Rh^I-Catalysed Formation of Two Conformational Diastereoisomers Due to a *cis*-Cyclohexane-1,2-diol Moiety. X-Ray Molecular Structure of Two Stereoisomers of 4′-Isopropenyl-7,9-dioxabicyclo[4.3.0]nonane-8-spiro-cyclohexan-3′-yl *p*-Bromobenzoate

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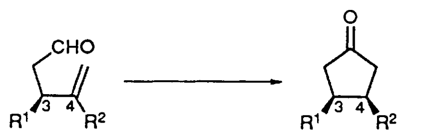
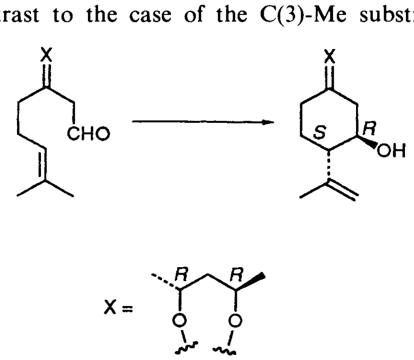
It is well known that *cis*-cyclohexane-1,2-diol and its mirror image are not superposable, but that these isomers are rapidly interconvertible by flipping from one chair conformation to the other. That is they exist as a pair of conformational enantiomers. Two aldehydes, 2-[8-(4-methylpent-3-enyl)-7,9-dioxabicyclononan-8-yl]ethanals, with the *cis*-cyclohexane-1,2-dioxy function at C(3) are cyclized by a Rh^I (Wilkinson) complex to give two conformational diastereoisomers due to the cyclohexane-1,2-diol moiety. Each conformational diastereoisomer of the title compound's parent alcohol yielded *trans*-3-hydroxy-4-isopropenylcyclohexanone and *cis*-cyclohexane-1,2-diol after deprotection with 5% aq. AcOH. Unambiguous stereochemistry of two of the parent alcohols was determined by X-ray crystallographic analysis of their *p*-bromobenzoates. The stereochemistry of the 1,3-dioxolane ring, including C(1) and C(2) of the *cis*-cyclohexane-1,2-diol and C(1′) of the *trans*-3-hydroxy-4-isopropenylcyclohexanone, was C(1′)-axial-O-axial-C(1) and C(1′)–equatorial–O–equatorial–C(2) for the two title compounds, and C(1′)-axial-O-equatorial-C(1) and C(1′)–equatorial–O–axial–C(2) for the other pair of isomers.

Regio- and stereo-specific C–C bond formation is essential in modern synthetic organic chemistry. It is well known that metal-catalysed C–C bond formation plays an important role in this field. Previously, we have reported that Rh^I-catalysed cyclizations are available for the preparation of *cis*-3,4-disubstituted cyclopentanones[1] from 3,4-disubstituted pent-4-enals (Scheme 1) and cyclohexanol derivatives[2,3] from oct-6-en-1-als. In the synthesis of cyclohexanol derivatives, 7-methyloct-6-enals[3] with a chiral acetal at the C(3)-position were diastereoselectively cyclized to only the *trans*-alcohol (Scheme 2), in contrast to the case of the C(3)-Me substrate which afforded a mixture of *cis*- and *trans*-alcohols. As a part of our studies on Rh^I-catalysed cyclization, the bulky *cis*-cyclohexane-1,2-diol was selected to examine the effect of substituents at the C(3)-position of oct-6-enals.

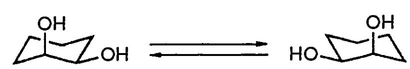


Scheme 1 *Reagent:* Rh^I complex



Scheme 2 *Reagent: Rh^I* complex

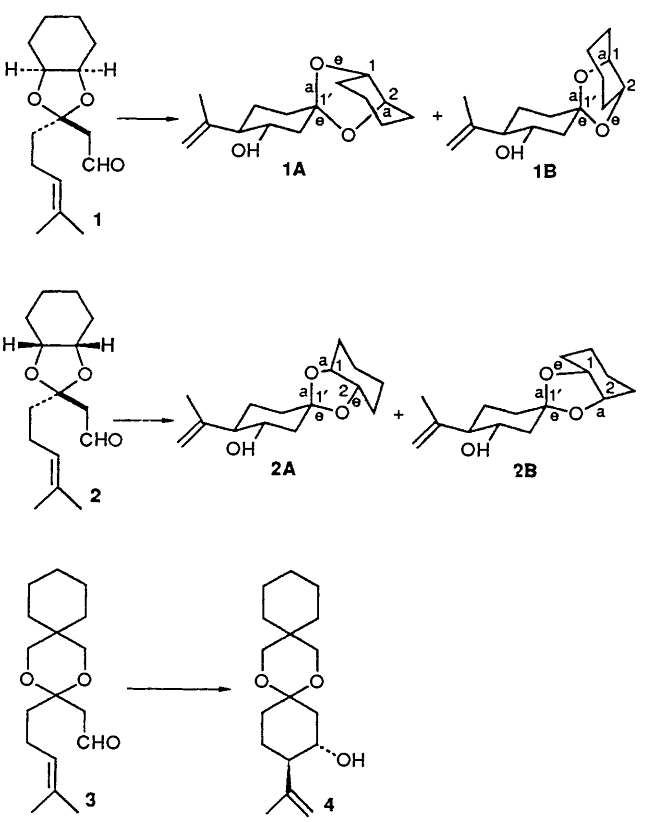
It is well known that although *cis*-cyclohexane-1,2-diol and its mirror image are not superposable, these isomers are rapidly interconvertible by the flipping of one chair conformation into the other (Scheme 3). That is to say, they exist as a pair of conformational enantiomers, which are impossible to isolate and whose optical purity cannot be measured. During our studies on Rh^I-catalysed cyclization we succeeded in the isolation of two conformational diastereoisomers derived from *cis*-cyclohexane-1,2-diol.[4]



Scheme 3

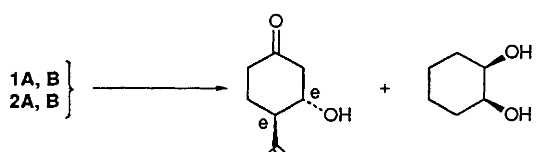
Chemistry.—*Rh^I-catalysed cyclization.* When aldehyde **1** or **2** with the *cis*-cyclohexane-1,2-dioxy function at the C(3)-position was heated at reflux in chloroform for 7 h in the presence of equimolar Rh^I (Wilkinson complex) each aldehyde afforded two cyclized products, **1A** (polar fraction, 19%) and **1B** (less polar fraction, 50%), or **2A** (polar fraction, 24%) and **2B** (less polar fraction, 26%), respectively (Scheme 4). Each isomer could be isolated by a flash silica gel column chromatography. It is noteworthy that $ZnBr_2$/benzene-catalysed cyclization of compound **2** at room temperature for 1 h afforded only isomer **2A** (65%), and isomer **2B** was not obtained. This interesting finding suggests that Rh^I-catalysed cyclization proceeds by a different mechanism to that pertaining in the case of the Lewis acid-catalysed reaction.[3,5] Stereochemistry of species **1A,B** and **2A,B** was unambiguously established on the basis of the following observations.

Structure determination and discussion. In the ^1H NMR spectrum of each cyclized product two olefinic protons appeared as a broad singlet at δ 4.90. On the basis of our previous findings[3c] that the two olefinic protons in the *trans*-3-hydroxy-4-isopropenylcyclohexane derivatives appear as a broad singlet, while one of the two olefinic protons in the *cis*-alcohol shifts



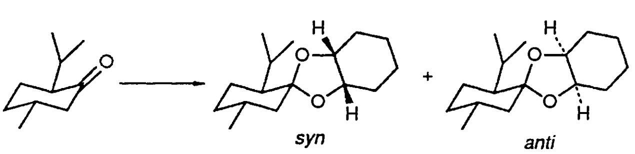
Scheme 4

remarkably upfield, isomers **1A** and **1B** as well as **2A** and **2B** were assigned to the 3,4-*trans* configuration. More definitive evidence for the *trans*-configuration was obtained by deprotection of each cyclized product with 5% aq. AcOH–tetrahydrofuran (THF) to afford *trans*-3-hydroxy-4-isopropenylcyclohexanone[3b] and *cis*-cyclohexane-1,2-diol (Scheme 5). Therefore the isomers of the cyclized products may be rationalized by taking the formation of conformational diastereoisomers into consideration.



Scheme 5 *Reagents:* aq. AcOH

Harada *et al.*[6] reported that ketalization of menthan-1-one with *cis*-cyclohexane-1,2-diol in the presence of trimethylsilyl trifluoromethanesulphonate (TMSOTf)[7] in CH_2Cl_2 afforded the *syn*- and the *anti*-ketal in ratio 6.8:1 (Scheme 6). In their behaviour on TLC and their ^{1}H NMR signal patterns the *syn*- and *anti*-spiroketals are similar to isomers **1B** and **2A**, respectively. In this ketalization the conformational diastereoisomers attributable to the *cis*-cyclohexanedioxy function were not obtained.



Scheme 6 *Reagents: cis*-cyclohexane-1,2-diol, TMSOTf, CH_2Cl_2

Each conformational diastereoisomer is similar in spectral data. More interesting findings concerning ^{1}H NMR spectrum

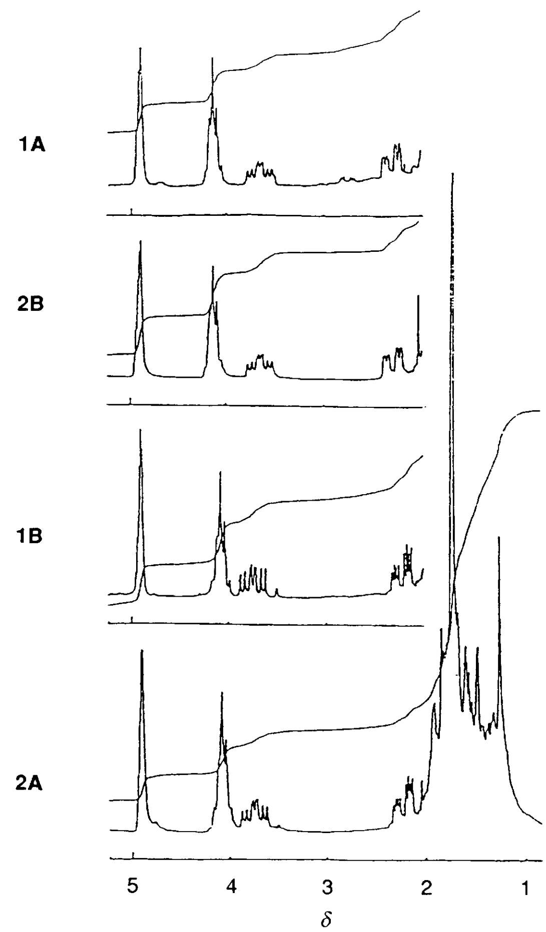
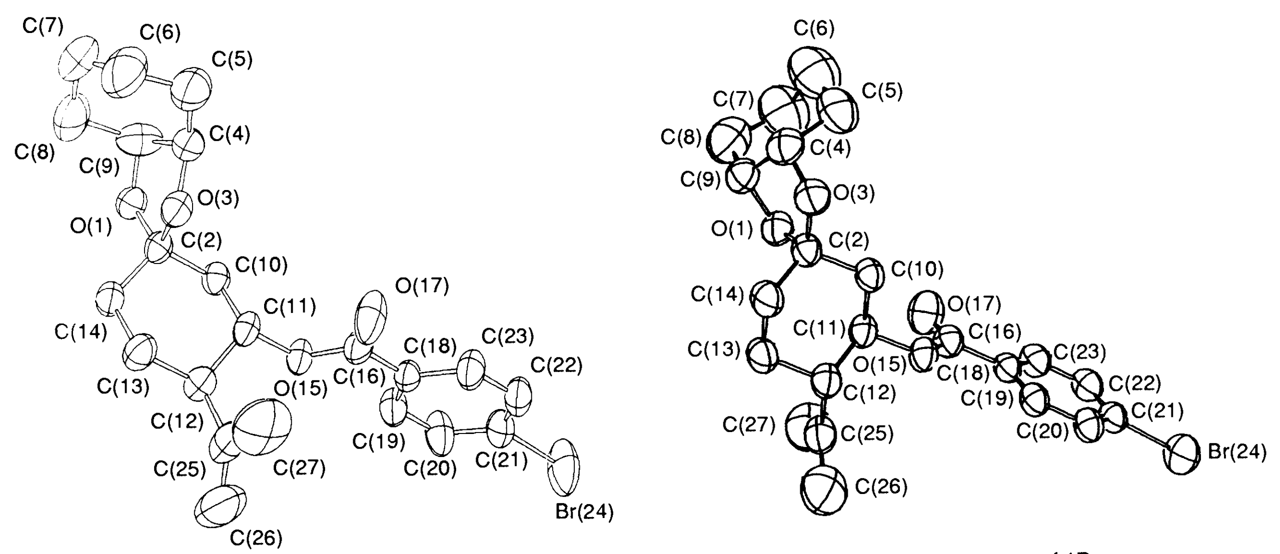


Fig. 1 ^{1}H NMR spectra of isomers **1A**, **2B**, **1B** and **2A**

of each isomer are that the most polar, **2A**, and the least polar, **1B**, in TLC showed remarkable similarity, as well as the case of isomers **2B** and **1A** (**2B** and **1A** have very close R_f-values) (Fig. 1). That is to say, two HC–O protons (**1B**: δ 4.073, **2A**: δ 4.096) of cyclohexane-1,2-dioxy function in isomers **1B** and **2A** appear as br s signals more upfield than those of the corresponding isomers (**1A**: δ 4.133, **2B**: δ 4.125). One HC–O proton (**1B**: δ 3.732, **2A**: δ 3.729) of the alcohol function was observed as a br t signal at lower field than those of isomers **1A** (δ 3.661) and **2B** (δ 3.659). Unambiguous stereochemistry of isomers **2A** and **1B** was determined, after converting them into *p*-bromobenzoates (*p*-bromobenzoate of **1B**: m.p. 80 °C, *p*-bromobenzoate of **2A**: m.p. 146 °C), by X-ray crystallographic analysis (Fig. 2). In species **1B** and **2A**, the C(1) and C(2) of the *cis*-cyclohexane-1,2-dioxy function and the C(1′) of the *trans*-3,4-disubstituted cyclohexane form the 1,3-dioxolane ring, and two cyclohexane rings are linked by two bonds of the C(1′)–axial–O–axial–C(1) and C(1′)–equatorial–O–equatorial–C(2) conformations. The same stereochemistry in the dioxolane ring (conformational enantiomers in the 1,3-dioxolane ring) of compounds **1B** and **2A** accounts for the remarkable similarity in their ^{1}H NMR spectra. Therefore, the stereochemistry of the 1,3-dioxolane ring in species **1A** and **2B**, which are extremely similar in the ^{1}H NMR spectra, should be C(1′)–axial–O–equatorial–C(1) and C(1′)–equatorial–O–axial–C(2).

Interconversion of isomers **2A** and **2B** (or **1A** and **1B**) was not observed even at reflux (8 h) in toluene or benzene, indicating that each isomer is thermodynamically stable. However, treatment of isomer **1A** (or **1B**) with large excess of zinc bromide/benzene at room temperature for 30 h afforded an equilibrium mixture of isomers **1A** and **1B**. A similar equilibrium was also observed upon identical treatment of **2A** (or



p-Bromobenzoate of **2A** *p*-Bromobenzoate of **1B**

Fig. 2 ORTEP Drawings of *p*-bromobenzoates of species **1B** and **2A**

2B). In further treatment of each conformational diastereoisomer with the Wilkinson complex in refluxing benzene no interconversion was observed. This finding suggests that each conformational diastereoisomer was directly formed under the Rh^{I}-catalysed cyclization reaction conditions employed, and was not produced by isomerization of one diastereoisomer.

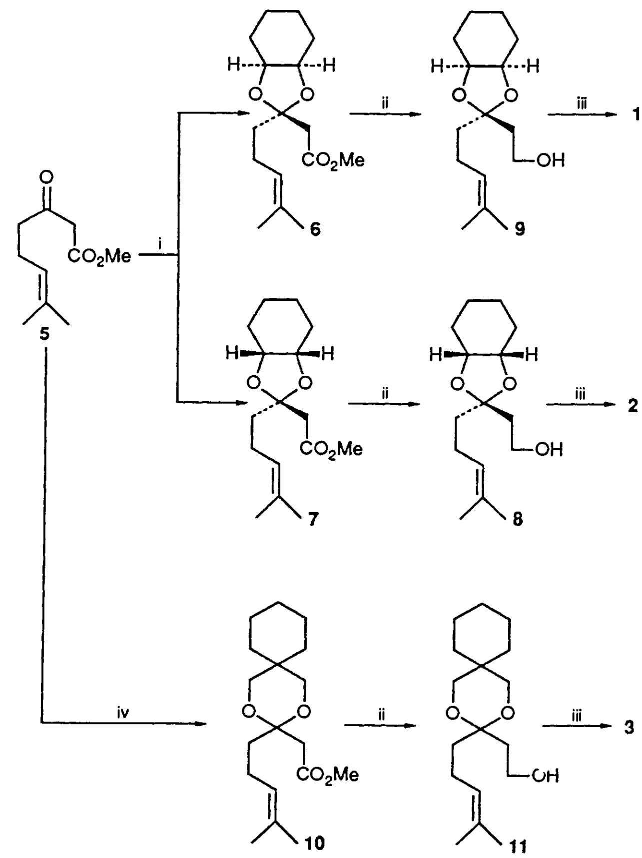
To examine the formation of another type of conformational diastereoisomer, the aldehyde **3** with a cyclohexane-1,1-dimethoxy function at C(3) was submitted to Rh^{I}-catalysed cyclization, but this reaction resulted in the formation of only one isomer.

The mechanistic pathways for the Rh^{I}-catalysed cyclization have not been established.

Synthesis of substrates. Methyl 7-methyl-3-oxooct-6-enoate **5** [3b] and *cis*-cyclohexane-1,2-diol in benzene were refluxed for 12 h in the presence of toluene-*p*-sulphonic acid (PTSA) under azeotropic conditions. Silica gel column chromatography of the crude product afforded a less polar fraction **6** and a more polar fraction **7** in the ratio 4:6 (99% yield). The relative configuration of the cyclohexane ring to the methyl ester was determined to be as shown in Scheme 7 by analysis (CH_2O_2 and HC–O) of the nuclear Overhauser effect difference spectra (NOEDS) of species **6** and **7**. Reduction of each ester (**6** and **7**) with $LiAlH_4$ afforded the corresponding alcohol **9** (85%) and **8** (95%), and subsequent oxidation [pyridinium chlorochromate (PCC)] afforded the corresponding aldehyde **1** (37%) and **2** (44%). Ketalization of compound **5** with cyclohexane-1,1-dimethanol in the presence of PTSA afforded compound **10** (84%), and subsequent reduction with $LiAlH_4$ followed by PCC oxidation gave the aldehyde **3** (70% from **10**).

Experimental

General Procedures.—IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-PS-100 or a GX-270 spectrometer. Coupling constants are reported in Hz. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Each reaction was carried out under N_2 and was monitored by TLC (silica gel 60F-254 plates). For gravity column chromatography, silica gel (Merck, Kieselgel 60, 70–230 mesh) was used and, for flash column chromatography, 230–400 mesh silica gel was used. All organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure on a rotary evaporator. Unless otherwise indicated, each product was obtained as an oil. The Wilkinson complex was prepared by J. F. Normant's procedure.[8] The purity of all title compounds was judged to be $\geqslant 95\%$ by TLC and GC. Details of X-ray crystallographic analysis of isomers **1B** and **2A** are given in supplementary material.*



Scheme 7 *Reagents:* i, H^+, cyclohexane-1,2-diol; ii, $LiAlH_4$; iii, PCC; iv, H^+, cyclohexane-1,1-dimethanol

* *Supplementary material available.* Tables of crystallographic analysis of **1B** and **2A** are available from the Cambridge Crystallographic Data Centre (see Instructions for Authors, section 5.6.3, in the January issue).

Rh[I] *(Wilkinson)-catalysed Cyclization*.—A mixture of Wilkinson complex (550 mg, 0.594 mmol) and the aldehyde **1** (151 mg, 0.594 mmol) in $CHCl_3$ (50 cm^3) was heated at reflux for 7 h under N_2. After removal of the solvent under reduced pressure the residue was diluted with diethyl ether and the precipitate was filtered off. The ether layer was concentrated under reduced pressure to leave a mixture of isomers **1A** and **1B**, which could be separated by flash column chromatography. The fraction eluted with hexane–AcOEt (7:1) afforded isomer **1B** (80 mg, 50%) as an oil. The second fraction, eluted with hexane–AcOEt (3:1), afforded isomer **1A** (32 mg, 19%) as an oil.

In a manner similar to that described for the cyclization of aldehyde **1**, identical cyclization of aldehyde **2** (170 mg) with the Wilkinson complex (631 mg) in $CHCl_3$ (60 cm^3) afforded a mixture of isomers **2A** and **2B**, which could be separated by flash column chromatography. The fraction eluted with hexane–AcOEt (6:1) afforded isomer **2B** (52 mg, 26%), and the second fraction, eluted with hexane–AcOEt (2:1), gave isomer **2A** (40 mg, 24%).

Similarly, Rh[I]-catalysed cyclization of aldehyde **3** (283 mg) with Wilkinson complex (935 mg) afforded the cyclized product **4** (163 mg, 58%) as an oil.

Compound **1A**: ν_{max}(neat)/cm^{-1} 3400, 1640, 1440, 1350, 1240, 1120 and 1040; δ_H($CDCl_3$) 1.257–2.397 (15 H, m), 1.763 (3 H, d, *J* 1.2, Me), 2.171–2.397 (1 H, br d), 3.661 (1 H, br t, HCO), 4.133 (2 H, br s, cyclohexanedioxy) and 4.922 (2 H, br s, $=CH_2$); *m*/*z* (relative intensity) 252 (M^+) (6.9), 234 (11.8), 169 (432.2), 153 (775.8), 140 (448.9), 98 (187.2), 81 (1000.0), 79 (276.3), 69 (136.4), 55 (529.9) and 43 (48.0); HRMS (Found: M^+, 252.1745. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Compound **1B**: ν_{max}(neat)/cm^{-1} 3500, 1640, 1442, 1350, 1240, 1120 and 1040; δ_H($CDCl_3$) 1.255–2.326 (15 H, m), 1.741 (3 H, d, *J* 0.8, Me), 2.132–2.326 (1 H, br d), 3.732 (1 H, br t, HCO), 4.073 (2 H, br s, cyclohexanedioxy) and 4.917 (2 H, br s, $=CH_2$); *m*/*z* 252 (M^+) (6.3), 234 (10.8), 169 (422.9), 153 (787.8), 140 (447.0), 98 (309.1), 81 (1000.0), 79 (406.8), 69 (313.9), 55 (660.6) and 43 (397.1); HRMS (Found: M^+, 252.1739. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Compound **2A**: ν_{max}(neat)/cm^{-1} 3450, 1645, 1445, 1355, 1305, 1240, 1120, 1045 and 1035; δ_H($CDCl_3$) 1.255–2.301 (15 H, m), 1.732 (3 H, s, Me), 2.167–2.317 (1 H, br d), 3.729 (1 H, br t, HCO), 4.096 (2 H, br s, cyclohexanedioxy) and 4.906 (2 H, br s, $=CH_2$); *m*/*z* 252 (M^+) (29.9), 234 (29.5), 169 (479.3), 153 (875.9), 140 (474.2), 98 (187.2), 81 (1000.0), 79 (128.8), 69 (187.2), 55 (410.1) and 43 (48.0); HRMS (Found: M^+, 252.1704. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Compound **2B**: ν_{max}(neat)/cm^{-1} 3450, 1645, 1445, 1355, 1195, 1135, 1045 and 1030; δ_H($CDCl_3$) 1.259–2.392 (15 H, m), 1.745 (3 H, s, Me), 2.171–2.392 (1 H, br d), 3.659 (1 H, br t, HCO), 4.125 (2 H, br s, cyclohexanedioxy) and 4.909 (2 H, br s, $=CH_2$); *m*/*z* 252 (M^+) (6.3), 234 (14.9), 169 (1000.0), 153 (120.7), 140 (198.2), 99 (208.0), 98 (118.0), 81 (640.0), 79 (100.5), 69 (97.8), 55 (165.8) and 43 (397.1); HRMS (Found: M^+, 252.1741. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Compound **4**: ν_{max}(neat)/cm^{-1} 3450, 1640, 1445, 1060 and 750; δ_H($CDCl_3$) (GX-270) 1.232–1.862 (15 H, m), 1.715 (3 H, t, *J* 0.6, Me), 1.985 (1 H, m), 2.183 (1 H, m), 2.768 (1 H, br d), 3.617 (5 H, m, 2 × CH_2O and CHO) and 4.902 (2 H, br s, $=CH_2$); *m*/*z* 280 (M^+) (13.0), 262 (20.7), 235 (111.8), 197 (514.5), 109 (515.8) and 83 (1000); HRMS (Found: M^+, 280.2057. Calc. for $C_{17}H_{28}O_3$: 280.2037).

p-*Bromobenzoates of Isomers* **1B** *and* **2A**.—*p*-Bromobenzoates were prepared by standard methods by using *p*-bromobenzoyl chloride–pyridine, and each product was purified by silica gel column chromatography, and was then recrystallized from hexane (**1B**) or EtOH (**2A**). The benzoates of compounds **1A** and **2B** were obtained as an oily substance.

p-*Bromobenzoate of Compound* **1B**: m.p. 80 °C; ν_{max}(Nujol)/cm^{-1} 1710, 1640, 1585, 1440, 1265 and 1100; δ_H($CDCl_3$) 1.304–1.956 (13 H, m), 1.704 (3 H, t, *J* 2.5, Me), 2.191–2.453 (2 H, m), 4.088 (2 H, m, CHO), 4.721 (1 H, m, C=CH), 4.787 (1 H, m, C=CH), 5.274 (1 H, dt, *J* 4.6, 10.9, CHOCO) and 7.466–7.905 (4 H, ArH); *m*/*z* 436 (M^+), 434, 205, 185, 183, 153, 140, 98, 81 and 55; HRMS (Found: M^+, 436.1058, 434.1102. Calc. for $C_{22}H_{27}BrO_4$: M, 436.1073, 434.1093).

p-*Bromobenzoate of compound* **2A**: m.p. 146 °C; ν_{max}(Nujol)/cm^{-1} 1705, 1630, 1580, 1430, 1250 and 1085; δ_H($CDCl_3$) 1.333–1.931 (13 H, m), 1.699 (3 H, t, *J* 1.1, Me), 2.208–2.510 (2 H, m), 4.151 (2 H, m, CHO), 4.711 (1 H, m, C=CH), 4.768 (1 H, m, C=CH), 5.17 (1 H, dt, *J* 4.6, 11.1, CHOCO) and 7.478–7.909 (4 H, m, ArH); *m*/*z* 436 (M^+), 434, 353, 351, 207, 153, 140, 98, 81 and 55; HRMS (Found: M^+, 436.1081, 434.1072. Calc. for $C_{22}H_{27}BrO_4$: M, 436.1073, 434.1093).

Crystal Data for the p-*Bromobenzoate of Compound* **1B**.—$C_{22}H_{27}BrO_4$, M=435.4, triclinic, $a = 11.450(2)$, $b = 11.791(2)$, $c = 8.969(1)$ Å, $\alpha = 110.14(1)$, $\beta = 111.68(1)$, $\gamma = 80.44(1)°$, $V = 1055.4(3)$ Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda = 1.5418$ Å), space group $P\bar{1}$, $Z = 2$, $D_x = 1.37$ g cm^{-3}, $\mu = 28.45$ cm^{-1} for Cu-$K\alpha$ radiation.

Data Collection and Processing for the p-*Bromobenzoate of Compound* **1B**.—Enraf–Nonius CAD-4 diffractometer, $\omega/2\theta$ mode with ω scan width = 1.00 + 0.14 tanθ, ω scan speed 1.6–5.5 deg min^{-1}, graphite-monochromated Cu-$K\alpha$ radiation; 3300 reflections measured ($0 < \theta \leqslant 30°$, $\pm h$, $\pm k$, l), 2948 unique reflections with $I > 2.3\sigma(I)$, absorption correction not applied.

Structure Analysis and Refinement for the p-*Bromobenzoate of Compound* **1B**.—The structure was solved by direct methods (MULTAN 82[9a]) and successive Fourier syntheses. Refinement was by block-diagonal least-squares with anisotropic temperature factors. Hydrogen atoms were located from the difference Fourier maps and were refined isotropically. The weighting scheme was $w = 2.944 - 0.123\,|F_o|$ for $|F_o| < 5.14$, $w = 2.437$ for $5.14 \leqslant |F_o| \leqslant 27.95$ and $w = (11.745 - 1.333\,|F_o| + 0.033\,|F_o|^2)^{-1}$ for $|F_o| > 27.95$. Final *R*- and R_w-values were 0.046 and 0.052. Calculations were performed with the SDP program package[9b] and UNICS III program system.[9c] The atomic scattering factors were taken from International Tables for X-ray Crystallography.[9d] Atomic co-ordinates are given in Table 1.

Crystal Data for the p-*Bromobenzoate of Compound* **2A**.—$C_{22}H_{27}BrO_4$, M = 435.1, monoclinic, $a = 17.628(7)$, $b = 16.339(4)$, $c = 16.378(6)$ Å, $\beta = 118.39(3)°$, $V = 4149(3)$ Å^3, space group $C2/c$, $Z = 8$, $D_x = 1.39$ g cm^{-1}, μ(Cu-$K\alpha$) = 31.7 cm^{-1}, crystal dimension ~0.4 × 0.3 × 0.3 mm.

Data Collection and Processing for the p-*Bromobenzoate of Compound* **2A**.—Data set was collected on a Rigaku AFC-5 diffractometer using $\omega/2\theta$ scanning and graphite-monochromated Cu-$K\alpha$ radiation. 2946 Out of 3543 unique data measured ($1.0 < \theta < 75°$, $+h$, $+k$, $\pm l$) had $F \geqslant 3\sigma(F)$ and were used in subsequent structure solution and refinement.

Structure Analysis and Refinement for the p-*Bromobenzoate of Compound* **2A**.—The structure was solved by direct methods (MULTAN 78[10a]) and successive Fourier syntheses. Refinement was by block-diagonal least-squares with anisotropic temperature factors. Hydrogen atoms were located from the difference Fourier maps and were refined isotropically. The weighting scheme was $w = 1/(0.0025F_o{}^2 + 0.05F_o + 1.25)$ and

Table 1 Final atomic co-ordinates ($\times 10^5$) for the bromobenzoate of compound **1b**

Atom	x	y	z
O(1)	63 302(20)	67 560(20)	11 603(27)
C(2)	52 404(27)	75 283(26)	120 404(37)
O(3)	53 423(19)	85 565(18)	116 103(27)
C(4)	66 535(31)	86 460(32)	119 536(46)
C(5)	68 340(44)	94 199(37)	110 055(71)
C(6)	64 716(54)	88 057(46)	91 287(72)
C(7)	71 548(58)	75 988(49)	87 680(74)
C(8)	67 994(44)	67 910(37)	94 861(56)
C(9)	70 719(31)	73 238(33)	113 988(48)
C(10)	40 496(28)	69 024(27)	107 947(36)
C(11)	28 917(27)	76 793(26)	110 091(38)
C(12)	28 534(29)	80 401(27)	127 873(40)
C(13)	40 749(31)	86 708(31)	140 297(39)
C(14)	52 423(30)	78 862(32)	138 389(39)
O(15)	17 946(19)	69 650(18)	98 933(25)
C(16)	11 613(28)	71 484(27)	84 149(39)
O(17)	14 119(25)	78 838(24)	79 312(33)
C(18)	741(26)	63 526(26)	74 240(35)
C(19)	−1 631(28)	54 893(27)	79 988(36)
C(20)	−12 098(30)	48 007(29)	70 840(38)
C(21)	−20 041(28)	49 791(29)	55 909(37)
C(22)	−17 705(29)	58 049(30)	49 674(38)
C(23)	−7 256(30)	64 881(29)	58 973(39)
Br(24)	−34 982(4)	41 109(4)	43 783(5)
C(25)	16 932(33)	88 070(31)	130 340(47)
C(26)	11 519(50)	85 819(43)	140 319(75)
C(27)	12 494(48)	97 874(46)	123 124(75)

Table 2 Final atomic co-ordinates ($\times 10^4$) for the bromobenzoate of compound **2A**

Atom	x	y	z
O(1)	7215(2)	3871(2)	7308(2)
C(2)	6318(2)	3755(2)	6683(2)
O(3)	5877(2)	4220(2)	7062(2)
C(4)	6459(3)	4243(3)	8050(3)
C(5)	6225(4)	4885(4)	8536(4)
C(6)	6412(5)	5734(4)	8328(6)
C(7)	7297(6)	5826(4)	8516(5)
C(8)	7516(4)	5248(4)	7952(5)
C(9)	7314(3)	4302(4)	8097(3)
C(10)	6088(2)	2855(2)	6643(3)
C(11)	5137(2)	2729(2)	5971(3)
C(12)	4913(3)	3006(2)	5006(3)
C(13)	5154(2)	3913(3)	5051(3)
C(14)	6094(2)	4075(2)	5730(3)
O(15)	4957(2)	1857(1)	5953(2)
C(16)	4409(2)	1624(2)	6262(3)
O(17)	4050(3)	2092(2)	6523(3)
C(18)	4276(2)	729(2)	6222(2)
C(19)	4692(3)	191(2)	5927(3)
C(20)	4526(3)	−639(3)	5886(4)
C(21)	3944(3)	−912(2)	6158(3)
C(22)	3542(3)	−397(3)	6483(3)
C(23)	3719(3)	425(3)	6517(3)
Br(24)	3654(1)	−2037(1)	6063(1)
C(25)	3983(3)	2859(3)	4283(4)
C(26)	3831(4)	2478(5)	3499(4)
C(27)	3305(4)	3168(6)	4451(5)

the final residuals were $R = 0.067$ and $R_w = 0.10$. Calculations were performed with the DIRECT-SEARCH program system.[10b] The atomic scattering factors were taken from International Tables for X-ray Crystallography.[9d] Atomic co-ordinates are given in Table 2.

Methyl 2-{1αH,6αH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*[4.3.0]*nonan*-8β-*yl*}*acetate* **6** *and Methyl* 2-{1βH,6βH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*[4.3.0]*nonan*-8β-*yl*}-*acetate* **7**.—A mixture of methyl 7-methyl-3-oxooct-6-enoate **5** (2.30 g) and *cis*-cyclohexane-1,2-diol (4.16 g) in benzene was refluxed in the presence of PTSA (trace) under azeotropic conditions. Reaction was monitored by TLC. The reaction mixture was washed and dried, then removal of solvent under reduced pressure afforded a mixture of compounds **6** and **7**, which could be separated by column chromatography on silica gel. The fractions eluted with hexane–AcOEt (9:1) and with hexane–AcOEt (7:1) afforded compound **6** (1.32 g, 37%) and compound **7** (2.18 g, 62%), respectively.

Compound **6**: ν_{max}(neat)/cm^{-1} 1742, 1435, 1210, 1095 and 1035; δ_H($CDCl_3$) 1.259–2.171 (12 H, m), 1.610 (3 H, d, *J* 1.0, Me), 1.674 (3 H, d, *J* 1.0, Me), 2.818 (2 H, s, CH_2CO), 3.701 (3 H, s, OMe), 4.144 (2 H, t, *J* 3.9, CHO) and 5.098 (1 H, t, *J* 8.1, C=CH); *m*/*z* 282 (M^+), 199, 110, 101, 99, 81, 74 and 69; HRMS (Found: M^+, 282.1854. Calc. for $C_{16}H_{26}O_4$: M, 282.1830).

Compound **7**: ν_{max}(neat)/cm^{-1} 1740, 1435, 1230, 1100 and 1040; δ_H($CDCl_3$) 1.259–2.242 (12 H, m), 1.656 (3 H, d, *J* 4.9, Me), 1.699 (3 H, d, *J* 4.2, Me), 2.686 (2 H, s, CH_2CO), 3.684 (3 H, s, OMe), 4.184 (2 H, t, *J* 3.8, CHO) and 5.147 (1 H, t, *J* 6.8, C=CH); *m*/*z* 282 (M^+), 209, 199, 110, 101, 81, 74 and 69; HRMS (Found: M^+, 282.1854. Calc. for $C_{16}H_{26}O_4$: M, 282.1830).

2-{1αH,6αH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*-[4.3.0]*nonan*-8β-*yl*}*ethanol* **9** *and* 2-{1βH,6βH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*[4.3.0]*nonan*-8β-*yl*}*ethanol* **8**.—A solution of compound **6** (1.28 g) in diethyl ether (10 cm^3) was added to a stirred suspension of $LiAlH_4$ (0.18 g) in diethyl ether (20 cm^3) at room temperature, and the mixture was stirred for 12 h. Usual work-up afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with hexane–AcOEt (5:1) afforded compound **9** (1.01 g, 85%). In a manner similar to that described for the reduction of ester **6**, compound **7** (2.13 g) could be reduced to the alcohol **8** (1.90 g, 95%).

Compound **8**: ν_{max}(neat)/cm^{-1} 3440, 1445, 1100 and 1045; δ_H($CDCl_3$) 1.180–2.176 (12 H, m), 1.620 (3 H, s, Me), 1.688 (3 H, d, *J* 5.0, Me), 2.921 (1 H, t, *J* 5.4, OH), 3.743 (2 H, dd, *J* 5.1, 10.8, CH_2), 4.166 (2 H, m, CH_2O) and 5.126 (1 H, m, C=CH); *m*/*z* 254 (M^+), 236, 209, 171, 138, 105, 98, 81, 79, 69 and 55; HRMS (Found: M^+, 254.1869. Calc. for $C_{15}H_{26}O_3$: M, 254.1881).

Compound **9**: ν_{max}(neat)/cm^{-1} 3450, 1445, 1114, 1100 and 1045; δ_H($CDCl_3$) 1.259–2.088 (12 H, m), 1.584 (3 H, d, *J* 3.2, Me), 1.676 (3 H, d, *J* 1.4, Me), 3.029 (1 H, t, *J* 5.5, OH), 3.745 (2 H, dd, *J* 11.4, 5.8, CH_2), 4.166 (2 H, m, CH_2O) and 5.076 (1 H, m, C=CH); *m*/*z* 254 (M^+), 209, 171, 105, 98, 81, 73, 69 and 55; HRMS (Found: M^+, 254.1903. Calc. for $C_{15}H_{26}O_3$: M, 254.1881).

2-{1βH,6βH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*-[4.3.0]*nonan*-8β-*yl*}*ethanal* **2** *and* 2-{1αH,6αH-8α-(4-*Methylpent*-3-*enyl*)-7,9-*dioxabicyclo*[4.3.0]*nonan*-8β-*yl*}*ethanal* **1**.—A solution of Compound **9** (0.51 g) in CH_2Cl_2 (2 cm^3) was added dropwise to a stirred solution of PCC (0.65 g) and AcONa (0.05 g) in CH_2Cl_2 (2 cm^3) at room temperature under N_2. After 4 h, the reaction mixture was diluted with diethyl ether (50 cm^3) and the supernatant was separated from the black gum by decantation. The organic layer was passed through a short column of florisil, and the solvent was removed under reduced pressure to leave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with hexane–AcOEt (15:1) afforded the aldehyde **1** (0.19 g, 37%). In a similar procedure, oxidation of the alcohol **8** afforded aldehyde **2** in 44% yield.

Compound **1**: ν_{max}(neat)/cm^{-1} 1730, 1450, 1100 and 1040; δ_H-($CDCl_3$) 1.259–2.044 (12 H, m), 1.600 (3 H, s, Me), 1.673 (3 H, d, *J* 1.3, Me), 2.806 (2 H, d, *J* 3.1, CH_2), 4.184 (2 H, t, *J* 3.8, CHO), 5.067 (1 H, m, C=CH) and 9.876 (1 H, t, *J* 3.1, CHO); *m*/*z* 252

(M^+), 234, 209, 169, 140, 99, 81, 69 and 55; HRMS (Found: M^+, 252.1749. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Compound **2**: ν_{max}(neat)/cm^{-1} 1730, 1445, 1100 and 1040; δ_H($CDCl_3$) 1.257–2.282 (12 H, m), 1.688 (3 H, s, Me), 1.770 (3 H, s, Me), 2.729 (2 H, d, *J* 3.1, CH_2), 4.176 (2 H, m, CHO), 5.121 (1 H, m, C=CH) and 9.743 (1 H, t, *J* 3.1, CHO); *m/z* 252 (M^+), 234, 210, 169, 140, 99, 81, 80, 69 and 55; HRMS (Found: M^+, 252.1741. Calc. for $C_{15}H_{24}O_3$: M, 252.1724).

Methyl 2-{3-(4-*Methylpent*-3-*enyl*)-2,4-*dioxaspiro*[5.5]*undecan*-3-*yl*} *acetate* **10**.—A mixture of keto ester **5** (5.00 g) and cyclohexane-1,1-dimethanol (4.60 g) in benzene (90 cm^3) was refluxed for 15 h in the presence of PTSA (trace) under azeotropic conditions. The reaction mixture was washed and dried, then removal of the solvent under reduced pressure afforded an oily residue, which was purified by silica gel column chromatography. The fraction eluted with hexane–AcOEt (15:1) afforded compound **10** (7.05 g, 84%), ν_{max}(neat)/cm^{-1} 1720, 1450, 1435, 1240, 1085 and 1015; δ_H($CDCl_3$) 1.436–2.179 (14 H, m), 1.626 (3 H, s, Me), 1.681 (3 H, d, *J* 1.0, Me), 2.809 (2 H, s, CH_2CO), 3.632 (4 H, s, CH_2O × 2), 3.689 (3 H, s, OMe) and 5.117 (1 H, m, C=CH); *m/z* 310 (M^+), 279, 227, 183, 109, 74 and 55; HRMS (Found: M^+, 310.2163. Calc. for $C_{18}H_{30}O_4$: M, 310.2142).

2-{3-(4-*Methylpent*-3-*enyl*)-2,4-*dioxaspiro*[5.5]*undecan*-3-*yl*}*ethanol* **11**.—In a standard procedure, reduction of ester **10** (4.34 g) with $LiAlH_4$ (0.53 g) in diethyl ether afforded compound **11** (3.70 g, 94%), ν_{max}(neat)/cm^{-1} 3450, 1650, 1455, 1070 and 900; δ_H(GX270) ($CDCl_3$) 1.098–2.044 (16 H, m), 1.621 (3 H, d, *J* 0.7, Me), 1.697 (3 H, d, *J* 1.2, Me), 3.051 (1 H, t, *J* 5.7, OH), 3.627 (4 H, s, CH_2O × 2), 3.849 (2 H, m, CH_2O) and 5.125 (1 H, m, C=CH); *m/z* 282 (M^+), 264, 237, 199 and 109; HRMS (Found: M^+, 282.2219. Calc. for $C_{17}H_{30}O_3$: M, 282.2193).

2-{3-(4-*Methylpent*-3-*enyl*)-2,4-*dioxaspiro*[5.5]*undecan*-3-*yl*}*ethanal* **3**.—In a manner similar to that described for the oxidation of the alcohol **9** to the aldehyde **1**, oxidation of compound **11** (0.50 g) with PCC (0.57 g) afforded the aldehyde **3** (0.37 g, 75%) as an oil, ν_{max}(neat)/cm^{-1} 1720, 1640, 1450, 1065 and 890; δ_H(GX270) ($CDCl_3$) 1.186–2.112 (14 H, m), 1.601 (3 H, d, *J* 3.6, Me), 1.688 (3 H, d, *J* 1.0, Me), 2.689 (2 H, d, *J* 2.9, CH_2CO), 3.637 (4 H, s, CH_2O × 2), 5.059 (1 H, m) and 9.847 (1 H, m, CHO); *m/z* 280 (M^+), 262, 237, 197 and 109; HRMS (Found: M^+, 280.2056. Calc. for $C_{17}H_{28}O_3$: M, 280.2037).

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