Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 10, pp. 1677–1684, 1997

Printed in Great Britain

PII: S0957-4166(97)00153-5

0957-4166/97 $17.00 + 0.00

Concise synthesis of (4*S*,5*S*)-4,5-(isopropylidenedioxy)-2-cyclopentenone and a novel C_2-symmetric ketone

Alan Armstrong * and Barry R. Hayter

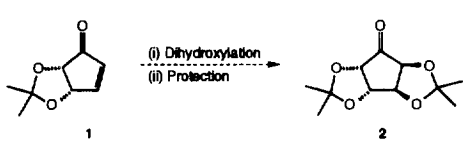
Department of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK

Abstract: A new and concise synthesis of the useful synthetic intermediate **1** is described which also allows access to a novel C_2-symmetric ketone **2**. The route relies on the Sharpless asymmetric dihydroxylation of fulvenes. © 1997 Elsevier Science Ltd

Introduction

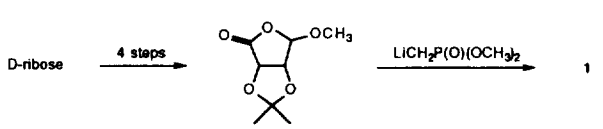
Despite having several potential uses in asymmetric synthesis, very few examples of chiral, C_2-symmetrical ketones are known.[1] As part of our investigations into asymmetric oxidation *via* chiral dioxiranes, we wished to examine the ketone **2** as a promoter of the epoxidation of alkenes by Oxone®.[2] Ketone **2** is conformationally well defined, and epimerisation α-to the carbonyl is prevented because of the high strain inherent in a *trans*-fused bicyclo[3.3.0] ring system. Moreover, we envisaged that the presence of α-oxygens should increase the susceptibility of the carbonyl to nucleophilic attack, a strategy that has since proved fruitful for Yang and co-workers.[3] A non-C_2-symmetric, fructose-derived ketone with similar design features to ours has recently been reported to provide excellent levels of enantioselectivity in the asymmetric epoxidation of *trans*-disubstituted alkenes.[4]

We expected that **2** could be accessed *via cis*-dihydroxylation of enone **1** with subsequent acetonide protection (Scheme 1). Enone **1** is an important synthetic intermediate, for example in prostaglandin synthesis, and so several routes have appeared in the literature for its preparation in enantiomerically pure form.[5] For example, D-ribose can be converted into 4 steps into the lactone **3**, which reacts with a lithiated phosphonate to give **1** (Scheme 2).[6] In our hands, however, this final step was extremely unreliable and gave low and variable yields (0–30%). A second reported route from D-ribose (Scheme 3) also gave low yields (27% in our hands) for the final step.[7] Hudlicky has reported a synthesis of **1** starting from **4**, the product of microbial *cis*-dihydroxylation of toluene (Scheme 4), but the final ring closure is again reported to be unreliable.[8] This problem is reduced if the chlorobenzene derivative is used instead.[9]



1 **2**

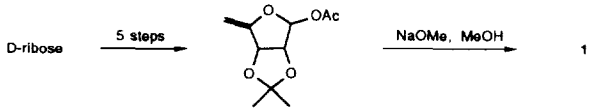
Scheme 1.



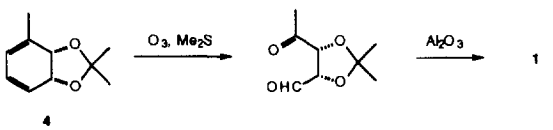
3

Scheme 2.

* Corresponding author. Email: Alan.Armstrong@nottingham.ac.uk



Scheme 3.



Scheme 4.

In view of our difficulties in obtaining reasonable quantities of enantiomerically enriched **1** by literature routes, we developed and report here a reliable new approach which also allowed access to our initial target, the C_2-symmetrical ketone **2**.

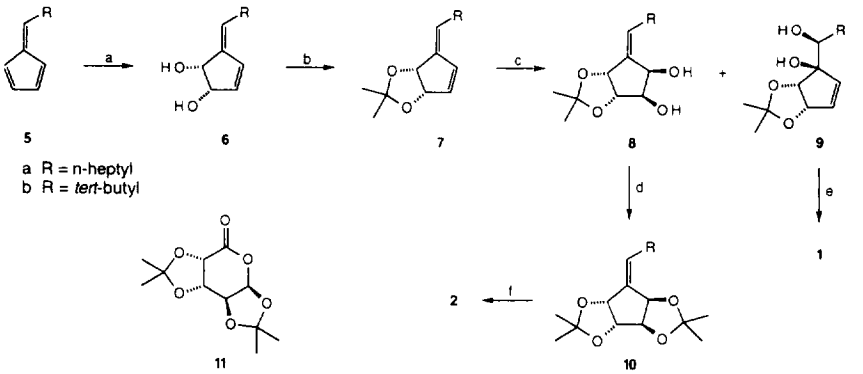
Results and discussion

Our route (Scheme 5) starts with the fulvene **5**, obtained by condensation of cyclopentadiene with an aliphatic aldehyde.[10] Our first experiments utilised the octaldehyde-derived fulvene **5a**. As reported by Sharpless,[11] asymmetric dihydroxylation of **5a** in the presence of the $(DHQD)_2PHAL$ ligand selectively occurs on the ring olefin *anti-* to the exocyclic alkene substituent, and subsequent acetonide protection of **6a** gives **7a**. Sharpless reports that this dihydroxylation proceeds with 80% ee.[11] We now wished to examine a second dihydroxylation of compounds of type **7** in the hope that this would offer a general and enantioselective approach to polyhydroxylated cyclopentane derivatives, including **2**. We hoped that second dihydroxylation of **7a** would be regioselective for either of the two olefins: both of the possible resulting diols would be synthetically useful (*vide infra*). In the event, osmylation of **7a** in the presence of an achiral ligand (quinuclidine) gave an inseparable 48:52 mixture of **8a** and **9a** according to ^1H NMR analysis of the crude reaction mixture (67% yield). Acid-catalysed reaction of this mixture with 2,2-dimethoxypropane effected selective protection of **8a**, allowing separation of **10a** from unreacted **9a**. The configuration of the exocyclic diol in **9a** is assigned based on the assumption that dihydroxylation of **7a** occurred predominantly on the less hindered, convex face of the bicyclic system.

As we had anticipated, both **9a** and **10a** proved synthetically useful. Periodate cleavage of diol **9a** gave the known enone **1**. Based on comparison of its optical rotation to the literature value, our material had 78% ee, which is in good agreement with the enantiomeric excess of 80% reported by Sharpless for the asymmetric dihydroxylation of **7a**.[11]

Despite several attempts, we were unable to effect dihydroxylation of enone **1** and so we examined **10a** as a potential precursor of our target C_2-symmetrical ketone **2**. We were pleased to find that ozonolysis of **10a** with reductive work-up (triphenylphosphine) gave **2**, presumed to have 78% ee.

We next examined *asymmetric* dihydroxylation of **7a** in the presence of the chiral ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, constituents of the commercial AD-mixes.[12] As well as potentially providing products with higher enantiomeric excess, it was hoped that this might improve the regioselectivity of the dihydroxylation in favour of one of the two alkenes. In the event, however, dihydroxylation of **7a** in the presence of $(DHQ)_2PHAL$ proceeded with no significant change in ratio of **8a** to **9a** (46:54). Conversion to the enone **1** and bisacetonide **10a** by the procedures described above and measurement of their optical rotation indicated that there had been no improvement in enantiomeric excess over the use of quinuclidine as ligand. Similarly, when $(DHQD)_2PHAL$ was used as ligand, there was little change in ratio of **8a** to **9a** (48:52) and no improvement of the enantiomeric



Scheme 5. *Reagents and Conditions*: **For compounds a (R=n-heptyl):** (a) $K_2Os(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, ^tBuOH, H_2O then Na_2SO_3, 36%; (b) 2,2-Dimethoxypropane, pTsOH, CH_2Cl_2, 93%; (c) $K_2Os(OH)_4$, quinuclidine, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, ^tBuOH, H_2O then Na_2SO_3; (d) 2,2-Dimethoxypropane, pTsOH, CH_2Cl_2; (e) $NaIO_4$, THF/H_2O, 18% over 3 steps from **7a**; (f) O_3 then Ph_3P, 15% over 3 steps from **7a**.
For compounds b (R=*tert*-butyl): (a) $K_2Os(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, ^tBuOH, H_2O then Na_2SO_3, 40%; (b) 2,2-Dimethoxypropane, pTsOH, CH_2Cl_2, 85%; (c) $K_2Os(OH)_4$, quinuclidine, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, ^tBuOH, H_2O then Na_2SO_3 (38% of **8a**, 31% of **9a**); (d) 2,2-Dimethoxypropane, pTsOH, CH_2Cl_2, 100%; (e) $NaIO_4$, THF/H_2O, 60%; (f) O_3 then Me_2S, 42%.

excess of **1** or **10a**. These results suggest that the influence of the chiral dihydroxylation system is low relative to that of the inherent chirality of **7a**.

In a final attempt to improve the regioselectivity of dihydroxylation of **7**, the route was repeated starting from the *tert*-butyl fulvene **5b**. While no improvement in regioselectivity or enantioselectivity of dihydroxylation was observed (78% yield of a 55:45 mixture of **8b**:**9b** using OsO_4, quinuclidine), the two diols **8b** and **9b** were now separable by flash chromatography. Based on determination of their specific rotation, both products had 84% ee. A single recrystallisation from ether–petrol improved the ee of **8b** to 93% and that of **9b** to 91%, again based on optical rotation measurements. Additional recrystallisation would doubtless have further increased the optical purities.

Periodate cleavage of **9b** did not occur at room temperature, but was cleanly effected upon heating to 55°C. Enone **1** was thus obtained in 60% yield. Acetonide protection of **8b** afforded **10b**. Ozonolysis of **10b** was lower yielding than for **10a**, and the product ratio was found to be dependent upon the work-up procedure. Use of triphenylphosphine as reducing agent afforded a complex mixture of which the lactone **11** (37%) was the major component. Quenching with dimethylsulfide as an alternative again gave **11** as the major product (49%), but also provided the desired ketone **2** (42%).

In conclusion, we have developed a concise and reliable route to the synthetically useful enone **1**, as well as the novel C_2-symmetrical ketone **2**, both in enantiomerically enriched form. We have found our route to **1** to be more amenable to the preparation of quantities of **1** than those already in the literature: an additional advantage is that it should be possible to obtain the other enantiomer of **1** by using the AD-mix-α reagent in the dihydroxylation of **5**.[11] The second dihydroxylation of the fulvene-derived acetonides **7** also offers a potential approach to other polyhydroxylated cyclopentane derivatives. Applications of the novel C_2-symmetrical ketone **2** in asymmetric synthesis are under investigation and will be reported elsewhere.

Experimental

General details

NMR spectra were recorded on Jeol GX 270, Jeol EX 270, Jeol EX 400, Bruker AM 400 or Bruker DRX 500 spectrometers. *J* values are measured in Hertz and are quoted to the nearest 0.5 Hz. Multiplicities in ^{13}C spectra were determined by DEPT experiments. Infra red spectra were recorded on

a Perkin–Elmer 1605 FT-IR spectrometer. Microanalyses were performed in the School of Chemistry, University of Bath, and the Department of Chemistry, University of Nottingham. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-310 spectrometer. Flash column chromatography was performed using Matrex silica Si. Where appropriate the silica was neutralised by flushing it once with a 1% solution of triethylamine. Petrol refers to light petroleum b.p. 40–60°C.

n-Heptylfulvene ***5a***

To a stirred solution of freshly cracked cyclopentadiene (20 ml, 0.244 mol) and octyl aldehyde (24 ml, 0.15 mol) in methanol (170 ml) was added pyrrolidine (20 ml, 0.24 mol). After 30 minutes acetic acid (15 ml, 0.26 mol) was added dropwise. The solution was stirred for 10 minutes, water (50 ml) was added, and the mixture was extracted three times with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a yellow oil. Flash column chromatography (petrol) yielded **5a** (20.4 g, 77%) as a yellow oil, ν_{max} (film)/cm^{-1} 2925, 1649, 1474, 1380; δ_H (270 MHz, $CDCl_3$) 6.57–6.41 (4H, m), 6.23–6.19 (1H, m), 2.57–2.49 (2H, dt, *J* 7.5, 7.5), 1.55–1.48 (2H, m), 1.43–1.28 (8H, m), 0.88 (3H, t, *J* 6.5).

*(1*R*,2*S*,5*E*)-5-Octylidene-cyclopent-3-ene-1,2-diol* ***6a***[11]

To a stirred biphasic mixture of water (225 ml) and *tert*-butanol (225 ml) was added potassium osmate dihydrate (343 mg, 0.93 mmol), potassium ferricyanide (48 g, 0.18 mol), $(DHQD)_2PHAL$ (1.13 g, 1.50 mmol), potassium carbonate (25 g, 0.18 mol) and methane sulfonamide (11 g, 0.12 mol). After 15 minutes fulvene **5a** (10.2 g, 0.06 mol) was added, and the reaction mixture stirred for a further 22 hours. Sodium sulfite (84 g, 0.59 mol) was added and the mixture stirred for a further 15 minutes before extracting three times into ethyl acetate. The combined organic extracts were washed with 2M KOH, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash column chromatography (40% ether–petrol) gave diol **6a** (4.34 g, 36%) as a colourless solid, $[\alpha]_D^{19}$ +63.7 (*c* 1.1, EtOH); δ_H (270 MHz, $CDCl_3$) 6.55 (1H, d, *J* 6.0), 6.05 (1H, dt, *J* 6.0, 1.5), 5.57 (1H, dt, *J* 6.5, 1.5), 4.59 (1H, m), 4.46 (1H, t, *J* 6.5), 2.37 (1H, d, *J* 6.5), 2.27 (1H, d, *J* 7.5), 2.16 (2H, dt, *J* 7.5, 7.5), 1.42–1.20 (10H, m), 0.88 (3H, t, *J* 7.0).

*(3*S*,4*R*,5*E*)-3,4-(Isopropylidenedioxy)-5-octylidenecyclopentene* ***7a***

To a solution of **6a** (4.67 g, 22.2 mmol) in dichloromethane (100 ml) at −5°C was added 2,2-dimethoxypropane (8 ml, 65 mmol) and *para*-toluenesulfonic acid (10 mg, 0.06 mmol). The reaction mixture was allowed to warm to room temperature while stirring for 3 hours. The solvent was removed and the residue purified by flash column chromatography (10% ether–petrol) to yield **7a** (5.15 g, 93%) as a colourless oil, $[\alpha]_D^{19}$ +114.0 (*c* 1.14, $CHCl_3$); ν_{max} (film)/cm^{-1} 2926, 2855, 1457, 1369, 1262, 1235, 1206, 1156, 1051; δ_H (270 MHz, $CDCl_3$) 6.46 (1H, d, *J* 6.0), 6.03 (1H, d, *J* 6.0), 5.66 (1H, t, *J* 7.5), 5.11 (1H, d, *J* 6.0), 4.88 (1H, d, *J* 6.0), 2.17 (2H, dt, *J* 7.5, 7.5), 1.41 (3H, s), 1.39 (3H, s), 1.20–1.35 (10H, m), 0.87 (3H, t, *J* 6.5); δ_C (67.9 MHz, $CDCl_3$) 142.0 (s), 134.6 (d), 131.4 (d), 127.6 (d), 111.0 (s), 82.8 (d), 79.7 (d), 31.8 (t), 29.5 (t), 29.23 (t), 29.18 (t), 29.12 (t), 27.4 (q), 25.9 (q), 22.6 (t), 14.4 (q); m/z (FAB$^+$) 250 (M^+, 5%), 235 (M–CH_3, 30), 193 (M–C_3H_5O, 100%); (Found: M^+, 250.1926. $C_{16}H_{26}O_2$ requires 250.1933).

*(1*R*,2*R*,3*R*,4*R*)-1,2:3,4-bis-(Isopropylidenedioxy)-5-octylidenecyclopentane* ***10a*** *and (4*S*,5*S*)-4,5-(isopropylidenedioxy)-2-cyclopentenone* ***1***

To a biphasic mixture of *tert*-butanol (11 ml) and water (11 ml) was added potassium osmate dihydrate (8 mg, 0.02 mmol), quinuclidine (3.6 mg, 0.05 mmol), potassium ferricyanide (1.29 g, 6.42 mmol), potassium carbonate (0.89 g, 6.42 mmol) and methane sulfonamide (204 mg, 4.28 mmol). The mixture was stirred at room temperature for 15 minutes and **7a** (536 mg, 2.14 mmol) added. The reaction mixture was stirred for 40 hours and sodium sulfite (2 g, 15.8 mmol) added. After a further 15 minutes, the mixture was extracted into ethyl acetate, dried over $MgSO_4$, filtered, and the

solvent removed under reduced pressure. Flash column chromatography (50% ether–petrol) yielded an inseparable mixture of diols **8a** and **9a** as a colourless solid (405 mg, 67%; **8a:9a**=42:58 by ^{1}H NMR) which was reacted on without further purification.

A solution of the mixture of diols prepared above (405 mg, 1.42 mmol) in dichloromethane (15 ml) was cooled to −5°C in an ice–salt bath and 2,2-dimethoxypropane (79μl, 0.64 mmol) and *para*-toluenesulfonic acid (5 mg) added. The reaction was stirred at −5°C for 4 hours, being monitored by taking aliquots and measuring the disappearance of the peak at 4.9 and the appearance of peaks at 5.04 and 5.12 ppm in the ^{1}H NMR spectrum. The reaction mixture was absorbed onto silica and purified by flash column chromatography. Elution with 5% ether–petrol gave **10a** (105 mg, 15% from **7a**) as a colourless oil, R_f 0.86 in 50% ether–petrol; $[\alpha]_D^{20}$ +96.4 (*c* 1.16, $CHCl_3$) @ *ca.* 78% ee. (Found C, 70.4; H, 9.95. $C_{19}H_{32}O_4$ requires C, 70.3; H; 9.95%); ν_{max} (film)/cm^{-1} 2986, 2927, 2855, 1456, 1379, 1370, 1238, 1161, 1067; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, t, *J* 7.5), 5.20 (1H, d, *J* 6.0), 4.98 (1H, d, *J* 5.5), 4.53 (1H, d, *J* 6.0), 4.48 (1H, d, *J* 5.5), 2.28–2.21 (2H, m), 1.40 (3H, s), 1.39 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 1.32–1.25 (10H, m), 0.88 (3H, t, *J* 7.0); δ_C (67.9 MHz, $CDCl_3$) 139.7 (s), 135.4 (d), 111.2 (s), 110.9 (s), 82.8 (d), 82.6 (d), 81.6 (d), 78.7 (d), 31.8 (t), 29.22 (t), 29.17 (t), 29.11 (t), 29.0 (t), 27.4 (q), 27.0 (q), 25.6 (q), 25.0 (q), 22.6 (t), 14.1 (q); m/z (FAB) 325 (MH^+, 12%), 323 ((M^+-1), 15), 309 (M^+-CH_3, 44), 209 (MH^+-2×acetone, 100).

Elution with 50% ether–petrol gave **9a** (210 mg), R_f 0.2 in 50% ether–petrol, contaminated with *ca.* 15% of **8a**. This was reacted on without further purification. NMR data for **9a**: δ_H (270 MHz, $CDCl_3$) 6.02 (1H, dd, *J* 6.0, 2.0), 5.76 (1H, d, *J* 6.0), 5.28 (1H, dd, *J* 6.0, 2.0), 4.54 (1H, d, *J* 6.0), 3.80–3.60 (1H, m), 3.00 (1H, s), 2.81 (1H, d, *J* 4.0), 1.61–1.28 (18H, m), 0.88 (3H, t, *J* 7.0); δ_C (67.9 MHz, $CDCl_3$) 136.3 (d), 135.0 (d), 113.5 (s), 87.8 (d), 87.8 (s), 84.3 (d), 74.1 (d), 32.2 (t), 30.3 (t), 30.0 (t), 29.6 (t), 27.3 (q), 26.5 (t), 25.7 (q), 23.0 (t), 14.4 (q).

To a stirred solution of the impure **9a** obtained above (180 mg) in tetrahydrofuran (10 ml) and water (2.5 ml) was added sodium periodate (280 mg, 1.31 mmol). After 18 hours the reaction mixture was extracted into ethyl acetate, washed with saturated sodium thiosulfate solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash column chromatography (25% EtOAc in petrol) gave **1** (50 mg, 18% from **7a**) as a colourless solid, $[\alpha]_D^{20}$ +55.9 (*c* 1.107, $CHCl_3$) (lit.[5c] $[\alpha]_D^{25}$ +71.3 (*c* 0.92, $CHCl_3$)). This suggests that the asymmetric dihydroxylation of **5a** proceeded with 78% ee. δ_H (270 MHz, $CDCl_3$) 7.60 (1H, dd, *J* 6.0, 2.0), 6.20 (1H, d, *J* 6.0), 5.25 (1H, dd, *J* 5.5, 2.0), 4.45 (1H, d, *J* 5.5), 1.40 (6H, s).

(2S,3S,4S,5S)-2,3:4,5-bis-(Isopropylidenenedioxy)cyclopentanone **2**

10a (84 mg, 0.26 mmol) was dissolved in dichloromethane (5 ml) and the solution cooled to −78°C. Ozone-enriched O_2 was bubbled through the solution until a deep blue colour persisted, followed by a stream of O_2 until the blue colour disappeared. Triphenylphosphine (250 mg, 0.95 mmol) was added, and the reaction was stirred for 30 minutes while allowing to warm to room temperature. The solvent was removed under reduced pressure. Flash column chromatography (25% ether–petrol) gave **2** (58 mg, 98%) as a white solid, m.p. 72–80°C. $[\alpha]_D^{20}$ +124.3 (*c* 0.63, $CHCl_3$) @ *ca.* 78% ee; ν_{max} (film)/cm^{-1} 2986, 1780, 1375, 1212, 1150, 1060; δ_H (270 MHz, $CDCl_3$) 4.68 (2H, d, *J* 5.0), 4.58 (2H, d, *J* 5.0), 1.41 (6H, s), 1.36 (6H, s); δ_C (67.9 MHz, $CDCl_3$) 208.5 (s), 113.0 (s), 77.8 (d), 77.5 (d), 26.6 (q), 24.6 (q); m/z (EI) 228 (M^+, 6%), 213 (M^+-CH_3, 8%), 100 (100%); Found: M^+, 228.0998. $C_{11}H_{16}O_5$ requires: M, 228.0998.

(1R,2R,3R,4R)-3,4-(Isopropylidenedioxy)-5-(2′,2′-dimethylpropylidene)-1,2-cyclopentanediol ***8b*** *and (1R,1′S,4S,5S)-1-(1′-hydroxy-2′,2′-dimethylpropyl)-4,5-(isopropylidenedioxy)-cyclopent-2-enol* ***9b***

(i) Dihydroxylation of fulvene ***5b***[11]

To a stirred biphasic mixture of water (370 ml) and *tert*-butanol (370 ml) at room temperature were added potassium osmate dihydrate (328 mg, 0.89 mmol), potassium ferricyanide (72.8 g, 221 mmol), $(DHQD)_2PHAL$ (918 mg, 1.18 mmol), potassium carbonate (30.6 g, 221 mmol) and methane

sulfonamide (14.2 g, 0.15 mol). After 15 minutes fulvene **5b**[10] (10.0 g, 74.5 mmol) was added, and the reaction mixture stirred for a further 22 hours. Sodium sulfite (112 g, 0.89 mol) was added and the mixture stirred for a further 15 minutes before extracting three times into ethyl acetate. The combined organics were washed with 2M KOH, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash column chromatography (40% ether–petrol) gave **6b** (5.00 g, 40%) as a pale, viscous oil which was reacted on without further purification. ^1H NMR: δ_H (270 MHz, $CDCl_3$) 6.77 (1H, d, *J* 6.5), 6.07 (1H, d, *J* 6.0), 5.58 (1H, s), 4.52–4.46 (1H, m), 4.42–4.36 (1H, m), 2.34 (1H, d, *J* 7.0), 2.25 (1H, d, *J* 7.5), 1.14 (9H, s).

(ii) Acetonide protection of ***6b***

To a solution of **6b** (5.00 g, 29.6 mmol) in acetone (150 ml) in an ice–salt bath was added 2,2-dimethoxypropane (13 ml, 105 mmol) and *para*-toluenesulfonic acid (10 mg, 0.06 mmol). The reaction was stirred for 1 hour and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (5% ether–petrol) to yield **7b** (5.15 g, 85%) as a colourless oil which was reacted on without further purification. ν_{max} (film)/cm^{-1} 2957, 1458, 1368, 1205, 1050; δ_H (270 MHz, $CDCl_3$) 6.67 (1H, d, *J*6.0), 6.05 (1H, dt, *J*6.0, 2.0), 5.68 (1H, br s), 5.02 (1H, dd, *J*5.5, 2.0), 4.84 (1H, d, *J*5.5), 1.41 (3H, s), 1.39 (3H, s), 1.16 (9H, s); δ_C (67.9 MHz, $CDCl_3$) 139.4 (s), 138.6 (d), 135.8 (d), 132.2 (d), 110.9 (s), 82.3 (d), 82.0 (d), 34.4 (s), 31.5 (q), 28.0 (q), 26.5 (q).

(iii) Dihydroxylation of ***7b***

To a stirred, biphasic mixture of *tert*-butanol (125 ml) and water (125 ml) was added potassium osmate dihydrate (37 mg, 0.10 mmol), potassium ferricyanide (24.7 g, 76.2 mmol), quinuclidine (28 mg, 0.26 mmol), potassium carbonate (10.4 g, 74.3 mmol), and methane sulfonamide (2.38 g, 25 mmol). The mixture was stirred for 15 minutes, diene **7b** (5.10 g, 25 mmol) was added, and the reaction was stirred for a further 46 hours. Sodium sulfite (37.5 g, 0.30 mmol) was added, and after a further 60 minutes the mixture was extracted into ethyl acetate. The combined organics were washed with 2M KOH solution, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash column chromatography (40% ether–petrol) yielded two compounds. The less polar compound **9b** (1.88 g, 31%), R_f 0.3, 50% ether–petrol, was isolated as a colourless solid, m.p. 70–76°C, $[\alpha]_D^{20}$ +86.5 (*c* 0.992, MeOH) @ 84% ee. (Found C, 64.2; H, 9.00. $C_{13}H_{22}O_4$ requires C, 64.4; H; 9.15%). ν_{max} (film)/cm^{-1} 3375, 3302, 2949, 1374, 1259, 1056; δ_H (270 MHz, $CDCl_3$) 6.06 (1H, dt, *J* 6.0, 1.0), 6.00 (1H, dd, *J* 6.0, 2.0), 5.23 (1H, ddd, *J* 5.5, 2.0, 1.0), 4.46 (1H, d, *J* 5.5), 3.62 (1H, d, *J* 5.5), 2.89 (1H, s), 2.85 (1H, d, *J* 5.5), 1.45 (3H, s), 1.36 (3H, s), 1.07 (9H, s); δ_C (67.9 MHz, $CDCl_3$) 137.1 (d), 134.4 (d), 112.0 (s), 89.2 (d), 88.0 (s), 83.3 (d), 79.3 (d), 36.0 (s), 28.3 (q), 27.6 (q), 26.2 (q); m/z (FAB) 243 (MH^+, 8%), 185 (MH^+-^{t}Bu, 100%).

A single recrystallisation (ether /petrol) gave colourless needles (1.29 g, 22%), m.p. 76–78°C, $[\alpha]_D^{19}$ +93.7 (*c* 1.002, MeOH) @ 91% ee. This value of 91% ee was obtained by conversion to enone **1** and comparison of the optical rotation of the resulting sample of **1** to the literature value. The ee of the unrecrystallised sample of **9b** was then estimated by comparing its optical rotation to that of recrystallised **9b**.

The more polar compound **8b** (2.27 g, 38%), R_f 0.15 in 50% ether–petrol, was isolated as a colourless solid m.p. 90–95°C, $[\alpha]_D^{20}$ +76.6 (*c* 0.984, MeOH) @ 84% ee; ν_{max} (film)/cm^{-1} 3350, 2958, 1371, 1207, 1070; δ_H (270 MHz, $CDCl_3$) 5.90 (1H, t, *J* 1.5), 4.93 (1H, d, *J* 6.5), 4.89 (1H, br d, *J* 4.5), 4.45 (1H, dd, *J* 6.5, 5.0), 4.06 (1H, br d, *J* 5.0), 3.25 (1H, d, *J* 4.5), 2.62 (1H, br s), 1.46 (3H, s), 1.41 (3H, s), 1.18 (9H, s); δ_C (67.9 MHz, $CDCl_3$) 146.4 (d), 135.2 (s), 112.5 (s), 83.8 (d), 81.8 (d), 78.5 (d), 71.4 (d), 34.0 (s), 30.6 (q), 27.7 (q), 25.7 (q); m/z (FAB) 265 (MNa^+, 8%), 243 (MH^+, 15), 185 (MH^+-^{t}Bu, 26), 167 (M^+–^{t}Bu–H_2O, 100%); Found: MH^+, 243.1596. $C_{13}H_{23}O_4$ requires: 243.1548.

A single recrystallisation from ether/petrol gave colourless plates (1.76 g, 29%), m.p. 100–102°C, $[\alpha]_D^{19}$ +84.7 (*c* 0.990, MeOH) @ 93% ee. This value of 93% ee was obtained by conversion to ketone

2 and comparison of the optical rotation of the resulting sample of **2** to that obtained previously. The ee of the unrecrystallised sample of **8b** was then estimated by comparing its optical rotation to that of recrystallised **8b**.

*Enone **1** from diol **9b***

To a solution of **9b** after recrystallisation (91% ee) (188 mg, 0.78 mmol) in tetrahydrofuran (4 ml) and water (2 ml) was added $NaIO_4$ (332 mg, 1.55 mmol). The solution was heated to 55°C for 18 hours. The resultant suspension was cooled to room temperature, filtered through celite, extracted into ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash column chromatography (25% ether–petrol) gave enone **1** (72 mg, 60%) as a colourless solid, $[\alpha]_D^{20}$ +64.8 (*c* 1.10, $CHCl_3$) @ 91% ee, identical by ^1H NMR to the sample prepared previously.

*(1R,2R,3R,4R)-1,2:3,4-bis-(Isopropylidenedioxy)-5-(2′,2′-dimethylpropylidene)cyclopentane **10b***

To a solution of diol **8b** after recrystallisation (93% ee) (1.75 g, 7.22 mmol) in acetone (75 ml) at 0°C was added 2,2-dimethoxypropane (5 ml, 41 mmol) and *para*-toluenesulfonic acid (10 mg). After 1 hour the solvent was removed under reduced pressure. Flash column chromatography (10% ether–petrol) gave **10b** (2.03 g, 100%) as colourless needles, m.p. 31–32°C. $[\alpha]_D^{20}$ +173.9 (*c* 0.74, MeOH) @ 93% ee. (Found C, 67.8; H, 9.45. $C_{16}H_{26}O_4$ requires C, 68.1; H, 9.30%); ν_{max} (film)/cm^{-1} 2955, 1370, 1209, 1162, 1067, 874; δ_H (270 MHz, $CDCl_3$) 5.83 (1H, t, *J* 1.5), 5.38 (1H, dt, *J* 6.0, 1.5), 4.96 (1H, br d, *J* 5.5), 4.53 (1H, d, *J* 6.0), 4.41 (1H, dd, *J* 5.5, 0.5), 1.41 (3H, s), 1.38 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 1.18 (9H, s); δ_C (67.9 MHz, $CDCl_3$) 144.8 (d), 136.6 (s), 111.4 (s), 110.5 (s), 82.8 (d), 82.6 (d), 82.3 (d), 78.1 (d), 34.0 (s), 30.4 (q), 27.7 (q), 26.9 (q), 26.1 (q), 24.7 (q); m/z (EI) 282 (M^+, 2%) 267 (M^+–CH_3, 38), 209 (75%).

*Ozonolysis of bis-acetonide **10b**: preparation of (3S,4S,5S,6R)-3,4:5,6-bis-(isopropylidenedioxy)-tetrahydropyran-2-one **11** and ketone **2***

(a) Reductive workup using triphenylphosphine quench

A solution of **10b** (156 mg, 0.55 mmol) in dichloromethane (5 ml) was cooled to −78°C. Ozone was bubbled through until a deep blue colour was observed, followed by a stream of O_2 until the blue colour disappeared. Triphenylphosphine (1.0 g, 3.8 mmol) was added, and the solution allowed to warm to room temperature. The solution was stirred for 18 hours, and the solvent removed under reduced pressure. Flash column chromatography gave **11** (46 mg, 37%) as a white solid, m.p. 92–94°C, $[\alpha]_D^{20}$ +24.3 (*c* 1.058, $CHCl_3$) @ 93% ee; ν_{max} (film)/cm^{-1} 2988, 2922, 2851, 1752, 1456, 1375, 1213, 1157, 1110, 1062, 1012; δ_H (500 MHz, $CDCl_3$) 5.92 (1H, d, *J* 2.5), 4.68 (1H, dd, *J*5.5, 2.5), 4.56 (1H, d, *J* 5.5), 4.37 (1H, t, *J* 2.5), 1.49 (3H, s), 1.46 (3H, s), 1.42 (3H, s), 1.40 (3H, s); δ_C (125 MHz, $CDCl_3$) 166.2 (s), 112.8 (s), 111.6 (s), 99.1 (d), 74.1 (d), 71.9 (d), 70.5 (d), 27.5 (q), 26.7 (q), 25.6 (q), 25.1 (q); m/z (CI) 243 (M^+, 5%), 229 (M^+–CH_3, 15); Found: M–CH_3^+, 229.0712. $C_{11}H_{16}O_6$ requires: 229.0713.

(b) Reductive workup using dimethylsulfide quench

A solution of **10b** (505 mg, 1.79 mmol) in dichloromethane (100 ml) was cooled to −78°C. A stream of ozone was bubbled through until a deep blue colour was observed, followed by a stream of O_2 until the blue colour disappeared. Dimethylsulfide (5 ml, 68.8 mmol) was added. The solution was stirred at −78°C for 5 minutes, then allowed to warm to room temperature over 2 hours. The solvent was removed under reduced pressure. Flash column chromatography (10–70% ether–petrol) gave **11** (213 mg, 49%) as a white solid and **2** (170 mg, 42%) as a white solid, m.p. 74–80°C, $[\alpha]_D^{20}$ +133.5 (*c* 1.025, $CHCl_3$) @ 93% ee, identical by ^1H NMR to the sample prepared previously.

Acknowledgements

We thank the EPSRC, the DTI and a consortium of chemical companies for funding of this work through the LINK Asymmetric Synthesis Second Core Programme. We are grateful to Dr. G. Potter (Chiroscience) and Mr. T. Lowdon (Hicksons) for useful discussions. We also thank Prof. K.B. Sharpless (Scripps) for helpful advice, and Dr. N.J. Turner (Edinburgh) for synthetic information and a sample of the enone **1**.

References

1. For example: McIntosh, J.M.; Cassidy, K.C. *Tetrahedron: Asymmetry* **1991**, *2*, 1053–1062. Delucchi, D.; Fabris, F. *Synlett* **1993**, 275–276.
2. Denmark, S.E.; Forbes, D.C.; Hays, D.S.; DePue, J.S.; Wilde, R.G. *J. Org. Chem.* **1995**, *60*, 1391–1407.
3. Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491–492.
4. Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.
5. It should be noted that there are several elegant literature routes that involve desymmetrisation or resolution of an intermediate or of **1** itself. For example: (a) Johnson, C.R.; Penning, T.D. *J. Am. Chem. Soc.* **1988**, *110*, 4726–4735. (b) Johnson, C.R.; Esker, J.L.; Van Zandt, M.C. *J. Org. Chem.* **1994**, *59*, 5854–5855. (c) Siddiqi, S.M.; Schneller, S.W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1993**, *12*, 185–198. (d) Deardorff, D.R.; Shambayate, S.; Myles, D.C.; Heerding, D. *J. Org. Chem.* **1988**, *53*, 3614–3615.
6. Hill, J.M.; Hutchinson, E.J.; Le Grand, D.M.; Roberts, S.M.; Thorpe, A.J.; Turner, N.J. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1483–1487.
7. Ohrui, H.; Konno, M.; Meguro, H. *Agric. Biol. Chem.* **1987**, *51*, 625–626.
8. Hudlicky, T.; Luna, H.; Barbierei, G.; Kwart, L.D. *J. Am. Chem. Soc.* **1988**, *110*, 4735–4741.
9. Hudlicky, T.; Natchus, M.G.; Nugent, T.C. *Synth. Commun.* **1992**, *22*, 151–157.
10. Stone, K.J.; Little, D.R. *J. Org. Chem.* **1984**, *49*, 1849–1853.
11. Wang, Z.-M.; Kakiuchi, K.; Sharpless, K.B. *J. Org. Chem.* **1994**, *59*, 6895–6897.
12. For a review of the Sharpless asymmetric dihydroxylation, see: Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(Received in UK 24 March 1997)