Phosphonomethylation of Cyclohexene Oxides

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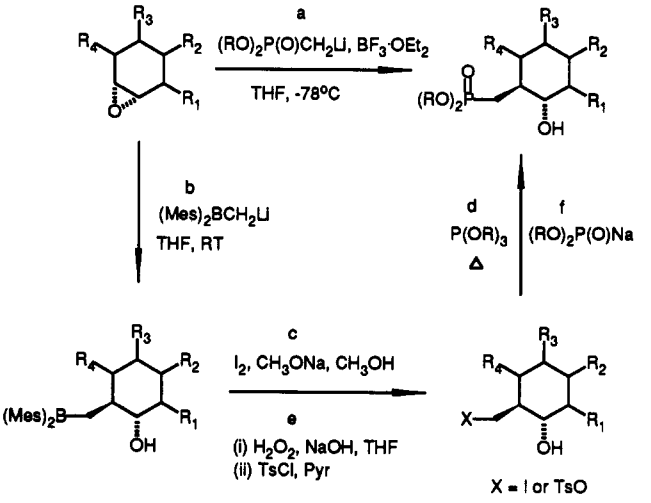
The tradeoff between synthetic directness and regioselectivity during oxirane ring opening is examined for two strategies used to phosphonomethylate cyclohexene oxide and substituted cyclohexene oxides derived from quinic acid and *myo*-inositol. Direct phosphonomethylation of the cyclohexene oxides utilizes diisopropyl lithiomethanephosphonate ($(C_3H_7O)_2P(O)CH_2Li$) in combination with boron trifluoride. Another more indirect route to phosphonomethylation begins with reaction of the cyclohexene oxides with (lithiomethyl)dimesitylborane (Mes_2BCH_2Li). In both reactions, boron plays a key role as either a Lewis acid during opening of the oxirane (diisopropyl lithiomethanephosphonate/boron trifluoride) or as a stabilizer of an adjacent carbanion in the attacking nucleophile [(lithiomethyl)dimesitylborane]. Regioselectivities for oxirane ring opening using diisopropyl lithiomethanephosphonate/boron trifluoride can be quite modest. By contrast, oxirane ring openings employing (lithiomethyl)dimesitylborane are uniform in the high degree of regioselectivity which is achieved. Factors which might influence the observed regioselectivities during nucleophilic attack on the cyclohexene oxides are also discussed.

During efforts to synthesize carbaphosphonate substrate analogues for 3-dehydroquinate (DHQ) synthase, a one step phosphonomethylation procedure (step a, Scheme I) was developed.[1] Cyclohexene oxides derived from quinic acid (such as **2**, Table I) were treated at −78 °C in tetrahydrofuran with an equimolar combination[2] of diisopropyl lithiomethanephosphonate and boron trifluoride etherate.[3] Ring opening proceeded with high regioselectivity and good overall yield. Phosphonomethyl products were ultimately converted into potent inhibitors of DHQ synthase.[1,4] In route to synthesis of carbaphosphonate substrate analogues and reactive intermediate analogues for inhibition of *myo*-inositol phosphate synthase, phosphonomethylation of a cyclohexene oxide (**3**, Table I) derived from *myo*-inositol was required. Reaction at −78 °C of the cyclohexene oxide derived from *myo*-inositol with a nearly stoichiometric concentration of the diisopropyl lithiomethanephosphonate and boron trifluoride combination failed to afford any phosphonomethylated product. A survey of the literature to find a solution to this synthetic impasse failed to provide relevant alternatives. Since our initial report of direct phosphonomethylation of quinate-derived cyclohexene oxides, the only progress in extending the scope of the reaction had been in monosubstituted oxirane systems.[5] This prompted a renewed examination of strategies relevant to phosphonomethylation of cyclohexene oxides.

As a first step, parameters associated with reaction of the cyclohexene oxides with the diisopropyl lithiomethanephosphonate/boron trifluoride combination were varied. The impact of reaction condition changes on both

Scheme I



reactivity and regioselectivity were of particular interest. A less-direct route to phosphonomethylation was also examined (Scheme I) which employed initial reaction of the cyclohexene oxide with (lithiomethyl)dimesitylborane.[6] Replacement of the dimesitylborane in the ring-opened intermediate with a suitable leaving group could be followed by Arbuzov[7] (steps c and d, Scheme I) or Michaelis–Becker[7] methodology (steps e and f, Scheme I) to assemble the phosphonomethyl functionality. As with the diisopropyl lithiomethanephosphonate/boron trifluoride combination, the reactivity of (lithiomethyl)dimesitylborane with cyclohexene oxide (**1**, Table I) and substituted cyclohexene oxides derived from quinic acid (**2**, Table I) and *myo*-inositol (**3**, Table I) was studied. The regioselectivities of oxirane ring openings were also established.

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(3) For use of boron trifluoride in organolithium reactions see: Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(4) Montchamp, J.-L.; Piehler, L. T.; Tolbert, T. J.; Frost, J. W. *BioMed. Chem. Lett.* **1993**, *3*, 1403.

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(6) (a) Pelter, A.; Bugden, G.; Rosser, R. *Tetrahedron Lett.* **1985**, *26*, 5097. (b) Pelter, A.; Vaughan-Williams, G. F.; Rosser, R. M. *Tetrahedron* **1993**, *49*, 3007.

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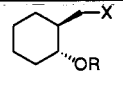
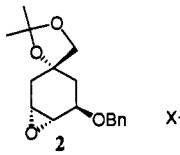
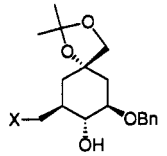
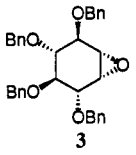
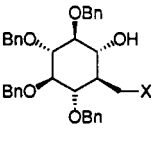
Table I. Reaction of Substituted and Unsubstituted Cyclohexene Oxides with $(RO)_2P(O)CH_2Li/BF_3$ and with Mes_2BCH_2Li

oxirane	product	entry	X	R	yield[a]
 1		1	$P(O)(OiPr)_2$	Ac	71
		2	OH	H	82[b]
		3	I	H	92
 2		4	$P(O)(OiPr)_2$		79[c,d]
		5	OH		92[c]
		6	I		46[c]
 3		7a	$P(O)(OiPr)_2$		49[e]
		7b	$P(O)(OMe)_2$		61[e]
		8	OH		89[c]
		9	I		35[c]

[a] All yields are relative to oxirane and are based on isolated, pure product. Satisfactory analytical data was obtained for all new compounds. [b] See ref 6. [c] A single regioisomer was obtained. [d] See ref 1a. [e] Regioisomeric mixture.

Results

In the absence of boron trifluoride, reaction of cyclohexene oxides derived from quinic acid with diisopropyl lithiomethanephosphonate failed to yield detectable ring-opened product. Even cyclohexene oxide failed to react with diisopropyl lithiomethanephosphonate in the absence of boron trifluoride. Cyclohexene oxide, like quinate-derived cyclohexene oxide, did react with the combination of diisopropyl lithiomethanephosphonate and boron trifluoride to give a 71% yield of phosphonomethylated product (entry 1, Table I). This is a combined yield for the oxirane ring opening and the subsequent acetylation which was used to expedite product purification.

Although the cyclohexene oxide derived from *myo*-inositol failed to react with diisopropyl lithiomethanephosphonate/boron trifluoride at −78 °C, ring opening did occur when an excess of reagents and higher reaction temperatures were used (entry 7a, Table I). An approximately 1:1 ratio of phosphonomethylated regioisomers was formed. The cyclohexene oxide derived from *myo*-inositol also underwent oxirane ring opening to yield a mixture of regioisomers when reacted with an excess of dimethyl lithiomethanephosphonate/boron trifluoride (entry 7b, Table I). Formation of regioisomers was not unique to phosphonomethylation of the cyclohexene oxide derived from *myo*-inositol. Mixtures of regioisomers were also observed during reaction of the combination of diisopropyl lithiomethanephosphonate and boron trifluoride with the cyclohexene oxide derived from quinic acid when reaction temperatures were allowed to rise above −78 °C. Regioisomers produced by reaction of the substituted cyclohexene oxides with dialkyl lithiomethanephosphonates/boron trifluoride were readily purified by silica gel chromatography. Assignment of structures to the regioisomers formed from reactions of the cyclohexene oxide derived from *myo*-inositol with the dialkyl lithiomethanephosphonate and boron trifluoride combinations utilized two dimensional homonuclear ($^1H,^1H$) COSY and heteronuclear ($^1H,^{13}C$) HETCOR experiments.

The attenuated reactivity of diisopropyl lithiomethanephosphonate/boron trifluoride with the cyclohexene oxide of *myo*-inositol and the loss of regioselectivity prompted the examination of the more indirect route to phosphonomethylation (Scheme I) which hinged on the reactivity of (lithiomethyl)dimesitylborane. While the diisopropyl lithiomethanephosphonate/boron trifluoride combination utilized boron as a Lewis acid, (lithiomethyl)-dimesitylborane employs boron to stabilize an adjacent carbanion.[8] (Lithiomethyl)dimesitylborane has previously been primarily used for hydroxymethylation of oxiranes in acyclic systems although the reactivity of cyclohexene oxide with the reagent is precedented.[6]

Oxirane ring opening upon reaction with (lithiomethyl)-dimesitylborane was observed for all of the cyclohexene oxides. Only one regioisomer was formed from the cyclohexene oxides derived from quinic acid and *myo*-inositol even though these oxirane ring openings were run at room temperature. Oxidative workup[6] afforded the desired hydroxymethylated ring systems (entries 2, 5, and 8; Table I). Although these hydroxymethyl groups could readily be converted into functionality suitable for Arbuzov or Michaelis–Becker reactions, iodinolysis[9] of the ring-opened organoborane intermediates was elaborated as an alternate route to the phosphonomethyl functionality. Unpurified reaction products resulting from reaction of cyclohexene oxide or quinate-derived cyclohexene oxide were treated with iodine and sodium methoxide[9a] to afford iodomethylated product (entries 3 and 6; Table I). Higher yields for iodomethylation were achieved if the ring-opened organoborane was purified prior to iodinolysis. For instance, the overall yield for conversion of quinate-derived cyclohexene oxide into iodomethylated product was increased from 46 to 69% when the ring-opened organoborane intermediate was purified on silica gel prior to iodinolysis. Purification of the ring-opened organoborane immediately prior to iodinolysis was essential for successful iodomethylation of *myo*-inositol-derived cyclohexene oxide (entry 9, Table I). Iodinolysis in this instance required a switch to reaction conditions employing iodine monochloride[9b] and methanol.

For the reaction of quinate-derived cyclohexene oxide with (lithiomethyl)dimesitylborane, NMR assignment of relative stereochemistry was straightforward for hydroxymethylated or iodomethylated products. NMR was inadequate for assigning relative stereochemistry in the hydroxymethylated and iodomethylated products resulting from reaction of (lithiomethyl)dimesitylborane with *myo*-inositol-derived cyclohexene oxide. Fortuitously, diffractable crystals were obtained for the ring-opened organoborane intermediate (Figure 1) which was routinely purified.[9c] This allowed subsequent assignment of relative stereochemistry in the hydroxymethylated and iodomethylated products. Surprisingly, a ring-opened dimesitylborane was not the product of oxirane ring opening. The ring-opened intermediate, instead, was a cyclic oxaborinane (Figure 1). This is consistent[10] with in-

(8) (a) Pelter, A.; Smith, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 2.2, p 487. (b) Pelter, A.; Singaram, B.; Warren, L.; Wilson, J. W. *Tetrahedron* **1993**, *49*, 2965. (c) Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 623.

(9) (a) Brown, H. C.; Rathke, M. W.; Rogic, M. M.; De Lue, N. R. *Tetrahedron* **1988**, *44*, 2751. (b) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1980**, *45*, 3578. (c) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(10) Utimoto, K.; Uchida, K.; Nozaki, H. *Tetrahedron Lett.* **1973**, 4527.

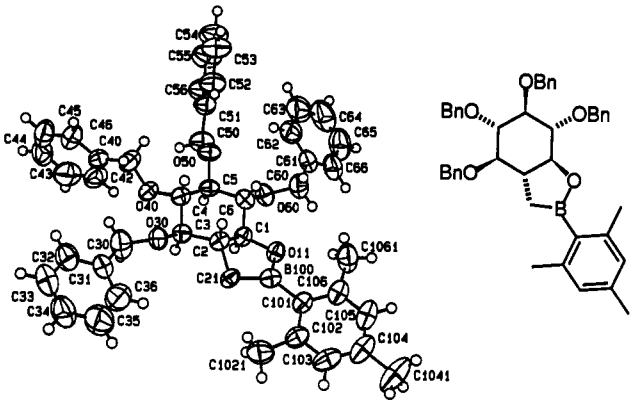
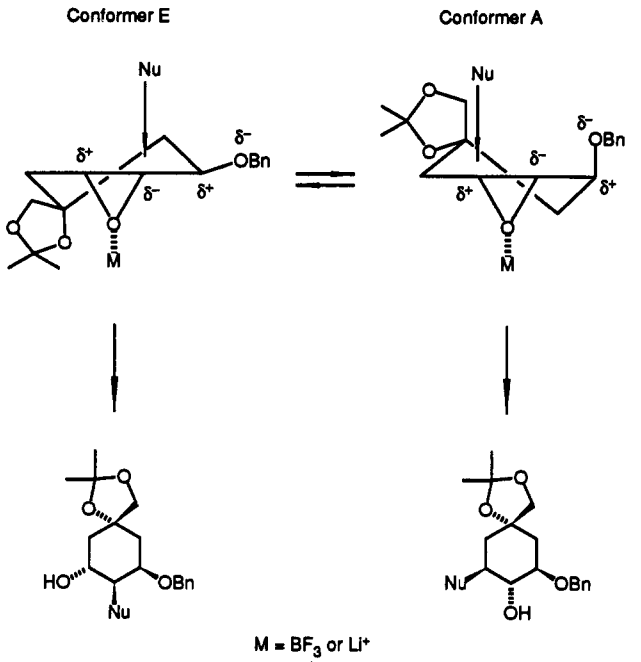


Figure 1. ORTEP of the X-ray crystal structure of the product formed by reaction of (lithiomethyl)dimesitylborane with *myo*-inositol-derived cyclohexene oxide 3.

Scheme II

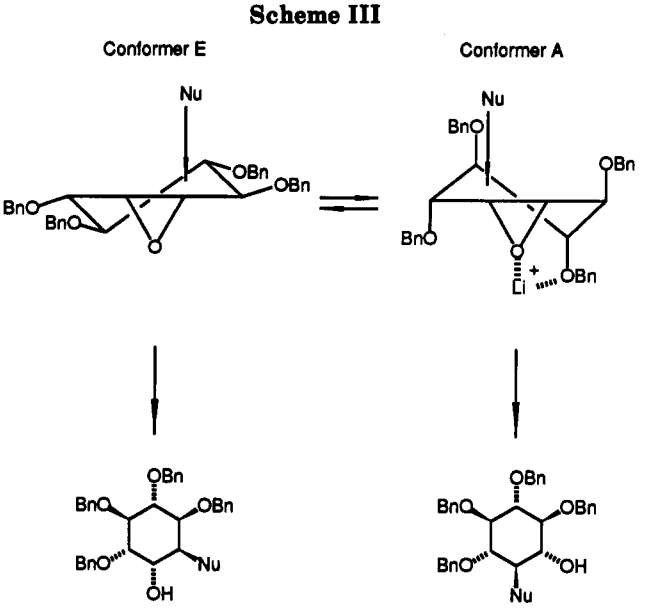


tramolecular borate formation after initial dimesitylboromethylation. Protonolysis would then lead to boron–carbon bond cleavage and formation of mesitylene. The iodinolyses may have benefited from the reduced steric hindrance around the boron of the cyclic oxaborinanes relative to the sterically hindered boron in a dimesitylboromethyl intermediate.

Discussion

The regioselectivity observed during heteromethylation was identical for reaction of the cyclohexene oxide derived from quinic acid with diisopropyl lithiomethanephosphonate/boron trifluoride and with lithiomethyldimesitylborane. Product regioisomers were suggestive of a transition state (Scheme II) involving transdiaxial attack[11] by the nucleophile on the cyclohexene oxide conformer having predominantly axial substitution. This regioselectivity is likely due to polarization[12] of the bond between the C-5 carbon and oxirane oxygen caused by inductive effects of the benzyloxy group attached at C-3. Transdiaxial attack at the partially electropositive C-5 carbon requires attack via conformer A of Scheme II. The lack of oxirane ring opening when cyclohexene oxides are reacted with diisopropyl lithiomethanephosphonate in the absence of boron trifluoride provides evidence for complexation of the BF_3 boron with the oxirane oxygen in the ring-opening transition state. Involvement of a complex between the BF_3 boron and carbanion of the methyl dialkylphosphonate seems unlikely based on literature studies.[3] Lithium also appears to complex to the oxirane oxygen in the transition state involving quinate-derived cyclohexene oxide and (lithiomethyl)dimesitylborane based on observed reactivity and regioselectivity. Although complexes with the oxirane oxygen are implicated along with polarization of one of the carbon–oxygen bonds of the oxirane, carbonium ion intermediacy during ring opening is unlikely. This follows from the lack of *cis*-substituted ring-opened products during reaction of the quinate-derived cyclohexene oxide with either dialkyl lithiomethanephosphonates or (lithiomethyl)dimesitylborane.

Scheme III



While regioselectivity was largely relaxed in the reaction of *myo*-inositol-derived cyclohexene oxide with the dialkyl lithiomethanephosphonates, the regioselectivity observed for the reaction of this same cyclohexene oxide with (lithiomethyl)dimesitylborane suggested reaction via a transition state where transdiaxial, nucleophilic attack is occurring on axially substituted conformer A (Scheme III). The indicated dominance of axially substituted conformers in the ring opening transition states for both quinate-derived and *myo*-inositol-derived cyclohexene oxides is noteworthy. However, the factors responsible for the dominance of axially substituted conformers in the transition states are likely different for the two substituted cyclohexene oxides. The *myo*-inositol-derived cyclohexene oxide has two adjacent benzyloxy substituents. These substituents likely inductively destabilize formation of a complex between the boron trifluoride or lithium with the oxirane oxygen. Diminished boron trifluoride complexation at −78 °C probably accounts for the diminished

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(12) Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, Ed.; Wiley: New York, 1972; Vol. 2, p 1.

reactivity of diisopropyl lithiomethanephosphonate. An absence of preferential polarization of either of the oxirane carbon–oxygen bonds may account for the relaxed regioselectivity during reactions of dialkyl lithiomethanephosphonate/boron trifluoride with the cyclohexene oxide derived from *myo*-inositol. The regioselectivity observed with (lithiomethyl)dimesitylborane might reflect lithium simultaneously binding to the oxirane oxygen and the ether oxygen of one of the benzyloxy groups (see Scheme III).[13] This bridging complex could stabilize the axially substituted conformer (Scheme III). In numerous reactions, lithium is precedented[14] to be a divalent ligand while boron trifluoride appears to be primarily a univalent ligand.[15] Failure of the boron trifluoride to form a bridging complex to stabilize the axially substituted conformer (Scheme III) may be an additional reason for the relaxed regioselectivity observed for the reactions of *myo*-inositol-derived cyclohexene oxide with the dialkyl lithiomethanephosphonates.

An apparent tradeoff exists between synthetic directness and regioselectivity in the reactions of cyclohexene oxides **1–3** with dialkyl lithiomethanephosphonates and (lithiomethyl)dimesitylborane. (Lithiomethyl)dimesitylborane's reactivity was uniformly high irrespective of whether the cyclohexene oxide was unsubstituted (**1**, Table I) or fully substituted (**3**, Table I). This reactivity did not come at the price of sacrificed regioselectivity as evidenced by the high regioselectivities observed for oxirane ring openings in both quinate-derived (**2**, Table I) and *myo*-inositol-derived (**3**, Table I) cyclohexene oxides. The reactivities of the cyclohexene oxides varied considerably with diisopropyl lithiomethanephosphonate in the presence of boron trifluoride. When the cyclohexene oxide (such as **3**, Table I) was refractory toward attack by diisopropyl lithiomethanephosphonate/boron trifluoride at −78 °C, reaction temperatures had to be increased and the regioselectivity of oxirane ring opening diminished. This change in regioselectivity may be of use depending on the phosphonomethylated product targeted for synthesis. However, while increasing temperature relaxed the degree of regioselectivity to afford approximately 1:1 ratios of regioisomers, a complete switch in regioselectivity was not observed. As for synthetic directness, reaction of the cyclohexene oxides with (lithiomethyl)dimesitylborane followed by oxidation or iodinolysis is a circuitous phosphonomethylation route (Scheme I). The yield of pure, phosphonomethylated regioisomer may not be an improvement over the yield of directly phosphonomethylated product (Scheme I) obtained after purification of regioisomeric mixtures. Therefore, while regioselectivity may be sacrificed for synthetic directness, advantage can be taken of the reaction of cyclohexene oxides with diisopropyl lithiomethanephosphonate/boron trifluoride which affords phosphonomethylated, ring-opened products in a single step.

Experimental Section

General Chemistry. See reference 1a for general experimental information. Solutions of (lithiomethyl)-dimesitylborane in THF were freshly prepared (using mesityllithium as the base) as described by Pelter et al.[8c] The following is a representative procedure: To a solution of mesityl bromide (1.50 g, 7.47 mmol) in THF (15 mL) cooled at −78 °C was added *tert*-butyllithium in pentane (1.7 M, 8.8 mL, 15.0 mmol) under N_2. The solution became yellow and salts rapidly formed. After 15 min, the cold bath was replaced by a water bath at rt. After an additional 15 min, the homogeneous orange solution was cannulated into a solution of methyldimesitylborane[8b] (1.80 g, 6.79 mmol) in THF (10 mL) at rt. The pale orange solution slowly turned darker and was stirred for 1 h at rt before use.

Table I. Entry 1. *trans*-1-Acetoxy-2-[(diisopropoxyphosphinyl)methyl] cyclohexane. A solution of *n*-butyllithium in hexane (1.42 M, 5.6 mL, 8.0 mmol) was cooled to −78 °C, and freshly distilled, dry THF (6 mL) was added, under N_2. Diisopropyl methanephosphonate (1.44 g, 8.0 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 10 min and boron trifluoride etherate (0.98 mL, 8.0 mmol) was added slowly. The mixture immediately became turbid. Addition of cyclohexene oxide **1** (0.390 g, 4.0 mmol) followed 5 min later. Slowly, the mixture became clear and after 20 min, the reaction mixture was quenched at −78 °C with saturated aqueous $NaHCO_3$. The cold bath was removed and the mixture was allowed to warm to rt. Water (10 mL) was added and the aqueous layer was extracted with ether/hexane (1:1, v/v, 3 × 15 mL) and $CHCl_3$ (1 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to yield 1.36 g of a clear oil. This crude product was dissolved in pyridine (1.7 mL, 21.2 mmol) and acetic anhydride (1.0 mL, 10.6 mmol) was added via syringe under N_2. After 12 h at rt, the solvent was removed under high vacuum and the residue was azeotroped with toluene (3×). Purification by flash chromatography (1:1 ethyl acetate/hexane, v/v) gave a colorless oil (0.950 g, 71% based on cyclohexene oxide): ^{1}H NMR ($CDCl_3$) δ 4.62–4.80 (m, 2 H), 4.42 (ddd, J = 11, 11, 4 Hz, 1 H), 2.20–2.35 (m, 1 H), 2.04 (s, 3 H), 1.59–2.08 (m, 8 H), 1.44 (ddd, 17, 15, 10 Hz, 2 H), 1.34 (s, 6 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 76.4 (J_{POCC} = 17 Hz), 69.6 (J_{POC} = 5 Hz), 69.5 (J_{POC} = 5 Hz), 37.1 (J_{PCC} = 4 Hz), 31.3, 31.0, 29.3 (J_{PC} = 143 Hz), 24.7, 24.0, 23.7 (J_{POCC} = 4 Hz), 20.9; IR (neat, NaCl) 1736 (s), 1452 (s), 1142 (s); MS *m/z* (rel inten) EI 177 (100), 176 (62); CI 322 (15), 321 (M + H$^+$, 100); HRMS (CI) calcd for $C_{15}H_{29}O_5P$ (M + H$^+$) 321.1831, found 321.1828. Anal. Calcd for $C_{15}H_{29}O_5P$: C, 56.23; H, 9.12. Found: C, 56.18; H, 9.12.

Table I. Entry 3. *trans*-2-(Iodomethyl)cyclohexan-1-ol.[16] A freshly prepared solution of (lithiomethyl)-dimesitylborane (see General Chemistry) in THF (0.25 M, 14 mL, 3.50 mmol) was added slowly via syringe to cyclohexene oxide **1** (0.320 g, 3.26 mmol) in THF (10 mL) at rt and under Ar. After 2.5 h, anhydrous methanol (1 mL) was added, followed by addition of iodine (2.83 g, 11.1 mmol) directly as a solid under Ar. The flask was shielded from light, and sodium methoxide (0.610 g, 11.3 mmol) in methanol (15 mL) was slowly cannulated into the reaction mixture. After 5 h, the mixture was quenched with aqueous sodium thiosulfate. The aqueous layer was then saturated with NaCl followed by extraction with ether (3×). The combined organic layers were dried over $MgSO_4$

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(14) For examples, see: (a) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. (b) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.

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and concentrated to a heterogeneous oil. Purification by radial chromatography (2-mm layer, hexane, ethyl acetate) yielded the iodide (0.720 g, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.20–3.50 (m, 3 H), 2.57 (s, 1 H), 1.90–2.05 (m, 1 H), 1.65–1.90 (m, 3 H), 1.00–1.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 73.3, 45.5, 35.2, 31.5, 24.9, 24.8, 14.4; IR (film, NaCl) 3356 (br); MS *m/z* (rel inten) EI 240 (M^+, 5), 95 (100); CI 241 (M + H^+, 10), 223 (100); HRMS (EI) calcd for $C_7H_{13}IO$ (M^+) 240.0011, found 240.0016.

Table I. Entry 5. [5*S*-(5α,7β,8α,9β)]-7-(Benzyloxy)-2,2-dimethyl-9-(hydroxymethyl)-1,3-dioxaspiro[4.5]-decan-8-ol. Cyclohexene oxide **2**[1a] (1.32 g, 4.53 mmol) in THF (20 mL) was cannulated into a (lithiomethyl)-dimesitylborane solution (See General Chemistry) in THF (0.2 M, 30 mL, 6.80 mmol) at rt. After 2 h, anhydrous methanol (8.0 mL) was added. Aqueous NaOH (1 N, 20 mL) was added and the flask was cooled to 0 °C. Aqueous hydrogen peroxide (30 wt %, 8 mL) was then added carefully. The cold bath was removed at the end of the addition. After 18 h, the reaction mixture was poured into saturated aqueous Na_2CO_3. The aqueous layer was extracted with ether (3×), and the combined organic layers were dried over $MgSO_4$ and concentrated to an oil. Purification by radial chromatography (4 mm thickness, 1:5 ethyl acetate/hexane, 1:1 ethyl acetate/hexane, v/v) yielded the title compound (1.34 g, 92%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.20–7.35 (m, 5 H), 4.64 (d, J = 12 Hz, 1 H), 4.53 (d, J = 12 Hz, 1 H), 3.69 (s, 2 H), 3.25–3.75 (m, 6 H), 2.14 (ddd, J = 13, 3, 3 Hz, 1 H), 1.90–2.10 (m, 1 H), 1.61 (ddd, J = 13, 3, 3 Hz, 1 H), 1.15–1.35 (m, 2 H), 1.34 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.4, 128.4, 127.8, 127.7, 109.6, 79.8, 79.5, 76.6, 73.9, 71.3, 65.4, 39.4, 38.6, 36.1, 26.9, 26.8; IR (film, NaCl) 3386 (br), 1454 (s), 1432 (m), 1116 (s), 1070 (s); MS *m/z* (rel inten) EI 91 (100); CI 324 (17), 323 (M + H^+, 100); HRMS (CI) calcd for $C_{18}H_{26}O_5$ (M + H^+) 323.1859, found 323.1849. Anal. Calcd for $C_{18}H_{26}O_5 \cdot {}^1/_4H_2O$: C, 66.13; H, 8.17. Found: C, 66.27; H, 8.17.

Table I. Entry 6. [5*S*-(5α,7β,8α,9β)-7-(Benzyloxy)-2,2-dimethyl-9-(iodomethyl)-1,3-dioxaspiro[4.5]decan-8-ol. A solution of cyclohexene oxide **2**[1a] (0.360 g, 1.24 mmol) in THF (5 mL) was slowly added to a THF solution (See General Chemistry) of (lithiomethyl)dimesitylborane (0.155 M, 12 mL, 1.86 mmol) under Ar. After 2 h at rt, anhydrous methanol (2 mL) was added, followed by addition of iodine (1.610 g, 12.4 mmol) in one portion. The flask was shielded from light, and sodium methoxide (0.334 g, 12.4 mmol) in methanol (5 mL) was added. After 19 h at rt, the mixture was quenched with aqueous sodium thiosulfate. The aqueous layer was extracted with ether (3×), and the combined organic layers were dried over $MgSO_4$ and concentrated to a heterogeneous oil. Purification by radial chromatography (2-mm thickness, 1:5 ethyl acetate/hexane, 1:1 ethyl acetate/hexane, v/v) yielded the iodide (0.249 g, 46%): ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.67 (d, J = 11 Hz, 1 H), 4.49 (d, J = 11 Hz, 1 H), 3.77 (s, 2 H), 3.69 (ddd, J = 12, 9, 4 Hz, 1 H), 3.53 (dd, J = 10, 5 Hz, 1 H), 3.42 (dd, J = 10, 3 Hz, 1 H), 3.28 (ddd, J = 9, 9, 1 Hz, 1 H), 2.62 (d, J = 1 Hz, 1 H), 2.18 (ddd, J = 13, 4, 3, 1 H), 1.77 (ddd, J = 13, 3, 3 Hz, 1 H), 1.50–1.70 (m , 1 H), 1.25–1.40 (m, 2 H), 1.38 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 128.4, 127.8, 109.8, 79.7, 79.3, 75.8, 73.9, 71.4, 40.4, 38.7, 38.0, 27.2, 27.1, 13.8; IR (film, NaCl) 3464 (br), 1454 (m), 1074 (s); MS *m/z* (rel inten) EI 91 (100); CI 434 (15), 433 (M + H^+, 92), 341 (100); HRMS (EI) calcd for $C_{18}H_{25}O_4I$ (M^+) 432.0798, found 432.0780. Anal. Calcd for $C_{18}H_{25}O_4I$: C, 50.01; H, 5.83. Found: C, 50.13; H, 5.87.

Table I. Entry 7a. Regioisomer I: [1*R(1α,2β,-3α,4β,5α,6β)]-2,3,4,5-Tetrakis(benzyloxy)-6-[(diisopropoxyphosphinyl)methyl]cyclohexan-1-ol. Regioisomer II: [1*S**(1α,2α,3β,4α,5β,6β)]-2,3,4,5-Tetrakis-(benzyloxy)-6-[(diisopropoxyphosphinyl)methyl]-cyclohexan-1-ol.** A solution of *n*-butyllithium in hexane (1.6 M, 0.97 mL, 1.56 mmol) was added to THF (5 mL) at −78 °C under N_2. To this solution was slowly added a solution of diisopropyl methanephosphonate (0.28 g, 1.56 mmol) in THF (5 mL). This solution was stirred for 30 min at −78 °C. Boron trifluoride etherate (0.19 mL, 1.56 mmol) was added immediately followed by a solution of cyclohexene oxide **3**[17] (0.16 g, 0.31 mmol) in THF (5 mL). The solution was stirred at −78 °C for 3 h. More boron trifluoride etherate (0.19 mL, 1.56 mmol) was added. The solution was then warmed to −40 °C and stirred for 12 h. Saturated aqueous $NaHCO_3$ was then added. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine followed by water and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude was first purified by flash chromatography (1:1 ethyl acetate/hexane, v/v) and then by radial chromatography (2-mm thickness of silica gel, 1:1 ethyl acetate/hexane, v/v). The faster eluting regioisomer **I** was isolated as an oil which slowly solidified at rt (0.063 g, 0.088 mmol, 28% yield). The slower eluting regioisomer **II** was isolated as an oil (0.045 g, 0.065 mmol, 21% yield).

Regioisomer I: ^{1}H NMR ($CDCl_3$) δ 7.20–7.40 (m, 20 H), 4.55–5.05 (m, 11 H), 3.30–3.90 (m, 4 H), 1.80–2.35 (m, 3 H), 1.50 (br, 1 H), 1.25–1.50 (m, 19 H); ^{13}C NMR ($CDCl_3$) δ 139.1, 138.8, 138.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 86.0, 85.2, 82.8, 79.7 (J_{PCC} = 7 Hz), 75.8, 75.6, 75.1, 73.8 (J_{PCCC} = 3 Hz), 72.0, 71.8, 70.9 (J_{POC} = 7 Hz), 70.6 (J_{POC} = 7 Hz), 41.7 (J_{PCC} = 4 Hz), 25.3 (J_{PC} = 141 Hz), 24.3, 24.2, 24.1, 24.0; IR (neat NaCl) 3380 (w), 1460 (m), 1450 (s), 1210 (s); MS, *m/z* (rel inten) EI 91 (100); CI 703 (M + H^+, 25), 107 (100); HRMS (CI) calcd for $C_{41}H_{52}O_8P$ (M + H^+) 703.3400, found 703.3400. Anal. Calcd for $C_{41}H_{51}O_8P$: C, 70.07; H, 7.31. Found: C, 70.31; H, 7.05.

Regioisomer II: ^{1}H NMR ($CDCl_3$) δ 7.00–7.45 (m, 20 H), 4.40–4.80 (m, 10 H), 3.90–4.05 (m, 1 H), 3.55–3.80 (m, 2 H), 3.25–3.45 (m, 2 H), 2.60–2.80 (m, 1 H), 2.45 (br, 1 H), 2.00–2.30 (m, 1 H), 1.00–1.60 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.6, 138.4, 137.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 81.7, 81.5, 79.7, 78.1 (J_{PCCC} = 13Hz), 76.0, 75.9, 75.5, 72.4 (J_{POC} = 7 Hz), 70.6, 70.2 (J_{POC} = 7 Hz), 67.8, 35.5 (J_{PCC} = 4 Hz), 25.1 (J_{PC} =134 Hz), 24.1, 24.0, 23.9; IR (neat NaCl) 3550 (s), 1460 (s), 1402 (s), 1255 (m); MS, *m/z* (rel inten) EI 91 (100); CI 704 (29), 703 (M + H^+, 100); HRMS (CI) calcd for $C_{41}H_{52}O_8P$ (M + H^+) 703.3400, found 703.3386. Anal. Calcd for $C_{41}H_{51}O_8P \cdot H_2O$: C, 68.30; H, 7.41. Found: C, 68.03; H, 7.23.

Table I. Entry 7b. Regioisomer I: [1*R(1α,2β,-3α,4β,5α,6β)]-2,3,4,5-Tetrakis(benzyloxy)-6-[(dimethoxyphosphinyl)methyl]cyclohexan-1-ol. Regioisomer II: [1*S**(1α,2α,3β,4α,5β,6β)]-2,3,4,5-Tetrakis-(benzyloxy)-6-[(dimethoxyphosphinyl)methyl]-cyclohexan-1-ol.** A solution of *n*-butyllithium in hexane (1.6 N, 8.45 mL, 13.5 mmol) was added to THF (20 mL) at −78 °C under N_2. To this solution was slowly added a

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solution of dimethyl methanephosphonate (1.67 g, 13.5 mmol) in THF (25 mL). The resulting solution was stirred for 30 min at −78 °C. Boron trifluoride etherate (1.66 mL, 13.5 mmol) was added, immediately followed by a solution of cyclohexene oxide **3**[17] (2.35 g, 4.50 mmol) in THF (25 mL). The solution was stirred at −78 °C for 3 h. After that time, more boron trifluoride etherate (1.66 mL, 13.5 mmol) was added. The solution was allowed to warm to rt and was stirred for 12 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer extracted with ether. The combined organic layers were washed with brine followed by water and then were dried over $MgSO_4$. The crude product was purified by flash chromatography (1:1 ethyl acetate/hexane, v/v) and then by radial chromatography (2-mm plate, 1:1 ethyl acetate/hexane, v/v). The faster eluting regioisomer **I** was isolated as an oil (0.99 g, 1.54 mmol, 34%) which slowly solidified at rt. The slower eluting regioisomer **II** was obtained as an oil (0.77 g, 1.19 mmol, 27%) which also slowly solidified at rt.

Regioisomer I: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 20 H), 4.80–5.05 (m, 7 H), 4.67 (d, J = 11 Hz, 1 H), 3.75 (d, J = 2 Hz, 3 H), 3.70 (d, J = 2 Hz, 3 H), 3.40–3.65 (m, 5 H), 1.80–2.40 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.4, 138.3, 138.2, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 86.0, 85.1, 82.7, 79.4 (J_{PCCC} = 7 Hz), 75.8, 75.6, 75.5, 75.1, 73.1 (J_{PCCC} = 3 Hz), 52.7 (J_{POC} = 7 Hz), 52.3 (J_{POC} = 7 Hz), 41.4 (J_{PCC} = 4 Hz), 22.6 (J_{PC} = 139 Hz); IR (neat NaCl) 3550 (w), 3360 (s), 1452 (s), 1260 (s); MS, m/z (rel inten) EI 91 (100); CI 647 (M + H^+, 5), 615 (100); HRMS (FAB) calcd for $C_{37}H_{44}O_8P$ (M + H^+) 647.2774, found 647.2768. Anal. Calcd for $C_{37}H_{43}O_8P \cdot {}^1/_3H_2O$: C, 68.08; H, 6.74. Found: C, 68.09; H, 7.17.

Regioisomer II: ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 20 H), 4.60–4.90 (m, 8 H), 4.40–4.50 (m, 1 H), 4.12 (ddd, J = 12, 5, 3 Hz, 1 H), 3.87 (dd, J = 9, 9 Hz, 1 H), 3.69 (d, J = 5 Hz, 3 H), 3.64 (d, J =5 Hz, 3 H) 3.63–3.70 (m, 1 H), 3.51 (dd, J = 9, 9 Hz, 1 H), 2.97 (b, 1 H), 2.70–2.95 (m, 1 H), 2.35, (ddd, J = 20, 16, 3 Hz, 1 H), 1.45 (ddd, J = 17, 16, 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.2, 137.8, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 81.5, 81.3, 79.4, 77.8 (J_{PCCC} = 13 Hz), 75.6, 75.3, 72.3, 67.7, 52.3 (J_{POC} = 7 Hz), 52.1 (J_{POC} = 7 Hz), 35.5 (J_{PCC} = 4 Hz), 19.9 (J_{PC} = 143 Hz); IR (neat NaCl) 3545 (m), 3400 (s), 1455 (s), 1370 (m), 1255 (s); MS, m/z (rel inten) EI 91 (100); CI 648 (37), 647 (M + H^+, 100); FAB 648 (15), 647 (36); HRMS (FAB) calcd for $C_{37}H_{44}O_8P$ (M + H^+) 647.2774, found 647.2767. Anal. Calcd for $C_{37}H_{43}O_8P \cdot {}^1/_2H_2O$: C, 67.77; H, 6.76. Found: C, 67.77; H, 6.76.

Table I. Entry 8. [1*R(1α,2β,3α,4β,5α,6β)]-2,3,4,5-Tetrakis(benzyloxy)-6-(hydroxymethyl)cyclohexan-1-ol.** To a solution of cyclohexene oxide **3**[17] (1.44 g, 2.00 mmol) in THF (25 mL) was added a (lithiomethyl)-dimesitylborane solution (See General Chemistry) in THF (1.28 M, 15 mL, 20 mmol) at rt, under N_2. After 12 h, saturated aqueous $NaHCO_3$ and ether (20 mL) were added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The intermediate was purified by radial chromatography (2-mm thickness, 1:5 ethyl acetate/hexane, v/v) to yield a white solid which recrystallized from CCl_4 (1.41 g). To a solution of this intermediate (0.21 g) in THF (5 mL) under nitrogen were added methanol (2 mL) followed by aqueous NaOH (5 N, 0.16 mL, 0.81 mmol). The solution was then chilled to 0 °C and aqueous hydrogen peroxide (30 wt %) (0.50 mL, 0.81 mmol) was slowly added. The mixture was then stirred at rt for 6 h. Saturated aqueous $NaHCO_3$ was added, followed by ether. The organic phase was washed with brine, followed by water, and then dried over $MgSO_4$. After removal of the solvents under reduced pressure, the diol was purified by radial chromatography (2-mm thickness of silica gel, 1:1 ethyl acetate/hexane, v/v). The diol was obtained as an oil (0.15 g, 0.27 mmol, 89%) which slowly solidified at rt: ^1H NMR ($CDCl_3$) δ 7.20–7.30 (m, 20 H), 4.80–5.00 (m, 6 H), 4.60–4.75 (m, 2 H), 3.91 (dd, J = 11, 3 Hz, 1 H), 3.73 (dd, J = 11, 4 Hz, 1 H), 3.60 (dd, J = 9, 9 Hz, 1 H), 3.50–3.55 (m, 2 H), 3.35–3.45 (m, 2 H), 2.30 (br, 2 H), 1.60–1.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.6, 138.5, 138.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 86.3, 85.1, 83.2, 77.5, 75.7 (2C), 75.5, 75.3, 70.5, 60.4, 46.0; IR (neat NaCl), 3535 (b), 3340 (b), 1450 (w), 1258 (s); MS, m/z (rel inten) EI 91 (100); CI 555 (M + H^+, 4), 107 (100); HRMS (CI) calcd for $C_{35}H_{38}O_6$ (M + H^+) 555.2747, found 555.2736. Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.09; H, 6.90. Found: C, 75.52; H, 6.95.

Table I. Entry 9. [1*R(1α,2β,3α,4β,5α,6β)]-2,3,4,5-Tetrakis(benzyloxy)-6-(iodomethyl)cyclohexan-1-ol.** To a solution of cyclohexene oxide **3**[17] (3.00 g, 5.73 mmol) in THF (25 mL) was added a (lithiomethyl)-dimesitylborane solution (see General Chemistry) in THF (0.72 M, 25 mL, 28.6 mmol) under N_2 at rt. After 12 h, a solution of sodium acetate in methanol (1 M, 57.3 mL, 57.3 mmol) was added, followed by a solution of ICl in methanol (1 M, 28.6 mL, 28.6 mmol). After 30 min at rt, saturated aqueous $NaHCO_3$ was added followed by ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane, 1:1, v/v) afforded an intermediate which was then dissolved in anhydrous tetrahydrofuran. A solution of sodium acetate in anhydrous methanol (1 M, 57.3 mL, 57.3 mmol) was then added under N_2 followed by a solution of ICl in methanol (1 M, 28.6 mL, 28.6 mmol). After 8 h at rt, saturated aqueous $NaHCO_3$ was added followed by ether. The organic layer was washed with brine and then with water and dried over $MgSO_4$. The solvents were removed, and the residue was purified by radial chromatography (4-mm thickness of silica gel, ethyl acetate/hexane, 1:5, v/v) to afford the iodide as a white solid (1.33 g, 2.00 mmol, 35%): ^1H NMR ($CDCl_3$) δ 7.20–7.45 (m, 20 H), 4.60–5.05 (m, 8 H), 3.65–3.80 (m, 3 H), 3.40–3.65 (m, 4 H), 2.38 (br, 1 H), 1.00–1.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.2, 138.1, 128.7, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 85.7, 84.5, 83.1, 79.5, 75.9, 75.8, 75.7, 75.5, 70.9, 43.9, 10.4; IR (neat NaCl), 3535 (m), 3450 (w), 1452 (s); MS, m/z (rel inten) EI 91 (100); CI 574 (11), 573 (46), 181 (100); HRMS (CI) calcd for $C_{35}H_{37}O_5I$ (M − H^+) 663.1608, found 663.1601. Anal. Calcd for $C_{35}H_{37}O_5I$: C, 63.26; H, 5.61. Found: C, 63.47; H, 5.63.

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