueous layer extracted with ethyl acetate (3 × 30 ml). The combined organic solutions were dried and evaporated to leave the *trans*-(*E*)-*cyclopentanol* **11a** (0.432 g, 87%) as an oil, ν_{max}/cm^{-1} 3352, 2957, 2928, 2871 and 968; δ_H (250 MHz) 0.89 (3H, t, *J* 6.9, CH_3), 1.21–2.19 (13H, m), 2.21–2.31 (1H, m, 2-H), 3.77–3.85 (1H, m, 1-H), 5.31 (1H, dd, *J* 15.3 and 8.0, 1′-H) and 5.52 (1H, ddd, *J* 15.3, 6.7 and 6.7, 2′-H); δ_C (67.5 MHz) 13.9 (CH_3), 21.0, 22.1, 29.9, 31.6, 32.3, 33.3 (all CH_2), 51.8 (2-CH), 78.5 (1-CH), 131.3 (=CH) and 131.8 (=CH); *m*/*z* 168 (M^+, 4%), 150 (70), 121 (34), 97 (66), 93 (40), 84 (72), 79 (68), 67 (89) and 55 (100) [Found: M^+, 168.1500].

(1α,2β,*E*)-2-(Hex-1-enyl)cyclohexanol 11b

By the foregoing method, starting with the acetylenic alcohol **10b** (0.40 g), the *trans*-(*E*)-*cyclohexanol* **11b** (0.324 g, 80%) was obtained as an oil, ν_{max}/cm^{-1} 3330, 2928, 2856 and 970; δ_H (400 MHz) 0.89 (3H, t, *J* 7.1, CH_3), 1.14–1.83 (14H, m), 2.01–2.04 (1H, m, 2-H), 2.51 (1H, br s, OH), 3.18 (1H, ddd, *J* 9.9, 9.9 and 4.2, 1-H), 5.24 (1H, dd, *J* 15.3 and 8.8, 1′-H) and 5.58 (1H, ddd, *J* 15.3, 6.8 and 6.8, 2′-H); δ_C (100 MHz) 14.0 (CH_3), 22.3, 24.9, 25.4, 31.6, 31.7, 32.4, 33.7 (all CH_2), 50.3 (2-CH), 73.1 (1-CH), 132.0 (=CH) and 133.7 (=CH); *m*/*z* 164 ($M^+ - H_2O$, 37%), 121 (30), 111 (33), 98 (46), 81 (68), 79 (69), 67 (100) and 55 (86) [Found: $M^+ - H_2O$, 164.1587. $C_{12}H_{20}$ requires *M*, 164.1565].[14]

(1α,2β,*Z*)-2-(Hex-1-enyl)cyclopentanol 12a

Quinoline (18.6 μl) was added to a stirred suspension of 5% palladium on barium sulfate (0.02 g) in ethyl acetate (5 ml). After 20 min at ambient temperature, the hydroxyacetylene **10a** (0.40 g) was added and the resulting suspension vigorously stirred under an atmosphere of hydrogen for 3 h then filtered through Kieselguhr. The combined filtrate and ethyl acetate washings were washed with 1 M hydrochloric acid (10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml) then dried and evaporated to leave the *trans*-(*Z*)-*cyclopentanol* **12a** (0.37 g, 92%) as an oil, ν_{max}/cm^{-1} 3340, 3000, 2954, 2871 and 730; δ_H (250 MHz) 0.90 (3H, t, *J* 6.9, CH_3), 1.23–2.43 (13H, m), 2.57–2.72 (1H, m, 2-H), 3.78–3.80 (1H, m, 1-H), 5.21 (1H, dd, *J* 10.8 and 8.0, 1′-H) and 5.47 (1H, ddd, *J* 10.8, 6.3 and 6.3, 2′-H); δ_C (67.5 MHz) 13.9 (CH_3), 21.3, 22.3, 27.3, 30.5, 32.1, 33.4 (all CH_2), 46.6 (2-CH), 79.3 (1-CH), 131.5 (=CH) and 131.9 (=CH); *m*/*z* 168 (M^+, 3%), 150 (77), 121 (84), 93 (61), 79 (87), 67 (97) and 55 (100) [Found: M^+, 168.1501. $C_{11}H_{20}O$ requires *M*, 168.1514].

(1α,2β,*Z*)-2-(Hex-1-enyl)cyclohexanol 12b

By the foregoing method, Lindlar reduction of the hydroxyacetylene **10b** (1.82 g) gave the *trans*-(*Z*)-*cyclohexanol* **12b** (1.71 g, 93%) as an oil, ν_{max}/cm^{-1} 3421, 2998, 2930, 2856 and 730; δ_H (400 MHz) 0.90 (3H, t, *J* 6.9, CH_3), 1.11–2.24 (15H, m), 2.27 (1H, br s, OH), 3.20 (1H, ddd, *J* 9.8, 9.8 and 4.4, 1-H), 5.17 (1H, dd, *J* 10.9 and 9.9, 1′-H) and 5.58 (1H, ddd, *J* 10.9, 7.4 and 7.4, 2′-H); δ_C (67.5 MHz) 13.9 (CH_3), 22.3, 24.7, 25.1, 27.4, 31.4, 32.0, 33.4 (all CH_2), 44.7 (2-CH), 73.7 (1-CH), 131.6 (=CH) and 133.1 (=CH); *m*/*z* 182 (M^+, 8%), 164 (75), 135 (44), 121 (94), 96 (54), 81 (78), 79 (64), 67 (100) and 55 (86) [Found: M^+, 182.1689. $C_{12}H_{22}O$ requires *M*, 182.1671].[14]

(1β,2β,*E*)-2-(Hex-1-enyl)cyclopentanol 14a

Diethyl azodicarboxylate (4.62 ml, 26.5 mmol) was added dropwise during 5 min to a stirred solution of the hydroxyacetylene **10a** (1.00 g, 6.01 mmol), triphenylphosphine (7.57 g, 28.9 mmol) and 4-nitrobenzoic acid (4.82 g, 28.9 mmol) in dry benzene (100 ml) at ambient temperature. After 24 h, the solvent was evaporated and the residue subjected to CC (25% ether–petrol) to give the *nitrobenzoate ester* **13a** (1.88 g, 99%) as a yellow oil, ν_{max}/cm^{-1} 3044, 2959, 2934, 2870, 2739, 1719, 1529, 1349 and 747; δ_H (250 MHz) 0.67 (3H, t, *J* 6.8, CH_3), 0.90–2.10 (12H, m), 2.80–2.82 (1H, m, 2-H), 5.42–5.43 (1H, m, 1-H) and 8.16–8.25 (4H, m, Ar-H); δ_C (67.5 MHz) 13.4 (CH_3), 18.3, 21.7, 22.2, 30.9, 31.3, 31.6 (all CH_2), 36.2 (2-CH), 78.2 (1-CH), 78.2 (1′(2′)-C), 83.0 (2′(1′)-C), 123.3 (2 × ArCH), 130.7 (2 × ArCH), 136.2 (ArC), 150.4 (ArC) and 164.0 (CO); *m*/*z* [CI–CH_4] 316 (M^+ + H), 286, 279, 263, 194 and 138.

The foregoing ester **13a** (0.08 g, 0.25 mmol) was reduced using lithium aluminium hydride–bis(tetrahydrofuran) complex (0.65 ml of a 1.0 M solution in toluene, 0.65 mmol) exactly as described above for the reduction of hydroxyacetylene **11a** to give the *cis*-(*E*)-*cyclopentanol* **14a** (0.038 g, 92%) as an oil, ν_{max}/cm^{-1} 3408, 2956 and 971; δ_H (250 MHz) 0.90 (3H, t, *J* 6.7, CH_3), 1.16–2.10 (12H, m), 2.37–2.46 (1H, m, 2-H), 4.08–4.12 (1H, m, 1-H), 5.54 (1H, dd, *J* 15.6 and 11.0, 1′-H) and 5.56 (1H, ddd, *J* 15.6, 5.9 and 5.9, 2′-H); δ_C (67.5 MHz) 13.9 (CH_3), 22.0, 22.2, 27.9, 31.7, 32.5, 33.8 (all CH_2), 48.7 (2-CH), 75.4 (1-CH), 128.4 (=CH) and 133.5 (=CH); *m*/*z* 168 (M^+, 2%), 150 (39), 121 (22), 111 (27), 97 (50), 93 (30), 79 (59), 67 (72), 55 (82) and 41 (100) [Found: M^+, 168.1476].

(1β,2β,*E*)-2-(Hex-1-enyl)cyclohexanol 14b

Mitsunobu reaction of the cyclohexanol **10b** (1.94 g, 10.6 mmol) exactly as described above, but with a final purification by CC in 3% ether–petrol gave the *nitrobenzoate ester* **13b** (3.01 g, 89%) as a yellow oil, ν_{max}/cm^{-1} 3054, 2935, 2861, 2228, 1723, 1607, 1529, 1343 and 873; δ_H (250 MHz) 0.84–0.89 (3H, m, CH_3), 1.40–2.32 (14H, m), 2.95–3.13 (1H, m, 2-H), 5.05–5.15 (1H, m, 1-H) and 8.26–8.28 (4H, m, Ar-H); δ_C (67.5 MHz) 13.5 (CH_3), 18.3, 21.8, 22.0, 22.9 28.0, 29.7, 31.1 (all CH_2), 32.9 (2-CH), 74.4 (1-CH), 79.2 (1′(2′)-C), 85.0 (2′(1′)-C), 123.4 (2 × ArCH), 130.7 (2 × ArCH), 138.7 (ArC), 151.3 (ArC) and 164.0 (CO); *m*/*z* 329 (M^+, 1%), 260 (9), 162 (78), 150 (100), 104 (96), 91 (51) and 76 (53) [Found: M^+, 329.1637. $C_{19}H_{23}NO_4$ requires *M*, 329.1627] [Found: C, 69.3; H, 7.2; N, 4.4. $C_{19}H_{23}NO_4$ requires C, 69.3; H, 7.0; N, 4.3%].

Reduction of the foregoing ester **13b** (0.075 g, 0.23 mmol) as described above gave the *cis*-(*E*)-*cyclohexanol* **14b** (0.040 g, 95%) as an oil, ν_{max}/cm^{-1} 3403, 2929, 2857 and 975; δ_H (250 MHz) 0.90 (3H, t, *J* 7.0, CH_3), 1.22–2.26 (16H, m), 3.78–3.80 (1H, m, 1-H), 5.51–5.55 (2H, m, 1′- and 2′-H); δ_C (100 MHz) 13.9 (CH_3), 21.2, 22.2, 24.1, 26.5, 31.8, 32.0, 32.6 (all CH_2), 44.3 (2-CH), 69.7 (1-CH), 130.7 (=CH) and 132.7 (=CH); *m*/*z* 182 (M^+, 3%), 164 (51), 121 (41), 111 (39), 98 (61), 91 (43), 79 (65), 67 (100) and 55 (82) [Found: M^+, 182.1642].

cis-2-(Hex-1-ynyl)cyclopentanol 15a

The nitrobenzoate **13a** (1.00 g, 3.17 mmol) was added to a solution of sodium hydroxide (0.634 g, 15.9 mmol) in 95% methanol and the resulting solution stirred at ambient temperature overnight, then the bulk of the solvent was evaporated. The residue was partitioned between water (15 ml) and ether (20 ml) and the separated aqueous layer extracted with ether (2 × 20 ml). The combined ether solutions were dried and evaporated. CC (5% ethyl acetate–petrol) then gave the *hydroxyacetylene* **15a** (0.40 g, 76%) as an oil, ν_{max}/cm^{-1} 3472, 2956, 2872 and 2233; δ_H (270 MHz) 0.98 (3H, t, *J* 7.1, CH_3), 1.23–2.13 (13H, m), 2.69–2.71 (1H, m, 2-H) and 4.16–4.20 (1H, m, 1-H); δ_C (67.5 MHz) 13.5 (CH_3), 18.4, 21.9, 22.2, 30.4, 31.1, 32.9 (all CH_2), 38.4 (2-CH), 74.0 (1-CH), 78.8 (1′(2′)-C) and 84.6 (2′(1′)-C); *m*/*z* 166 (M^+, 2%), 148 (11), 119 (59), 106 (46), 91 (58), 80 (100), 79 (56) and 67 (61) [Found: M^+, 166.1351].

cis-2-(Hex-1-ynyl)cyclohexanol 15b

Saponification of the nitrobenzoate **13b** (2.00 g) exactly as described above gave, after CC (17% ethyl acetate–petrol) the *hydroxyacetylene* **15b** (0.89 g, 79%) as a colourless oil, ν_{max}/cm^{-1} 3420, 2933, 2858 and 2362; δ_H (270 MHz) 1.01 (3H, t, *J* 6.9, CH_3), 1.26–2.33 (15H, m), 2.70–2.88 (1H, m, 2-H) and 3.70–3.72 (1H, m, 1-H); δ_C (67.5 MHz) 13.6 (CH_3), 18.4, 21.9, 22.3, 22.7, 29.1, 31.2, 31.3 (all CH_2), 35.9 (2-CH), 69.8 (1-CH), 79.5 (1′(2′)-C) and 84.4 (2′(1′)-C); *m*/*z* 180 (M^+, 10%), 162 (8), 137 (32), 120 (29), 105 (39), 91 (65), 79 (85), 67 (100) and 55 (54) [Found: M^+, 180.1490].

(1β,2β,*Z*)-2-(Hex-1-enyl)cyclopentanol 16a

Lindlar reduction of the cyclopentanol **15a** (0.90 g), exactly as described above, gave the *cis*-(*Z*)-*cyclopentanol* **16a** (0.85 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 3380, 3010, 2957, 2871 and 748; δ_H (400 MHz) 0.91 (3H, t, *J* 7.1, CH_3), 1.21–2.11 (13H, m), 2.67–2.74 (1H, m, 2-H), 4.13–4.15 (1H, m, 1-H), 5.39 (1H, dd, *J* 10.9 and 7.3, 1′-H) and 5.57 (1H, ddd, *J* 10.9, 7.3 and 7.3, 2′-H); δ_C (100 MHz) 13.9 (CH_3), 22.3 (× 2), 27.7, 30.1, 31.9, 34.4 (all CH_2), 43.6 (2-CH), 75.9 (1-CH), 128.7 (=CH) and 133.0 (=CH); *m*/*z* 168 (M^+, 2%), 150 (73), 121 (65), 93 (61), 79 (100), 67 (89) and 55 (87) [Found: M^+, 168.1539] [Found: C, 78.1; H, 12.3. $C_{11}H_{20}O$ requires C, 78.5; H, 12.0%].

(1β,2β,*Z*)-2-(Hex-1-enyl)cyclohexanol 16b

Lindlar reduction of the cyclohexanol **15b** (0.40 g), exactly as described above, gave the *cis*-(*Z*)-*cyclohexanol* **16b** (0.38 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 3394, 3009, 2930, 2856 and 733; δ_H (250 MHz) 0.90 (3H, t, *J* 6.9, CH_3), 1.31–2.07 (15H, m), 2.58–2.61 (1H, m, 2-H), 3.74–3.77 (1H, m, 1-H) and 5.48–5.53 (2H, m, 1′- and 2′-H); δ_C (67.5 MHz) 13.9 (CH_3), 21.6, 22.3, 23.4, 27.4, 28.2, 32.0, 32.1 (all CH_2), 39.4 (2-CH), 70.7 (1-CH), 129.5 (=CH) and 132.2 (=CH); *m*/*z* 182 (M^+, 5%), 164 (67), 135 (35), 121 (63), 107 (28), 98 (54), 93 (39), 79 (77), 67 (100) and 55 (85) [Found: M^+, 182.1663].

General procedure for iodocyclisations

Sodium hydrogen carbonate (0.28 g, 3.33 mmol) was stirred with the homoallylic alcohol (1.11 mmol) in dry acetonitrile (6 ml) at 0 °C for 5 min then iodine (0.845 g, 3.33 mmol) was added in one portion and stirring continued for the time stated, maintaining the mixture at 0 °C with exclusion of light. The mixture was then diluted with ether (10 ml) and washed with saturated aqueous sodium thiosulfate (10 ml). The aqueous washings were extracted with ether (3 × 20 ml) and the combined organic solutions dried and evaporated. The residue was purified by CC using the specified solvents.

(2β,3α,3aα,6aβ)-2-Butyl-3-iodohexahydro-2*H*-cyclopenta[*b*]-furan 17

By the general procedure, iodocyclisation of the *trans*-(*E*)-cyclopentanol **11a** (0.22 g, 1.19 mmol) for 48 h, followed by CC (5% ether–petrol) gave the (*2β,3α,3aα,6aβ*)-*iodofuran* **17** (0.102 g, 29%) as a colourless oil, ν_{max}/cm^{-1} 2956, 2934, 2867, 1123 and 1084; δ_H (400 MHz) 0.92 (3H, t, *J* 7.2, CH_3), 1.19–2.18 (12H, m), 2.46 (1H, dddd, *J* 11.7, 11.5, 11.3 and 6.5, 3a-H), 3.65 (1H, dd, *J* 11.5 and 8.0, 3-H), 3.73 (1H, ddd, *J* 11.3, 11.3 and 6.5, 6a-H) and 4.69 (1H, ddd, *J* 8.0, 8.0 and 3.7, 2-H); δ_C (100 MHz) 13.9 (CH_3), 20.1, 22.6 (both CH_2), 24.8 (3-CH), 25.7, 25.9, 28.1, 33.3 (all CH_2), 61.9 (3a-CH), 86.8 (2-CH) and 98.0 (6a-CH); *m*/*z* 294 (M^+, 3%), 208 (37), 149 (5), 110 (12), 81 (100), 79 (11), 67 (23) and 55 (13) [Found: M^+, 294.0492. $C_{11}H_{19}IO$ requires *M*, 294.0481].

NOE data: 2-H–3a-H (5.4%); 3-H–6a-H (5.3%).

(2β,3α,3aα,7aβ)-2-Butyl-3-iodooctahydrobenzofuran 18

By the general procedure, iodocyclisation of the *trans*-(*E*)-cyclohexanol **11b** (0.20 g, 1.10 mmol) for 1.3 h, followed by CC (5% ether–petrol) gave the (*2β,3α,3aα,7aβ*)-*iodofuran* **18** (0.332 g, 98%) as a colourless oil, ν_{max}/cm^{-1} 2931, 2856, 1120, 1094 and 1075; δ_H (400 MHz) 0.92 (3H, t, *J* 7.2, CH_3), 1.02 (1H, dddd, *J* 12.3, 12.3, 12.3 and 3.7, 4-H_{ax}), 1.26–1.81 (12H, m), 1.97–2.00 (1H, m, 4-H_{eq}), 2.00–2.07 (1H, m, 7-H_{eq}), 3.15 (1H, ddd, *J* 10.5, 10.5 and 4.0, 7a-H), 3.52 (1H, dd, *J* 11.2 and 8.1, 3-H) and 4.20 (1H, ddd, *J* 8.1, 8.1 and 3.9, 2-H); δ_C (100 MHz) 14.0 (CH_3), 22.7, 24.4, 25.3, 27.2, 28.2 (all CH_2), 29.9 (3-CH), 31.5, 33.2 (both CH_2), 56.2 (3a-CH), 80.7 (2-CH) and 87.1 (7a-CH); *m*/*z* 308 (M^+, 2%), 251 (35), 222 (22), 181 (55), 163 (17), 124 (84), 95 (100) and 81 (31) [Found: M^+, 308.0657. $C_{12}H_{21}IO$ requires *M*, 308.0637] [Found: C, 46.8; H, 6.7. $C_{12}H_{21}IO$ requires C, 46.7; H, 6.9%].

NOE data: 2-H–3a-H_{ax} (4.2%); 3-H–7a-H_{ax} (5.6%); 3-H–4-H_{ax} (4.0%); 4-H_{ax}–7a-H_{ax} (5.8%); 7-H_{eq}–7a-H_{ax} (3.7%).

Alternative cyclisation conditions. *i*) The *trans*-(*E*)-cyclohexanol **11b** (0.20 g, 1.10 mmol) was cyclized by the general procedure but using powdered sodium hydroxide (0.132 g, 3.33 mmol) as base in place of sodium hydrogen carbonate. Work-up after 1.5 h followed by CC gave the (*2β,3α,3aα,7aβ*)-*iodofuran* **18** (0.308 g, 91%) which displayed spectroscopic and analytical data identical to the foregoing sample.

ii) The *trans*-(*E*)-cyclohexanol **11b** (0.20 g, 1.10 mmol) was cyclized by the general procedure but in the absence of any base. Work-up after 1.5 h followed by CC gave the (*2β,3α,3aα,7aβ*)-*iodofuran* **18** (0.271 g, 80%) which displayed spectroscopic and analytical data identical to the foregoing sample.

iii) To a stirred solution of the *trans*-(*E*)-cyclohexanol **11b** (0.500 g, 2.74 mmol) in dry dichloromethane (20 ml) was added *N*-iodosuccinimide (0.679 g, 3.02 mmol) and the resulting solution stirred in the dark for 5 h then the solvent evaporated. The residue was triturated with ether (20 ml) and the resulting suspension filtered and the filtrate evaporated. CC gave the (*2β,3α,3aα,7aβ*)-*iodofuran* **18** (0.670 g, 79%) which displayed spectroscopic and analytical data identical to the foregoing sample.

iv) The *trans*-(*E*)-cyclohexanol **11b** (0.20 g, 1.10 mmol) was cyclized by the general procedure but using triethylamine (0.46 ml, 3.30 mmol) as base in place of sodium hydrogen carbonate. After 30 h at 0 °C, no tetrahydrofuran formation could be detected by either TLC or ^{1}H NMR analysis.

v) The *trans*-(*E*)-cyclohexanol **11b** (0.20 g, 1.10 mmol) was cyclized by the general procedure but using *N*,*N*-diisopropylethylamine (Hünig's base; 0.575 ml, 3.30 mmol) as base in place of sodium hydrogen carbonate. After 30 h at 0 °C, no tetrahydrofuran formation could be detected by either TLC or ^{1}H NMR analysis.

(2α,3α,3aα,7aβ)-2-Butyl-3-iodooctahydrobenzofuran 20

By the general procedure, iodocyclisation of the *trans*-(*Z*)-cyclohexanol **12b** (0.22 g, 1.21 mmol) for 16 h, followed by CC (17% ether–petrol) gave the (*2α,3α,3aα,7aβ*)-*iodofuran* **20** (0.28 g, 75%) as a colourless oil, ν_{max}/cm^{-1} 2933, 2857 and 1116; δ_H (400 MHz) 0.92 (3H, t, *J* 7.2, CH_3), 1.03 (1H, dddd, *J* 12.3, 12.2, 11.7 and 3.7, 4-H_{ax}), 1.16–1.52 (9H, m), 1.66 (1H, dddd, *J* 11.7, 11.0, 10.8 and 3.1, 3a-H), 1.76–1.83 (2H, m), 2.02–2.10 (2H, m, 4- and 7-H_{eq}), 3.00 (1H, ddd, *J* 10.8, 10.4 and 3.9, 7a-H), 3.75 (1H, ddd, *J* 8.2, 8.2 and 3.9, 2-H) and 4.07 (1H, dd, *J* 11.0 and 8.2, 3-H); δ_C (100 MHz) 14.1 (CH_3), 22.6, 24.5, 25.5, 27.4, 28.8, 31.4 (all CH_2), 33.5 (3-CH), 39.1 (CH_2), 55.5 (3a-CH), 77.9 (2-CH) and 82.2 (7a-CH); *m*/*z* 251 (M^+ − Bu, 11%), 222 (14), 181 (13), 124 (28), 95 (100), 85 (20), 67 (25) and 55 (20); *m*/*z* [CI − NH_3] 326 (M^+ + NH_4), 309 (M^+ + H), 258, 240 and 181 [Found: C, 46.6; H, 6.9. $C_{12}H_{21}IO$ requires C, 46.7; H, 6.9%].

NOE data: 2-H–3-H (11.6%); 2-H–7a-H_{ax} (5.7%); 2-α-CH_2–3a-H (4.3%); 3-H–7a-H_{ax} (5.2%).

(2β,3α,3aα,6aα)-2-Butyl-3-iodohexahydro-2*H*-cyclopenta-[*b*]furan 21 and (2α,3β,3aα,6aα)-2-butyl-3-iodohexahydro-2*H*-cyclopenta[*b*]furan 22

By the general procedure, iodocyclisation of the *cis*-(*E*)-cyclopentanol **14a** (0.050 g, 0.297 mmol) for 1.5 h, followed by CC (1% ether–petrol) gave i) the (*2β,3α,3aα,6aα*)-*iodofuran* **21** (0.044 g, 50%) as a colourless oil, ν_{max}/cm^{-1} 2955, 2928, 2859, 1123 and 1103; δ_H (400 MHz) 0.91 (3H, t, *J* 7.1, CH_3), 1.26–1.93 (12H, m), 2.97–2.99 (1H, m, 3a-H), 3.20 (1H, dd, *J* 9.7 and 7.5, 3-H), 3.74 (1H, ddd, *J* 7.5, 7.5 and 0.4, 2-H) and 4.45 (1H, dd, *J* 6.9 and 5.7, 6a-H); δ_C (100 MHz) 13.9 (CH_3), 22.7, 23.0, 28.2, 30.7, 30.8 (all CH_2), 32.2 (3-CH), 33.6 (CH_2), 55.5 (3a-CH), 83.8 (6a-CH) and 86.5 (2-CH); *m/z* [CI–NH_3] 295 (M^+ + H), 207, 168 and 92 and ii) the (*2α,3β,3aα,6aα*)-*iodofuran* **22** (0.035 g, 40%) as a colourless oil, ν_{max}/cm^{-1} 2956, 2925, 2860, 1131 and 1089; δ_H (400 MHz) 0.91 (3H, t, *J* 7.2, CH_3), 1.25–1.90 (11H, m), 1.92–2.01 (1H, m, 6–H), 2.73 (1H, dddd, *J* 9.5, 8.9, 6.7 and 6.5, 3a-H), 3.82 (1H, ddd, *J* 7.2, 7.2 and 2.6, 2-H), 3.89 (1H, dd, *J* 9.5 and 7.2, 3-H) and 4.54 (1H, ddd, *J* 6.5, 6.2 and 3.4, 6a-H); δ_C (100 MHz) 14.0 (CH_3), 22.7, 24.9, 28.1, 31.6 (all CH_2), 32.9 (3-CH), 33.8 (CH_2), 35.6 (6-CH_2), 48.4 (3a-CH), 82.8 (6a-CH) and 83.5 (2-CH); *m/z* [CI − NH_3] 312 (M^+ + NH_4), 295 (M^+ + H), 167 and 91.

By the general procedure, iodocyclisation of the *cis*-(*E*)-cyclopentanol **14a** (0.100 g, 0.601 mmol) for 5 h at −78 °C in a mixture of acetonitrile (3 ml) and dichloromethane (12 ml) gave the same two iodofurans (**21** and **22**) (0.156 g, 88%) in a ratio of 1.3:1 which exhibited spectroscopic data identical to the foregoing compounds.

NOE data: (*2β,3α,3aα,6aα*)-*iodofuran* **21** 2-H–3a-H (3.4%); 2-H–6a-H (4.1%); 3a-H–6a-H (7.4%); (*2α,3β,3aα,6aα*)-*iodofuran* **22** 3-H–3a-H (11.7%); 3a-H–6a-H (7.6%).

(2β,3α,3aα,7aα)-2-Butyl-3-iodooctahydrobenzofuran 23

By the general procedure, iodocyclisation of the *cis*-(*E*)-cyclohexanol **14b** (0.080 g, 0.44 mmol) for 5 h, followed by CC (1% ether–petrol) gave the (*2β,3α,3aα,7aα*)-*iodofuran* **23** (0.115 g, 73%) as a colourless oil mixed with an inseparable isomer, in a ratio of 5:1. The mixture showed ν_{max}/cm^{-1} 2930, 2855, 1146, 1116 and 1088; *m/z* [FAB] 309 (M^+ + H, 15%), 211 (8), 181 (24), 154 (41), 137 (32), 95 (38), 81 (65), 69 (59) and 55 (100) [Found: C, 46.7; H, 6.8%]. The major isomer **23** showed δ_H (400 MHz) 0.92 (3H, t, *J* 7.2, CH_3), 1.30–1.74 (14H, m), 2.35–2.43 (1H, m, 3a-H), 3.66 (1H, dd, *J* 6.6 and 5.1, 3-H), 4.04–4.08 (1H, m, 7a-H) and 4.26 (1H, ddd, *J* 7.0, 7.0 and 5.1, 2-H); δ_C (100 MHz) 14.0 (CH_3), 21.4, 22.9, 23.2, 27.3, 28.3, 29.1 (all CH_2), 32.1 (3-CH), 34.7 (CH_2), 49.9 (3a-CH), 75.5 (7a-CH) and 88.7 (2-CH). The minor isomer (**24**) showed δ_C (100 MHz) 14.0 (CH_3), 19.9, 22.9, 25.0, 28.4, 28.9 (all CH_2), 33.1 (3-CH), 33.9, 34.7 (both CH_2), 43.0 (3a-CH), 74.5 (7a-CH) and 84.5 (2-CH).

By the general procedure, iodocyclisation of the *cis*-(*E*)-cyclohexanol **14b** (0.100 g, 0.549 mmol) for 2.5 h at −78 °C in a mixture of acetonitrile (3 ml) and dichloromethane (12 ml) gave the same two iodofurans (**23** and **24**) (0.166 g, 98%) in a ratio of 10:1 which exhibited spectroscopic data identical to the foregoing compounds.

NOE data for (*2β,3α,3aα,7aα*)-*iodofuran* **23**: 2-H–3a-H (2.8%); 2-H–7a-H (4.1%); 3a-H–7a-H (6.3%).

(2α,3α,3aα,6aα)-2-Butyl-3-iodohexahydro-2*H*-cyclopenta-[*b*]furan 25

By the general procedure, iodocyclisation of the *cis*-(*Z*)-cyclopentanol **16a** (0.050 g, 0.297 mmol) for 24 h, followed by CC (5% ether–petrol) gave the (*2α,3α,3aα,6aα*)-*iodofuran* **25** (0.084 g, 96%) as a colourless oil, ν_{max}/cm^{-1} 2956, 2930, 2871, 2864 and 1153; δ_H (400 MHz) 0.91 (3H, t, *J* 7.1, CH_3), 1.25–1.90 (12H, m), 3.04 (1H, ddd, *J* 6.5, 6.5 and 3.5, 2-H), 3.13–3.19 (1H, m, 3a-H), 4.20 (1H, dd, *J* 3.5 and 2.0, 3-H) and 4.76 (1H, ddd, *J* 5.4, 5.4 and 2.6, 6a-H); δ_C (100 MHz) 14.0 (CH_3), 22.6, 25.3, 28.1, 32.6, 34.5, 36.4, (all CH_2), 40.3 (3-CH), 56.4 (3a-CH), 80.8 (2-CH) and 83.1 (6a-CH); *m/z* [FAB] 295 (M^+ + H, 3%), 167 (27), 136 (23), 109 (27), 95 (42), 81 (55), 69 (76), 57 (97) and 55 (100) [Found: C, 45.1; H, 6.7. $C_{11}H_{19}IO$ requires C, 44.9; H, 6.5%].

NOE data: 2-H–3-H (7.2%); 3-H–3a-H (4.0%); 3a-H–6a-H (7.2%).

(2α,3α,3aα,7aα)-2-Butyl-3-iodooctahydrobenzofuran 26

By the general procedure, iodocyclisation of the *cis*-(*Z*)-cyclohexanol **16b** (0.156 g, 0.856 mmol) for 22 h, followed by CC (5% ether–petrol) gave the (*2α,3α,3aα,7aα*)-*iodofuran* **26** (0.248 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 2931, 2858 and 1119; δ_H (400 MHz) 0.91 (3H, t, *J* 7.1, CH_3), 1.16–2.07 (14H, m), 2.49–2.61 (1H, m, 3a-H), 3.63 (1H, ddd, *J* 6.2, 6.2 and 4.4, 2-H), 4.32 (1H, dd, *J* 4.4 and 1.9, 3-H) and 4.52 (1H, app. q, *J* 3.8, 7a-H); δ_C (100 MHz) 14.0 (CH_3), 20.4, 22.6, 23.5, 28.2, 28.4 (× 2), 39.6 (all CH_2), 41.1 (3-CH), 50.7 (3a-CH), 74.5 (7a-CH) and 79.0 (2-CH); *m/z* [FAB] 309 (M^+ + H, 14%), 291 (16), 181 (45), 165 (40), 109 (44), 95 (72), 81 (81), 67 (67) and 55 (100) [Found: C, 46.6; H, 6.9. $C_{12}H_{21}IO$ requires C, 46.7; H, 6.9%]

NOE data: 2-H–3-H (8.5%); 3-H–3a-H (4.2%); 3a-H–7a-H (8.5%).

(2β,3α,3aα,7aβ)-3-Bromo-2-butyloctahydrobenzofuran 33

N-Bromosuccinimide (0.351 g, 1.97 mmol) was added in one portion to a stirred solution of the *trans*-(*E*)-cyclohexanol **11b** (0.30 g, 1.65 mmol) in dry carbon tetrachloride (10 ml) at ambient temperature. The resulting mixture was refluxed for 4 h, then cooled and the solvent evaporated. CC (5% ether–petrol) of the residue gave the (*2β,3α,3aα,7aβ*)-*bromofuran* **33** (0.297 g, 69%) as a colourless oil, ν_{max}/cm^{-1} 2937, 2859, 1095 and 1076; δ_H (250 MHz) 0.92 (3H, t, *J* 6.9, CH_3), 1.02–2.12 (15H, m), 3.22 (1H, ddd, *J* 10.6, 10.5 and 4.0, 7a-H), 3.57 (1H, dd, *J* 10.7 and 7.6, 3-H) and 4.08 (1H, ddd, *J* 7.6, 7.6 and 4.3, 2-H); δ_C (62.5 MHz) 14.1 (CH_3), 22.7, 24.2, 25.4, 26.9, 28.2, 32.0, 34.0 (all CH_2), 54.1 (3(3a)-CH), 54.9 (3a(3)-CH), 80.6 (2(7a)-CH) and 86.1 (7a(2)-CH); *m/z* 262 (M^+ (Br^{81}), 6%), 260 (M^+ (Br^{79}), 6), 205 (39), 203 (41), 176 (36), 174 (38), 123 (38), 95 (100), 81 (95) and 67 (53) [Found: C, 55.2; H, 7.6. $C_{12}H_{21}BrO$ requires C, 55.4; H, 8.1%].

(2α,3β,3aα,7aβ)-2-Butyl-3-formyloxyoctahydrobenzofuran 34

To a stirred solution of the (*2α,3α,3aα,7aβ*)-*iodofuran* **20** (0.060 g, 0.195 mmol) in dry *N*,*N*-dimethylformamide (10 ml) was added silver tetrafluoroborate (0.076 g, 0.39 mmol). The resulting mixture was stirred at 70 °C for 48 h, then cooled, diluted with ether (10 ml) and filtered through Kieselguhr. The solid was washed with ether (2 × 5 ml) and the combined filtrates washed with 1 M hydrochloric acid (15 ml), saturated aqueous sodium bicarbonate (15 ml) and brine (15 ml) then dried and evaporated. CC (10% ether–petrol) separated the *formyloxy-THF* **34** (0.028 g, 64%) as a colourless oil, ν_{max}/cm^{-1} 2932, 2860, 1726, 1174 and 1067; δ_H (400 MHz) 0.92 (3H, t, *J* 7.0, CH_3), 1.19–1.23 (1H, m, 7-H_{eq}), 1.30–1.35 (1H, m, 3a-H), 1.21–1.82 (12H, m), 2.17–2.20 (1H, m, 7-H_{ax}), 3.41 (1H, ddd, *J* 10.6, 10.6 and 3.9, 7a-H), 3.83 (1H, dd, *J* 6.6 and 6.6, 2-H), 5.08 (1H, app. d, *J* 5.1, 3-H) and 8.08 (1H, app. s, CHO); δ_C (100) 14.0 (CH_3), 22.7, 23.9, 25.4, 27.7, 29.7, 31.7, 34.0 (all CH_2), 48.2 (3a-CH), 79.0, 80.3, 85.0 (all CH) and 160.6 (CO); *m/z* 180 (M^+ − HCO_2H, 11%), 169 (22), 138 (56), 123 (29), 112 (37), 94 (100), 79 (39), 69 (21), 67 (25) and 55 (25) [Found: M^+ − HCO_2H, 180.1499. $C_{12}H_{20}O$ requires *M*, 180.1514]; *m/z* [FAB] 197 (M^+ + H − HCO, 16%), 181 (34), 123 (21), 107 (37), 95 (27), 81 (36), 68 (34) and 56 (57) [Found: M^+ + H − HCO, 197.1567. $C_{12}H_{21}O_2$ requires *M*, 197.1542].

NOE data: 2-H–3-H (2.7%); 2-H–7a-H (4.7%); 3-H–3a-H (13.6%).

(2β,3β,3aα,7aβ)-2-Butyl-3-formyloxyoctahydrobenzofuran 35

The foregoing method starting with the (*2β*,*3a*,*3aα*,*7aβ*)-*iodofuran* **18** (0.049 g, 0.161 mmol) gave the *formyloxy-THF* **35** (0.028 g, 77%) as a colourless oil, ν_{max}/cm^{-1} 2934, 2861, 1727 and 1174; δ_H (400 MHz) 0.89 (3H, t, *J* 7.1, CH_3), 1.17–1.21 (1H, m, 7-H_{eq}), 1.56–1.64 (1H, m, 3a-H), 1.17–1.80 (12H, m), 2.09–2.19 (1H, m, 7-H_{ax}), 3.52 (1H, ddd, *J* 10.8, 10.8 and 4.0, 7a-H), 4.15 (1H, ddd, *J* 8.5, 4.2 and 4.2, 2-H), 5.52 (1H, dd, *J* 4.2 and 4.0, 3-H) and 8.16 (1H, app. s, CHO); δ_C (100 MHz) 14.0 (CH_3), 22.7, 23.9, 24.4, 25.3, 28.6, 29.7, 32.0 (all CH_2), 49.7 (3a-CH), 75.3, 79.5, 81.4 (all CH) and 160.4 (CO); *m*/*z* [FAB] 227 (M^+ + H, 14%), 226 (6), 225 (32), 181 (100), 154 (24), 137 (30), 107 (22), 95 (44), 85 (61), 81 (63), 66 (44) and 54 (63) [Found: M^+ + H, 227.1657. $C_{13}H_{23}O_3$ requires *M*, 227.1647].

NOE data: 2-H–3-H (9.8%); 2-H–3a-H (6.4%); 3-H–3a-H (6.9%); 7-H_{eq}–7a-H_{ax} (6.2%).

(2β,3β,3aα,7aβ)-3-Azido-2-butyloctahydrobenzofuran 40

Sodium azide (0.042 g, 0.649 mmol) was added in one portion to a stirred solution of (*2β*,*3a*,*3aα*,*7aβ*)-*iodofuran* **18** (0.200 g, 0.649 mmol) in dry *N*,*N*-dimethylformamide (15 ml) and the resulting mixture heated at 110 °C for 73 h (TLC monitoring). The cooled solution was diluted with ether (20 ml) and water (20 ml) and the resulting layers separated. The aqueous layer was extracted with ether (2 × 20 ml) and the combined organic solutions washed with water (4 × 20 ml) then dried and evaporated. CC (5% ether–petrol) of the residue gave the *azide* **40** (0.091 g, 63%) as a colourless oil, ν_{max}/cm^{-1} 2936, 2861, 2101 and 1146; δ_H (400 MHz) 0.92 (3H, t, *J* 7.1, CH_3), 1.19–1.25 (1H, m, 7-H_{eq}), 1.57–1.64 (1H, m, 3a-H), 1.20–1.80 (12H, m), 2.04–2.14 (1H, m, 7-H_{ax}), 3.44 (1H, ddd, *J* 11.9, 10.6 and 4.0, 7a-H), 3.98 (1H, dd, *J* 4.2 and 4.0, 3-H) and 4.07–4.12 (1H, m, 2-H); δ_C (67.5 MHz) 14.0 (CH_3), 22.8, 23.9, 24.9, 25.3, 28.7, 30.9, 31.9 (all CH_2), 50.8 (3a-CH), 66.9 (3-CH), 79.2 and 82.1 (2- and 7a-CH) and 160.4 (CO); *m*/*z* 167 (M^+ − Bu, 3%), 138 (9), 108 (22), 85 (68), 82 (48), 67 (100), 57 (50) and 54 (38) [Found: C, 64.5; H, 9.4; N, 18.4. $C_{12}H_{21}N_3O$ requires C, 64.5; H, 9.5; N, 18.8%].

NOE data: 2-H–3-H (11.4%); 2-H–3a-H (5.0%); 3-H–3a-H (8.6%).

(2β,3β,3aα,7aβ)-2-Butyl-3-(phenylsulfanyl)octahydrobenzofuran 41

Sodium hydride (0.020 g of a 60% dispersion in oil, 0.487 mmol) was washed with dry pentane (3 × 3 ml) and dried under a flow of nitrogen. A solution of thiophenol (50 µl, 0.487 mmol) in dry *N*,*N*-dimethylformamide (10 ml) was then added dropwise and the resulting mixture stirred for 10 min at ambient temperature. A solution of the (*2β*,*3a*,*3aα*,*7aβ*)-*iodofuran* **18** (0.100 g, 0.324 mmol) in dry *N*,*N*-dimethylformamide (5 ml) was then added and the resulting mixture heated at 55 °C for 30 h (TLC monitoring). The cooled mixture was carefully diluted with water (10 ml) and extracted with ether (2 × 10 ml). The combined extracts were washed with water (4 × 10 ml) then dried and evaporated. CC (1% ether–petrol) separated the *sulfide* **41** (0.043 g, 45%) as a colourless oil, ν_{max}/cm^{-1} 3057, 2932, 2858, 1146 and 1075; δ_H (400 MHz) 0.81 (3H, t, *J* 7.1, CH_3), 1.05–1.19 (1H, m, 7-H_{eq}), 1.06–1.74 (11H, m), 1.44 (1H, dddd, *J* 12.1, 12.1, 12.1 and 3.4, 4-H_{ax}), 1.80–1.87 (1H, m, 3a-H), 2.07–2.10 (1H, m, 7-H_{ax}), 3.49 (1H, ddd, *J* 10.6, 10.6 and 5.9, 7a-H), 3.78 (1H, dd, *J* 5.0 and 5.0, 3-H), 4.19–4.24 (1H, m, 2-H), 7.05–7.25 (3H, m) and 7.31 (2H, d, *J* 7.3); δ_C (100 MHz) 14.0 (CH_3), 22.8, 23.9, 25.3 (all CH_2), 26.6 (4-CH_2), 28.9 (CH_2), 32.1 (7-CH_2), 32.7 (CH_2), 51.3 (3a-CH), 55.2 (3-CH), 79.8 (7a-CH), 82.2 (2-CH), 126.0 (4′-CH), 128.8 (2 × 3′-CH), 130.0 (2 × 2′-CH) and 137.2 (1′-C); *m*/*z* [FAB] 291 (M^+ + H, 64%), 290 (86), 289 (54), 204 (85), 181 (66), 123 (45), 95 (87), 81 (76), 68 (67) and 56 (100) [Found: M^+, 290.1703. $C_{18}H_{26}OS$ requires *M*, 290.1704].

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