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An asymmetric synthesis of enantiopure chair and twist *trans*-cyclooctene isomers

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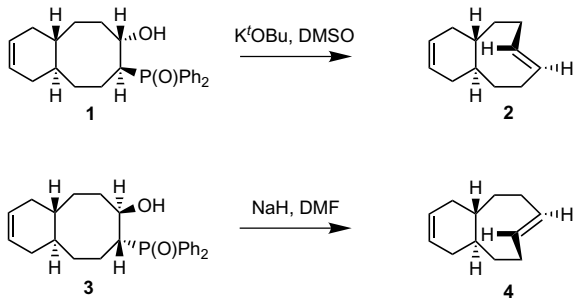
Abstract—A pair of enantiopure chair and twist *trans*-cyclooctenes isomers were prepared by regioselective Sharpless asymmetric dihydroxylation of the central olefin of (*E*)-1,5,9-dectriene triene, with subsequent ring-closing metathesis to form an enantiomerically pure *cis*-cyclooctene. Epoxidation and ring-opening with lithium diphenylphosphide gives after oxidation two diastereomeric hydroxyphosphine oxides. Separate *syn*-elimination of these diastereomers gives enantiomerically pure chair and twist *trans*-cyclooctenes. A discussion of the molecular motion required to achieve the chair and twist isomers is discussed with reference to the X-ray crystal structure obtained for the hydroxyphosphine oxide leading to the chair *trans*-cyclooctene.

1. Introduction

Twist ("Crown") **A** Chair **B**

trans-Cyclooctene[1] demonstrates molecular asymmetry as a consequence of restricted rotation of the olefinic hydrogens through the hexamethylene chain and was first resolved into its enantiomers by Cope via diastereomeric platinum complexes.[2] Theoretical methods suggest that *trans*-cyclooctene exists preferentially in the so-called twist (or 'crown') conformation **A**,[3] and this has been substantiated by X-ray crystallographic evidence of derivatives.[4] An alternative, albeit less stable, 'chair' conformation **B** for *trans*-cyclooctenes has also been suggested and the first examples—(4*E*,10*Z*)-bicyclo[6.4.0]dodecadiene **2** is representative—were reported by Newton and Whitham in 1979.[5] The locked chair *trans*-cyclooctene **2** was obtained by restricting the partial conformation about C-4, C-5, C-6 and C-7 in the cyclooctane ring of precursor **1** by incorporation of a *trans*-fused six-membered ring at the 5 and 6 positions and *syn*-elimination of the β-hydroxyphosphine oxide to install a *trans* double bond between C-1 and C-2 (Scheme 1). *syn*-Elimination from the diastereomeric hydroxyphosphine oxide **3** gave instead the twist isomer **4**. The chair *trans*-cyclooctenes were prepared by synthetic routes that delivered racemates, but enantiomerically pure **2** and **4** were also prepared by fractional crystallisation of diastereomeric cyclooctane menthoxyacetate derivatives early in the synthetic route.[6] However, to the best of our knowledge there have been no further reports on the synthesis of chair *trans*-cyclooctenes. We report herein the direct asymmetric synthesis of a pair of enantiomerically pure chair and twist *trans*-cyclooctene isomers **5c** and **5t** with a *trans*-fused



Scheme 1. *syn*-Eliminations to give chair *trans*-cyclooctene **2** and twist *trans*-cyclooctene **4**.

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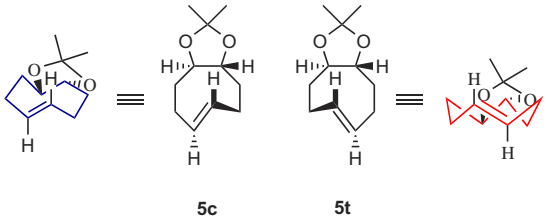
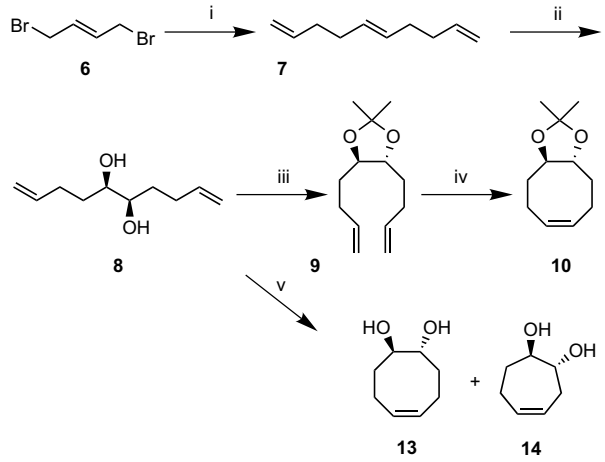
bicyclo[6.3.0]undecane skeleton,[†] by use of the Sharpless catalytic asymmetric dihydroxylation reaction, ring-closing metathesis, and *syn*-elimination of diastereomeric β-hydroxyphosphine oxides as the key steps.



5c **5t**

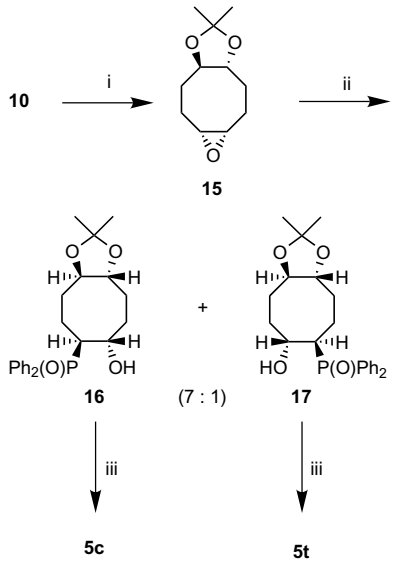
2. Results and discussion

On the basis of literature precedent it was considered that ring-closing metathesis[7] could be employed to construct the requisite eight-membered ring of **5c** and **5t** (albeit initially with a *cis* double bond requiring subsequent transformation to a *trans* double bond). Several examples of eight-membered carbocyclic ring-formation by ring-closing metathesis have now been reported,[8] including the (unexpected) direct formation of a (twist) *trans*-cyclooctene.[9] The ring-closing metathesis substrate **9** was prepared by double coupling of allyl magnesium bromide to commercially available dibromide **6** to give *E*-triene **7** in an improved 72% yield compared to the 49% isolated yield originally reported[10] (Scheme 2). Sharpless asymmetric dihydroxylation with β-AD mix using methanesulfonamide to promote nonterminal double-bond selectivity[11] gave the (*R*,*R*)-diol **8**[12] (61%, >96% ee by Mosher ester analysis—see Section 4.5). Acetonide formation proceeded smoothly under standard conditions to provide acyclic diene **9** (86%). We note an order of magnitude difference in the specific rotation value recorded for this compound compared to the one reported in the literature.[13] After some optimisation, ring-closing metathesis of diene **9** was found to proceed to the desired eight-membered ring compound **10**[14] at a concentration of 0.024 M in 2 h using 2 mol% of Grubbs catalyst $(Cl)_2(PCy_3)_2Ru{=}CHPh$ **11**[15] (Cy = cyclohexyl) in refluxing dichloromethane solution (89%). An essentially identical result was obtained using 2 mol% of the *N*-heterocyclic carbene containing benzylidene $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ **12**[16] ($IMesH_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) under the same conditions. *cis*-Cyclooctene **10** displays six resonances in the ^{13}C NMR spectrum as required for a C_2 symmetric system with the olefinic carbons resonating at 129.6 ppm. Ring-closing metathesis of diol **8** was also attempted. Surprisingly, regardless of the catalyst used (**11** or **12**), although the expected eight-membered ring diol **13**[17] was present in the reaction mixture (19% isolated yield), the seven-membered diol **14** was isolated as the major product instead (33%). This result can be added to the growing list of examples of unexpected methylene loss in a ring-closing metathesis event.[18,19]



Scheme 2. Reagents and conditions: (i) Mg, allyl bromide, Et_2O, 18 h (72%); (ii) β-AD mix, $MeSO_2NH_2$, ^tBuOH–H_2O, 7 h, 0 °C (61%, >96% ee); (iii) $Me_2C(OMe)_2$, cat. TsOH, acetone, 18 h (86%); (iv) 2 mol% **11**, CH_2Cl_2, 2 h (89%); (v) cat. **11** or cat. **12**, CH_2Cl_2.

Epoxidation of *cis*-olefin **10** with *m*CPBA gave epoxide **15** (Scheme 3) in good yield (85%). Epoxide ring-opening with lithium diphenylphosphide followed by in situ oxidation with hydrogen peroxide[20] gave diastereomeric phosphine oxides **16** and **17** in a 7:1 ratio after purification (61% combined yield).



Scheme 3. Reagents and conditions: (i) *m*CPBA, CH_2Cl_2, 2 h (85%); (ii) $LiPPh_2$, THF, 24 h then AcOH, H_2O_2, 4 h (61%); (iii) NaH, DMF (**5c**: 91%; **5t**: 55%).

The major isomer **16** was confirmed as the (1*R*,4*S*,5*S*,8*R*)-diastereoisomer by X-ray crystallography. In Whitham's work,[5] the two possible diastereo-

[†] Each of the *trans*-cyclooctenes **5c** and **5t** is drawn in two representations. The pair of central molecules are represented so that there is no ambiguity about their relative and absolute *configurations*. The alternative representations (flanking on either side) serve to illustrate the *conformation* of the chair **5c** (the eight ring chair conformation is highlighted in blue) and the twist **5t** isomer (the eight ring twist—or 'crown'—conformation is highlighted in red).

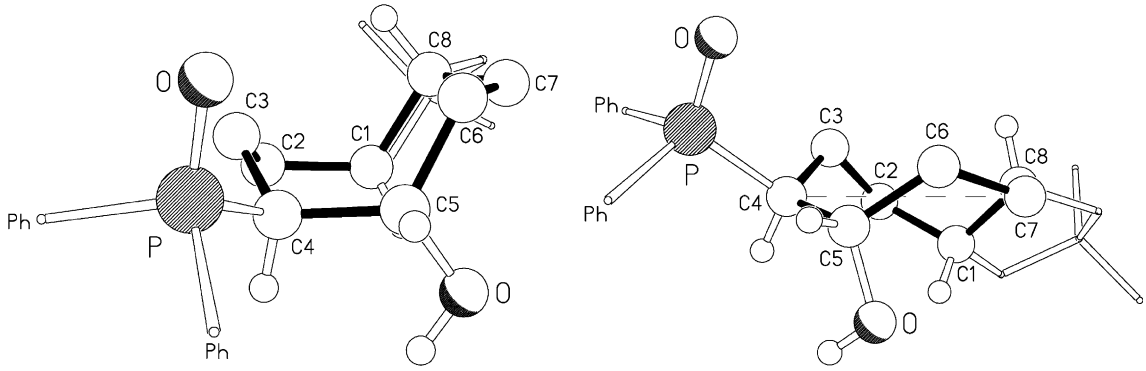


Figure 1. View of the eight-membered ring in **16** showing the boat-chair conformation and the pseudo-mirror plane that bisects the C2–C3–C4 and C6–C7–C8 angles (left); view of the eight-membered ring in **16** showing the λ twist of the C5–C6 bond with respect to the plane of C4, C7 and the centre of the C5–C6 bond (right).

meric isomers **1** and **3** were reported to be obtained in equal quantities from the ring-opening of an epoxide. This difference may arise from a pseudo-*trans*-diaxial ring-opening on a preferred conformation of epoxide **10** imposed by the bicyclo[6.3.0]undecane framework.

In the solid state, the eight-membered ring of major diastereoisomer **16** has a boat-chair conformation (Fig. 1, left) with a pseudo-mirror plane bisecting the C2–C3–C4 and C6–C7–C8 angles (i.e., in the plane of the paper); the bulky diphenylphosphine oxide moiety adopts an equatorial position. In order to undergo the *syn*-elimination step to form the corresponding *trans*-cyclooctene the axial alcohol on C5 has to be aligned with the phosphine oxide on C4. Examination of CPK models has shown that this can only occur *exo* to the eight-membered ring, an *endo* pathway being far too hindered. As can be seen (Fig. 1, right), in the solid state the C5–C6 bond has a λ twist[21] with respect to the plane of C4, C7 and the centre of the C5–C6 bond. The simplest molecular motion to align the PO and OH units in a *syn* fashion is merely a flip of the twist of the C5–C6 bond from λ to δ (i.e., C5 moves 'up' and C6 moves 'down', which changes the C5 alcohol from an axial to an equatorial disposition). This leads to a chair conformation for the resultant *trans*-cyclooctene (i.e., **5c**). Assuming an analogous boat-chair structure for the other diastereoisomer of the phosphine oxide, **17**, (with the bulky diphenylphosphine oxide again equatorial), the C5–C6 bond has a δ twist, and flipping this to λ to achieve a *syn* alignment of the PO and OH units leads to a twist conformation for the subsequent *trans*-cyclooctene (i.e., **5t**).

By consideration of the above analysis and by analogy with Whitham's work, phosphine oxide **16** would be expected to undergo *syn*-elimination on treatment with base to give the chair *trans*-cyclooctene **5c**, and the phosphine oxide **17** to give twist *trans*-cyclooctene **5t**. Using Shea and Kim's conditions[22] both diastereoisomers **16** and **17** underwent smooth elimination (Scheme 3) to give chair *trans*-cyclooctene **5c** (91%), $[\alpha]_D = -178.4$, and twist *trans*-cyclooctene **5t** (55%), $[\alpha]_D = +90.9$, respectively (cf. *cis*-cyclooctene **10**, $[\alpha]_D = -89.4$). Inspection of the chemical shifts for the olefinic carbons in the ^{13}C NMR spectra is instructive and the characteristic shifts further confirm the above assignments. For chair *trans*-cyclooctene **5c** the chemical shift was found to be 135.6 ppm. This compares with a value of 136.8 ppm reported for chair *trans*-cyclooctene **2**.[5] Chemical shifts of 133.2 and 133.8 ppm are the respective values for **5t** and twist cyclooctene **4** (cf. *trans*-cyclooctene: 133.9 ppm[22]). In the ^1H NMR spectrum the olefin protons resonate at 5.83 ppm for **5c** (and 5.77 ppm in **2**) and 5.42 ppm for **5t** (and 5.40 ppm for **4**).

Treatment of either **5c** and **5t** with 4,4-dibromo-2,6-*tert*-butylcyclohexa-2,5-dienone[23] in $CDCl_3$ resulted in isomerisation to the *cis*-cyclooctene **10** thereby corroborating the skeletal identity of the *trans*-cyclooctenes. This process presumably occurs by initial transfer of Br^+ from the dienone to the alkene forming a *trans* bromonium ion, bromonium ion ring-opening to give a carbocation, bond rotation, ring-closure to form a *cis* bromonium ion and finally transfer of Br^+ back to the phenoxide. After 26.5 h the twist-cyclooctene **5t** had undergone 23% isomerisation to olefin **10**, while the isomerisation process with the chair cyclooctene **5c** had proceeded to 82%, showing that the twist *trans*-cyclooctene **5t** is less reactive than the chair **5c** under these conditions and qualitatively confirming their relative conformational stabilities.[24] In neither case was the possible competing isomerisation from twist to chair (or chair to twist) *trans*-cyclooctenes observed.

3. Conclusion

In conclusion, we have shown that regioselective Sharpless asymmetric dihydroxylation of (*E*)-1,5,9-decatriene, followed by subsequent ring-closing metathesis and *syn*-elimination of hydroxyphosphine oxides provides a convenient synthetic route to enantiomerically pure chair and twist *trans*-cyclooctenes that were previously inaccessible. Analysis of the X-ray crystal structure of the chair *trans*-cycloalkene precursor **16** shows that in order to align the two groups for *syn*-elimination, the

chair–boat conformation with a C5–C6 λ twist must undergo a bond rotation to give the δ twist leading to chair *trans*-cyclooctene **5c**.

4. Experimental

4.1. Materials and methods

Et_2O and THF were distilled from sodium and potassium, respectively, in the presence of benzophenone. CH_2Cl_2 was distilled from CaH_2. DMF was distilled from $MgSO_4$. All other reagents were used as received. Concentrated refers to removal of solvent under reduced pressure on a rotary evaporator. Analytical thin-layer chromatography (TLC) was carried out on silica gel $F_{254/366}$ 60 Å plates with visualisation using UV light (254 nm) or potassium permanganate as appropriate. Chromatography was performed using BDH 33–70 μm grade silica gel.

Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm using the 589.3 nm D-line of sodium. Solutions were prepared using spectroscopic grade solvents and concentrations (*c*) are quoted in g/100 mL. Melting points were recorded on a Reichart Thermovar melting point apparatus and are uncorrected. Fourier transform infrared (IR) spectra were recorded through Diffuse Reference Infrared Fourier Transform Spectroscopy (DRIFTS) or as thin films on NaCl plates using a Mattson 500 FTIR spectrometer. ^{1}H NMR were recorded at 270 MHz on a Jeol GSX-270 spectrometer or at 300 MHz on a 300 MHz Bruker DRX spectrometer. ^{13}C NMR were recorded at 68 and 75 MHz on a Jeol GSX-270 spectrometer or a 300 MHz Bruker DRX spectrometer, respectively. ^{31}P NMR were recorded at 202.5 MHz on a Bruker AM500 spectrometer. NMR samples were run in the indicated solvents and were referenced internally. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. The following abbreviations are used for the multiplicity of NMR signals: br = broad, s = singlet, d = doublet, t = triplet, m = multiplet. Low Resolution Mass Spectra (MS) [EI CI] and High Resolution Mass Spectra (HRMS) were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service. Elemental analyses were carried out by the University of North London Analytical Service.

4.2. (*E*)-1,5,9-Decatriene 7

To a suspension of Mg (16.8 g, 702 mmol) stirring in Et_2O (300 mL) under N_2 was added dropwise allyl bromide (40.5 mL, 468 mmol) to maintain an exotherm. After 3 h the reaction mixture was transferred to a fresh flask and cooled to 0 °C. *trans*-1,4-Dibromo-2-butene **6** (25.0 g, 117 mmol) in Et_2O (100 mL) was added dropwise and the reaction allowed to stir overnight. The reaction mixture was quenched carefully with acetic acid (3 mL) in water (10 mL) and diluted with ice water (700 mL). The organic layer was separated, washed with 10% aqueous $NaHCO_3$ solution (2×200 mL) and brine (1×300 mL), dried over $MgSO_4$ and concentrated to yield 15 g of pale yellow oil. The residue was chromatographed (petroleum ether) to give triene **7** (11.5 g, 72%) as a colourless oil: bp 169–171 °C [lit.,[10] 69–70 °C/18 mmHg]; $R_f = 0.60$ (petroleum ether); FTIR (NaCl plate) ν_{max} 3078, 1641 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.81 (2H, ddt, $J = 17.0$, 10.3, 6.1 Hz), 5.45–5.43 (2H, m), 5.04–4.93 (4H, m), 2.09 (8H, br s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.5, 130.0, 114.6, 33.9, 32.1.

4.3. (5*R*,6*R*)-5,6-Dihydroxydeca-1,9-diene 8

A suspension of β-AD mix (122 g, 1.4 g/mmol of olefin) and methanesulfonamide (8.7 g, 88 mmol) stirring in ^{t}BuOH (430 mL) and water (430 mL) was cooled to 0 °C. Triene **7** (11.9 g, 87 mmol) was added and the reaction mixture stirred for 7 h at 0 °C. Sodium sulfite (131 g) was added to quench the reaction and the mixture was allowed to warm to room temperature before extracting with EtOAc (650 mL). The organic layers were combined, washed with brine (400 mL), dried over $MgSO_4$ and concentrated to yield 14.8 g of pale yellow oil. The residue was chromatographed (petroleum ether–EtOAc, 2:3) to give diol **8** (9.0 g, 61%) as a colourless oil: $[\alpha]_D^{25} = +21.3$ (*c* 4.0, $CHCl_3$) [lit.,[12] +22.0 (*c* 4, $CHCl_3$)]; $R_f = 0.45$ (petroleum ether–EtOAc; 1:2); FTIR (NaCl plate) ν_{max} 3650–3100, 3078, 1641 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.79 (2H, ddt, $J = 17.0$, 13.4, 6.7 Hz), 5.07–4.93 (4H, m), 3.45–3.37 (2H, m), 2.47 (2H, br s), 2.27–2.05 (4H, m), 1.59–1.46 (4H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.3, 115.1, 73.9, 32.7, 30.0; MS (CI$^+$) 188 $(M+NH_4)^+$, 170 $(M)^+$; HRMS calcd for $C_{10}H_{22}NO_2$ 188.1651, found 188.1646.

4.4. (5*S*,6*S*)-5,6-Dihydroxydeca-1,9-diene

Following the above procedure for the dihydroxylation of triene **7** but using α-AD mix gave the corresponding (*S*,*S*)-enantiomer (24%) as a colourless oil; $[\alpha]_D^{25} = -20.1$ (*c* 4.0, $CHCl_3$) [lit.,[12] −21.3 (*c* 3.30, $CHCl_3$)].

4.5. Ee determination of diol 8 by Mosher ester analysis[25]

To a solution of (*R*)-MTPA (250 mg, 1.1 mmol) and DMF (1 drop) stirring in hexane (4 mL) at room temperature was added freshly distilled oxalyl chloride (442 μL, 5.1 mmol). After 1 h the organic layer was decanted off and concentrated to yield (*S*)-MTPA–Cl, verified by ^{1}H NMR in CD_2Cl_2. A solution of (*S*)-MTPA–Cl in CD_2Cl_2 (0.42 M, 0.8–1 mL), was added to diol **8** (16 mg, 0.094 mmol) stirring in CD_2Cl_2 (0.3 mL) with triethylamine (148 μL, 1.1 mmol) and 4-dimethylaminopyridine (1 mg, 0.0082 mmol). The reaction was monitored by TLC (petroleum ether–EtOAc, 1:2) and ^{1}H NMR. After 18 h the reaction was quenched with HCl (0.1 M, 10 mL), extracted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (1×15 mL), dried over $MgSO_4$ and concentrated to yield the corresponding Mosher diesters. The residue was analysed by ^{1}H and ^{13}C NMR.

Mosher's diester derived from (*R*,*R*)-diol **8**: ^{1}H NMR (270 MHz, toluene-d_8) δ 7.67–7.58 (4H, d, J = 6.9 Hz), 7.15–6.96 (6H, m), 5.54 (2H, ddt, J = 19.6, 10.5, 6.7 Hz), 5.24–5.18 (2H, m), 4.96–4.88 (4H, m), 3.40 (6H, s), 1.87–1.79 (4H, m), 1.68–1.55 (2H, m), 1.52–1.39 (2H, m); ^{13}C NMR (68 MHz, toluene-d_8) δ 166.0, 137.2, 136.5, 132.1, 129.5, 125.2, 124.8, 124.4, 115.7, 74.9, 55.1, 29.9, 29.0.

Mosher's diester derived from (*S*,*S*)-diol **8**: ^{1}H NMR (270 MHz, toluene-d_8) δ 7.67–7.53 (4H, d, J = 6.9 Hz), 7.15–6.96 (6H, m), 5.53 (2H, ddt, J = 19.6, 10.5, 6.7 Hz), 5.16–5.10 (2H, m), 4.96–4.88 (4H, m), 3.38 (6H, s), 1.91–1.80 (4H, m), 1.64–1.53 (4H, m); ^{13}C NMR (68 MHz, toluene-d_8) 165.7, 137.2, 136.4, 132.3, 129.5, 125.2, 124.8, 124.4, 115.7, 74.4. 55.1, 29.3, 28.9.

The ee of diol **8** was determined by integration of the resolved resonances in the ^{1}H NMR spectrum between 5.24 and 5.10 (*H*CO) or 3.40 and 3.38 (O*Me*) ppm. The ^{13}C NMR spectra showed diagnostic signals for di-Mosher's ester of the (*R*,*R*) isomer at 74.9 and for the (*S*,*S*)-isomer at 74.4 ppm.

4.6. (4*R*,5*R*)-4,5-Dibut-3-enyl-2,2-dimethyl-1,3-dioxacyclopentane 9

A solution of diol **8** (3.5 g, 21 mmol), 2,2-dimethoxypropane (40 mL) and toluene-*p*-sulfonic acid (182 mg, 5 mol%) in acetone (40 mL) was stirred at room temperature for 18 h. CH_2Cl_2 (120 mL) was added and the reaction mixture washed with saturated aqueous $NaHCO_3$ solution (2 × 80 mL). The organic layer was extracted, washed with brine (2 × 80 mL), dried over $MgSO_4$ and concentrated to yield acetonide **9** (3.72 g, 86%) as a colourless oil: $[\alpha]_D^{25} = +27.0$ (c 0.7, $CHCl_3$) [lit.,[13] +3.05 (c 0.7, $CHCl_3$)]; R_f = 0.80 (petroleum ether–EtOAc; 1:2); FTIR (NaCl plate) ν_{max} 3078, 1642 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.78 (2H, ddt, J = 17.0, 13.4, 6.7 Hz), 5.04–4.87 (4H, m), 3.64–3.57 (2H, m), 2.30–2.01 (4H, m), 1.62–1.52 (4H, m), 1.33 (6H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.1, 114.9, 108.0, 80.2, 32.1, 30.2, 27.3; MS (CI$^+$) 211 (M+H)$^+$. HRMS calcd for $C_{13}H_{23}O_2$ 211.1698, found 211.1694.

4.7. (*Z*)-(1*R*,8*R*)-10,10-Dimethyl-9,11-dioxabicyclo-[6.3.0]undec-4-ene 10

A solution of acetonide **9** (3.64 g, 17.3 mmol) and Grubbs catalyst **11** (285 mg, 2 mol%) stirring in CH_2Cl_2 (725 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and concentrated directly onto silica. The residue was chromatographed (petroleum ether–Et_2O; 85:15) to give *cis*-cyclooctene **10** (2.82 g, 89%) as a colourless oil: $[\alpha]_D^{25} = -89.4$ (c 1.89, $CHCl_3$) [lit.,[14] −98.9 (c 1.89, $CHCl_3$)]; R_f = 0.40 (petroleum ether–Et_2O; 4:1); FTIR (NaCl plate) ν_{max} 3017 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.66–5.55 (2H, m), 3.93–3.83 (2H, m), 2.28–2.02 (6H, m), 1.50–1.38 (2H, m) 1.32 (6H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 129.6, 107.4, 80.9, 31.7, 27.0, 21.9; MS (CI$^+$) 183 (M+H)$^+$. HRMS calcd for $C_{11}H_{19}O_2$ 183.1385, found 183.1388.

4.8. Ring-closing metathesis of (5*R*,6*R*)-5,6-dihydroxydeca-1,9-diene 8

A solution of diol **8** (619 mg, 3.64 mmol) and ruthenium benzylidene **12** (114 mg, 5 mol%) in CH_2Cl_2 (750 mL) was refluxed for 2 h. The reaction mixture was allowed to cool, concentrated onto silica and chromatographed (petroleum ether–EtOAc; 1:3) to give first *(Z)-(1R,2R)-cyclohept-4-ene-1,2-diol* ***14*** (156 mg, 33%) as a colourless oil: $[\alpha]_D^{25} = -14.5$ (c 0.20, CH_2Cl_2); R_f = 0.25 (petroleum ether–EtOAc; 1:3); FTIR (NaCl plate) ν_{max} 3750–3050, 3025, 1653 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.89–5.81 (1H, m), 5.69–5.60 (1H, m), 3.46 (1H, dt, J = 8.4, 3.9 Hz), 3.28 (1H, dt, J = 7.2, 3.8 Hz), 3.00 (2H, br s), 2.31–1.90 (5H, m), 1.41–1.34 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 133.8, 126.6, 79.3, 74.1, 32.7, 32.5, 23.0; MS (CI$^+$) 146 (M+NH$_4^+$); HRMS calcd for $C_7H_{16}NO_2$ 146.1181, found 146.1179, and second *(Z)-(1R,2R)-cyclooct-5-ene-1,2-diol* ***13*** (98 mg, 19%). An authentic sample of *(Z)-(1R,2R)-cyclooct-5 ene-1,2-diol* ***13*** was prepared for comparison by deprotection of acetonide **10**. A solution of acetonide **10** (100 mg, 0.56 mmol), and *para*-toluenesulfonic acid (123 mg, 0.72 mmol) in methanol (1.8 mL) and water (0.8 mL) was heated to 70 °C for 72 h. The reaction mixture was allowed to cool, EtOAc (30 mL) was added and the mixture washed with saturated aqueous sodium hydrogencarbonate solution (2 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over $MgSO_4$, concentrated and chromatographed (petroleum ether–EtOAc; 1:1) to give diol **13** (59 mg, 76%) as a colourless oil: $[\alpha]_D^{25} = -18.0$ (c 0.20, $CHCl_3$) [lit.,[17] 18.2 (c 0.20, $CHCl_3$)]; R_f = 0.20 (petroleum ether–EtOAc; 1:2); FTIR (NaCl plate) ν_{max} 3550–3050, 3015 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.63–5.52 (2H, m), 3.69–3.60 (2H, m), 2.82 (2H, br s), 2.41–2.24 (2H, m), 2.19–2.02 (4H, m), 1.61–1.50 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 129.2, 74.0, 33.5, 22.8. MS (CI$^+$) 160 (M+NH$_4$)$^+$. HRMS calcd for $C_8H_{18}NO_2$ 160.1338, found 160.1334.

4.9. (1*R*,4*R**,6*S**,9*R*)-11,11-Dimethyl-5,10,12-trioxatricyclo[7.3.0^{4,6}]dodecane 15

To a solution of *m*CPBA (50–55%, 6.07 g, 17.6–19.3 mmol) stirring in CH_2Cl_2 (50 mL) was added *cis*-alkene **10** (2.56 g, 14.1 mmol) in CH_2Cl_2, controlling the resulting exotherm with an ice bath. After 2 h stirring at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (3 × 50 mL). The organic layer was washed with saturated aqueous sodium sulfite solution (3 × 50 mL), water (2 × 50 mL), dried over $MgSO_4$ and concentrated to give epoxide **15** (2.38 g, 85%) as a colourless oil: $[\alpha]_D^{25} = -86.3$ (c 1.3, $CHCl_3$); R_f = 0.40 (petroleum ether–EtOAc; 3:2); FTIR (NaCl plate) ν_{max} 2982, 2937, 2869 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.87 (1H, ddd, J = 11.1, 7.9, 4.9 Hz), 3.65 (1H, ddd, J = 10.7, 7.9, 3.0 Hz), 2.91–2.81 (2H, m), 2.29–2.05 (4H, m), 1.65–1.37 (2H, m) 1.30 (6H, s), 1.24–1.07 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 107.5, 81.2, 80.5, 54.6, 54.1, 30.3, 29.2, 26.9, 26.8, 23.9, 22.5; MS (CI$^+$) 199 (M+H)$^+$. HRMS calcd for $C_{11}H_{19}O_3$ 199.1334, found 199.1339; Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.39; H, 8.94.

4.10. (1*R*,4*S*,5*S*,8*R*)-4-Diphenylphosphinoyl-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undecan-5-ol 16 and (1*R*,4*R*,5*R*,8*R*)-4-diphenylphosphinoyl-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undecan-5-ol 17

To a stirred solution of lithium diphenylphosphide[26] (~6.5 mmol) in THF (10 mL) at 0 °C was added dropwise epoxide **15** (857 mg, 4.3 mmol) in dry THF (5 mL). The reaction mixture was allowed to stir for 24 h at room temperature, cooled to 0 °C and glacial acetic acid (1 mL) followed by hydrogen peroxide (38%, 1.8 mL, 23 mmol) in water (6 mL) was added. After 4 h the mixture was extracted with CH_2Cl_2 (80 mL), washed with water (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$ and concentrated to yield a white solid (2.3 g). Trituration with Et_2O followed by recrystallisation (EtOH–H_2O) afforded β-hydroxyphosphine oxide **16** (920 mg, 53%) as a white crystalline solid: mp 174–176 °C; $[\alpha]_D^{25} = -77.3$ (*c* 2.15, $CHCl_3$); $R_f = 0.22$ (MeOH–CH_2Cl_2; 1:19); FTIR (CH_2Cl_2) ν_{max} 3500–3100, 3051 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.80–7.69 (4H, m), 7.57–7.48 (6H, m), 4.26 (1H, br s), 4.21–4.13 (1H, m), 3.95 (1H, ddd, $J = 10.3$, 8.6, 5.0 Hz), 3.50 (1H, m), 2.51 (1H, m), 2.08–1.61 (6H, m), 1.52–1.31 (2H, m), 1.38 (3H, s), 1.32 (3H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 132.5, 132.4, 132.3, 131.2 (d, $J_{C-P} = 9.4$ Hz), 129.3 (d, $J_{C-P} = 95.1$ Hz), 128.9 (d, $J_{C-P} = 11.4$ Hz), 128.8 (d, $J_{C-P} = 11.4$ Hz), 107.1, 82.4, 79.9, 69.1 (d, $J_{C-P} = 2.1$ Hz), 40.1 (d, $J_{C-P} = 68.5$ Hz), 29.6 (d, $J_{C-P} = 11.4$ Hz), 29.1 (d, $J_{C-P} = 7.3$ Hz), 27.1, 27.0, 24.8, 19.8; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 43.5 ppm; MS (CI^+) 401 $(M+H)^+$. HRMS calcd for $C_{23}H_{30}O_4P$ 401.1882, found 401.1886; Anal. Calcd for $C_{23}H_{29}O_4P$: C, 68.98; H, 7.30. Found: C, 69.09; H, 7.38. *Crystal data for* **16**: $C_{23}H_{29}O_4P$, $M = 400.43$, orthorhombic, $P2_12_12_1$ (no 19), $a = 5.7316(4)$, $b = 12.3013(11)$, $c = 29.435(2)$ Å, $V = 2075.3(3)$ Å^3, $Z = 4$, $D_c = 1.282$ g/cm^3, μ(Cu-Kα) = 1.384 mm^{-1}, $T = 293$ K, colourless thin platy needles; 1920 independent measured reflections, F^2 refinement, $R_1 = 0.045$, $wR_2 = 0.115$, 1701 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 130°$], 231 parameters. The absolute structure of **16** was determined by a combination of *R*-factor tests [$R_1^+ = 0.0452$, $R_1^- = 0.0501$] and by use of the Flack parameter [$x^+ = +0.00(5)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 233570. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. The ether triturants were evaporated and the residue chromatographed (MeOH–CH_2Cl_2; 4:96) to give diastereoisomeric hydroxyphosphine oxide **17** (132 mg, 8%) as a white crystalline solid: mp 74–76 °C; $[\alpha]_D^{25} = +26.7$ (*c* 0.06, $CHCl_3$); $R_f = 0.29$ (MeOH–CH_2Cl_2; 1:19) FTIR (CH_2Cl_2) ν_{max} 3500–3100, 3056 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.77–7.65 (4H, m), 7.60–7.40 (6H, m), 5.26 (1H, s), 4.21 (1H, dd, $J = 15.7$, 8.8 Hz), 4.13–4.03 (1H, m), 3.82 (1H, ddd, $J = 11.1$, 9.0, 4.6 Hz), 2.55 (1H, ddt, $J = 13.4$, 6.7, 3.5 Hz), 2.36 (1H, tt, $J = 9.5$, 8.3 Hz), 2.21–2.12 (1H, m), 2.01–1.87 (1H, m), 1.86–1.59 (2H, m), 1.54–1.41 (1H, m), 1.37 (3H, s), 1.34 (3H, s), 1.29–1.06 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 132.7 (d, $J_{C-P} = 5.2$ Hz), 132.6, 132.5 (d, $J_{C-P} = 2.6$ Hz), 131.4 (d, $J_{C-P} = 97.6$ Hz), 131.2 (d, $J_{C-P} = 9.4$ Hz), 129.1 (d, $J_{C-P} = 11.9$ Hz), 128.7 (d, $J_{C-P} = 94.5$ Hz), 128.7 (d, $J_{C-P} = 10.9$ Hz), 107.4, 79.2, 78.9, 68.6 (d, $J_{C-P} = 3.6$ Hz), 45.0 (d, $J_{C-P} = 68.0$ Hz), 35.2 (d, $J_{C-P} = 10.9$ Hz), 27.8 (d, $J_{C-P} = 13.0$ Hz), 27.2, 27.0, 26.4, 21.5; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 44.6 ppm; MS (CI^+) 401 $(M+H)^+$. HRMS calcd for $C_{23}H_{30}O_4P$ 401.1882, found 401.1884; Anal. Calcd for $C_{23}H_{29}O_4P$: C, 68.98; H, 7.30. Found: C, 68.83; H, 7.14.

4.11. (*E*)-Chair-(1*R*,8*R*)-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene 5c

To NaH (60%, 48 mg, 1.2 mmol) stirring in dry DMF (4 mL) at 0 °C under N_2 was slowly added phosphine oxide **16** (400 mg, 1 mmol) in dry DMF (2 mL). The reaction mixture was stirred for 1.5 h at room temperature, and the resulting white precipitate was filtered and washed with hexane (2 × 10 mL). The combined organics were washed with saturated aqueous NH_4Cl solution (2 × 35 mL), water (2 × 20 mL), brine (1 × 20 mL), dried over $MgSO_4$ and concentrated to yield chair *trans*-cyclooctene **5c** (166 mg, 91%) as a clear oil: $[\alpha]_D^{22} = -178.4$ (*c* 1.84, $CDCl_3$); FTIR (KBr) ν_{max} 3007, 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.90–5.75 (2H, m), 3.66–3.58 (2H, m), 2.50–2.37 (2H, m), 2.21–2.01 (4H, m), 1.96–1.82 (2H, m), 1.30 (6H, s). ^{13}C NMR (68 MHz, $CDCl_3$) δ 135.6, 105.3, 83.3, 39.5, 27.0, 25.5; MS (CI^+) 183 $(M+H)^+$. HRMS calcd for $C_{11}H_{19}O_2$ 183.1385, found 183.1388.

4.12. (*E*)-Twist-(1*R*,8*R*)-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene 5t

Following the procedure used above for the preparation of **5c**, phosphine oxide **17** (37 mg, 0.093 mmol) in dry DMF (0.4 mL) was treated with NaH (60%, 5 mg, 0.11 mmol) in dry DMF (0.8 mL) to yield twist *trans*-cyclooctene **5t** (9.3 mg, 55%) as a pale yellow oil: $[\alpha]_D^{25} = +90.9$ (*c* 0.30, $CDCl_3$); FTIR (KBr) ν_{max} 3004 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.43–5.41 (2H, m), 3.73–3.67 (2H, m), 2.31–2.17 (6H, m), 1.79–1.70 (2H, m), 1.32 (6H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 133.2, 106.6, 84.6, 38.2, 31.7, 26.7.

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