Spiro Hydantoin Aldose Reductase Inhibitors Derived from 8-Aza-4-chromanones

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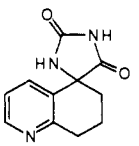
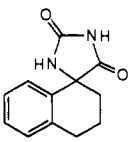
A series of spiro hydantoins derived from 8-azachromanones (2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-ones) has been prepared and tested for aldose reductase inhibitory activity. The standard Bucherer–Bergs conditions had to be drastically modified to increase yields from less than 1% to an acceptable 50% range. One of the most potent compounds was *cis*-6′-chloro-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′H-pyrano[2,3-*b*]pyridine]-2,5-dione; resolution of this compound showed that the 2′*R*,4′*S* enantiomer **16** was the most active spiro hydantoin in this series with an IC_{50} of 7.5×10^{-9} against human placenta aldose reductase.

Previous efforts from these laboratories have shown that spiro hydantoins derived from cyclic aromatic ketones have excellent in vitro and in vivo activity as aldose reductase inhibitors, an activity of potential interest in the therapy of chronic complications of diabetes mellitus.[1,2] We have found earlier (Table V of ref 2) that spiro hydantoin **1** derived from 6-aza-1-tetralone is at least as active as 1-tetralone derivative **2**. The finding that 4-chromanone-derived spiro hydantoins **3** have excellent biological activity[2] made the 8-aza-4-chromanone-derived spiro hydantoins **4** (X = hydrogen, halogen) attractive targets.



1



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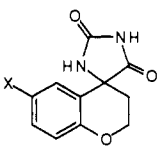

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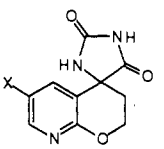

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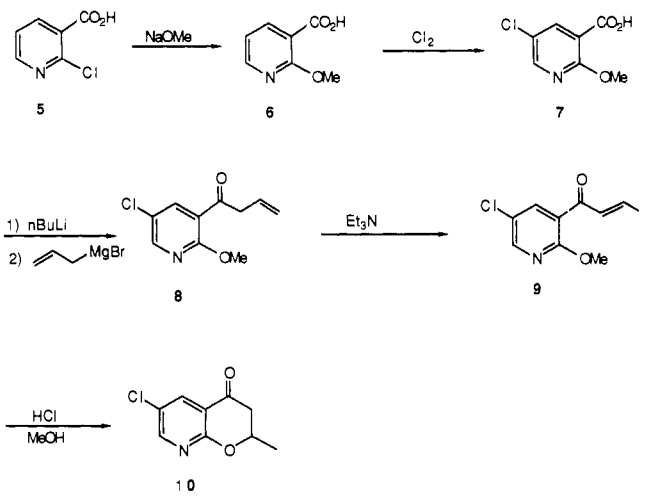
Chemistry

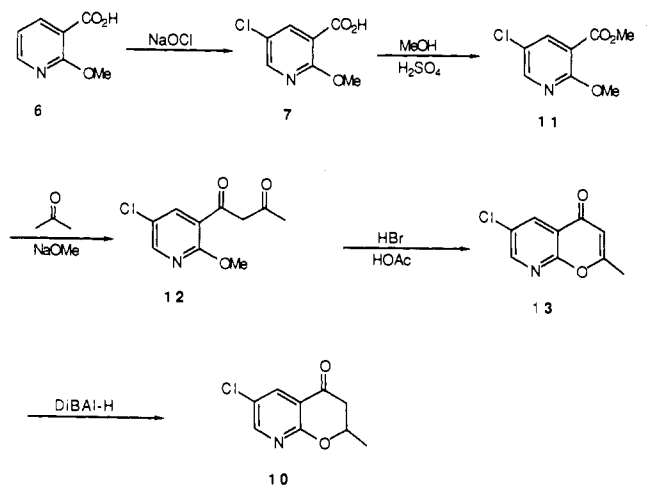
When 2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one was subjected to the standard Bucherer–Bergs conditions (KCN, ammonium carbonate, ethanol–water, heating to 60 °C with or without $NaHSO_3$) no spiro hydantoin was isolated! In hindsight, the reasons for this failure are clear: under these reaction conditions very little product is formed, and in this particular case the reaction product is water soluble and would have been easily lost during the aqueous workup. However, the analogous 6-chloro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one gave under these reaction conditions a 0.4% yield of the desired hydantoin. Biological testing of this spiro hydantoin showed excellent activity, warranting a more extensive effort to develop a practical synthesis of this compound and to prepare congeners of it.

Initially we prepared 6-chloro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (**10**) as shown in Scheme I by allylmagnesium bromide addition to **7**, followed by equilibration of the double bond and cyclization of **9**. However, the synthesis of **10** shown in Scheme II lent itself better to scale-up. Key improvements were the chlorination of **6** with sodium hypochlorite in a homogeneous

Scheme I



Scheme II



system[3] instead of the chlorination with chlorine gas in an aqueous suspension of starting material and product, which is difficult to stir.[4] Furthermore, condensation of **11** with acetone, followed by cyclization and reduction, gave a significant yield improvement over the older route. When we turned our attention to exploring the Bucherer–Bergs reaction step, a series of experiments showed that the reaction product was stable under the reaction conditions but that the starting material **10** underwent side reactions, presumably via a retro-Michael reaction, to give water-soluble byproducts. Finely powdering the solid ingredients, adding sodium bisulfite, replacing the ethanol–water sol-

(1) Sarges, R.; Bordner, J.; Dominy, B. W.; Peterson, M. J.; Whipple, E. B. *J. Med. Chem.* **1985**, *28*, 1716.
(2) Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1988**, *31*, 230.
(3) Goddard, C. J. US Patent 4,716,231, Dec. 29, 1987; *Chem. Abstr.* **1988**, *108*, P167321*r*.
(4) Kuhla, D. E.; Sarges, R. US Patent 3,879,403, Apr. 22, 1975; *Chem. Abstr.* **1975**, *82*, P72792*a*.

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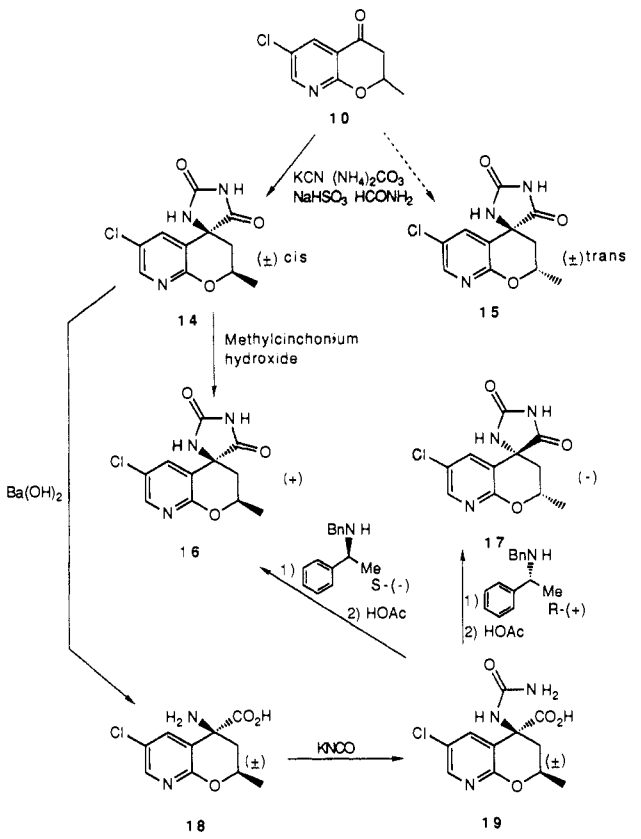
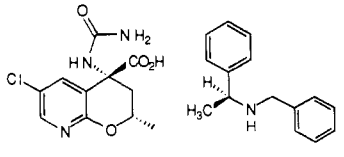
Scheme III



vent system with acetamide or formamide, and lowering the reaction temperature all helped to improve the yield of hydantoin to some extent. The best reaction conditions ultimately found were as follows: use of 2 mol of KCN and 7 mol of ammonium carbonate per mole of ketone, addition of 1 mol of $NaHSO_3$, use of formamide as the solvent (lower melting point than acetamide), and running of the reaction at a maximum temperature of 50 °C for 3 days. These conditions resulted consistently in 50% yields of hydantoin.

The major product obtained in this manner from **10** is the racemic cis (2′-methyl, 4′-NH *cis*) hydantoin **14** (Scheme III). The cis configuration of **14** was proven by the X-ray analysis of compound **20** (vide infra). Only very



20

small amounts of trans racemate **15** could be obtained by preparative HPLC of the pooled mother liquors of **14**. Racemic trans isomer **15** proved to be much less potent as an aldose reductase inhibitor than racemic cis isomer **14**.

Since aldose reductase has a highly stereoselective binding site for spiro hydantoins,[1] it was of interest to resolve **14** into its enantiomers. This was accomplished in two ways. The more efficient route utilizes methylcinchonium hydroxide[5] to obtain high yields of the salt of the biologically more active (+)-isomer **16**. Fractional crystallization of acidified mother liquors of this salt gave the (−)-enantiomer **17**. Alternatively, hydrolysis of **14** to the amino acid **18**, followed by reaction with KNCO gave hydantoic acid **19**. Treatment of **19** with (*S*)-(−)-*N*-benzyl-α-methylbenzylamine gave a resolved salt which was isolated and ring-closed under acidic conditions to give good yields of **16**. The mother liquor of the (*S*)-(−)-*N*-benzyl-α-methylbenzylamine salt of **19** deposited the crystalline compound **20**. These crystals of **20** proved suitable for X-ray analysis, shown in Figure 1 of the supplementary material.[6] According to the X-ray analysis, **20** was the (*S*)-(−)-*N*-benzyl-α-methylbenzylamine salt of the 2*S*,4*R* enantiomer of **19**. Since acid treatment of **20** gave **17**, these findings established the configuration of **17** as 2′*S*,4′*R*, and therefore the configuration of **16** as 2′*R*,4′*S*. Conversely, **17** was obtained in good yield by treatment of **19** with (*R*)-(+)-*N*-benzyl-α-methylbenzylamine, followed by acid-catalyzed cyclization.

A more elegant route to 2′*R*,4′*S* enantiomer **16** would be the conversion of chiral **10** [(2*R*)-8-aza-6-chloro-2-methyl-4-chromanone] to the hydantoin. We have proven the feasibility of this route by showing that the chiral center of this ketone is preserved under our Bucherer–Bergs conditions: hydrolysis of **16** to the amino acid, oxidation with *N*-chlorosuccinimide to the 8-aza-4-chromanone, and conversion to the hydantoin gave exclusively **16**. Efforts to prepare (2*R*)-8-aza-6-chloro-2-methyl-4-chromanone on a large scale by an independent synthesis with chiral precursors have been successful.[7]

Compound **21**, the bromo analogue of **14**, was prepared in an analogous fashion starting with 5-bromo-2-methoxynicotinic acid.[4] Fluoro analogue **22** was similarly prepared from methyl 5-fluoro-2-methoxynicotinate, obtained by nitration of methyl 2-methoxynicotinate, followed by reduction with $SnCl_2$ and diazotization in the presence of H_2SiF_6. 6′-Hydrogen analogue **23**, the target of our initial synthesis attempt, was obtained readily by hydrogenolysis of **14** in the presence of triethylamine.

The desmethyl analogue of **14** was produced via a Claisen condensation between methyl 5-chloro-2-methoxynicotinate and ethyl acetate, followed by decarboalkoxylation to give the acetyl derivative. This was then condensed with ethyl formate, cyclized, and reduced to afford the 8-azachromanone, which was converted to **24**.

N-Oxides of **14** and **16** were obtained by treatment of these spiro hydantoins with 30% hydrogen peroxide in acetic acid to afford **25** and **26**, respectively.

Biological Results and Discussion

These compounds were evaluated for their in vitro inhibitory activity against aldose reductase isolated from human placenta and for their ability to inhibit sorbitol formation in the nerve and lens of a streptozotocinized rat model after oral administration.[8] These biological data are summarized in Table I. It is apparent that chloro compound **14** is a more potent inhibitor of human placenta aldose reductase in vitro than its bromo, fluoro, or hydrogen analogues. A similar structure–activity relationship (SAR) trend for the 6-substituents had been observed earlier in the corresponding chroman series, measuring inhibitory activity against bovine lens aldose reductase.[2] On the other hand, while sorbinil and 2-methylsorbinil have similar in vitro activity against human placenta aldose

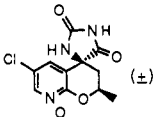
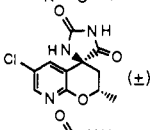
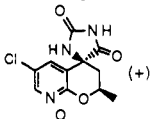
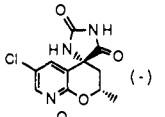
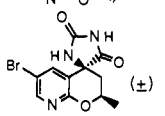
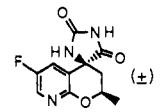
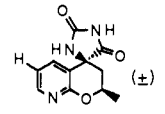
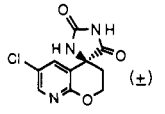
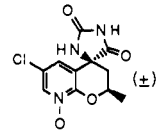
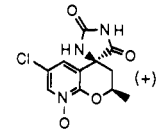
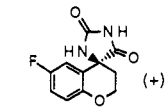
(5) Major, R. T.; Finkelstein, J. *J. Am. Chem. Soc.* **1941**, *63*, 1368.

(6) We are grateful to Dr. J. Bordner of Pfizer Central Research for this determination.

(7) Murtiashaw, C. W.; Pezzullo, S. L.; Breitenbach, R.; Goldstein, S. W.; Sarges, R., manuscript in preparation.

(8) Peterson, M. J.; Sarges, R.; Aldinger, C. E.; MacDonald, D. P. *Metab. Clin. Exp.* **1979**, *28* (Suppl. 1), 456.

Table I

		IC_{50},[a] μM	in vivo (% inhibn)[b] dose, mg/kg	nerve	lens
14	 (±)	0.025 (0.0096–0.068)	0.25 5.0	38 ± 3.6[c] 98 ± 0.6[c]	13 ± 4.6 89 ± 2.3
15	 (±)	0.89 (0.45–1.76)	0.25	12.8 ± 10.4	31.8 ± 3.9[c]
16	 (+)	0.0075 (0.0027–0.021)	0.1 0.5 1.0	8.7 ± 17.0 55.8 ± 11.6[c] 87.5 ± 5.6[c]	13.8 ± 19.3 55.5 ± 4.2[c] 88.2 ± 4.0[c]
17	 (-)	3.09 (1.38–6.96)	1.0	-9.5 ± 5.5	-10.6 ± 6.4
21	 (±)	0.50 (0.26–0.98)	1.0	72.7 ± 3.9[c]	67.4 ± 4.2[c]
22	 (±)	1.13 (0.57–2.24)	-	-	-
23	 (±)	7.22 (3.12–16.7)	1.0	18.2 ± 2.7	33.9 ± 4.2[c]
24	 (±)	6.45 (2.80–14.9)	1.0	37.0 ± 3.2[c]	46.1 ± 14.2
25	 (±)	0.13 (0.059–0.28)	1.0	37.6 ± 4.8[c]	19.9 ± 7.9
26	 (+)	0.95 (0.48–1.88)	-	-	-
sorbinil	 (+)	0.17 (0.085–0.33)	0.15 0.25 0.75 1.5	29.0 ± 5.9[c] 50.0 ± 9.8[c] 72.7 ± 2.8[c] 90.9 ± 2.5[c]	12.3 ± 10.0 38.1 ± 10.6[c] 44.2 ± 7.8[c] 73.4 ± 3.2[c]

[a] IC_{50} with 95% confidence limits for inhibition of human placenta aldose reductase. [b] Percent inhibition (mean ± SEM) of sorbitol accumulation versus untreated diabetic controls in nerve and lens of streptozotocinized rat.[8] Streptozotocin (85 mg/kg, iv) was administered at 0 h, the test compounds were given orally at 4, 7, and 24 h at the doses indicated, sorbitol was assayed at 27 h. [c] Significantly different from untreated diabetic controls at $P < 0.05$.

reductase,[10] removal of the 2′-methyl group of **14** decreases activity. Cis diastereomer **14** is clearly more active than trans diastereomer **15**. Resolution of **14** showed that 2′*R*,4′*S* isomer **16** is far more active than its enantiomer **17**. The *N*-oxides, compounds **25** and **26**, are potential metabolites of **14** and **16**[9] and showed diminished in vitro activity and, surprisingly, more potency for the racemic compound.

The in vitro activity of **16** is expressed as in vivo activity, when measured by sorbitol reduction in the nerve and lens in the streptozotocinized rat model. However, relative to sorbinil, the 10-fold greater in vitro activity of **16** leads only to a smaller increase in in vivo potency in the lens, possibly reflecting in part a shorter plasma half-life in rats: 3.5 h for compound **16** versus 5.5 h for sorbinil.[9] Nevertheless, compound **16** is one of the most potent spiro hydantoins known.[10]

Experimental Section

Melting points are uncorrected and were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian T-60, EM-390, XL-300 or Bruker WM-250 instruments with TMS as internal standard or referenced to residual proto-

(9) Ronfeld, R. A., unpublished studies.
(10) Sarges, R. *Trends in Medicinal Chemistry*; Mutschler, E., Winterfeldt, E. Eds.; Proceedings of the 9th International Symposium on Medicinal Chemistry, Berlin 1986, VCH: Weinheim, 1987; pp 551–564.

solvent peaks, as appropriate for the instrument. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Analytical Department of Pfizer Central Research.

Ketone Syntheses. 6-Chloro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (10). 5-Chloro-2-methoxynicotinic acid (7) was obtained from 2-methoxynicotinic acid (6) by chlorination with Cl_2[4] or, more conveniently, with NaOCl.[3] Thus 217 g (1.42 mol) of 2-methoxynicotinic acid was added in portions to a well-stirred solution of 2.5 L of 5.25% NaOCl (Clorox) cooled to 10 °C, while the internal temperature was kept below 28 °C with external cooling. After stirring at room temperature overnight, the solution was acidified with 12 N HCl to pH 2 and the precipitated solids were filtered, washed with water, and dried to give 201 g (75%) of 5-chloro-2-methoxynicotinic acid (7). A solution of 9.3 g (0.05 mol) of 7 in 350 mL of tetrahydrofuran in a flame-dried reaction flask with a N_2 blanket was cooled to 5 °C and treated dropwise with 31.25 mL (0.05 mol) of 1.6 M *n*-butyllithium in hexane, while the internal temperature was kept below 15 °C. After stirring at 0 °C for 30 min, the resultant slurry was treated dropwise with 50 mL (0.05 mol) of 1 M allylmagnesium bromide in Et_2O, and the internal temperature was kept below 15 °C. After stirring at 0 °C for 1 h, the mixture was poured into water and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, and evaporated to an oil (crude 8), which was dissolved in 100 mL of EtOH and treated with 3 mL of triethylamine. After stirring at room temperature overnight, the solvent was evaporated and the residue was purified by flash chromatography on 400 g of SiO_2, using hexane–EtOAc 95:5 as the eluant to give 3.0 g (29%) of 5-chloro-3-crotonyl-2-methoxypyridine [9: ^{1}H NMR ($CDCl_3$) δ 2.0 (d, 3 H), 3.9 (s, 3 H), 6.5–7.3 (m, 2 H), 7.7 (d, 1 H), 8.1 (d, 1 H)] as an oil, which solidified on standing. A solution of 9.0 g (0.042 mol) of 9 in 100 mL of EtOH was treated with 100 mL of EtOH saturated at 0 °C with HCl gas, and the mixture was heated at reflux overnight. After evaporation in vacuo the residue was chromatographed on 600 mL of SiO_2 with $CHCl_3$ to give 6.5 g (78%) of 6-chloro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (10) as a light yellow solid: mp 84–7 °C; MS *m/e* 197, 199; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, *J* = 2.8 Hz, H7), 8.17 (d, *J* = 2.8 Hz, H5), 4.73 (app dq, *J* = 6.3, 5.8 Hz, H2), 2.75 (dd, *J* = 18 Hz, 0.6 Hz, H3eq), 2.72 (dd, *J* = 18 Hz, 5.8 Hz, H3ax), 1.59 (d, *J* = 6.3 Hz, CH_3).

Alternatively, 10 was prepared by converting 5-chloro-2-methoxynicotinic acid (7) to its methyl ester by adding 3 mL of concentrated H_2SO_4 to a suspension of 100 g (0.533 mol) of acid 7 in 100 mL of MeOH and heating the reaction mixture to reflux for 3 h. Upon cooling, the precipitated crystalline ester was collected and washed with MeOH to give 59.5 g (55%) of 11. Concentration of the mother liquor allowed for the isolation of an additional 18.4 g (17%) of 11: mp 86–7 °C; MS *m/e* 201, 203; ^{1}H NMR ($CDCl_3$) δ 8.24 (d, *J* = 2.7 Hz, H6), 8.12 (d, *J* = 2.7 Hz, H4), 4.02 (s, OCH_3), 3.90 (s, OCH_3). Anal. ($C_8H_8ClNO_3$) C, H, N. To a solution of 63.0 g of ester 11 (0.312 mol) and THF (300 mL) was added 27.4 mL of acetone (0.373 mol), followed by 20.1 g of sodium methoxide (0.373 mol). After stirring overnight, the thick slurry was collected via vacuum filtration and washed with 100 mL of EtOAc. Drying the product under vacuum afforded 72.7 g (92%) of crude 1-(5-chloro-2-methoxy-3-pyridyl)butane-1,3-dione (12) as the sodium salt, which was used directly in the next step. To a solution of 44.5 g (0.177 mol) of sodium salt 12 in 650 mL of acetic acid at 102 °C was added 48% HBr (65 mL). The oil-bath temperature and level was adjusted so as to maintain an internal reaction temperature of 98–102 °C for 15 min. The orange solution was then cooled in ice until it had reached ambient temperature and then poured into ice water (2 L) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with water (2 × 250 mL) and then with 250-mL portions of 2% NaOH until the washings were basic. The organic solution was dried ($MgSO_4$) and concentrated to give 19.3 g (56%) of 6-chloro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (13): mp 141–4 °C; MS *m/e* 195, 197; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, *J* = 2.7 Hz, H7), 8.50 (d, *J* = 2.7 Hz, H5), 6.23 (app d, *J* = 0.7 Hz, H3), 2.46 (d, *J* = 0.6 Hz, CH3). To a solution of 25.1 g of chromenone (13) (0.128 mol), THF (154 mL), and CH_2Cl_2 (615 mL) at −70 °C was added 166 mL of 1 M diisopropylaluminum hydride in toluene solution over 20 min. After stirring the reaction mixture for 4 h at −70 °C, it was quenched by the dropwise addition of 15 g of acetic acid in THF (15 mL). The solution was allowed to warm to ambient temperature, poured into 1 L of water, and adjusted to pH 2 with dilute HCl. The organic layer was removed and the aqueous solution was extracted with CH_2Cl_2 (500 mL). The combined organic layers were washed with water (2 × 500 mL), 2% NaOH (2 × 500 mL), and water (500 mL) and then dried ($MgSO_4$) and concentrated to give 23.4 g (93%) of 6-chloro-2-methyl-2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-one (10): mp 84–6 °C.

6-Bromo-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one. A solution of 1.0 g (4.3 mmol) of 5-bromo-2-methoxynicotinic acid[4] in 10 mL of MeOH was treated with 50 μL of H_2SO_4 and refluxed to give the methyl ester [0.695 g, 66%; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 3.9 (s, 3 H), 8.2 (d, 1 H), 8.4 (d, 1 H)]. This methyl ester (508 mg; 1.73 mmol) was converted in 73.5% yield, as described above for the chloro analogue, to the butane-1,3-dione derivative, which was cyclized in 63% yield to 6-bromo-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one as a yellow solid: mp 130–2 °C; NMR (DMSO-d_6) δ 2.42 (s, 3 H), 6.35 (s, 1 H), 8.5 (d, 1 H), 8.8 (d, 1 H). LAH reduction of this material gave a 26% yield of the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.45 (d, 3 H), 2.7–2.9 (m, 2 H), 4.75 (m, 1 H), 8.2 (d, 1 H), 8.5 (d, 1 H).

6-Fluoro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one. To 8.6 g (50 mmol) of methyl 2-methoxynicotinate in 25 mL of trifluoroacetic anhydride was added portionwise a total of 6.0 g of ammonium nitrate (75 mmol). After stirring for 2 h, the reaction was poured into 30 mL of ice water and the solid material was collected. This material was then dissolved in CH_2Cl_2; the organic layer was separated from residual water, dried ($MgSO_4$), and concentrated to give 6.5 g (61%) of methyl 5-nitro-2-methoxynicotinate: mp 98–9.5 °C; MS *m/e* 212; ^{1}H NMR ($CDCl_3$) δ 9.18 (d, *J* = 2.7 Hz, H6), 8.92 (d, *J* = 2.8 Hz, H4), 4.17 (s, OCH_3), 3.95 (s, OCH_3). A mixture of 1.08 g (5.09 mmol) of this nitropyridine and 5.64 g (25 mmol) of $SnCl_2 \cdot 2H_2O$ in 10 mL of EtOAc was heated to reflux for 20 min. The resulting thick suspension was then poured into ice water (50 mL) and adjusted to pH 7 with $NaHCO_3$. This mixture was then extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$) and concentrated to afford 0.80 g (85%) of methyl 5-amino-2-methoxynicotinate: mp 109–10.5 °C; MS *m/e* 182; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 3.0 Hz, H6), 7.57 (d, *J* = 3.0 Hz, H4), 3.95 (s, OCH_3), 3.87 (s, OCH_3). To a solution of 1.50 g (8.06 mmol) of this amine and ethanol (25 mL) was added 12 mL of a 23% H_2SiF_6 solution. After cooling in ice, the white salt was collected by vacuum filtration. The salt was then suspended in HOAc (25 mL) and enough butyl nitrite was added in a dropwise fashion to cause all of the salt to dissolve. The yellow solution was then diluted with ether (40 mL) and cooled in ice to cause precipitation of the diazonium salt, which was collected under a blanket of nitrogen (550 mg, 20%); mp 124–7 °C dec. This white salt was then suspended in xylenes (10 mL) and heated to 130 °C for 15 min, cooled to room temperature, filtered, and concentrated to give crude methyl 5-fluoro-2-methoxynicotinate. Radial chromatography (15% EtOAc/hexanes) provided 210 mg (14%) of impure methyl 5-fluoro-2-methoxynicotinate; MS *m/e* 185; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, *J* = 3.1 Hz, H6), 7.91 (dd, *J* = 7.9, 3.1 Hz, H4), 4.02 (s, OCH_3), 3.91 (s, OCH_3). This material was converted to the title compound, 6-fluoro-2,3-dihydro-2-methyl-4*H*-pyrano-[2,3-*b*]pyridin-4-one, via the intermediate pyridylbutane-1,3-dione (87%), which was cyclized (26%) and reduced (25%) as described above for compound 10: ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* = 3.0 Hz, H7), 7.53 (dd, *J* = 8.0, 3.0 Hz, H5), 4.55 (dq, *J* = 6.5, 2.0 Hz, H2), 2.65 (s, H3), 2.50 (d, *J* = 2.0 Hz, H3), 1.48 (d, *J* = 6.5 Hz, CH_3).

6-Chloro-2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-one. To a solution of 17.1 g (85 mmol) of 7 and THF (100 mL) was added 12.5 mL (128 mmol) of EtOAc and 6.0 g (111 mmol) of sodium methoxide, and the reaction mixture was then heated to reflux for 3 h. After cooling to room temperature, the fine white precipitate was isolated by vacuum filtration, suspended in 100 mL water, and adjusted to pH 1 with dilute HCl. This was extracted with ether (2 × 50 mL), dried ($MgSO_4$) and filtered to afford 11.7 g (57%) of methyl 3-(5-chloro-2-methoxy-3-pyridyl)-3-oxopropionate; mp 59–61.5 °C; MS *m/e* 243, 245; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, *J* = 2.7 Hz, H6′), 8.17 (d, *J* = 2.7 Hz, H4′, 6.12 (s, H2),

4.02 (s, OCH_3), 3.73 (s, OCH_3). A mixture of 10.0 g (41.4 mmol) of this propionate was refluxed with 100 mL of 1 N NaOH for 1 h. The reaction mixture was cooled to room temperature and stirred overnight, then adjusted to pH 1 with concentrated HCl and extracted with ether (2 × 100 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and filtered to give 4.98 g (65%) of 5-chloro-2-methoxy-3-acetylpyridine: MS *m/e* 185, 187; ^1H NMR ($CDCl_3$) δ 8.23 (d, J = 2.7 Hz, H6), 8.06 (d, J = 2.7 Hz, H4), 4.04 (s, OCH_3), 2.63 (s, $COCH_3$). To a solution of 4.60 g (24.8 mol) of this ketone, 6.0 mL (74.6 mmol) of ethyl formate, and THF (50 mL) was cautiously added 1.43 g of sodium hydride (50%, 29.8 mmol). After stirring for 64 h, the yellow precipitate was collectd by vacuum filtration and washed with 20 mL of EtOAc. This crude sodium salt was dissolved in 73 mL of acetic acid and heated to 100 °C and 7.3 mL of 48% HBr was then added to the hot solution. After stirring for 15 min the reaction mixture was cooled to room temperature, poured into 100 mL of water, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 50 mL of 2% NaOH and 50 mL of water, dried ($MgSO_4$), and concentrated to give 1.70 g (38%) of 6-chloro-4*H*-pyrano[2,3-*b*]pyridin-4-one: mp 134–6 °C; MS *m/e* 181, 183; ^1H NMR ($CDCl_3$) δ 8.64 (d, J = 2.7 Hz, H7), 8.53 (d, J = 2.7 Hz, H5), 7.97 (d, J = 6.2 Hz, H2), 6.41 (d, J = 6.2 Hz, H3). To a solution of 1.00 g (5.50 mmol) of this chromenone, 18 mL of THF and 36 mL of toluene at −78 °C was added 6.0 mL of a 1.0 M DIBAL-H solution in toluene. The reaction mixture was stirred at −78 °C for 2.5 h and then quenched by the addition of 0.51 mL of HOAc in 3 mL of THF. After warming to room temperature, it was poured into 100 mL of water, adjusted to pH 2 with dilute HCl, and extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 715 mg (71%) of the title compound: mp 120–3 °C; MS *m/e* 183, 185; ^1H NMR ($CDCl_3$) δ 8.40 (d, J = 2.7 Hz, H7), 8.19 (d, J = 2.7 Hz, H5), 4.67 (t, J = 6.5 Hz, H2), 2.86 (t, J = 6.5 Hz, H3).

Hydantoin Syntheses. 6′-Chloro-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione (14 and 15). A mixture of 39.3 g (0.2 mol) of 6-chloro-2,3-dihydro-2-methylpyrano[2,3-*b*]pyridin-4-one, 26 g (0.4 mol) of KCN, 134.4 g of (1.4 mol) ammonium carbonate, 25 g (0.24 mol) of sodium bisulfite and 400 mL of formamide were heated in an autoclave under stirring to 50 °C for 3 days. After cooling to room temperature, the mixture was diluted with 3 L of water and filtered. The filtrate was acidified with concentrated HCl to pH 2.5 and allowed to stir at room temperature for 30 min. The precipitated solids were collected by filtration, air-dried, and recrystallized from $CHCl_3$–MeOH 9:1 to give 26.6 g (50%) of the racemic cis isomer 14 (2′-Me, 4′-NH cis; 2′*R*,4′*S*/2′*S*,4′*R*) of the title compound in three crops: mp >250 °C; ^1H NMR (DMSO-d_6) δ 1.35 (d, 3 H), 1.8 (t, 1 H), 2.35 (d, 1 H), 4.9 (m, 1 H, characteristic for H-2′ of the cis isomer), 7.75 (d, 1 H), 8.15 (d, 1 H), 8.35 (s, 1 H), 11.1 (b s, 1 H). Anal. ($C_{11}H_{10}ClN_3O_3$) C, H, N.

The mother liquor contained a small amount of the trans isomer 15 (2′-Me, 4′-NH trans; 2′*S*,4′*S*/2′*R*,4′*R*) which was isolated by preparative HPLC using multiple injections on a Zorbax Silica Prep column, 2.12 cm × 25 cm, and eluting with 5% MeOH in $CHCl_3$. Collection of the more polar fractions gave 40 mg of crude trans isomer. After recrystallization from EtOAc–hexane, there was obtained 26.5 mg of 15: mp >250 °C°; ^1H NMR (DMSO-d_6) δ 1.35 (d, 3 H), 1.8 (t, 1 H), 2.35 (d, 1 H), 4.4 (m, 1 H, characteristic for H-2′ of the trans isomer), 7.7 (d, 1 H), 8.25 (d, 1 H), 8.8 (s, 1 H), 11.1 (b s, 1 H).

Resolution of the Racemic Cis Isomer To Give 16 and 17. Racemic cis isomer 14 (965 mg, 3.6 mmol) was added to a solution of 1.18 g (3.6 mmol) of methylcinchonium hydroxide in 24 mL of water, prepared according to the method of Major and Finkelstein.[5] Evaporation of this mixture in vacuo, followed by crystallization of the residue from 2-propanol–isopropyl ether, gave 919 mg of a white solid, which was collected by filtration, while the mother liquor was saved. This solid material was recrystallized from 2-propanol to give 680 mg (65%) of the enantiomerically pure 2′*R*,4′*S* salt. A 400-mg sample of this salt was treated with 17 mL of 1 N HCl and extracted with 3 × 10 mL of EtOAc. The EtOAc extracts were combined, dried, and evaporated to give 172 mg of a white solid, which was recrystallized from EtOAc–hexane to give 129 mg of the desired 2′*R*,4′*S* compound 16: mp >250 °C; $[\alpha]^{20}_D$ = +235.7° (*c* = 1, MeOH). Anal. ($C_{11}H_{10}ClN_3O_3$) C, H, N.

The saved original mother liquor was concentrated in vacuo to give 990 mg of a white solid, 890 mg of which was treated with 10 mL of 1 N HCl and extracted with 3 × 15 mL of EtOAc. The EtOAc washings were combined, dried, and evaporated to a residue, which on treatment with EtOAc–hexane deposited 120 mg of a racemic crop. Concentration of its mother liquor, followed by crystallization from EtOAc–hexane gave 142.6 mg of the pure 2′*S*,4′*R* compound 17: mp >250°; $[\alpha]^{20}_D$ = −226.3° (*c* = 1, MeOH). Anal. ($C_{11}H_{10}ClN_3O_3$) C, H, N.

Alternatively, the racemic cis isomer can be resolved via the hydantoic acids. Thus 2.67 g (0.01 mol) of racemic cis isomer was heated under reflux with 15.8 g (0.05 mol) of $Ba(OH)_2 \cdot 8H_2O$ in 100 mL of water for 4 days. After cooling, the mixture was diluted with water and treated dropwise with a solution of 4.8 g (0.05 mol) of ammonium carbonate. The precipitated solids were filtered and washed with water, and the filtrate was evaporated in vacuo to give a residue which was crystallized from MeOH to yield 1.4 g (58%) of a first crop of *cis*-4-amino-6-chloro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridine-4-carboxylic acid (18): mp 200–3 °C; MS *m/e* 242. Anal. ($C_{10}H_{11}ClN_2O_3 \cdot {}^3/_4H_2O$) C, H, N.

A solution of 1.0 g (0.004 mol) of this material in 220 mL of water was adjusted to pH 5 with 1 N HCl and treated portionwise over 1 h with 640 mg (0.008 mol) of KOCN while the pH was kept at 5 with 1 N HCl. After stirring overnight the pH had increased to 8 and was readjusted to 3 with 1 N HCl. The precipitated solids were collected, washed with water, and air-dried to give 570 mg (50%) of *cis*-hydantoic acid 19: mp 209–10 °C dec; MS *m/e* 285. Anal. ($C_{11}H_{12}ClN_3O_4 \cdot {}^1/_2H_2O$) C, H, N.

A slurry of 2.5 g (8.75 mmol) of this material in 25 mL of MeOH was treated with 1.85 g (8.75 mmol) of (*S*)-(−)-*N*-benzyl-α-methylbenzylamine [Norse]. The resultant solution was allowed to evaporate slowly at room temperature until crystals formed. The crystals were collected by filtration and washed with MeOH to yield 2.1 g (97%) of crude (2*R*,4*S*)-hydantoic acid salt, mp 168–170 °C dec. The mother liquor was saved. Recrystallization of the solids from MeOH gave a first crop of 1 g (46%) of the pure salt: mp 175–7 °C dec; $[\alpha]^{20}_D$ = +58.7° (*c* = 1, MeOH). Anal. ($C_{11}H_{12}ClN_3O_4 \cdot C_{15}H_{17}N \cdot {}^1/_4H_2O$) C, H, N.

A 500-mg (1 mmol) batch of this material was dissolved in 5 mL of glacial acetic acid and heated at 90 °C for 4 h. After cooling, the mixture was diluted with water and extracted with EtOAc. The extract was dried and evaporated to give 260 mg (97%) of 2′*R*,4′*S* isomer 16: $[\alpha]^{20}_D$ = +205.4° (*c* = 1, MeOH).

The saved mother liquor of the hydantoic acid salt deposited after 3 days at room temperature 87 mg of the (*S*)-(−)-*N*-benzyl-α-methylbenzylamine salt of the 2*S*,4*R* enantiomer of hydantoic acid 19: mp 164–5 °C; $[\alpha]^{20}_D$ = −67.6° (*c* = 1. MeOH). Anal. ($C_{11}H_{12}ClN_3O_4 \cdot C_{15}H_{17}N \cdot CH_3OH$) C, H, N. Single-crystal X-ray analysis of this material established the 2*S*,4*R* configuration of this compound, and treatment with glacial acetic acid resulted in formation of 2′*S*,4′*R* enantiomer 17.

Conversely, treatment of racemic *cis*-hydantoic acid 19 with (*R*)-(+)-*N*-benzyl-α-methylbenzylamine [Norse] gave the salt of the (2*S*,4*R*)-hydantoic acid, after recrystallization from MeOH: mp 175–7 °C; $[\alpha]^{20}_D$ = −62.7°. Anal. ($C_{11}H_{12}ClN_3O_4 \cdot C_{15}H_{17}N \cdot {}^1/_4H_2O$) C, H, N. This material could in turn be converted by treatment with acetic acid to 2′*S*,4′*R* enantiomer 17.

The enantiomeric purity of hydantoins 16 and 17 was established by HPLC analysis on a Cyclobond 1 (acetylated cyclodextran, Astec) column, 1 cm × 45 cm, using 80% of a pH 4 buffer (water containing 0.4% triethylamine and 0.3% acetic acid) and 20% MeOH as eluant. This system separates these compounds nicely, with 16 eluting first.

6′-Bromo-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione (21). A mixture of 361 mg (1.49 mmol) of 6-bromo-2,3-dihydro-2-methylpyrano[2,3-*b*]-pyridin-4-one, 194 mg (2.98 mmol) of KCN, 1.0 g (10.5 mmol) of ammonium carbonate, 155 mg (1.49 mmol) of sodium bisulfite, and 10 mL of formamide was heated in a round-bottom flask, sealed with a wired-on ground-glass stopper [**NOTE**: this reaction should be carried out behind a safety shield; pressures of 40 psi develop in the flask], to 40–45 °C overnight. After dilution with 10 mL of water, acidification to pH 3, and filtration was obtained 177 mg of crude product. Recrystallization from 2-propanol/

isopropyl ether gave 116 mg (25%) of **21**: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 1.45 (d, 3 H), 1.8 (t, 1 H), 2.35 (d, 1 H), 4.9 (m, 1 H), 7.8 (d, 1 H), 8.25 (d, 1 H), 8.3 (s, 1 H), 11.1 (b s, 1 H); MS *m/e* 311, 313. Anal. ($C_{11}H_{10}BrN_3O_3$) C, H, N.

6′-Fluoro-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione (22). To 110 mg (0.61 mmol) of 6-fluoro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]-pyridin-4-one was added 1 mL of formamide, 0.40 g (5 mmol) of powdered ammonium carbonate, 62 mg (0.6 mmol) of sodium bisulfite, and 78 mg (1.2 mmol) of powdered potassium cyanide. The reaction vessel was sealed with a wired-on ground-glass stopper and heated to 51 °C for 24 h and then kept at ambient temperature for 5 days. After diluting with 10 mL of water, the solution was adjusted to pH 3 and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and recrystallized twice from methanol–chloroform (1:9) to afford 28 mg (16%) of 22: mp 231–2.5 °C; MS *m/e* 251; ^{1}H NMR (DMSO-d_6) δ 11.0 (b s, NH), 8.40 (s, NH), 8.17 (d, *J* = 3.0 Hz, H7′), 7.70 (dd, *J* = 8.3, 3.0 Hz, H5′), 4.87 (ddq, *J* = 1.7, 6.4, 12 Hz, H2′), 2.35 (dd, *J* = 1.7, 14 Hz, H3′eq), 1.83 (dd, *J* = 12, 14 Hz, H3′ax), 1.37 (d, *J* = 6.3 Hz, CH_3). Anal. ($C_{11}H_{10}FN_3O_3 \cdot {}^1/_3CHCl_3$) C, H, N.

2′,3′-Dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione (23). A mixture of 0.5 g (1.8 mmol) of 14, 377 mg (3.6 mmol) of triethylamine, 50 mg of 10% Pd/C, and 10 mL of MeOH was hydrogenated at atmospheric pressure and room temperature overnight. Removal of the catalyst, evaporation of the solvent, and trituration of the residue with $CHCl_3$ gave 450 mg (86%) of **23**: mp 150 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.45 (d, 3 H), 1.8 (t, 1 H), 2.3 (d, 1 H), 4.9 (m, 1 H), 7.0 (m, 1 H), 7.6 (d of d, 1 H), 8.1 (d of d, 1 H), 8.35 (s, 1 H), 11.1 (b s, 1 H). Anal. ($C_{11}H_{11}N_3O_3 \cdot 0.4CHCl_3$) C, H, N.

6′-Chloro-2′,3′-dihydrospiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione (24). To 715 mg (3.89 mmol) of 6-chloro-2,3-dihydropyrano[2,3-*b*]pyridin-4-one in 7 mL of formamide was added 2.58 g (26.8 mmol) of powdered ammonium carbonate, 0.40 g (3.8 mmol) of sodium bisulfite and 0.50 g (7.7 mmol) of potassium cyanide. The reaction vessel was sealed with a wired-on ground-glass stopper and heated to 52 °C for 15 h. After cooling to ambient temperature, the solution was diluted with 30 mL of water and acidified to pH 3 with concentrated HCl. The precipitated solid was collected by vacuum filtration, washed with water, and dried to afford 848 mg (86%) of crude **24**; after recrystallization from MeOH–$CHCl_3$, an analytical sample had the following: mp 265–6 °C; MS *m/e* 253, 255; ^{1}H NMR (DMSO-d_6) δ 11.1 (b s, NH), 8.59 (s, NH), 8.23 (d, *J* = 2.6 Hz, H7′), 7.77 (d, *J* = 2.6 Hz, H5′), 4.64 (ddd, *J* = 3.1, 8.6, 12 Hz, H2′), 4.37 (ddd, *J* = 3.7, 6.6, 12 Hz, H2′), 2.31 (ddd, *J* = 3.1, 6.6, 14 Hz, H3′), 2.13 (ddd, *J* = 3.7, 8.6, 14 Hz, H3′). Anal. ($C_{10}H_8ClN_3O_3 \cdot CHCl_3$) C, H, N.

6′-Chloro-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione 8′-Oxide (25). A mixture of 100 mg (0.37 mmol) of 14, 3 mL of HOAc, and 1 mL of 30% H_2O_2 was heated to 85 °C overnight. After cooling and dilution with water, the precipitated solids were collected to give 30 mg (29%) of **25**: mp >250 °C; MS *m/e* 283, 285. Anal. ($C_{11}H_{10}ClN_3O_4$) C, H, N.

(2′*R*,4′*S*)-6′-Chloro-2′,3′-dihydro-2′-methylspiro[imidazolidine-4,4′-4′*H*-pyrano[2,3-*b*]pyridine]-2,5-dione 8′-Oxide (26). This compound was prepared in 38% yield by the above procedure from **16**: mp >250 °C; MS *m/e* 238, 285. Anal. ($C_{11}H_{10}ClN_3O_4$) C, H, N.

Pilot Experiment Regarding the Preservation of Chirality at C-2. A 350-mg (0.7 mmol) batch of the (*S*)-(−)-*N*-benzyl-α-methylbenzylamine salt of the 2*R*,4*S* isomer of the hydantoic acid **19** was hydrolyzed to the amino acid with 1.1 g (3.5 mmol) of $Ba(OH)_2 \cdot 8H_2O$ according to the procedure of Cue et al.[11] After a workup with ammonium carbonate, the amino acid solution in water was treated portionwise at pH 4.5 with 93 mg (0.7 mmol) of *N*-chlorosuccinimide to give ultimately, after extraction with $CHCl_3$, 60 mg (43%) of the 2*R* isomer of ketone **10** (NMR identical with that of authentic **10**). This material was subjected to the Bucherer–Bergs conditions described above, to yield 23 mg (28%) of crude **16**; NMR was identical with that of **16**; HPLC analysis of this material on Cyclobond 1 (acetylated cyclodextran, Astec), using 2.5% MeOH, 0.2% triethylamine, and 0.2% HOAc in H_2O as eluant, showed only a major peak for **16**, with less than 1% of its enantiomer **17** present. This establishes that the chirality at C-2 is preserved under the Bucherer–Bergs conditions.

Biological Methods. Enzyme Preparation. Aldose reductase was partially purified from human placentae by a modification of Hayman and Kinoshita's[12] purification of rat lens aldose reductase. Freshly obtained human placentae were homogenized in 3 volumes of 0.1 M potassium phosphate buffer, pH 7.0, containing 5 mM 2-mercaptoethanol and centrifuged for 20 min at 33000*g* at 4 °C. The supernatant was subjected to a 50% to 75% ammonium sulfate fractionation and the resulting pellets were pooled, resuspended in a minimum volume of buffer, and dialyzed overnight. The dialysate was chromatographed on a DEAE-cellulose column (2 cm × 25 cm) and aldose reductase was eluted with a linear salt gradient (0–1 M NaCl). Peak fractions containing aldose reductase activity were pooled and aliquots stored frozen.

Assay Procedure. Enzyme activity was assayed with an Abbott VP bi-chromatic clinical analyzer which measured the decrease in the rate of NADPH oxidation at 340 nm at 25 °C over 10 min in a reaction mixture of 0.25 mL of 50 mM potassium phosphate buffer (pH 7.1) containing 0.4 M ammonium sulfate, 0.067 mM NADPH, and 1.0 mM *dl*-glyceraldehyde. Sufficient enzyme was added to produce a rate of NADPH oxidation equal to 4 milliunits (unit equal to 1 μmol of NADPH oxidized at 25 °C per min). The coefficient of variation for this assay over a 4-year period was approximately 12%.

In Vivo Model. According to the method of Peterson et al.,[8] rats were made diabetic by the injection of 85 mg/kg of streptozotocin at 0 h; test compounds were administered by oral gavage at 4, 7, and 24 h. The sorbitol content of sciatic nerves and lenses were determined at 27 h. Results were expressed as the mean (±SEM) percent inhibition of sorbitol accumulation versus untreated diabetic controls. Statistical significance was calculated on the basis of the absolute levels of sorbitol in the treated and untreated diabetic groups by using Student's *t* test.

Statistical Analysis. The IC_{50} value was calculated for each compound as follows

$$(IC_{50})_i = \bar{x}_i + [(50 - \bar{y}_i)/\beta]$$

where IC_{50} is the concentration associated with 50% inhibition of enzyme activity, and $\bar{x}_i$ and $\bar{y}_i$ are the mean concentration and percent inhibition, respectively, of the i^{th} compound; and β is the common slope of the dose–response relationship, estimated by analysis of covariance (ANOCOVA) of pooled data from all compounds in the experiment, using only data within the dose-proportional range. The 95% confidence interval (CI_{95}) for each compound was calculated as follows

$$(CI_{95})_i = \bar{x}_i + [(50 \pm w_i) - \bar{y}_i]/\beta$$

$$w_i = 2s_{yx}\sqrt{(1/n_i) + (\Delta_i/s_{xx})}$$

$$\Delta i = ((IC_{50})_i - \bar{x}_i)^2$$

$$s_{xx} = \sum x_i^2 - n_i\bar{x}_i^2$$

where n_i is the number of data points for the i^{th} compound, and s_{yx} is the standard error of the estimate of $\bar{y}_i$. This analysis assumes that the percent inhibition is a linear function of the logarithm of concentration within the dose-proportional range and that the slope of the line is the same for all compounds in the experiment. Observations are assumed to be mutually independent and of equal weight. Error in measuring inhibition is assumed to be normally distributed and approximately equal throughout the dose range for all compounds.

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Myers and the contributions to data analysis by Daniel Gans.

Registry No. **6**, 16498-81-0; **7**, 54916-65-3; **8**, 126578-29-8; **9**, 126578-30-1; **10**, 126578-31-2; **11**, 82060-51-3; **12**·Na, 122433-56-1; **13**, 122433-39-0; **14**, 122433-33-4; **15**, 122442-60-8; **16**, 126642-39-5; **16**·methylcinchonium hydroxide, 126642-40-8; **17**, 126642-41-9; **18**, 126578-32-3; **19**, 126720-80-7; (2*R*,4*S*)-**19**·(*S*)-(−)-*N*-benzyl-α-methylbenzylamine, 126642-43-1; (2*S*,4*R*)-**19**·(*S*)-(−)-*N*-benzyl-α-methylbenzylamine, 126642-45-3; (2*S*,4*R*)-**19**·(*R*)-(+)-*N*-benzyl-α-methylbenzylamine, 126720-72-7; **20**, 126720-73-8; **21**, 122433-34-5; **22**, 122433-36-7; **23**, 122433-35-6; **24**, 122454-50-6; **25**, 122518-01-8; **26**, 126642-46-4; 6-bromo-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one, 126578-33-4; 5-bromo-2-methoxynicotinic acid, 54916-66-4; methyl 5-bromo-2-methoxynicotinate, 122433-41-4; 1-(5-chloro-2-methoxy-3-pyridyl)butane-1,3-dione, 122433-42-5; 6-bromo-2-methyl-4*H*-pyrano[2,3-*b*]pyridin-4-one, 122433-43-6; 6-fluoro-2,3-dihydro-2-methyl-4*H*-pyrano[2,3-*b*]-pyridin-4-one, 126578-34-5; methyl 2-methoxynicotinate, 67367-26-4; methyl 5-nitro-2-methoxynicotinate, 122433-50-5; methyl 5-amino-2-methoxynicotinate, 122433-51-6; methyl 5-fluoro-2-methoxynicotinate, 122433-52-7; pyridylbutane-1,3-dione, 3594-37-4; 6-chloro-2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-one, 122433-49-2; methyl 3-(5-chloro-2-methoxy-3-pyridyl)-3-oxopropionate, 122433-45-8; 5-chloro-2-methoxy-3-acetylpyridine, 122433-46-9; 6-chloro-4*H*-pyrano[2,3-*b*]pyridin-4-one, 122433-48-1; methylcinchonium hydroxide, 122518-07-4; (*S*)-(−)-*N*-benzyl-α-methylbenzylamine, 17480-69-2; (*R*)-(+)-*N*-benzyl-α-methylbenzylamine, 38235-77-7; aldose reductase, 9028-31-3.

Supplementary Material Available: Additional experimental data concerning the X-ray analysis of compound **20** (9 pages). Ordering information is given on any current masthead page.