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A practical route to both enantiomers of bicyclo[3.3.0]oct-2-en-7-one and their use for the synthesis of key trisubstituted cyclopentanes

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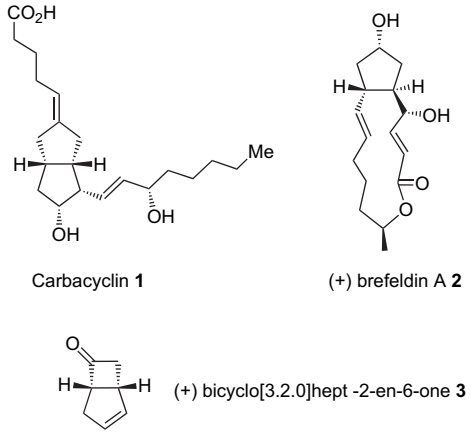
Celebrating the 80th birthday of Professor E.J. Corey who first prepared brefeldin A in 1976

Abstract

We describe new methodology for the synthesis of both enantiomers of 7,7-dichlorobicyclo[3.2.0]hep-2-en-6-one and conversion of these compounds into stereochemically defined bicyclo[3.3.0]oct-2-en-7-ones and thence trisubstituted cyclopentanes. These are key intermediates for the synthesis of prostanoids, brefeldin and other cyclopentane-containing natural products.

1. Introduction

The cyclopentane ring is a commonly encountered constituent of many biologically important compounds, e.g., carbacyclin **1** and brefeldin A **2** (from *Penicillium decumbens*), which are two examples of compounds that have been the targets of innumerable synthetic endeavours. The chiral bicyclo[3.2.0]-hept-2-en-6-one **3** has often been used for the synthesis of prostanoids and could, in principle, also be useful for elaboration into brefeldin A (Scheme 1). In this paper we provide full details of a new practical route for the synthesis of a range of other chiral intermediates that could be used for the synthesis of these natural products and other cyclopentane-containing natural products.



Scheme 1. Structures of carbacyclin **1**, (+) brefeldin A **2** and bicyclo[3.2.0]-hept-2-en-6-one **3**.

2. Results and discussion

The cycloaddition of dichloroketene to cyclopentadiene is a tried and tested route for the synthesis of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one **4** and this compound is then usually reduced to the requisite ketone **3** using zinc and acetic acid. Resolution of this bicyclic ketone has been achieved using fermenting Baker's yeast,[1] porcine pancreatic lipase,[2] and other enzymes,[3] but we wondered whether the dichloroketone might be a viable substrate for a classical resolution via diastereoisomers, and this indeed proved to be the case (Scheme 2). After stereoselective reduction of this ketone with sodium borohydride the resultant alcohol **5** was converted into the diastereoisomeric camphanate esters **6a**,**b** by reaction with (−)-camphanoyl chloride, and these could be efficiently separated using flash chromatography (Fig. 1). The yield of the mixture of diastereoisomers was 96% and the yields of the discrete diastereoisomers after chromatography were ca. 40% each on the gram scale.

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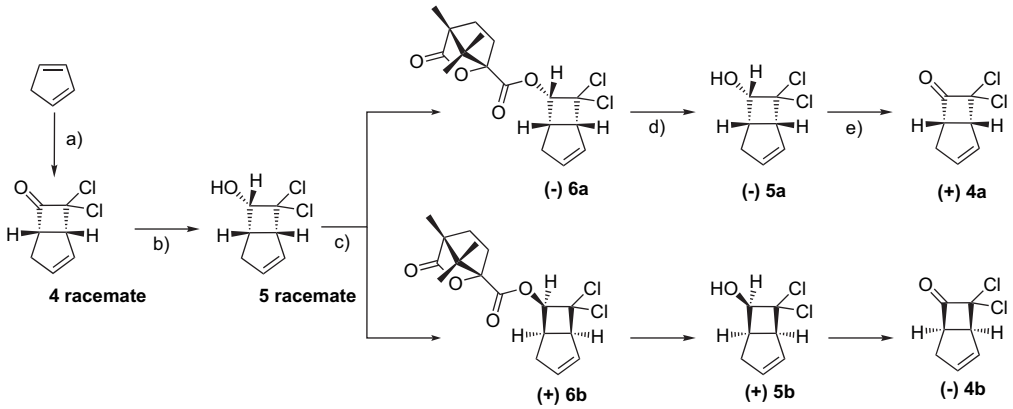
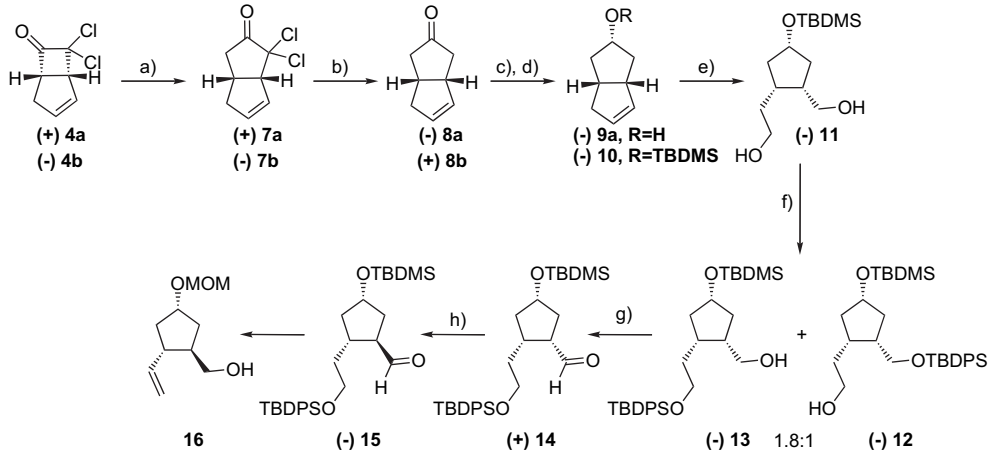


Scheme 2. Resolution of 7,7-dichlorobiyclo[3.2.0]hept-2-en-6-one **4** via the diastereoisomeric camphanate esters **6a** and **6b**; (a) dichloroacetyl chloride, Et_3N, hexane, rt, overnight, 85%; (b) $NaBH_4$, MeOH, 0 °C to rt, 1 h 30 min , 65%; (c) (1*S*)camphanic acid chloride, DCM, DMAP, 0 °C to rt, overnight, 37% for **6a**, 39% for **6b**; (d) $LiAlH_4$, THF, 0 °C to rt, overnight, 60/63%; (e) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C to rt, 1 h 10 min, 71/77%.

Reduction of these with lithium aluminium hydride provided the discrete enantiomers of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-ol **5a**,**b** with $[\alpha]_D$ −137 and +139, and thence using Swern oxidation to produce the original ketone now as pure enantiomers **4a**,**b** with $[\alpha]_D$ +84 and −81. Roberts and co-workers have reported resolution of **5a**,**b** using 3α,20β-hydroxysteroid dehydrogenase (from *Streptomyces hydrogenas*)[4] and recorded an $[\alpha]_D$ of −155 for enantiomer **5a**. Our method thus provides a complementary gram scale and non-enzymatic route to these important compounds.

Figure 1. X-ray structures of camphanate derivatives **6a** and **6b**.

The key reaction for an approach to brefeldin A (shown in Scheme 3) now involved a ring expansion reaction of the (+)-enantiomer **4a** using diazomethane and this provided the 8,8-dichlorobicyclo[3.3.0]oct-2-en-7-one **7a**, which could be reduced with zinc and acetic acid to yield the key bicyclo[3.3.0]oct-2-en-7-one **8a**. This has been reported previously by Kashihara and co-workers,[5] who recorded an $[\alpha]_D$ of −161 while our $[\alpha]_D$ was −138. We have no explanation for this discrepancy since our sample was of high purity. However, reduction with lithium aluminium hydride provided primarily the *endo* alcohol **9a** (57% isolated yield) together with around 17% of the *exo* alcohol, which could be recycled, and the $[\alpha]_D$ for compound **9a** was −74, which agreed very well with the value of −75 recorded by Kashihara. Alcohol **9a** was protected as its TBDMS-ether **10** prior to ozonolytic cleavage of the double bond to yield (after reduction of the ozonide with sodium borohydride) the trisubstituted cyclopentane **11**. Various methods were tried for selective protection of the alcohols but this was not possible and the two isomers **12** and **13** were produced after reaction with *tert*-butyldiphenylsilyl chloride. The latter was oxidised



Scheme 3. Synthesis of the chiral intermediate **15** for an approach to (+) brefeldin A. (a) CH_2N_2, Et_2O, 0 °C, 3 h, 74%; (b) Zn, AcOH, 70 °C, 1 h 30 min, 95%; (c) $LiAlH_4$, THF, 0 °C, 1 h, 57% (+17% *exo* isomer); (d) TBDMSOTf, Et_3N, DCM, rt, 1 h, quantitative; (e) (1) O_3, DCM/MeOH 2:1, −78 °C; (2) $NaBH_4$, DCM/MeOH 2:1, 66–77%; (f) (1) NaH, THF, rt, 10 min; (2) TBDPSCl, THf, rt, 20 h, 60%; (g) Dess–Martin periodinane, DCM, 1 h 30 min, 90%; (h) DBU, THF, rt, 4 h, 88%.

to the aldehyde **14**, which could be epimerised with DBU to yield the key intermediate **15**. This has the correct absolute stereochemistry and appropriate functionality for conversion into intermediates like **16**, which have been used to prepare brefeldin and analogues via a short synthetic sequence[6] involving an INOC reaction as the key step. These are of considerable interest due to the fascinating spectrum of biological activities possessed by the parent natural product and we hope to prepare a small library of such analogues for biological evaluation.

In summary, we have produced multigram quantities of both enantiomers of 7,7-dichloro[3.2.0]hept-2-en-6-one via classical resolution of camphanate esters, and then used these for the synthesis of a range of stereochemically defined trisubstituted cyclopentanes, which have potential for the synthesis of natural products and related structures.

3. Experimental

3.1. General

All solvents were dried before use. Dichloromethane and methanol were either distilled from calcium hydride under nitrogen or argon or used after drying on a high pressure alumina column device (MBRAUN). Tetrahydrofuran was either dried by distillation in the presence of sodium and benzophenone or used after drying on a high pressure alumina column device. Hexane was used after drying on a high pressure alumina column device. P.E. refers to the fraction of petroleum ether boiling range 60–80 °C. Thin layer chromatography was used to monitor reactions using Polygram® SIL G/UV254 precoated plastic sheets with a 0.2 mm layer of silica gel containing fluorescent indicator UV254. Plates were visualised using a 254 nm UV lamp and potassium permanganate stain. Flash column chromatography was carried out using Sorbsil® (or Fluorochem®) C60 silica gel (40–60 mesh) with the eluent or the gradient of eluents reported. NMR spectra were recorded using Bruker Avance300 or Bruker DRX500 spectrometers. Samples were dissolved in $CDCl_3$ with tetramethylsilane as a reference. IR spectra were recorded using a Perkin–Elmer RXI FT-IR system spectrometer. Samples were dissolved in chloroform with the indicated concentration and optical rotations were recorded at 20 °C on a Perkin–Elmer model 341 polarimeter. Mass spectra were recorded on a VG Autospec spectrometer and were carried out by Analytical Services, Queen's University of Belfast. Melting points were recorded on a Stuart melting point apparatus and are uncorrected.

3.2. X-ray crystallography[7]

Single crystal X-ray crystallographic data were collected using a Bruker SMART diffractometer with graphite monochromated Mo Kα radiation. The crystal stability was monitored and there was no significant decay (±1%). Data were collected at low temperature ca. 153 K. Omega/phi scans were employed for data collection and Lorentz and polarisation corrections were applied. The structures were solved by direct methods and all non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen was added at idealised positions, subsequent refinement uses a riding model with atomic displacement parameters fixed at 1.2 U_{eq} of the atom to which they are attached (1.5 U_{eq} for methyl groups). The function minimised for *wR*2 was $S[w(|F_o|^2-|F_c|^2)]$ with reflection weights $w^{-1}=[\sigma^2|F_o|^2+(g_1P)^2+g_2P]$ where $P=[\max|F_o|^2+2|F_c|^2]/3$ for all F^2. The SAINT[1] and SHELXTL[2] PC packages were used for data collection, reduction, structure solution and refinement. Additional material available from the Cambridge Structural Database includes atomic co-ordinates, thermal parameters, remaining bond lengths and angles, and structure factors (CCDC numbers: 646816 and 646817).

3.3. Synthesis of (±)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one **4**

A solution of triethylamine (21 mL, 149 mmol, 1.1 equiv) in hexane (250 mL) was added dropwise to a solution of freshly distilled cyclopentadiene (30 mL, 455 mmol, 3 equiv) and dichloroacetyl chloride (14 mL, 145 mmol) in hexane (450 mL). The mixture was vigorously stirred at room temperature overnight. The precipitate of triethylamine hydrochloride was removed by filtration and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography and 22 g (85%) of (±)-7,7-dichlorobiyclo [3.2.0] hept-2-en-6-one **4** was obtained as a yellow oil. R_f: 0.44 (EtOAc/P.E. 1:9); ν_{max}/cm^{-1}: 1806.6 (C=O), 1028, 753 (HC=CH), 730 (C–Cl); δ_H ($CDCl_3$): m (6.04–6.05, 1H, H_2), m (5.79–5.81, 1H, H_3), ddd (4.26, 1H, H_5, $J_{5/4}$=8.7 Hz, $J_{5/1}$=7.5 Hz, $J_{5/4'}$=1.1 Hz), m (4.06–4.08, 1H, H_1), m (2.79–2.84, 1H, $H_{4equatorial}$), ddddd (2.57, 1H, H_{4axial}, $J_{4/4'}$=17.5 Hz, $J_{4/5}$=8.7 Hz, $^4J_{4/1}\sim J_{4/2}\sim J_{4/3}\sim$2.1 Hz); δ_C ($CDCl_3$): 197.8 (C_6), 136.8 (C_2), 128.8 (C_3), 88.0 (C_7), 59.6 (C_1), 58.6 (C_5), 35.2 (C_4); *m/z* (EIMS): 181 (MH^+ (^{37}Cl), 6), 180 (M^+ (^{37}Cl), 7), 179 (MH^+ (^{35}Cl, ^{37}Cl), 16), 178 (M^+ (^{35}Cl, ^{37}Cl), 35), 177 (MH^+ (^{35}Cl), 27), 176 (M^+ (^{35}Cl), 55), 150 (43), 149 (37), 148 (66), 147 (44), 143 (M^+-Cl (^{35}Cl), 32), 141 (M^+-Cl (^{37}Cl), 100), 140 (51); $C_7H_6Cl_2O$ requires 175.9795, found: 175.9792.

3.4. Synthesis of (±)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-ol **5**

A solution of the dichloroketone **4** (15 g, 84.3 mmol) in methanol (400 mL) was cooled to 0 °C before addition of small portions of sodium borohydride (7.97 g, 210.7 mmol, 2.5 equiv). The mixture was stirred at room temperature for 1 h 30 min, and 1 M HCl was added until the white precipitate formed was dissolved. The solution was concentrated under vacuum and the residue was extracted with EtOAc. The combined organic extracts were washed with brine and dried with $MgSO_4$. After evaporation of the solvent and purification by flash chromatography (EtOAc/P.E. 1:9), 9.72 g (65%) of *endo*-dichloro-alcohol **5** was obtained as a colourless oil. R_f: 0.33 (EtOAc/P.E. 1:9); ν_{max}/cm^{-1}: 3437 (br), 1117 (C–O–C), 769, 723 (C–Cl); δ_H ($CDCl_3$): m (6.06–6.09, 1H, $H_{2\ or\ 3}$), m (5.77–5.79, 1H, $H_{2\ or\ 3}$), ddd (4.53, 1H, H_6, $J_{6/OH}$=9.5 Hz,

$^3J_{5/6}$=7.5 Hz, $^4J_{6/1}$=3.3 Hz), m (3.92–3.93, 1H, H_1), dddd (qd like) (3.41, 1H, H_5, $J_{5/1}\sim J_{5/6}\sim J_{5/4}$=8.0 Hz, $J_{5/4'}$=1.5 Hz), m (2.65–2.68, 1H, $H_{4'}$), m (2.39–2.45, 1H, H_4), d (2.28, 2.30, 1H, OH, J=9.5 Hz); δ_C ($CDCl_3$): 138 ($C_{2\text{ or }3}$), 131 ($C_{2\text{ or }3}$), 91 (C_7), 81 (C_5), 65 (C_1), 38 (C_6), 32 (C_4). Note: no mass spectrum could be obtained with this compound, i.e., EI, CI, electrospray, FAB did not give the expected mass. In the best case, the mass obtained in CI corresponded to a dimeric compound.

3.5. Synthesis of (−)-endo-(1S)-camphanic acid (1S,5R,6R)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-yl ester **6a** and (+)-endo-(1S)-camphanic acid (1R,5S,6S)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-yl ester **6b**

Camphanic acid chloride (6 g, 27.7 mmol, 1.1 equiv) was added to a solution of the alcohol **5** (4.5 g, 25.2 mmol) and DMAP (28 g, 230 mmol, 9 equiv) in DCM (250 mL) at room temperature and the mixture was stirred overnight. The mixture was washed with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine and then dried over $MgSO_4$ and 8.7 g (96%) of the diastereoisomeric mixture was obtained. The two diastereoisomers were separated by portions of 3 g by successive flash chromatography and 3.51 g (39%) of (+) camphanate ester **6b** and 3.24 g (37%) of (−) camphanate ester **6a** were obtained as white solids. Data for **6b**: R_f: 0.25 (EtOAc/P.E. 2:8); ν_{max}, cm^{-1}: 2968 (alkyl), 1789 (C=O lactone), 1763 (C=O ester), 1261, 1108.5 and 1055 (C−O), 728 (C−Cl); dr: 100%; $[\alpha]_D$ +58.5 (*c* 0.75); mp: 122/123 °C; δ_H ($CDCl_3$): m (6.03–6.07, 1H, H_2), m (5.71–5.75, 1H, H_3), dd (5.54, 1H, H_6, $^4J_{6/1}$=2.8 Hz, $J_{6/5}$=7.9 Hz), m (3.97–4.00, 1H, H_1), dddd (qd like) (3.52, 1H, H_5, $J_{5/4'}$=1.9 Hz, $J_{5/1}\sim J_{5/6}\sim J_{5/4}\sim$8.5 Hz), m (2.59–2.61, $H_{4equatorial}$), m (2.43–2.53, 2H, H_{4axial} and $H_{15equatorial}$), m (2.00–2.05, 1H, $H_{15axial}$), m (1.89–1.93, 1H, $H_{14equatorial}$), m (1.69, 1H, $H_{14axial}$), s (1.12, 3H, CH_3), s (1.06, 3H, CH_3), s (1.03, 3H, CH_3); δ_C ($CDCl_3$): 178.5 (C_9), 166.7 (C_{12}), 137.1 (C_2), 129.0 (C_3), 91.5 (C_7), 87.5 (C_{10}), 81.1 (C_6), 65.5 (C_1), 55.4 (C_{13} or C_{16}), 54.7 (C_{13} or C_{16}), 36.3 (C_5), 32.9 (C_4), 31.3 (C_{15}), 29.1 (C_{14}), 17.1 and 17.3 (2Me), 10.1 (Me); *m/z* (EIMS): 363 (MH^+ (^{37}Cl), 6), 361 (MH^+ (^{35}Cl, ^{37}Cl), 35), 359 (MH^+ (^{35}Cl), 49), 343 (7), 341 (8), 315 (8), 313 (13), 295 (19), 293 (27), 249 (8), 247 (12), 182 (13), 181 (33), 153 (61), 137 (19), 135 (27), 125 (64), 109 (34), 97 (42), 83 (77), 66 (100); $C_{17}H_{20}Cl_2O_4$ requires 358.0738, found: 358.0733. Crystal data for $C_{17}H_{20}Cl_2O_4$ (**6b**): M=359.23, monoclinic, space group $P2_1$, a=12.109(2) Å, b=9.9216(16) Å, c=14.911(3) Å, β=103.640(7), U=1741.0(6) $Å^3$, Z=4, μ=0.389 mm^{-1}, R_{int}=0.0305. A total of 20,188 reflections were measured for the angle range $1.8<2\theta<57$ and 7749 independent reflections were used in the refinement. The final parameters were $wR2$=0.1441 and $R1$=0.0578 [$I>2\sigma I$]. Data for **6a**: R_f: 0.20 (EtOAc/P.E. 2:8); ν_{max}, cm^{-1}: 2970 (alkyl), 1791 (C=O lactone), 1762 (C=O ester), 1261, 1107.1 and 1055.2 (C−O), 722.5 (C−Cl); dr: 100%; $[\alpha]_D$ −78.5 (*c* 0.61); mp: 82/84 °C; δ_H ($CDCl_3$): m (6.04–6.07, 1H, H_2), m (5.72–5.75, 1H, H_3), dd (5.56, 1H, H_6, $^4J_{6/1}$=2.9 Hz, $J_{6/5}$=7.7 Hz), m (3.97–4.01, 1H, H_1), dddd (3.51, 1H, H_5, $J_{5/6}\sim J_{5/1}\sim J_{5/4}$=7.7 Hz, $J_{5/4'}$= 2.3 Hz), m (2.39–2.55, 3H, $H_{4equatorial}$, H_{4axial} and $H_{15equatorial}$), m (2.05–2.09, 1H, $H_{15axial}$), ddd (1.93, 1H, $H_{14equatorial}$, J_1=13.2 Hz, J_2=10.5 Hz, J_3=4.5 Hz), m (1.68–1.72, 1H, $H_{14axial}$), s (1.12, 3H, CH_3), s (1.10, 3H, CH_3), s (1.01, 3H, CH_3); δ_C ($CDCl_3$): 178.4 (C_9), 166.3 (C_{12}), 137.1 (C_2), 129.0 (C_3), 91.2 (C_7), 87.4 (C_{10}), 80.7 (C_6), 65.5 (C_1), 55.2 (C_{13} or C_{16}), 54.7 (C_{13} or C_{16}), 36.3 (C_5), 32.8 (C_4), 31.5 (C_{15}), 29.3 (C_{14}), 17.0 (2Me), 10.0 (Me); *m/z* (EIMS): 363 (MH^+ (^{37}Cl), 7), 361 (MH^+ (^{35}Cl, ^{37}Cl), 15), 360 (M^+ (^{35}Cl, ^{37}Cl), 32), 359 (MH^+ (^{35}Cl), 52), 343 (6), 341 (9), 315 (9), 313 (14), 295 (24), 293 (36), 249 (9), 247 (14), 182 (15), 181 (40), 153 (75), 137 (25), 135 (34), 125 (78), 109 (45), 97 (50), 83 (83), 66 (100); $C_{17}H_{20}Cl_2O_4$ requires 358.0738, found: 358.0735. Crystal data for $C_{17}H_{20}Cl_2O_4$ (**6a**): M=359.23, orthorhombic, space group $P2_12_12_1$, a=6.488(8) Å, b=12.224(15) Å, c=44.23(6) Å, U=3508(8) $Å^3$, Z=8, μ=0.386 mm^{-1}, R_{int}=0.1091. A total of 25,535 reflections were measured for the angle range $1.8<2\theta<50$ and 6185 independent reflections were used in the refinement. The final parameters were $wR2$=0.2785 and $R1$=0.0999 [$I>2\sigma I$].

3.6. Synthesis of (−)-7,7-dichlorobiyclo[3.2.0]hept-2-en-6-ol **5a** and (+)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-ol **5b**

A solution of (−) camphanate ester **6a** (3.3 g, 9.18 mmol) in THF (10 mL) was added dropwise at 0 °C to a suspension of lithium aluminium hydride (383 mg, 10.1 mmol, 1.1 equiv) in THF (20 mL), and the mixture was stirred at room temperature for 18 h. The excess of lithium aluminium hydride and the complex were decomposed at 0 °C with wet THF. A 2 M sulfuric acid solution was added dropwise and the mixture was heated at 60 °C for 30 min. The aqueous layer was extracted with ether and the combined organic layers were washed with water, brine and dried with $MgSO_4$. After evaporation and flash chromatography (EtOAc/P.E. 2:8), 986 mg of (−) alcohol **5a** (60%) and recovered starting material were obtained. The same reaction was carried out with the other diastereoisomer **6b** (4.36 g) and 1.34 g (63%) of (+) alcohol **5b** was obtained. Same analytical data as **5**; **5a**: $[\alpha]_D$ −137, (lit.[4]: $[\alpha]_D$ −155); **5b**: $[\alpha]_D$ +139.6 (*c* 0.56).

3.7. Synthesis of (+)-(1R,5S)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one **4a** and (−)-(1S,5R)-7,7-dichlorobicyclo-[3.2.0]hept-2-en-6-one **4b**

DMSO (1.1 mL, 15.31 mmol, 3 equiv) in DCM (25 mL) was stirred at room temperature under argon. After 5 min, the mixture was cooled to −78 °C using a dry ice/acetone bath. Oxalyl chloride (890 μL, 10.2 mmol, 2 equiv) was added dropwise and the mixture was stirred for 10 min. A solution of the (−) alcohol **5a** (914 mg, 5.10 mmol) in DCM (7 mL) was added dropwise and then the mixture was stirred for 30 min. Triethylamine (2.84 mL, 20.4 mmol, 4 equiv) was added and the mixture was stirred for 10 min at −78 °C, then 30 min at room temperature. Water, followed by DCM was added and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine and dried with $MgSO_4$.

After evaporation of the solvents and flash chromatography (EtOAc/P.E. 1:9), 691 mg (77%) of (+) ketone **4a** was obtained as a yellow oil. The same reaction was carried out with the other enantiomer **5b** (1.30 g) and 0.92 g (71%) of the (−) ketone **4b** was obtained. Same analytical data as **4**; $[\alpha]_D$ +83.9 (*c* 0.79) for **4a**, $[\alpha]_D$ −81 (*c* 0.75) for **4b**.

*3.8. Synthesis of (+)-(1R,5S)-8,8-dichlorobicyclo[3.3.0]oct-2-en-7-one **7a** and (−)-(1S,5R)-8,8-dichlorobicyclo-[3.3.0]oct-2-en-7-one **7b***

A solution of KOH (6.1 g, 108.9 mmol, 30 equiv) in water/ethanol (11/12 mL) was heated to 65 °C without stirring. A solution of Diazald (7.3 g, 36.3 mmol, 10 equiv) in ether (65 mL) was added dropwise so that the reflux rate of addition equalled the reflux rate of distillation. After complete addition, the distillation was maintained until the distillate became colourless. The resulting solution of diazomethane was poured into a solution of the ketone **4a** (610 mg, 3.40 mmol) in ether (7 mL), and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with acetic acid until disappearance of the yellow colour. The solvent was removed under vacuum and the crude mixture was purified by flash chromatography (EtOAc/P.E. 1:9), and 480 mg (74%) of 8,8-dichlorobicyclo[3.3.0]oct-2-en-7-one **7a** were obtained as a colourless oil. The same reaction was carried out with the other enantiomer **4b** (900 mg) and 700 mg (78%) of (−) dichloroketone **7b** was obtained as a colourless oil. R_f: 0.36 (EtOAc/P.E. 1:9); ν_{max}, cm^{-1}: 2917 (C−H), 1766 (C=O), 1139, 804, 774.; δ_H ($CDCl_3$): m (5.94−5.95, 1H, $H_{2\ or\ 3}$), m (5.69−5.70, 1H, $H_{2\ or\ 3}$), m (3.90, 1H, H_1), m (3.10−3.14, 1H, H_5), dd (3.03, 1H, $H_{6'}$, $J_{6/6'}$=19.5 Hz, $J_{6'/5}$=10.3 Hz), m (2.75−2.80, 1H, H_4), br d (2.30−2.33, 1H, $H_{4'}$, J=17 Hz), dd (2.00, 1H, H_6, $J_{6/6'}$=19.5 Hz, $J_{5/6}$=5.3 Hz); δ_C ($CDCl_3$): 201.6 (C_7), 135.0 (C_2), 128.7 (C_3), 87.6 (C_8), 64.5 (C_1), 41.3 (C_4), 38.9 (C_6), 33.9 (C_5); *m/z* (EIMS): 194 (M^+ (^{37}Cl), 8), 192 (M^+ (^{35}Cl, ^{37}Cl), 37), 190 (M^+ (^{35}Cl), 52), 179 (10), 177 (17), 169 (13), 161 (17), 157 (32), 155 (83), 149 (52), 147 (27), 141 (21), 127 (33), 125 (44), 119 (19), 115 (26), 113 (48), 105 (21), 91 (65), 89 (18), 85 (26), 79 (58), 78 (100), 72 (42), 66 (19), 64 (63), 62 (30), 59 (16); $C_8H_8Cl_2O$ requires 189.9952, found: 189.9956; $[\alpha]_D$ +1.27 (*c* 1.11) for **7a**, $[\alpha]_D$ −1.28 (*c* 1.25) for **7b**.

*3.9. Synthesis of (−)-(1R,5S)-bicyclo[3.3.0]oct-2-en-7-one **8a** and (+)-(1S,5R)-bicyclo[3.3.0]oct-2-en-7-one **8b***

A solution of the dichloroketone **7a** (450 mg, 2.35 mmol) in acetic acid (2 mL) was added dropwise to a suspension of zinc powder (924 mg, 14.1 mmol, 6 equiv) in acetic acid (1.5 mL). An exothermic reaction occurred. After complete addition, the mixture was heated to 70 °C for 1 h 30 min. The mixture was cooled to room temperature and ether was added. After filtration over Celite, the pad was washed with ether and water, and the aqueous layer was extracted with ether. The combined organic layers were washed with 2 M Na_2CO_3 until pH 7, then with brine. After drying with $MgSO_4$, the solvent was removed under vacuum and 272 mg (95%) of the ketone **8a** was obtained as a colourless oil. The product was used without further purification. The same reaction was carried out with the other enantiomer **7b** (600 mg) and 338 mg of ketone **8b** was obtained as a colourless oil. R_f: 0.28 (EtOAc/P.E. 2:8); ν_{max}, cm^{-1}: 2924, 2850 (C−H), 1742 (C=O), 1402, 1258, 1159, 1027, 723; δ_H ($CDCl_3$): m (5.73−5.75, 1H, H_2), m (5.62−5.63, 1H, H_3), m (3.41−3.42, 1H, H_1), m (2.93−3.00, 1H, H_5), ddddd (2.70, 1H, H_{4axial}, $J_{4/4'}$=16.5 Hz, $J_{4/5}$=7.6 Hz, $^4J_{4/1} \sim J_{4/2} \sim J_{4/3} \sim$ 2.5 Hz), m (2.44−2.53, 2H, H_{6axial} and H_{8axial}), m (2.20−2.27, 2H, $H_{4equatorial}$ and $H_{8equatorial}$), ddd (2.00, 1H, $H_{6equatorial}$, $J_{6/6'}$= 19.0 Hz, $J_{6/5}$=7.5 Hz, J_3=1.5 Hz); δ_C ($CDCl_3$): 220.6 (C_7), 134.5 (C_2), 130.8 (C_3), 46.7 (C_1), 45.3 (C_6), 43.0 (C_8), 40.5 (C_4), 37.4 (C_5); $[\alpha]_D$ −137.5 (*c* 0.96) for **8a**, $[\alpha]_D$ +132.2 (*c* 0.99) for **8b** (lit.[5]: $[\alpha]_D$ −160.5).

*3.10. Synthesis of (−)-(1R,5S,7S)-bicyclo[3.3.0]oct-2-ene-7-ol **9a** and (+)-(1S,5R,7R)-bicyclo[3.3.0]oct-2-ene-7-ol **9b***

A solution of the ketone **8a** (240 mg, 2.00 mmol) in dry THF (6 mL) was added to a 1 M solution of lithium aluminium hydride (2.2 mL, 2.2 mmol, 1.1 equiv) in THF (4 mL) at 0 °C. The mixture was stirred for 1 h and 85 μL of water was added dropwise, followed by the addition of 85 μL of a 15% NaOH solution. The mixture was stirred for 5 min, water was added (250 μL) and the mixture was heated at reflux for 30 min. The white precipitate was filtered and the solution was concentrated under vacuum. The crude product was purified by flash chromatography and 136 mg of (−) alcohol **9a** (57%) and 40 mg (17%) of the *exo* isomer were obtained as colourless oils. Similarly, **8b** was converted into **9b**. Data for compound **9a**: R_f: 0.25 (EtOAc/P.E. 2:8); ν_{max}, cm^{-1}: 3342 (OH), 2931−2849 (C−H), 1085−1060 (C−O); δ_H ($CDCl_3$): m (5.76−5.79, 1H, H_2), m (5.64−5.67, 1H, H_3), m (4.19−4.21, 1H, H_7), m (3.19−3.20, 1H, H_1), m (2.69−2.74, 2H, H_5 and H_{4axial}), m (2.26−2.31, 1H, $H_{4equatorial}$), m (2.18, 1H, H_{6axial}), m (1.99−2.01, 1H, H_{8axial}), br s (1.77, 1H, OH), m (1.56−1.58, 1H, $H_{8equatorial}$), m (1.48−1.49, 1H, $H_{6equatorial}$); δ_C ($CDCl_3$): 136.6 (C_2), 129.4 (C_3), 75.5 (C_7), 49.8 (C_1), 44.6 (C_6), 41.5 (C_4), 41.1 (C_8), 38.5 (C_5); $[\alpha]_D$ −73.6 (*c* 0.75) for **9a**, $[\alpha]_D$ +73.8 (*c* 0.70) for **9b** (lit.[5]: $[\alpha]_D$ −75.4).

*3.11. Synthesis (−)-(1R,5S,7S)-bicyclo[3.3.0]oct-2-ene-7-oxy-tert-butyldimethylsilane **10***

tert-Butyldimethylsilyl-trifluoromethanesulfonate (340 μL, 1.47 mmol, 1.4 equiv) was added dropwise at 0 °C to a solution of the alcohol **9a** (130 mg, 1.05 mmol) in DCM/Et_3N (5.5 mL, 350 μL, 2.52 mmol, 2.4 equiv). The mixture was stirred at room temperature for 2 h. Water was added and the organic layer was extracted with DCM. The combined organic layers were washed with brine and dried with $MgSO_4$. The product was purified by flash chromatography (EtOAc/P.E. 2:8) and 250 mg (quantitative) of silyl ether **10** was obtained as a pale yellow oil. R_f: 0.79 (EtOAc/P.E. 2:8); ν_{max}, cm^{-1}: 2929, 2857 (C−H), 1255 (Si−Me), 1112 (Si−O), 836 (Si−O), 774; $[\alpha]_D$ −38.8 (*c* 0.69); δ_H ($CDCl_3$): m (5.66−5.67,

1H, H_2), m (5.56–5.57, 1H, H_3), m (4.06–4.15, 1H, H_7), m (3.01–3.03, 1H, H_1), m (2.52–2.61, 2H, H_5 and H_{4axial}), m (2.06–2.21, 3H, $H_{4equatorial}$, H_{6axial}, H_{8axial}), m (1.28–1.35, 2H, $H_{8equatorial}$, $H_{6equatorial}$), s (0.89, 9H, $(CH_3)_3$), s (0.05–0.07, 3H+3H, CH_3); δ_C ($CDCl_3$): 135.1 (C_2), 128.1 (C_3), 74.6 (C_7), 48.2, (C_1), 43.7 (C_6), 41.2 (C_4), 40.2, (C_8), 37.9 (C_5), 26.1–26.3 (*t*-Bu), 18.5 (CMe_3), −2.53, −4.36 (Me_2); *m/z* (EIMS): 239 (MH^+), 206 (25), 192 (9), 190 (10), 181 (8), 177 (19), 164 (29), 153 (26), 152 (33), 150 (38), 141 (20), 140 (33), 139 (43), 138 (37); $C_{14}H_{27}OSi$ (MH^+) requires 239.1831, found: 239.1826.

*3.12. Synthesis of 2-[(1R,2S,4S)-4-(tert-butyl-dimethyl-silanyloxy)-2-(tert-butyl-diphenyl-silanyloxymethyl)-cyclopentyl]-ethanol **12** and {(1S,2R,4S)-4-(tert-butyl-dimethyl-silanyloxy)-2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclopentyl}-methanol **13***

Ozone was bubbled through a solution of the silyl ether **10** (250 mg, 1.05 mmol) in DCM/MeOH 2:1 (15 mL) at −78 °C until a bright blue colour persisted. Solid sodium borohydride (400 mg, 10.5 mmol, 10 equiv) was added and the mixture was allowed to warm slowly to room temperature over 3 h. The solution was concentrated under vacuum and water was added. The product was extracted with Et_2O, and the combined organic layers were washed with brine, and then dried over $MgSO_4$. The crude product (colourless oil) (188 mg, 66%) was pure enough and was used without further purification for the next step. Sodium hydride (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2 equiv) was added to a solution of the diol **11** (68 mg, 0.25 mmol) in THF (2 mL). The resulting mixture was stirred for 10 min before the addition of *tert*-butyldiphenylsilyl chloride (65 μL, 0.25 mmol, 1 equiv), and the mixture was stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride and water, and the product was extracted with Et_2O. The combined organic layers were washed with brine, then dried over $MgSO_4$. The two regioisomers were separated by flash chromatography (EtOAc/P.E. 1:9) and 50 mg of the monoprotected diol **13**, 27 mg of the monoprotected diol **12** and recovered starting material were obtained as colourless oils (60% overall). Data for **13**: ν_{max}, cm^{-1}: 3368 (OH), 2930, 2858 (C–H), 1472–1428, 1257 (C–O–C), 1113–822.0–701 (Si–O); δ_H ($CDCl_3$): m (7.66–7.68, 4H, Ar), m (7.37–7.42, 6H, Ar), m (4.28–4.29, 1H, H_4), m (3.65–3.71, 4H, $CH_2OTBDPS$, CH_2OH), br s (3.33, 1H, OH), m (2.09–2.16, 1H, H_2), m (2.00–2.06, 3H, H_1 and H_3, H_5), m (1.88–1.94, 1H, $CH_2CH_2OTBDPS$), m (1.70–1.76, 1H, $CH_2CH_2OTBDPS$), br d (1.55, 1H, $H_{3'}$, $J_{3/3'}$=11.0 Hz), m (1.32–1.37, 1H, $H_{5'}$), s (1.05, 9H, $(CH_3)_3$), s (0.88, 9H, $(CH_3)_3$), s (0.05–0.6, 3H+3H, CH_3); δ_C ($CDCl_3$): 136.0 (Ar_o), 134.4 (Ar_i), 129.9 (Ar_p), 128.0 (Ar_m), 73.5 (C_4), 64.2 ($CH_2OTBDPS$), 64.0 (CH_2OH), 43.2 (C_2), 43.0 (C_3), 41.5 (C_5), 38.3 (C_1), 33.8 ($CH_2CH_2OTBDPS$), 27.3–26.2 (*t*-Bu), 19.6–18.4 ($C(Me)_3$), −4.42, −4.51 (2s, $SiMe_2$); *m/z* (CIMS): 513 (MH^+), 391 (15), 275 (39); $C_{30}H_{49}O_3Si_2$ (MH^+) requires 513.322028, found: 513.322723; $[\alpha]_D$ −0.42 (*c* 2.15). Data for **12**: ν_{max}, cm^{-1}: 3349.7 (OH), 2930.0, 2857.5 (C–H), 1472.0–1428.2, 12,555.6 (C–O–C), 1112, 836, 775, 701 (Si–O); δ_H ($CDCl_3$): m (7.70–7.72, 4H, Ar), m (7.41–7.46, 6H, Ar), m (4.20–4.22, 1H, H_4), m (3.57–3.80, 4H, CH_2OH, $CH_2OTBDPS$), m (2.18–2.25, 1H, H_1), m (1.97–2.11, 3H, H_2, H_3 and H_5), m (1.80–1.91, 1H, $CH_2CH_2OTBDPS$), m (1.55–1.64, 1H, $CH_2CH_2OTBDPS$), m (1.40–1.49, 2H, $H_{3'}$, $H_{5'}$), s (1.08, 9H, $(CH_3)_3$), s (0.88, 9H, $(CH_3)_3$), s (0.04–0.05, 3H+3H, CH_3); δ_C ($CDCl_3$): 136.0 (Ar_o), 134.2 (Ar_i), 129.9 (Ar_p), 128.0 (Ar_m), s (73.2, 1C, C_4), 65.3 (CH_2OH), 62.8 ($CH_2OTBDPS$), 43.3 (C_1), 41.7 (C_5), 39.2 (C_3), 36.9 (C_2), 33.5 ($CH_2CH_2OTBDPS$), 27.3–26.3 (*t*-Bu), 19.6–18.4 ($C(Me)_3$), −4.34, −4.38 (2s, $SiMe_2$); *m/z* (CIMS): 513 (MH^+, 100), 275 (25), 257 (75), $C_{30}H_{49}O_3Si_2$ (MH^+) requires 513.3220, found: 513.3223; $[\alpha]_D$ −8.96 (*c* 1.15).

*3.13. Synthesis of (1S,2R,4S)-4-(tert-butyl-dimethyl-silanyloxy)-2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclopentanecarbaldehyde **14***

Dess–Martin periodinane (75 mg, 0.175 mmol, 2 equiv) was added to a solution of the monoprotected diol **13** (45 mg, 0.088 mmol) in DCM (2 mL) at room temperature, and the mixture was stirred for 2 h. The reaction was quenched with a saturated sodium metabisulfite solution and a saturated solution of sodium hydrogen carbonate. The product was extracted with DCM and the combined organic layers were washed successively with water and brine. The extracts were dried over $MgSO_4$ and the crude product (40 mg, 90%) was used without purification for the next step. ν_{max}, cm^{-1}: 2930, 2857 (C–H), 1722 (CHO), 1472–1428, 1259 (C–O–C), 776.7–702.3 (Si–O); $[\alpha]_D$ +0.27 (*c* 1.5); δ_H ($CDCl_3$): d (9.83, 1H, CHO, *J*=4.4 Hz), m (7.66–7.68, 4H, Ar), m (7.41–7.44, 6H, Ar), m (4.28–4.29, 1H, H_4), m (3.65–3.71, 2H, $CH_2OTBDPS$), m (2.64–2.73, 1H, H_1), m (2.32–2.46, 1H, H_2), m (2.00–2.16, 2H, H_3 and H_5), m (1.82–1.97, 2H, $H_{5'}$, $CH_2CH_2OTBDPS$), m (1.62–1.74, 1H, $CH_2CH_2OTBDPS$), m (1.40–1.47, 1H, $H_{3'}$), s (1.07, 9H, $(CH_3)_3$), s (0.89, 9H, $(CH_3)_3$), s (0.06–0.07, 3H+3H, CH_3); δ_C ($CDCl_3$): 205.7 (CHO), 136.0 (Ar_o), 134.2 (Ar_i), 130.0 (Ar_p), 128.1 (Ar_m), 73.5 (C_4), 63.1 ($CH_2OTBDPS$), 53.3 (C_1), 42.1 (C_3), 37.8 (C_2), 37.3 (C_5), 34.5 ($CH_2CH_2OTBDPS$), 27.3–26.2 (*t*-Bu), 19.6–18.4 ($C(Me)_3$), −4.4 s ($SiMe_2$); *m/z* (CIMS): 529 (MH^++NH_4^+, 30), 528 (M^++NH_4^+, 64), 512 (MH^+, 39), 511 (M^+, 80), 497 (40), 453 (18), 433 (33), 391 (53), 321 (36), 301 (30), 255 (100), 216 (16); $C_{30}H_{47}O_3Si_2$ (MH^+) requires 511.306178, found: 511.305298.

*3.14. Synthesis of (1R,2R,4S)-4-(tert-butyl-dimethyl-silanyloxy)-2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclopentanecarbaldehyde **15***

DBU (22 μL, 0.147 mmol, 2.5 equiv) was added to a solution of the aldehyde **14** (30 mg, 0.059 mmol) in THF (1.5 mL) and the mixture was stirred for 4 h at room temperature. The reaction was quenched carefully with a 1 M HCl solution until pH 4. The product was extracted with Et_2O, and the combined

organic extracts were washed with $NaHCO_3$, then with brine and were dried over $MgSO_4$. After evaporation of the solvent, 26 mg of product **15** was obtained (88%) as a colourless oil. ν_{max}, cm^{-1}: 2957, 2929–2857 (C–H), 1725 (CHO), 1472–1428, 1259 (C–O–C), 739–702 (Si–O); $[\alpha]_D$ −7.68 (*c* 1.25); δ_H ($CDCl_3$): d (9.60, 1H, CHO, $J_{CHO/1}$=2.8 Hz), m (7.66–7.68, 4H, Ar), m (7.38–7.40, 6H, Ar), m (4.21–4.23, 1H, H_4), m (3.64–3.71, 2H, $CH_2OTBDPS$), dddd (2.68, 1H, H_1, $J_1 \sim J_2 \sim J_3$=8.5 Hz, $J_{1/CHO}$=2.8 Hz), m (2.27–2.31, 1H, H_2), m (2.01–2.07, 1H, H_3), m (1.94–1.99, 1H, H_5), m (1.66–1.84, 3H, $CH_2CH_2OTBDPS$, $H_{5'}$), m (1.28–1.36, 1H, $H_{3'}$), s (1.04, 9H, $(CH_3)_3$), s (0.86, 9H, $(CH_3)_3$), s (0.03, 3H+3H, CH_3); δ_C ($CDCl_3$): 202.5 (CHO), 135.0 (Ar_o), 133.8 (Ar_i), 128.6 (Ar_p), 126.7 (Ar_m), 72.1 (C_4), 61.5 ($CH_2OTBDPS$), 55.0 (C_1), 40.9 (C_3), 37.9 ($CH_2CH_2OTBDPS$), 35.4 (C_5), 34.3 (C_2), 25.8–24.8 (*t*-Bu), 19.1–17.8 ($C(Me)_3$), 0.00 to −5.8 s ($SiMe_2$); *m/z* (CIMS): 529 ($MH^+ + NH_4^+$, 30), 528 ($M^+ + NH_4^+$, 64), 512 (MH^+, 39), 511 (M^+, 80), 497 (40), 453 (18), 433 (33), 391 (53), 321 (36), 301 (30), 255 (100), 216 (16); $C_{30}H_{47}O_3Si_2$ (MH^+) requires 511.306178, found: 511.305298.

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References and notes

1. Newton, R. F.; Paton, J.; Reynolds, D. P.; Young, S.; Roberts, S. M. *J. Chem.Soc., Chem. Commun.* **1979**, 908–909.
2. Cotterill, I. C.; MacFarlane, E. L. A.; Roberts, S. M. *J. Chem.Soc., Perkin Trans. 1* **1988**, 3387–3391.
3. Dawson, M. J.; Lawrence, G. C.; Lilley, G.; Todd, M.; Noble, D.; Green, S. M.; Roberts, S. M.; Wallace, T. W.; Newton, R. F.; Carter, M. C.; Hallet, P.; Paton, J.; Reynolds, D. R.; Young, S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2119–2125.
4. Davies, H. G.; Gartenmann, T. C. C.; Leaver, J.; Roberts, S. M.; Turner, M. K. *Tetrahedron Lett.* **1986**, *27*, 1093–1094.
5. Kashihara, H.; Suemune, H.; Kawahara, T.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1663–1667.
6. Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Doi, T.; Kim, S. *J. Org. Chem.* **2002**, *67*, 772–778.
7. Sheldrick, G. M. *SHELXTL: An Integrated System for Data Collection, Processing, Structure Solution and Refinement*; Bruker Analytical X-ray Systems: Madison, WI, 1998.