Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 9, pp. 2721-2724, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00350-3

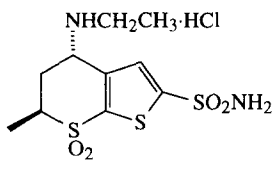
β-Butyrolactone as a Chiral Building Block in Organic Synthesis: A Convenient Synthesis of MK-0507 Keto Sulfone

Orin Tempkin*‡, Thomas J. Blacklock‡, J. Andrew Burke, and Maria Anastasia°

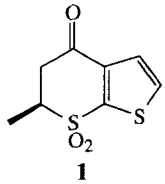
Merck Manufacturing Division
Technical Operations
P. O. Box 2000
Rahway, NJ 07065

Abstract: The nucleophilic ring opening of (*R*)-β-butyrolactone **2** with 2-thiophenethiolate is the key step in a straightforward stereospecific synthesis of keto sulfone **1**, a precursor to carbonic anhydrase inhibitor MK-0507.Copyright © 1996 Elsevier Science Ltd

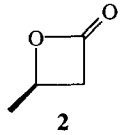
Keto sulfone **1** is a promising intermediate for the preparation of MK-0507 (Trusopt®), a new and potent topically active carbonic anhydrase inhibitor developed for the treatment of elevated intraocular pressure, symptomatic of glaucoma.[1] The previous synthesis of MK-0507, described in a 1993 publication by Blacklock



MK-0507



1



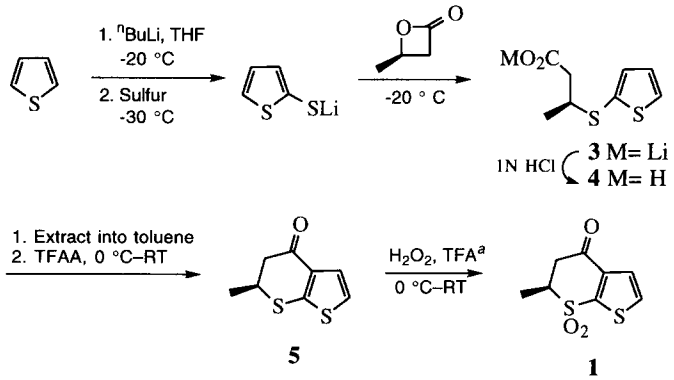
2

and Sohar et al., began with an S_N2 displacement reaction of methyl (*R*)-3-(4-toluenesulfonyloxy)butyrate with lithium 2-thiophenethiolate, followed by hydrolysis of the methyl ester and TFAA-promoted cyclization.[2] In the course of streamlining the commercial-scale synthesis of MK-0507, we developed a simplified route to the keto sulfone which features as a key step the ring-opening of (*R*)-β-butyrolactone **2** (4-methyl-2-oxetanone), a versatile chiral starting material. The ring-opening reaction of β-butyrolactone with organosulfur nucleophiles has been investigated by Seebach and co-workers[3] and typically occurs at C-4 of the lactone with inversion of configuration. A recent Merck patent outlined a similar method applied to the synthesis of (*S*)-3-(thien-2-ylthio)butyric acid analogs.[4]

(*R*)-β-butyrolactone was prepared by asymmetric hydrogenation of diketene, an inexpensive starting material, in the presence of a chiral ruthenium(II)–BINAP catalyst according to the method of Takaya et al.[5] Hydrogenation of diketene in CH_2Cl_2 or THF with 0.1–0.2 mol% $Ru_2Cl_4[(S)\text{-BINAP}]_2\cdot NEt_3$[11] provided high yields of (*R*)-β-butyrolactone in 89–92% ee.[6,12] Optically active β-butyrolactone is not, to our knowledge, commercially available, and the asymmetric hydrogenation method is currently the most practical approach.[13]

Lithium 2-thiophenethiolate was prepared as previously described[2] by adding powdered sulfur to 2-thienyllithium in THF (Scheme I). Neat (*R*)-β-butyrolactone[5] (90% ee[6]) was slowly added to this reaction mixture at -20 °C. Cleavage of the lactone by 2-thiophenethiolate was monitored by HPLC and proceeded smoothly to completion in < 1 h, resulting in a dark orange solution of the lithium carboxylate **3**. THF was evaporated in vacuo[7]; the residue was acidified with 1N HCl, and the free acid (*S*)-**4** was then extracted into toluene. Trifluoroacetic anhydride (TFAA)-promoted cyclization on the crude carboxylic acid[8] proceeded as expected[2] in toluene to afford **5**. Aqueous hydrogen peroxide was immediately added to the *same reaction mixture* to effect oxidation of the sulfide to the (*S*)-keto sulfone **1**.[9] The biphasic mixture was stirred vigorously at room temperature until conversion to the sulfone was complete. The crude product was recrystallized from

Scheme I



[a]Residual TFA from previous step.

ethyl acetate and hexane, giving white crystals of **1** in 50–60% overall yield from thiophene. This sulfone was obtained in 90% ee, determined by chiral HPLC analysis[10]; assignment of the (*S*)-configuration was confirmed by comparison of its optical rotation to that of a reference sample (>98% ee) obtained by the earlier method.[2]

In conclusion, we have demonstrated a concise synthesis of the MK-0507 keto sulfone[14] highlighted by the nucleophilic ring opening of (*R*)-β-butyrolactone, a useful butyrate equivalent and chiral building block. In this new procedure, multiple steps are carried out in the same reaction vessel, and product is not isolated until the keto sulfone stage. The acid wash and solvent switch to toluene that are required before the cyclization reaction are minor modifications to an otherwise "one pot" process[15]: the recovery of **4** is quantitative, and the cyclization reaction with TFAA may be conducted on the concentrated (and azeotropically dried) toluene extracts. We are currently modifying the procedure for larger scale production. In conjunction with this goal, future studies will also be directed toward obtaining (*R*)-β-butyrolactone of enantiomeric purity greater than 90% ee.

EXPERIMENTAL

General. NMR spectra were recorded on a Varian XL-300 spectrometer in $CDCl_3$, with TMS as an internal standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin layer chromatography was performed on 0.25 mm silica gel F254 plates (Merck). Details for the HPLC analysis of MK-0507 intermediates are described in reference 2.

(*R*)-β-Butyrolactone was prepared according to reference 5, using $[RuCl_2(BINAP)]_2{\cdot}NEt_3$ (prepared by the method described in reference 11).[12] The ee of the β-butyrolactone was determined by chiral GC analysis[6] using a Chiradex G-BP capillary column available from Advanced Separation Technologies.

(*S*)-5,6-Dihydro-6-methylthieno[2,3-*b*]thiopyran-4-one 7,7-dioxide: keto sulfone 1.
Thiophene (10.5 g, 0.125 mol) was dissolved in THF (150 mL) and cooled to -20° C. ^{n}Butyllithium (63 mL of a 2M solution in pentane, 0.126 mol, 1 eq) was added dropwise over 10 min, and the resulting yellow solution was stirred an additional 1 h at -20 °C. Sulfur (4.01 g, 0.125 mol, 1 eq) was then added in small portions. When addition was complete, the orange-yellow solution was allowed to stir at -20° C until reaction was complete by TLC (<1 h). At this point, β-butyrolactone (10.8 g, 0.125 mol, 1 eq) was added by syringe. The orange solution was then allowed to warm up to room temperature.

The solvents were removed by rotary evaporation, and the the reaction mixture was evaporated twice from toluene (2 x ca. 50 mL) to remove traces of THF[7]. The residual orange semisolid was suspended in toluene (70 mL) and, with rapid stirring, 1N HCl solution (60-70 mL) was added until the pH of the aqueous layer was 1-2. The acidic solution was extracted with toluene (4 x 75 mL), and the combined organic layers were concentrated, leaving the acid **4** as an orange oil. The ee of the acid may be checked at this stage.[8]

The oil was dissolved in toluene (625 mL) and cooled to 0 °C. Trifluoroacetic anhydride (26.2 g, 0.125 mol, 1 eq) was slowly added and the reaction mixture gradually darkened. After addition, the cooling bath was removed and the solution was warmed to room temperature. When cyclization was shown to be complete by TLC or HPLC[2], the solution was re-cooled to 0 °C and hydrogen peroxide (40 mL of a 30% aqueous solution, 0.392 mol, 3.1 eq) was slowly added to the reaction mixture. The biphasic mixture was warmed to room temperature and stirred vigorously until oxidation to the sulfone (via the sulfoxide) was complete.[2]

The mixture was re-cooled to 0 °C and saturated aqueous sodium sulfite solution (50-70 mL) was very cautiously added (exotherm) until the aqueous layer tested negative to KI/ starch paper. Water (50 mL) was added, and the aqueous layer was extracted into toluene (3 x 100 mL). The organic layers were concentrated, giving a dark oil which was solidified by evaporation from hexane (50 mL). The crude **1** was recrystallized from 1:1 ethyl acetate-hexane, giving the crystalline keto sulfone (14.9 g, 68.9 mmol) in 55% overall yield from thiophene.

mp 108-111 °C. $[\alpha]_D^{25}$ -13.1 (c 1.2, CH_3CN). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, 3H, J= 6.8 Hz, C<u>H</u>$_3$), 3.22 (m, 2H, AB of ABX, C<u>H</u>$_2$CO), 3.85 (m, 1H, X of ABX, C<u>H</u>CH$_3$), 7.49 (d, 1H, J= 5.1 Hz, Ar<u>H</u>), 7.62 (d, 1H, J= 5.1 Hz, Ar<u>H</u>). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.74, 44.70, 57.99, 126.17, 130.68, 139.88, 146.82, 186.58. Exact mass for $C_8H_8O_3S_2$ requires: 238.9812 (for MNa^+); found 238.9820.

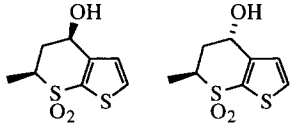
Determination of enantiomeric excess and assignment of stereochemistry.[10] The enantiomeric excess of the keto sulfone was determined to be 90% by chromatographic analysis using a Chirapak AS column (Chiral Technologies) using 90:10 hexane:(isopropyl alcohol containing 1v% water) as the mobile phase at a flow rate of 0.7 ml/min with the column oven operated at 40 °C and the detector at 255 nm. The retention times for the enantiomers were 27.8 and 32.2 min. The amount of the keto sulfone loaded onto the column should not exceed 2.5 μg to obtain satisfactory resolution. Assignment of the (*S*)-configuration was secured by comparison of the optical rotation to that of a reference sample (>98% ee) obtained by the earlier method.[2]

Acknowledgements: We thank Dr. Anthony King and the Merck high pressure laboratory for carrying out the diketene hydrogenations, and Drs. Lynn Brown and Joseph Auerbach for insightful discussions.

REFERENCES AND NOTES

‡Current address: Sandoz Pharmaceuticals Corporation, 59 Rt. 10, East Hanover, NJ 07936.
°Current address: Pharmacia Biotech Inc., 800 Centennial Avenue, Piscataway, NJ 08855.

1. Kaufman, P. L.; Robin, A. L.; Weinreb, R. N.; Crawford, K.; Shaw, B. *Drugs* **1991**, *41*, 514.
2. Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672.
3. (a) Breitschuh, R.; Seebach, D. *Synthesis* **1992**, 83. (b) Breitschuh, R.; Seebach, D. *Synthesis* **1992**, 1170.
4. Blacklock, T. J.; Shinkai, I. U.S. Patent 4 968 815, **1990**.
5. (a) Ohta, T.; Miyake, T.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1725. (b) Takaya, H.; Ohta, T.; Kumobayashi, H. U.S. Patent 5 306 834, **1994**. (c) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, 60, 357.
6. The ee of the β-butyrolactone was determined by chiral GC analysis. Konig, W.A., Krebber, R., Mishnic, P. *J. High Resolut. Chromatogr.* **1989**, *12(11)* , 732-738.
7. The presence of THF is deleterious in the TFAA-mediated cyclization step.
8. The ee of the acid **4** was determined as the 3,5-dimethylanilide derivative using a column containing the (*R,R*) GEM CSP (Regis Technologies) using 90:10 hexane: THF as the mobile phase. The acid (1eq) was dissolved in 2 ml of CH_2Cl_2 and to this was added 1.1 eq of EEDQ. After 30 min, 1.1 eq of 3,5-dimethylaniline was added and allowed to react for 15 min. The organic layer was washed sequentially with two 10 ml portions of 1 N HCl, two 10 ml portions of water and 10 ml of saturated $NaHCO_3$. The organic layer was then analyzed.
9. The oxidation in this case does not require sodium tungstate, an additive described in the 1993 procedure. This modification was developed by Dr. D. J. Mathre of Merck Process Research.
10. The ee was verified by an ee determination on the corresponding *cis* hydroxy sulfone **6a**[14], using the same chromatographic parameters as those for the keto sulfone assay except that the detector was operated at 240 nm. The retention times for the enantiomers were 50.2 min and 61.3 min. The amount of the hydroxy sulfone loaded onto the column should not exceed 2.0 μg to obtain satisfactory resolution.
11. For the preparation of the Ru(II)–BINAP catalyst, see: King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.
12. Butyric acid, a minor side product from the hydrogenation of diketene, was removed by shaking the reaction mixture with saturated $NaHCO_3$(aq).
13. Optically active β-butyrolactone has previously been prepared by the resolution and lactonization of 3-bromobutyric acid: Shelton, J. R.; Lando, J. B.; Agostini, D. E. *J. Polym. Sci., Part B* **1971**, *9*, 173. Seebach described a synthesis in 25% yield of the (*S*)-isomer of the lactone, via pyrolysis of an orthoester derivative of (*R*)-3-hydroxybutyric acid: Breitschuh, R.; Seebach, D. *Chimia* **1990**, *44*, 216 and references therein. Lenz et al. also recently published a five-step synthesis of the (*S*)-enantiomer (>97% ee) starting from poly[(*R*)-β-hydroxybutyrate] (PHB): Zhang, Y.; Gross, R. A.; Lenz, R. W. *Macromolecules* **1990**, *23*, 3206.
14. The keto sulfone **1** was reduced to the corresponding hydroxy sulfones **6a** and **6b** (98:2 *cis*:*trans*) in quantitative yield using $NaBH_4$ in EtOH. The hydroxy sulfones may be epimerized to a mixture favoring the *trans* isomer using conditions described in reference 2. We are seeking new methods to selectively convert **1** to the *trans* hydroxy sulfone **6b** which is desired for the next step.



6a **6b**

15. The synthetic and environmental significance of "one-pot" reactions has recently been reviewed: Hall, N. *Science* **1994**, *266*, 32.

(*Received in USA* 17 *July* 1996)