Asymmetric Synthesis of CDP840 by Jacobsen Epoxidation. An Unusual Syn Selective Reduction of an Epoxide

J. E. Lynch,* W.-B. Choi, H. R. O. Churchill, R. P. Volante, R. A. Reamer, and R. G. Ball†

Department of Process Research and Department of Molecular Design and Diversity, Merck Research Laboratories, PO Box 2000, Rahway, New Jersey 07065

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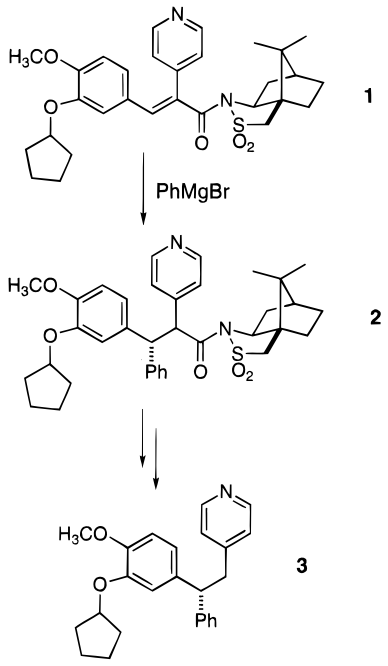
An asymmetric synthesis of the PDE IV inhibitor, CDP840 (**3**) is reported. The absolute stereochemistry was controlled by a Jacobsen epoxidation of the *Z* triaryl olefin **8** (89% ee) or the *E* triaryl olefin **9** (48% ee). The disparate results in stereocontrol were interpreted in terms of the "skewed side-on approach model" proposed by Jacobsen. $LiBH_4 \cdot BH_3$ reduction of the epoxides was found to proceed with retention of configuration.

The phosphodiesterases (PDE) are a family of enzymes in which at least five different isozymes have been characterized. These isozymes are distinct in their cellular distribution and also in their affinity for cyclic AMP and cyclic GMP. The discovery of isozyme-selective inhibitors has facilitated the elucidation of the separate roles each isotype plays in cellular function. PDE IV in particular is believed to be the dominant isozyme present in inflammatory cells and in airway smooth muscle. Inhibition of PDE IV leads to an increase in the concentration of cAMP resulting in suppression of a broad range of cellular function in inflammatory cells.[1] This has generated a great deal of interest in selective PDE IV inhibitors as potential antiasthmatic agents.

We wish to report an asymmetric synthesis of CDP840 (**3**), a selective inhibitor of PDE IV.[2] **3** has previously been obtained in enantiomerically pure form by the 1,4 addition of phenylmagnesium bromide to the chiral diarylacrylate **1** (Scheme 1) or by additions to other chiral Michael acceptors.[3]

We were interested in probing other synthetic routes that did not require the use of a stoichiometric, covalently bound chiral auxiliary. The Jacobsen epoxidation of olefin **8** or **9** seemed an attractive possibility.[4] Although this introduces two carbon−oxygen bonds where we require two carbon−hydrogen bonds, the well precedented stereocontrol of the oxidation and the general ease of benzylic C−O bond hydrogenolysis attenuated our concern about the circuitousness of this strategy. Mixtures of *E* and *Z* olefins were prepared in a straightforward manner as shown in Scheme 2.

Scheme 1



Grignard addition to aldehyde **4** followed by oxidation[5] and picoline addition gave carbinol **7**. Dehydration of **7** gave variable ratios of *Z* and *E* olefin isomers, depending on solvent. When the elimination was performed in toluene a 4:1 ratio (**9**:**8**) was obtained; when the elimination was performed in THF a 2.5:1 ratio was obtained. The olefins, **8** and **9**, were efficiently separated by fractional crystallization. Crystallization of the mixture of methanesulfonic acid salts gave pure *E* olefin **9** (MSA salt), 70% from the toluene elimination; treatment of the mother liquors with aqueous NaOH followed by crystallization of the resulting free base from ethyl acetate gave the pure *Z* olefin (26% from the THF elimination). The configuration of each olefin was determined by ^{1}H NOE difference experiments. The olefin isomers were readily interconvertible under strongly acidic conditions (12 N HCl) and in principle a process to convert the mixture to

† Department of Molecular Design and Diversity.

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(2) Celltech Therapeutics Ltd, US Patent No. 5,608,070.

(3) (a) Celltech Therapeutics Ltd, US Patent No. 5,622,977. (b) Use of the acrylamide with *cis*-2-aminoindanolacetonide as the Michael acceptor, Choi, W.-B; Churchill, H.; Lynch, J. E. Unpublished results. Use of a vinyl phenyl sulfoxide as the chiral Michael acceptor, Houpis, I.; Molina, A.; Dorsiotis, I.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 7131.

(4) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.

(5) Murahashi, S.−I.; Naota, T. *Adv. in Metal-Org. Chem.* **1994**, *3*, 225 and refs therein. Tanaka, M.; Kobayashi, T.; Sakakura, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 518. Agarwal, D. D.; Jain, R.; Sangha, P.; Rastogi, R. *Indian J. Chem.* **1993**, *32B*, 381. Miller, R. A.; Li, W.; Humphrey, G. *R. Tetrahedron Lett.* **1996**, *37*, 3429.

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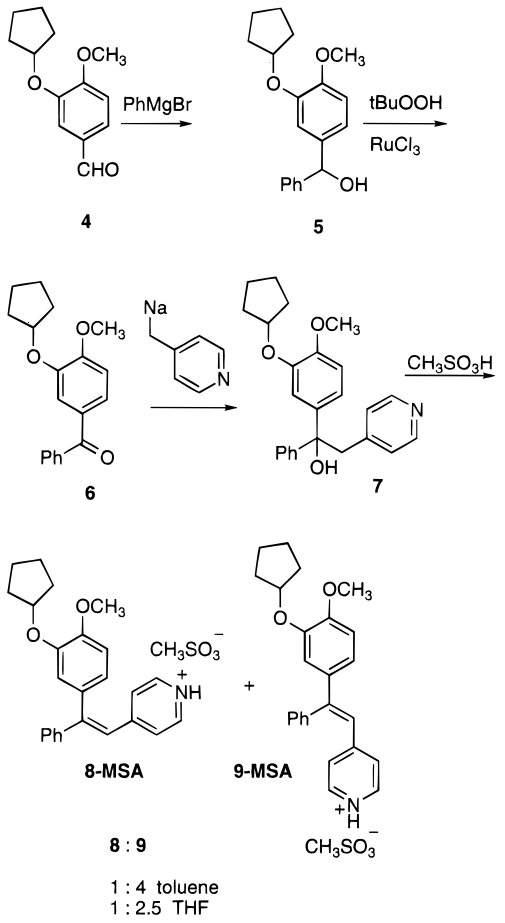
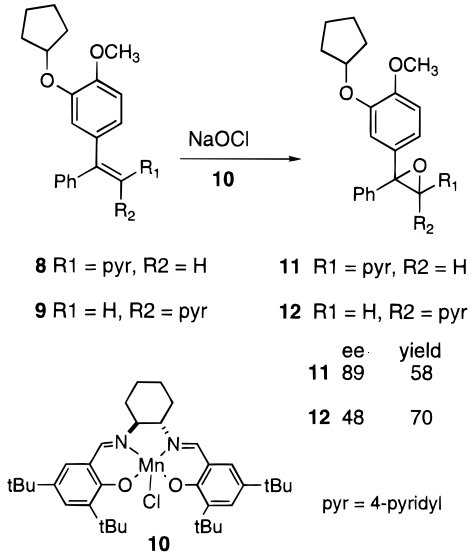
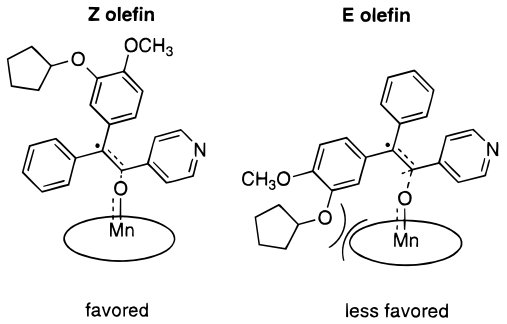
Scheme 2



Scheme 3



Scheme 4



a single isomer could be developed; however, such a process was not reduced to practice.[6]

Jacobsen epoxidation reactions of both **8** and **9** (free bases) were stereospecific i.e., the *Z* olefin gave only the syn epoxide and the *E* olefin gave only the anti epoxide (the relative configurations of each epoxide were likewise determined by ^{1}H NOE difference measurements). Treatment of **8** and **9** with NaOCl solution in the presence of *S,S* salen Mn(III) complex **10** (1 mol %) and 4-(3-phenylpropyl)pyridine *N*-oxide[7] at −10 °C to 0 °C provided the epoxides **11** and **12**, respectively. Although somewhat sensitive to silica gel, the purified epoxides were isolated by flash chromatography. The enantiomers of **11** and **12** were each prepared by the same method using the *R,R* salen complex. Chiral HPLC showed a 94.5:5.5 ratio of enantiomers in the case of **11** (89% ee) and 48% ee in the case of **12**. In addition to showing a lesser degree of stereoselectivity, epoxidation of **9** also proceeded more slowly compared to epoxidation of **8**; after 3 h reaction time HPLC showed 80% conversion of **8** versus only 10% conversion of **9** under identical conditions.

The disparate results in asymmetric induction can be understood in terms of the "skewed side-on approach" model proposed by Jacobsen (Scheme 4).[4] In this model that face of the olefin which can avoid severe steric interactions with the catalyst ligand approaches the catalyst in a skewed manner such that interactions with the disubstituted end of the double bond are minimized. In the case of the *E* olefin the additional steric hindrance of the large cyclopentyloxy substituent in the "favored" approach raises the activation energy of this transition state and results in both lower enantioselectivity and also the observed slower rate of reaction.

Attempted hydrogenolyses of the epoxides with Ni(Ra)[8] were nonselective giving complex mixtures of products. However, a 1:1 mixture of $LiBH_4$ and BH_3−THF cleanly reduced epoxide **11** at the more substituted carbon providing the alcohol **13** as the pyridine borane complex.[9] It was found that crystallization of **13** from hexane: ethyl acetate (8:3) improved the enantiomeric purity to >99% ee (46% yield from **11**). Treatment of **12** under identical conditions produced the corresponding pyridine complex of alcohol **14** as the major product, however, in much lower yield (Scheme 5). HPLC analysis of the crude reduction mixtures showed that **11** was reduced with 66:1 selectivity (**13**:*ent*-**14**) and **12** was reduced with 8:1 selectivity (**14**:*ent*-**13**). Heating **13** or **14** in 4:1 toluene:

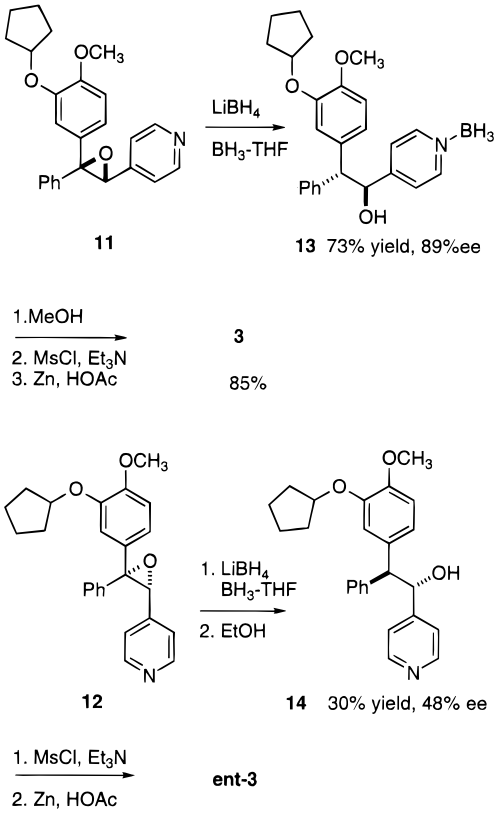
(6) Dissolution of either pure olefin in 12 N HCl leads to a rapid equilibration to ~60:40 mixture of the two olefins (~30 min, 22 °C).

(7) Senanayake, C.; Smith, G. B.; Ryan, K. M.; Fredenburg, L.; Liu, J.; Roberts, F. E.; Hughes, D. L., Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 3271.

(8) King, S. B.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 5611. Cope, A. C.; McKervey, M. A.; Weinshenker, N. M.; Kinnel, R. B. *J. Org. Chem.* **1970**, *35*, 2918. Roberts, R. M.; Bantel, K. H.; Low, C. E. *J. Org. Chem.* **1973**, *38*, 1903.

(9) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1968**, *90*, 2686. Other methods for reduction of epoxides at the more substituted carbon have also been reported. Hutchins, R. O.; Taffer, I. M.; Burgoyne, W., *J. Org. Chem.* **1981**, *46*, 5214. Ranu, B. C.; Das, A. R. *J. Chem. Soc., Chem Commun.* **1990**, 1334. Guanti, G., Banfi, L.; Merlo, V.; Narisano, E. *Tetrahedron* **1994**, *50*, 2219. Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004. Taber, D. F.; Louey, J. P. *Tetrahedron* **1995**, *51*, 4495 and refs therein.

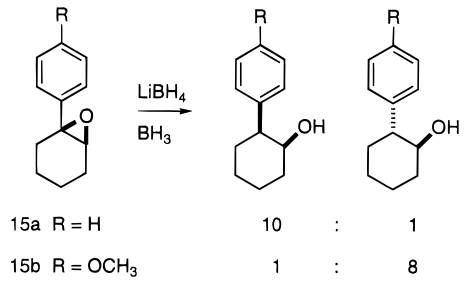
Scheme 5



MeOH or in ethanol at reflux for 2 h followed by vacuum concentration provided the free hydroxypyridines. Chiral HPLC showed no loss in enantiomeric purity when compared to the starting epoxides.

The final deoxygenation was accomplished by one-pot mesylation (Et_3N, MsCl) followed by Zn/acetic acid reduction, providing CDP840 in 85% yield. We were surprised to find that the enantiomer of **13** which was prepared using the *R,R* salen complex ultimately gave the undesired enantiomer of CDP840, and that the isomer generated with the *S,S* catalyst had the necessary configuration to give CDP840. We had incorrectly predicted the opposite result based on the Jacobsen model for the epoxidation and that the borane/borohydride reduction would proceed with inversion of stereochemistry at the reacting center. At the time it was not clear which of these assumptions was incorrect. However, recrystallization of **13** from ethanol provided a crystal suitable for X-ray analysis[17] which allowed assignment of the relative stereochemistry of the two chiral centers. This result coupled with NOE determination of the epoxide structure proved that the reduction had proceeded with retention of configuration! Brown has reported that reduction of 1-phenylcyclopentene oxide with BH_3−THF and BF_3 gave predominantly *trans*-2-phenylcyclopentanol (an apparent syn reduction).[10] However, the use of the strong acid, BF_3, is likely to lead to rearrangement of the epoxide to 2-phenylcyclopentanone and Brown reports that, indeed, reduction of this ketone gave the same ratio of *cis*- and *trans*-2-phenylcyclopentanols (1:4.6) as obtained by reduction of the epoxide.[10] The reductions of **11** and **12** reported here cannot proceed via a ketone intermediate since both epoxides would give the same ketone and on reduction would necessarily give the same diastereomeric ratio of products.

Scheme 6



Some solvolysis reactions of phenyl-substituted epoxides, and particularly of 4-methoxyphenyl-substituted epoxides are known to occur predominantly with retention of configuration (syn substitution).[11,12] To our knowledge this is the first documented case of a hydride reduction of an epoxide with retention of configuration.[13] We thus chose to investigate the reduction of other phenyl substituted epoxides under identical conditions as used for **11** and **12** (Scheme 5). In contrast to **11** and **12**, reduction of phenylcyclohexene oxide (**15a**) by this method did not occur at −20 °C, even after 5 h. After an overnight age at ambient temperature HPLC analysis showed 74% of *cis*-2-phenylcyclohexanol (the result of inversion). Inspection of the crude ^1H NMR spectrum revealed about a 10:1 ratio of cis:trans isomers (Scheme 6). Reduction of 4-methoxyphenylcyclohexene oxide (**15b**),[12] however, was rapid at −20 °C. HPLC showed two major products in an 8:1 ratio. After the usual aqueous workup, ^1H NMR confirmed the major isomer was in fact the *trans*-cyclohexanol,[14] the product of retention of configuration.

Based on previous reports on the "syn" substitution of epoxides and on the dramatic difference in the rate of reduction of **15a** vs **11**, **12**, and **15b**, it is likely that a carbonium ion intermediate is involved in the reductions with retention of configuration. Apparently, the additional stability provided by the *p*-methoxy group is required to make the carbonium ion accessible under these conditions. One can invoke alkoxide delivery of the reducing agent as an explanation for the observed syn selectivity. However, it is not clear what species delivers the hydride; borohydride and borane are known to react reversibly to form a diborohydride ($B_2H_7^-$) in diglyme.[15] It is possible this species may be involved in the reaction, although free borane is more Lewis acidic and would more easily lead to carbonium ion formation. Control experiments showed the reduction requires both BH_3 and $LiBH_4$, no reaction was observed with the latter alone and although a slow reaction with BH_3 alone occurred, it did not produce the same products.

In summary, a catalytic asymmetric synthesis of CDP840 has been demonstrated. The results of the

(10) Brown, H. C.; Yoon, N. M. *Chem. Commun.* **1968**, 1549.

(11) Battistini, C.; Balsamo, A.; Berti, G.; Crotti, P.; Macchia, B.; Macchia, F. *J. Chem. Soc., Chem. Commun.* **1974**, 712. Imuta, M.; Ziffer, H. *J. Am. Chem. Soc.* **1979**, *101*, 3990.

(12) Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1973**, *29*, 2183.

(13) Reductions of chiral benzylic alcohols with Raney Ni are known to proceed with retention of configuration in some cases. See ref 8.

(14) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607.

(15) Brown, H. C.; Tierney, P. A. *J. Am. Chem. Soc.* **1958**, *80*, 1552. Brown, H. C.; Stehle, P. F.; Tierney, P. A. *J. Am. Chem. Soc.* **1957**, *79*, 2020. Duke, B. J.; Howarth, O. W.; Kenworth, J. G. *Nature* **1964,** *202*, 81.

Jacobsen epoxidation of olefins **8** and **9** are in accord with the "skewed side-on approach" model both in terms of the direction and degree of asymmetric induction and the relative rate of reaction. A highly selective hydride reduction of an epoxide with retention of configuration has been documented.

Experimental Section

General. Solvents and reagents were used as received from the vendor. "Dry" refers to solvents stored over 3A molecular sieves for at least 16 h prior to use. HPLC analysis were performed on a Zorbax C8-RX column (250 × 4.6 mm) eluting with CH_3CN and 0.1% aqueous H_3PO_4 mixtures in proportions such that the desired analyte was eluted in 3−15 min with UV detection at 210 nm. NMR and IR spectra were recorded in $CDCl_3$ solution unless otherwise specified.

α-[3-(Cyclopentyloxy)-4-methoxyphenyl]benzenemethanol, 5. Isovanillin (100 g, 0.65 mol) and potassium carbonate (138.2 g, 1.12 mol) were added to DMF (600 mL) portionwise at rT. The mixture was heated to 60 °C, and cyclopentyl bromide (112 mL, 1.12 mol) was added over 30 min at 60 °C. The mixture was aged at 60 °C for 14 h. The mixture was cooled to rT, and water (600 mL) was added in one portion. The solution was stirred for 30 min. The mixture was extracted twice with toluene (800, 400 mL). The combined organic layers were washed with a dilute HCl aqueous solution (0.2 N, 800 mL) and with water (2 × 600 mL). The organic layer was concentrated to 1 L in volume. To the above toluene solution was added phenylmagnesium bromide solution in ether (230 mL, 3 M) at −10 °C, and the mixture was aged for 30 min below 0 °C. Aqueous HCl (1 N) solution (700 mL) and ethyl acetate (700 mL) were added successively, and the layers were separated. The organic layer was washed with water (2 × 500 mL) and concentrated to dryness. Crystallization of the crude alcohol in 1:6 ethyl acetate:hexanes mixture (1.4 L) gave 167.8 g of a white solid (87% yield). ^{1}H NMR δ 7.4−7.2 (m, 5H); 6.92 (d, J = 2 Hz, 1H); 6.88 (dd, J = 7, 2 Hz, 1H); 6.81 (d, J = 7 Hz, 1H); 5.26 (d, J = 4 Hz, 1H); 4.75 (m, 1H); 3.82 (s, 3H); 2.49 (d, J = 4 H, 1H (O−H)); 2.0−1.75 (m, 6H); 1.7−1.5 (m, 2H). ^{13}C NMR δ 149.5, 147.7, 144.1, 136.6, 128.4, 127.4, 126.5, 119.0, 113.6, 111.9, 80.4, 76.0, 56.1, 32.8$_3$, 32.7$_9$, 24.10. IR 3600(s). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.41; H, 7.45.

3-(Cyclopentyloxy)-4-methoxybenzophenone, 6. $RuCl_3 \cdot H_2O$ (0.63 g) was added to a solution of alcohol **5** (50.0 g, 0.168 mol) in 10:1 THF:H_2O (198 mL). The solution was heated to 40 °C in an oil bath, and 70% *tert*-butyl hydroperoxide (10 mL, 73 mmol) was added. The ensuing exothermic reaction caused the solution to warm slowly to 60 °C and *tert*-butyl hydroperoxide (80 mL, 0.584 mol) addition continued at a rate (45 min) sufficient to maintain a gentle reflux. LC analysis showed 74% conversion to ketone **6**. Additional *tert*-butyl hydroperoxide (52 mL, 0.380 mol) was added at 45 °C (without any observed temperature increase), and the solution was allowed to stir at ambient temperature for 24 h. LC analysis indicated 97% conversion. The solution was diluted with MTBE (250 mL) and quenched with 10% $NaHSO_3$ solution (250 mL), and the organic layer was then washed with 5% $NaHCO_3$ (100 mL) and water (100 mL), dried ($MgSO_4$), filtered, and concentrated to a thick slurry (160 mL). Hexanes (300 mL) was added slowly, and the slurry was stirred at ambient temperature for 30 min, cooled to 0 °C, filtered, washed with hexane (100 mL), and dried in vacuo overnight, giving 44.2 g of white solid (89% yield). ^{1}H NMR δ 7.78 (m, 2H); 7.57 (m, 1H); 7.48 (m, 3H); 7.38 (m, 1H); 6.89 (d, J = 8 Hz, 1H); 4.85 (m, 1H); 3.92 (s, 3H), 2.05−1.75 (m, 6H); 1.70−1.55 (m, 2H). ^{13}C NMR δ 195.8, 154.0, 147.5, 138.4, 131.8, 130.1, 129.7, 128.1, 125.1, 115.6, 110.4, 80.5, 56.1, 32.8, 24.1. IR 1650. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.82; H, 6.80.

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)ethanol, 7. NaHMDS (2.21 M in THF, 11.5 mL, 25.4 mmol) was added to 4-picoline (2.46 mL, 25.3 mmol) in dry THF (50 mL) at 22 °C. The solution was aged for 1 h at 22 °C, and ketone **6** (5.05 g, 17.0 mmol) in THF (50 mL) was added. The solution was aged 2 h; LC analysis showed 0.5% ketone remaining. Hexanes (100 mL) and water (50 mL) were added, the mixture was stirred vigorously for 10 min, and the layers were separated. The organic layer was concentrated to a white solid that was then triturated in MTBE (40 mL). The resulting slurry was stirred overnight, filtered, washed with MTBE (15 mL), and dried, giving a white solid (6.10 g, 92%). ^{1}H NMR δ 8.13 (m, 2H); 7.38 (m, 2H); 7.33−7.99 (m, 3H); 6.88 (m, 2H); 6.32−6.22 (m, 3H); 4.61 (m, 1H); 3.79 (s, 4H, includes hydroxyl H); 3.52 (s, 2H); 1.87−1.65 (m, 6H); 1.62−1.45 (m, 2H). ^{13}C NMR δ 149.0, 148.6, 147.1, 146.6, 146.4, 138.9, 128.1, 127.1, 126.3, 118.5, 114.1, 111.2, 80.4, 77.7, 56.0, 47.6, 32.7$_4$, 32.6$_6$, 24.0. IR: 3600. HRMS, *m/z* Calcd for $C_{25}H_{27}NO_3$ (M^+) 389.1991, found 389.1978.

(*E*-1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)ethene, 9. Carbinol **7** (38.9 g, 100 mmol) was suspended in toluene (200 mL) at 18 °C. Methanesulfonic acid (19.6 mL, 300 mmol) was added in one portion, T = 30 °C after addition. The mixture was stirred 2 h, and LC showed complete conversion. THF (200 mL) was added, and after stirring 1 h the mixture was filtered. The solid was washed with 1:1 THF:toluene (70 mL) and dried to afford 29.5 g of pure *E* olefin MSA salt (63%). The salt (11.9 g, 25.4 mmol) was partitioned between EtOAc (100 mL), saturated Na_2CO_3 solution (50 mL), and water (50 mL). The organic layer was washed with water (50 mL) and concentrated to an oil (10.0 g, 105%). The oil was crystallized from EtOAc (50 mL) by addition of hexanes (200 mL), giving an off-white solid (5.9 g, 62%); a second crop gave 2.8 g (30%) of comparable purity. ^{1}H NMR δ 8.33 (m, 2H); 7.36 (m, 3H); 7.18 (m, 2H); 6.90−6.78 (m, 6H); 4.69 (m, 1H); 3.86 (s, 3H); 1.90−1.74 (m, 6H); 1.65−1.51 (m, 2H). ^{13}C NMR δ 150.6, 149.5, 147.4, 147.0, 145.0, 139.5, 135.1, 130.1, 128.8, 128.1, 123.7, 123.5, 120.8, 114.8, 111.5, 80.6, 56.1, 32.8, 24.1. IR: 1600, 1515. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.58; H, 6.76; N, 3.67.

(*Z*)-1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)ethene, 8. MSA (7.0 mL, 108 mmol) was added to carbinol **7** (20.9 g, 53.6 mmol) in THF (150 mL). The solution was refluxed 4 h and was then concentrated to dryness. The residue was triturated in 10:1 methyl isobutyl ketone (MIBK):MeOH (220 mL), and the resulting solid was filtered (12.3 g of *E* isomer, 49%). The mother liquors were concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (150 mL). NaOH (2 N) (50 mL) was added, and the mixture was stirred for 10 min. The organic layer was concentrated to a thick oil; EtOAc (45 mL) was added, and the mixture was stirred for 2 h at 22 °C. The resulting slurry was cooled to 0 °C, stirred an additional 30 min, filtered, washed with cold EtOAc, and dried giving an off-white solid, 5.18 g (26%). ^{1}H NMR δ 8.38 (d, J = 7 Hz, 2H); 7.36 (m, 5H); 6.92 (d, J = 7 Hz, 2H); 6.83 (d, J = 8 Hz, 1H); 6.81 (s, 1H); 6.68 (m, 2H); 4.57 (m, 1H); 3.88 (s, 3H); 1.8−1.65 (m, 6H); 1.57−1.48 (m, 2H). ^{13}C NMR δ 150.1, 149.6, 147.7, 147.1, 145.2, 142.6, 131.6, 128.4, 128.3, 127.9, 124.7, 123.8, 122.6, 117.1, 112.0, 80.3, 56.0, 32.6, 24.1. IR 1600, 1510. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.50; H, 6.77; N, 3.60.

***syn*-(1*S*,2*S*)-1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)-ethylene Oxide, 11.** CH_2Cl_2 (8 mL) was added to a mixture of olefin **8** (2.40 g, 6.46 mmol), *S*,*S* salen Mn complex **10** (48 mg, 0.075 mmol), and 4-(3-phenylpropyl)pyridine *N*-oxide (64 mg, 0.03 mmol), and the dark mixture was cooled to 0 °C. A solution of NaOCl (1.72 M, 13 mL, 22.4 mmol) and 5 N NaOH (0.4 mL, 2 mmol) was added over 1.5 h (via syringe pump), and the mixture was stirred at 0 °C for 22 h. The mixture was diluted with MTBE (10 mL), the resulting emulsion was filtered, and the layers were separated. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to a dark oil (2.17 g). Flash chromatography (1:1 EtOAc:hexanes) gave the epoxide (1.58 g) in 91% purity (3.72 mmol, 58%); the epoxide coelutes with unreacted **8** and an overoxidized byproduct. LC on Chiracel OD (75:25 hexane:iPA 1 mL/min showed a major enantiomer at 5.5 min (80 A%) and a minor one at 11.1 min (4.4 A%) 89.6%

ee. ^{1}H NMR δ 8.41 (d, J = 6 Hz, 2H); 7.33 (bs, 5H); 6.99 (d, J = 6 Hz, 2H); 6.72 (s, 2H); 6.65 (s, 1H); 4.56 (m, 1H); 4.28 (s, 1H); 3.79 (s, 3H); 1.9−1.48 (m, 8H). ^{13}C NMR δ 149.7, 149.3, 147.0, 144.7, 140.4, 128.5, 128.2, 127.0, 126.3, 121.73, 121.66, 116.0, 111.4, 80.4, 68.8, 66.7, 55.9, 32.7, 32.5, 24.1, 24.0. IR 1260. HRMS, m/z Calcd for $C_{25}H_{25}NO_3$: 387.1834. Found: 387.1817. A nearly enantiomerically pure sample was obtained from an oxidation which proceeded to only 85% conversion. Following chromatography, a crystalline solid separated from the concentrated fractions; this mixture was slurried in 4:1 hexane:EtOAc, and the solid was filtered. LC analysis showed this solid was a 2:1 mixture of **11** (racemic):8. Careful preparative TLC of the mother liquors provided a sample of 99.7% ee. $[\alpha]^{36}_D$ −16.2 (*c* 1.34, EtOH).

***anti*-(1*R*,2*S*-1-[3-(Cclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)-ethylene Oxide, 12.** NaOCl (1.72 M) (26 mL, 44.7 mmol) containing 5 N NaOH (0.8 mL, 4 mmol) was added to a solution of olefin **9** (4.80 g, 12.9 mmol), *S*,*S* Mn salen complex **10** (96 mg, 0.15 mmol), and 4-(3-phenylpropyl)pyridine *N*-oxide (128 mg, 0.6 mmol) in CH_2CL_2 (16 mL) over 40 min at 0 °C. After 18 h, additional **10** (48 mg) and 4-(3-phenylpropyl)pyridine *N*-oxide (128 mg) was added; 4 h later a third portion of catalyst (48 mg) was added and the mixture was stirred an additional 3 h. LC analysis showed 87:5 ratio of **12**:**9**. Hexane (16 mL) was added, and the layers were separated. The organic layer was washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated to an oil. Flash chromatography gave the epoxide **12** (3.60 g, 69% yield). LC on Chiracel OJ, 80:20 hexane:EtOH showed a major isomer at 5.50 min, 73.5%, and a minor isomer at 7.22 min, 25.5% (48% ee). The sample crystallized on standing; the solid was slurred in 4:1 hexane:EtOAc (25 mL) and filtered, giving 1.90 g of crystalline epoxide. Chiral LC analysis showed 10% ee. The mother liquors were evaporated to an oil (1.70 g) shown to be 95% ee. ^{1}H NMR δ 8.48 (d, J = 6 Hz, 2H); 7.22 (m, 5H); 6.98 (d, J = 6 Hz, 2H); 6.89 (s, 1H); 6.80 (s, 2H); 4.72 (m, 1H); 4.39 (s, 1H); 3.83 (s, 3H); 2.0−1.7 (m, 6H); 1.7−1.5 (m, 2H). ^{13}C NMR δ 150.0, 149.2, 147.8, 144.6, 135.0, 132.4, 128.9, 128.1, 128.0, 121.6, 119.3, 112.7, 111.5, 80.5, 69.1, 66.5, 56.1, 32.8_4, 32.7_7, 24.1. IR 1265. Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.26; H, 6.47; N, 3.54.

(1*R*,2*R*-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-phenyl-1-(4-pyridyl)ethanol BH_3 Complex, 13. $LiBH_4$ (66 mg, 3 mmol) was dissolved in 1 M BH_3·THF (10 mL, 10 mmol). A solution of the 1*S*,2*S* epoxide **11** (1.23 g, 3.17 mmol) in THF (5 mL) was cooled to −20 °C, and 6.5 mL of the $LiBH_4/BH_3$ solution was added dropwise such that the temperature did not rise above −10 °C. The solution was aged at −20 °C for 3 h, and then MeOH (2.5 mL) was added dropwise. Hexanes (10 mL), EtOAc (10 mL), and water (20 mL) were added with vigorous stirring. The organic layer was separated and concentrated to a yellow solid. The solid was broken up and stirred with 8:3 hexanes: EtOAc (11 mL) at 22 °C for 1 h, cooled to 0 °C, filtered, washed with hexanes, and dried, giving a white solid (590 mg) (mp 83−93 °C dec, ^{1}H NMR analysis showed 18 mol % = 5 wt % EtOAc which could not be removed by drying in vacuum at 25 °C, 44% yield). The mother liquors and wash were concentrated and flash chromatographed (2:1 hexanes:EtOAc), giving an additional 338 mg of oil (27%). ^{1}H NMR δ 8.31 (d, J = 7 Hz, 2H); 7.35 (m, 4H); 7.29 (m, 1H); 7.23 (d, J = 7 Hz, 2H); 6.70 (d, J = 8 Hz, 1H); 6.63 (dd, J = 8, 2 Hz, 1H); 6.57 (d, J = 2 Hz, 1H); 5.41 (dd, J = 9, 3 Hz, 1H); 4.59 (m, 1H); 4.02 (d, J = 9 Hz, 1H); 3.76 (s, 3H); 2.68 (d, J = 3 Hz, 1 H); 2.9−2.1 (bs, 3H); 1.9−1.68 (m, 6H); 1.68−1.50 (m, 2H). ^{13}C NMR δ 155.7, 149.2, 147.5, 146.7, 139.4, 132.2, 129.1, 128.7, 127.5, 123.3, 120.7, 115.8, 112.1, 80.6, 75.1, 59.4, 56.0, 32.8, 32.6, 24.1. IR 3700−3100, 2370. Anal. Calcd for $C_{25}H_{30}BNO_3$: C, 74.45; H, 7.50; N, 3.47. Found: C, 73.53; H, 7.56; N, 3.34 (consistent with 5 wt % EtOAc contamination). HRMS, m/z Calcd for $C_{25}H_{30}BNO_3$: 403.2319. Found: 403.2369. A crystal suitable for X-ray analysis was obtained from the above crystalline salt. A slurry of **13** (10 mg) in EtOH (absolute, 0.3 mL) was warmed briefly in a 45 °C oil bath (10 s); a small amount remained undissolved. The mixture was allowed to stand overnight at ambient temperature, giving clear, prism-shaped crystals, mp 123 °C dec.

13-Free Base. The borane complex (338 mg, 80% ee, oil from above) was refluxed in 4:1 toluene:MeOH (10 mL) for 8 h, and LC analysis showed complete conversion. The solution was then concentrated redissolved in fresh 4:1 toluene:methanol and concentrated again giving an oil (311 mg, 95%). Chiral LC (Chiracel OJ, 60:40 hexane: EtOH 1 mL/min, 35 °C, 280 nm) showed a major isomer at 5.4 min (87.7%) and a minor isomer at 8.4 min (9.3%), 80% ee. Treatment of the crystalline material from above in the same manner provided an oil in 100% yield, and chiral LC showed a major isomer at 5.4 min (94.8%) and the minor isomer at 8.4 min (0.4%), 99.2% ee. ^{1}H NMR δ 8.45 (m, 2H), 7.39 (m, 4H), 7.35−7.28 (m, 1H), 7.10 (m, 2H), 6.69 (d, J = 8 Hz, 1H), 6.65 (dd, J = 8, 2 Hz, 1H), 6.61 (d J = 2 Hz, 1H), 5.33 (d, J = 9 Hz, 1H), 4.58 (m, 1H), 4.10 (d, J = 9 Hz, 1H), 3.77 (s, 3H), 2.25 (bs, 1H), 2.0−1.5 (m, 8H). ^{13}C NMR δ 152.0, 149.2, 148.9, 147.3, 140.4, 133.3, 128.8, 128.5, 127.1, 122.0, 120.8, 116.0, 111.9, 80.5, 75.7, 59.4, 56.0, 32.9, 32.6, 24.1. [a]$^{33}_D$ +119 (*c* 1.65, EtOH) for the 99.2% ee sample. HRMS, m/z Calcd for $C_{25}H_{27}NO_3$: 389.1991. Found: 389.1993.

(1*S*,2*R*-2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-phenyl-1-(4-pyridyl)ethanol, 14. The $LiBH_4-BH_3$ solution (prepared as for **13**, 6 mL) was added to epoxide **12** (1.03 g, 2.66 mmol) in dry THF (3 mL) at −30 °C at such a rate that the temperature did not exceed −15 °C. The solution was aged 1 h at −30 °C, and then 2 h at −20 °C, and then MeOH (2.5 mL) was added dropwise. Hexanes (10 mL), EtOAc (10 mL), and water (20 mL) were added with vigorous stirring. The organic layer was dried (Na_2SO_4) and concentrated to an oil; LC analysis showed 55 area % **14**−BH_3 and 6.7% **13**. The crude oil was chromatographed on silica gel (2:1 hexane: EtOAc) and the purified oil, 89:11 **14**−BH_3:**13** (331 mg, 31%) was dissolved in EtOH (10 mL) and heated at reflux 10 h, concentrated, redissolved in EtOH (10 mL), and concentrated again. Chiral LC showed 93% ee. ^{1}H NMR δ 8.25 (m, 2H), 7.23−7.10 (m, 5H), 7.08 (m, 2H), 6.39−6.25 (m, 3H), 5.30 (d, J = 8 Hz, 1H), 4.69 (m, 1H), 4.10 (d, J = 8 HZ, 1H), 3.8 (bs, 1H), 3.78 (s, 3H), 1.9−1.7 (m, 6H), 1.7−1.5 (m, 2H). ^{13}C NMR δ 152.3, 149.1, 149.0, 147.6, 141.4, 132.2, 128.5_1, 128.4_6, 126.7, 121.9, 121.1, 116.3, 112.1, 80.5, 75.3, 59.1, 56.0, 32.9, 32.8, 24,1. IR:3585, 1602, 1510, 1266. Combustion analysis was obtained for the benzenesulfonic acid salt. Benzenesulfonic acid (105 mg, 0.66 mmol) was added to the alcohol **14** (235 mg, 0.60 mmol) in EtOAc (1.5 mL), giving a clear solution. The solution was allowed to stand at ambient temperature for 1 h. The resulting crystalline salt was collected by filtration, washed with EtOAc (5 mL), and dried overnight in vacuo (305.4 mg, 0.55 mmol, 92%). Anal. Calcd for $C_{31}H_{33}N0_6S$: C, 67.99; H, 6.07; N, 2.56. Found: C, 67.55; H, 6.04; N, 2.40.

(2*R*)-1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-phenyl-2-(4-pyridyl)ethane, 3, CDP840. Triethylamine (15.6 mg, 0.15 mmol) was added to the free base **13** (89.6% ee, 30 mg, 0.077 mmol) in CH_2Cl_2 (0.25 mL) at 0 °C. Methanesulfonyl chloride (13.2 mg, 0.116 mmol) was added, and the solution was aged 30 min. LC showed 95.4% mesylate and 4% **13**. The CH_2Cl_2 was evaporated, the residue was dissolved in acetic acid (0.5 mL), and zinc dust (15 mg, 0.23 mmol) was added. LC analysis showed 72% conversion to CDP840 after 10 min. The mixture was allowed to stir 10 h, giving 95% CDP840:5% **13**. The mixture was diluted with methyl *tert*-butyl ether (5 mL) and water (2 mL), and 5 N NaOH was added dropwise to pH 11. The layers were separated, the organic layer was concentrated to an oil (40 mg) that was purified by prep TLC (2:1 hexane:EtOAc), giving 24.4 mg of oil (85%). Chiral LC showed two peaks 6.36 min, 95% and 9.48 min, 5% (90% ee). An authentic sample of CDP840 showed a single peak on the same LC system at 6.35 min. A sample of **13** of 99.0% ee similarly treated gave CDP840 also in 99.0% ee.

1-(4-Methoxyphenyl)cyclohexene Oxide (15b).[12] K_2CO_3 (1 g) and then 1-(4-methoxyphenyl)cyclohexene (448 mg, 2.38 mmol) were added to a 0.14 M solution of dimethyldioxirane (34 mL, 4.76 mmol) in acetone (prepared as described by Adam *et al.*[16]) at 0 °C. After 10 min, HPLC showed complete reaction.

(16) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

The mixture was filtered and concentrated. The residue was dissolved in $CDCl_3$ (3 mL) and dried over K_2CO_3; concentration gave a clear oil that crystallized on standing, mp 45−46 °C. ^{1}H NMR 7.30 (d, J = 9.7 Hz, 2H); 6.88 (d, J = 9.7 Hz, 2H); 3.79 (s, 3H); 3.07 (m, 1H); 2.25 (ddd (ABXY), J = 14, 9, 6 Hz, 1H); 2.11 (m (ABXY), 1H); 1.98 (m, 2H); 1.7−1.4 (m, 3H); 1.4−1.2 (m, 2H). ^{13}C NMR δ 158.8, 134.7, 126.6, 113.7, 62.0, 59.9, 55.3, 29.0, 24.8, 20.2, 19.9.

(17) The author has 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.

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Supporting Information Available: X-ray data for compound **13** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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