Enantioselective Synthesis of 5-LO Inhibitor Hydroxyureas. Tandem Nucleophilic Addition−Intramolecular Cyclization of Chiral Nitrones

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An enantioselective synthesis of chiral hydroxyurea based 5-lipoxygenase inhibitors is reported via a five-step sequence in about 30% overall yield. The synthesis is based on a novel tandem nucleophilic addition−intramolecular cyclization reaction in which a chiral nitrone functions as the electrophilic acceptor species. A mannose-based chiral auxiliary controls the diastereoselectivity of the reaction in an 8:1 ratio. After the auxiliary removal and appropriate functionalization, a single recrystallization afforded the target structures in >99% ee.

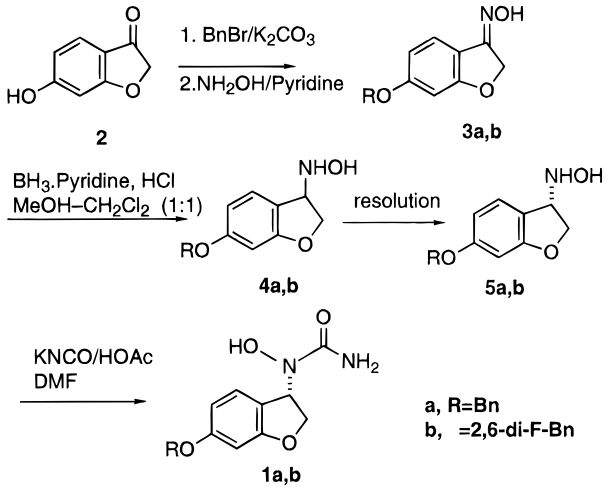
Introduction

The leukotrienes have been implicated as mediators in a number of inflammatory and vascular diseases. Inhibition of their biosynthesis therefore has been considered to hold promise in the therapeutic intervention of such diseases as asthma, allergy, and a host of others and has been in the intense focus of pharmaceutical research.[1] The enzyme 5-lipoxygenase (5-LO) plays a central role in the biosynthesis of leukotrienes by catalyzing first the transformation of arachidonic acid to 5-HPETE and then to leukotriene-A_4.[2a] This central role has prompted several companies to initiate research programs toward the discovery of drugs that would act as inhibitors of this highly pivotal enzyme, and as the result of this intense effort several drugs are now in development.

Zileuton of Abbott Pharmaceuticals is the first selective 5-LO inhibitor on the market having received approval from the FDA. Structurally, the compound contains a chiral hydroxylamine moiety, and clinically the compound is marketed as a racemate. Its chemical synthesis, biological activities, and clinical data have been extensively described in the literature.[2b]

SmithKline Beecham has also been developing agents that have shown very high inhibitory potency toward the 5-LO enzyme.[3ab] These compounds, **1a** and **1b** (SB 202235 and 210661), also contain the hydroxyurea pharmacophore but now attached to a dihydrobenzofuran moiety. The molecules are chiral, and our decision to develop only the active enantiomer posed a major synthetic challenge. Clearly, finding a chemical process based on either an efficient resolution or an enantioselective synthesis was the fundamental objective of this program.

Scheme 1



In this communication we wish to report on the extensive chemical development effort that was expended on the synthesis of **1a** and **1b** culminating in an efficient enantioselective synthesis capable of affording the compounds in five steps, in 30% overall yield and >99% ee.

I. The First Generation Synthesis

The initial racemic synthesis is shown in Scheme 1. Benzofuranone **2** was prepared from resorcinol and chloroacetonitrile by the method of Shriner[4] in 72% yield. Conversion of **2** to the benzyl-substituted oximes **3a** and **3b** was achieved via standard methods in 81% and 94% yields, respectively. Reduction of the oximes to the hydroxylamines was carried out by applying a procedure originally devised by Kikugawa[5] involving treatment of a (1:1) CH_2Cl_2/MeOH solution of **3** with a 5-fold excess of the borane−pyridine complex in the presence of HCl. The reaction routinely delivered the desired racemic hydroxylamines **4a** and **4b** in better than 80% yield.

Resolution of the racemic compound was first accomplished via derivatization and chromatography.[3a] While this method was successful in generating sufficient

† Chemical Development.
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(1) Brooks, C. D.; Summers, J. B. *J. Med. Chem.* **1996**, *39*, 2629.
(2) (a) Samuelsson, B. *Science* **1983**, *220*, 568. (b) Brooks, D. W.; Carter, G. W. In *The Search for Antiinflammatory Drugs;* Merluzzi, V. J., Adams, J., Eds.; Burkhauser: Boston, 1995; Chapter 5.
(3) (a) Garigipati, R. S.; Sorenson, M. E.; Erhardt, K. F.; Adams, J. L. *Tetrahedron Lett.* **1993**, *35*, 5537. (b) Adams, J. L.; Garigipati, R. S.; Sorenson, M.; Schmidt, S. J.; Brian, W. R.; Newton, J. F.; Tyrrell, K. A.; Garver, E.; Yodis, L. A.; Chabot-Fletcher, M.; Tzimas, M.; Webb, E. F.; Breton, J. J.; Griswold, D. E. *J. Med. Chem.* **1996**, *39*, 5035.
(4) Shriner, R. L.; Grosser, F. *J. Am. Chem. Soc.* **1942**, *64*, 382.
(5) Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkins Trans. 1* **1979**, 643.

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enantiomerically pure materials for biological differentiation the low throughput of the process prevented its use for clinical development. A more practical solution was provided by the finding that careful salt formation with mandelic acid could accomplish an efficient resolution of racemic precursor **4a** in about 30−35% yield and 96−98% ee. Resolution of **4b**, however, was somewhat more difficult on account of the lack of reproducibility of the enantiopurity of the mandelic acid salts which varied over the range of 34−92% ee. Recrystallization of these salts from EtOAc, however, always consistently brought the enantiomeric excess to >95%. As far as we know this is the first time that the feasibility of classical resolution of hydroxylamines has been documented in the literature.

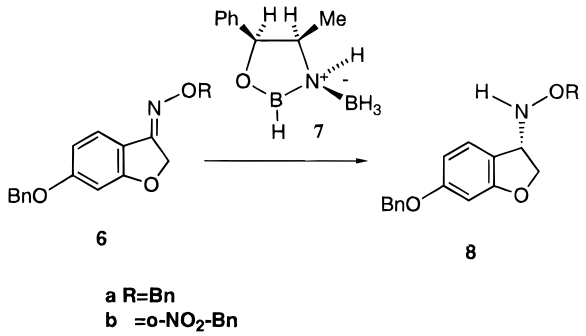
Conversion of the enantiomerically pure hydroxylamines **5a** and **5b** to the final hydroxyureas was performed via the addition of KOCN/HOAc in DMF solution. The reaction provided almost analytically pure substances in excess of 90% yield that could be further purified to >99.0% optical purity by recrystallization from hot DMF/TBME. The resolution process together with the overall simplicity of the synthesis finally afforded us the means to prepare both compounds (**1a** and **1b**) in multikilogram quantities, thus fulfilling our initial objective. Having reached this initial goal, we could now turn our attention to the invention of a more economical synthesis based on the enantioselective generation of the chiral hydroxylamine moiety.

II. Enantioselective Synthesis

Our first attempts explored the feasibility of generating chiral hydroxylamines via the enantioselective reduction of oxime ethers. Although highly effective asymmetric reductions of oxime ethers to optically active amines have been reported in recent years,[6] useful enantioselective conversions of oxime ethers into *O*-substituted hydroxylamines have been relatively neglected. As far as we know no such successful transformations have been described.[7] A method reported by Burk et al.[8] involving a highly efficient and enantioselective reduction of benzoyl hydrazones to hydrazines by analogy appeared to have potential for the reduction of oximes to hydroxylamines. The analogous benzoyl oxime was readily prepared; however, the reduction was not successful. Even though we were able to fully reproduce Burk's reported results on his hydrazone substrates, the oximes totally inhibited the reaction.

After surveying several other chiral reducing agents for the asymmetric reduction of variously substituted 6-(benzyloxy)-2,3-dihydrobenzofuran 3-oximes, we found that reagent **7**, first reported by Sakito[7] and prepared from norephedrine and borane, reduced the *O*-(*o*-nitrobenzyl) ether **6b** in respectable yields (55%) to the corresponding optically active *O*-(*o*-nitrobenzyl) hydroxylamine and with *excellent enantioselectivity (99% ee)*. Similarly, reductive conversion of the *O*-benzyl oxime **6a** was also successful with 89.2% ee and in 63% yield.

Scheme 2



a R=Bn
b =o-NO_2-Bn

It is noteworthy that neither the reagent of Corey[9] nor several related reagents were able to carry out the reductions under identical conditions. Unfortunately, our success in finding these reductive conditions[10] for the enantioselective formation of substituted hydroxylamines did not lead to an efficient solution to the problem of chiral synthesis. Numerous attempts at the selective removal of hydroxylamino substituents resulted in removal of both benzyl substituents in the molecule. Surprisingly, attempted rebenzylation at the phenolic hydroxyl could also not be accomplished. These results were found not only with the penultimate intermediates **8** but also with their corresponding hydroxylurea derivatives. These results forced us to pursue our goal in a different direction.

The addition of carbon-bearing nucleophiles to nitrones having a chiral auxiliary to form chiral hydroxylamines was first noted by Chang and Coates.[12] These workers explored the addition of organometallic reagents to *inter alia* chiral β-methoxy-α-phenylethyl-substituted nitrones. Impressive diasteroselectivities were observed. This approach was further progressed by Hu and Schwartz[13] in their enantioselective synthesis of chiral hydroxylamines via the addition of Grignard reagents to nitrones bearing gulofuranosyl moieties. The very high diastereoselectivities obtained and the mild conditions required for auxiliary removal (the highly oxygen rich character of the aryl moiety in **5a** and **5b** makes these molecules inherently acid labile) prompted us to initiate an investigation into applying Schwartz's method (interestingly it now appears from the literature[14] that three research groups independently came to this same conclusion as witnessed by subsequent publications).

The route we have envisaged is shown in Scheme 3. Conceptually, it involves a tandem nucleophilic addition of dimethylsulfoxonium ylide to the benzaldehyde-based nitrones **11a** and **11b** and cyclization of the *in situ* generated intermediates. Commercially, readily avail-

(6) (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (b) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1548. (c) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1859. (d) Itsuno, S.; Nakano, M.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615. (e) Itsuno, S.; Tanaka, K.; Ito, K. *Chem. Lett.* ***1986***, 1133−1136. (f) Gibbs, D. E.; Barnes, D. *Tetrahedron Lett.* **1990**, *31*, 5555.

(7) Suzukamo et al. in their description of the asymmetric reduction of oxime ethers to amines allude (in the notes to Table 1) to the possibility of obtaining methyl ethers of hydroxylamines which were not characterized: Sakito, Y.; Yoneyoshi, Y.; Suzukamo, G. *Tetrahedron Lett.* **1988**, 223−224.

(8) Burk, M.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266

(9) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(10) Dougherty, J. T.; Flisak, J. R.; Liu, L.; Tucker, L.; Lantos, I.; Hayes, J. *Tetrahedron*: *Asymm.* **1997**, *8*, 497.

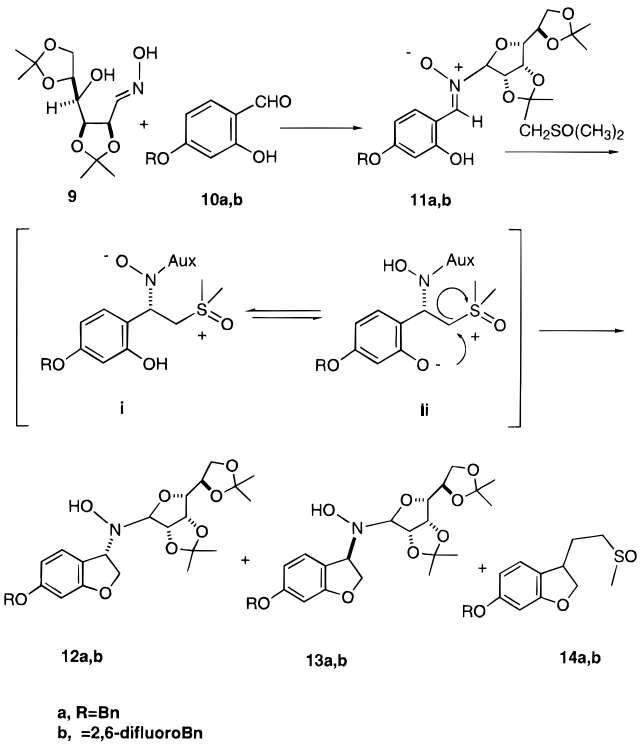
(11) Flisak, J. R; Lantos, I.; Liu, Li.; Matsuoka, R. T.; Mendelson, W. L.; Tucker, L. M.; Villani, A. J.; Zhang, W.-Y. *Tetrahedron Lett.* **1996**, *37*, 4639.

(12) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464.

(13) Hu, X.; Schwartz, M. A. Book of Abstracts, 204th National Meeting of the American Chemical Society, Washington, D.C., 1992; ORGN 5.

(14) (a) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35*, 1011. (b) Basha, A.; Henry, R.; Maclaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103.

Scheme 3



able mannose bis-acetonide **9** was chosen as the chiral auxiliary, and the success of the sulfur ylide addition was anticipated based on the work of Pyne and Hajipour.[15] We were also hoping that the inherently exceptional leaving group ability of dimethyl sulfoxide would allow the initial adduct to undergo spontaneous cyclization.

In the event, the crystalline mannose-bearing nitrones **11a** and **11b** were prepared by condensation of **9** (an approximately 1:1 mixture of the oxime and the cyclic hydroxylamine) with benzaldehyde **10a** and **10b**[16] in 80% yield. A slurry of nitrone **11a** in toluene was treated with a solution of dimethylsulfoxonium methylide[17] in THF at −10 °C, and after warming the resulting solution to 10 °C it afforded a mixture of diastereomeric *N*-glycosides, **12a** and **13a**, in relative ratios of about 7.5−8.0 to 1 (isolated yields ca 65−75%; solution yields >90%). Identical reaction was carried out for **11b** in THF, affording a similar ratio of diastereomers. With both substrates, the diastereoselectivity of the reaction is temperature and concentration dependent; the lower the temperature and the less concentrated the reaction mixture, the higher the diastereoselectivity. The condensation−cyclization reaction is extremely sluggish at temperatures below 0 °C. We currently believe that mechanistically, the reaction involves initial condensation of the methylide with the nitrone, tautomerization of the proton from the phenol to the hydroxylamine moiety, and five-membered ring cyclization with the elimination of dimethyl sulfoxide (as shown in Scheme 3). The phenol moiety of *N*-glycosyl nitrones **11** is not deprotonated by the methylide during the condensation−cyclization reaction because only 1 equiv of methylide is needed for the reaction to take place. If the *N*-glycosyl nitrone is pretreated with 1 equiv of potassium *tert*-butoxide before methylide addition, the subsequent condensation-cyclization reaction is shut down completely. On the other hand, if one pretreats the *N*-glycosyl nitrone with 1 equiv of potassium *tert*-butoxide and subsequently with trimethylsulfoxonium iodide at temperatures above 40 °C, the condensation−cyclization reaction proceeds, albeit with much lower levels of diastereoselectivity due to the rather high reaction temperature required.

Only one major side-product is formed in these reactions, sulfoxides **14a** and **14b** (Scheme 4),[18] which could be minimized to <3% by treating the nitrones with no more than 1 equiv of dimethylsulfoxonium methylide at relatively low temperatures (ca. −10 °C).

The diastereoselectivity seen in the initial condensation step of the addition of dimethylsulfoxonium methylide to the various *N*-glycosyl nitrones was rationalized via the Vasella transition state model[19] known as the "kinetic anomeric effect". Vasella has used this model to describe both additions of phosphorus nucleophiles and 1,3-dipoles to *N*-glycosyl nitrones and observed selectivities similar to what we observed in the methylide condensation. The argument is schematically represented in Scheme 5.

The sterically less congested "*O-endo*" conformer of the nitrone reacts preferentially over the "*O-exo*" conformer. The nucleophile adds from the "*syn*" face because the liberated p-orbital electrons have a stabilizing anomeric interaction with the C(1)−O bond in the glycosyl moiety.

We attempted to obtain the final hydroxy ureas **1a** and **1b** in a single-pot operation by removing the mannose chiral auxiliary with dilute HCl and after the pH was adjusted at 4.0 reacting the resulting hydroxylamines with KOCN as shown in Scheme 6.

Surprisingly, this one-pot procedure afforded, in addition to 70−75% yields of the target compounds, a few percent of the (benzyloxy)benzofuran and a small percentage of an isomer **15** resulting from carbamoylation of the hydroxyl group. A much more efficient conversion could be readily demonstrated, however, by treatment of the **12a** and **12b** mixtures with $NH_2OH{\cdot}HCl$ in refluxing ethanol. Simply cooling the reaction mixture to 0 °C precipitated the enantioenriched hydroxylamines in 75% yield from the corresponding nitrones. Furthermore, concentration of the mother liquors enabled us to recover the chiral auxiliary suitable for reuse. Conversion of the hydroxylamines to **1a** (SB 202235) and **1b** (SB 210661) was carried out using the original protocol of treatment with KOCN in the presence of acetic acid (Scheme 1). Using this protocol no isomer or benzofuran was generated, and the crude products were obtained in 96% and 85% yields, respectively, and 77% ee. The enantiomeric purity of the product was improved to 99% by one recrystallization from 2-propanol.

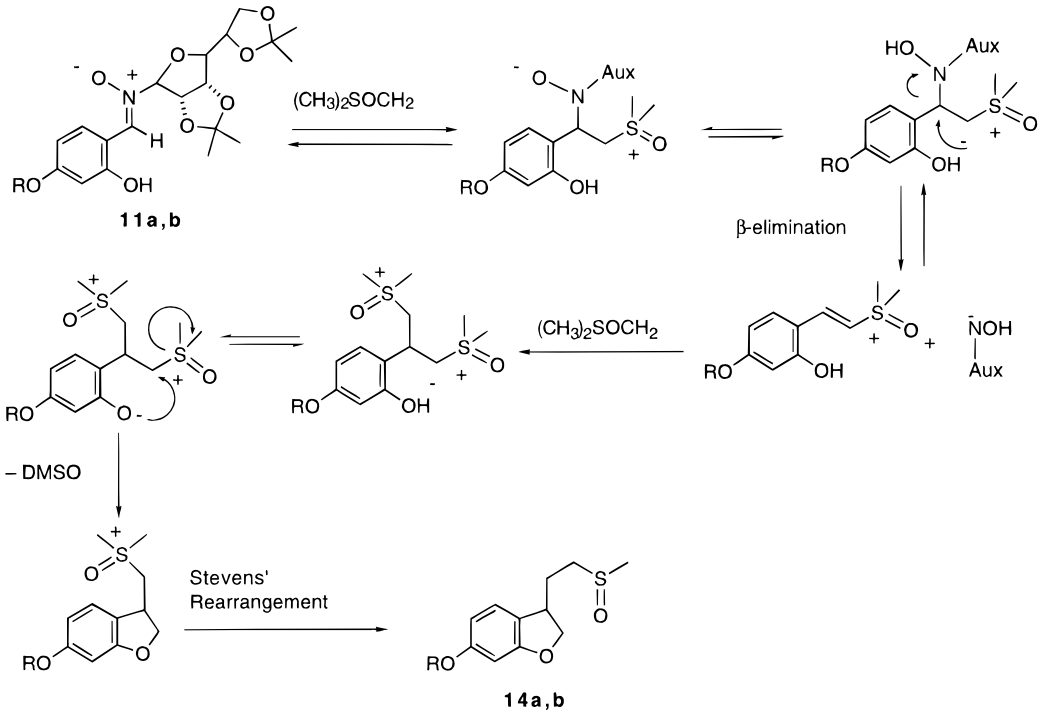
Conclusion

In summary, an efficient six-step enantioselective synthesis of two related hydroxyurea lipoxygenase inhibitors **1a** and **1b** has been devised using the readily

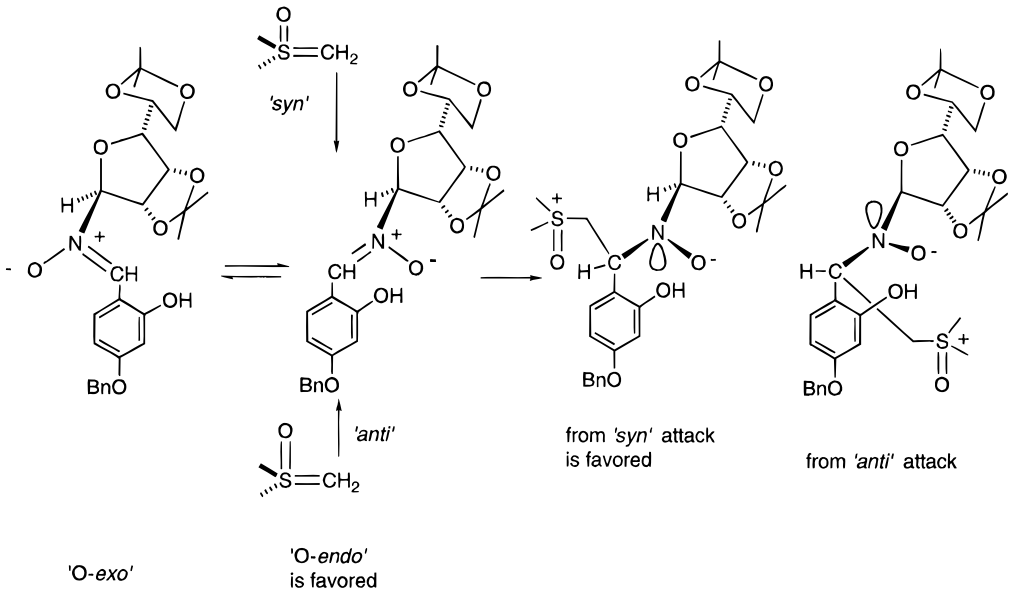
(15) Pyne, S. G.; Hajipour, A. R. *Tetrahedron Lett.* **1992**, *48*, 9385
(16) Mendelson, W. *Synth. Commun.* **1996**, *26*, 593.
(17) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. Corey, E. J., Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) For a recent review on dimethylsulfoxonium methylide, see Gologobov, Y. G.; Nesmeyano, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609.

(18) The formation of **14a,b** was postulated as arising from a five-step reaction sequence shown in Scheme 4. Following initial condensation, α,β-elimination of the chiral auxiliary occurs. This is followed by a 1,4-addition of a second equivalent of methylide, cyclization, and Stevens rearrangement to afford the sulfoxide side-product.
(19) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33 and references cited therein.
(20) Ng, J. S. *Synth. Commun.* **1990**, *20*, 1193 and references cited therein.

Scheme 4



Scheme 5



available protected mannose oxime as chiral auxiliary. The synthesis is based on a novel nucleophilic addition−intramolecular cyclization reaction and proceeds in 30% overall yield and >99% ee. An additional feature is the almost complete recovery of the auxiliary.

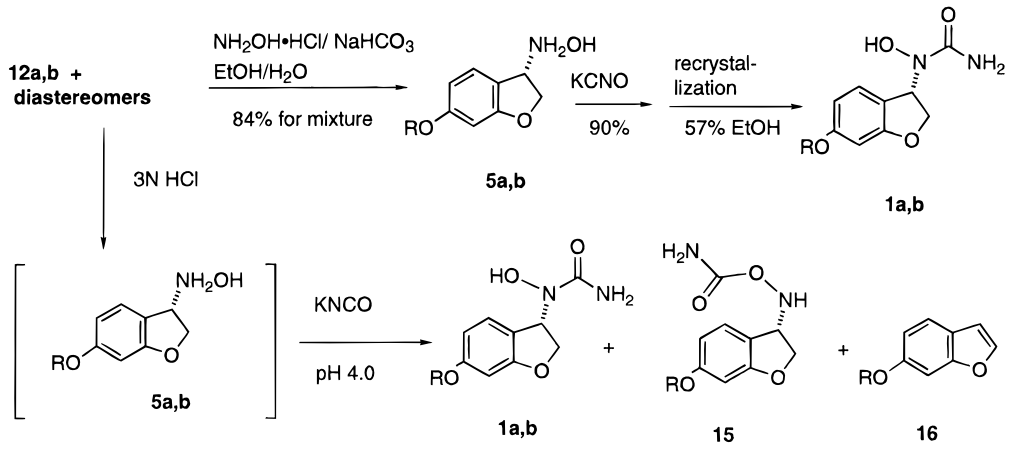
Experimental Section

General Remarks. NMR spectra are listed in ppm and were measured in relation to internal TMS standard in the solvent indicated. Commercial starting materials were obtained from Aldrich Chemical Co. Melting points were uncorrected.

6-(Benzyloxy)-3-oxo-2,3-dihydrobenzofuran. To a solution of **2**[4] (363 g, 2.42 mol) in DMF (4 L) were added anhyd K_2CO_3 (668 g, 4.84 mol) and BnBr (582 g, 3.40 mol) with stirring at rt over the period of 30 min. The reaction mixture was stirred for an additional 3 h and was poured into cold water (12 L). The precipitated solids were collected by filtration and dried *in vacuo*, obtaining 554 g of the desired compound (100%). ^{1}H NMR (DMSO-d_6, 300 MHz) 7.52 (d, J = 8.7 Hz, 1H), 7.41 (m, 5H), 6.90 (bs, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.22 (s, 2H), 4.76 (s, 2H). IR (KBr) 3070, 3040, 1710, 1610, 1446, 1320 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C,73.86; H, 5.05.

6-(Benzyloxy)-3-oximido-2,3-dihydrobenzofuran (3a). To a solution of the 6-benzyloxy compound from the above experiment (24 g, 0.1 mol) and anhyd NaOAc (24.6 g 0.30 mol) in 95% EtOH (216 mL) was added hydroxylamine hydrochloride (NH_2OH·HCl) (14.6 g, 0.21 mol). The mixture was heated under reflux for 1 h. The solution was cooled to about 60 °C, and an additional portion of NH_2OH·HCl (5.60 g, 0.080 mol) was added. After refluxing the solution for an 1 h, it was cooled to rt and poured into water (534 mL). The precipitated solids were filtered and dried *in vacuo* at 50 °C, yielding 21 g of **3a** (83%). ^{1}H NMR (DMSO-d_6, 300 MHz) 11.0 (s, 1H), 7.45−7.30 (m, 6H), 6.70 (s, 1H), 6.64 (dd, J = 8.4, 2.1 Hz, 1H), 5.12

Scheme 6



(s, 4H). IR (KBr) 3418, 2922, 1615, 1261 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.64; H, 5.17; N, 5.50.

Preparation of 6-[(2,6-Difluorophenyl)methoxy]-2,3-dihydrobenzofuran-3-one. A solution of **2**[4] (200.0 g, 1.332 mol) was obtained in DMF (1 L) by heating to 33 °C. After being cooled to rt, K_2CO_3 (248.5 g, 1.798 mol) was added. In a separate flask 2,6-difluorobenzyl bromide (331 g, 1.598 mol) was dissolved in DMF (200 mL). This solution was transferred over a 20 min period to the stirring reaction mixture containing the benzofuranone. The reaction mixture was stirred for 1.5 h at rt and was then added to water (5 L), causing crystallization of the product. The slurry was stirred for 30 min, and the pale yellow solid was filtered and rinsed with water (6 L) followed by EtOH (1 L). The product was dried *in vacuo*, isolating 356 g (96.7%), mp 134.0−138.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.57 (bd, J = 7.1 Hz, 1H), 7.41−7.33 (m, 1H), 7.00−6.91 (m, 2H), 6.78−6.71 (m, 2H), 5.17 (s, 2H), 4.62 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) 197, 175, 166, 161, 132, 124, 114, 111, 111, 111, 97, 75, 58. IR (KBr) 3075, 1700, 1610, 1595, 1454, cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_2O_3$: C, 64.98; H, 3.63. Found: C, 64.57; H, 3.33.

Preparation of 6-[(2,6-Difluorophenyl)methoxy]-2,3-dihydrobenzofuran-3-one Oxime (3b). To a stirred solution of 6-[(2,6-difluorophenyl)methoxy]-2,3-dihydrobenzofuran-3-one (340 g, 1.231 mol) and NH_2OH·HCl (118 g, 1.698 mol) in EtOH (2.57 L) was added NaOAc (135.3 g, 1.65 mol). The reaction mixture was refluxed for 3 h and allowed to cool to rt. The cooled reaction mixture was poured into H_2O (3.42 L), causing crystallization. The slurry was stirred for 30 min, and the product was filtered. The product was rinsed with hexane (3.67 L) and dried at 40 °C *in vacuo*. Isolated 338 g of **3b** (94.3%), mp 166−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 11.1 (s, 1H), 7.48 (bd, J = 7 Hz, 1H), 7.45−7.26 (m, 1H), 7.0−6.88 (m, 2H), 6.68−6.50 (m, 2H), 5.14 (s, 2H), 5.11 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) 166, 161, 161, 154, 131, 122, 113, 112, 111, 109, 97, 71, 58. IR (KBr) 3311, 2945, 1616, 1595, 1470 cm^{-1}. Anal. Calcd for $C_{15}H_{11}F_2NO_3$: C, 61.85; H, 3.80; N, 4.81. Found C, 61.74; H, 3.45; N, 4.60.

***N*-[3-[6-(Benzyloxy)-2,3-dihydrobenzofuranyl]]hydroxylamine (4a).** To a solution of **3a** (505 g, 1.98 mol) in MeOH:CH_2Cl_2 (1:1, 10 L) was added BH_3−pyridine (808 g, 8.69 mol). The resulting mixture was dropwise treated with 6 N HCl (1.5 L) over 1.15 h, and the reduction proceeded for 18 h at rt. The clear-yellow solution was concentrated at reduced pressure to a thick oil, which was cooled to 0−5 °C, and 3 N HCl was cautiously added. The precipitated HCl salts were filtered and suspended in cold H_2O. The pH of the suspension was adjusted to 10.5 first by the addition of 50% NaOH solution to pH 8 and then concd NH_3. The solid hydroxylamine was filtered and dried in vacuo, yielding 440 g of **4a** (86%). ^{1}H NMR (DMSO-d_6, 400 Hz) 7.54 (br s, 1H), 7.41 (m, 4H), 7.27 (d, J = 8.0 Hz, 1H), 6.51 (dd, J = 8.0, 2.3 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 5.08 (s, 2H), 4.55 (dd, J = 6.7, 4.0 Hz, 1H), 4.48 (br s, 2H). ^{13}C NMR (DMSO-d_6) 161, 159, 137, 128(2C), 127, 127(2C), 126, 118, 106, 96, 75, 69, 62. IR (KBr) 3423, 3100−2800, 1620, 1600, 1289, 1184 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.45; H, 5.81; N, 5.38.

The 2,6-difluoro compound 4b was prepared in a similar fashion from **3b** in 85% yield. ^{1}H NMR (DMSO-d_6) 7.53 (tt, J = 8.3, 6.5 Hz, 1H), 7.43 (br s, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 2H), 6.51 (br m, 2H), 5.03 (s, 2H), 4.55 (dd, J = 6.5, 4.4 Hz, 1H), 4.49 (m, 2H). ^{13}C NMR (DMSO-d_6) 161.9, 161.2 (2C), 159.8, 131.6, 126.3, 119.2, 112.2, 111.7 (2C), 106.5, 96.4, 75.7, 62.5, 57.8. IR (KBr) 3440, 3100−2800, 1626, 1598, 1288, 1235, 1187 cm^{-1}. Anal. Calcd for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.45; H, 4.39; N, 4.83.

Resolution of Racemic 4a and 4b. To **4a** (50 g, 0.194 mol) in MeOH (1.4 L) was added a solution of (+)-S-mandelic acid (29.57 g, 0.194 mol) in MeOH (45 mL), and the mixture was heated for 30 min to obtain a clear-yellow solution. The solution was allowed to slowly cool to rt over 2.5 h and then stirred for an additional 4 h. The precipitated salts were filtered, washed with EtOAc, and dried, affording 24.4 g (0.06 mol, 30%). The isolated salts (20 g, 0.049 mol) were covered with H_2O (208 mL) and EtOAc (520 mL), and concd NH_3 solution was slowly added with constant stirring until a pH of 9.5 was obtained. The layers were separated, the aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic solution was concentrated under reduced pressure until a white suspension was obtained. Hexane (415 mL) was added, and the suspension was stirred in an ice-bath for 1 h to complete crystallization. The crystalline product was filtered, yielding after drying 12.2 g of **5a** (97%). $[\alpha]^{25}_D$ = +24.04 (*c* 1.0, DMSO). ^{1}H NMR (DMSO-d_6) 7.35−7.44 (m, 6H), 7.23 (d, J = 8.9, 1H), 6.50 (bs, 1H), 6.45 (bd, 1H), 5.89 (bs, 1H), 5.05 (s, 2H), 4.52 (t, 1H), 4.47 (bs, 1H), 4.45 (bs, 1H). ^{13}C NMR (DMSO-d_6) 161, 159, 137, 128 (2C), 127, 127 (2C), 126, 118, 106, 96, 75, 69, 62. IR (KBr) 3435, 3252, 3100, 3000−2800, 1625, 1599, 1281, 1150 cm^{-1}; MS m/z 258 $(M + H)^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.83; H, 5.91; N, 5.51.

Compound 5b was Prepared Similarly. $[\alpha]^{25}_D$ = +21.15 (*c* 1.0, DMSO); 1H NMR (DMSO-d_6) 7.50 (m, J = 6.6 Hz, 1H), 7.45 (s, 1H), 7.23 (d, J = 8.9 Hz, 1H), 7.16 (t, J = 8.3, 7.8 Hz, 2H), 6.49 (bs, 1H), 6.47 (bd, 1H), 5.92 (bs, 1H), 5.05 (s, 2H), 4.52 (t, 1H), 4.47 (bs, 1H) 4.45 (br s, J = 5.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) 161, 161(2C), 159, 131, 126, 119, 112, 111(2C), 106, 96, 75, 62, 57. IR (KBr) 3440, 3250, 3140, 1627, 1597, 1284, 1234, 1155 cm^{-1}. MS m/z 294 $(M + H)^+$. Anal. Calcd for $C_{15}H_{13}NO_3F_2$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.28; H, 4.48; N, 4.79.

***N*-[3-[6-(Benzyloxy)-2,3-dihydrobenzofuranyl]]-*N*-hydroxyurea (1a).** To a stirred solution of **5a** (152 g, 0.59 mol) in DMF (767 mL) and AcOH (53.27 g, 0.89 mol) was added a solution of KOCN (72.0 g, 0.89 mol) in H_2O (133 mL) at 0 °C in one portion. A white suspension of the product formed almost immediately which became a viscous mixture within 15 min. TBME (3000 mL) was added and stirring continued for an additional 1 h while the mixture was cooled to 0−5 °C. The product was filtered and recrystallized from DMF:TBME

(1:3) mixture, yielding 154 g of **1a** (87.3%), mp 174−5 °C. $[\alpha]^{25}_D = +97.22$ (*c* 1.0, DMSO). ^{1}H NMR (DMSO-d_6) 9.12 (s, 1H), 7.42 (dd, J = 8.5, 1.8 Hz, 2H), 7.37 (dd, J = 7.0, 8.5 Hz, 2H), 7.31 (tt, J = 6.9, 1.7 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.50 (dd, J = 8.3, 2.3 Hz, 1H), 6.48 (br s, 2H), 6.45 (d, J = 2.1 Hz, 1H), 5.79 (dd, J = 9.1, 4.2 Hz, 1H), 5.05 (s, 2H), 4.55 (dd, J = 9.5, 9.3 Hz, 1H), 4.46 (dd, J = 9.7, 4.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 162, 161, 160, 137, 128(2C), 127, 127(2C), 125, 117, 107, 96, 73, 69, 58. IR (KBr) 3462, 3323, 3263, 3175, 3100−2800, 1643, 1626, 1295, 1169, 1135, cm^{-1}. MS *m*/*z* 301 $(M + H)^+$, 318 $(M + NH_4)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.88; H, 5.42; N, 9.33.

Preparation of *N*-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)[2-hydroxy-4-(phenylmethoxy)phenyl]-methanimine *N*-Oxide (11a). To a solution of 4-(benzyloxy)-2-hydroxybenzaldehyde[16] (91.4 g, 0.401 mol) and (2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)hydroxylamine (100.0 g, 0.364 mol) in toluene (640 mL) at rt was added tributylamine (74.3 g, 0.401 mol). The reaction was heated at reflux for 6 h, and the water was removed via a Dean−Stark trap. After the reaction was cooled to rt, heptanes (250 mL) was added to facilitate crystallization. The mixture was further cooled to 10 °C, and stirred for 1 h. The product was filtered, rinsed with heptanes (2 × 250 mL), and dried at reduced pressure to give the desired nitrone, as a pale yellow powder. Isolated 165.0 g (corrected 92.2%), mp 144.5−145.5 °C; $[\alpha]^{25}_D = {}^+7.85$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) 13.4 (s, 1H), 7.52 (s, 1H), 7.45−7.38 (m, 5H), 6.98−6.96 (d, J = 8.5 Hz, 1H), 6.51−6.48 (m, 2H) , 5.47 (s, 1H), 5.32−5.31 (d, J = 6.0 Hz, 1H), 5.06 (s, 2H), 5.01 (dd, J = 6.0, 3.9 Hz, 1H), 4.66 (dd, J = 6.9, 3.9 1H), 4.44 (dd, J = 6.9, 5.9 Hz, 1H), 4.15−4.12 (m, 2H), 1.56 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) 164, 162, 139, 136, 134, 128, 128, 127, 113, 109, 108, 108, 104, 101, 85, 84, 80, 73, 70, 66, 26, 26, 25, 24. IR (KBr) 3018, 1617, 1384, 1215 cm^{-1}. Anal. Calcd for $C_{26}H_{31}NO_8$: C, 64.45; H, 6.24; N, 2.89. Found: C, 64.07, H, 6.37; N, 2.76.

Preparation of 2,6-Difluoro-*N*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)[2-hydroxy-4-(phenylmethoxy)phenyl]methanimine *N*-Oxide (11b). A solution of 2,6-difluorobenzyl bromide (100.0 g, 0.483 mol) and KI (2.4 g, 15 mmol) in acetonitrile (200 mL) was added to a stirred solution of 2,4-dihydroxybenzaldehyde (68.1 g, 0.499 mol) and $NaHCO_3$ (45.5 g, 0.542 mol) in acetonitrile (420 mL) which was heated to 60 °C. The reaction mixture was then heated at reflux for 16 h and cooled to 25 °C, and water (250 mL) was added. The solution was extracted into toluene (1600 mL). The organic layer was washed with water (500 mL), and the acetonitrile and water were distilled off until the internal temperature reached 111−2 °C. The mixture was cooled to 25 °C, and (2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)hydroxylamine (**9**) (149.1 g, 0.542 mol) and tributylamine (100.5 g, 0.542 mol) were added. The reaction mixture was refluxed for 6 h with azeotropic removal of water via a Dean−Stark trap. The reaction mixture was cooled to 25 °C, and heptanes (250 mL) was added to facilitate crystallization. The pale-yellow crystals were filtered, rinsed with heptanes (2 × 250 mL), and dried under vacuum. The overall yield of **11b** starting from 2,6-difluorobenzyl bromide was 174.6 g (69.4%), mp 157.5−159.0 °C. $[\alpha]^{25}_D = +43.5$ ° (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz) 13.4 (s, 1H), 7.54 (s, 1H), 7.37 (m, 1H), 7.01−6.95 (m, 3H), 6.59 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 5.51 (s, 1H), 5.36 (d, J = 6.0 Hz, 1H), 5.15 (s, 2H), 5.01−4.99 (m, 1H), 4.68−4.65 (m, 1H), 4.45−4.43 (m, 1H), 4.15−4.12 (m, 2H), 1.55−1.38 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) 164, 162, 161, 139, 134, 131, 113, 112, 111, 109, 109, 108, 103, 101, 85, 84, 80, 73, 66, 57, 26, 25, 25, 24. IR (neat) 3018, 1617, 1596, 1473, 1215 cm^{-1}. Anal. Calcd for $C_{26}H_{29}F_2NO_8$: C, 59.88; H, 5.61; N, 2.69. Found: C, 59.75; H, 5.66; N, 2.93.

Preparation of Dimethylsulfoxonium Methylide in Tetrahydrofuran. A solution of potassium *tert*-butoxide (312 mL, 0.500 mol, a 1.60 M solution in THF) was added to THF (1.06 L) at rt with stirring, and the resulting solution was heated to 40 °C. Trimethylsulfoxonium iodide (121 g, 0.550 mol) was added, and the resulting white slurry was stirred at 40 °C until all the tBuOK had been consumed, usually 20 min. [The disappearance of tBuOK was monitored by treating solutions of iminostilbene in THF (10−20 mg of iminostilbene/10 mL of THF) with samples of the reaction mixture; a color change of the iminostilbene solution upon treatment implies the presence of excess potassium *tert*-butoxide.] The reaction mixture was cooled to rt and then filtered to remove KI and excess trimethylsulfoxonium iodide. The molarity of the dimethylsulfoxonium methylide filtrate solution was determined via titration against standard aqueous HCl solutions to the phenolphthalein endpoint. The methylide was then used without further purification. The ylide was also prepared following the procedure of Corey.[17a]

Preparation of (*S*)-(+)-*N*-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)[2,3-dihydro-6-(phenylmethoxy)-3-benzofuranyl]hydroxylamine (12a). A solution of dimethylsulfoxonium methylide in THF (52.9 mL, 100 mmol, a 1.89 M solution in THF) was added to a stirred slurry of nitrone *N*-(2,3:5,6-di-*O*-isopropylidine-α-D-mannofuranosyl)[2-hydroxy-4-(phenylmethoxy)phenyl]methanimine *N*-oxide **11a** (48.6 g, 100 mmol) in toluene (447 mL) at −10 °C. The rate of methylide addition was such that the reaction temperature never rose above −5 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 2 h and then stirred at +10 °C for 19 h at which point the reaction was 96% complete. The reaction mixture was cooled to 0 °C and treated with an additional quantity of the solution of dimethylsulfoxonium methylide (2.1 mL, 4.0 mmol, a 1.89 M solution in THF), and the reaction mixture was warmed to 10 °C and stirred for 5 h. The reaction was then concentrated *in vacuo*. The residual yellowish-gold colored solid was dissolved in ethyl acetate (500 mL), washed with water (2 × 250 mL), dried over magnesium sulfate, and filtered. The solution was then filtered through a pad of silica gel to remove any sulfoxide side-product and concentrated *in vacuo*. The crude product was recrystallized from toluene (250 mL) and hexane (400 mL) to afford **11a**, 33.7 g (67.5%) as a 7.0 to 1 mixture of diastereomers. HPLC (Zorbax SBC8, $CH_3OH/H_2O/CH_3CN$/0.5 M ammonium acetate 5.72:2.25:1:1, 1.5 mL/min) t_R (major diastereomer) 17.8 min; t_R (minor diastereomer 15.3 min.

For the major diasteromer: $[\alpha]^{25}_D = +18.9°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19−7.43 (m, 6H), 6.46−6.55 (m, 2H), 5.03 (s, 2H), 4.92−4.95 (m, 1H), 4.82−4.86 (m, 2H), 4.68−4.74 (m, H), 4.55 (bs, 1H), 4.50 (s, 1H), 4.30−4.36 (m, 2H), 4.06−4.14 (m, 2H), 1.49 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) 162, 161, 136, 128, 127, 127, 126, 117, 112, 109, 107, 98, 97, 84, 84, 80, 73, 73, 70, 66, 65, 26, 26, 25, 24. Anal. Calcd for $C_{27}H_{31}F_2NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 64.93; H, 6.76; N, 2.99.

Preparation of (S)-(+)-*N*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-2,3-dihydro-6-[(2,6-difluorophenyl)methoxy]-3-benzofuranylhydroxylamine (12b). A solution of dimethylsulfoxonium methylide (545 mL, 200 mmol, a 0.367 M solution in THF) was diluted with THF (455 mL) at rt to afford a final methylide solution with an approximate concentration of 0.2 M. The solution was cooled to −10 °C. Solid nitrone **11b** (104.3 g, 200 mmol) was added with stirring at such a rate that the reaction temperature never rose above −5 °C. After the addition was complete, the reaction mixture was warmed to +7 °C over a period of 45 min and then stirred for 15 h at +7 °C. After 15 h, the reaction was about 87% complete. The reaction mixture was cooled to −10 °C and treated with an additional quantity of the solution of dimethylsulfoxonium methylide (70.85 mL, 26 mmol, a 0.367 M solution in THF) at such a rate that the reaction temperature never rose above −5 °C. After the addition was complete, the reaction mixture was warmed to +7 °C and stirred for 4 h. The reaction was determined to be complete at this point based upon complete consumption of starting material. The reaction mixture was used in the next step without further purification. The reaction afforded approximately 104 g (HPLC weight-based solution assay, 97% yield) of **12b** as a 8 to 1 ratio of diastereomers with the desired diastereomer being the major product. For the major diasteromer (**12b**): ^{1}H NMR (C_3D_6O, 360 MHz) 7.61 (bs, 1H), 7.58−7.50 (m, 1H), 7.26−7.23 (m, 1H), 7.16−7.08 (m, 2H), 6.58−6.55 (m, 1H), 6.50 (bs, 1H), 5.17 (s, 2H), 5.02 (d, 1H, J = 3.6 Hz), 4.89−4.84 (m, 3H), 4.79−4.76

(m, 1H), 4.54−4.46 (m, 2H), 4.32 (dd, 1H, J = 3.6, 3.6 Hz), 4.13−4.08 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (C_3D_6O, 90.6 MHz) 163, 163, 161 131, 127, 118, 113, 111, 111, 108, 107, 98, 96, 85, 84, 81, 74, 74, 66, 65, 58, 26, 25, 25, 24. Anal. Calcd for $C_{27}H_{31}F_2NO_8$: C, 60.56; H, 5.83; N, 2.62. Found: C, 59.57; H, 5.92; N, 2.57.

Preparation of (S)-*N*-[6-(Benzyloxy)-2,3-dihydrobenzofuran-3-yl]hydroxylamine (5a) (removal of the mannose auxiliary from isolated 12a with NH_2OH·HCl). To a solution of $NaHCO_3$ (2.90 g, 34.5 mmol) in 60 mL of water was slowly added hydroxylamine hydrochloride (2.60 g, 37.4 mmol). The resulting solution was added to a suspension of **12a** (4.7 g, 9.4 mmol) as a 8 to 1 mixture of diastereomers in EtOH (60 mL). The mixture was refluxed for 80 min and then cooled to rt in 1 h. The white suspension was filtered, washed with water (50 mL) and hexanes (50 mL), and dried at 40 °C *in vacuo*, yielding 2.32 g of **5a** as a white solid in 96.0% yield and 98.6% ee $[\alpha]^{25}_D = +24.04$ (*c* 1.0, DMSO). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.83; H, 5.91; N, 5.51.

The mother liquor from the filtration was concentrated to remove EtOH and then extracted with EtOAc (3 × 75 mL). Combined EtOAc extract was washed with water (70 mL), dried over $MgSO_4$, filtered, and evaporated to a residue which was crystallized from EtOAc (6 mL)/hexanes (55 mL) to give **9** as a white solid (2.30 g, 8.4 mmol, 89.4% yield).

Preparation of (S)-*N*-[6-[(2,6-Difluorophenyl)methoxy]-2,3-dihydrobenzofuran-3-yl]hydroxylamine, 5b (from crude reaction mixture of 12b). The reaction mixture of **12b** (20.2 g, 37.7 mmol) was concentrated under reduced pressure to an oil of a 8 to 1 ratio of diastereomers. EtOH (65 mL) was added, and a solution of $NaHCO_3$ (11.3 g, 134 mmol) and NH_2OH·HCl (10.1 g, 146 mmol) in water (65 mL). The resulting suspension was refluxed for 1.5 h, cooled to rt, and stirred for 1.5 h. The resulting white suspension was treated with water (110 mL) for 10 min and filtered. The solid product was washed with water (220 mL) and hexanes (220 mL) and dried at 40 °C *in vacuo* to yield a yellow solid containing 10.1 g of **5b** and its enantiomer in 91.1% yield and 72% ee $[\alpha]^{25}_D = +21.15$ (*c* 1.0, DMSO).

Conversion of 12a Directly to (S)-*N*-[6-(Benzyloxy)-2,3-dihydrobenzofuran-3-yl]-*N*-hydroxyurea (1a) without Isolating 5a. A solution of the mannosylhydroxylamine **12a** (1.9 g, 3.8 mmol) in DMF (20 mL) and water (4 mL) was cooled to about 25 °C. To this stirred solution was added 1 N HCl (7.0 mL, 7 mmol) over 50 min, the water bath was removed, and the mixture was stirred at rt for 2 h. The reaction was cooled to about 5 °C, and the pH was adjusted to about 4.5 by treatment with 6 N NaOH (0.5 mL, 3 mmol) and HOAc (0.24 mL, 4.2 mmol). A solution of KOCN (0.34 g, 4.2 mmol) in water (2 mL) was added and stirring continued at about 5 °C for 30 min. The reaction mixture was treated with water (16 mL), and the resulting slurry was stirred for 10 min at about 5 °C. The white precipitate was filtered, washed with water (10 mL) and hexanes (20 mL), and dried at 40 °C *in vacuo* to yield 0.88 g of **1a** and its enantiomer as a white solid in 77.9% yield and 90.4% ee. This crude **1a** (0.46 g, 1.55 mmol, 90.4% ee) was recrystallized from DMF (3.73 mL)/TBME (10.5 mL) to yield purified **1a** (0.42 g, 1.4 mmol, 99.7% ee, 94.6% yield).

Preparation of 1b. To a solution of **5b** (9.6 g, 32.9 mmol, 72% ee) in DMF (73 mL) was added HOAc (3.51 mL, 61.4 mmol). The resulting solution was cooled in an ice bath to ∼5 °C. A solution of KOCN (5.0 g, 61.4 mmol) in water (9 mL) was added at such a rate that the internal temperature did not exceed 15 °C. After stirring at ∼5 °C for 30 min, water (208 mL) was added and the resulting suspension was stirred at 20−25 °C for 1 h. The precipitated solids were filtered, washed with water (200 mL) and hexanes (200 mL), and then dried at 40 °C *in vacuo* to yield **1b** as a very light-yellow solid (9.9 g 29.5 mmol, 74% ee, 90.9% yield).

Recrystallization of 1b. To crude **1b** (38.4 g, 74.2% ee) was added 2-propanol (950 mL). The resulting suspension was heated to a clear solution and refluxed for 5 min and then slowly cooled to rt in 3 h with minimum stirring (the reaction mixture was seeded with **1b** at 65 °C). The product was filtered, washed with hexanes (1100 mL), and dried at 40 °C in vacuo to yield **1b** as a white solid (26.5 g, 75.8% yield, no R isomer was detected). $[\alpha]^{25}_D = +87.53$ (*c* 1.0, DMSO). ^{1}H NMR (DMSO-d_6) 9.12 (s, 1H), 7.50 (m, J = 6.6 Hz, 1H), 7.16 (t, J = 8.3, 8.0 Hz, 2H), 7.08 (d, J = 8.5 Hz, 1H), 6.51 (dd, J = 2.5 Hz, 2H), 6.48 (br s, 2H), 5.79 (dd, J = 9.2, 4.2 Hz, 1H), 5.05 (s, 2H), 4.57 (t, J = 9.2 Hz, 1H), 4.47 (dd, J = 9.7, 4.2 Hz, 1H). ^{13}C NMR (DMSO-d_6) 162, 161, 161(2C), 159, 131, 125, 118, 112, 111(2C), 106, 96, 73, 58, 57. IR (KBr) 3465, 3323, 3262, 3176, 3100−2800, 1642, 1627, 1233, 1165, 1109 cm^{-1}. MS m/z 337 $(M + H)^+$, 359 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_4F_2$: C, 57.15; H, 4.20; N, 8.33. Found: C, 57.10; H, 4.12; N, 8.17.

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