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Single Enantiomer Epoxides by Bromomandelation of Prochiral Alkenes

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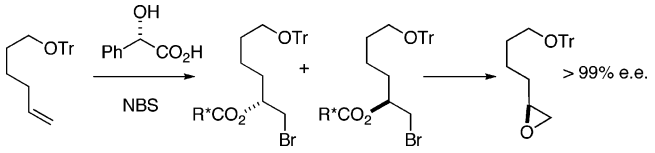
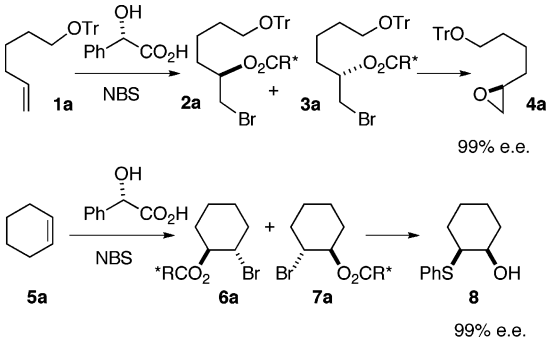


A combination of mandelic acid and *N*-bromosuccinimide efficiently converts prochiral alkenes into a readily separable 1:1 mixture of the bromomandelates. The diastereomerically pure bromomandelates are then converted into a variety of enantiomerically pure products. Terminal alkenes are converted into enantiomerically pure epoxides. Cyclohexene is converted into enantiomerically pure *cis*-2-azidocyclohexanol and *cis*-2-phenylthiocyclohexanol.

Introduction

Sharpless asymmetric epoxidation[1a] and asymmetric dihydroxylation[1b] are workhorses of modern organic synthesis. More recently, Jacobsen epoxidation[2a] and Shi epoxidation[2b] have also become important. Epoxides of terminal alkenes, however, cannot be prepared directly in acceptable enantiomeric excess with any of these protocols. Enantiomerically enriched epoxides of such alkenes are currently derived by catalytic asymmetric hydrolysis of the racemic epoxides.[3] The epoxides of simple cyclic alkenes such as **5a** are prochiral. Enantiomerically enriched products from such epoxides are currently accessed by chiral catalytic nucleophilic opening[4] or by resolution.[5] We have found (Scheme 1) that mandelic acid reacts with terminal alkenes such as **1a** in the presence of NBS to give the readily separated 1:1 mixture of diastereomeric secondary mandelates **2a** and **3a**. The diastereomeric bromomandelates from cyclic alkenes are also readily separated. This provides a facile entry to chiral pool starting materials such as **4a** and **8**.

SCHEME 1



Results and Discussion

We envisioned that conversion of alkene **1a** to the bromohydrin followed by esterification with an enantiomerically pure acid could lead to a separable mixture of diastereromeric bromo esters. The known[6] HPLC separation of diastereomeric secondary mandelates led us to this inexpensive ($0.23/mmol), easily handled acid. We were pleased to observe that the (*S*)-mandelates **2a** and **3a** of the enantiomeric secondary bromohydrins derived from **1a** were readily separated by silica gel

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(1) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(2) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

(3) For leading references to the catalytic kinetic enantioselective opening of terminal epoxides, see: (a) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360. (b) Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952.

(4) For leading references to the catalytic enantioselective opening of cyclohexene epoxide, see: (a) McCleland, B. W.; Nugent, W. A.; Finn, M. G. *J. Org. Chem.* **1998**, *63*, 6656. (b) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.

(5) Ami, E.; Ohrui, H. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 2150.

(6) (a) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548. (b) For the use of *O*-methyl mandelate esters to resolve preformed halohydrins, see: Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966.

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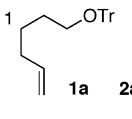
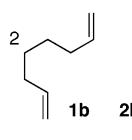
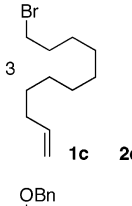
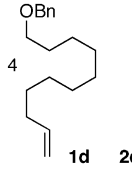
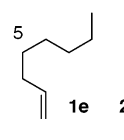
TABLE 1. Bromomandelation of Terminal Alkenes

Alkene	Bromomandelates	(%)[a]	Epoxide	(%)[b]
1 	**1a**	**2a**	**3a**	53	**4a**	92
2 	**1b**	**2b**	**3b**	49[c]	**4b**	89[d]
3 	**1c**	**2c**	**3c**	52	**4c**	86
4 	**1d**	**2d**	**3d**	51	**4d**	87[e]
5 	**1e**	**2e**	**3e**	53	**4e**	94[f]

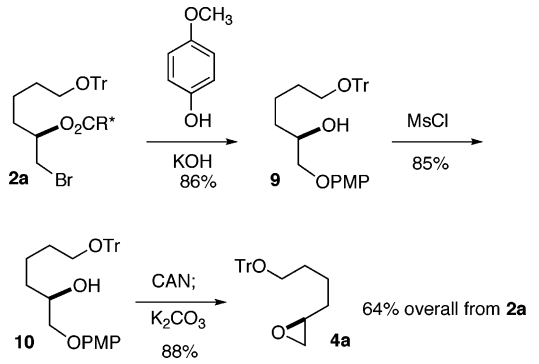
[a] Yield of a 1:1 mixture of secondary mandelates, based on starting alkene. A small amount (~25%) of the mixture of the primary mandelates was also formed. [b] Yield of epoxide from diastereomer **3** of bromomandelate. [c] NBS was the limiting reagent. [d] Ref 9. [e] Ref 10. [f] Ref 11.

chromatography.[7] Methanolysis of **3a** delivered the epoxide **4a** as a single enantiomer (99% ee, chiral HPLC).

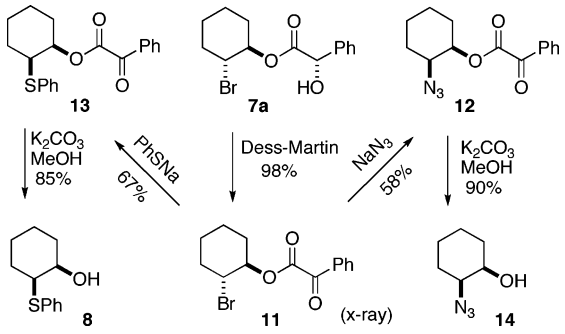
The success of this separation led us to devise a one-step protocol for the conversion of an alkene to the mixture of bromomandelates. To our surprise, we found that in contrast to halolactonization, intermolecular alkene bromoesterification had not been developed as a synthetic method.[8] We have found that the key was the use of the hindered pyridine 2,6-lutidine as the base for the reaction. For simple terminal alkenes, the mixture of bromomandelates formed efficiently, and the diastereomeric secondary mandelates were indeed easy to separate. For example, from alkene **1a**, TLC R_f values, (isolated yields): **3a** 0.62, (26%), **2a** 0.54 (27%), were followed by the 1:1 mixture of the primary mandelates 0.46 (25%). Other monosubstituted alkenes (Table 1) worked equally well. The diastereomers **2** and **3** were readily distinguished by ^{1}H NMR of the methines: for **2**, δ 3.47−3.50 and for **3** δ 3.35−3.39. Relative configurations were assigned by analogy to **3b**, **3d**, and **3e**, each of which led to an epoxide of known optical rotation.

Both of the diastereomers **2a** and **3a** could be converted to the same enantiomer of the epoxide **4a**. Direct exposure of **3a** to KOH gave **4a** (92% yield, Table 1). Exposure of **2a** (Scheme 2) to 4-methoxyphenol in the presence of KOH gave the alcohol **9**. The derived mesylate **10** was deprotected[12] to give, after cyclization, the same enantiomer **4a** of the epoxide (64% yield overall from **2a**). The net yield of the enantiomerically pure epoxide **4a** from the alkene **1a** was thus 41%, comparable to the yield expected from alkene epoxidation followed by enantioselective hydrolysis.

SCHEME 2



SCHEME 3



A substantial advantage of this approach is that it provides the single enantiomer epoxides (**4a**−**4e**) directly from the chromatographically pure bromomandelates. The diastereomers **2** and **3** are readily distinguishable by TLC and by ^{1}H NMR. There is no need to monitor a catalyst-mediated enantioselective hydrolysis by the more cumbersome and expensive methods of chiral HPLC or chiral GC. On a larger scale, the individual diastereomers of the bromomandelates can alternatively be purified by cystallization (Table 2, entry 2). Furthermore, for low molecular weight epoxides, the diastereomerically pure bromomandelate precursors are more convenient to store and to handle than are the epoxides themselves.

Encouraged by these results, we undertook (Table 2) the bromomandelation of prochiral cyclic alkenes. Again, the bromomandelates were readily separable [From **5a**, TLC R_f values (isolated yields): **7a** 0.51 (40%) and **6a** 0.40 (41%)]. Consistently, the ^{1}H NMR chemical shifts of the brominated methines of **7a**−**7e** were downfield (δ 0.13 to δ 0.33) from the ^{1}H NMR chemical shifts of the brominated methines of **6a**−**6e**.

We briefly investigated nucleophilic displacement on **7a**. The secondary bromide of **7a** (Scheme 3) participated more ef-

(7) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

(8) (a) For bromoacetoxylation of a terminal alkene, see: Srikrishna, A.; Sundarababu, G. *Tetrahedron* **1991**, *47*, 481. (b) For bromoacetoxylation of cyclohexene, see: Dulcère, J. P.; Rodríguez, J. *Synlett* **1992**, 347.

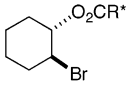
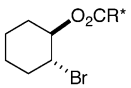
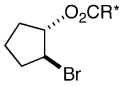
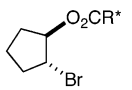
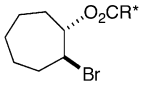
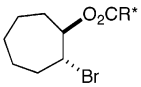
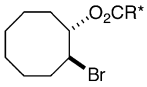
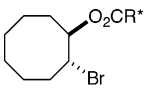
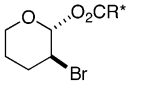
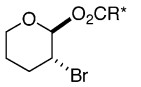
(9) Herb, C.; Dettner, F.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, *13*, 728.

(10) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779.

(11) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; Konig, W. A.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487.

(12) Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389.

TABLE 2. Bromomandelation of Cyclic Alkenes

	Alkene	Secondary Bromomandelates[b]		Yield (%)[a]
1				81
	5a	**6a**	**7a**	
2				84
	5b	**6b**[c]	**7b**[c]	
3				88
	5c	**6c**	**7c**	
4				87
	5d	**6d**	**7d**	
5				55
	5e	**6e**	**7e**	

[a] Yields based on limiting alkene. [b] Relative configurations assigned in analogy to **6a** and **7a**. [c] Diastereomers separated by low temperature differential crystallization.

ficiently in nucleophilic displacement after oxidation to the corresponding ketone **11**. It is particularly noteworthy that these displacements, to give **12** and **13**, led to the enantiomerically pure cis derivatives **8**[13] and **14**,[5,14] not directly available by other means. Indeed, the simple alcohol **8**[13] had not previously been described in an enantiomerically pure form. X-ray analysis of crystalline **9** allowed assignment of the absolute configuration of **7a**.

Conclusion

The route to chiral pool starting materials that we have described here is operationally simple and routinely delivers 99% e.e. products. We expect that it will have broad applications in exploratory synthesis.

Experimental Section

Bromomandelation of Terminal Alkenes: Method A. A mixture of (*S*)-mandelic acid (350 mg, 2.3 mmol) and 2,6-lutidine (278 mg, 2.6 mmol) in dry CH_2Cl_2 (4 mL) was purged with N_2 for 10 min. Alkene (1.00 mmol) was added. After stirring for another 2 min, NBS (267 mg, 1.5 mmol) was added in one portion while the solution was cooled by a water bath. The mixture was kept stirring overnight, then loaded onto a TLC mesh silica gel column and eluted.

Method B. A mixture of (*S*)-mandelic acid (305 mg, 2.0 mmol) and 2,6-lutidine (268 mg, 2.5 mmol) in dry CH_2Cl_2 (4 mL) was purged with N_2 for 10 min. Alkene (4 mmol) was added. After stirring for another 2 min, NBS (178 mg, 1.00 mmol) was added in one portion while the solution was cooled by a water bath. The mixture was kept stirring for overnight, then loaded onto a TLC mesh silica gel column and eluted.

From 342 mg of **1a**, Method A. Ester **3a** (colorless oil, 149 mg, 26%); TLC $R_f = 0.62$ (25% MTBE/petroleum ether); $[\alpha]^{20}_D$ +21.9 ($c = 1.35$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (m, 2H), 1.66 (m, 4H), 3.06 (t, $J = 6.4$ Hz, 2H), 3.24 (m, 2H), 3.35 (d, $J = 6.0$ Hz, 1H), 5.04 (m, 1H), 5.16 (d, $J = 6.0$ Hz, 1H), 7.20−7.38 (m, 12H), 7.43 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 144.4, 138.1, 86.5, 63.0, 33.1, 32.3, 29.6, 21.9; d 128.8, 128.7, 128.7, 127.9, 127.1, 126.7, 74.6, 73.0; IR (cm^{-1}) 3499, 1736, 1597, 1491, 1448, 1182, 1068, 763, 746; HRMS calcd for $C_{33}H_{33}BrNaO_4$ (M + Na): 595.1460, found: 595.1457.

Ester **2a** (colorless oil, 155 mg, 27%); TLC $R_f = 0.54$ (25% MTBE/petroleum ether); $[\alpha]^{20}_D$ +31.3 ($c = 1.20$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (m, 2H), 1.42 (m, 4H), 2.83 (dt, $J =$ 2.0 and 6.4 Hz, 2H), 3.39 (dd, $J = 6.0$ and 11.4 Hz, 2H), 3.47 (dd, $J = 6.0$ and 11.0 Hz, 1H), 5.02 (m, 1H), 5.17 (d, $J = 5.6$ Hz, 1H), 7.20−7.34 (m, 12H), 7.41 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 144.4, 138.3, 86.5, 63.2, 33.5, 32.4, 29.5, 21.3; d 128.8, 128.7, 128.6, 127.9, 127.0, 126.6, 74.6, 73.0; IR (cm^{-1}) 3466, 1737, 1596, 1491, 1448, 1181, 1068, 763, 746; HRMS calcd for $C_{33}H_{33}BrNaO_4$ (M + Na): 595.1460, found: 595.1442.

The primary esters (1:1) were also eluted. TLC $R_f = 0.46$ (25% MTBE/petroleum ether).

From 178 mg of NBS, Method B. Ester **3b** (colorless oil, 79 mg, 23%), TLC $R_f = 0.68$ (30% Et_2O/petroleum ether); $[\alpha]^{20}_D$ +34.7 ($c = 0.95$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28−1.49 (m, 4H), 1.71 (m, 2H), 2.05 (m, 2H), 3.28 (m, 2H), 3.37 (d, $J = 6.0$ Hz, 1H), 4.94−5.10 (m, 3H), 5.20 (d, $J = 6.4$ Hz, 1H), 5.77 (m, 1H), 7.35 (m, 3H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 138.1, 115.0, 33.6, 33.1, 32.4, 28.5, 24.5; d 138.5, 128.7, 128.7, 126.7, 74.7, 73.1; IR (cm^{-1}) 3469, 1737, 1454, 1181, 1067, 912, 732; HRMS calcd for $C_{16}H_{20}BrO_2$ (M − OH): 323.0647, found: 323.0632.

Ester **2b** (white solid, mp 53−54 °C, 89 mg, 26%).; TLC $R_f =$ 0.61 (30% Et_2O/petroleum ether); $[\alpha]^{20}_D$ +66.6 ($c = 0.9$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94 (m, 2H), 1.16 (m, 2H), 1.54 (m, 2H), 1.82 (m, 2H), 3.43 (m, 2H), 3.50 (dd, $J = 4.8$ and 11.2 Hz, 1H), 4.90 (m, 2H), 5.04 (m, 1H), 5.21 (d, $J = 5.6$ Hz, 1H), 5.63(m, 1H), 7.35 (m, 3H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 138.4, 114.8, 33.6, 33.5, 32.4, 28.4, 24.0; d 138.5, 128.7, 126.7, 74.7, 73.0; IR (cm^{-1}) 3438, 1734, 1455, 1203, 1101, 912, 737; HRMS calcd for $C_{16}H_{20}BrO_2$ (M − OH): 323.0647, found: 323.0638. The primary esters (1:1) were also eluted. TLC $R_f = 0.57$ (30% Et_2O/petroleum ether).

Epoxide Formation, Method A. To a solution of diastereo/pure bromomandelate (1 equiv) in methanol (0.1 M) was added K_2CO_3 (5 equiv), and the mixture was stirred at rt for 20 min. When the reaction was complete (monitored by TLC), methanol was removed at reduced pressure, and Et_2O was added. The mixture was filtered with Et_2O, and the combined filtrate was concentrated. The residue was chromatographed to provide enantio-enriched epoxide.

Epoxide **4a**: (Method A, colorless solid, mp 54−55 °C, 63 mg, 92%), from 110 mg of **3a**, TLC $R_f = 0.40$ (10% Et_2O/petroleum ether); $[\alpha]^{20}_D$ −7.2 ($c = 1.0$, $CHCl_3$); enantiomeric excess was measured to be 99.0% by HPLC using a CHIRALDALCEL OD column, eluting at 1 mL/min with 99.0/1.0 hexane/isopropanol, monitored at 250 nm, retention time: 7.75 min (*R*-epoxide), 8.77 min (*S*-epoxide). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45−1.73 (m, 6H), 2.43 (dd, $J = 2.8$ and 4.8 Hz, 1H), 2.72 (dd, $J = 4.0$ and 4.8 Hz, 1H), 2.88 (m, 1H), 3.07 (t, $J = 6.4$ Hz, 2H), 7.20 (m, 3H), 7.29 (m, 6H), 7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 86.5, 63.4, 47.2, 32.5, 29.9, 22.9; d 128.8, 127.8, 127.0, 52.4; IR

(13) Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, *108*, 3718.

(14) For the use of an enantiomerically pure *cis*-2-aminocyclohexanol as an effective ligand for the enantioselective reduction of a ketone, see: Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320.

(cm^{-1}) 1596, 1490, 1448, 1219, 1154, 1076, 1032, 899, 747; HRMS calcd for $C_{25}H_{26}O_2$ (M^+): 358.1933, found: 358.1918.

Synthesis of Epoxide 4a from Ester 2a. A mixture of **2a** (145 mg, 0.25 mmol), KOH (70 mg, 1.25 mmol), and 4-methoxyphenol (155 mg, 1.25 mmol) in dry THF (1.25 mL) in a thick-walled tube was purged with N_2 for 10 min. This tube was sealed and heated to 95 °C for 16 h with magnetic stirring. The cooled mixture was partitioned between ethyl acetate and 5% aqueous NaOH. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the alcohol **9** (colorless oil, 105 mg, 0.22 mmol, 86%). TLC R_f = 0.34 (40% MTBE/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41−1.72 (m, 6H), 2.47 (d, J = 2.4 Hz, 1H), 3.08 (t, J = 6.4 Hz, 2H), 3.71 (s, 3H), 3.86 (dd, J = 2.8 and 9.2 Hz, 1H), 3.93 (m, 1H), 6.81 (s, 4H), 7.20 (m, 3H), 7.27 (t, J = 6.8 Hz, 6H), 7.44 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 152.8, 144.5, 86.4, 73.0, 63.4, 32.9, 30.0, 22.3; d 128.7, 127.8, 126.9, 115.6, 114.8, 70.2, 55.8.

A mixture of alcohol **9** (105 mg, 0.22 mmol), DMAP (3 mg, 0.024 mmol), and Et_3N (67 mg, 0.66 mmol) in dry CH_2Cl_2 was cooled to 0 °C, and mesyl chloride (38 mg, 0.33 mmol) was added in one portion. The solution was kept stirring overnight, then partitioned between water and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the mesylate **10** (white crystals, mp 123−124 °C, 104 mg, 0.19 mmol, 85%), TLC R_f = 0.34 (40% MTBE/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47−1.83 (m, 6H), 3.08 (m, 5H), 3.76 (s, 3H), 4.01 (m, 2H), 4.94 (m, 1H), 6.81 (m, 4H), 7.21 (m, 3H), 7.29 (t, J = 7.2 Hz, 6H), 7.43 (d, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5, 152.2, 144.4, 86.5, 70.1, 63.1, 31.6, 29.7, 21.9; d 128.8, 127.9, 127.0, 115.6, 115.0, 81.7, 55.8, 38.8.

The mixture of mesylate **10** (104 mg, 0.19 mmol) in THF/H_2O (4:1, 1.25 mL) was cooled to −5 °C, and ammonium cerium nitrate (312 mg, 0.57 mmol) was added in one portion. The reaction was monitored by TLC, and after 30 min, the reaction mixture was partitioned between water and ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was redissolved in MeOH (2 mL), and K_2CO_3 (105 mg, 0.76 mmol) was added in one portion. After 20 min, the reaction was complete (monitored by TLC). Methanol was removed at reduced pressure, and the residue was filtered with Et_2O. The combined filtrate was concentrated, and the residue was chromatographed to provide enantioenriched expoxide **4a** (58 mg, 0.16 mmol, 88%; overall yield from **2a** was 64%). The enantiomeric excess was measured to be 99.0% under the conditions outlined previously.

Epoxide Formation, Method B. To a solution of diastereo/pure bromomandelate (1 equiv) in dry Et_2O (0.1 M) was added KOH pellets (4 equiv), and the mixture was stirred for 2−3.5 h (monitored by TLC). When the reaction was complete, the reaction mixture was filtrated with Et_2O. The filtrate was concentrated, and the residue was distilled bulb-to-bulb (pot = 110−130 °C, 150 mmHg) to give the epoxide as a clear oil.

Epoxide **4b** (Method B, colorless oil, 205 mg, 89%), from 625 mg of **3b**, TLC R_f = 0.71 (25% Et_2O/petroleum ether); $[\alpha]^{20}_D$ −9.9 (c = 1.3, $CHCl_3$), lit $[\alpha]^{20}_D$ −10.1 (c = 1.50, CH_2Cl_2). Data identical with those reported.[8]

Bromomandelation of Cyclic Alkenes. A mixture of (*S*)-mandelic acid (609 mg, 4.0 mmol), 2,6-lutidine (535 mg, 5.0 mmol), and alkene (2.0 mmol) in dry CH_2Cl_2 (6 mL) was stirred for 10 min. NBS (356 mg, 2.0 mmol) was added in one portion while the solution was cooled by a water bath. The mixture was stirred overnight, added to a TLC mesh silica gel column, and eluted.

From 164 mg of **5a**. Ester **7a** (colorless oil, 250 mg, 40%), TLC R_f = 0.51 (30% Et_2O/petroleum ether); $[\alpha]^{20}_D$ +14.7 (c = 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (m, 3H), 1.62 (m, 2H), 1.90 (m, 2H), 2.34 (m, 1H), 3.42 (d, J = 5.6 Hz, 1H), 3.96 (m, 1H), 4.96 (dt, J = 4.4 and 9.6 Hz, 1H), 5.22 (d, J = 5.2 Hz, 1H), 7.34 (m, 3H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 138.4, 35.6, 30.7, 25.4, 23.1; d 128.7, 128.6, 126.8, 77.9, 73.0, 52.1; IR (cm^{-1}) 3447, 1732, 1453, 1186, 1067, 734; HRMS calcd for $C_{14}H_{17}O_3$ (M − Br): 233.1178, found: 233.1188.

Ester **6a** (white solid, mp 88−89 °C, 259 mg, 41%); TLC R_f = 0.40 (30% Et_2O/petroleum ether); $[\alpha]^{20}_D$ +126.1 (c = 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (m, 1H), 1.45 (m, 2H), 1.72 (m, 3H), 2.15 (m, 2H), 3.42 (d, J = 5.6 Hz, 1H), 3.82 (dt, J = 4.4 and 8.8 Hz, 1H), 4.93 (m, 1H), 5.18 (d, J = 5.6 Hz, 1H), 7.34 (m, 3H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 138.1, 35.1, 30.7, 25.0, 23.1; d 128.6, 128.6, 126.9, 77.7, 73.2, 51.4; IR (cm^{-1}) 3435, 1733, 1451, 1182, 1067, 733; HRMS calcd for $C_{14}H_{17}O_3$ (M − Br): 233.1178, found: 233.1179.

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Supporting Information Available: Experimental details, spectra for all new compounds, and CIF file for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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