Addition of Organometallic Reagents to *N*-Glycosyl Nitrones. Enantioselective Syntheses of (+)-(*R*)- and (−)-(*S*)-Zileuton

Anwer Basha,† Rodger Henry,‡ Maureen A. McLaughlin,§ James D. Ratajczyk,† and Steven J. Wittenberger*,§

Leukotriene Biosynthesis, Department 47K/AP10, Process Chemistry, Department 45L/AP10; Structural Chemistry, Department 418/AP9; Pharmaceutical Products Division, Abbott Laboratories, One Abbott Park Road, Abbott Park, Illinois 60064-3500

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5-Lipoxygenase is the initiatory enzyme in the biosynthesis[1] of leukotrienes which are implicated as mediators in disease states[2] such as asthma, allergy, psoriasis, and inflammatory bowel disease. Discovered at Abbott Laboratories,[3] zileuton (±)-**1** (ABT-077, (±)-*N*-(1-benzo[*b*]-thien-2-ylethyl)-*N*-hydroxyurea)[4] is the first selective 5-lipoxygenase inhibitor to establish efficacy for this new class of therapeutic agents in asthma[5] and ulcerative colitis.[6] Several syntheses of this important new clinical candidate, in both the racemic[7] and enantiomerically enriched[8] forms, have appeared in the literature. Herein are reported the complementary approaches to (+)-(*R*)- and (−)-(*S*)-zileuton (**1**) that rely on the diastereoselective addition of an organometallic reagent to a mannose-derived *N*-glycosyl nitrone as the key step in the syntheses.

Nitrones are known to react with organometallic reagents to yield *N*-hydroxylamines.[9–11] Coates et al. reported the diastereoselective addition of Grignard reagents to nitrones bearing α-stereogenic centers.[12] Vasella et al. have published a series of papers describing the addition reactions of phosphorus nucleophiles and cycloaddition reactions of dipolarophiles with *N*-glycosyl nitrones.[13] During the course of our studies, Schwartz and Hu presented their results regarding the addition of Grignard reagents to *N*-gulofuranosyl-*C*-aryl nitrones to produce *N*-hydroxylamine products with high diastereoselectivity.[14] This work was extended recently by Rohloff, Alfredson, and Schwartz for the syntheses of (+)-(*R*)-zileuton and the pyrido analogue, (+)-(*R*)-RS-27871.[8b]

Application of the Vasella transition state model[13] of cyclo- and nucleophilic addition to *N*-glycosyl nitrones, termed the "kinetic anomeric effect" guided our choice of chiral auxiliary. D-Mannose was converted to the diacetonide **2** with acetone and phosphorus pentoxide. Treatment of the lactol **2** with *N*-hydroxylamine hydrochloride and sodium acetate in ethanol provided reproducibly high yields (81–83% from D-mannose) of mannose oxime **4**.[15] The ratio of *syn*/*anti* oxime isomers is dependent upon the solvent.[16]

The oxime **4** is in equilibrium with the hydroxylamine tautomer **3** as evidenced by the ready formation of the *N*-mannofuranosyl-*C*-methyl nitrone **5** upon exposure of *N*-mannofuranosyl(hydroxylamine) **3/4** to acetaldehyde in dichloromethane containing sodium sulfate at ambient temperature.[17] Treatment of nitrone **5** with metalated benzo[*b*]thiophene[18] produced the diastereomeric addition products **6a** and **6b**. Improved diastereoselectivity was observed for the Grignard reagent (**6a/6b**, 9.2:1, 73% yield from **3/4**) relative to the organolithium (**6a/6b**, 2.2:1, 70% yield). Coates and Chang[12] demonstrated that suitably situated alkoxy groups enhanced the diastereoselective addition of organometallic reagents (presumably through chelation) to nitrones and that different ratios of diastereomers were produced from magnesium and lithium reagents; however, these differences were variable and also dependent on nitrone structure, reaction temperature, and solvent. In the present example of nitrone **5**, the subtle changes in the complex transition state structures (in going from the organolithium to the Grignard reagent) responsible for the observed enhancement in diastereoselectivity are not clear. The stereochemistry of the major addition adduct **6a** was proven by X-ray crystallographic analysis[19] and through correlation with authentic (+)-(*R*)-zileuton **1**.

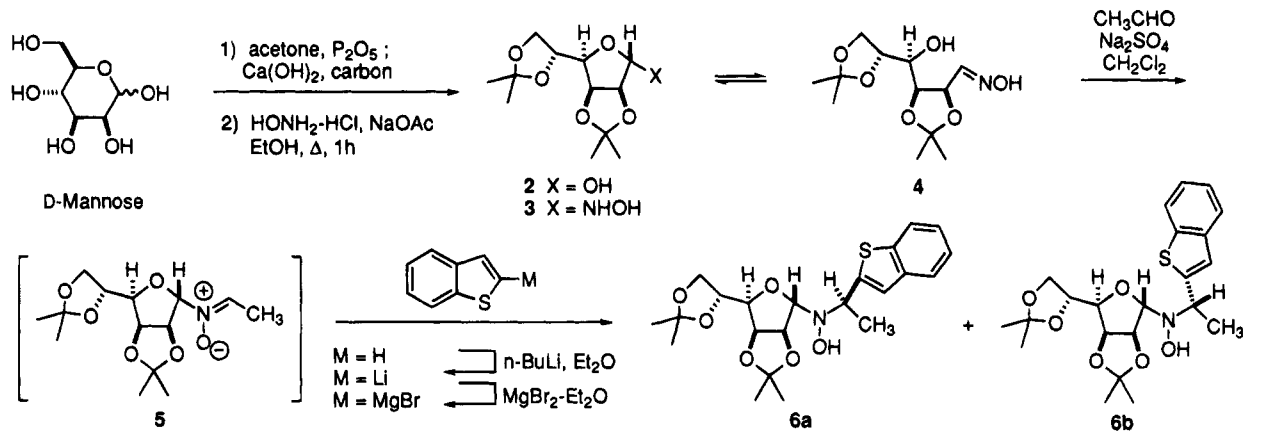
Ideally, conditions were sought that would hydrolyze the *N*-glycoside **6a** to liberate the α-chiral *N*-hydroxylamine **7** and provide the auxiliary in a reusable form. The glycosidic auxiliary of **6a** proved to be quite sensitive to acidic hydrolysis conditions. Treatment under a variety of conditions resulted in no reaction (e.g. 3:1:1 HOAc/THF/H_2O; saturated aqueous NH_4Cl/MeOH solution) or in degradation of the diacetonide-lactol auxiliary (e.g. aqueous HCl/MeOH; HCO_2H/MeOH/H_2O). *N*-Hydroxylamine hydrochloride in methanol-water solution effectively hydrolyzed the *N*-glycosidic linkage to give **7**; following short reaction times (i.e. 2 h) significant quantities of the *N*-mannose oxime **3/4** could be isolated. Longer reaction times resulted in decomposition of the

† Leukotriene Biosynthesis.
‡ Structural Chemistry.
§ Process Chemistry.

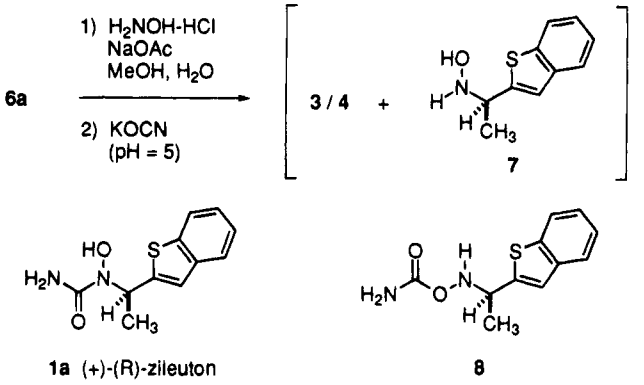
(1) (a) Samuelsson, B. *Science* **1983**, *120*, 568. (b) Cashman, J. R.; Oliva, S. L. *Drugs Today* **1988**, *24*, 723–732.
(2) Lewis, R. A.; Austen, K. F.; Soberman, R. J. *N. Engl. J. Med.* **1991**, *323*, 645.
(3) Summers, J. B.; Gunn, B. P.; Brooks, D. W. U.S. Patent 4,873,-259, Oct. 10, 1989.
(4) Brooks, D. W.; Bell, R. L.; Carter, G. W.; Dube, L. M.; Rubin, P. D. *Drugs Future* **1993**, *18* (7), 616–618.
(5) Isreal, E.; Drazen, J.; Pearlman, H.; Cohn, J.; Rubin, P. *J. Allergy Clin. Immunol.* **1992**, *89*, 236.
(6) Collawn, C.; Rubin, P.; Perez, H.; Bobadilla, J.; Cabrera, G.; Reyes, E.; Borovoy, J.; Kershenobich, D. *Am. J. Gasteroenterol.* **1992**, *87*, 342.
(7) Racemic syntheses of zileuton: (a) Kolasa, T.; Brooks, D. W. *Synthetic Commun.* **1993**, *23*, 743–748. (b) Basha, A.; Ratajczyk, J. D.; Brooks, D. W. *Tetrahedron Lett.* **1991**, *32*, 3783–3786.
(8) Asymmetric synthesis of (+)-(*R*)-zileuton: (a) Hsiao, C.-N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629–2632. (b) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35* (7), 1011–1014.
(9) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495.
(10) Basha, A.; Ratajczyk, J. D.; Brooks, D. W. *Tetrahedron Lett.* **1991**, *32* (31), 3783–3786.
(11) Schwartz, M. A.; Hu, X. *Tetrahedron Lett.* **1992**, *33* (13), 1689–1692.
(12) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464–3474, 3475–3483.
(13) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33–58, and references therein.
(14) Hu, X.; Schwartz, M. A. *Abstracts of Papers*, 204th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 1992; ORGN 5.
(15) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273–1295.
(16) In $CDCl_3$ the oxime **4** exists as a mixture of the *syn* and *anti* isomers (ca. 1:7 ratio) while in DMSO-d_6 and CD_3OD only one isomer is apparent by ^1H NMR.
(17) Torssell, K.; Zeuthen, O. *Acta. Chem. Scand., Ser. B* **1978**, *B32*, 118–124.
(18) Lumma, W. C., Jr.; Dutra, G. A.; Voeker, C. A. *J. Org. Chem.* **1970**, *35* (10), 3442–3444.
(19) ORTEP structure of **6a** included in supplementary material. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

0022-3263/94/1959-6103$04.50/0

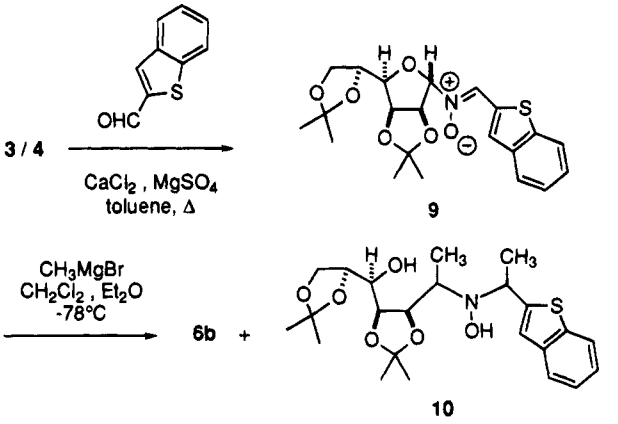
Scheme 1



Scheme 2



Scheme 3



auxiliary, presumably through loss of the acetonide protecting groups. Sodium acetate was added as a buffer to raise the pH of the reaction mixture. The reaction proceeded slower but was much cleaner, nearly devoid of any baseline material (TLC) indicative of acetonide hydrolysis.

The intermediate *N*-hydroxylamine **7** was not isolated. The reaction mixture was treated with potassium cyanate to selectively carbamoylate **7** in the presence of *N*-mannofuranosyl(hydroxylamine) **3/4**. In the aqueous methanolic reaction medium, **3/4** exists primarily in the oxime tautomer **4** which explains the selectivity observed. Following workup and chromatography, the *N*-mannose oxime **3/4** was recovered (95% yield). Two acylation products were isolated; (+)-zileuton (**1**) (60% yield) and the O-acylation product **8** (20% yield) which could be observed (TLC) to isomerize to **1** on heating in toluene over several hours. The (+)-(*R*)-zileuton (**1**) produced was shown to be ≥98% ee by chiral HPLC analysis.[20]

(−)-(*S*)-Zileuton was prepared by reversal of the nitrone and Grignard substituents. A mixture of benzo[*b*]-thiophene-2-carboxaldehyde, *N*-mannofuranosyl(hydroxylamine) **3/4**, anhydrous calcium chloride, and anhydrous magnesium sulfate was heated at reflux in toluene. The *C*-aryl nitrone **9** was isolated (46% yield) after eluting the reaction mixture from a silica gel column with 2% methanol in dichloromethane. Treatment of a dichloromethane solution of nitrone **9** at −78 °C with ethereal methylmagnesium bromide followed by ethanol quench and aqueous workup provided a mixture of the expected hydroxylamine **6b** (63% yield after flash chromatography) and the bis-addition product **10** (ca. 10−15% yield) as the major identifiable products, each a single diastereomer, and some unreacted nitrone **9** (ca. 15−20%). The epimeric hydroxylamine **6a** could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture.[21] Interestingly, when the nitrone **9** was treated with a tetrahydrofuran solution of methylmagnesium chloride in dichloromethane at −40 to ~0 °C only the bis-addition product **10** was isolated in 93% yield.[22]

The crude ethereal methylmagnesium chloride reaction mixture was stirred with ethanolic HCl to hydrolyze the *N*-glycosidic linkage and provide the hydroxylamine (56% yield). Carbamoylation with trimethylsilyl isocyanate (THF, rt) followed by hydrolysis gave (−)-(*S*)-zileuton in 44% yield.

N-Glycosyl-*C*-alkyl and -*C*-aryl nitrones are effective intermediates for the preparation of enantiomerically enriched α-chiral *N*-hydroxylamines and their derivatives. The methodolgy has successfully led to the enantioselective syntheses of (+)-(*R*)- and (−)-(*S*)-zileuton (**1**) on a laboratory scale. By application of the kinetic anomeric effect model in conjunction with the variety of commercially available carbohydrate derivatives, either enantiomer of an α-chiral hydroxylamine derivative is predictably accessible via this methodology.

Experimental Section

General. Reactions were routinely performed under an inert atmosphere (nitrogen or argon). Analytical thin-layer chroma-

(20) Chiral HPLC conditions: Chiralpak AD 4.6 × 250, 90:10 hexane:ethanol at 1.0 mL/min. Detection: λ = 254 nm, t_R: (+)-(*R*)-isomer = 12.6 min, (−)-(*S*)-isomer = 21.2 min.

(21) Coincidentally, this hydroxylamine epimer **6a** has the same R_f as both the starting nitrone **9** and the bis-addition product **10** in the TLC systems we commonly used.

(22) At −78 °C, ≥90% starting nitrone was recovered with a minor amount (≤10%) of the bis-addition product **10** observed in the crude ^{1}H NMR spectrum.

tography (TLC) was performed using E. Merck silica gel 60 F-254 glass-backed plates, 250 μm thickness. Flash chromatography was performed using E. Merck Kieselgel 60 (230–400 mesh) and elutent systems are listed as v/v %.

2,3:5,6-Di-*O*-isopropylidene-D-mannose Oxime (3/4). A 2-L, three-necked, round-bottom flask equipped with an overhead stirrer is charged with acetone (1.11 L, HPLC grade) and D-mannose (Aldrich, mixture of anomers, 100.2 g, 0.556 mol). P_2O_5 (19 g, 0.133 mol) is added in portions and the mixture is stirred overnight (25 h). $Ca(OH)_2$ (74 g, 1.0 mol) and activated carbon (37 g) are added and the mixture is stirred ca. 20 min before it is filtered through a cake of diatomaceous earth, rinsing thoroughly with acetone. The light yellow filtrate is evaporated to dryness in vacuo leaving 139.1 g of 2,3:5,6-di-*O*-isopropylidene-D-mannose (**2**) as a light yellow solid.

The above crude lactol **2** (139.1 g, 0.537 mol) is dissolved in absolute EtOH (750 mL). $NH_2OH{\cdot}HCl$ (55.6 g, 0.80 mol) and $NaOAc{\cdot}3H_2O$ (65.7 g, 0.80 mol) are added and the mixture is warmed to 65–70 °C for 1 h. After cooling to room temperature, the bulk of the EtOH (ca. 525 mL) is removed in vacuo and the residue is partitioned between EtOAc (1 L) and saturated $NaHCO_3$ solution (0.5 L). The organic layer is washed with saturated $NaHCO_3$ solution (0.5 L). The combined aqueous portions are extracted with EtOAc (2 × 250 mL) and the combined organics are washed with brine (500 mL) and dried ($MgSO_4$ + activated carbon). Filtration and evaporation afforded 125.6 g (82% yield) 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (**3/4**) as a light yellow solid: mp 137–138 °C; $[\alpha]^{24}_D = -159.9°$ (c = 2.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.23 (s, 3H), 1.28 (s, 6H), 1.44 (s, 3H), 3.17 (t, 1H, J = 7 Hz), 3.80–3.95 (m, 3H), 4.49 (dd, 1H, J = 1, 8 Hz), 4.58 (d, 1H, J = 8 Hz), 5.19 (dd, 1H, J = 5, 8 Hz), 6.93 (d, 1H, J = 4 Hz), 11.11 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 24.7, 25.3, 26.1, 26.8, 66.2, 69.5, 71.6, 75.5, 76.8, 85.4, 108.2, 149.9; IR ($CDCl_3$) 3570, 3340, cm^{-1}; HRMS (FAB) m/e calcd 276.1447, found 276.1430. Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.54; H, 7.62; N, 5.07.

***N*-(2,3:5,6-Di-*O*-isopropylidene-D-mannofuranosyl)-*N*-(β-((*R*)-1-(2-benzothienyl)ethyl))hydroxylamine (6a).** A mixture of oxime **3/4** (5.04 g, 18.3 mmol), acetaldehyde (2.05 mL, 36.6 mmol), and Na_2SO_4 (3.94 g, 27.7 mmol) in CH_2Cl_2 (37 mL) was stirred at ambient temperature for 1.67 h. The reaction was filtered and evaporated to dryness. In the meantime, to a solution of thianaphthalene (4.85 g, 34.3 mmol) in ether (24 mL) was added n-BuLi (1.45 M, 24 mL, 34.8 mmol). After 55 min $MgBr_2{\cdot}OEt_2$ (8.94 g, 34.6 mmol) was added in three portions to give a ca. 0.7 M suspension of 2-benzothienylmagnesium bromide. To the nitrone dissolved in CH_2Cl_2 (30 mL) at −78 °C was added the suspension of Grignard reagent via double-ended needle at such a rate as to maintain a reaction temperaure ≤−65 °C. The reaction was allowed to warm to ca. −45 °C over 50 min and then was quenched with water. The mixture was partitioned between CH_2Cl_2 and 5% $KHSO_4$ solution (100 mL ea). The aqueous portion was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organics were washed with saturated $NaHCO_3$ solution (100 mL) and then brine (100 mL) and dried ($MgSO_4$). Filtration and evaporation of solvent left 9.3 g yellow oil which was flash chromatographed (25% EtOAc/hexane) to give **6a** (5.25 g, 66% yield) and **6b** (0.57 g, 7% yield). **6a**: mp 99–101°C; $[\alpha]^{24}_D = +114°$ (c = 3.3, $CHCl_3$); R_f = 0.35 (1:2 EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 1.40 (s, 6H), 1.49 (s, 3H), 1.62 (d, 3H, J = 7 Hz), 4.12 (d, 2H, J = 6 Hz), 4.28–4.39 (m, 2H), 4.59 (q, 1H, J = 7 Hz), 4.65 (s, 1H), 4.85 (dd, 1H, J = 3, 6 Hz), 4.92 (br s, 1H), 4.96 (d, 1H, J = 6 Hz), 7.19 (s, 1H), 7.25–7.35 (m, 2H), 7.68–7.7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 24.2, 25.4, 25.8, 26.9, 58.1, 66.8, 73.9, 80.7, 84.1, 84.7, 96.9, 109.1, 112.2, 122.2, 122.3, 123.4, 124.1 (2C), 139.3, 139.7, 145.4; IR ($CDCl_3$) 3570, 3400 cm^{-1}; MS (DCI/NH_3) 436 $(M + H)^+$. Anal. Calcd for $C_{12}H_{29}NO_6S$: C, 60.67; H, 6.71; N, 3.22; S, 7.36. Found: C, 59.88; H, 6.55; N, 3.01; S, 6.87.

(+)-(*R*)-Zileuton (1a). A mixture of **6a** (1.01 g, 2.32 mmol), $NaOAc{\cdot}3H_2O$ (0.47 g, 3.45 mmol), and $NH_2OH{\cdot}HCl$ (0.244 g, 3.51 mmol) in CH_3OH/water (3/1 v/v, 12 mL) was stirred at ambient temperature overnight (19 h). KOCN (0.285 g, 3.51 mmol) was added and the mixture was stirred 2.5 h. The mixture was concentrated in vacuo and partitioned between EtOAc and water (20 mL ea), and the aqueous portion was extracted with EtOAc (2 × 20 mL). The combined organics were dried (Na_2SO_4), filtered, and evaporated. Flash silica chromatography provided oxime **3/4** (600 mg, 94% yield), *O*-carbamoyl product **8** (101 mg, 18% yield), and (+)-(*R*)-zileuton (**1a**) (332 mg, 60% yield). **8**: mp 104–105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (d, 3H, J = 7 Hz), 4.63 (q, 1H, J = 7 Hz), 5.0–5.6 (br s, 2H), 6.5–7.0 (br s, 1H), 7.27 (s, 1H), 7.28–7.39 (m, 2H), 7.70–7.75 (m, 1H), 7.79–7.83 (m, 1H); MS (DCI/NH_3) 254 $(M + NH_4)^+$. Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.92; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.24; H, 5.27; N, 11.88; S, 13.56. (+)-(*R*)-**1a**: mp 148–149 °C; $[\alpha]^{24}_D = +47.0°$ (c = 1.1, MeOH); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.51 (d, 3H, J = 7 Hz), 5.57 (q, 1H, J = 7 Hz), 6.45 (s, 2H), 7.26 (s, 1H), 7.28–7.36 (m, 2H), 7.75–7.79 (s, 1H), 7.86–7.90 (m, 1H), 9.24 (s, 1H); MS (DCI/NH_3) 254 $(M + NH_4)^+$. Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.92; H, 5.12; N, 11.86; S, 13.57. Found: C, 55.96; H, 5.16; N, 11.56; S, 13.64.

***N*-(2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl)-*C*-(2-benzo[*b*]thienyl)nitrone (9).** A mixture of oxime **3/4** (5.0 g, 18.2 mmol) and benzo[*b*]thiophene-2-carboxaldehyde (3.0 g, 18.5 mmol) was refluxed in toluene (100 mL) in the presence of anhydrous $CaCl_2$ (10 g) and anhydrous $MgSO_4$ (5 g) over 3 h. The reaction mixture was evaporated, applied to a flash silica gel column, and eluted with 2% CH_3OH/CH_2Cl_2 to afford nitrone **9** (3.5 g, 46% yield). **9**: mp 222–223 °C; $[\alpha]^{24}_D = +54.9°$ (c = 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 1.41 (s, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 4.12–4.17 (m, 2H), 4.43 (ddd, 1H, J = 6, 7, 11 Hz), 4.68 (dd, 1H, J = 4, 7 Hz), 5.02 (dd, 1H, J = 4, 6 Hz), 5.38 (d, 1H, J = 6 Hz), 5.55 (s, 1H), 7.37–7.48 (m, 2H), 7.78 (s, 1H), 7.82–7.86 (m, 1H), 7.89–7.94 (m, 1H), 8.12 (s, 1H); MS (DCI/NH_3) 420 $(M + H)^+$, 437 $(M + NH_4)^+$. Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34; S, 7.64. Found: C, 59.98; H, 6.02; N, 3.19; S, 7.60.

***N*-(2,3:5,6-Di-*O*-isopropylidene-D-mannofuranosyl)-*N*-(β-((*S*)-1-(2-benzothienyl)ethyl))hydroxylamine (6b).** To a solution of nitrone **9** (503 mg, 1.20 mmol) in anhydrous CH_2Cl_2 (8 mL) chilled to −78 °C was added CH_3MgBr (3.0 M ether, 2.0 mL, 6.0 mmol). After 3 h EtOH (1.5 mL) was added and the mixture was allowed to warm to rt and partitioned between EtOAc and water (25 mL ea). The layers were separated and the aqueous portion was extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (1 × 20 mL), dried (Na_2SO_4), filtered, and evaporated leaving crude *N*-hydroxylamine **6b**. Purification by flash silica gel chromatography (20–25% EtOAc/hexane) gave 345 mg of *N*-hydroxylamine **6b** (66% yield) mp 115 °C; $[\alpha]^{24}_D = -10°$ (c = 2.3, $CHCl_3$); R_f = 0.45 (1:2 EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.49 (d, 3H, J = 7 Hz), 1.52 (s, 3H), 4.05–4.15 (m, 2H), 4.30–4.38 (m, 2H), 4.57 (q, 1H, J = 7 Hz), 4.69 (s, 1H), 4.85–4.90 (m, 1H), 5.00 (s, 1H), 5.03 (d, 1H, J = 6 Hz), 7.21 (s, 1H), 7.28–7.39 (m, 2H), 7.68–7.73 (m, 1H), 7.78–7.83 (m, 1H); MS (DCI/NH_3) 436 $(M + H)^+$.

(−)-(*S*)-Zileuton (1b). The crude *N*-hydroxylamine **6b** was stirred with ethanolic HCl (10 mL) for ca. 2 h at rt followed by evaporation in vacuo. The residue was treated with 3 N HCl (15 mL) and extracted with EtOAc. The aqueous portion was basified with K_2CO_3 (solid) to pH 7–8 and extracted with EtOAc (2 × 25 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated to give 115 mg of hydroxylamine **7b** (56% yield). A solution of **7b** (57 mg, 0.3 mmol) in THF (20 mL) was treated with TMSNCO (0.2 mL, mmol) at rt for 5 h followed by the addition of several drops of water and stirred 30 min longer. The mixture was concentrated in vacuo and the residue was triturated under CH_2Cl_2, collected, washed with a little CH_2Cl_2, and dried to give 31 mg (−)-(*S*)-zileuton **1b** (44% yield). (−)-(*S*)-**1b**: mp 149.5–150.5 °C; $[\alpha]^{24}_D = -46.6°$ (c = 1, MeOH).

Bis-Addition Product 10. To a slurry of nitrone **9** (1.00 g, 2.38 mmol) chilled to −40 °C was added CH_3MgCl (3 M THF, 2.90 mL, 6.75 mmol). After ca. 30 min at −40 °C, the reaction was warmed to −5 °C over about 50 min when it was quenched with water (20 mL). The pH was adjusted to ca. 7 with aqueous HCl solution and then extracted with EtOAc (3 × 25 mL). The combined organics were washed with brine (1 × 50 mL) then dried (Na_2SO_4), filtered, and evaporated. Flash silica gel chromatography provided 1.00 g of **10** (93% yield) as a white foam. **10**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (d, 3H, J = 7 Hz), 1.37 (s, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 1.54 (d, 3H, J = 7 Hz), 1.56 (s, 3H), 3.42–3.49 (m, 1H), 3.56 (q, 1H, J = 7 Hz), 4.08–4.17 (m, 1H), 4.18–4.27 (m, 2H), 4.30 (dd, 1H, J = 2, 7 Hz), 4.33–4.42 (m, 2H), 5.5–6.0 (br s, 1H), 5.63 (br s, 1H), 7.23 (s,

1H), 7.24–7.35 (m, 2H), 7.68–7.73 (m, 1H), 7.78–7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 21.0, 25.0, 25.1, 26.3, 27.0, 54.5, 60.1, 67.8, 71.5, 75.1, 77.4, 81.8, 108.7, 109.1, 121.4, 122.4, 123.3, 123.9, 124.0, 139.2, 139.4, 147.1; MS (DCI/NH_3) 451 $(M + H)^+$.

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Supplementary Material Available: ORTEP structure of **6a** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.