The Synthesis of a Chiral Hexaphenyl-18-crown-6 Derivative

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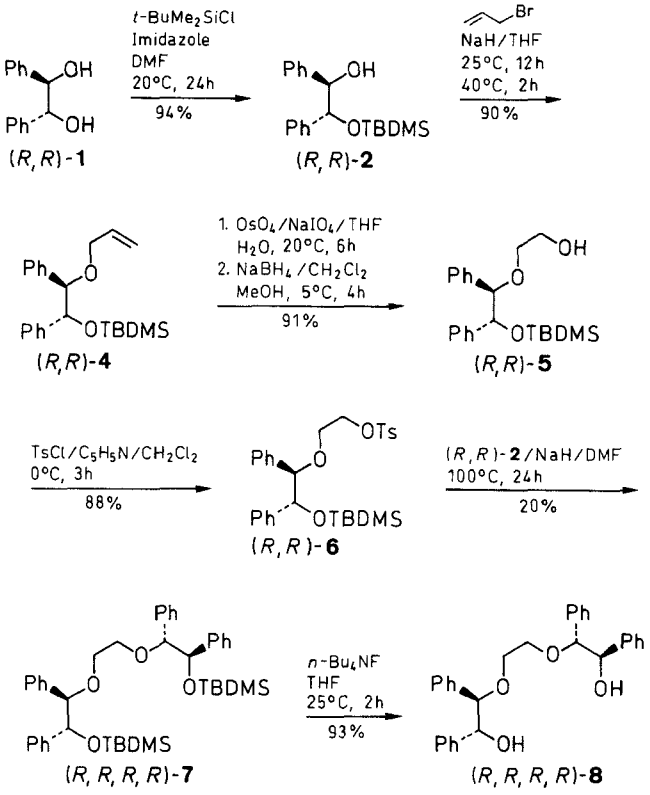
The stereospecific synthesis of (2*R*,3*R*,8*R*,9*R*,14*R*,15*R*)-2,3,8,9,14,15-hexaphenyl-1,4,7,10,13,16-hexaoxacyclooctadedecane [(*R*,*R*,*R*,*R*,*R*,*R*)-**12**] from (*R*,*R*)-hydrobenzoin [(*R*,*R*)-**1**] is reported. The ability of (*R*,*R*,*R*,*R*,*R*,*R*)-**12** to act as a chiral solid–liquid phase-transfer catalyst in an asymmetric Michael addition is compared with the efficiencies of other chiral di- and tetra-substituted 18-crown-6 derivatives, both with respect to product conversions and chirality transfers from catalysts to products.

Chiral crown ethers[1] cannot only differentiate[2,3] between the enantiomers of racemic substrates on complex formation, but they can also behave[1–5] as chiral reagents or catalysts during enantioselective reactions carried out on appropriate substrates. Thus, both enantiomers (*R*,*R*,*R*,*R* and *S*,*S*,*S*,*S*) of 2,3,11,12-tetraphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane[6–10] have been used as chiral auxiliaries in *stoichiometric amounts* to form[1,4,5,11,12] 1:1 adducts with borane–ammonia that are able[1,4,5,12,13] to effect enantioselective reductions of prochiral aromatic ketones – PhCOR where R = Me, Et, *i*-Pr, *t*-Bu – to the corresponding (*S* and *R*) aromatic secondary alcohols with enantiomeric excesses of up to 90%. They have also been employed as chiral auxiliaries in *catalytic amounts* to form potassium cyanide complexes[14] that are capable[4,5] of catalysing the asymmetric addition of cyanide ion to benzaldehyde as a substrate in the presence of benzoyl chloride as a trapping reagent to produce the optically active, benzoylated cyanohydrin in 40% enantiomeric excess. In view of these encouraging results, we were curious to find out if the enantiomeric excesses in these different reactions could be enhanced further by using either (2*R*,3*R*,8*R*,9*R*,14*R*,15*R*)-2,3,8,9,14,15-hexaphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane [(*R*,*R*,*R*,*R*,*R*,*R*)-**12**] or its 2*R*,3*R*,8*R*,9*R*,14*S*,15*S* isomer as the chiral auxiliaries. In this paper, we describe the stereospecific syntheses of (*R*,*R*,*R*,*R*,*R*,*R*)-**12** starting from the now readily-available[15] (*R*,*R*)-hydrobenzoin [(*R*,*R*)-**1**] and compare its performance with related chiral crown ethers as a chiral catalyst in the asymmetric Michael addition[16–18] of methyl phenylacetate to methyl acrylate.

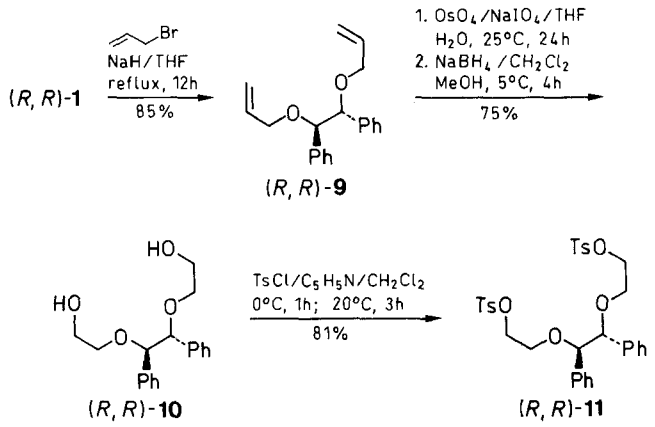
The strategy[1] we adopted for the stereospecific synthesis (Schemes 1–3) of (*R*,*R*,*R*,*R*,*R*,*R*)-**12** is similar to one we employed previously[19,20] in the construction of a chiral 20-crown-6 derivative from carbohydrate precursors. Thus, from (*R*,*R*)-**1**, the chiral diol (*R*,*R*,*R*,*R*)-**8** was prepared in seven steps (Scheme 1) and the chiral bistosylate (*R*,*R*)-**11** in four steps (Scheme 2). Thereafter, base-promoted cyclization of these two building blocks afforded the (*R*,*R*,*R*,*R*,*R*,*R*)-hexaphenyl-18-crown-6 derivative (*R*,*R*,*R*,*R*,*R*,*R*)-**12** in one step (Scheme 3).

Monoprotection of (*R*,*R*)-**1** using an equimolar amount of *tert*-butyldimethylsilyl chloride and excess of imidazole in dimethylformamide (DMF) proceeded efficiently with the production of the monosilyl ether (*R*,*R*)-**2** in 94% yield after its separation by silica gel chromatography from a trace (2.3%) of the disilyl ether (*R*,*R*)-**3**. Treatment of (*R*,*R*)-**2** in THF with allyl bromide in the presence of sodium hydride as base afforded the allyl ether (*R*,*R*)-**4** in 90% yield. Lemieux oxidation (OsO_4–$NaIO_4$) of (*R*,*R*)-**4** in aqueous tetrahydrofuran (THF), followed by in situ reduction ($NaBH_4$) of the product in dichloromethane–methanol gave (91%) the alcohol (*R*,*R*)-**5**, which was treated with tosyl chloride in pyridine–dichloromethane to afford the tosylate (*R*,*R*)-**6**, as a crystalline compound in 88% yield. The reaction of (*R*,*R*)-**2** with (*R*,*R*)-**6** to give the disilyl ether (*R*,*R*,*R*,*R*)-**7**, as a low-melting solid, in THF in the presence of sodium hydride as base could only be achieved after many attempts in a modest 20% yield. However, deprotection of (*R*,*R*,*R*,*R*)-**7** with tetrabutylammonium fluoride in THF proceeded smoothly (93%) to afford the required diol (*R*,*R*,*R*,*R*)-**8** as a crystalline compound.



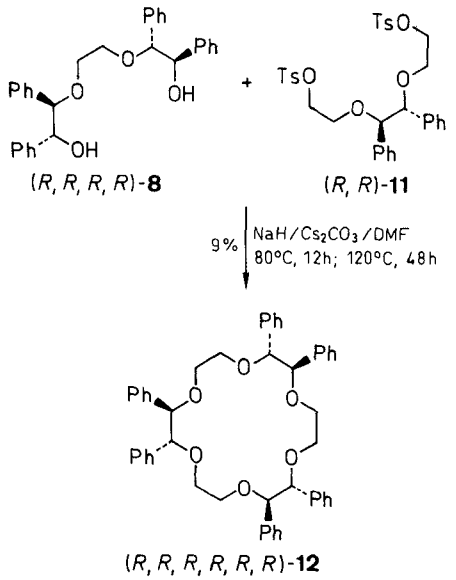
Scheme 1

The reaction (Scheme 2) of (*R*,*R*)-**1** in THF with excess of allyl bromide in the presence of sodium hydride as base gave (85%) the diallyl ether (*R*,*R*,*R*,*R*)-**9**, which was subjected to Lemieux oxidation and in situ reduction, as described previously for the monoallyl ether (*R*,*R*)-**4**. The diol (*R*,*R*)-**10**, which was isolated in 75% yield, afforded (81%) the required bistosylate (*R*,*R*)-**11**, again using the same conditions as those employed in the tosylation of the alcohol (*R*,*R*)-**5**.



Scheme 2

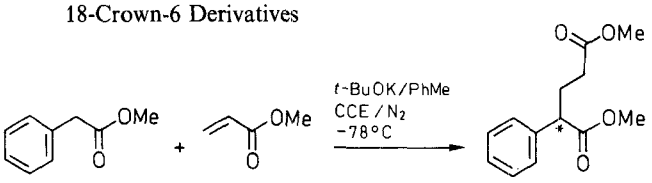
The cyclization (Scheme 3) of (*R,R,R,R*)-**8** with (*R,R*)-**11** in DMF in the presence of sodium hydride as base proved to be low yielding (9%), even when caesium carbonate was added to the reaction mixture in considerable excess. In this context, it is worth noting that all attempts to prepare (2*R*,3*R*,8*R*,9*R*,14*S*,15*S*)-2,3,8,9,14,15-hexaphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane by reacting (*R,R,R,R*)-**8** with the *S,S* enantiomer of **11** were unsuccessful. The (*R,R,R,R,R,R*)-hexaphenyl-18-crown-6 derivative (*R,R,R,R,R,R*)-**12** was fully characterized by FABMS and by ^1H and ^{13}C NMR spectroscopies. The D_3 symmetry of the molecule is supported by the appearance for (*R,R,R,R,R,R*)-**12** of: (a), only one signal – a singlet – in its ^1H NMR spectrum at δ 4.81 for the six homotopic methine protons; and (b), only one signal in its broad-band decoupled ^{13}C NMR spectrum at δ 85.9 for the six homotopic carbon atoms carrying phenyl groups on the 18-membered ring.

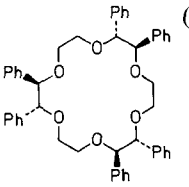
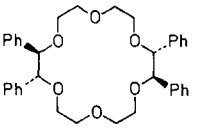
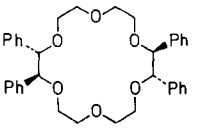
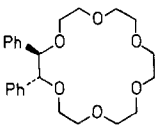
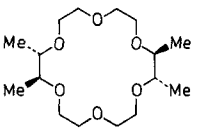
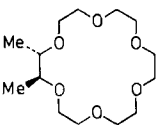


Scheme 3

In view of the relatively small amount (30 mg) of (*R,R,R,R,R,R*)-**12** which was available to us, we decided to evaluate its performance as a chiral catalyst (20 mol percent) in the asymmetric Michael addition of methyl phenylacetate to methyl acrylate. The results are shown in the Table 1. They reveal that this (*R,R,R,R,R,R*)-hexaphenyl-18-crown-6 derivative causes the reaction to proceed very slowly, yielding only 14% of the Michael addition product with the modestly low enantiomeric excess of 36% in favour of the *R* enantiomer. The *R,R,R,R* and *S,S,S,S* isomers [(*R,R,R,R*)-**13** and (*S,S,S,S*)-**13**] with the 2,3,11,12-tetraphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane constitution not only afforded the Michael addition product in the slightly higher percentage enantiomeric excesses of 39 (*R*) and 41 (*S*) respectively, but the reactions were also very much more efficient, going in 95% and 96% yields, respectively. The high yield (92%) was maintained with (2*R*,3*R*)-2,3-diphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane [(*R,R*)-**14**] but the enantiomeric excess switched to 20% in favour of the *S* enantiomer. Even the diphenyl and tetraphenyl-18-crown-6 derivatives do not quite match the corresponding dimethyl- and tetramethyl-18-crown-6 derivatives as enantioselective catalysts for this asymmetric

Table. The Asymmetric Michael Addition of Methyl Phenylacetate to Methyl Acrylate Catalyzed by a Selection of Chiral 18-Crown-6 Derivatives



Chiral Crown Ether (CCE)		Yield (%)	Enantiomeric Excess (%)	Preferred Configuration (*)
	(*R,R,R,R,R,R*)-**12**	14[a]	36[a]	*R*[a]
	(*R,R,R,R*)-**13**	95[a]	39[a]	*R*[a]
	(*S,S,S,S*)-**13**	96[a]	41[a]	*S*[a]
	(*R,R*)-**14**	92[a]	20[a]	*S*[a]
	(*S,S,S,S*)-**15**	89[b]	56[b]	*R*[b]
	(*S,S*)-**16**	95[b]	79[b]	*S*[b]

[a] This work.
[b] Ref. 18.

Michael addition (Table). In this case, (*S,S,S,S*)-**15** favours the *R* product, whereas (*R,R*)-**16** favours the *S* product. It is clear that the factors, which influence the absolute stereochemistry of the asymmetric Michael addition[21] promoted by the catalysts listed in the Table require detailed investigation by appropriate molecular modelling techniques.

TLC Analyses were performed on silica gel plates (Merck Kieselgel 60 F_{254}) and the spots were visualized under UV light. Column chromatography was carried out using Merck Kieselgel 60 (9385) as the stationary phase. Melting points were determined using a Reichart hot-stage apparatus, and are uncorrected. Optical rotations were measured at 589 nm (sodium D line) on a Perkin-Elmer 141 polarimeter.

Mass spectra were recorded on either a Kratos MS25 or MS80 mass spectrometer. ^{1}H- and ^{13}C NMR spectra were obtained on a Bruker AM250 spectrometer.

(1*R*,2*R*)-1,2-Diphenyl-2-(*tert*-butyldimethylsilyloxy)ethanol [(*R,R*)-2] and (1*R*,2*R*)-1,2-Diphenyl-1,2-bis(*tert*-butyldimethylsilyloxy)ethane [(*R,R*)-3]:

A solution of *tert*-butyldimethylsilyl chloride (3.02 g, 20 mmol) in dry DMF (10 mL) was added dropwise with stirring to a solution of (*R,R*)-hydrobenzoin [(*R,R*)-**1**] (4.28 g, 20 mmol) and imidazole (2.74 g, 40 mmol) in dry DMF (100 mL). Stirring was continued for 24 h at 20 °C. The solvent was evaporated under vacuum and the crude product was separated by column chromatography on silica gel using light petroleum (bp 40–60 °C) to give (*R,R*)-**2** and (*R,R*)-**3**.

(*R,R*)-**2**: Yield: 6.20 g (94%); colourless oil; $[\alpha]_D$ −35° (*c* = 1.5, Me_2CO).

EIMS: *m/z* (%) = 311 (M−OH, 1), 271 (8), 221 (28), 179 (11), 149 (5), 115 (10), 105 (16), 91 (10), 73 (100), 59 (10).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.20, −0.03 (2 s, 3H each, $SiMe_2CMe_3$), 0.93 (s, 9H, $SiMe_2CMe_3$), 4.60, 4.65 (AB system, J_{AB} = 6.2 Hz, 2H, PhCHOH and PhCHOSi), 7.05–7.25 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = −5.33, −4.74 ($SiMe_2CMe_3$), 18.1 ($SiMe_2CMe_3$), 25.7 ($SiMe_2CMe_3$), 79.2, 80.7 (PhCHOH and PhCHOSi), 127.0, 127.4, 127.5, 127.7, 139.9, 140.7 (PhCHOH and PhCHOSi).

(*R,R*)-**3**: Yield: 150 mg (2.3%); mp 35–37 °C; $[\alpha]_D$ −56° (*c* = 1.5, Me_2CO).

EIMS: *m/z* (%) = 385 (M−CMe_3, 31), 221 (75), 179 (23), 163 (16), 147 (67), 133 (16), 73 (100), 59 (38).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.20, −0.07 (2 s, 6H each, 2 $SiMe_2CMe_3$), 0.87 (s, 18H, 2 $SiMe_2CMe_3$), 4.74 (s, 2H, 2 PhCHOSi), 7.03–7.16 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = −5.09, −4.93 ($SiMe_2CMe_3$), 18.2 ($SiMe_2CMe_3$), 25.9 ($SiMe_2CMe_3$), 79.4 (PhCHOSi), 126.9, 127.0, 127.6, 141.4 (Ph).

(5*R*,6*R*)-5,6-Diphenyl-4-oxa-6-(*tert*-butyldimethylsilyloxy)-1-hexene [(*R,R*)-4]:

The monosilyl derivative (*R,R*)-**2** (4.93 g, 15 mmol) was treated with 80% NaH in oil (450 mg, 15 mmol) suspended in THF (80 mL) at 25 °C under nitrogen. The mixture was stirred until all the NaH had been consumed. Allyl bromide (2.72 g, 22.5 mmol) in THF (20 mL) was added dropwise to this solution during 1 h. The reaction mixture was stirred at 25 °C for 12 h and then at 40 °C for 2 h before it was filtered at the pump. The solvent was evaporated under vacuum below 40 °C and the crude product was subjected to column chromatography (SiO_2) using light petroleum (bp 40–60 °C)–EtOAc (20:1) as eluant to afford (*R,R*)-**4** as a colourless oil.

(*R,R*)-**4**: Yield: 5.00 g (90%); $[\alpha]_D$ −38.9° (*c* = 1.2, Me_2CO).

FABMS: *m/z* (%) = 311 (M−$OCH_2CH{=}CH_2$, 90), 253 (12), 237 (11), 221 (100), 195 (12), 179 (28), 165 (26).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.11, 0.04 (2 s, 3H each, $SiMe_2CMe_3$), 0.87 (s, 9H, $SiMe_2CMe_3$), 3.80–4.03 (m, 2H, $OCH_2CH{=}CH_2$), 4.39 (d, *J* = 6.2 Hz, 1H, PhCHOCH$_2$), 4.81 (d, *J* = 6.2 Hz, 1H, PhCHOSi), 5.07–5.27 (m, 2H, $OCH_2CH{=}CH_2$), 5.76–5.92 (m, 1H, $OCH_2CH{=}CH_2$), 6.95–7.15 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = −5.01, −4.87 ($SiMe_2CMe_3$), 18.3 ($SiMe_2CMe_3$), 25.8 ($SiMe_2CMe_3$), 70.0 ($OCH_2CH{=}CH_2$), 78.8 (PhCHOSi), 86.3 (PhCHOCH$_2$), 116.0 ($OCH_2CH{=}CH_2$), 126.9 ($OCH_2CH{=}CH_2$), 127.2, 127.3, 127.4, 127.5, 128.0, 135.2, 138.8, 141.3 (PhCHOCH$_2$ and PhCHOSi).

(4*R*,5*R*)-4,5-Diphenyl-3-oxa-5-(*tert*-butyldimethylsilyloxy)-1-pentanol [(*R,R*)-5]:

OsO_4 (1 mL of a 4.0 wt% solution in *t*-BuOH) was added with stirring to a solution of (*R,R*)-**4** (4.8 g, 13 mmol) in THF–H_2O (40 mL, 3:1). The mixture was stirred at 20 °C for 2 h and then $NaIO_4$ (7.0 g, 33 mmol) was added portionwise during the next 2 h. The reaction mixture was stirred for a further 2 h and then the solvents were evaporated under vacuum. The resulting paste was added to a CH_2Cl_2–MeOH solvent mixture (80 mL, 1:1) which was cooled to 5 °C while stirring vigorously. Then, $NaBH_4$ (3.0 g, 79 mmol) was added cautiously during 2 h and stirring was continued for a further 2 h. Again, the solvents were evaporated under vacuum and then CH_2Cl_2 (50 mL) was added. The resulting suspension was filtered under suction and the precipitate was washed with CH_2Cl_2 (2 × 15 mL). The combined organic phase was extracted with saturated aqueous NaCl (3 × 25 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting oil was subjected to column chromatography (SiO_2) using light petroleum (bp 60–80 °C)–EtOAc (10:1) as eluant to give (*R,R*)-**5** as a pale yellow oil.

(*R,R*)-**5**: Yield: 4.4 g (91%); $[\alpha]_D$ −34.2° (*c* = 1.0, Me_2CO).

FABMS: *m/z* (%) = 311 (M−OCH_2CH_2OH, 67), 253 (7), 241 (47), 221 (100), 197 (40), 180 (32), 167 (23).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.19, −0.06 (2 s, 3H each, $SiMe_2CMe_3$), 0.83 (s, 9H, $SiMe_2CMe_3$), 1.90 (brs, 1H, OH), 3.30–3.72 (ABCD system, 4H, OCH_2CH_2OH), 4.36 (d, *J* = 6.2 Hz, 1H, PhCHOCH$_2$), 4.75 (d, *J* = 6.2 Hz, 1H, PhCHOSi), 7.00–7.20 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = −5.01 ($SiMe_2CMe_3$), 18.2 ($SiMe_2CMe_3$), 25.8 ($SiMe_2CMe_3$), 61.8 (OCH_2CH_2OH), 70.5 (OCH_2CH_2OH), 79.2 (PhCHOSi), 87.6 (PhCHOCH$_2$), 127.2, 127.5, 127.7, 127.7, 138.7, 141.3 (PhCHOCH$_2$ and PhCHOSi).

(1*R*,2*R*)-1,2-Diphenyl-1-(*tert*-butyldimethylsilyloxy)-5-(*p*-toluenesulfonyloxy)-3-oxapentane [(*R,R*)-6]:

The alcohol (*R,R*)-**5** (3.3 g, 8.9 mmol) was stirred in CH_2Cl_2–C_5H_5N (35 mL, 6:1) at 0 °C and *p*-toluenesulfonyl chloride (1.9 g, 10 mmol) was added during 1 h. The reaction mixture was stirred for 2 h at 0 °C and then it was allowed to warm up slowly to 25 °C during a further 2 h. Ice-water (25 mL) was added with stirring to the reaction mixture. The organic layer was washed with cold 2 M HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered. The filtrate was concentrated to give a crude product which was purified by column chromatography (SiO_2) using CH_2Cl_2–hexane (1:1) as eluant to afford (*R,R*)-**6** as a white solid.

(*R,R*)-**6**: Yield: 4.1 g (88%); mp 76–78 °C; $[\alpha]_D$ +16.2° (*c* = 0.5, Me_2CO).

FABMS: *m/z* (%) = 549 (M+Na, 1), 527 (M+1, 0.5), 435 (15), 395 (29), 305 (25), 273 (3), 200 (100), 181 (17).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.16, −0.02 (2 s, 3H each, $SiMe_2CMe_3$), 0.82 (s, 9H, $SiMe_2CMe_3$), 2.45 (s, 3H, C_6H_4Me), 3.50–3.55 (m, 2H, $OCH_2CH_2OSO_2$), 4.03–4.17 (m, 2H, $OCH_2CH_2OSO_2$), 4.26 (d, *J* = 6.2 Hz, 1H, PhCHOCH$_2$), 4.70 (d, *J* = 6.2 Hz, 1H, PhCHOSi), 6.86–7.17 (m, 10H, 2 Ph), 7.29–7.30 and 7.73–7.79 (AA'BB' system, 4H, $MeC_6H_4SO_2$).

^{13}C NMR ($CDCl_3$/TMS): δ = −5.04, −4.97 ($SiMe_2CMe_3$), 18.2 ($SiMe_2CMe_3$), 21.6 (C_6H_4Me), 25.8 ($SiMe_2CMe_3$), 66.8 ($OCH_2CH_2OSO_2$), 69.1 ($OCH_2CH_2OSO_2$), 78.6 (PhCHOSi), 87.7 (PhCHOCH$_2$), 127.0, 127.2, 127.3, 127.5, 127.5, 127.9, 127.9, 129.7, 133.3, 138.0, 141.0, 144.6 (PhCHOCH$_2$, PhCHOSi and $MeCC_6H_4SO_2$).

(1*R*,2*R*,7*R*,8*R*)-1,2,7,8-Tetraphenyl-3,6-dioxa-1,8-bis(*tert*-butyldimethylsilyloxy)octane [(*R*,*R*,*R*,*R*)-7]:
The mono-silyl derivative (*R*,*R*)-**2** (3.23 g, 9.8 mmol) was dissolved in dry DMF (60 mL) and treated with 80% NaH in oil (295 mg, 9.8 mmol). The mixture was stirred at 25 °C under nitrogen until it was clear. The tosylate (*R*,*R*)-**6** (5.18 g, 9.8 mmol) in dry DMF (10 mL) was added rapidly to this solution. The reaction mixture was stirred for 24 h at 100 °C and the solvent was evaporated off under reduced pressure. The crude product was dissolved in CH_2Cl_2 (50 mL) and washed with cold 2 M HCl, water, dried ($MgSO_4$), and filtered. The filtrate was concentrated to afford a yellow oil which was subjected to flash chromatography (SiO_2), eluting with CH_2Cl_2–light petroleum (bp 60–80 °C) (2:1) to give (*R*,*R*,*R*,*R*)-**7** as colourless crystals.

(*R*,*R*,*R*,*R*)-**7**: Yield: 1.34 g (20%); mp 65–66 °C; $[\alpha]_D$ −34.2° (*c* = 1.1, Me_2CO).

FABMS: *m*/*z* (%) = 705 (M + Na, 1), 311 (100), 253 (9), 221 (74).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.13, 0.01 (2 s, 6H each, 2 $SiMe_2CMe_3$), 0.86 (s, 18H, 2 $SiMe_2CMe_3$), 3.38–3.60 (A_2B_2 system, 4H, OCH_2CH_2O), 4.34 (d, *J* = 6.0 Hz, 2H, 2 $PhCHOCH_2$), 4.76 (d, *J* = 6.0 Hz, 2H, 2 PhCHOSi), 6.92–7.15 (m, 20H, 4 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = −4.94, −4.83 ($SiMe_2CMe_3$), 18.3 ($SiMe_2CMe_3$), 25.9 ($SiMe_2CMe_3$), 69.0 (OCH_2CH_2O), 78.7 (PhCHOSi), 87.3 ($PhCHOCH_2$), 126.9, 127.0, 127.1, 127.4, 127.5, 127.6, 128.1, 138.8, 141.3 (PhCHOCH$_2$ and PhCHOSi).

(1*R*,2*R*,7*R*,8*R*)-1,2,7,8-Tetraphenyl-3,6-dioxa-1,8-octanediol [(*R*,*R*,*R*,*R*)-8]:
Bu_4NF (0.70 g, 2.7 mmol) was added to a solution of (*R*,*R*,*R*,*R*)-**7** (0.50 g, 0.73 mmol) in THF (30 mL). The reaction mixture was stirred for 2 h at 25 °C. The solution was evaporated and the crude product was purified by column chromatography (SiO_2) with $CHCl_3$–MeOH (30:1) as eluant to afford (*R*,*R*,*R*,*R*)-**8** as colourless crystals.

(*R*,*R*,*R*,*R*)-**8**: Yield: 0.31 g (93%); mp 135–136 °C; $[\alpha]_D$ +42.5° (*c* = 2.0, $CHCl_3$).

FABMS: *m*/*z* (%) = 477 (M + Na, 69), 454 (M, 3), 419 (6), 311 (9), 257 (4), 241 (100), 221 (8).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.49–3.71 (A_2B_2 system, 4H, OCH_2CH_2O), 3.86 (br s, 2H, 2 OH), 4.32 (d, *J* = 8.5 Hz, 2H, 2 $PhCHOCH_2$), 4.75 (d, *J* = 8.5 Hz, 2H, 2 PhCHOH), 6.98–7.24 (m, 20H, 4 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = 68.4 (OCH_2CH_2O), 78.7 (PhCHOH), 88.2 ($PhCHOCH_2$), 127.3, 127.6, 127.7, 127.8, 128.0, 137.7, 139.2 (PhCHOCH$_2$ and PhCHOH).

(5*R*,6*R*)-5,6-Diphenyl-4,7-dioxa-1,9-decadiene [(*R*,*R*)-9]:
(*R*,*R*)-**1** (4.28 g, 20 mmol) was dissolved in dry THF (200 mL) and treated with 80% NaH in oil (1.25 g, 42 mmol). The mixture was stirred for 1 h at 30 °C under nitrogen. Then, a solution of allyl bromide (8.47 g, 70 mmol) in THF (20 mL) was added dropwise during 2 h with stirring. The reaction mixture was warmed up to 40 °C for 2 h and then heated under reflux for 12 h, before being concentrated down to a residue under vacuum. The residue was extracted into CH_2Cl_2 (100 mL) and the CH_2Cl_2 extract was washed with water (2 × 30 mL), saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated under vacuum to yield a pale brown oil which was subjected to column chromatography (SiO_2) with light petroleum–EtOAc (10:1) as eluant. (*R*,*R*)-**9** was isolated as a colourless oil.

(*R*,*R*)-**9**: *Yield: 5.2 g (85%).*

FABMS: *m*/*z* (%) = 237 (M − $OCH_2CH{=}CH_2$, 100), 219 (13), 207 (9), 195 (17), 179 (21), 167 (39).

^{1}H NMR ($CDCl_3$/TMS): 3.82–4.52 (m, 4H, 2 $OCH_2CH{=}CH_2$), 4.53 (s, 2H, 2 $PhCHOCH_2$), 5.07–5.27 (m, 4H, 2 $OCH_2CH{=}CH_2$), 5.77–5.93 (m, 2H, 2 $OCH_2CH{=}CH_2$), 7.01–7.19 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = 70.2 ($OCH_2CH{=}CH_2$), 85.0 ($PhCHOCH_2$), 116.3 ($OCH_2CH{=}CH_2$), 127.4 ($OCH_2CH{=}CH_2$), 127.6, 127.9, 135.0, 138.8 (Ph).

(4*R*,5*R*)-4,5-Diphenyl-3,6-dioxa-1,8-octanediol [(*R*,*R*)-10]:
A solution of (*R*,*R*)-**9** (5.88 g, 20 mmol) and OsO_4 (150 mg, 0.59 mmol) in THF–H_2O (40 mL, 3:1) was stirred at 25 °C for 2 h and $NaIO_4$ (25 g, 117 mmol) was added portionwise over the following 2 h. The reaction mixture was stirred overnight and the solvent was evaporated off under vacuum. The resulting paste was dissolved in CH_2Cl_2–MeOH (80 mL, 1:1) which was stirred vigorously and cooled to 5 °C. Then, $NaBH_4$ (4.5 g, 119 mmol) was added cautiously during 1 h and stirring was continued for a further 3 h. Again, the solvents were evaporated under vacuum and CH_2Cl_2 (80 mL) was added. The suspension was filtered at the pump and the residue was washed with further portions of CH_2Cl_2 (2 × 15 mL). The combined organic phase was washed with 2 M HCl, water, saturated aqueous NaCl, dried ($MgSO_4$), and filtered. The filtrate was concentrated under vacuum and the resulting brown oil was subjected to column chromatography (SiO_2) using $CHCl_3$–MeOH (10:1) as eluant to give (*R*,*R*)-**10** as an oil.

(*R*,*R*)-**10**: Yield: 4.5 g (75%); $[\alpha]_D$ −19° (*c* = 0.8, $CHCl_3$).

FABMS: *m*/*z* (%) = 325 (M + Na, 13), 303 (M + 1, 3), 241 (58), 197 (100), 179 (22), 167 (23).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.42–3.77 (ABCD system, 8H, 2 OCH_2CH_2O), 3.48 (brs, 2H, 2 OH), 4.48 (s, 2H, 2 $PhCHOCH_2$), 7.01–7.18 (m, 10H, 2 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = 61.6 (OCH_2CH_2OH), 71.0 (OCH_2CH_2OH), 86.7 ($PhCHOCH_2$), 127.5, 127.8, 128.0, 138.2 (Ph).

(4*R*,5*R*)-4,5-Diphenyl-1,8-bis(*p*-toluenesulfonyloxy)-3,6-dioxaoctane [(*R*,*R*)-11]:
The diol (*R*,*R*)-**10** (2.8 g, 9.3 mmol) was stirred in CH_2Cl_2–C_5H_5N (35 mL, 6:1) at 0 °C and *p*-toluenesulfonyl chloride (3.8 g, 20 mmol) was added during 1 h. The reaction mixture was allowed to warm up slowly to 20 °C and then it was stirred for a further 1 h. Ice-water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was then washed with cold 2 M HCl, saturated aqueous $NaHCO_3$, water, dried (Na_2SO_4), and filtered. The filtrate was concentrated under vacuum to afford a residue, which was subjected to flash chromatography (SiO_2) with light petroleum (bp 60–80 °C)–EtOAc (3:2) as eluant, affording (*R*,*R*)-**11** as a clear oil.

(*R*,*R*)-**11**: Yield: 4.6 g (81%); $[\alpha]_D$ −4.6° (*c* = 0.5, Me_2CO).

FABMS: *m*/*z* (%) = 633 (M + Na, 6), 395 (15), 307 (17), 200 (100), 180 (10).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.43 (s, 6H, 2 C_6H_4Me), 3.50–3.64 (m, 4H, 2 $OCH_2CH_2OSO_2$), 4.02–4.17 (m, 4H, 2 $OCH_2CH_2OSO_2$), 4.35 (s, 2H, 2 $PhCHOCH_2$), 6.85–7.15 (m, 10H, 2 Ph), 7.28–7.33 and 7.72–7.77 (AA'BB' system, 8H, 2 $MeC_6H_4SO_2$).

^{13}C NMR ($CDCl_3$/TMS): δ = 21.5 (C_6H_4Me), 67.0 ($OCH_2CH_2OSO_2$), 69.2 ($OCH_2CH_2OSO_2$), 86.2 ($PhCHOCH_2$), 127.2, 127.6, 127.8, 128.0, 129.7, 133.0, 137.5, 144.6 (PhCHOCH$_2$ and $MeC_6H_4SO_2$).

(2*R*,3*R*,8*R*,9*R*,14*R*,15*R*)-2,3,8,9,14,15-Hexaphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane [(*R*,*R*,*R*,*R*,*R*,*R*)-12]:
The diol (*R*,*R*,*R*,*R*)-**8** (205 mg, 0.45 mmol) was dissolved in dry DMF (50 mL) and treated with 80% NaH in oil (27 mg, 0.90 mmol). The suspension was stirred at 30 °C under nitrogen until it became clear. Then, the ditosylate (*R*,*R*)-**11** (300 mg, 0.49 mmol) in dry DMF (20 mL) and Cs_2CO_3 (200 mg) were added rapidly with stirring. The temperature was raised to 80 °C for 12 h and then to 120 °C for 48 h. The solvent was evaporated under vacuum to give a residue which was dissolved in water (50 mL) and extracted into $CHCl_3$ (3 × 30 mL). The combined organic extracts were washed with 2 M HCl, water, dried (Na_2SO_4), and filtered. The filtrate was concentrated to a residue, which was subjected to column chromatography (SiO_2) with gradient elution using $CHCl_3$–MeOH (60:1 to 10:1). Recrystallization of the crude product from hexane afforded (*R*,*R*,*R*,*R*,*R*,*R*)-**12** as a white crystalline solid.

(*R*,*R*,*R*,*R*,*R*,*R*)-**12**: Yield: 30 mg (9%); mp 154–155 °C; $[\alpha]_{436}$ +16.9 (*c* = 0.52, Me_2CO).

FABMS: m/z (%) = 759 (M + K, 28), 743 (M + Na, 100), 721 (M, 2), 391 (13), 241 (43), 203 (13).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.55–3.70 (ABCD system, 12 H, 3 OCH_2CH_2O), 4.81 (s, 6 H, 6 PhC<u>H</u>OCH_2), 7.04–7.15 (m, 30 H, 6 Ph).

^{13}C NMR ($CDCl_3$/TMS): δ = 68.9 (OCH_2CH_2O), 85.9 (Ph<u>C</u>$HOCH_2$), 127.3, 127.6, 128.2, 138.9 (Ph).

General Procedure for the Catalysed Michael Additions:
A solution of methyl phenylacetate (3.75 mmol) in dry toluene (3 mL) was added dropwise during 15 min to a suspension of *t*-BuOK (0.5 mmol) in dry toluene (14 mL). While stirring under nitrogen, the mixture was cooled down to − 78 °C before adding the chiral crown ether (0.5 mmol). After 30 min, methyl acrylate (2.5 mmol) in dry toluene (3 mL) was added dropwise during 15 min. The reaction mixture was stirred for 5 h at − 78 °C before being poured into water (30 mL) saturated with NH_4Cl. The toluene layer was separated and the aqueous layer was extracted with additional toluene. The combined toluene solutions were dried ($MgSO_4$) and concentrated under vacuum to give a crude product which was subjected to column chromatography (SiO_2) with light petroleum (bp 60–80 °C)–CH_2Cl_2 (4:1 to 1:1) as eluant, affording the pure Michael addition product as shown in Table 1. Percentage enantiomeric excesses for the Michael addition products were obtained by measuring the optical activity at the sodium D line and were based on the *S* isomer having a maximum value[16–18] of $[\alpha]_D$ + 89° (EtOH) when it is enantiomerically pure. The chiral crown ether which remained on the column was recovered by elution with $CHCl_3$–MeOH (10:1). In all cases, the chiral crown ethers had the same specific rotations after the experiment as before it.

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