Supporting Information

Design, Development and Scale-Up of a Selective *meso*-Epoxide Desymmetrization Process

David L. Varie, Christopher Beck, Sandra K. Borders, Molly D. Brady, Jason S. Cronin, Tracy K. Ditsworth, David A. Hay, David W. Hoard, Richard C. Hoying, Ryan J. Linder, Richard D. Miller, Eric D. Moher, Jacob R. Remacle, John A. Rieck III*

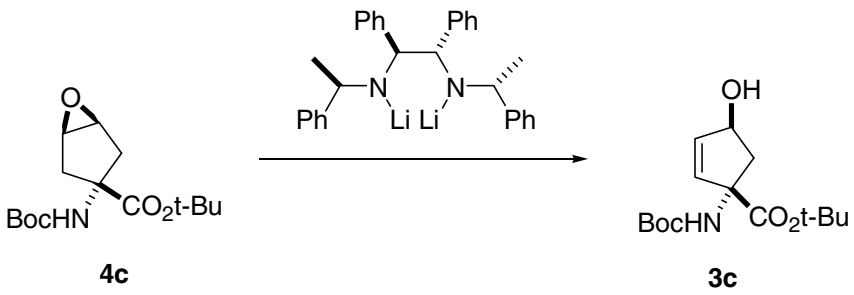
Chemical Product Research and Development, Eli Lilly and Co., Indianapolis, IN 46285

David D. Anderson, Paul N. Dodson, Mindy B. Forst, Duane A. Pierson, Joseph A. Turpin

Analytical Sciences Research and Development, Eli Lilly and Co., Indianapolis, IN 46285

Isolation and spectroscopic data for epoxide **4c**. Epoxide **4c** was isolated from the mother liquor of a **4b** crystallization by chromatography on silica gel with 2:1:1 hexanes/MTBE/CH_2Cl_2 eluent (R_f **4b** = 0.61; R_f **4c** = 0.39) as a white solid, mp 135-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ3.59 (s, 1H), 2.83 (d, J = 14.9 Hz, 2H), 2.10 (m, 2H),1.50 (s, 9H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 154.5, 81.5, 79.9, 64.5, 56.7, 38.6, 28.3, 27.8.

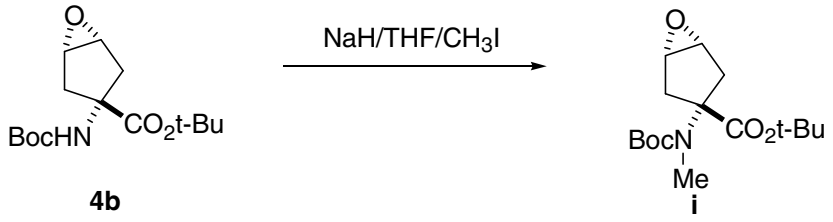
Preparation of alcohol **3c**.



4c **3c**

Diamine **13** (617 mg, 1.47 mmol) was dissolved in 5 mL dry THF under N_2 and cooled to -10 °C. *n*-BuLi (1.6 M in hexanes, 1.85 mL, 2.96 mmol) was added dropwise. The red solution was stirred for 45 min. A solution of epoxide **4c** (209 mg, 0.70 mmol) in 3 mL of THF was added via syringe. The reaction was stirred at 0 °C for 18 h, diluted with 10 mL of MTBE and quenched with 5 mL of 1N HCl. The mixture was allowed to warm to room temperature and filtered to remove the HCl salt of diamine **13**. The filter cake was washed with 10 mL MTBE and the layers of the filtrate were separated. The organic layer was washed with saturated NaCl solution, dried with Na_2SO_4 and concentrated to yield 366 mg of an oil containing alcohol **3c** and diamine **13**. The oil was purified by flash chromatography on silica gel (eluent 1:1:1 hexanes:MTBE:CH_2Cl_2) to provide 75 mg (36% yield) of alcohol **3c** as a colorless oil, which crystallized on standing. Chiral HPLC assay: 61.8% ee. (Chiralpak OD; 90:10 hexane:i-PrOH; 1 mL/min; 210 nm; major enantiomer t_R = 7.4 min; minor enantiomer t_R = 6.5 min.) ^{1}H NMR (500 MHz, $CDCl_3$) δ6.21 (m, 1H), 5.81 (m, 1H), 5.32 (bs, 1H), 4.87 (m, 1H), 2.96 (bs, 1H - OH), 2.60 (d, *J* = 14.3, Hz, 1H), 2.35 (m, 1H), 1.51 (s, 9H), 1.48 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.1, 154.7, 138.9, 134.0, 83.0, 79.9, 76.0, 70.7, 45.4, 28.3, 27.8.

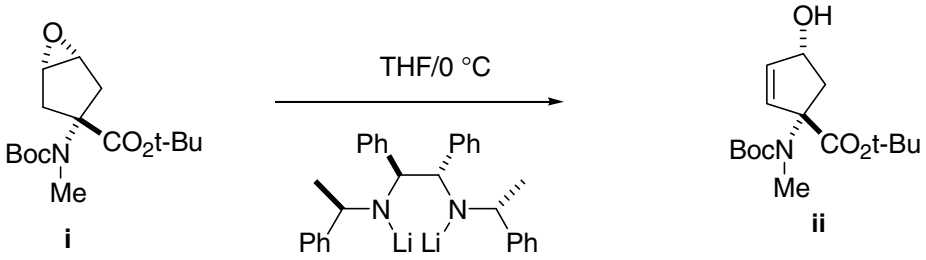
Preparation of *N*-Methyl-*N*-BOC epoxide **i.**



4b **i**

NaH (60 wt % in oil, 0.96 g, 40 mmol) was stirred in 20 mL dry THF under N_2 and then allowed to stand. THF was removed via syringe and 20 mL of new THF was added. Epoxide **4b** (6.00 g, 20 mmol) in 15 mL THF was added to the NaH slurry at -78 °C. The cooling bath was removed and the reaction mixture was stirred 1.5 h at 22 °C. A solution of CH_3I (12.48 mL, 200 mmol) in 20 mL THF was added and the reaction mixture was heated 40 °C for 3 h. The reaction mixture was cooled to 0 °C and 30 mL of cold 1 N HCl solution was added dropwise. The mixture was diluted with 50 mL MTBE and the layers were separated. The aqueous layer was extracted with 3 x 25 mL MTBE. The combined organic layers were washed with 3 x 25 mL saturated NaCl solution, dried (Na_2SO_4) and concentrated under vacuum to give 5.99 g (95% yield) of epoxide **i**, as a waxy solid, which was used without further purification. Purification of a sample on silica gel (2:1 hexanes MTBE) gave a white solid, mp 77-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 2H), 2.90 and 2.86 (broad singlets, 3H, *N*-Me rotamers), (s, 2H), 2.45 (AB quartet, J = 16 Hz, 4H), 1.42 (s, 9H), 1.39 (s, 9H). ^{1}H NMR (100 MHz, $CDCl_3$) δ 173.0 (quat.), 155.7 (quat.), 80.6 (quat.), 79.7 (quat.), 68.1 (quat.), 56.4 (2 x CH), 38.7, (CH_2), 37.5 (CH_2), 31.2 (CH_3), 28.4 (CH_3), 27.7 (CH_3). MS (ES): *m/z* 214 (*M*-BOC + H).

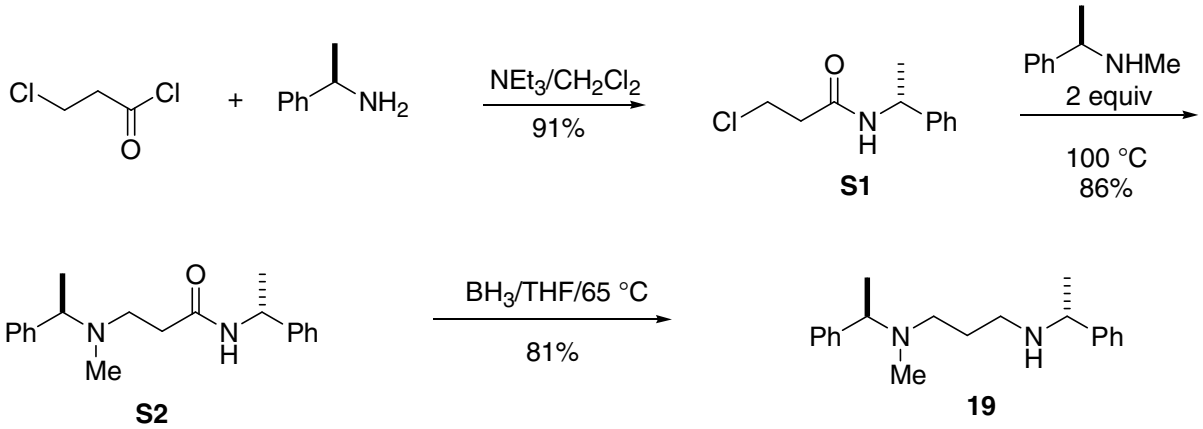
Rearrangement of epoxide **i** to alcohol **ii**.



i diLi-**13** (1.2 equiv) **ii**

Diamine **13** (1.61 g, 3.82 mmol) was dissolved in 10 mL dry THF under N_2. The solution was cooled to -10 °C and *n*-BuLi (1.6 M in hexanes, 4.78 mL, 7.66 mmol) was added via syringe. The solution was stirred 45 min at 0 °C. A solution of epoxide i (1.00 g, 3.19 mmol) in 10 mL THF was added over 20 min and the reaction mixture was stirred for 5 h at 0 °C. The reaction mixture was then added to a solution of 25 mL 1N HCl and 30 mL water at 0 °C. The mixture was extracted with 3 x 25 mL MTBE. The combined organic layers were washed with 2 x 25 mL 1 N HCl, followed by 25 mL saturated NaCl solution, dried (Na_2SO_4), and concentrated under vacuum to obtain 0.99 g of an oil, containing the desired product and residual diamine **13**. The oil was chromatographed on silica gel (eluent 1:1 hexanes:MTBE, R_f of **ii** = 0.22) to yield 0.54 g (54% yield) of alcohol **ii** as a colorless oil. Chrial HPLC assay: 85.1% ee. (Assay conditions: Chiralpak AD column at 30 °C; 7% IPA/hexane with 0.1% diethylamine; 1 mL/min; 210 nm.). t_R = 9.2 and 8.5 min for major and minor enantiomer, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 5.2, 2 Hz, 1H), 5.82 (d, *J* = 5 Hz), 4.93 (bs, 1H), 3.53 (dd, *J* = 13.6, 6.8 Hz), 2.91 (s, 3H), 2.00 (bs, 1H, -OH), 1.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.1, 139.1, 131.8, 81.2, 75.4, 47.0, 45.0, 31.3, 28.4, 27.9.

Scheme S1. Preparation of diamine ***(R,R)*-19**

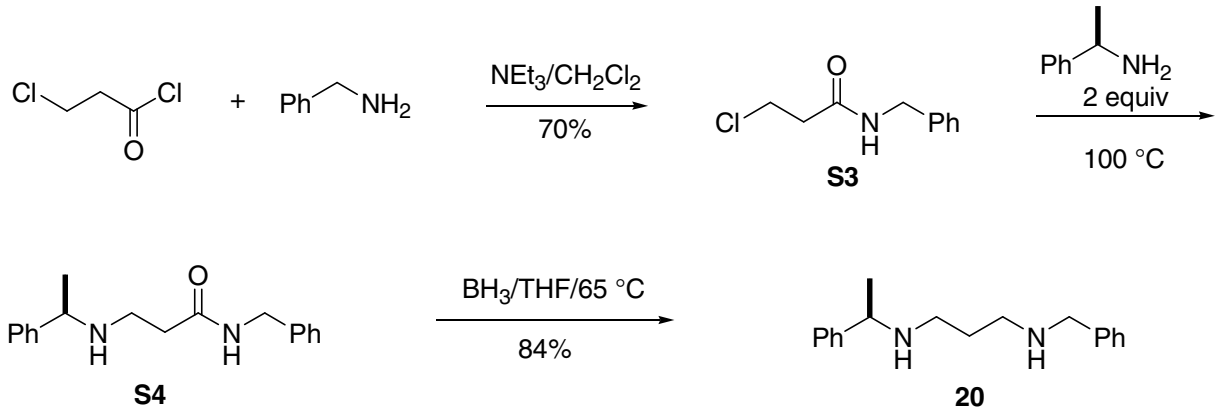


Diamine ***(RR)*-19** was prepared as shown in Scheme S1 and purified by Kugelrohr distillation (140-50 °C, 0.3 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.2 (m, 10H), 3.71 (q, *J* = 6.4 Hz, 1H), 3.52 (q, *J*

= 6.9 Hz, 1H), 2.51 (m, 1H), 2.40 (m, 2H), 2.28 (m, 1H), 1.63 (m, 2H), 2.16 (s, 3H), 1.33 (overlapping doublets, 6H).

Diamine ***(R)*-20** was prepared as shown in Scheme S2 and was purified by Kugelrohr distillation (110-125 °C, o.15 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.2 (m, 10H), 3.76 (s, 2H), 3.74 (q, *J* = 6.6 Hz, 1H), 2.65 (m, 2H), 2.56 (m, 1H), 2.46 (m, 1H), 1.66 (m, 2H), 1.47 (m, 1H), 1.34 (d, *J* = 6.6 Hz, 6H).

Scheme S2. Preparation of diamine ***(R)*-20**



Diamine ***(R,R)*-21** was prepared as shown in Scheme S3 and purified by Kugelrohr distillation (195 °C, 0.1 mm Hg). NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 8H), 7.23 (m, 2H), 3.76 (s, 2H), 3.67 (q, *J* = 6.6 Hz, 2H), 2.32 (m, 2H), 2.23 (m, 2H), 1.7 (m, 1H), 1.33 (bs, 1H), 1.33 (d, *J* = 6.5 Hz, 6H), 0.86 (s, 6H).

Scheme S3. Preparation of diamine (***R,R*)-21**