Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4639-4642, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00922-7

Enantioselective Synthesis of a 5-LO Inhibiting Hydroxyurea. Construction of the Dihydro-benzofuran Nucleus by Tandem Nucleophilic Addition and Intramolecular Cyclization.

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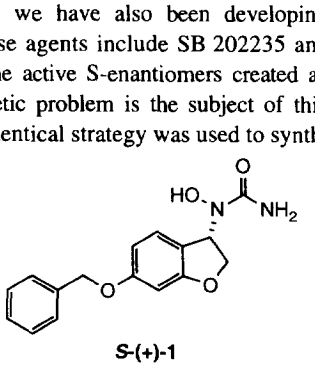
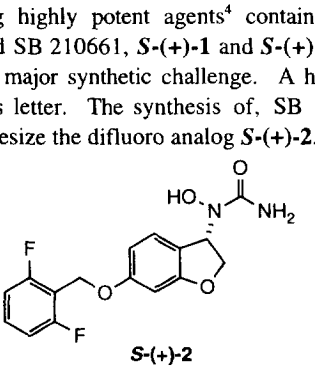
Abstract: An enantioselective synthesis of a 5-LO inhibiting chiral hydroxyurea is described based on the nucleophilic addition of dimethylsulfoxonium ylide to a nitrone bearing a mannose-derived chiral auxiliary. The dihydrobenzofuran skeleton is then constructed by a spontaneous cyclization of the initial adduct, thus completing a tandem nucleophilic addition-cyclization protocol. Copyright © 1996 Elsevier Science Ltd

Inhibition of leukotriene biosynthesis has been the focus of intense research efforts at several pharmaceutical companies. Towards this end, much attention has been paid to the discovery and development of 5-lipoxygenase (5-LO) inhibitors.[1] The synthesis of hydroxyurea based inhibitors has been reported by several laboratories;[2,3] among these, the racemic drug Zileuton of Abbott Laboratories is under FDA review. At SmithKline Beecham, we have also been developing highly potent agents[4] containing the hydroxyurea pharmacophore. These agents include SB 202235 and SB 210661, ***S*-(+)-1** and ***S*-(+)-2**, respectively. The decision to develop the active S-enantiomers created a major synthetic challenge. A high yielding practical solution to this synthetic problem is the subject of this letter. The synthesis of, SB 202235, ***S*-(+)-1** is presented below; an identical strategy was used to synthesize the difluoro analog ***S*-(+)-2**.



***S*-(+)-1**

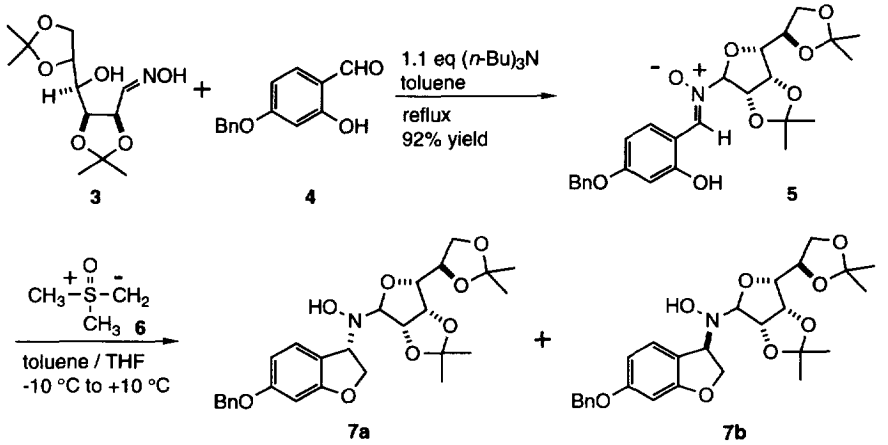


***S*-(+)-2**

Based upon several reports from the literature,[5] we felt that some type of nucleophilic addition to a nitrone containing a chiral sugar auxiliary would provide the best strategy with which to install the stereogenic center in hydroxyurea **1**. The problem of dihydrofuran ring construction could then be solved in a subsequent intramolecular cyclization if the incoming nucleophile contained a suitable leaving group. This idea was put into practice by employing dimethylsulfoxonium methylide[6] **6** as the reacting nucleophile (Scheme 1). Mannose bis-acetonide oxime **3** (a 1:1 mixture of furanose hydroxylamine:oxime) was condensed with 4-benzyloxy-2-hydroxybenzaldehyde **4** (1.1 eq tributylamine, toluene, reflux, Dean-Stark conditions, 6 h) to afford nitrone **5**[7] in 92% yield. A subsequent slurry of nitrone **5** in toluene was treated at -10 °C with a THF solution of dimethylsulfoxonium methylide. Once the methylide addition was complete, the reaction mixture was warmed

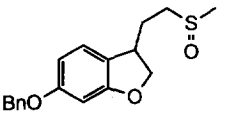
to 10 °C and afforded an 8:1 mixture of diastereomeric adducts **7a** and **7b** in 65-75% isolated yield. The estimated solution yield of adducts **7a**[7] and **7b** averaged between 90-95%.

Scheme 1



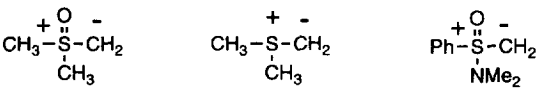
The diastereoselectivity of this addition-cyclization reaction is enhanced at lower reaction temperatures (and concentrations). Addition of the methylide to the nitrone is slightly exothermic. The reaction is extremely sluggish at temperatures below 0 °C. Hence, the methylide addition is conducted at subzero temperatures with subsequent warming of the reaction temperature.

This reaction temperature protocol also helped to limit the production of sulfoxide **8**, the only major by-product formed in the reaction. The presence of this sulfoxide side-product is thought to arise from a multi-step reaction sequence involving at least two equivalents of dimethylsulfoxonium methylide. Adding no more than one equivalent of methylide relative to the nitrone substrate was found to be the major factor in keeping the yield of undesired sulfoxide **8** below 3%.

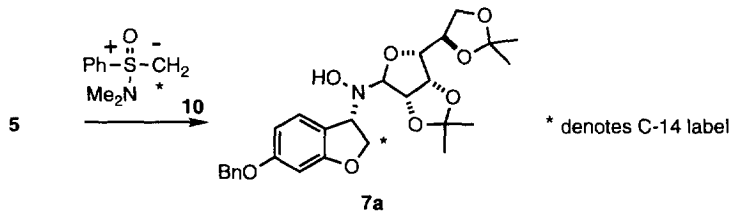


8

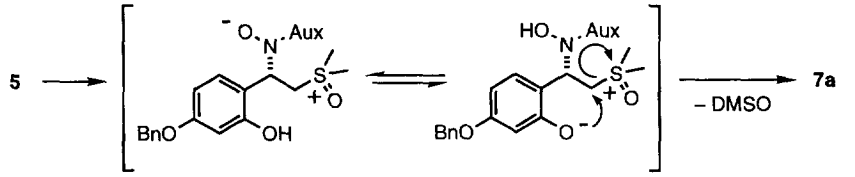
The phenol portion of nitrone **5** is not deprotonated by the methylide during the condensation because only one equivalent of the ylide is needed. Ylides that are more basic than dimethylsulfoxonium methlylide **6** and which deprotonate the phenol group, such as dimethylsulfonium ylide **9**, do not undergo the tandem condensation-cyclization reaction no matter how many equivalents of ylide are added. Similarly, if the phenol group is deprotonated before addition of dimethylsulfoxonium methylide, the condensation is shut down. In accordance with these observations, ylides which are less basic than dimethylsulfoxonium methylide, such as (dimethylamino)methylphenyloxosulfonium ylide **10**,[8] can participate in this tandem reaction (7.4 to 1 diastereoselectivity; 89% estimated solution yield). Moreover, ylide **10** is superior to ylide **6** in radiolabelling experiments because there is only one carbon from the former ylide that can be transferred in the tandem reaction. Mechanistically, we believe that cyclization with dimethylsulfoxonium methylide involves dimethylsulfoxide expulsion which is preceded by the transfer of a proton from the phenolic to the hydroxylamino oxygen (Scheme 2).



6 **9** **10**



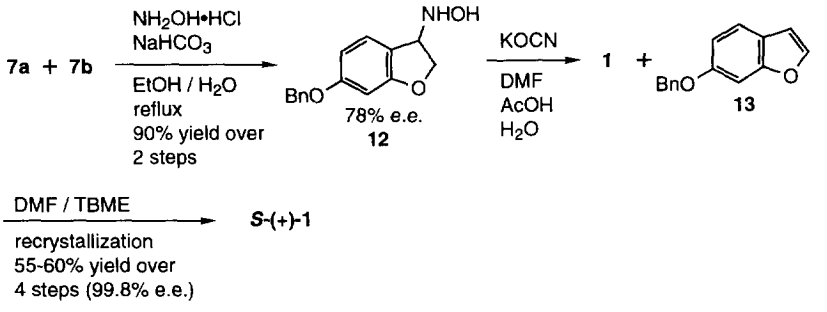
Scheme 2



Unmasking the hydroxylamine group of the diastereomixture **7a** and **7b** to afford hydroxylamine **12** and its enantiomer and conversion to the hydroxyurea was first attempted by mild acid treatment followed by treatment with potassium cyanate in DMF. The chiral auxiliary, however, could not be recovered in reusable form using this strategy. We later found that unmasking of the hydroxylamine can be conveniently carried out by the addition of hydroxylamine hydrochloride. Treating **7a** and **7b** with hydroxylamine hydrochloride in the presence of sodium bicarbonate in refluxing ethanol-water followed with cooling to 0 °C precipitated the enantio-enriched hydroxylamine **12**[9] in nearly quantitative yield. Because the estimated solution yields of adducts **7a** and **7b** were much higher than the isolated yields, isolation of the adducts was soon abandoned after experiments indicated that the impurities present in the crude condensation-cyclization reaction mixture did not impede the unmasking reaction. Using this latter strategy, enantio-enriched hydroxylamine **12** was isolated in 90% yield (78% e.e) over the two steps. After hydroxylamine **12** was isolated via filtration, the chiral auxiliary **3** was extracted from the mother liquor for recycling purposes using ethyl acetate. Recrystallization (ethyl acetate/hexane) of the crude afforded a 90% yield of recovered chiral auxiliary **3** (>99.9% w/w purity).

Conversion of the hydroxylamine **12** (78% e.e.) to the corresponding hydroxyurea **1** was performed by reaction with potassium cyanate in DMF solution to which an equivalent of HOAc was added. One recrystallization of the crude **1** from DMF-TBME was sufficient to afford the desired product in 55-60% yield over the final four steps (i.e. from nitrone **5**). The *S*-(+)-**1**[10] produced was shown to be 99.8% e.e. by chiral HPLC analysis.[11] The absolute stereochemistry of the final product was proven by X-ray crystallographic analysis and through correlation with material made via another route. This recrystallization also removed the small amount (<3%) of benzofuran **13** also formed in the final transformation.

Scheme 3



Acknowledgment: The authors wish to acknowledge the efficient and highly professional support they received from members of the Analytical Sciences department; in particular, Dr. Charlie DeBrosse for the NMR data and Ms. Edith Reich for the elemental analyses.

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7. (**7a**) mp 131.8-133.0 °C; $[\alpha]_D^{20}$ = +18.9 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.19 (m, 6 H), 6.55-6.46 (m, 2 H), 5.03 (s, 2 H), 4.95-4.92 (m, 1 H), 4.86-4.82 (m, 2 H), 4.74-4.68 (m, 1-H), 4.55 (bs, 1 H), 4.50 (dd, 1 H), 4.36-4.30 (m, 2 H), 4.14-4.06 (m, 2 H), 1.49 (s, 3 H), 1.46 (s, 3-H), 1.39 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.48, 161.10, 136.85, 128.58, 127.97, 127.43, 126.40, 117.01, 112.34, 109.11, 107.67, 98.46, 97.13, 84.74, 84.59, 80.87, 73.84, 73.67, 70.29, 66.69, 65.27, 26.83, 26.04, 25.31, 24.38. Anal. Calcd for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.99. Found: C, 64.93; H, 6.76; N, 2.99.
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9. (**12**) $[\alpha]_D^{20}$ = +24.04 (*c* = 1.0, DMSO); IR (KBr pellet, cm^{-1}) 3435, 3252, 3100, 3000-2800, 1625, 1599, 1281, 1150, 809, 733, 695; ^1H NMR (DMSO-d_6, ppm) 7.35-7.44 (m, 6H), 7.23 (d, J = 8.9, 1H), 6.50 (br. s, J = 2.3 Hz, 1H), 6.45 (br. d, 1H), 5.89 (br. s, 1H), 5.05 (s, 2H), 4.52 (t, 1H), 4.47 (br. s, J = 6.0 Hz, 1H), 4.45 (br. s, J = 5.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, ppm) 161.9, 159.9, 137.1, 128.4 (2C), 127.7, 127.5 (2C), 126.2, 118.7, 106.7, 96.6, 75.7, 69.3, 62.6. MS, m/e 258 $(M+ H)^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.83; H, 5.91; N, 5.51.
10. (**1**) $[\alpha]_D^{20}$ = +97.22 (*c* = 1.0, DMSO); IR (KBr pellet, cm^{-1}) 3462, 3323, 3263, 3175, 3100-2800, 1643, 1626, 1295, 1169, 1135, 1111, 1008, 836, 778, 733; ^1H NMR (DMSO-d_6, ppm) 9.12 (s, 1H), 7.42 (dd, J = 8.5, 1.8 Hz, 2H), 7.37 (dd, J = 7.0, 8.5 Hz, 2H), 7.31 (tt, J = 6.9, 1.7 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.50 (dd, J = 8.3, 2.3 Hz, 1H), 6.48 (br. s, 2H), 6.45 (d, J = 2.1 Hz, 1H), 5.79 (dd, J = 9.1, 4.2 Hz, 1H), 5.05 (s, 2H), 4.55 (dd, J = 9.5, 9.3 Hz, 1H), 4.46 (dd, J = 9.7, 4.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, ppm) 162.0, 161.8, 160.1, 137.1, 128.4 (2C), 127.8, 127.6 (2C), 125.5, 117.8, 107.2, 96.4, 73.2, 69.4, 58.9. MS, m/e 301 $(M+ H)^+$, 318 $(M+ NH_4)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.88; H, 5.42; N, 9.33.
11. Chiral purity of >99.8% e.e. was verified by HPLC upon comparison with a racemic reference sample synthesized via a non-asymmetric route (Chiralcel OJ, 4.6 mm x 250 mm, 50:50 hexane:ethanol (200 proof), λ = 215 nm, flow 1.0 mL/min).

(*Received in USA* 20 *February* 1996; *revised* 30 *April* 1996; *accepted* 7 *May* 1996)