Single Enantiomer Epoxides by Bromomandelation of Prochiral Alkenes

Douglass F. Taber* and Jiang-lin Liang
Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716
Taberdf@udel.edu
Received September 1, 2006

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 epoxidation1a and asymmetric dihydroxylation1b are workhorses of modern organic synthesis. More recently, Jacobsen epoxidation2a and Shi epoxidation2b 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 opening4 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.

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 diastereomeric bromoesters. The known6 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

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
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 haloalkylation, intermolecular alkene bromoesterification had not been developed as a synthetic method. 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 Rf 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 1H 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 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.

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 1H 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 crystallization (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 Rf values (isolated yields): 7a 0.51 (40%) and 6a 0.40 (41%)]. Consistently, the 1H NMR chemical shifts of the brominated methines of 7a–7e were downfield (δ 0.13 to δ 0.33) from the 1H 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-

---

**TABLE 1. Bromomandelation of Terminal Alkenes**

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Bromomandelates (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Epoxide (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1b</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1c</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1d</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1e</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>2 OTr, 3 OTr&lt;sup&gt;*&lt;/sup&gt;</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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. <sup>b</sup> Yield of epoxide from diastereomer 3 of bromomandelate. <sup>c</sup> NBS was the limiting reagent. 

---

TABLE 2. Bromomandelation of Cyclic Alkenes

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Secondary Bromomandelates</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>6a</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6e</td>
<td>55</td>
</tr>
</tbody>
</table>

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

Consequence

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 (305 mg, 2.0 mmol) and 2,6-lutidine (268 mg, 2.5 mmol) in dry CH₂Cl₂ (4 mL) was purged with N₂ for 10 min. Alkene (4 mmol) was added. After stirring for stilling 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 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 Rf = 0.62 (25% MTBE/petroleum ether); [α]<sub>D</sub> +21.9 (c = 1.35, CHCl₃); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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, 127.9, 127.1, 126.7, 74.6, 73.0; IR (cm⁻¹) 3499, 1736, 1597, 1491, 1448, 1182, 1068, 763, 746; HRMS calcld for C₁₅H₂₁BrNaO (M + Na): 595.1460, found: 595.1457.

Ester 2a (colorless oil, 155 mg, 27%); TLC Rf = 0.54 (25% MTBE/petroleum ether); [α]<sub>D</sub> +31.3 (c = 1.20, CHCl₃); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 100 MHz): δ 173.4, 144.4, 138.3, 86.5, 63.2, 33.5, 32.4, 29.5, 21.8, 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 calcld for C₁₅H₂₁BrNaO (M + Na): 595.1460, found: 595.1442.

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

From 178 mg of NBS, Method B. Ester 3b (colorless oil, 79 mg, 23%); TLC Rf = 0.68 (30% EtO/petroleum ether); [α]<sub>D</sub> +34.7 (c = 0.95, CHCl₃); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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, 1203, 1101, 1067, 912, 732; HRMS calcld for C₁₅H₂₁BrO₂ (M + OH): 323.0647, found: 323.0632.

Ester 2b (white solid, mp 53–54 °C, 89 mg, 26%); TLC Rf = 0.61 (30% EtO/petroleum ether); [α]<sub>D</sub> +66.6 (c = 0.93, CHCl₃); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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 calcld for C₁₅H₂₀BrO₂ (M + OH): 323.0647, found: 323.0638. The primary esters (1:1) were also eluted. TLC Rf = 0.57 (30% EtO/petroleum ether).

Epoxide Formation, Method A. To a solution of diastereopure bromomandelate (1 equiv) in methanol (0.1 M) was added K₂CO₃ (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 Et₂O was added. The mixture was filtered with Et₂O, 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 Rf = 0.40 (10% EtO/petroleum ether); [α]<sub>D</sub> +7.2 (c = 1.0, CHCl₃); enantiomeric excess was measured to be 99% by HPLC using a CHIRALDICAL C₁₅ column, eluting at 1 ml/min with 99:0.1 hexane/isopropanol, monitored at 250 nm, retention time: 7.75 min (R-epoxide), 8.77 min (S-epoxide). 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 100 MHz): δ 144.5, 86.5, 63.4, 47.2, 32.5, 29.9, 22.9; d 128.8, 128.7, 127.0, 52.4; IR

Hz, 6H); 13 C NMR (CDCl3, 100 MHz): δ 141.1–1.72 (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, 1H), 7.44 (d, J = 7.2 Hz, 6H); 13 C NMR (CDCl3, 100 MHz): δ 154.1, 152.8, 144.5, 86.4, 73.0, 63.4, 32.9, 30.0, 22.3; δ 128.7, 127.8, 126.9, 115.0, 81.7, 55.8, 38.8. A mixture of alcohol 9 (105 mg, 0.22 mmol), DMAP (3 mg, 0.024 mmol), and Et3N (67 mg, 0.66 mmol) in dry CH2Cl2 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 CH2Cl2. The combined organic extract was dried (Na2SO4) and concentrated. The residue was chromatographed to give the mesylate 10 (white crystals, mp 123–124 °C, 104 mg, 0.19 mmol, 85%), TLC Rf = 0.34 (40% MTBE/petroleum ether); 1H NMR (CDCl3, 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 (CDCl3, 100 MHz): δ 154.5, 152.2, 144.4, 86.5, 70.1, 63.1, 31.6, 29.7, 21.9; δ 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/H2O (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 (Na2SO4) and concentrated. The residue was redissolved in MeOH (2 mL), and K2CO3 (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 Et2O. The combined filtrate was concentrated, and the residue was chromatographed to give enantioenriched epoxide 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 Et2O (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 filtered with Et2O. 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 Rf = 0.71 (25% Et2O/petroleum ether); [α]20D +9.9 (c = 1.3, CHCl3), lit [α]20D −10.1 (c = 1.50, CH2Cl2). 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 CH2Cl2 (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 64 mg of 5a. Ester 7a (colorless oil, 250 mg, 40%), TLC Rf = 0.51 (30% Et2O/petroleum ether); [α]20D +14.7 (c = 1.65, CHCl3); 1H NMR (CDCl3, 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 (CDCl3, 100 MHz): δ 172.9, 138.4, 35.6, 30.7, 25.4, 23.1; δ 128.7, 128.6, 126.8, 77.9, 73.0, 52.1; IR (cm⁻¹) 3447, 1732, 1453, 1186, 1067, 734; HRMS calcd for C17H17O4 (M – Br): 233.1178, found: 233.1188.

Ester 6a (white solid, mp 88–89 °C, 259 mg, 41%); TLC Rf = 0.40 (30% Et2O/petroleum ether); [α]20D +126.1 (c = 1.65, CHCl3); 1H NMR (CDCl3, 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 (CDCl3, 100 MHz): δ 172.9, 138.1, 35.1, 30.7, 25.0, 23.1; δ 128.6, 128.6, 126.9, 77.7, 73.2, 51.4; IR (cm⁻¹) 3435, 1733, 1451, 1182, 1067, 733; HRMS calcd for C12H12O3 (M – Br): 220.0583, found: 220.0582.

**Acknowledgment.** This work was supported by the National Institutes of Health (GM 60287). We thank Andrea J. Passarelli for a crucial experiment.

**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.

**JO061818R**