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From 2-Aminomethyl-1,4-benzodioxane Enantiomers to Unichiral 2-Cyano- and 2-Carbonyl-Substituted Benzodioxanes via Dichloroamine

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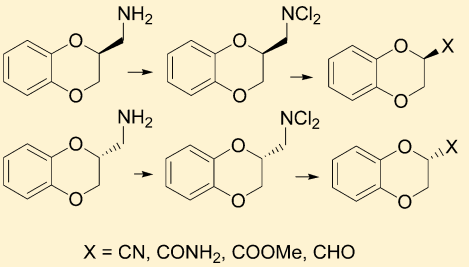
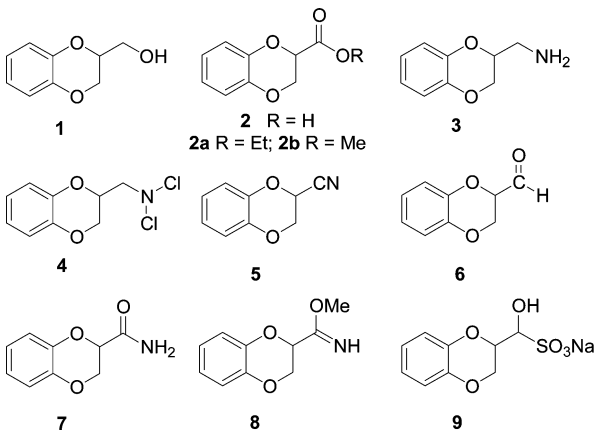
Supporting Information

ABSTRACT: 2-Substituted 1,4-benzodioxanes, such as 2-cyano-, 2-methoxycarbonyl-, 2-aminocarbonyl-, and 2-formyl-1,4-benzodioxane, are key synthons that for the most part are never described as enantiomers or are inadequately characterized for enantiomeric purity. They were prepared by quantitative N,N-dichlorination of (*R*)- and (*S*)-2-aminomethyl-1,4-benzodioxane and successive functional group conversions in high yields without any racemization of the stereogenic benzodioxane C(2).



2-Substituted 1,4-benzodioxanes are widely used chiral synthons because they occur as a key substructure in a variety of compounds, many of which are of biological interest in different areas.[1] D_2 antagonists,[2] subtype-selective adrenergic antagonists,[3] and neuronal nicotinic agonists[4] are only a few examples. Recently, the wide range of interesting pharmacological properties of 2-substituted 1,4-benzodioxanes has stimulated the development of new synthetic approaches. Significant examples are the palladium-catalyzed enantioselective cyclization of phenolic (*E*)-allylic trichlorocetamidates to give the *S* enantiomer of 2-vinyl-1,4-benzodioxane with 92−94% enantiomeric excess[5] or the use of "chiral pool" member (*S*)-ethyl lactate for the asymmetric synthesis of the 1,4-benzodioxane lignans eusiderins.[6] Historically, the two most accessible and synthetically versatile 2-substituted 1,4-benzodioxanes in unichiral form are 2-hydroxymethyl-1,4-benzodioxane (**1**) and 1,4-benzodioxane-2-carboxylic acid or ethyl ester (**2** and **2a**). The former can be prepared from the racemate of the latter by reduction and successive enzymatic resolution[7] or vice versa[8] or from the enantiomers of C3 synthetic units, which in turn are available from the "chiral pool"[9] or from the respective racemates by classical[10] or enzymatic resolution[11] or from prochiral precursors through a stereoselective reaction.[12] The latter are readily synthesized from catechol and 2,3-dibromopropionate[13] and then resolved as the ester or the acid by various methods such as entrainment,[14] enzymatic resolution,[8,15] or selective crystallization of diastereomeric salts.[16] In this context, we have recently reported that mandelic acid efficiently resolves 2-aminomethyl-1,4-benzodioxane (**3**),[17] whose racemate is as easily accessible as that of **2**.[2,18] Such a successful procedure prompted us to consider the enantiomers of **3** as precursors not only of more substituted amines but also of other 2-substituted 1,4-benzodioxanes that are valuable as synthetic intermediates. In particular, we thought to prepare derivatives such as 2-cyano-1,4-benzodioxane (**5**), 1,4-benzodioxane-2-carboxaldehyde (**6**), 1,4-benzodioxane-2-carboxamide (**7**), and methyl 1,4-benzodioxane-2-carboxylate (**2b**), whose enantiomers have never been described or which have never been prepared from **3**.



For this purpose, we needed a very simple, mild, and efficient way of oxidizing amine **3**. This was suggested to us by our recent research on N-chlorination with safe and cheap trichloroisocyanuric acid (TCCA)[19] or sodium dichloroisocyanurate[20] and the subsequent dehydrochlorination of amines and amides, which are key synthetic precursors of important biologically active unichiral compounds.[21]

Therefore, the first reaction we studied was the N-chlorination of the enantiomers of **3**. A ratio of 0.67 mol of TCCA per mol of (*S*)-**3** quantitatively gives the corresponding

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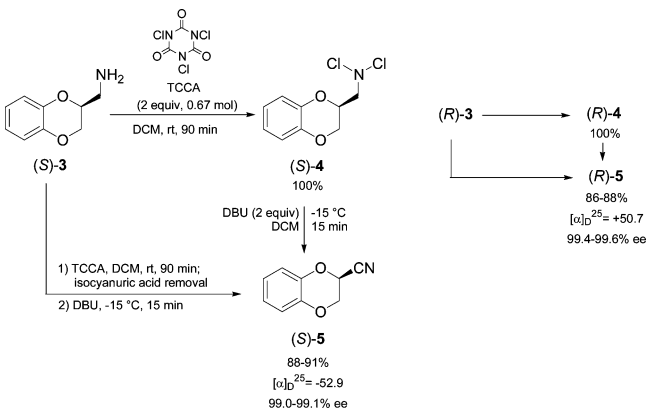
N,*N*-dichloroamine (*S*)-**4** after 1 h at room temperature in methanol, in which TCCA is freely soluble. However, at the end of the reaction, the formed isocyanuric acid cannot be completely removed by filtration because it precipitates only partially. Its residual presence in the reaction filtrate hampers the accurate dosage of the base, which is necessary for the subsequent dehydrohalogenation to give the nitrile; the base has to be neither deficient nor in excess of 2 equiv on pain of nitrile racemization. Thus, we opted to use dichloromethane to effect one-pot double chlorination and dehydrochlorination without isolating the intermediate dichloroamine and without nitrile racemization. In fact, isocyanuric acid is highly insoluble in dichloromethane and quantitatively removable. The reaction was rather slow because of the modest solubility of TCCA, but its rate could be sensibly increased simply by using finely powdered TCCA and a higher amount of solvent. After 90 min at room temperature, (*S*)-**3** was quantitatively converted into the corresponding dichloroamine (*S*)-**4**, which was isolated by filtering off the isocyanuric acid and evaporating the dichloromethane to give the product as an oil that is unstable at room temperature but stable at 4 °C for weeks (Scheme 1).

Scheme 1. N,N-Dihalogenation and Dehydrohalogenation of 2-Aminomethyl-1,4-benzodioxane Enantiomers To Give (*S*)- and (*R*)-2-Cyano-1,4-benzodioxane[a]



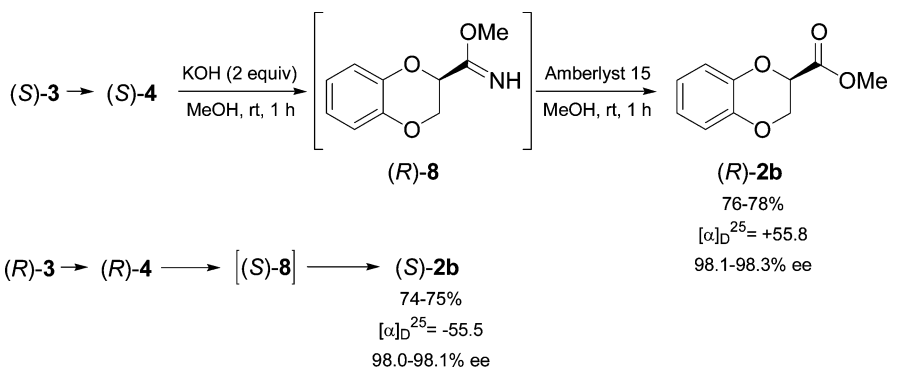
[a]Dichlorination of 1 mol of substrate required 0.67 mol of TCCA, equivalent to 0.67 × 3 = 2 mol of chlorine.

Alternatively, the filtered reaction mixture was directly subjected to the treatment with a base to give the nitrile (*S*)-**5**. In order of increasing basicity, we tested triethylamine (TEA), *N*,*N*-diisopropylethylamine (DIPEA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). TEA and DIPEA produced appreciable dehydrochlorination at room temperature. However, the isolated yields of the nitrile were lower than 50% as a result of the formation of byproducts. At 0 °C, TEA and DIPEA were practically ineffective. On the contrary, DBU was able to efficiently dehydrochlorinate (*S*)-**4** under very mild conditions: 2 mol of DBU reacted with 1 mol of dichloroamine at −15 °C for 15 min to give (*S*)-**5** as a crystalline solid, higher melting than *rac*-**5**, in 91% yield after chromatographic purification. (*R*)-**5** and *rac*-**5** were prepared in the same manner from (*R*)-**3** and *rac*-**3**, respectively (Scheme 1). No literature data are available for the enantiomers of **5**. Therefore, the symmetrical rotations we measured for (*S*)-**5** and (*R*)-**5** needed to be supplied with the corresponding enantiomeric excesses, which were found to be 99.1 and 99.6%, respectively, by chiral HPLC analysis. Such values demonstrate that the two reactions, N-dichlorination and didehydrochlorination, do not imply any racemization under the selected conditions.

Double dehydrochlorination of intermediate **4** was also performed with 2 equiv of KOH in methanol. Such a treatment afforded the corresponding methyl imidate **8**, which could be readily converted into methyl ester **2b** by simple addition of a strongly acidic resin (Amberlyst-15) to the reaction solution after it was filtered to remove precipitated KCl. As **3** is quantitatively dichlorinated and **8** does not need to be isolated, this way makes feasible the straightforward conversion of the amines (*S*)-**3**, (*R*)-**3**, and *rac*-**3** into the methyl esters (*R*)-**2b**, (*S*)-**2b**, and *rac*-**2b**, respectively, in 72−78% yield (Scheme 2). The HPLC enantiomeric excesses of 98.3 and 98.1% determined for (*R*)-**2b** and (*S*)-**2b** proved that the conversion of the amine into the ester occurred without racemization. These results make the resolution of *rac*-**3**[17] followed by transformation into (*R*)-**2b** and (*S*)-**2b** an alternative route that is not less convenient than *rac*-**2** resolution followed by esterification of the resolved acids.[16]

The successive challenge was to convert the efficiently obtained enantiomers of **5** into other useful synthetic intermediates with unchanged enantiomeric purity. The enantiomers of 1,4-benzodioxane-2-carboxamide **7** have never been described apart from one report on (*S*)-**7**, which was observed to be recoverable with 94% enantiomeric excess and in 50% yield as the unreacted substrate from the claimed enantioselective hydrolysis of *rac*-**7** by a *Rhodococcus erythropolis* amidase.[22] Conventional methods for hydration of nitriles can

Scheme 2. Conversion of (*S*)- and (*R*)-2-Aminomethyl-1,4-benzodioxane into Methyl 1,4-Benzodioxane-2-carboxylate Enantiomers via Dichloroamine and Methyl Imidate



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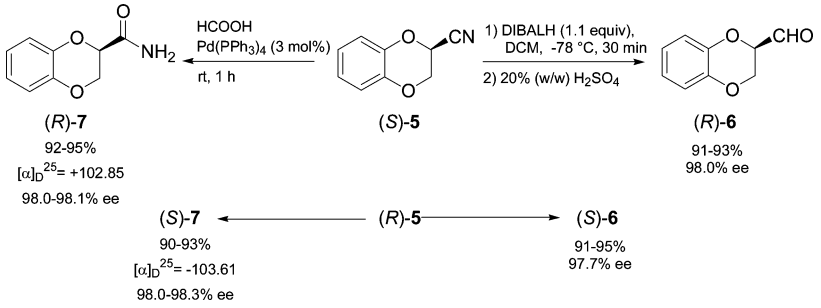
Scheme 3. Conversion of (*S*)- and (*R*)-2-Cyano-1,4-benzodioxane into 1,4-Benzodioxane-2-carboxamide and 1,4-Benzodioxane-2-carboxaldehyde Enantiomers[a]

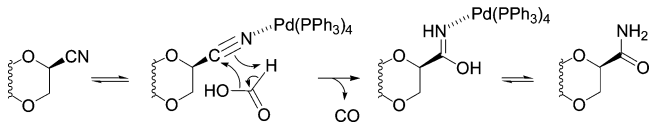


[a]The aldehyde enantiomeric excess was indirectly determined by chiral HPLC analysis after conversion to Bertagnini's salt and reduction to the alcohol.

present difficulties;[23] several protocols using enzymes,[24] heterogeneous catalysts,[25] or transition-metal complexes[26] have been developed. In searching for mild transformations of nitriles into carbonyl and carboxyl derivatives, our attention had been previously drawn to aqueous formic acid and PtO_2. These are reported to efficiently convert nitriles into aldehydes at 60 °C through intermediate imines resulting from the addition of hydrogen liberated by formic acid.[27] When performed on our substrate **5**, such a reaction yielded the amide **7** instead of the aldehyde **6** in 80% yield after chromatographic purification. The reaction product was the same also when anhydrous in place of aqueous formic acid was used, whereas the amide was not formed in the absence of PtO_2 or when aqueous formic acid was replaced with aqueous acetic acid. After ascertaining that anhydrous formic acid and the catalyst were necessary and sufficient to effect the reaction, we tried using palladium(0). In the presence of Pd/C, the amide formation was slow and incomplete, but the conversion of **5** into **7** was quantitative after 1 h at room temperature when the reaction was performed simply by adding 3% $Pd(PPh_3)_4$ to the nitrile solution in anhydrous formic acid. At room temperature, the presence of $Pd(PPh_3)_4$ was proved to be indispensable. Under such conditions, selected as the best ones, *rac*-**5**, (*S*)-**5**, and (*R*)-**5** were converted into *rac*-**7**, (*R*)-**7**, and (*S*)-**7**, respectively, and isolated in 89−95% yield after chromatographic purification (Scheme 3). Chiral HPLC analysis showed >98% ee for both (*R*)- and (*S*)-**7**.

To our knowledge, no other nitrile−amide conversions by treatment with formic acid have been reported in the literature. It is reasonable that palladium coordinates to the nitrile nitrogen, enhancing the electrophilicity of the nitrile carbon. Furthermore, the formation of the amide instead of the aldehyde suggests that formic acid would serve as a water source instead of a hydrogen source, decomposing to CO instead of CO_2,[28] and that the imidic acid is intermediately formed and then tautomerizes to the amide (Scheme 4). Water resulting from previous decomposition of formic acid could be the nucleophilic species, or alternatively, decomposition to CO could follow the nucleophilic attack by an intact formic acid molecule: water addition to nitrile is the net result in both cases. Anyhow, it is interesting to compare the $Pd(PPh_3)_4$-catalyzed reaction in formic acid with that in acetic acid, which cannot act as a water source. In formic acid, the quantitative conversion of the nitrile into the amide takes place in 1 h independent of the water addition, whereas it requires 7 h in 80% aqueous acetic acid and no fewer than 18 h in commercial glacial acetic acid. It is reasonable to conclude that the presence of water is superfluous in formic acid but determinant in acetic acid if we observe such a reaction time increment by replacing aqueous acetic acid with commercial glacial acetic acid, where there is a trace amount of water.

Scheme 4. Proposed Mechanism of Nitrile Hydration by Treatment with Formic Acid in the Presence of $Pd(PPh_3)_4$



1,4-Benzodioxane-2-carboxaldehyde (**6**) has never been characterized either as a racemate or as single enantiomers. The reduction of nitrile to imine, which failed when formic acid was used, was successfully performed with DIBALH in dichloromethane; **6** could be obtained by hydrolysis of the intermediate iminoalane in quantitative yield (Scheme 3). The reduction was performed on both *rac*-**5** and the two enantiomers of **5**. It is known that the aldehydes are generally unstable. Indeed, **6** was stable in the course of the reaction workup and in dichloromethane solution at 4 °C for weeks, but it rapidly degraded at room temperature and also at 4 °C when dichloromethane was completely evaporated. Nevertheless, its quantitative formation was well-evidenced by TLC on silica gel and by ^1H and ^{13}C NMR analyses in $CDCl_3$ on samples collected from dichloromethane solution and analyzed immediately after removal of the dichloromethane under vacuum. However, we needed a derivative that would allow the aldehyde (a) to be indefinitely stored undissolved, (b) to be easily regenerated or directly used without regeneration, and (c) to have its enantiomeric excess be directly or indirectly ascertained. Bertagnini's salt[29] was just what we needed: the adducts **9** formed from sodium bisulfite and (*S*)-**6** and (*R*)-**6** are stable solids that were easily obtained in >90% yield without purification steps (Scheme 5). The nucleophilic addition of bisulfite to the carbonyl group was not diastereoselective: nearly equimolar mixtures of epimers at the new stereocenter were obtained from (*S*)-**6** and (*R*)-**6**, as proved by the respective ^1H NMR spectra, where the hydroxyl proton appears as two well-distinct and equally integrating doublets.

Regeneration of (*S*)-**6** and (*R*)-**6** from the bisulfite adducts was carried in quantitative yield according to a literature method (Scheme 5).[30] Reduction of the bisulfite adducts of (*S*)-**6** and (*R*)-**6** by treatment with sodium borohydride in methanol provided 2-hydroxymethyl-1,4-benzodioxanes (*R*)-**1**

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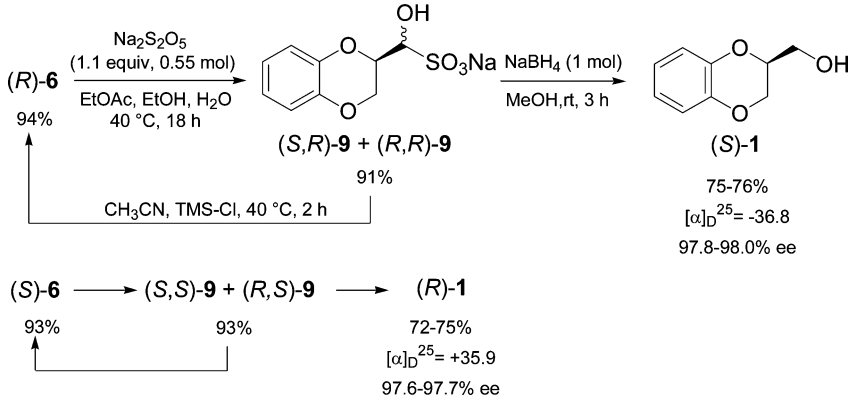
Scheme 5. Conversion of (*R*)- and (*S*)-1,4-Benzodioxane-2-carboxaldehyde into Bisulfite Adducts, Reduction to (*S*)- and (*R*)-2-Hydroxymethyl-1,4-benzodioxane, and Regeneration of the Aldehydes



and (*S*)-**1**, respectively, in high yields (Scheme 5). Chiral HPLC analysis of (*R*)-**1** and (*S*)-**1** showed enantiomeric excesses near 98%, thus demonstrating that the conversion of (*R*)-**5** and (*S*)-**5** into the respective aldehydes does not imply racemization, and neither does the subsequent derivatization to Bertagnini's salts and the final reduction of the latter.

In conclusion, simple methods are reported for the conversion of the ready available enantiomers of 2-aminomethyl-1,4-benzodioxane into 2-cyano- and 2-carbonyl-substituted benzodioxanes, which are useful unichiral synthons. The reactions, carried out under mild conditions, proceed in high to excellent yields and, what is more important, without racemization.

EXPERIMENTAL SECTION

General Procedures. All chemicals and solvents were used as received from commercial sources or prepared as described in the literature. Anhydrous formic acid was prepared according to standard literature procedures. Flash chromatography was performed by using silica gel 60 (40−63 μm). TLC analyses were carried out on aluminum plates precoated with silica gel 60 F254 (layer thickness, 0.2 mm) and visualized with UV light; R_f values are given for guidance. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz using an FT-NMR spectrometer. Chemical shifts are reported in parts per million relative to residual solvent ($CHCl_3$ or DMSO) as an internal standard. The atmospheric pressure ionization (API) mass spectra of (*S*)-**4** and (*R*)-**6** bisulfite adduct were acquired using a high-resolution electrostatic field mass spectrometer (Orbitrap) with up to 100 000 resolving power and 5 ppm mass accuracy; the mass spectrum of the intermediate (*R*)-**8** was acquired using a triple-quadrupole mass spectrometer. Melting points were determined by differential scanning calorimetry (DSC) and correspond to the peak maximum. Optical rotations were determined in a 1 dm cell of 1 mL capacity. Enantiomeric excesses were determined by chiral HPLC analyses, and compounds were detected at 276 or 280 nm.

(*S*)-2-*N*,*N*-Dichloroaminomethyl-1,4-benzodioxane [(*S*)-4]. Trichloroisocyanuric acid (938 mg, 4.03 mmol) was added to a solution of (*S*)-**3** (1.00 g, 6.05 mmol) in DCM (30 mL) at 0 °C. The mixture was stirred for 90 min at room temperature and then cooled to −15 °C. The precipitated isocyanuric acid was filtered off, and the filtrate was concentrated under vacuum to give (*S*)-**4** as a light-yellow oil in quantitative yield. TLC (cyclohexane/EtOAc 9:1) R_f = 0.73; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (dd, *J* = 5.8 Hz, 13.5 Hz, 1H), 4.02 (dd, *J* = 5.8 Hz, 13.5 Hz, 1H), 4.08 (d, *J* = 5.8 Hz, 1H), 4.30 (dd, *J* = 2.5 Hz, 11.6 Hz, 1H), 4.58 (dq, *J* = 2.5 Hz, 5.8 Hz, 1H), 6.83−6.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.5, 70.8, 74.8, 117.5, 117.8, 122.1, 122.3, 142.4, 143.1; HRMS (ESI) *m*/*z* calcd for $C_9H_{10}Cl_2NO_2$ (MH^+) 234.00831, found 234.00776. Anal. Calcd for $C_9H_9Cl_2NO_2$ (234.08): C, 46.18; H, 3.88; Cl, 30.29; N, 5.98. Found: C, 46.27; H, 3.93; Cl, 30.18; N, 5.92.

(*R*)-2-*N*,*N*-Dichloroaminomethyl-1,4-benzodioxane [(*R*)-4]. Obtained from (*R*)-**3** in quantitative yield as described for (*S*)-**4**. The ^{1}H NMR and ^{13}C NMR data were identical to those of (*S*)-**4**.

***rac*-2-*N*,*N*-Dichloroaminomethyl-1,4-benzodioxane (*rac*-4).** Obtained from *rac*-**3** in quantitative yield as described for (*S*)-**4**. The ^{1}H NMR and ^{13}C NMR data were identical to those of (*S*)-**4**.

(*S*)-2-Cyano-1,4-benzodioxane [(*S*)-5]. A solution of DBU (1.8 mL, 12.00 mmol) in DCM (2 mL) was added dropwise to a solution of (*S*)-**4** (1.40 g, 5.98 mmol) in DCM (10 mL) at −10 °C. The mixture was stirred for 15 min, and then 1 N HCl (10 mL) was added. The layers were separated, and the organic phase was dried over Na_2SO_4 and concentrated under vacuum to give the crude nitrile. Purification on silica gel (cyclohexane/AcOEt 9:1) yielded (*S*)-**5** as a white solid. The yields ranged between 88% (850 mg) and 91% (880 mg). TLC (cyclohexane/EtOAc 9:1) R_f = 0.33; mp = 62.21 °C; $[\alpha]_D^{25}$ = −52.9 (*c* 1, $CHCl_3$); 99.0−99.1% ee (determined by HPLC analysis on a Kromasyl AmyCoat column, 250 mm × 4.6 mm i.d.; hexane/EtOH 95:5; 0.8 mL/min; 276 nm; $t_R \approx 21$ min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 2.75 Hz, 11.55 Hz, 1H), 4.42 (dd, *J* = 3.85 Hz, 11.55 Hz, 1H), 5.11 (dd, *J* = 2.75 Hz, 3.85 Hz, 1H), 6.95 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.1, 64.9, 115.0, 117.8, 118.2, 122.9, 123.5, 140.7, 142.5. Anal. Calcd for $C_9H_7NO_2$ (161.16): C, 67.08; H, 4.38; N, 8.69. Found: C, 66.92; H, 4.40; N, 8.66.

(*R*)-2-Cyano-1,4-benzodioxane [(*R*)-5]. Obtained from (*R*)-**4** in 86−88% yield as described for (*S*)-**5**. Mp = 64.62 °C; $[\alpha]_D^{25}$ = +50.7 (*c* 1, $CHCl_3$); 99.4−99.6% ee (determined by HPLC analysis as described for (*S*)-**5**; $t_R \approx 19$ min); the ^{1}H NMR and ^{13}C NMR data were identical to those of (*S*)-**5**.

***rac*-2-Cyano-1,4-benzodioxane (*rac*-5).** Obtained from *rac*-**4** in 86−89% yield as described for (*S*)-**5**. Mp = 56.14 °C; the ^{1}H NMR and ^{13}C NMR data were identical to those of (*S*)-**5**.

(*R*)-1,4-Benzodioxane-2-carboxaldehyde [(*R*)-6]. A 1 M solution of DIBALH in toluene (6.8 mL) was added to a solution of (*S*)-**5** (1.00 g, 6.20 mmol) in DCM (10 mL) at −78 °C. The resulting mixture was stirred at this temperature for 30 min. After dilution with DCM (20 mL), 2 M H_2SO_4 (5 mL) was slowly added. The layers were separated, and the organic phase was dried and concentrated under vacuum to give (*R*)-**6** as a clear oil. The yields ranged between 91% (930 mg) and 93% (950 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, *J* = 3.85 Hz, 2H), 4.64 (t, *J* = 3.85 Hz, 1H), 6.90 (m, 3H), 7.02 (m, 1H), 9.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.4, 76.8, 117.8, 117.9, 122.5, 142.2, 143.5, 199.1. The neat product quickly degraded at room temperature but was stable for several days if dissolved in DCM (ca. 20% w/v).

(*S*)-1,4-Benzodioxane-2-carboxaldehyde [(*S*)-6]. Obtained from (*R*)-**5** in 91−95% yield as described for (*R*)-**6**. The ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-**6**.

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***rac*-1,4-Benzodioxane-2-carboxaldehyde (*rac*-6).** Obtained from *rac*-**5** in 92−96% yield as described for (*R*)-**6**. The ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-**6**.

(*R*)-1,4-Benzodioxane-2-carboxamide [(*R*)-7]. $Pd(PPh_3)_4$ (214 mg, 0.18 mmol) was added to a solution of (*S*)-**5** (1.00 g, 6.20 mmol) in formic acid (9 mL). After 1 h of stirring, ethyl acetate and $NaHCO_3$ saturated aqueous solution were added. The layers were separated, and the organic phase was repeatedly washed with $NaHCO_3$ saturated solution until neutral pH was reached. The organic phase was dried with Na_2SO_4 and concentrated under vacuum to give the crude amide. Purification on silica gel (cyclohexane/AcOEt 6:4) gave (*R*)-7 as a white solid. The yields ranged between 92% (1.03 g) and 95% (1.06 g). TLC (cyclohexane/EtOAc 9:1) R_f = 0.56; mp = 138.88 °C; $[\alpha]_D^{25}$ = +102.85 (*c* 1, MeOH); 98.0−98.1% ee (determined by HPLC analysis on a Kromasyl AmyCoat column, 250 mm × 4.6 mm i.d.; hexane/MeOH/2-propanol 78:20:2; 0.3 mL/min; 280 nm; $t_R \approx 30$ min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, *J* = 7.15 Hz, 11.55 Hz, 1H), 4.53 (dd, *J* = 2.75 Hz, 11.55 Hz, 1H), 4.70 (dd, *J* = 2.75 Hz, 7.15 Hz, 1H), 6.12 (br s, 1H), 6.54 (br s, 1H), 6.86−6.95 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 65.4, 73.2, 117.7, 118.0, 122.1, 122.2, 142.9, 143.7, 169.7. Anal. Calcd for $C_9H_9NO_3$ (179.18): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.11; H, 5.09; N, 7.79.

(*S*)-1,4-Benzodioxane-2-carboxamide [(*S*)-7]. Obtained from (*R*)-**5** in 90−93% yield as described for (*R*)-7. Mp = 140.35 °C; $[\alpha]_D^{25}$ = −103.61 (*c* 1 MeOH); ee 98.0−98.3% (determined by HPLC analysis as described for (*R*)-7; $t_R \approx 36$ min); the ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-7.

***rac*-1,4-Benzodioxane-2-carboxamide (*rac*-7).** Obtained from *rac*-**5** in 89−93% yield as described for (*R*)-7. Mp = 141.04 °C; the ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-7.

(*R*)-Methyl 1,4-Benzodioxane-2-carboxylate [(*R*)-2b]. KOH solution in methanol (1 M, 12.0 mL, 12.00 mmol) was added dropwise to a solution of (*S*)-**4** (1.40 g, 5.98 mmol) in MeOH (10 mL) at −15 °C. The mixture was allowed to reach room temperature and stirred for 1 h. TLC analysis (cyclohexane/ethyl acetate 8:2) showed complete conversion into (*R*)-methyl 1,4-benzodioxane-2-imidate [(*R*)-**8**] (R_f = 0.18). The mixture was cooled to −15 °C and filtered to remove precipitated KCl. Amberlyst-15 ion-exchange resin (1.53 g, 7.20 mequiv) was added to the filtrate, and the mixture was stirred for 30 min. After the resin was filtered off, the filtrate was concentrated under vacuum to give the crude methyl ester, which was purified by chromatography on silica gel (cyclohexane/ethyl acetate 8:2), yielding (*R*)-**2b** as a white solid. The yields ranged between 76% (885 mg) and 78% (908 mg). TLC (cyclohexane/EtOAc 8:2) R_f = 0.43; mp = 77.6 °C;[16] $[\alpha]_D^{25}$ = +55.8 (*c* 1, $CHCl_3$); 98.1−98.3% ee (determined by HPLC analysis on a Kromasyl AmyCoat column, 250 mm × 4.6 mm i.d.; hexane/MeOH/2-propanol 78:18:4; 0.4 mL/min; 280 nm; $t_R \approx 16$ min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.37 (d, *J* = 3.85 Hz, 2H), 4.84 (t, *J* = 3.85 Hz, 1H), 6.86−6.98 (m, 3H), 7.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 65.1, 71.2, 117.5, 117.6, 122.1, 122.4, 142.5, 143.2, 168.8. (*R*)-**8**: oil resulting from the concentration of an aliquot of the methanolic solution after removal of KCl; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.04 (dd, *J* = 7.15 Hz, 11.55 Hz, 1H), 4.43 (dd, *J* = 2.75 Hz, 11.55 Hz, 1H), 4.61 (dd, *J* = 2.75 Hz, 7.15 Hz, 1H), 6.87 (m, 3H), 7.00 (m, 1H), 7.92 (br s, 1H, exchanges with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.8, 65.7, 71.2, 117.6, 117.6, 122.2, 122.4, 142.2, 143.2, 167.8; MS (ESI) *m*/*z* calcd for $C_{10}H_{12}NO_3$ (MH^+) 194.08, found 194.1. Anal. Calcd for $C_{10}H_{11}NO_3$ (193.20): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.02; H, 5.78; N, 7.23.

(*S*)-Methyl 1,4-Benzodioxane-2-carboxylate [(*S*)-2b]. Obtained from (*R*)-**4** in 74−75% yield as described for (*R*)-**2b**. Mp = 76.91 °C;[16] $[\alpha]_D^{25}$ = −55.5 (*c* 1, $CHCl_3$), ee 98.0−98.1% (determined by HPLC analysis as described for (*R*)-**2b**; $t_R \approx 14$ min); the ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-**2b**.

***rac*-Methyl 1,4-Benzodioxane-2-carboxylate (*rac*-2b).** Obtained from *rac*-**4** in 72−76% yield as described for (*R*)-**2b**. Mp = 50.09 °C;[16] the ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-**2b**.

(*R*)-1,4-Benzodioxane-2-carboxaldehyde Bisulfite Adduct. Sodium metabisulfite (600 mg, 3.16 mmol), (*R*)-**6** (950 mg, 5.78 mmol), ethyl acetate (5 mL), ethanol (4 mL), and water (1 mL) were mixed and stirred at 40 °C overnight. After ethyl acetate (3 mL) was added and the mixture was cooled to 0 °C, the precipitated sodium α-hydroxymethanesulfonate (1.18 g, 4.40 mmol) was isolated by filtration as a white solid. The filtrate was concentrated, and the residue was triturated in hot ethyl acetate and collected by filtration to give an additional amount (238 mg, 0.89 mmol) of the desired product. The overall yield was 91%. The bisulfite adduct, which decomposed about 160 °C, was a nearly equimolar mixture of two diastereomers epimeric at the newly formed stereocenter. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.90−4.09 (m, 2H), 4.30 (dd, J_1 = 1.92 Hz, J_2 = 5.8 Hz, ∼0.5H), 4.39 (pseudo d, J_1 = 8.8 Hz, ∼0.5H), 4.55 (m, ∼0.5H), 4.67 (dd, J_1 = 2.2 Hz, J_2 = 11.6 Hz, ∼0.5H), 5.72 (d, J_1 = 5.8 Hz, ∼0.5 H, exchanges with D_2O), 6.05 (d, J_1 = 5.5 Hz, ∼0.5 H, exchanges with D_2O), 6.75−6.85 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 65.1, 66.2, 74.5, 75.0, 82.0, 83.8, 117.3, 117.5, 117.7, 117.8, 121.6, 121.8, 143.7, 143.9, 144.0, 144.5; HRMS (ESI) *m*/*z* calcd for $C_9H_9O_6S^-$ ($M - Na^+$) 245.01253, found 245.01329.

(*S*)-1,4-Benzodioxane-2-carboxaldehyde Bisulfite Adduct. Obtained from (*S*)-**6** in 93% yield as a nearly equimolar mixture of two diastereomers with the *S* configuration at the dioxane stereocenter and epimeric at the newly formed stereocenter, as described for the bisulfite adduct of (*R*)-**6**. The ^{1}H NMR and ^{13}C NMR data were identical to those of the bisulfite adduct of (*R*)-**6**.

Regeneration of (*R*)-6 and (*S*)-6 from the Respective Bisulfite Adducts. Both of the bisulfite adducts (1.10 g, 4.10 mmol) were combined with CH_3CN (20 mL) and TMS-Cl (1.3 mL, 10.25 mmol) and heated at 40 °C for 2 h. The mixtures were allowed to cool to room temperature. Ethyl acetate and water were added, and the layers were separated. The organic phases were dried with Na_2SO_4 and concentrated under vacuum to give (*R*)-**6** and (*S*)-**6** as clear oils (94% and 93% yield, respectively). The ^{1}H NMR and ^{13}C NMR data were identical to those of (*R*)-**6** and (*S*)-**6** obtained from (*S*)-**4** and (*R*)-**4**, respectively.

(*S*)-2-Hydroxymethyl-1,4-benzodioxane [(*S*)-1]. $NaBH_4$ (141 mg, 3.73 mmol) was added to a solution of the bisulfite adduct of (*R*)-**6** (1.00 g, 3.73 mmol) in methanol (8 mL), and the suspension was stirred for 3 h at room temperature. The solvent was evaporated under vacuum, and the residue was partitioned between water and DCM. The layers were separated, and the organic phase was dried with Na_2SO_4 and concentrated to give (*S*)-**1** as a white solid. The yields ranged between 75% (464 mg) and 76% (471 mg). Mp = 75.82 °C;[16] $[\alpha]_D^{25}$ = −36.8 (*c* 0.1, EtOH); 97.8−98.0% ee (determined by HPLC analysis on a Kromasyl AmyCoat column, 250 mm × 4.6 mm i.d.; hexane/EtOH 95:5; 1.2 mL/min; 280 nm; $t_R \approx 14$ min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (br s, 1H, exchange with D_2O), 3.82−3.93 (m, 2H), 4.07−4.14 (m, 1H), 4.24−4.32 (m, 2H), 6.83−6.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.0, 65.4, 73.7, 117.5, 117.5, 121.8, 121.9, 143.2, 143.3.

(*R*)-2-Hydroxymethyl-1,4-benzodioxane [(*R*)-1]. Obtained from the bisulfite adduct of (*S*)-**6** in 72−75% yield as described for (*S*)-**1**. Mp = 74.82 °C;[16] $[\alpha]_D^{25}$ = +35.9 (*c* 0.1, EtOH); 97.6−97.7% ee (determined by HPLC analysis as described for (*S*)-**1**; $t_R \approx 17$ min); the ^{1}H NMR and ^{13}C NMR data were identical to those of (*S*)-**1**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra, HRMS spectra, DSC curves, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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