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Diastereoselective Reaction of a Grignard Reagent with Chiral Imides: A Practical Preparation of a Key Intermediate in the Synthesis of Ifetroban Sodium

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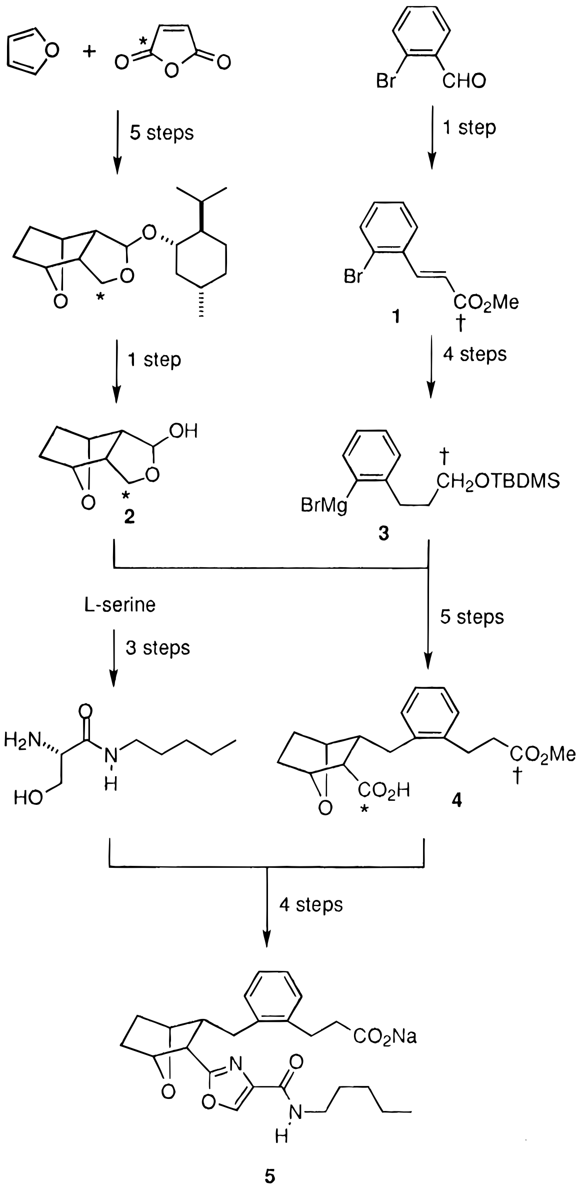
Abstract:

A novel and highly efficient synthesis of [1*S*-(1α,2α,3α,4α)]-2-[[2-(3-methoxy-3-oxopropyl)phenyl]methyl]-7-oxabicyclo[2.2.1]-heptane-3-carboxylic acid (A), a key intermediate in the synthesis of ifetroban sodium, BMS-180291, is described. Reaction of chiral imides such as [2(*S*),3aα,4*β*,7*β*,7aα]-hexahydro-2-(1-phenylethyl)-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione (B) with the Grignard reagent derived from 2-(2-bromophenyl)-1,3-dioxolane and subsequent *in situ* transformations give [2*S*-(2α,3aα,4*β*,7*β*,7aα)]-2-(octahydro-3-oxo-4,7-epoxyisobenzofuran-1-yl)benzaldehyde, converted in two steps to A. Efficient syntheses of B from furan and maleic anhydride are described.

Scheme 1



Ifetroban sodium (BMS-180291, **5**, a single enantiomer) is a long-acting, orally bioavailable, highly selective thromboxane A2 receptor antagonist with potent antithrombotic and anti-ischemic activity.[1] Cardioprotective in myocardial ischemia and reperfusion injury in animal models,[2] ifetroban sodium currently is in human clinical trials. In support of the necessary preclinical and early clinical trials, the synthesis of multikilogram quantities of ifetroban sodium was required. The original sequence,[1] although lengthly (23 steps) and inefficient (the overall yield via the longest linear sequence was less than 3%), was utilized (with minor modifications and some important improvements[3]) for the preparation of ~20 kg of ifetroban sodium. However, it was immediately apparent that continued development of the compound as a clinical candidate would require a much more practical synthesis.

Notable inefficiencies present in the original synthesis (Scheme 1) are rooted in oxidation-state readjustments and in attainment of a single enantiomer via a resolution process. Specifically, the carboxylic acid present in key intermediate **4** is derived from the carbon atom [indicated by the asterisks (*) in Scheme 1] present in hemiacetal **2** in the alcohol oxidation state, this carbon atom in turn originating from one of the carbonyl groups of maleic anhydride. The carboxylate ester [indicated by the daggers (†) in Scheme 1] present in key intermediate **4** is derived from the protected primary alcohol present in **3**, the carbon atom of the primary alcohol having been introduced earlier as an ester in **1**. Thus, two reduction−oxidation sequences are utilized in redundant conversions. Also, as a consequence, the alcohol in **3** requires protection. Therefore, five steps potentially could be saved by maintenance of these carbon atoms in their original oxidation states. An alternative to the resolution

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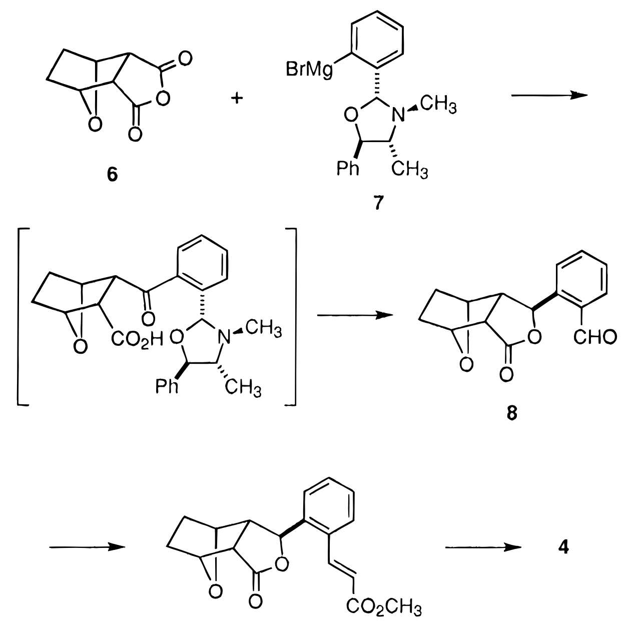
(1) Misra, R. N.; Brown, B. B.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J.; Floyd, D. M.; Sprague, P. W.; Morrison, R. A.; Ridgewell, R. E.; White, R. E.; DiDonato, G. C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M. L.; Ogletree, M. L. *BioMed. Chem. Lett.* **1992**, *2*, 73.

(2) Gomoll, A. W.; Schumacher, W. A.; Ogletree, M. L. *Pharmacology* **1995**, *50*, 92. Gomoll, A. W.; Grover, G. J.; Ogletree, M. L. *J. Cardiovasc. Pharmacol.* **1994**, *24*, 960.

(3) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494−4496.

S1083-6160(96)00034-5 CCC: $14.00

Scheme 2

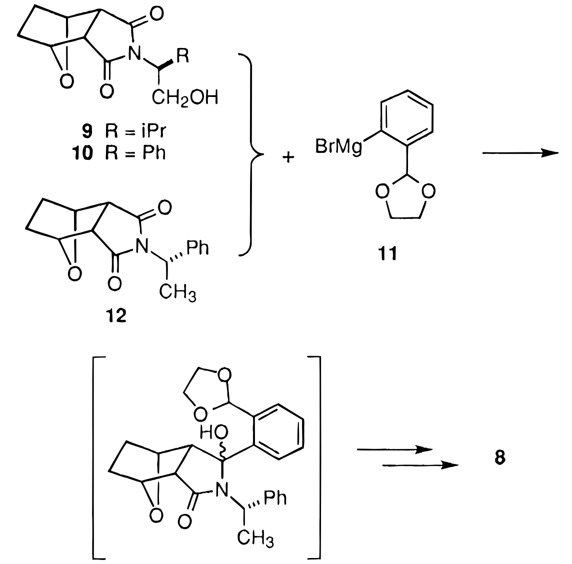


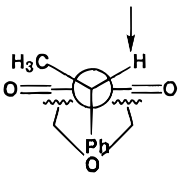
sequence would present an opportunity to considerably improve the logistics, or throughput, since resolutions are inherently inefficient, particularly in the absence of an efficient recycle strategy, with a maximum theoretical yield of 50%. With these thoughts in mind, a program was initiated to devise a direct synthesis of the desired enantiomer of intermediate **4** in which its functionalities are introduced and subsequently maintained in the correct oxidation states.

One solution to this problem has been described previously (Scheme 2).[4] Desymmetrization of *meso*-anhydride **6** with the chiral Grignard reagent **7** provided lactone aldehyde **8** after *in situ* borohydride reduction and acidification; **8** was obtained in reasonable yield and with very high enantiomeric purity. Conversion of **8** to **4** was accomplished via chain extension followed by concurrent reduction and hydrogenolysis.

Described below is an alternate approach for the synthesis of **8** in which the chirality of the reacting partners is reversed, *i.e.*, reaction of a chiral imide with an achiral Grignard reagent. This sequence ultimately proved to be much more efficient than that depicted in Scheme 2. Although the reactions of Grignard reagents with achiral imides[5] and chiral imides derived from tartaric acid[6] and malic acid[7] have been reported in the literature, no examples were found in which the chirality is derived from the amine moiety. Treatment of the chiral imides **9** or **10** (Scheme 3) prepared from either (*S*)-valinol or (*S*)-phenylglycinol first with 1 equiv of EtMgBr followed by 1 equiv of Grignard reagent **11**[8] produced a complex product mixture, presumably due to equilibration between the keto and hemiketal isomers. In order to simplify analysis, the crude reaction mixture was reduced *in situ* by addition of EtOH and NaBH$_4$ followed by sequential acidification, solvent exchange to toluene, and heating to form lactone aldehyde **8** in ~65% yields with enantiomeric ratios of ~86:14 (the desired enantiomer predominating) and with high diastereoselectivities at the alcohol carbon atom. Note that generation of a single isomer at the alcohol carbon atom rendered isolation and purification of the product **8** more efficient than if a mixture of isomers had been obtained; this result, as recognized previously,[4] is a consequence of the presence of magnesium ion, derived from the Grignard reagent, during the reduction step. Most importantly, imide **12**, derived from the more readily available (and considerably less expensive) (*S*)-methylbenzylamine, produced the same enantiomer of **8** with greater selectivity (94:6 in the reaction mixture, >99:1 after crystallization directly from the reaction mixture) and in higher yield (89%). Note that the phenyl group of **12** has stereochemistry opposite to that of **10**, but both **10** and **12** produce the same enantiomer of **8**. Presumably, **12** reacts via attack of the Grignard reagent from the less hindered face of the imide (that opposite the oxa bridge) and at the less hindered carbonyl group of the most reactive conformation (see **13**, a Newman projection along the N−C bond of the imide substituent). On the other hand, **10** reacts via the most reactive conformation of the cyclic magnesium alkoxide as shown in **14**, complexation with magnesium activating the indicated carbonyl group toward reaction.

Scheme 3





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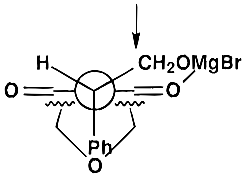

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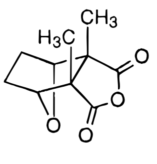

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Efforts were next focused on the development of a practical and efficient synthesis of imide **12**. Of concern was the use of anhydride **6**, particularly as an isolated, dry solid intermediate. Earlier experience had demonstrated that **6** was a potent irritant, causing inflammation and severe swelling on accidental skin exposure (*cf.* cantharidin, **15**).

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[4] Real, S. D.; Kronenthal, D. R.; Wu, H. Y. *Tetrahedron Lett.* **1993**, *34*, 8063.

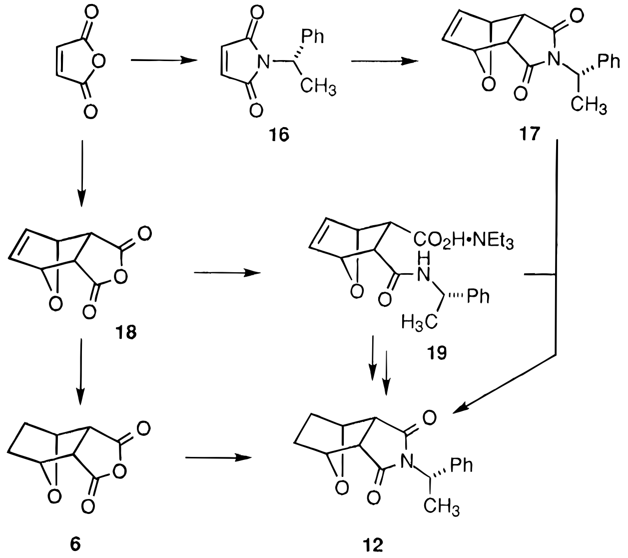
[5] Hitchings, G. J.; Helliwell, M.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 83. Nishio, T.; Yamamoto, H. *J. Heterocycl. Chem.* **1995**, *32*, 883.

[6] Yoda, H.; Katagiri, T.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 6771. Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451.

[7] Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 7329.

[8] Tomcufcik, A. S.; Wright, W. B., Jr.; Meyer, W. E. U.S. Patent 4,892,885, Jan 9, 1990.

Scheme 4



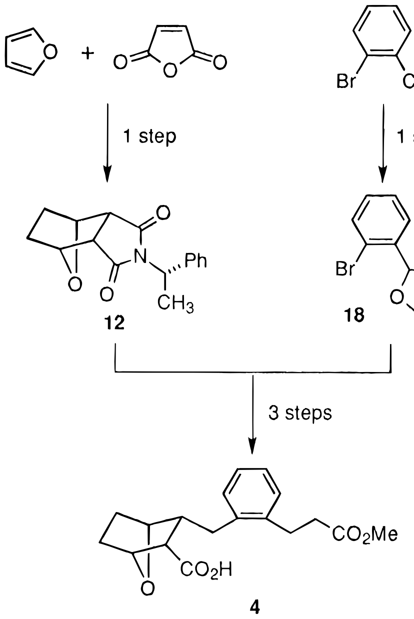
The inhalation risk associated with handling **6** as a dry (and dusty) solid, especially on a large scale, was especially daunting. One approach (Scheme 4) involved reaction of maleic anhydride with (*S*)-methylbenzylamine, Et_3N, and Ac_2O in refluxing THF to give maleimide **16**[9] in 64% distilled yield. Diels−Alder reaction (3 equiv of furan, 0.3 equiv of $AlCl_3$) in DCM at 25 °C for 20 h produced *exo* isomer **17** in 88% crystallized yield; the use of $AlCl_3$ proved necessary to effect equilibration of the kinetic ~3:1 *endo*:*exo* isomer ratio of the thermodynamically preferred *exo* isomer. Hydrogenation (H_2, Pd/C, EtOAc) gave imide **12** in 95% crystallized yield. A second approach involved Diels−Alder reaction between maleic anhydride and furan (6 equivs) followed by treatment of the resulting anhydride **18** (*endo*−*exo* equilibration occurs at room temperature without catalyst) with (*S*)-methylbenzylamine and Et_3N in *n*-BuOAc to generate **19** (as a 1:1 mixture of diastereomers). *In situ* hydrogenation (H_2, Pd/C, *n*-BuOAc) followed by cyclization (refluxing *n*-BuOAc) gave **12** in 85% crystallized yield overall. A third approach involved Diels−Alder reaction between maleic anhydride and furan in EtOAc or toluene, decantation of the supernatant from the crystalline **18**, and addition of acetonitrile and hydrogenation (H_2, Pd/C) followed by reaction with (*S*)-methylbenzylamine to give **12** in 80−95% crystallized yield. The latter two sequences, although consisting of three operations, are considered as one step each, since they can be performed in one pot and involve isolation only of imide **12**.

Thus, the synthesis (Scheme 5) of key intermediate **4** has been dramatically reduced from 16 steps (see Scheme 1) to five steps, and the yield has been increased 10-fold from 5% to 52%; the overall synthesis of ifetroban sodium has been cut virtually in half (from 23 steps to 12), and the yield (via the longest linear sequence) improved from 3% to 28%.

Experimental Section

^1H NMR spectra were recorded at 270 or 500 MHz (^{13}C at 67.8 MHz) and are reported in parts per million downfield from internal TMS. Solvents were ACS reagent grade; starting materials and reagents were obtained from Aldrich or Lancaster. THF was distilled from sodium benzophenone ketyl prior to use. Melting points are uncorrected, and optical rotations were measured at ambient temperature.

Scheme 5



Synthesis of 4. Into a 250-mL flask under Ar were placed **8** (9.44 g, 36.5 mmol), LiCl (1.7 g, 40.2 mmol), and acetonitrile (145 mL). With magnetic stirring, trimethyl phosphonoacetate (7.32 g, 40.2 mmol) was added *via* syringe followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.01 mL, 40.2 mmol). The solution became cloudy, and the temperature of the reaction rose to 42 °C. After 75 min, the mixture was poured into saturated aqueous $NaHCO_3$ (500 mL) and extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and dried under vacuum to provide 11.36 g (98.9% yield) of a yellow, crystalline solid. This material was placed into a 250-mL flask and dissolved in THF (35 mL) and MeOH (70 mL). With magnetic stirring, Pearlman's catalyst (1.14 g) was added. The flask was evacuated and then connected to a balloon filled with H_2. The reaction mixture was stirred for 2 h, and a second portion of Pearlman's catalyst (1.14 g) was added. The flask was evacuated and connected to the balloon filled with H_2. After another 2 h, the balloon was removed and Celite (2.0 g) was added to the mixture, which was stirred for 10 min. The mixture was filtered through a Celite pad (45 × 25 mm), and the pad was washed with MeOH (50 mL). The filtrate was evaporated to provide a yellow oil. The oil was dissolved in CH_2Cl_2 (100 mL) and dried over $MgSO_4$. The solution was filtered, concentrated, and dried under vacuum to provide 11.8 g of crude **4**, which was dissolved in 120 mL of EtOAc and treated with 1.2 g of Darco KB activated carbon by heating to reflux for 2 min and then cooling. Celite (2.4 g) was added and the mixture stirred for 10 min and then filtered through a pad of Celite (45 × 25 mm). The pad was washed with EtOAc (50 mL). The filtrate was evaporated, and the residue was crystallized from hot EtOAc (23 mL) and heptane (46 mL) with seeding. After cooling to room temperature, additional heptane (65 mL) was added,

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[9] Braish, T. F.; Fox, D. E. *Synlett* **1992**, 979.

and the mixture was let stand at 4 °C overnight. The resulting crystals were filtered, washed with heptane (50 mL), and dried under vacuum to give 9.97 g (85.7%) of **4**: mp 93−94 °C; $[\alpha]_D = +46.5°$ (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1709, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (m, 1H), 1.50 (m, 1H), 2.45 (m, 2H), 2.57 (m, 3H) 2.75 (dd, 1H, J = 3.67, 13.75 Hz), 2.91 (d, 1H, J = 9.17 Hz), 2.96 (t, 2H, J = 7.33 Hz), 3.65 (s, 3H), 4.30 (d, 1H, J = 4.58 Hz), 4.88 (d, 1H, J = 4.58 Hz), 7.15 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 27.3, 28.7, 29.2, 31.9, 34.8, 48.5, 51.6, 52.2, 77.6, 78.4, 126.4, 126.6, 128.8, 130.2, 138.0, 138.6, 173.3, 177.3 ppm. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 68.01; H, 6.99.

Synthesis of 8 from 12. Compound **20**[8] was dissolved in THF (30.0 mL) in an oven-dried, Ar-purged, 100-mL flask. Mg turnings (2.1 g, 87.5 mmol) were charged into a separate oven-dried, Ar-purged, 100-mL three-necked flask equipped with a condenser. To the Mg turnings was added a portion (5.0 mL) of the above solution of **20**. The reaction self-initiated within 5 min. The remaining solution of **20** was added to the flask over 40 min so as to maintain a gentle reflux. When the addition was complete, the mixture was stirred for another 1 h at room temperature to give Grignard reagent **11**.

Imide **12** (10.0 g, 36.9 mmol) was added to an oven-dried, Ar-purged, 250-mL three-necked flask equipped with an addition funnel and a mechanical stirrer. The imide was suspended in THF (14 mL) and the mixture cooled in an ice−water bath. The solution of **11** prepared above (38.0 mL of a 1.94 M solution in THF, 73.7 mmol) was added dropwise over 40 min. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h. The ice−water bath was removed, and the reaction mixture was stirred for an additional 3 h at room temperature. The mixture was cooled to 0 °C with an ice−water bath, and EtOH (100 mL) was added. To this mixture was added solid $NaBH_4$ (3.3 g, 87.3 mmol) in six equal portions over 20 min. The ice−water bath was allowed to warm to room temperature, and the reaction mixture was stirred for 17 h. The reaction mixture was poured into 10% aqueous Na_2CO_3 (400 mL), and the mixture was extracted with EtOAc (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in toluene (50 mL) and refluxed for 3.0 h. The resulting solution was cooled to room temperature, and then 1 N NaOH (150 mL) and EtOH (38 mL) were added. The mixture was stirred vigorously for 4 h at room temperature and then was extracted with EtOAc (130 mL). The aqueous layer was mixed with THF (26 mL), and 10% HCl (70 mL) was added at room temperature. The resulting mixture was then stirred at room temperature for 14 h while a white precipitate formed. The reaction mixture was cooled to 0 °C for 1 h. The precipitate was filtered and washed with water (20 mL). The solid was dried under vacuum to give **8** (>99.9% ee) as a white solid (7.7 g, 81%): mp 135−136 °C; $[\alpha]_D = -185°$ (c 1.0, MeOH); IR (KBr) ν_{max} 3436 (br), 1752 (s), 1684 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.09 (s, 1H), 7.91 (dd, 1H, J = 1.8, 7.0 Hz), 7.45−7.75 (m, 3H), 6.08 (d, 1H, J = 2.9 Hz), 5.34 (d, 1H, J = 4.7 Hz), 4.91 (d, 1H, J = 4.7 Hz), 2.88 (d, 1H, J = 8.2 Hz), 2.29 (dd, 1H, J = 2.9, 8.2 Hz), 1.65−1.85 (m, 2H), 1.25−1.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 193.3, 177.6, 142.4, 136.4, 134.3, 131.8, 128.4, 125.0, 83.0, 82.1, 79.9, 52.5, 49.9, 28.1, 28.0 ppm. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.77; H, 5.48.

Synthesis of 8 from 9. Into a flame-dried, Ar-purged, 250-mL three-necked flask fitted with a condenser and a dropping funnel were placed Mg shot (2.25 g, 92.6 mmol) and freshly distilled THF (80 mL). The mixture was heated to reflux, and a small crystal of I_2 was added to the flask. Acetal **20**[8] (18.45 g, 80.5 mmol) was added to maintain vigorous refluxing. Once the addition was complete (∼20 min), the mixture was refluxed for an additional 25 min and then cooled to room temperature.

In a separate flame-dried, 500-mL flask were added compound **9** (10.0 g, 40.3 mmol) and THF (60 mL). The mixture was cooled in a −20 °C bath, and EtMgCl (21.2 mL of a 1.90 M solution in THF, 40.3 mmol) was added dropwise while the internal temperature was maintained below −10 °C. The mixture was then cooled in a −78 °C bath, and the Grignard solution prepared above (62.7 mL) was added *via* syringe while the internal temperature was maintained below −65 °C. The reaction mixture was allowed to warm slowly to room temperature over 5 h. To the mixture was added absolute EtOH (145 mL), and then $NaBH_4$ (3.05 g, 80.5 mmol) was added in one portion. The mixture was stirred at room temperature for 1 h and then carefully poured into aqueous saturated Na_2CO_3 (500 mL) and extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and dried under vacuum to provide 18.1 g of a crude oil. This material was dissolved in toluene (80 mL) and heated to reflux for 1.5 h. The mixture was cooled with an ice−water bath and diluted with EtOH (20 mL) and 1.0 M NaOH (80 mL). The mixture was stirred at room temperature for 4.5 h. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The aqueous layer was diluted with iPrOH (20 mL) and then adjusted to pH 1.05 with 1.0 M HCl (120 mL). The mixture was stirred at room temperature for 18 h and then diluted with THF (180 mL, added in 60-mL increments over 7 h) until the mixture was homogeneous. The solution was stirred overnight and then concentrated to remove volatile organics (160 mL) as a white solid formed. The material was filtered, washed with water (3 × 100 mL), and dried under vacuum to provide 6.9 g (67% yield) of **8** as a 96:4 mixture of enantiomers.

Synthesis of 8 from 10. Compound **8** was prepared from **10** in a manner similar to that described above from **9**. After crystallization, **8** was obtained in 71% yield with 99.9% ee.

Synthesis of 9. A 3-L, three-necked Morton flask, fitted with a condenser and a mechanical stirrer, was purged with Ar and then charged with (S)-valinol (50.0 g, 485 mmol) and THF (1000 mL). The mixture was stirred for 5 min until a homogeneous solution was obtained. Oxalic acid (43.1 g, 479 mmol) was added in one portion. Within 5 min a thick, white precipitate formed. An additional portion of THF (500 mL) was added to the flask. Anhydride **6** (77 g, 458 mmol) was added in one portion, followed by Et_3N (129 mL, 926 mmol). The mixture was heated to reflux for 18 h. After cooling, the resulting slurry was filtered. The filtrate was concentrated to a volume of ~1 L. The solution was poured into saturated aqueous $NaHCO_3$ (1 L) and extracted with CH_2Cl_2 (1 × 1000 mL, then 2 × 500 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and dried under vacuum to provide 94.8 g of crude **9**. This material was dissolved in hot EtOAc (250 mL) and diluted with hexane (570 mL) at reflux. The mixture was allowed to cool to room temperature. The resulting crystals were collected by filtration and washed with 2.4:1 hexane−EtOAc (2 × 100 mL) and hexane (2 × 100 mL). The material was dried for 2 days at ~80 mmHg at ambient temperature to provide 78.6 g (68%) of **9**: mp 107−108 °C; $[\alpha]_D = +6.70°$ (*c* 1.0, MeOH); IR (KBr) ν_{max} 3528.9 (s), 1757.3 (s), 1690.0 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.88 (t, 2H, $J = 3.0$ Hz), 4.09−3.90 (m, 1H), 3.80−3.70 (m, 2H), 2.94−2.89 (m, 3H), 2.44−2.32 (m, 1H), 1.89−1.79 (m, 2H), 1.62 (m, 2H), 1.02 (d, 3H, $J = 6.9$ Hz), 0.80 (d, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 178.67, 178.25, 79.41, 79.34, 61.87, 61.00, 49.80, 49.49, 28.67, 28.53, 25.93, 19.74, 19.62 ppm. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.57; H, 7.56; N, 5.54. The mother liquor was evaporated, and a second crop of 9.7 g (8%) was obtained from EtOAc (40 mL) and hexane (120 mL).

Synthesis of 10. Into a 2.0-L three-necked flask were charged **6** (34.1 g, 203 mmol), (*S*)-(+)-phenylglycinol (27.8 g, 203 mmol), oxalic acid (18.3 g, 203 mmol), and THF (500 mL). To the above suspension was added Et_3N (56 mL), and the mixture was heated to reflux for 8 h. The reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (300 mL). The resulting mixture was extracted with EtOAc (2 × 300 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated under vacuum. The residue was dissolved in EtOAc (100 mL) at 60 °C, and hexane (50 mL) was added. The resulting solution was cooled to room temperature and then stored at ~4 °C for 14 h. The white solid was filtered and dried under vacuum for 24 h to give **10** (48.7 g, 84%): mp 118−119 °C; $[\alpha]_D = -16.0°$ (*c* 1.3, $CHCl_3$); IR (KBr) ν_{max} 3430 (s), 1699 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.35−7.22 (m, 5H), 5.28 (dd, 1H, $J = 5.01, 4.22$ Hz), 4.92 (m, 2H), 4.47 (dd, 1H, $J = 8.32, 2.53$ Hz), 4.12 (dd, 1H, $J = 9.13, 5.83$ Hz), 3.95 (s, 2H), 1.89−1.82 (m, 2H), 1.69−1.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 178.4 (2C), 136.4, 129.1 (2C), 128.5 (2C), 127.9, 79.9 (2C), 62.3, 58.7, 50.2 (2C), 29.9, 29.0 ppm. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 66.89; H, 5.95; N, 4.88. Found: C, 66.83; H, 6.01; N, 5.06.

Synthesis of 12. Method 1. ***CAUTION***: *Nonisolated intermediate* ***18*** *is a potent irritant. Extreme precaution should be excerised to prevent exposure to solutions of* ***18*** *and to prevent aerosol formation during handling.* Furan (222 mL, 3.06 mol) was added under Ar to pulverized maleic anhydride (50.0, g, 0.510 mol) in a 2-L three-necked flask equipped with a mechanical stirrer and chilled in a cold water bath (without cooling, the addition is sufficiently exothermic to evaporate some of the furan). After the addition was complete, the flask was stoppered and the maleic anhydride was dissolved by stirring. The solution was let stand for 22 h without stirring, and then the resulting crystalline mass of **18** was suspended in *n*-BuOAc (500 mL). The mixture was chilled in an ice−water bath, and a mixture of Et_3N (71.1 mL, 0.510 mol) and (*S*)-(−)-α-methylbenzylamine (65.7 mL, 0.510 mol) was added dropwise over 15 min while the temperature was maintained at or below 10 °C. The suspension dissolved within 10 min, and the cold bath was removed. Pd/C (5%; 7.19 g) was added, and H_2 was sparged through the mixture for 2.5 h to give **6**. After sparging with N_2 for 15 min, the mixture was filtered through Celite and washed with *n*-BuOAc (4 × 10 mL) directly into a 1-L distillation flask. Furan and Et_3N were removed by distillation over 30 min (~250 mL, bp 88−122 °C), and then another 140 mL was distilled (bp ~124 °C) over 1.5 h. After cooling, the pot residue (~400 mL) was diluted with EtOAc and washed with 1 N HCl (300 mL), water (300 mL), 5% $NaHCO_3$ (300 mL), and brine (100 mL) and dried ($MgSO_4$). The extract was treated with Darco G-60 (14 g) and filtered through Celite. The filtrate was evaporated at a bath temperature of 50 °C until the residue weighed 300 g. The residue was heated on the steam bath while heptane (950 mL) was added slowly. Crystals started to form immediately. After 6 h the solid was collected on a filter, washed with cold heptane, and dried to give 117.6 g (85% yield) of **12**: mp 108−109 °C; $[\alpha]_D = -67°$ (*c* 5.08, $CHCl_3$); IR (KBr) ν_{max} 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.15 (m, 1H), 1.42 (m, 1H), 1.71 (m, 2H), 1.82 (d, 3H, $J = 7.0$ Hz), 3.33 (m, 2H), 4.83 (m, 2H), 5.37 (q, 1H, $J = 7.0$ Hz), 7.38 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 16.0, 25.8, 26.1, 50.3, 51.1, 78.2, 127.7, 128.0, 128.4, 139.1, 175.4 ppm. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.03; H, 6.31; N, 5.16.

Synthesis of 12. Method 2. $AlCl_3$ (0.199 g, 1.49 mmol) was added to imide **16**[9] (1.0 g, 4.98 mmol) and furan (1.08 mL, 14.9 mmol) in CH_2Cl_2 (16.6 mL) chilled in an ice−water bath under Ar. After 15 min the bath was removed, and the mixture was stirred overnight. A black precipitate formed. EtOAc (20 mL) and 1 N HCl (20 mL) were added and stirred for 10 min. The mixture was filtered through Celite with EtOAc to remove the solid. The filtrate was transferred to a separatory funnel, and the aqueous layer was separated. The organic layer was washed with 1 N HCl (20 mL), water (20 mL), 5% $NaHCO_3$ (20 mL), and brine (10 mL) and then dried over $MgSO_4$. Darco G-60 (0.5 g) was added and the mixture stirred for 30 min. The mixture was filtered through Celite and evaporated to ~25 mL. The residue was transferred with 25 mL of EtOAc into a hydrogenation flask containing 5% Pd/C (0.1 g). H_2 was sparged through the mixture for 1 h, and then N_2 was sparged for 15 min to remove excess H_2. Darco G-60 (0.5 g) was added and the mixture stirred for 30 min. The mixture was filtered through Celite with EtOAc and evaporated to give 1.27 g of crude **12**. The semisolid residue was dissolved in EtOAc (1.5 mL) and heptane (10 mL) by heating on a steam bath. The solution was let stand for 2 h at room temperature and then at 0 °C for 3 h. The crystals were filtered, washed with cold hexane, and dried overnight under vacuum to yield 1.12 g (83% yield) of **12**: mp 107−109 °C; $[\alpha]_D = -68°$ (*c* 1, $CHCl_3$).

Synthesis of 12. Method 3. ***CAUTION***: *Nonisolated intermediates* ***18*** *and* ***6*** *are potent irritants. Extreme* *precaution should be excerised to prevent exposure to solutions of **18** and **6** and to prevent aerosol formation during handling.* Maleic anhydride (500 g, 5.1 mol) and toluene (750 mL) were charged into a 22-L, three-necked flask equipped with a mechanical stirrer and thermometer under N_2. Furan (2078 g, 30.5 mol) was added dropwise over 1.5 h with stirring. Initially, the reaction temperature dropped from 18−19 °C to 12−14 °C (dissolution of the anhydride), and then it started to increase as reaction occurred; the internal temperature was maintained below 30 °C by cooling with an ambient temperature water bath. After 2 days, HPLC indicated completion of the reaction to form **18**, and acetonitrile (5 L) was added to dissolve the white slurry. Pd/C (5%; 60 g, 50% water-wet) was slurried in 500 mL of acetonitrile and transferred under N_2 to the reaction mixture. H_2 was sparged through the mixture with maximum agitation. A water bath was used to maintain the internal temperature below 40 °C. Reaction to give **6** was complete in 2−4 h (TLC). N_2 was sparged through the mixture for 15 min to displace remaining H_2, and the catalyst was removed by filtration through Celite. The cake was washed with 500 mL of acetonitrile. (*S*)-(−)-Methylbenzylamine (694 mL, 8.07 mol) and 4 L of toluene were added in one portion, and furan and acetonitrile were removed by distillation. After 9 h, reaction was complete (HPLC). The mixture was allowed to cool and then transferred to a phase splitter using another 2 L of toluene. The solution was washed sequentially with 3 L of 1 N HCl, 2 × 3 L of saturated aqueous $NaHCO_3$, and 3 L of brine. Each aqueous layer was backwashed with 500 mL of toluene. The combined organic layer was dried over $MgSO_4$ and treated with 200 g of Darco G-60. After filtration, the solution was concentrated to ∼2 L to give a thick slurry. Hexane (4 L) was added, and the mixture was stored overnight at 5 °C. The white solid was collected by filtration, washed with hexane (1 L), and then dried under vacuum to give **12** (1253 g, 90.6%) with an enantiomeric purity of 99.7%: mp 105−107°; $[\alpha]_D = -70.4°$ (*c* 1.07, $CHCl_3$).

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