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Enantioselective Synthesis of 5-LO Inhibitors Using a Gulofuranose Auxiliary[1]

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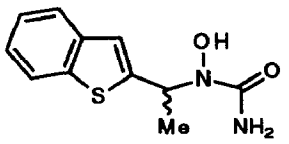
Abstract: *The pure R-(+)-enantiomer of 5-lipoxygenase inhibitor Zileuton was prepared by diastereoselective methyl Grignard addition to an aldonitrone bearing a D-gulofuranose-derived chiral auxiliary. Addition of the Lewis acid trimethylaluminum leads to a reversal of the alkylation stereochemistry and the potent pyrido analogue, R-(+)-RS-27871 was prepared in this way from an L-gulofuranose-derived nitrone.*

Zileuton **1** is a racemic N-(1-arylethyl)-N-hydroxyurea inhibitor of mammalian 5-lipoxygenase (5-LO) which is currently in clinical development by Abbott Laboratories as a treatment for asthma.[2] The Syntex compound, RS-27871, **2** is an optically active pyrido analogue, bearing the *R*-(+)-configuration, which shows higher potency and significantly longer metabolic half-life *in vitro*.[3] Several routes to racemic **1** have been described in the literature but only one enantioselective synthesis has appeared, a lengthy chiral pool approach starting from L-lactic acid.[2c] The lack of general enantioselective methodology for this class of compounds has been noted.[2e]



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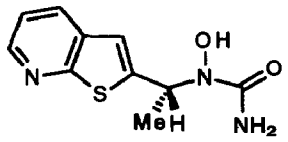

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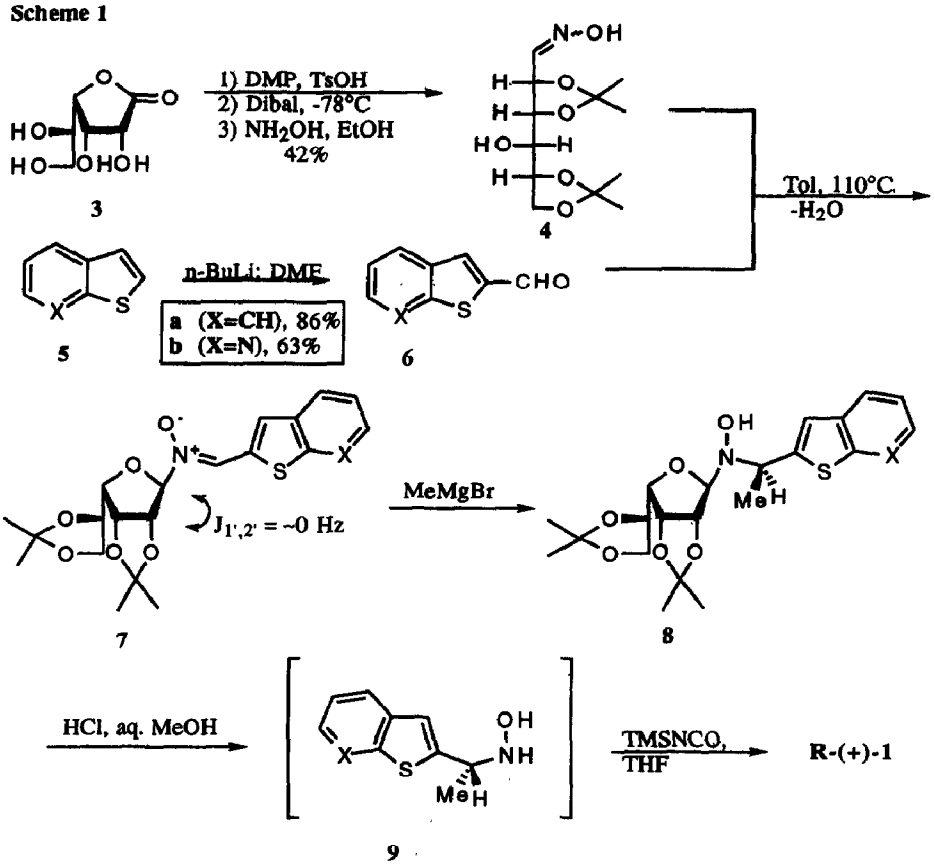
Schwartz and Hu have recently disclosed a novel synthesis of chiral benzylic amines and hydroxylamines based upon Grignard alkylation of nitrones bearing a 2,3:5,6-di-*O*-isopropylidene-gulofuranose auxiliary.[4] A particular advantage of the sugar gulose is that both of its enantiomers are readily prepared, and commercially available, in the form of the gulono-1,4-lactones. Related precedents were found in the preparation and diastereoselective cycloaddition reactions of sugar-derived aldonitrones which have been extensively studied by Vasella.[5] In addition, the utility of chelation-controlled stereoselective Grignard additions to amino alcohol-derived nitrones has been amply demonstrated by Coates.[6]

The synthesis of enatiomerically pure *R*-(+)-Zileuton was readily accomplished using the gulose auxiliary (Scheme 1). D-Gulono-1,4-lactone[7] **3** was protected as its diisopropylidene derivative (acetone, 2,2-dimethoxypropane, TsOH),[8] reduced to the lactol (Dibal, tol, -78°C)[9] and converted to a glassy 6:5 mixture of aldoximes **4** (hydroxylamine•HCl, sodium bicarbonate, aq. MeOH) in 42% overall yield. Thianaphthene **5a** was formylated (1.4 eq. n-BuLi, THF, -78°C; 4 eq. DMF)[10] to give aldehyde **6a** in 82% yield and this was

Scheme 1

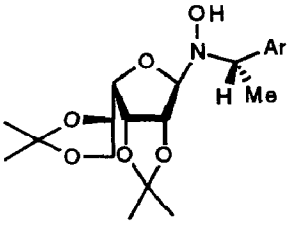


condensed with equimolar **4** in refluxing toluene under Dean-Stark conditions to afford the highly crystalline nitrone **7a**[11] in 78% yield. The β-configuration of the anomeric center was assigned based on observation of $J_{1'-2'}$ ~0 Hz in the ^{1}H-NMR[5b] and the Z-nitrone stereochemistry was supported by observation of a strong NOE between the benzylic and C1' hydrogens.

Treatment of a slurry of the nitrone **7a** with methylmagnesium bromide at 0°C (1.5 eq. ethereal MeMgBr, CH_2Cl_2, 1 h) gave a clear solution from which the sole monoalkylation product, **8a**[12] (>99% de), was isolated in 61% yield following silica gel chromatography. Acid cleavage of **8a** (1N HCl, MeOH, 0°C, 12h) afforded the hydroxylamine **9a** which was carbamoylated (TMSNCO, THF, 23°C) without purification to give *R*-(+)-**1** in 72% yield, after crystallization from CH_2Cl_2/MeOH/hexane.[13]

Preparation of optically pure RS-27871 **2** was initially found to be more difficult. Thieno[2,3-*b*]-pyridine **5b**[14] was formylated[15] and condensed with **4**, as above, to give nitrone **7b**[16] in 80% yield. Alkylation at 0°C with MeMgBr in CH_2Cl_2 gave a 64% yield of a mixture of monoalkylation products, with a disappointing 30% de favoring the desired *R*-epimer **8b**. The lower diastereoselectivity in this case presumably resulted from perturbation of the structured magnesium chelate by the pyrido ligand. At -78°C no reaction occurred (20 MeMgBr, 40h, CH_2Cl_2 or THF) due to the insolubility of **7b** (or **7a**) at low temperature.

Alternative organometallic reagents were screened in an attempt to raise the diastereoselectivity and this led to a serendipitous discovery. Addition of trimethylaluminum (1.2 eq 1M in hexane) to a CH_2Cl_2 slurry of **7b** gave no alkylation but instead formed a stable, soluble complex. The complex remained fully dissolved even on cooling to -78°C and Grignard addition at that temperature (1.5 eq ethereal MeMgBr, 0.5 h) unexpectedly afforded, as the major product, the *S*-epimer **10**[17] (63% yield, 82% de) revealing a *reversal of the alkylation facial selectivity from the uncomplexed experiments*.[18] Repetition of the sequence starting from L-gulono-1,4-lactone **ent-3**,[19] using aluminum-mediated Grignard addition, afforded the desired *R*-epimer, **ent-10**, in similar overall yield and de. Acid cleavage of **ent-10** gave **9b**, which upon carbamoylation afforded pure **2**[20] in 40% yield, after removal of a small amount of racemic material by crystallization.



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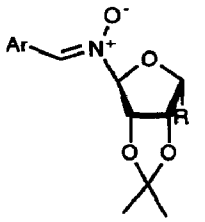
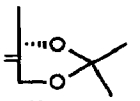


11 R = 

12 R = H

Ar = thieno[2,3-*b*]pyridin-2-yl-

Comparison with two closely related sugar auxiliaries implicated gulose's C5'-oxy substituent as a key stereocontrol element, despite its distance from the reaction center. Commercially available 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose was readily converted into its oximes and condensed with aldehyde **5b** (toluene, 110°C, 40 h) to give nitrone **11**[21] in 65% yield. In similar fashion, L-erythronic γ-lactone was converted into nitrone **12**.[22] Despite the obvious structural homologies of **11** and **12** with **7b** (or more specifically with **ent-7b**), methyl Grignard addition to these former nitrones, either with or without trimethylaluminum, proceeded with poor diastereoselectivity. Thus, Schwartz's identification of the gulofuranose auxiliary appears to be a key observation, with the trimethylaluminum-mediated reaction being a useful complement to the basic method in some cases.[23]

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11. (**7a**): mp 244-6°C (EtOAc/tol); $[\alpha]_D$ -14° (c 1.1, CH_2Cl_2); IR (KBr), 1563 cm^{-1}; FAB MS, *m/z* 420 (MH^+), 243, 285, 127; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (s, 1 H, N=CH), 7.92-7.80 (m, 2 H, ArH), 7.76 (s, 1H, Ar_3H), 7.46-7.38 (m, 2 H, ArH), 5.65 (s, 1 H, $C_1'H$), 5.37 (d, *J* = 6.1 Hz, 1 H, $C_2'H$), 4.94 (dd, *J* = 4.3, 6.1 Hz, 1 H, $C_3'H$), 4.65 (dd, *J* = 4.3, 8.1 Hz, 1 H, $C_4'H$), 4.39 (ddd, *J* = 6.6, 7.3, 8.1, 1 H, $C_5'H$), 4.25 (dd, *J* = 6.6, 8.5 Hz, $C_6'H$), 3.73 (dd, *J* = 7.3, 8.5 Hz, $C_6'H'$), 1.52 (s, 3 H, Me), 1.46 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.34 (s, 3 H, Me). Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.04; H, 5.76; N, 3.51.
12. (**8a**): mp 87°C (foam); $[\alpha]_D$ +38° (c 0.6, CH_2Cl_2); IR (KBr), 3440 cm^{-1}; MS *m/z* 435 ($M^{+\cdot}$), 377, 319, 161; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80-7.68 (m, 2 H, ArH), 7.35-7.25 (m, 2 H, ArH), 7.20 (s, 1 H, C_3H), 5.12 (s, 1 H, OH), 4.98 (d, *J* = 6.1 Hz, 1 H, $C_2'H$), 4.74 (dd, *J* = 4.2, 6.1 Hz, 1 H, $C_3'H$), 4.73 (s, 1 H, $C_1'H$), 4.70 (q, *J* = 6.6 Hz, 1 H, ArCHN), 4.36-4.18 (m, 3 H, $C_4'5'6'H$), 3.68 (dd, *J* = 6.5, 8.2 Hz, 1 H, $C_6'H'$), 1.50 (d, *J* = 6.6 Hz, 3 H, NCMe), 1.49 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.32 (s, 3 H, Me). Anal. Calcd for $C_{22}H_{29}NO_6S$: C, 60.67; H, 6.71; N, 3.22. Found: C, 60.72; H, 6.56; N, 3.33.
13. ((**R**)-(+)-**1**): mp 155-7°C (CH_2Cl_2/MeOH/hexane); $[\alpha]_D$ +46.8° (c 0.349, MeOH), [lit.[2c] $[\alpha]_D$ +50.3° (c 0.35, MeOH)]; IR (KBr), 3459, 3276, 1676 cm^{-1}; ^1H NMR (5% DMSO-d_6/$CDCl_3$, 300 MHz) δ 8.83 (s, 1 H, OH), 7.78-7.69 (m, 2 H, ArH), 7.33-7.24 (m, 3 H, ArH), 5.77 (q, *J* = 6.9 Hz, 1 H, ArCH), 5.50 (bs, 2 H, NH_2), 1.65 (d, *J* = 6.9 Hz, 3 H, Me). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 56.05; H, 5.10; N, 11.73. Chiral purity of >99.6% ee was verified by HPLC upon comparison with a racemic reference sample[2b] (Chiralcel OD-R, 4.6 mm x 25 cm, 35°C, 75% 0.5 M $NaClO_4$/25% CH_3CN, λ = 234 nm, flow 1 mL/min.).
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16. (**7b**): mp 254-5°C (EtOAc/tol); $[\alpha]_D$ -12.5° (c 1, CH_2Cl_2); IR (KBr), 1552 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.79 (s, 1 H, N=CH), 8.64 (dd, *J* = 1.6, 4.6 Hz, 1 H, C_6H), 8.30 (dd, *J* = 1.6, 8.2 Hz, 1 H, C_4H), 7.95 (s, 1 H, C_3H), 7.46 (dd, *J* = 4.6, 8.2 Hz, 1 H, C_5H), 5.94 (s, 1 H, $C_1'H$), 5.17 (d, *J* = 6.0 Hz, 1 H, $C_2'H$), 5.02 (dd, *J* = 4.0, 6.0 Hz, 1 H, $C_3'H$), 4.61 (dd, *J* = 4.2, 8.2 Hz, 1 H, $C_4'H$), 4.19-3.79 (m, 3 H, $C_5',_6'H$), 1.46 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.30 (s, 6 H, 2 x Me). Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.27; H, 5.68; N, 6.66.
17. (**10:8b**, 91:9 crystalline mixture): mp 161-2°C (EtOAc/hex); $[\alpha]_D$+110° (c 1, CH_2Cl_2); IR (KBr), 3430 cm^{-1}; MS *m/z* 436 ($M^{+\cdot}$), 378, 162; Anal. Calcd for $C_{21}H_{28}N_2O_6S$: C, 57.78; H, 6.46; N, 6.42. Found: C, 57.92; H, 6.47; N, 6.55. (**10**): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (dd, *J* = 1.4, 4.7 Hz, 1 H, C_6H), 7.94 (dd, *J* = 1.4, 8.0 Hz, 1 H, C_4H), 7.24 (dd, *J* = 4.7, 8.0 Hz, 1 H, C_5H), 7.21 (s, 1 H, C_3H), 6.26 (bs, 1 H, OH), 4.97 (d, *J* = 6.1 Hz, 1 H, $C_2'H$), 4.84 (s, 1 H, $C_1'H$), 4.78 (dd, *J* = 4.5, 6.1 Hz, 1 H, $C_3'H$), 4.71 (q, *J* = 6.5 Hz, 1 H, ArCHN), 4.38 (dd, *J* = 4.5, 8.1 Hz, $C_4'H$), 4.30-4.17 (m, 2 H, $C_5'6'H$), 3.70 (dd, *J* = 6.6, 8.0 Hz, $C_6'H$), 1.64 (d, *J* = 6.5 Hz, 3 H, NCMe), 1.48 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.38 (s, 3 H, Me), 1.25 (s, 3 H, Me).
18. Methyl Grignard addition to **7a** in the presence of trimethylaluminum gave **8a** in 20% de.
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20. (**2**): mp 158-60°C (MeOH/EtOAc); $[\alpha]_D$ +41° (c 0.2, MeOH); IR (KBr), 3475, 3150, 1693 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 9.32 (s, 1 H, OH), 8.49 (dd, *J* = 1.6, 4.7 Hz, 1 H, C_6H), 8.16 (dd, *J* = 1.6, 8.0 Hz, 1 H, C_4H), 7.38 (dd, *J* = 4.7, 8.0 Hz, 1 H, C_5H), 7.26 (d, *J* = 0.9 Hz, 1 H, C_3H), 6.52 (bs, 2 H, NH_2), 5.58 (dq, *J* = 0.9, 7.0 Hz, 1 H, ArCHN), 1.52 (d, *J* = 7.0 Hz, 3 H, Me). Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.61; H, 4.67; N, 17.70. Found: C, 50.64; H, 4.68; N, 17.74. Chiral purity of 96% ee was determined by HPLC (Chiral AGP, 4 mm x 10 cm, 23°C, 92% 10 mM KH_2PO_4/ 8 % MeOH, λ = 234 nm, flow 1 mL/min.).
21. (**11**): mp 248-51°C (EtOAc/tol); $[\alpha]_D$ + 58° (c 1, CH_2Cl_2); IR (KBr), 1553 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 56.69; H, 5.63; N, 6.61.
22. (**12**): mp 210-3°C (EtOAc/tol); $[\alpha]_D$ + 145° (c 0.6, CH_2Cl_2); IR (KBr), 1552 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.34; H, 5.18; N, 8.96.
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