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Diastereospecific Tandem Prins Cyclisation/Rearrangement Reactions for the Desymmetrisation of Cyclohexa-1,4-dienes

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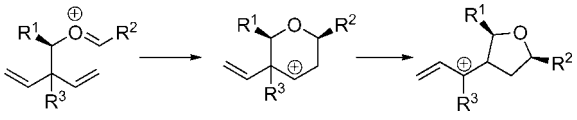
The Prins cyclisation has been used for the first time to desymmetrise a 1,4-diene. Products derived from both normal Prins and rearrangement pathways were obtained, all with complete stereocontrol.

Introduction

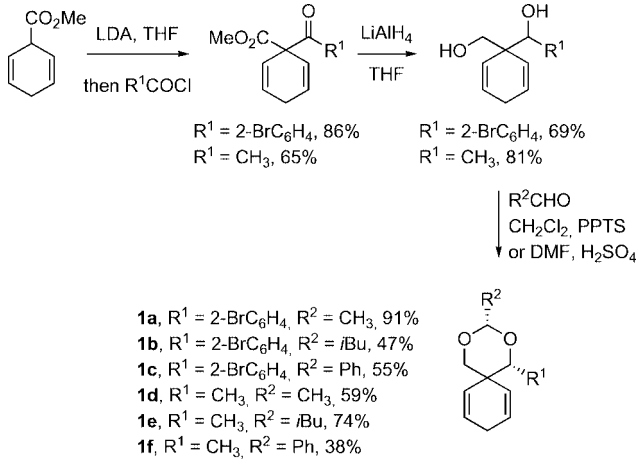
The Prins reaction of cyclic acetal derivatives permits an extremely versatile entry into highly functionalised tetrahydropyrans,[1] and has been widely used in total synthesis.[2] Because the initial product of the Prins cyclisation is a carbenium ion, there are a number of possibilities for rearrangement reactions. Notable among these is the Prins–pinacol sequence pioneered by the group of Overman.[3] Formation of an oxocarbenium ion from a doubly homoallylic alcohol derivative does not appear to have been reported, despite the potential of such cyclisations to distinguish between two diastereotopic double bonds in chiral substrates.[4] Such a reaction will lead to the initial formation of a homoallylic carbenium ion, which could potentially rearrange to the more stable allylic carbenium ion (Scheme 1). Of the numerous possible substrates for such a reaction, we have elected to study this process using 3,3-disubstituted cyclohexa-1,4-diene derivatives.[5] Our results show that a range of products are formed, all with complete diastereoselectivity with respect to the double bond attacked.



Scheme 1. Diastereoselective reactions of 1,4-dienes.

Results and Discussion

The requisite acetal substrates **1a**–**f** were prepared according to Scheme 2. Reactions with aliphatic aldehydes were carried out using sulfuric acid as catalyst; benzaldehyde acetals were formed using pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane. In all cases, acetals were formed with one diastereoisomer predominating. This is presumably the 1,3-*syn* diastereoisomer shown, although because the stereochemistry will be lost upon oxocarbenium ion formation, this aspect was not investigated.



Scheme 2. Preparation of cyclohexa-1,4-diene acetals **1a**–**f**.

The Prins reaction of compounds **1a** and **1b** was initially investigated using two equivalents of $TiCl_4$ as Lewis acid at –78 °C for either 2 or 4 h. This resulted in the formation of a 6.5:1 mixture of compounds **2a** and **3a** in the former case, while compound **2b** was the sole product in the latter case (Scheme 3). Product ratios were determined from the average integration of two or more peaks in the ^1H NMR spectra of the crude reaction mixtures. In both cases a small amount of 2-bromobenzaldehyde was observed in these NMR spectra. Upon purification by flash column chromatography, the major compounds **2a** or **2b** underwent elimination reactions to produce compounds **4a**,**b** and **5a**,**b**. Isolation of compound **3a** was uneventful. So far, attempts

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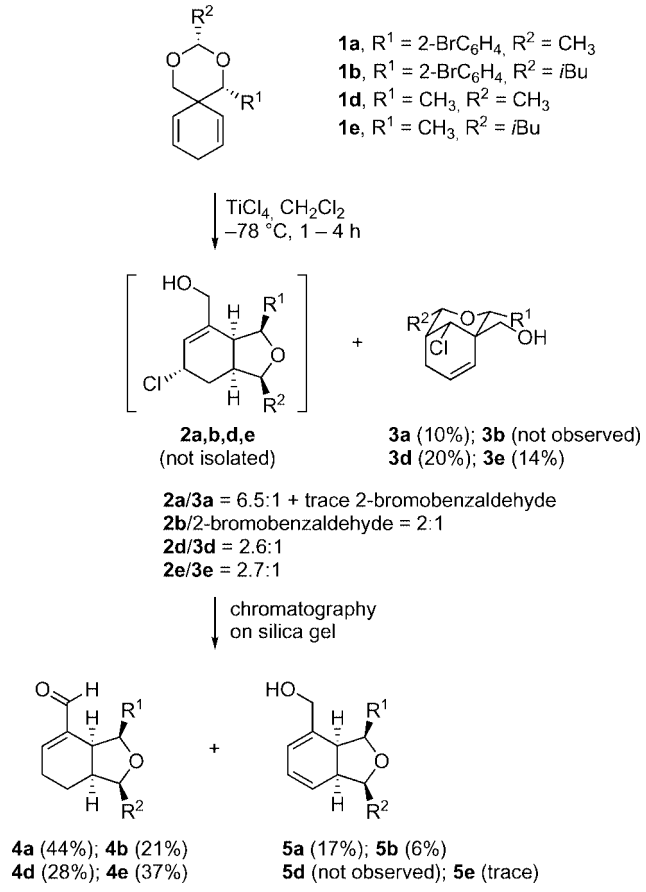
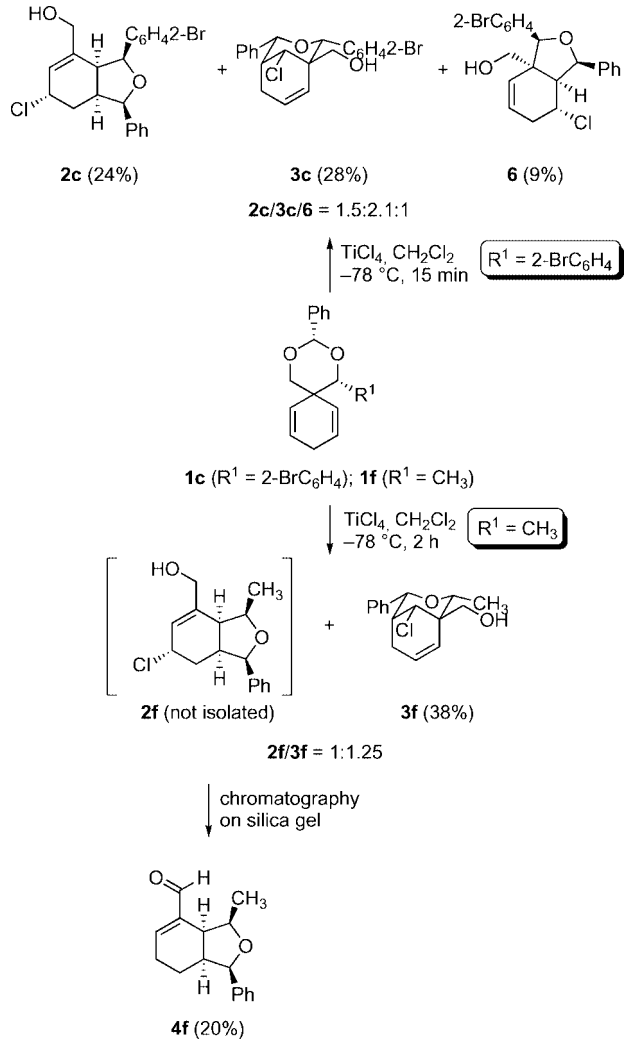
to derivatise compounds **2a** and **2b** (acetate, benzoate, TBS ether) have failed, with only the aldehydes identifiable in the reaction mixtures.



Scheme 3. Prins reaction of compounds **1a**,**b**,**d**,**e**.

Reaction of compounds **1d** and **1e** under similar conditions gave compounds **4d**,**e** as the sole aldehyde products after chromatography (Scheme 3). As above, the initial major products under these conditions were alcohols **2d**,**e**, although these did not survive chromatographic purification. In addition to the expected pyrans **3d**,**e**, compound **1d** also gave a small amount (2%) of the diene elimination product **5e**. All isolated compounds were identified by a combination of spectroscopic methods, with stereochemistry being elucidated by gradient NOESY NMR spectroscopy.

The two benzaldehyde acetals undergo similar reactions, albeit with subtle differences. Reaction of compound **1c** with titanium tetrachloride at –78 °C for only 15 min resulted in the formation of compounds **2c** and **3c**, along with compound **6**, in a ratio of 1.5:2.1:1, with isolated yields as shown in Scheme 4. Compound **3c** was characterised by single-crystal X-ray diffraction,[6] confirming the structure and stereochemistry (Figure 1). The tetrahydropyran ring is close to an ideal chair conformation, with substituents, where possible, in equatorial positions. Reaction of compound **1f** at –78 °C for 2 h gave a mixture of compounds **2f** and **3f**, from which compounds **3f** and **4f** were obtained after chromatography in 58% combined yield. Compound **4f** was identified by a combination of spectroscopic methods, while compound **3f** also gave crystals suitable for X-ray diffraction analysis.[6] The structure was found to be similar to that of compound **3c**.



Scheme 4. Prins reaction of compounds **1c** and **1f**.

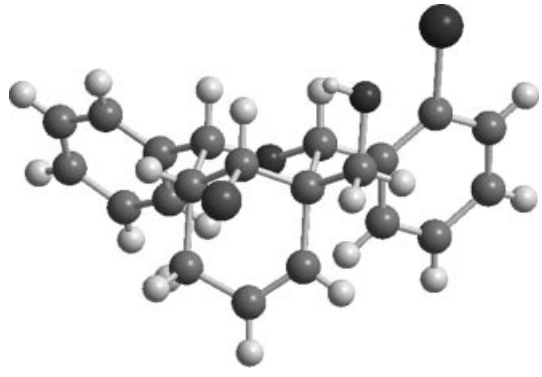
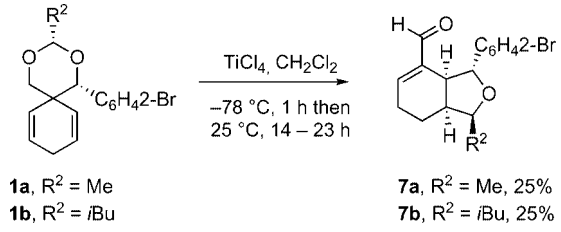


Figure 1. Structure of compound **3c** from X-ray data.

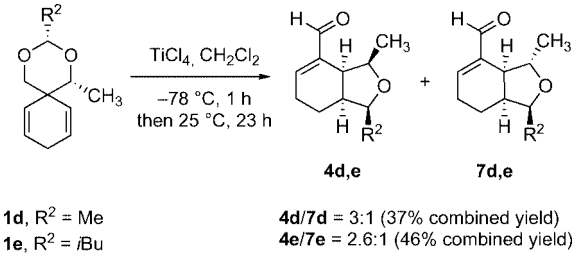
The failure of compound **2c** to undergo elimination upon chromatography is somewhat surprising, given the facile nature of this reaction with compounds **2a**–**b**,**d**–**f**. However, all of these reactions are entirely reproducible. In both of these cases, far more of the unrearranged products **3c** and **3f** were obtained.

When the reactions are warmed to room temperature and left to stir for 14 h or more, elimination to give the aldehydes **4** is favoured followed by epimerisation to varying extents as follows.[7] With compounds **1a** and **1b**, containing a benzylic ether moiety, epimerisation was complete, giving isomers **7a** and **7b** (Scheme 5). These are presumably formed by epimerisation of compounds **4a**,**b**, via the reversible formation of a benzylic carbenium ion.



Scheme 5. Extended Prins reaction of compounds **1a**,**b**.

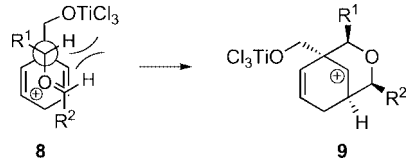
Treating acetals **1d** and **1e** with titanium tetrachloride under the same conditions gave a mixture of the aldehydes **4d**,**e** and a stereoisomer in a ratio of 2.6–3:1 (Scheme 6). As these could not be separated, it is impossible to unequivocally state the structure of the minor isomer. However, it seems likely that the epimerisation takes place at the 3-position via the homoallylic carbenium ion[8] rather than at the 1-position to give an unstabilised secondary carbenium ion. We therefore propose the structures **7d**,**e** for these minor diastereoisomers.



Scheme 6. Extended Prins reaction of compounds **1d**,**e**.

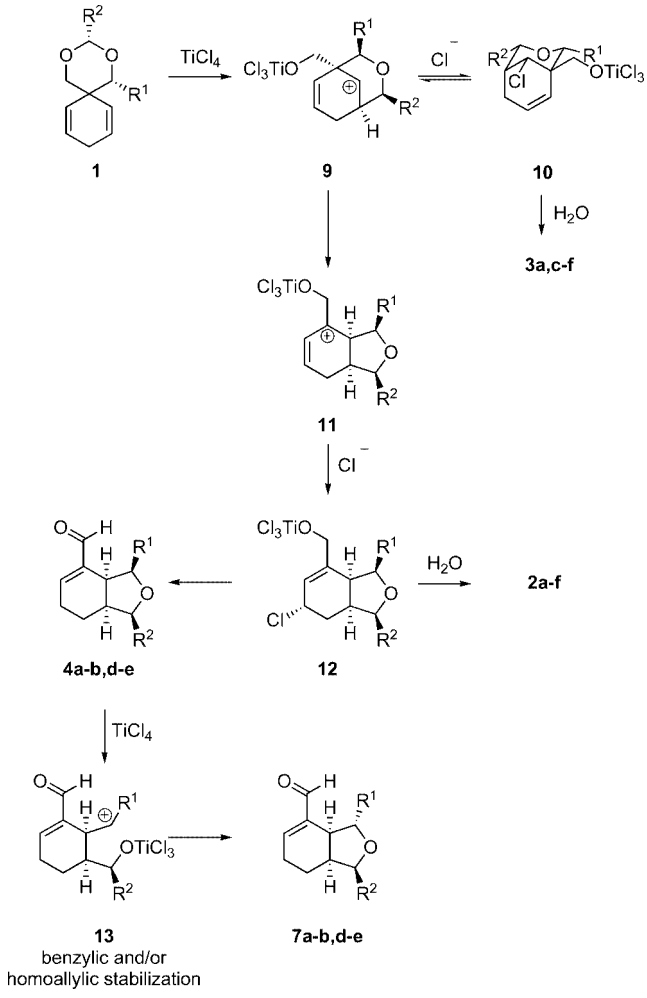
Subjecting benzaldehyde acetals **1c** and **1f** to these extended reaction conditions resulted solely in the formation of aromatic decomposition products.

The stereochemical outcome of all of these reactions can be explained by the structures **8** and **9** in Scheme 7. The controlling element is minimisation of $A^{1,3}$ strain[9] as shown on structure **8**. The predominant pathway is 6-*endo* cyclisation of the oxocarbenium ion **8** to give the intermediate **9**. Compound **6** arises from the 5-*exo* cyclisation, which is generally disfavoured,[10] and which was only observed in the cyclisation of substrate **1c**. Upon consideration of structure **8**, it seems conceivable that the combination of two aromatic rings causes unfavourable interactions with the hydroxymethyl and cyclohexadiene methylene hydrogen atoms. This could be alleviated by a slight anticlockwise rotation of the stereogenic carbon atom, bringing the oxocarbenium ion carbon into closer proximity with C-4. The smaller methyl group in substrate **1f** would account for our failure to observe a similar compound in this case.



Scheme 7. Rationalisation of the stereochemical outcome.

The mechanisms of the reactions are summarised in Scheme 8. Reaction of acetals **1** stereoselectively gives the secondary carbenium ion **9** via intermediate **8**. This can then undergo addition of chloride, possibly reversibly, to give compound **10**, leading to isolated compounds **3a**,**c**–**f**, or rearrangement to give allylic carbenium ion **11**. Addition of chloride then leads to intermediate **12** which undergoes hydrolysis to compounds **2a**–**f** as seen in the NMR spectra of crude reaction mixtures. Alternatively, upon extended stirring, intermediate **12** can undergo dehydrochlorination



Scheme 8. Mechanistic summary.

to give aldehydes **4a**–**b**,**d**–**e** which epimerise, via carbenium ion **13**, to give the more stable aldehydes **7a**–**b**,**d**–**e**. While presently racemic, all of these compounds arise from a diastereospecific discrimination between the two cyclohexa-1,4-diene double bonds. We cannot exclude the participation of an oxonia-Cope pathway[11] in the formation of intermediate **11** since the stereochemical outcome of such a pathway may well be similar.

Conclusions

In conclusion, the Prins reaction has been applied for the first time to desymmetrise the two diastereotopic double bonds of a 1,4-diene. While a number of products were obtained, the initial reaction was completely diastereoselective, reacting only at one of the two diastereotopic double bonds. This stereoselectivity can be rationalised by the minimisation of $A^{1,3}$ strain in the transition state as shown in structure **8**. Further developments of this reaction, and applications to total synthesis are underway in our laboratories, and will be reported in due course.

Experimental Section

General Experimental Points: Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded with a Fisons VG Platform II spectrometer and with a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded with a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or with a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Multiplicity in ^{1}H NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 micron.

Synthesis of Precursors to Acetals 1–2

Methyl 1-(2-Bromobenzoyl)cyclohexa-2,5-dienecarboxylate: *n*-Butyllithium (4.4 mL, 2.5 M solution in hexane, 11 mmol) was added to *i*Pr$_2$NH (1.5 mL, 10.7 mmol) at 0 °C. After stirring the resulting mixture for 30 min, the resulting gel was cooled to –78 °C and THF (10 mL) added. A solution of methyl cyclohexa-2,5-diene-1-carboxylate (1.5 g, 10.8 mmol) in THF (5 mL) was added and the stirring was continued for another 30 min. 2-Bromobenzoyl chloride (2.38 g, 10.8 mmol) was then added as a solution in THF (5 mL) and the reaction mixture was stirred for one hour at –78 °C, then at room temperature for 18 h. Aqueous hydrochloric acid (2 M, 50 mL) was added and the product extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude product as a brown waxy solid which was purified by flash chromatography (eluting with ethyl acetate/hexane, 1:6) to afford the title compound (2.98 g, 86%) as a pale yellow waxy solid, m.p. 43–45 °C. IR (neat): $\tilde{\nu}$ = 3051, 2952, 2882, 1741, 1705, 1433, 1286, 1231, 1052, 922, 737 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.49 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, one of aromatic CH), 7.24–7.14 (m, 3 H, aromatic CH), 6.03 (broad d, $^3J_{H,H}$ = 10.2 Hz, 2 H, 2 × alkene CH), 5.93 (broad d, $^3J_{H,H}$ = 10.2 Hz, 2 H, 2 × alkene CH), 3.78 (s, 3 H, O–CH_3), 2.63 (broad d, $^2J_{H,H}$ = 23.5 Hz, 1 H, one of ring CH_2), 2.45 (broad d, $^2J_{H,H}$ = 23.5 Hz, 1 H, one of ring CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.4 (C), 170.4 (C), 170.4 (C), 140.7 (C), 133.0 (CH), 130.7 (CH), 128.6 (2 × CH), 127.2 (CH), 126.5 (CH), 122.6 (2 × CH), 118.7 (C), 62.7 (C), 53.0 (CH_3), 26.1 (CH_2) ppm.

1-(2-Bromophenyl)-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]methanol: A solution of Methyl 1-(2-bromobenzoyl)cyclohexa-2,5-dienecarboxylate (2.98 g, 9.8 mmol) in dry THF (10 mL) was carefully added to a stirred suspension of $LiAlH_4$ (1.1 g, 28.9 mmol) in dry THF (20 mL) under nitrogen at room temperature in a flame-dried flask. After stirring for 1 h, excess $LiAlH_4$ was quenched with 15% aqueous NaOH solution and the stirring was continued at room temperature for 30 minutes. The resulting solution was filtered, washed with brine and concentrated under reduced pressure to afford a viscous yellow oil. Purification by flash chromatography (eluting with hexane/ethyl acetate, 2:1) afforded the title diol (1.9 g, 66%) as a colourless viscous oil. IR (neat): $\tilde{\nu}$ = 3374 cm^{-1} (broad), 3025, 2878, 2814, 1469, 1435, 1020, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.44 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.8 Hz, 1 H, aromatic CH), 7.41 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.1 Hz, aromatic CH), 7.24–7.18 (m, 1 H, aromatic CH), 7.03 (app td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.7 Hz, 1 H, aromatic CH), 6.00 (app. dtd, $^3J_{H,H}$ = 10.3, $^3J_{H,H}$ = 3.3, $^4J_{H,H}$ = 1.6 Hz, 1 H, one of CH=C*H*–CH_2), 5.83 (app. dq, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 5.77 (app. dtd, $^3J_{H,H}$ = 10.3, $^3J_{H,H}$ = 3.3, $^4J_{H,H}$ = 1.5 Hz, 1 H, one of CH=C*H*–CH_2), 5.56 (app. dq, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 2.0 Hz, 1 H, C*H*=CH–CH_2), 5.21 (s, 1 H, C*H*–OH), 3.79 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, one of CH_2–OH), 3.49 (d, $^3J_{H,H}$ = 10.5, 1 H, one of CH_2–OH), 2.49 (app. dtt, $^2J_{H,H}$ = 23.1, $^3J_{H,H}$ = 3.6, $^4J_{H,H}$ = 1.8 Hz, 1 H, one of ring CH_2), 2.25 (app. double quintet, $^2J_{H,H}$ = 23.1, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.7 Hz, 1 H, one of ring CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 139.9 (C), 132.3 (CH), 130.2 (CH), 129.6 (CH), 129.0 (CH), 128.5 (CH), 126.9 (CH), 125.8 (CH), 125.4 (CH), 123.9 (C), 76.3 (CH), 69.2 (CH_2), 48.8 (C), 26.7 (CH_2) ppm.

Methyl 1-Acetylcyclohexa-2,5-dienecarboxylate: *n*-Butyllithium (2.5 M solution in hexane, 29.0 mL, 72.4 mmol, 1.0 equiv.) was added to a cooled solution of *i*Pr$_2$NH (10.14 mL, 72.4 mmol, 1.0 equiv.) in dry THF (100 mL) at –78 °C. After stirring the resulting mixture for 30 min, a solution of methyl cyclohexa-2,5-diene-1-carboxylate (10 g, 72.4 mmol, 1.0 equiv.) in THF (10 mL) was added and the stirring was continued for another 30 min. Acetyl chloride (5.7 mL, 79.6 mmol, 1.1 equiv.) was added carefully and the reaction mixture was stirred for 1 h at –78 °C, then at room temperature for 18 h. Saturated ammonium chloride solution (20 mL) was added and the product was extracted three times with CH_2Cl_2 (40 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:9) afforded the title compound (8.5 g, 65%) as oil which solidified on standing to white crystals, m.p. 36–38 °C. IR (neat): $\tilde{\nu}$ = 3042, 2953, 2883, 1720, 1634, 1433, 1354, 1229, 1181, 1071, 942, 797 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.99–5.92 (m, 2 H, 2 × CH=CH–CH_2), 5.90–584 (m, 2 H, 2 × CH=CH–CH_2), 3.64 (s, 3 H, O–CH_3), 2.74–2.57 (m, 2 H, ring CH_2), 2.07 (s, 3 H, CH_3–C=O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 204.8 (C), 170.8 (C), 128.4 (2 × CH), 122.7 (2 × CH), 62.9 (C), 52.7 (CH_3), 26.1 (CH_2), 26.0 (CH_3) ppm.

1-[1-(Hydroxymethyl)cyclohexa-2,5-dienyl]ethanol: Methyl 1-acetylcyclohexa-2,5-dienecarboxylate (7.2 g, 39.8 mmol) in dry THF

(10 mL) was carefully added to a stirred suspension of $LiAlH_4$ (4.6 g, 122.4 mmol, 4.1 equiv.) in dry THF (30 mL) under nitrogen at room temperature in a flame-dried flask. After stirring for 18 h, 15% aqueous NaOH solution (4.7 mL) was added carefully followed by water (13.7 mL) and the stirring was continued at room temperature for two hours. Filtration and concentration under reduced pressure afforded a viscous yellow oil. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) afforded the title diol (4.98 g, 81%) as a colourless solid, m.p. 50–52 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3394 (broad), 3022, 2973, 2879, 1635, 1421, 1372, 1130, 1025, 904 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.99 (m, 1 H, one of CH=C*H*–CH_2), 5.88 (m, 1 H, one of CH=C*H*–CH_2), 5.68 (app. dd, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 5.36 (app. dd, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 3.75 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, C*H*–OH), 3.58 and 3.50 (AB quartet, $^2J_{H,H}$ = 10.5 Hz, C*H*$_2$–OH), 2.70–2.56 (m, 2 H, ring CH_2), 2.52 (broad s, 2 H, 2 × OH), 1.04 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 128.4 (CH), 127.9 (CH), 127.0 (CH), 125.5 (CH), 72.9 (CH), 69.6 (CH_2), 46.7 (C), 27.2 (CH_2), 19.1 (CH_3) ppm.

Synthesis of Acetals 1a–f

(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-methyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1a): Acetaldehyde (3.3 g, 4.2 mL, 75.6 mmol, 7 equiv.) was added to a solution of 1-(2-bromophenyl)-[1-(hydroxymethyl)-cyclohexa-2,5-dienyl]methanol (3.2 g, 10.8 mmol) in dry CH_2Cl_2 (50 mL). Pyridinium *p*-toluenesulfonate (1.09 g, 4.3 mmol, 0.4 equiv.) was added and the resulting mixture was stirred at room temperature under nitrogen for 72 h. The mixture was poured into water (50 mL) and the organic material was extracted into CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford **1a** (3.1 g, 91%) as an essentially-pure pale yellow oil which solidified upon standing into an off-white solid, m.p. 52–54 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3025, 2991, 2858, 2360, 1698, 1474, 1410, 1162, 1117, 1032, 911 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37 (m, 2 H, 2 × aromatic CH), 7.20–7.14 (m, 1 H, aromatic CH), 7.01 (app. td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.8 Hz, 1 H, aromatic CH), 6.21 (app. dq, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 5.74–5.68 (m, 1 H, one of CH=C*H*–CH_2), 5.65–5.59 (m, 1 H, one of CH=C*H*–CH_2), 5.48 (app. dq, $^3J_{H,H}$ = 10.1, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 5.08 (s, 1 H, CH–Ar), 4.94 (q, $^3J_{H,H}$ = 5.0 Hz, 1 H, OC*H*CH_3), 3.81 and 3.76 (AB quartet, $^2J_{H,H}$ = 11.0 Hz, 2 H, OCH_2), 2.34 (app. dtt, $^2J_{H,H}$ = 22.8, $^3J_{H,H}$ = 3.7, $^4J_{H,H}$ = 1.8 Hz, 1 H, one of ring CH_2), 1.90 (app. double quintet, $^2J_{H,H}$ = 22.8, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.6 Hz, 1 H, one of ring CH_2), 1.38 (d, $^3J_{H,H}$ = 5.0 Hz, 3 H, OCHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 137.3 (C), 131.9 (CH), 130.9 (CH), 128.9 (CH), 128.5 (CH), 126.4 (CH), 126.4 (CH), 126.3 (CH), 125.3 (CH), 123.6 (C), 100.2 (CH), 83.7 (CH), 76.5 (CH_2), 42.1 (C), 26.8 (CH_2), 21.1 (CH_3) ppm.

(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-isobutyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1b): 3-Methylbutyraldehyde (4.4 g, 5.5 mL, 50.8 mmol, 10 equiv.) was added to a solution of 1-(2-bromophenyl)-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]methanol (1.5 g, 5.1 mmol) in dry CH_2Cl_2 (25 mL). Pyridinium *p*-toluenesulfonate (0.77 g, 3.05 mmol, 0.6 equiv.) was added and the resulting mixture was stirred at room temperature under nitrogen for 4 d. The mixture was poured into water (50 mL) and the organic material was extracted into CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford a pale yellow oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 0.5:9.5) afforded **1b** (871 mg, 47%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3026, 2956, 2923, 2854, 1467, 1439, 1362, 1260, 1128, 1017, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.1 Hz, 1 H, aromatic CH), 7.36 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.8 Hz, 1 H, aromatic CH), 7.19–7.14 (m, 1 H, aromatic CH), 7.00 (app. td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.8 Hz, 1 H, aromatic CH), 6.19 (app. dq, $^3J_{H,H}$ = 10.4, $^4J_{H,H}$ = 1.9 Hz, 1 H, one of C*H*=CH–CH_2), 5.72–5.67 (m, 1 H, one of CH=C*H*–CH_2), 5.65–5.59 (m, 1 H, one of CH=C*H*–CH_2), 5.49 (app. dq, $^3J_{H,H}$ = 10.2, $^4J_{H,H}$ = 1.9 Hz, 1 H, one of CH=CH–CH2), 5.05 (s, 1 H, CH–Ar), 4.82 (t, $^3J_{H,H}$ = 5.4 Hz, 1 H, OCHO), 3.81 and 3.74 (AB quartet, $^2J_{H,H}$ = 11.0 Hz, 2 H, OCH_2), 2.35 (app. dtt, $^2J_{H,H}$ = 22.9, $^3J_{H,H}$ = 3.7, $^4J_{H,H}$ = 1.9 Hz, 1 H, one of ring CH_2), 1.89 (app. doubled quintet, $^2J_{H,H}$ = 22.9, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.7 Hz, 1 H, one of ring CH_2), 1.80 [app. nonet, $^3J_{H,H}$ = 6.7 Hz, 1 H, $(CH_3)_2CH$], 1.64–1.48 [m, 2 H, $(CH_3)_2CHCH_2$], 0.88 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH_3), 0.86 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 137.5 (C), 131.9 (CH), 131.0 (CH), 128.9 (CH), 128.4 (CH), 126.4 (CH), 126.3 (CH), 126.3 (CH), 125.4 (CH), 123.5 (C), 102.2 (CH), 83.8 (CH), 76.5 (CH_2), 43.7 (CH_2), 42.1 (C), 26.8 (CH_2), 23.8 (CH), 23.2 (CH_3), 22.8 (CH_3) ppm.

(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1c): Concentrated sulfuric acid (0.12 mL) was added to a solution of 1-(2-bromophenyl)-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]methanol (1.0 g, 3.39 mmol) and benzaldehyde (0.7 mL) in DMF (10 mL). The resulting mixture was stirred at room temperature under nitrogen for 6 d. Then the reaction mixture was poured into ice–water (100 mL) containing K_2CO_3 (180 mg) and the organic material was extracted into CH_2Cl_2 (3 × 20 mL). The combined extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 3:7) afforded **1c** (716 mg, 55%) as white crystals, m.p. 104–105 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3022, 2886, 2852, 1449, 1401, 1322, 1223, 1112, 1023, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.82 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 2 × aromatic CH), 7.75 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.6 Hz, 1 H, aromatic CH), 7.70 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 0.9 Hz, 1 H, aromatic CH), 7.67–7.58 (m, 3 H, 3 × aromatic CH), 7.48 (app. t, $^3J_{H,H}$ = 7.9 Hz, 1 H, aromatic CH), 7.32 (app. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.7 Hz, 1 H, aromatic CH), 6.65 (app. dq, $^3J_{H,H}$ = 10.3, $^4J_{H,H}$ = 1.6 Hz, 1 H, one of C*H*=CH–CH_2), 6.11–6.02 (m, 2 H, one of CH=C*H*–CH_2 and OCHO), 5.98 (broad d, $^3J_{H,H}$ = 10.1 Hz, 1 H, one of CH=C*H*–CH_2), 5.88 (app. dq, $^3J_{H,H}$ = 10.2, $^4J_{H,H}$ = 1.7 Hz, 1 H, one of C*H*=CH–CH_2), 5.62 (s, 1 H, CH–Ar), 4.30 (app. singlet, 2 H, OCH_2), 2.75–2.63 (m, 1 H, one of ring CH_2), 2.29–2.18 (m, 1 H, one of ring CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.3 (C), 137.2 (C), 131.9 (CH), 131.1 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (2 × CH), 126.6 (CH), 126.4 (CH), 126.3 (2 × CH), 126.1 (CH), 125.2 (CH), 123.6 (C), 102.5 (CH), 84.2 (CH), 76.9 (CH_2), 42.3 (C), 26.8 (CH_2) ppm.

1,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1d): Acetaldehyde (5 mL, 88.6 mmol, 19 equiv.) was added to a solution of 1-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]ethanol (711 mg, 4.6 mmol) in dry CH_2Cl_2 (20 mL). Pyridinium *p*-toluenesulfonate (500 mg, 2.0 mmol, 0.43 equiv.) was added and the resulting mixture was stirred at room temperature under nitrogen for 16 h. The mixture was poured into water (30 mL) and the organic material was extracted into CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford a pale yellow oil. Purification by flash chromatography (eluting with hexane/ethyl acetate, 9:1) afforded **1d** (mixture of two diastereoisomers) (631 mg, 59%) as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3014, 2978, 2840, 1450, 1408, 1377, 1232, 1179, 1145, 1037, 955,

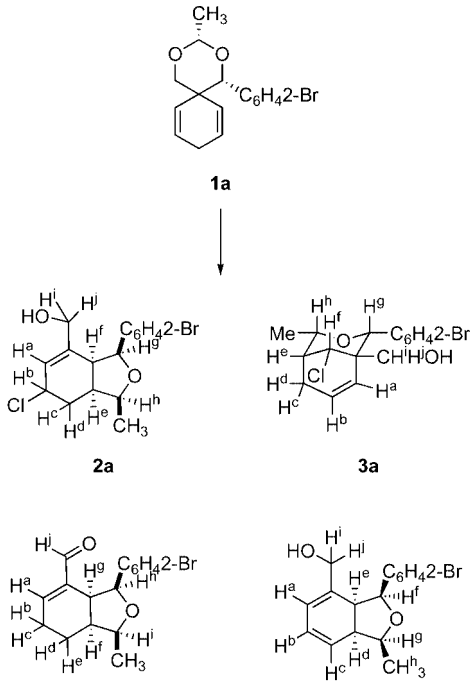
867 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.04–5.96 (m, 1 H, alkene CH), 5.89–5.77 (m, 2 H, 2 × alkene CH), 5.09–5.01 (m, 1 H, alkene CH), 4.70 (q, $^3J_{H,H}$ = 5.0 Hz, 1 H, OCHO), 3.65 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 3.52 (q, $^3J_{H,H}$ = 6.3 Hz, 1 H, OC*H*CH_3), 3.45 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 2.64–2.57 (m, 2 H, ring CH_2), 1.30 (d, $^3J_{H,H}$ = 5.0 Hz, 3 H, CH_3), 1.00 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 128.7 (CH), 126.6 (CH), 126.2 (CH), 125.3 (CH), 99.3 (CH), 79.2 (CH), 76.1 (CH_2), 39.7 (C), 27.4 (CH_2), 21.1 (CH_3), 16.9 (CH_3) ppm.

3-Isobutyl-1-methyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1e): 3-Methylbutyraldehyde (4.8 g, 5.9 mL, 50.8 mmol, 10 equiv.) was added to a solution of 1-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]-ethanol (855 mg, 5.5 mmol) in dry CH_2Cl_2 (25 mL). Pyridinium *p*-toluenesulfonate (834 mg, 3.3 mmol, 0.6 equiv.) was added and the resulting mixture was stirred at room temperature under nitrogen for 9 d. The mixture was poured into water (50 mL) and the organic material was extracted into CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 0.5:9.5) afforded **1e** (mixture of two diastereoisomers) (912 mg, 74%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3017, 2954, 2869, 1454, 1410, 1375, 1261, 1099, 800 cm^{-1}. ^1H NMR (400 MHz, CDCl3, 25 °C): δ = 5.99 (app. dd, $^3J_{H,H}$ = 10.4, $^4J_{H,H}$ = 1.7 Hz, 1 H, C*H*=CH–CH_2), 5.87–5.78 (m, 2 H, 2 × CH=C*H*–CH_2), 5.05 (app. dd, $^3J_{H,H}$ = 10.4, $^4J_{H,H}$ = 1.8 Hz, C*H*=CH–CH_2), 4.58 (t, $^3J_{H,H}$ = 5.4 Hz, 1 H, OCHO), 3.66 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 3.50 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, OC*H*CH_3), 3.45 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 2.70–2.53 (m, 2 H, ring CH_2), 1.76 [app. nonet, $^3J_{H,H}$ = 6.8 Hz, 1 H, $(CH_3)_2$C*H*], 1.55–1.39 (m, 2 H, [$(CH_3)_2$CHCH_2]), 0.99 [d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3], 0.85 [app. d, $^3J_{H,H}$ = 6.6 Hz, 6 H, 2 × CH_3] ppm. ^{13}C NMR [100 MHz, $CDCl_3$, 25 °C]: δ = 128.6 (CH), 126.7 (CH), 126.3 (CH), 125.2 (CH), 101.5 (CH), 79.3 (CH), 76.2 (CH_2), 43.7 (CH_2), 39.9 (C), 27.4 (CH_2), 23.9 (CH), 23.0 (CH_3), 22.7 (CH_3), 16.9 (CH_3) ppm.

(1*RS*,3*SR*)-1-Methyl-3-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (1f): Concentrated sulfuric acid (0.46 mL) was added to a solution of 1-[1-(hydroxymethyl)cyclohexa-2,5-dienyl]ethanol (2.0 g, 12.97 mmol) and benzaldehyde (2.83 mL) in DMF (20 mL). The resulting mixture was stirred at room temperature under nitrogen for 7 d. Then the reaction mixture was poured into ice-water (100 mL) containing K_2CO_3 (690 mg) and the organic material was extracted into CH_2Cl_2 (3 × 30 mL). The combined extracts were dried with Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 0.3:9.7) afforded **1f** (1.2 g, 38%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3033, 2978, 2840, 1452, 1400, 1373, 1161, 1132, 1087, 1021, 970, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.43 (m, 2 H, 2 × aromatic CH), 7.33–7.23 (m, 3 H, 3 × aromatic CH), 6.14 (app. dq, $^3J_{H,H}$ = 10.4, $^4J_{H,H}$ = 2.0 Hz, 1 H, one of C*H*=CH–CH_2), 5.91–5.83 (m, 2 H, m, 2 × CH=C*H*–CH_2), 5.50 (s, 1 H, O–CH–O), 5.12 (app. dq, $^3J_{H,H}$ = 10.4, $^4J_{H,H}$ = 2.0 Hz, one of C*H*=CH–CH_2), 3.83 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 3.74 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, OC*H*CH3), 3.66 (d, $^2J_{H,H}$ = 11.0 Hz, 1 H, one of OCH_2), 2.72–2.56 (m, 2 H, ring CH_2), 1.07 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.6 (C), 129.0 (CH), 128.9 (CH), 128.4 (2 × CH), 126.6 (CH), 126.3 (2 × CH), 126.2 (CH), 125.4 (CH), 102.0 (CH), 80.0 (CH), 76.6 (CH_2), 39.9 (C), 27.5 (CH_2), 17.0 (CH_3) ppm.

Prins Reactions

Prins Cyclisation of Acetaldehyde Acetal 1a at –78 °C for 4 h



Titanium tetrachloride (0.18 mL, 1.64 mmol) was carefully added to a cooled (–78 °C) solution of acetaldehyde acetal **1a** (235 mg, 0.73 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 4 h then carefully quenched with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the organic material extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow residue. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:5) afforded compound **5a** as a colourless oil (40 mg, 17%), compound **3a** as a pale yellow oil (26 mg, 10%) and compound **4a** as a colourless oil (104 mg, 44%), respectively. While compound **2a** was not isolated, its existence was evident from the data obtained from the crude reaction mixture.

[(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-methylisobenzofuran-4-yl]methanol (2a): This compound was not isolated pure. These data are obtained from the crude reaction mixture under the above conditions. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.44 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, aromatic CH), 7.22–7.17 (m, 1 H, aromatic CH), 7.10–7.02 (m, 2 H, 2 × aromatic CH), 5.84 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, H^a), 5.41 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H, H^g), 4.72–4.64 (m, 1 H, H^b), 4.10 (dq $^3J_{H,H}$ = 4.8, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^h), 3.48 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, H^i), 3.35–3.28 (m, 2 H, H^j and H^f), 2.70–2.61 (m, 1 H, H^e), 2.15–2.20 (m, 2 H, H^c and H^d), 1.30 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.9 (C), 138.0 (C), 132.5 (CH), 129.8 (CH), 129.4 (CH), 127.6 (CH), 125.0 (CH), 124.0 (C), 81.1 (CH), 76.9 (CH), 64.6 (CH_2), 53.9 (CH), 43.3 (CH), 36.9 (CH), 29.9 (CH_2), 14.8 (CH_3) ppm. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^e,H^f} {H^e,H^h} {H^e,H^g} {H^f,H^g} {H^f,H^h}.

[(1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-2-(2-Bromophenyl)-9-chloro-4-methyl-3-oxabicyclo[3.3.1]non-7-en-1-yl]methanol (3a): Pale yellow oil (26 mg, 10%). IR (CH_2Cl_2): $\tilde{\nu}$ = 3578, 3024, 2925, 1725, 1694, 1470,

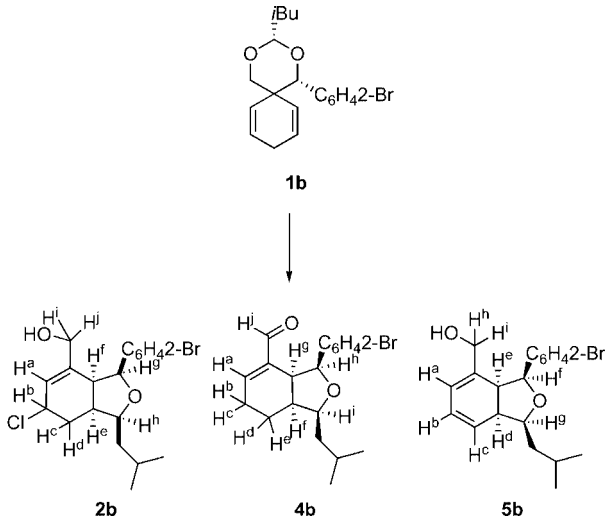
1440, 1386, 1204, 1084 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.2 Hz, 1 H, aromatic CH), 7.40 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.7 Hz, 1 H, aromatic CH), 7.23–7.17 (m, 1 H, aromatic CH), 7.08 (app. dt, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 7.6 Hz, 1 H, aromatic CH), 6.01 (app. dt, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 3.4 Hz, 1 H, H^b), 4.97 (s, 1 H, H^g), 4.81 (app. dq, $^3J_{H,H}$ = 9.9, $^4J_{H,H}$ = 1.9 Hz, 1 H, H^a), 4.68 (dd, $^3J_{H,H}$ = 3.3, $^4J_{H,H}$ = 1.5 Hz, 1 H, H^f), 3.89 (app. dq, $^3J_{H,H}$ = 1.7, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^h), 3.60 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, H^i), 3.22 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, H^j), 2.47–2.30 (m, 2 H, H^c and H^d), 2.12–2.06 (m, 1 H, H^e), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 137.5 (C), 132.3 (CH), 131.5 (CH), 130.3 (CH), 129.7 (CH), 127.3 (CH), 123.5 (C), 121.8 (CH), 80.7 (CH), 77.3 (CH), 63.2 (CH_2), 63.1 (CH), 46.5 (C), 41.1 (CH), 22.8 (CH_2), 18.9 (CH_3) ppm. MS (APCI): *m/z* (%) = 361 (13) [MH^+ ($^{81}Br^{37}Cl$)], 359 (48) [MH^+ ($^{79}Br^{37}Cl$)], 257 (44), 187 (65), 185 (75), 157 (25), 155 (65), 149 (29), 137 (100). HRMS (EI) $C_{16}H_{18}O_2{}^{79}Br^{35}Cl$ [MH^+] 356.0173; found 356.0167. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g} {H^f,H^h} {H^g,H^h}.

(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-methylisobenzofuran-4-carbaldehyde (4a): Colourless oil (104 mg, 44%). IR (CH_2Cl_2): $\tilde{\nu}$ = 2935, 1685, 1641, 1472, 1441, 1392, 1212, 1162, 1089, 1018 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.79 (s, 1 H, H^j), 7.38 (app. dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 1.1 Hz, 1 H, aromatic CH), 7.11–7.04 (m, 2 H, 2 × aromatic CH), 6.97–6.91 (app. ddd, *J* = 8.1, *J* = 6.5, *J* = 2.5 Hz, 1 H, aromatic CH), 6.75 (app. ddd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 3.3, $^4J_{H,H}$ = 1.0 Hz, 1 H, H^a), 5.54 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, H^h), 4.07 (dq, $^3J_{H,H}$ = 5.1, $^3J_{H,H}$ = 6.5 Hz, 1 H, H^i), 3.56 (m, 1 H, H^g), 2.45 (app. dq, $^2J_{H,H}$ = 19.1, $^3J_{H,H}$ = 4.8 Hz, 1 H, H^b), 2.32–2.24 (m, 1 H, H^f), 2.24 – 2.13 (m, 1 H, H^c), 1.80–1.63 (m, 2 H, H^d and H^e), 1.31 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.2 (CH), 151.0 (CH), 141.0 (C), 137.6 (C), 132.6 (CH), 130.3 (CH), 128.8 (CH), 126.5 (CH), 125.1 (C), 81.4 (CH), 77.1 (CH), 39.9 (CH), 39.5 (CH), 24.7 (CH_2), 20.2 (CH_2), 14.8 (CH_3) ppm. MS (APCI): *m/z* (%) = 323 (89) [MH^+ (^{81}Br)], 321 (100) [MH^+ (^{79}Br)], 305 (24), 303 (27), 279 (40), 277 (27), 243 (16), 229 (11), 185 (18). HRMS (ES$^+$) $C_{16}H_{18}{}^{79}BrO_2$ [MH^+] 321.0490; found 321.0480. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g} {H^f,H^i} {H^g,H^h} {H^g,H^i} {H^h,H^i}.

[(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,7a-tetrahydro-1-methylisobenzofuran-4-yl]methanol (5a): Slightly impure colourless oil (40 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.30 (m, 2 H, aromatic CH), 7.12 (apparent td, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.0 Hz, 1 H, aromatic CH), 7.00 (apparent td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.7 Hz, aromatic CH), 5.85 (ddd, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 5.5, $^4J_{H,H}$ = 2.6 Hz, 1 H, H^b), 5.74 (dd, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.6 Hz, 1 H, H^c), 5.69 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, H^a), 5.49 (d, $^3J_{H,H}$ = 9.8 Hz, 1 H, H^f), 4.24 (apparent quintet, $^3J_{H,H}$ = 6.1 Hz, 1 H, H^g), 3.69 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, H^i), 3.59 (dd, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 9.8 Hz, 1 H, H^e) 3.51 (d, $^2J_{H,H}$ = 11.5 Hz, H^j), 3.17 (apparent ddt, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.6 Hz, 1 H, H^d), 1.51 (broad s, 1 H, OH), 1.43 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3) ppm. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy.

Prins Cyclisation of 3-Methylbutyraldehyde Acetal 1b at –78 °C for 4 h

Titanium tetrachloride (0.18 mL, 1.64 mmol) was carefully added to a cooled (–78 °C) solution of 3-methylbutyraldehyde acetal **1b** (217 mg, 0.6 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 2 h then carefully quenched with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the organic material extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow residue. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:6) afforded compound **5b** as a colourless oil (12 mg, 6%) and compound **4b** as a colourless oil (46 mg, 21%). While compound **2b** was not isolated, its existence was evident from the data obtained from the crude reaction mixture.



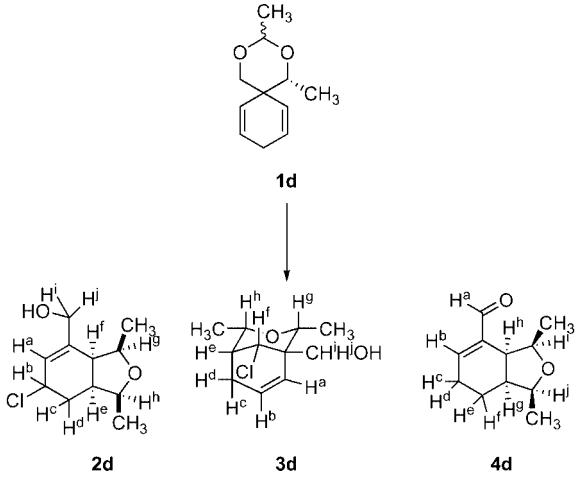
[(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-isobutylisobenzofuran-4-yl]methanol (2b): This compound was not isolated pure. These data are obtained from the crude reaction mixture under the above conditions. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.44 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, aromatic CH), 7.21–7.16 (m, 1 H, aromatic CH), 7.10–7.01 (m, 2 H, aromatic CH), 5.86 (dd, $^3J_{H,H}$ = 5.0, $^4J_{H,H}$ = 1.0 Hz, 1 H, H^a), 5.40 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H, H^g), 4.71–4.62 (m, 1 H, H^b), 4.00 (app. dt, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 4.9 Hz, 1 H, H^h), 3.51 (d, $^2J_{H,H}$ = 14.3 Hz, 1 H, H^i), 3.32 (d, $^2J_{H,H}$ = 14.3 Hz, 1 H, H^j), 3.30 (app. t, $^3J_{H,H}$ = 8.7 Hz, 1 H, H^f), 2.72–2.62 (m, 1 H, H^e), 2.14–2.03 (m, 2 H, H^c and H^d), 1.78–1.40 (m, 4 H, isobutyl CH_2, isobutyl CH and OH), 0.91 (app. d, $^3J_{H,H}$ = 5.0 Hz, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 141.0 (C), 138.2 (C), 132.5 (CH), 129.9 (CH), 129.4 (CH), 127.6 (CH), 124.8 (CH), 124.1 (C), 81.0 (CH), 76.4 (CH), 64.7 (CH_2), 54.1 (CH), 43.3 (CH), 38.3 (CH), 36.2 (CH), 29.9 (CH_2), 25.6 (CH), 23.3 (CH_3), 22.8 (CH_3) ppm.

(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-isobutylisobenzofuran-4-carbaldehyde (4b): Colourless oil (46 mg, 21%). IR (CH_2Cl_2): $\tilde{\nu}$ = 2952, 1687, 1641, 1469, 1367, 1208, 1160, 1026, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.79 (s, 1 H, H^j), 7.37 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, aromatic CH), 7.11–7.05 (m, 2 H, aromatic CH), 6.94 (app. ddd, *J* = 8.1, 6.0, 2.9 Hz, 1 H, aromatic CH), 6.72 (broad app. t, $^3J_{H,H}$ = 3.6 Hz, 1 H, H^a), 5.51 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, H^h), 3.95 (app. dt, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 5.1 Hz, 1 H, H^i), 3.54 (app. t, $^3J_{H,H}$ = 8.6 Hz, 1 H, H^g), 2.45 (app. dq, $^2J_{H,H}$ = 19.4, $^3J_{H,H}$ = 4.7 Hz, 1 H, H^b), 2.30–2.22 (m, 1 H, H^f), 2.22–2.11 (m, 1 H, H^c), 1.80–1.40 (m, 5 H, H^d, H^e, isobutyl CH_2 and isobutyl CH), 0.91 (app. d, $^3J_{H,H}$ = 6.6 Hz, 6 H, 2× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.2 (CH), 150.8 (CH), 141.1 (C), 137.8 (C), 132.6 (CH), 130.5 (CH), 128.7 (CH), 126.4 (CH), 125.1 (C), 81.2 (CH), 79.7 (CH), 39.8 (CH), 38.9 (CH), 38.4 (CH_2), 25.7 (CH), 24.7 (CH_2), 23.4 (CH_3), 22.8 (CH_3), 20.2 (CH_2) ppm. MS (ES$^+$): *m/z* (%) = 365 (100) [MH^+ (^{81}Br)], 363 (95) [MH^+ (^{79}Br)], 347 (18), 345 (17), 279 (25), 277 (23), 207 (54), 179 (19).

HRMS (ES$^+$) $C_{19}H_{24}{}^{79}BrO_2$ [MH$^+$] 363.0960; found 363.0946. Stereochemical assignment by comparison of NMR spectroscopic data with those of compound **4a**.

[(1*SR*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,7a-tetrahydro-1-isobutylisobenzofuran-4-yl]methanol (5b): Slightly impure colourless oil (12 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.33 (m, 2 H, aromatic CH), 7.12 (app. dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0 Hz, 1 H, aromatic CH), 7.04–6.95 (m, 1 H, aromatic CH), 5.83 (ddd, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 5.5, $^4J_{H,H}$ = 2.6 Hz, 1 H, H^b), 5.72 (dd, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 2.6 Hz, 1 H, H^c), 5.67 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, H^a), 5.46 (d, $^3J_{H,H}$ = 9.8 Hz, 1 H, H^f), 5.14 (app. dt, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 5.0 Hz, 1 H, H^g), 3.74 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, H^h), 3.56 (dd, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 9.8 Hz, 1 H, H^e), 3.52 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, H^i), 3.19 (apparent ddt, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 4.7, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.3 Hz, 1 H, H^d), 1.80 (broad s, 1 H, OH), 1.76–1.54 (m, 3 H, isobutyl CH_2 and isobutyl CH), 0.94 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3), 0.93 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH_3) ppm.

Prins Cyclisation of Acetaldehyde Acetal 1d at –78 °C for 1 h

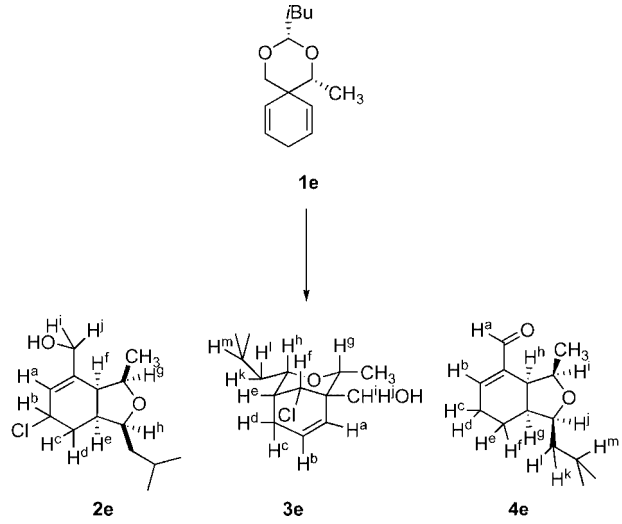


Titanium tetrachloride (0.32 mL, 2.9 mmol) was carefully added to a cooled (–78 °C) solution of acetaldehyde acetal **1d** (260 mg, 1.44 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 1 h, then carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the organic material was extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale brown oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:6) afforded compound **4d** as a yellow oil (73 mg, 28%) and compound **3d** as a pale yellow oil (61 mg, 20%), respectively. While compound **2d** was not isolated but its existence was evident from the data obtained from the crude reaction mixture.

((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2,4-dimethyl-3-oxabicyclo-[3.3.1]non-7-en-1-yl)methanol (3d): Pale yellow oil (61 mg, 20%). IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 2978, 1684, 1376, 1075, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.92 (app. dt, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 3.4 Hz, 1 H, H^b), 5.02 (app. dq, $^3J_{H,H}$ = 10.0, $^4J_{H,H}$ = 1.8 Hz, 1 H, H^a), 4.45 (app. dd, $^3J_{H,H}$ = 3.3, $^4J_{H,H}$ = 1.2 Hz, 1 H, H^f), 3.91 (d, $^2J_{H,H}$ = 11.2 Hz, 1 H, H^i), 3.72 (q, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^g), 3.70 (app. dq, $^3J_{H,H}$ = 1.7, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^h), 3.57 (d, $^2J_{H,H}$ = 11.2 Hz, 1 H, H^j), 2.33 (app. ddt, $^2J_{H,H}$ = 19.3, $^3J_{H,H}$ = 5.9, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.9 Hz, 1 H, H^c), 2.28–2.20 (m, 1 H, H^d), 2.00 –1.95 (m, 1 H, H^e), 1.17 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH^h), 1.09 (d, J = 6.3 Hz, 3 H, CH_3CH^g) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 130.8 (CH), 121.8 (CH), 76.5 (CH), 76.3 (CH), 63.5 (CH_2), 63.3 (CH), 45.6 (C), 41.2 (CH), 22.7 (CH_2); 19.0 (CH_3); 16.3 (CH_3) ppm. MS (CI): *m*/*z* (%) = 234 (100) [M + NH_4^+], 198 (79), 181 (48), 137 (27), 121 (27). HRMS (ES$^+$) $C_{11}H_{21}{}^{35}ClNO_2$ [MNH_4^+] 234.1255; found 234.1256. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g and/or H^h}.

(1*SR*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1,3-dimethylisobenzofuran-4-carbaldehyde (4d): Yellow oil (73 mg, 28%). IR (CH_2Cl_2): $\tilde{\nu}$ = 2924, 1686, 1458, 1375, 1259, 1165 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.40 (s, 1 H, H^a), 6.95 (broad singlet, 1 H, H^b), 4.39–4.30 (m, 1 H, H^i), 4.02–3.94 (m, 1 H, H^j), 3.18 (app. t, $^3J_{H,H}$ = 8.0 Hz, 1 H, H^h), 2.54–2.42 (m, 1 H, H^c), 2.28–2.15 (m, 1 H, H^d), 2.00–1.86 (m, 1 H, H^g), 1.76–1.67 (m, 1 H, H^e), 1.41–1.27 (m, 1 H, H^f), 1.18 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH^j), 0.87 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH^i) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.5 (CH), 152.8 (CH), 140.9 (C), 76.2 (CH), 74.8 (CH), 40.2 (CH), 39.4 (CH), 25.7 (CH_2), 19.8 (CH_3), 19.2 (CH_2), 15.1 (CH_3) ppm. MS (EI): *m*/*z* (%) = 180 (12) [M$^+$], 178 (37), 136 (100), 107 (98), 79 (98). HRMS (EI) $C_{11}H_{16}O_2$ [M$^+$] 180.1150; found 180.1161.

Prins Cyclisation of Isobutyl Acetal 1e at –78 °C for 2 h



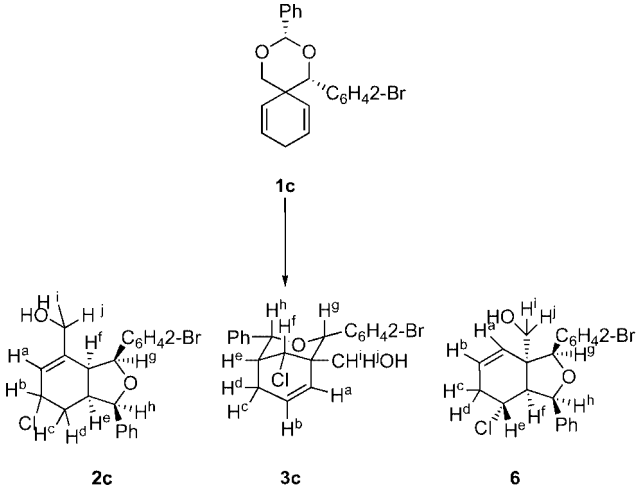
Titanium tetrachloride (0.18 mL, 1.6 mmol) was carefully added to a cooled (–78 °C) solution of isobutyl acetal **1e** (188 mg, 0.85 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 2 h, then carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the organic material extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:6) afforded compound **4e** as a yellow oil (70 mg, 37%), and compound **3e** as a pale yellow oil (31 mg, 14%), respectively. While compound **2e** was not isolated but its existence was evident from the data obtained from the crude reaction mixture.

((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-4-isobutyl-2-methyl-3-oxabicyclo[3.3.1]non-7-en-1-yl)methanol (3e): Pale yellow oil which solidified on standing (31, mg, 14%), m.p. 70–72 °C. IR (neat): $\tilde{\nu}$ = 3442 cm^{-1} (broad), 3024, 2955, 1467, 1369, 1107, 1042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.92 (app. dt, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 3.5 Hz, 1 H, H^b), 5.02 (app. dq, $^3J_{H,H}$ = 10.0, $^4J_{H,H}$ =

1.9 Hz, H^a), 4.48 (app. dd, $^3J_{H,H}$ = 3.2, $^4J_{H,H}$ = 1.3 Hz, 1 H, H^f), 3.91 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, H^i), 3.69 (q, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^g), 3.57 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, H^j), 3.56–3.51 (m, 1 H, H^h), 2.32 (app. ddt, $^2J_{H,H}$ = 19.3, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.7 Hz, 1 H, H^e), 2.24–2.16 (m, 1 H, H^d), 2.01–1.96 (m, 1 H, H^e), 1.67 (app. nonet, $^3J_{H,H}$ = 6.6 Hz, 1 H, H^m), 1.53 (app. ddd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^k), 1.16–1.10 (m, 1 H, H^l), 1.08 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3CH^g), 0.84 [d, $^3J_{H,H}$ = 6.4 Hz, 3 H, one of $(CH_3)_2CH$], 0.83 [d, $^3J_{H,H}$ = 6.4 Hz, 3 H, one of $(CH_3)_2CH$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 130.9 (CH), 121.9 (CH), 79.1 (CH), 76.4 (CH), 63.5 (CH and CH_2), 45.9 (C), 42.0 (CH_2), 40.2 (CH), 24.6 (CH), 23.2 (CH_2), 23.0 (CH_3), 22.5 (CH_3), 16.2 (CH_3) ppm. MS (CI): *m/z* (%) = 276 (100) [M + NH_4^+], 240 (50), 223 (22), 179 (23). HRMS (ES^+) $C_{14}H_{27}{}^{35}ClNO_2$ [MNH_4^+] 276.1725; found 276.1723. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g} {H^f,H^h} {H^g,H^h}.

(1*SR*,3*SR*,3a*SR*,7a*SR*)-1-Isobutyl-1,3,3a,6,7,7a-hexahydro-3-methylisobenzofuran-4-carbaldehyde (4e): Yellow oil (70 mg, 37%). IR (neat): $\tilde{\nu}$ = 2954, 1684, 1642, 1466, 1371, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.39 (s, 1 H, H^a), 6.94 (app. d, $^3J_{H,H}$ = 5.1 Hz, 1 H, H^b), 4.31 (app. dq, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^i), 3.86 (ddd, $^3J_{H,H}$ = 7.3, $^3J_{H,H}$ = 6.1, $^3J_{H,H}$ = 4.0 Hz, 1 H, H^j), 3.16 (app. t, $^3J_{H,H}$ = 8.1 Hz, 1 H, H^h), 2.45 (app. dtd, $^2J_{H,H}$ = 20.0, $^3J_{H,H}$ = 4.2, $^3J_{H,H}$ = 1.1 Hz, 1 H, H^c), 2.26–2.12 (m, 1 H, H^d), 1.90 (app. ddt, $^3J_{H,H}$ = 13.1, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 4.0 Hz, 1 H, H^g), 1.72–1.59 (m, 2 H, H^e and H^m), 1.47 (app. dt, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 7.2 Hz, 1 H, H^k), 1.41–1.27 (m, 2 H, H^f and H^l), 0.91–0.84 (m, 9 H, m, 3 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.5 (CH), 152.7 (CH), 141.0 (C), 78.7 (CH), 74.5 (CH), 39.4 (CH), 39.2 (CH), 38.8 (CH_2), 25.7 (CH_2), 25.5 (CH), 23.3 (CH_3), 22.8 (CH_3), 19.8 (CH_3), 19.3 (CH_2) ppm. MS (CI): *m/z* (%) = 222 (1) [M^+], 178 (26), 136 (59), 107 (81), 91 (100). HRMS (EI) $C_{14}H_{22}O_2$ [M^+] 222.1611; found 222.1623. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^g,H^h} {H^g,H^j} {H^h,H^i} {H^h,H^j} {H^i,H^j}.

Prins Cyclisation of Benzaldehyde Acetal 1c at –78 °C for 2 h



Titanium tetrachloride (0.16 mL, 1.5 mmol) was carefully added to a cooled (–78 °C) solution of benzaldehyde acetal **1c** (280 mg, 0.73 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 15 min, then carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the organic material extracted into CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellow solid. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:9) afforded compound **3c** as a colourless solid (85 mg, 28%), compound **6** as a pale yellow oil (30 mg, 9%) and compound **2c** as a pale yellow solid (74 mg, 24%), respectively.

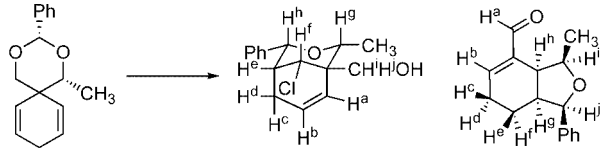
[(1*RS*,3*SR*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-6-chloro-1,3,3a,6,7,7a-hexahydro-1-phenylisobenzofuran-4-yl]methanol (2c): Pale yellow solid (74 mg, 24%) m.p. 50 –52 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3426 (broad), 3061, 3021, 2929, 1732, 1567, 1470, 1367, 1267, 1206, 1121, 916 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.82 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 2 × aromatic CH), 7.14 (m, 3 H, 3 × aromatic CH), 7.10–7.05 (m, 2 H, 2 × aromatic CH), 7.05–6.99 (m, 2 H, 2 × aromatic CH), 6.14 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, H^a), 5.36 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, H^g), 5.25 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, H^h), 3.53 (app. t, $^3J_{H,H}$ = 5.7 Hz, 1 H, H^f), 3.40–3.32 (m, 1 H, H^e), 3.32–3.26 (m, 1 H, H^b), 2.93 and 2.84 (AB quartet, $^2J_{H,H}$ = 13.5 Hz, 2 H, H^i and H^j), 2.01–1.89 (m, 2 H, H^c and H^d) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 139.0 (C), 136.4 (C), 135.9 (C), 132.6 (CH), 132.2 (CH), 130.9 (CH), 130.8 (CH), 129.1 (CH), 128.6 (CH), 127.6 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 121.3 (C), 83.6 (CH), 77.6 (CH), 64.7 (CH_2), 44.1 (CH), 37.7 (CH), 35.1 (CH), 29.6 (CH_2) ppm. MS (ES^+): *m/z* (%) = 402 (86) [MNH_4^+ – HCl, (^{81}Br)], 400 (89), 367 (84), 365 (100). HRMS (ES^+) $C_{21}H_{23}{}^{79}BrNO_2$ [MNH_4^+ – HCl] 400.0912; found 400.0909. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^e,H^f} {H^e,H^g} {H^e,H^h} {H^f,H^g} {H^f,H^h}.

[(1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-2-(2-Bromophenyl)-9-chloro-4-phenyl-3-oxabicyclo[3.3.1]non-7-en-1-yl]methanol (3c): Colourless solid (85 mg, 28%), m.p. 70–72 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3466, 3061, 3027, 2924, 1472, 1266, 1122, 1071, 1030, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.59 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.6 Hz, 1 H, aromatic CH), 7.49 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 0.9 Hz, 1 H, aromatic CH), 7.32–7.24 (m, 5 H, 5 × aromatic CH), 7.23–7.17 (m, 1 H, aromatic CH), 7.12 (app. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.7 Hz, 1 H, aromatic CH), 5.99 (app. dt, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 3.4 Hz, 1 H, H^b), 5.16 (s, 1 H, H^g), 4.92 (broad resonance, 2 H, H^h and H^f), 4.87 (app. dd, $^3J_{H,H}$ = 9.9, $^4J_{H,H}$ = 1.6 Hz, 1 H, H^a), 3.66 (dd, $^2J_{H,H}$ = 12.3, $^3J_{H,H}$ = 7.6 Hz, 1 H, H^i), 3.31 (dd, $^2J_{H,H}$ = 12.3, $^3J_{H,H}$ = 4.8 Hz, 1 H, H^j), 2.52–2.47 (m, 1 H, H^e), 2.19 (app. ddt, $^2J_{H,H}$ = 19.4, $^3J_{H,H}$ = 6.7, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.6 Hz, 1 H, H^c), 2.14–2.09 (m, 1 H, OH), 2.01–1.91 (m, 1 H, H^d) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 139.6 (C), 137.5 (C), 132.3 (CH), 131.6 (CH), 130.6 (CH), 129.8 (CH), 128.3 (2 × CH), 127.4 (CH), 127.3 (CH), 125.6 (2 × CH), 123.5 (C), 121.7 (CH), 82.4 (CH), 80.9 (CH), 63.2 (CH_2), 62.7 (CH), 46.6 (C), 41.1 (CH), 23.2 (CH_2) ppm. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Structure and stereochemistry confirmed by single-crystal X-ray diffraction.

[(1*RS*,3*SR*,3a*RS*,7*RS*,7a*SR*)-3-(2-Bromophenyl)-7-chloro-1,6,7,7a-tetrahydro-1-phenylisobenzofuran-3a-yl]methanol (6): Pale yellow oil (30 mg, 9%). IR (neat): $\tilde{\nu}$ = 3450, 3065, 3032, 2931, 1470, 1439, 1374, 1269, 1206, 1067, 1020, 909, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.6 Hz, 1 H, aromatic CH), 7.49 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 0.9 Hz, 1 H, aromatic CH), 7.42 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, 2 × aromatic CH), 7.35–7.22 (m, 4 H, 4 × aromatic CH), 7.12 (app. td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.6 Hz, 1 H, aromatic CH), 5.66 (app. dt, $^3J_{H,H}$ = 10.2, $^3J_{H,H}$ = 4.1 Hz, 1 H, H^b), 5.25 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, H^h), 5.23 (s, 1 H, H^g), 4.81 (app. dt, $^3J_{H,H}$ = 10.2, $^4J_{H,H}$ = 1.7 Hz, 1 H, H^a), 4.04–4.01 (m, 1 H, H^e), 3.89 and 3.83 (AB quartet, $^2J_{H,H}$ = 11.3 Hz, 2 H, H^i and H^j), 3.23 (app. t, $^3J_{H,H}$ = 7.0 Hz, 1 H, H^f), 2.20–2.06 (m, 2 H, H^c and H^d) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ =

137.6 (C), 137.2 (C), 132.6 (CH), 130.9 (CH), 129.4 (CH), 128.3 (2×CH), 127.7 (CH), 127.7 (CH), 127.2 (CH), 127.0 (CH), 126.5 (2×CH), 122.6 (C), 82.4 (CH), 81.3 (CH), 66.3 (CH_2), 55.4 (CH), 55.0 (C), 51.3 (CH), 32.5 (CH_2) ppm. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g and/or H^h} {H^g and/or H^h,H^i and/or H^j}. These data are ambiguous due to overlapping peaks. However, the assigned stereochemistry is consistent with the data, and with the proposed mechanistic model.

Prins Cyclisation of Benzaldehyde Acetal 1f at –78 °C for 15 min



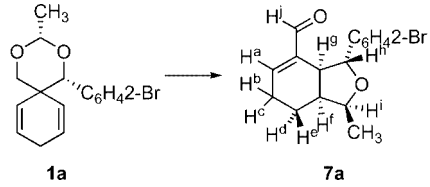
Titanium tetrachloride (0.17 mL, 1.5 mmol) was carefully added to a cooled (–78 °C) solution of benzaldehyde acetal **1f** (183 mg, 0.76 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for 15 min then carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the organic material extracted into CH_2Cl_2 (2×20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale brown oil. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:9) afforded the aldehyde **4f** as a colourless solid (36 mg, 20%) and alcohol **3f** as colourless crystals (80 mg, 38%), respectively.

[(1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2-methyl-4-phenyl-3-oxabicyclo[3.3.1]non-7-en-1-yl]methanol (3f): Colourless crystalline solid (80 mg, 38%), m.p. 144–145 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3429 (broad), 3030, 2924, 1653, 1451, 1387, 1368, 1310, 1250, 1119, 1058, 1031, 724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.16 (m, 5 H, 5×aromatic CH), 5.87 (app. dt, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 3.4 Hz, 1 H, H^b), 5.06 (app. dq, $^3J_{H,H}$ = 10.0, $^4J_{H,H}$ = 1.9 Hz, H^a), 4.70 (broad resonance, 2 H, H^h and H^f), 3.96 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, H^i), 3.90 (q, $^3J_{H,H}$ = 6.2 Hz, 1 H, H^g), 3.64 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, H^j), 2.42–2.36 (m, 1 H, H^e), 2.09 (app. ddt, $^2J_{H,H}$ = 19.3, $^3J_{H,H}$ = 6.7, $^3J_{H,H}$ and $^4J_{H,H}$ = 2.7 Hz, 1 H, H^c), 1.87–1.78 (m, 1 H, H^d), 1.20 (d, $^3J_{H,H}$ = 6.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.2 (C), 130.9 (CH), 128.2 (2×CH), 127.2 (CH), 125.6 (2×CH), 121.5 (CH), 81.7 (C), 77.1 (CH), 63.6 (CH_2), 63.1 (CH), 46.6 (C), 41.9 (CH), 23.2 (CH_2), 16.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 234 (8) [$M^+ - C_2H_4$], 198 (12), 181 (15), 107 (25), 91 (100). HRMS (EI) $C_{14}H_{15}{}^{35}ClO$ [$M - OC_2H_4$]$^+$ 234.0811; found 234.0829. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Structure and stereochemistry confirmed by single-crystal X-ray diffraction.

(1*RS*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-3-methyl-1-phenylisobenzofuran-4-carbaldehyde (4f): Pale yellow crystalline solid (36 mg, 20%), m.p. 94–96 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2966, 2925, 2885, 2805, 1671, 1637, 1449, 1172, 1092, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.40 (s, 1 H, H^a), 7.27 (m, 3 H, aromatic CH), 7.22–7.15 (m, 2 H, aromatic CH), 6.94 (app. d, $^3J_{H,H}$ = 4.8 Hz, 1 H, H^b), 5.04 (d, $^3J_{H,H}$ = 4.4 Hz, 1 H, H^j), 4.57 (dq, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^i), 3.39 (app. t, $^3J_{H,H}$ = 8.2 Hz, 1 H, H^h), 2.35 (app. dtd, $^2J_{H,H}$ = 20.0, $^3J_{H,H}$ = 5.3, $^3J_{H,H}$ = 1.3 Hz, 1 H, H^c), 2.21 (app. ddt, $^3J_{H,H}$ = 13.1, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 4.6 Hz, 1 H, H^g), 2.14–2.02 (m, 1 H, H^d), 1.18 (app. dq, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 5.3 Hz, 1 H, H^e), 1.09–1.01 (m, 1 H, H^f), 0.99 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.3 (CH), 152.9 (CH), 140.8 (C), 138.9 (C), 128.1 (2×CH), 127.0 (CH), 125.9 (2×CH), 82.1 (CH), 75.1 (CH), 41.6 (CH), 39.6 (CH), 25.7 (CH_2), 20.2 (CH_2), 20.0 (CH_3) ppm. MS (APCI): *m*/*z* (%) = 260 (100) [$M + NH_4^+$], 257 (54), 198 (13). HRMS (ES^+) $C_{16}H_{18}NaO_2$ [MNa^+] 265.1199; found 265.1200. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^g,H^h} {H^g,H^j} {H^h,H^i} {H^h,H^j}.

Prins Cyclisation of Acetaldehyde Acetal 1a at –78 °C for 1 h Followed by 25 °C for 23 h

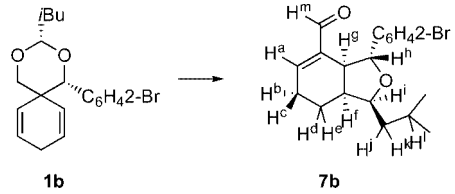
(1*SR*,3*RS*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-methylisobenzofuran-4-carbaldehyde (7a)



Titanium tetrachloride (0.22 mL, 2.0 mmol, 2 equiv.) was carefully added to a cooled (–78 °C) solution of acetaldehyde acetal **1a** (321 mg, 1.0 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. Saturated $NaHCO_3$ solution (5 mL) was added then followed by water (20 mL). The organic material was extracted into CH_2Cl_2 (2×20 mL). The combined extracts were dried with $MgSO_4$, and concentrated under reduced pressure to afford a golden yellow solid. Purification by flash chromatography (eluted in gradient mode from EtOAc/hexane, 1:9 to 5:5) afforded **7a** (80 mg, 25%) as a colourless solid, m.p. 132–135 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2942, 1682, 1422, 1378, 1163, 1012 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.29 (s, 1 H, H^j), 7.50 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.5 Hz, 1 H, aromatic CH), 7.34 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 0.9 Hz, 1 H, aromatic CH), 7.30 (app. td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 0.9 Hz, 1 H, aromatic CH), 7.04 (app. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.5 Hz, 1 H, aromatic CH), 6.81 (app. dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 2.3 Hz, 1 H, H^a), 5.07 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, H^h), 4.63 (dq, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^i), 3.16 (dd, $^3J_{H,H}$ = 9.5, $^3J_{H,H}$ = 5.8 Hz, H^g), 2.58 (app. dt, $^2J_{H,H}$ = 20.5, $^3J_{H,H}$ = 4.8 Hz, 1 H, H^b), 2.35–2.22 (m, 1 H, H^c), 2.12 (app. dq, $^3J_{H,H}$ = 13.3, $^3J_{H,H}$ = 4.6 Hz, 1 H, H^f), 1.80 (app. dt, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 4.9 Hz, 1 H, H^d), 1.65 (app. dq, $^3J_{H,H}$ = 5.4, $^2J_{H,H}$ and $^3J_{H,H}$ = 13.3 Hz, 1 H, H^e), 1.25 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.3 (CH), 150.3 (CH), 142.6 (C), 140.4 (C), 132.2 (CH), 128.8 (CH), 127.9 (CH), 127.8 (CH), 122.8 (C), 83.1 (CH), 78.6 (CH), 45.6 (CH), 41.4 (CH), 26.1 (CH_2), 18.8 (CH_2), 16.0 (CH_3) ppm. MS (APCI): *m*/*z* (%) = 323 (94) [MH^+ (^{81}Br)], 321 (100) [MH^+ (^{79}Br)], 241 (23), 165 (67), 146 (65). HRMS (ES^+) $C_{16}H_{18}O_2{}^{79}Br$ [MH^+] 321.0485; found 321.0489. Hydrogen connectivity fully supported by ^{1}H-^{1}H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g} {H^f,H^i} {H^g,H^i} {H^g,aromatic CH} {H^i,aromatic CH}. H^g and H^h also show a NOE correlation, but this is due to the conformation rather than an indication that they are on the same side of the tetrahydrofuran ring. The correlation between H^i and the aromatic CH with δ = 7.50 ppm is particularly diagnostic.

Prins Cyclisation of Isobutyraldehyde Acetal 1b at –78 °C for 1 h Followed by 25 °C for 14 h

(1*SR*,3*RS*,3a*SR*,7a*SR*)-3-(2-Bromophenyl)-1,3,3a,6,7,7a-hexahydro-1-isobutylisobenzofuran-4-carbaldehyde (7b)

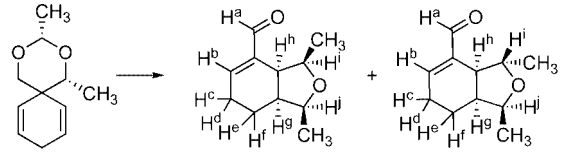


1b 7b

Titanium tetrachloride (0.22 mL, 2.0 mmol, 2 equiv.) was carefully added to a cooled (–78 °C) solution of isobutyl acetal **1b** (362 mg, 1.0 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen. The resulting mixture was stirred at this temperature for one hour then at room temperature for 14 h. Water (20 mL) was added and the organic material was extracted into CH_2Cl_2 (2 × 20 mL). The combined extracts were dried with $MgSO_4$, and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with EtOAc/hexane, 1:9) afforded **7b** (91 mg, 25%) as a yellow solid, m.p. 82–84 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3056, 2946, 1688, 1639, 1468, 1367, 1265, 1163, 1087, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.28 (s, 1 H, H^m), 7.48 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.5 Hz, 1 H, aromatic CH), 7.35–7.29 (m, 2 H, 2 × aromatic CH), 7.07–7.02 (m, 1 H, aromatic CH), 6.80 (app. dd, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 2.2 Hz, 1 H, H^a), 5.06 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, H^h), 4.51 (app. dt, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 4.9 Hz, 1 H, H^i), 3.13 (app. dd, $^3J_{H,H}$ = 8.8, $^3J_{H,H}$ = 5.9 Hz, 1 H, H^g), 2.59 (app. dt, $^2J_{H,H}$ = 20.3, $^3J_{H,H}$ = 4.9 Hz, 1 H, H^b), 2.35–2.23 (m, 1 H, H^c), 2.18–2.07 (m, 1 H, H^f), 1.85–1.60 (m, 3 H, H^d, H^e and H^l), 1.60–1.48 (m, 1 H, H^j), 1.40–1.32 (m, 1 H, H^k), 0.92 (app. t, $^3J_{H,H}$ = 6.1 Hz, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 192.3 (CH), 150.1 (CH), 142.9 (C), 140.5 (C), 132.2 (CH), 128.8 (CH), 127.8 (2 × CH), 122.8 (C), 82.9 (CH), 81.2 (CH), 45.5 (CH), 40.9 (CH), 39.5 (CH_2), 26.1 (CH_2), 25.6 (CH), 23.4 (CH_3), 22.7 (CH_3), 18.9 (CH_2) ppm. Hydrogen connectivity fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations {H^f,H^g} {H^f,H^i} {H^g,H^i} {H^g,aromatic CH} {H^i,aromatic CH}.

Prins Cyclisation of Acetaldehyde Acetal 2a at –78 °C for 1 h then 25 °C for 23 h

(1*SR*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1,3-dimethylisobenzofuran-4-carbaldehyde (4d) and (1*SR*,3*SR*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1,3-dimethylisobenzofuran-4-carbaldehyde (7d)

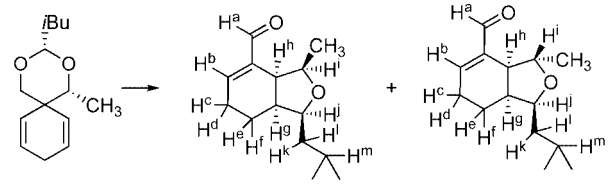


1d 4d 7d

Titanium tetrachloride (0.44 mL, 4.0 mmol, 2 equiv.) was carefully added to a cooled (–78 °C) solution of acetaldehyde acetal **1d** (360.5 mg, 2.0 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. water (20 mL) was added and the organic material was extracted into CH_2Cl_2 (3 × 20 mL). The combined extracts were dried with $MgSO_4$, and concentrated under reduced pressure to afford brown oil. Purification by flash chromatography (eluting with EtOAc/hexane, 1:9) afforded compounds **4d** and **7d** as an inseparable 3:1 mixture (133 mg, 37%) as a pale yellow solid, m.p. 38–56 °C (mixture of two diastereoisomers). IR (CH_2Cl_2): $\tilde{\nu}$ = 2974, 2939, 2879, 1682, 1640, 1457, 1422, 1372, 1216, 1165, 1095, 934 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.40 (s, 1 H, H^a of major isomer), 9.38 (s, 1 H, H^a of minor isomer), 6.95 (app. broad d, $^3J_{H,H}$ = 5.1 Hz, 1 H, H^b of major isomer), 6.83 (app. dd, $^3J_{H,H}$ = 5.6, $^3J_{H,H}$ = 3.2 Hz, 1 H, H^b of minor isomer), 4.34 (dq, $^3J_{H,H}$ = 9.9, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^i of major isomer), 4.20 (dq, $^3J_{H,H}$ = 4.2, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^j of minor isomer), 3.97 (dq, $^3J_{H,H}$ = 4.1, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^j of major isomer), 3.72 (dq, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^i of minor isomer), 3.18 (app. t, $^3J_{H,H}$ = 8.2 Hz, 1 H, H^h of major isomer), 2.75 (app. t, $^3J_{H,H}$ = 6.3 Hz, 1 H, H^h of minor isomer), 2.53–2.42 (m, 2 H, H^c of both isomers), 2.27–2.14 (m, 2 H, H^d of both isomers), 1.97–1.84 (m, 2 H, H^g of both isomers), 1.75–1.66 (m, 2 H, H^e of both isomers), 1.47–1.28 (m, 2 H, H^f of both isomers), 1.35 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3 of minor isomer), 1.18 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3 of major isomer), 1.16 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3 of minor isomer), 0.87 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3 of major isomer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.5 (CH of major isomer), 194.1 (CH of minor isomer), 152.8 (CH of major isomer), 152.6 (CH of minor isomer), 141.7 (C of minor isomer), 140.9 (C of major isomer), 79.5 (CH of minor isomer), 76.2 (CH of major isomer), 75.6 (CH of minor isomer), 74.8 (CH of major isomer), 44.0 (CH of minor isomer), 41.3 (CH of minor isomer), 40.2 (CH of major isomer), 39.4 (CH of major isomer), 25.9 (CH_2 of minor isomer), 25.7 (CH_2 of major isomer), 22.1 (CH_3 of minor isomer), 19.8 (CH_3 of major isomer), 19.2 (CH_2 of major isomer), 18.8 (CH_2 of minor isomer), 15.4 (CH_3 of minor isomer), 15.1 (CH_3 of major isomer) ppm. Hydrogen connectivity of both the major and minor isomers fully supported by ^1H-^1H COSY NMR spectroscopy. Diagnostic NOESY correlations for the major isomer **4d** {H^g,H^h} {H^g,H^j} {H^h,H^i} {H^h,H^j}.

Prins Cyclisation of Isobutyl Acetal 1e at –78 °C for 1 h then 25 °C for 23 h

(1*SR*,3*RS*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1-isobutyl-3-methylisobenzofuran-4-carbaldehyde (4e) and (1*SR*,3*SR*,3a*SR*,7a*SR*)-1,3,3a,6,7,7a-Hexahydro-1-isobutyl-3-methylisobenzofuran-4-carbaldehyde (7e)



1e 4e 7e

Titanium tetrachloride (0.12 mL, 1.1 mmol, 2 equiv.) was carefully added to a cooled (–78 °C) solution of isobutyraldehyde acetal **1e** (117 mg, 0.53 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. Water (20 mL) was added and the organic material was extracted into CH_2Cl_2 (3 × 15 mL). The combined extracts were dried with $MgSO_4$, and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with EtOAc/hexane, 0.7:9.3) afforded compounds **4e** and **7e** as an inseparable 2.6:1 mixture (153 mg, 46%) as a sticky yellow oil. IR (CH_2Cl_2): $\tilde{\nu}$ = 2956, 2865, 1682, 1644, 1468, 1371, 1260, 1162, 1095, 951 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.39 (s, 1 H, H^a of major isomer), 9.37 (s, 1 H, H^a of minor isomer), 6.94 (app. broad d, $^3J_{H,H}$ = 4.8 Hz, 1 H, H^b of major isomer), 6.82 (app. dd, $^3J_{H,H}$ = 5.2, $^3J_{H,H}$ = 1.7 Hz, 1 H, H^b of minor isomer), 4.31 (dq, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 6.4 Hz, 1 H, H^i of major isomer), 4.10–4.04 (m, 1 H, H^j of minor isomer), 3.85 (ddd, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 6.4, $^3J_{H,H}$ = 4.1 Hz, 1 H, H^j of major isomer), 3.67 (dq, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 6.1 Hz, 1 H, H^i of minor

isomer), 3.15 (app. t, $^3J_{H,H}$ = 8.0 Hz, 1 H, H^h of major isomer), 2.73 (app. t, $^3J_{H,H}$ = 6.1 Hz, 1 H, H^h of minor isomer), 2.46 (m, 2 H, H^c of both isomers), 2.29–2.14 (m, 2 H, H^d of both isomers), 2.00–1.85 (m, 2 H, H^g of both isomers), 1.71–1.58 (m, 4 H, H^e and H^m of both isomers), 1.51–1.41 (m, 2 H, H^k of both isomers), 1.40–1.25 (m, 4 H, H^f and H^l of both isomers), 1.34 (d, $^3J_{H,H}$ = 6.1 Hz, 3 H, CH_3 of minor isomer), 0.90–0.84 [m, 15 H, CH_3 of major isomer and $(CH_3)_2$–CH of both isomers] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.5 (CH of major isomer), 194.2 (CH of minor isomer), 152.8 (CH of major isomer), 152.5 (CH of minor isomer), 141.8 (C of minor isomer), 141.0 (C of major isomer), 79.2 (CH of minor isomer), 78.7 (CH of major isomer), 78.1 (CH of minor isomer), 74.5 (CH of major isomer), 44.0 (CH of minor isomer), 40.6 (CH of minor isomer), 39.4 (CH of major isomer), 39.2 (CH of major isomer), 38.9 (CH_2 of minor isomer), 38.7 (CH_2 of major isomer), 25.9 (CH_2 of minor isomer), 25.7 (CH_2 of major isomer), 25.6 (CH of minor isomer), 25.5 (CH of major isomer), 23.3 (CH_3 of major isomer), 23.2 (CH_3 of minor isomer), 22.9 (CH_3 of minor isomer), 22.8 (CH_3 of major isomer), 22.1 (CH_3 of minor isomer), 19.9 (CH_3 of major isomer), 19.3 (CH_2 of major isomer), 18.9 (CH_2 of minor isomer) ppm. Hydrogen connectivity of both the major and minor isomers fully supported by ^1H-^1H COSY NMR spectroscopy.

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