Pergamon

Tetrahedron Letters 39 (1998) 8579–8580

TETRAHEDRON LETTERS

Synthesis of Chiral Tetrahydropyrrolo[2,1-b]thiazol-5(6H)-ones[1]

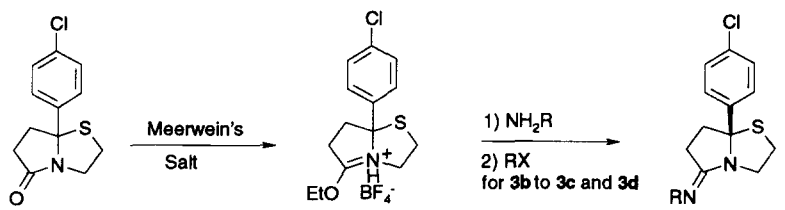
Thomas D. Aicher,* Douglas C. Knorr, Howard C. Smith

Metabolic & Cardiovascular Diseases, Novartis Institute for Biomedical Research, 556 Morris Avenue, Summit, New Jersey 07901

Received 28 July 1998; revised 3 September 1998; accepted 9 September 1998

Abstract: In our investigations of potential hypoglycemic agents,[2] it was desired to evaluate optically pure tetrahydropyrrolo[2,1-β]thiazol-5-ones. A novel, practical synthesis of each enantiomer of **1** via formation, separation, and hydrolysis of diastereomeric amidine derivatives is described.

In our investigations of hypoglycemic agents, it was desired to evaluate optically pure tetrahydropyrrolo[2,1-b]thiazol-5(6H)-ones.[2] Members of this class of compounds have displayed a number of diverse pharmacological activities including anti-HIV and anti-inflammatory activity.[3] The racemate of **1** was readily synthesized via a condensation of 3-(4-chlorobenzoyl)-propionic acid and cysteamine in near quantitative yield. This desirable brief synthesis employed two achiral components and there is no obvious way to induce enantioselectivity. Since **1** is a neutral compound, formation of a salt is not feasible. While a derivative of **5** could potentially be resolved, the propensity of the asymmetric center to racemize in the free amine may fatally flaw this approach. Separation of similar HIV-1 reverse transcriptase inhibitors using a chiral stationary phase has been demonstrated by Mertens *et al.*[3] The chromatography group of Novartis successfully developed such a separation of **1** for analytical purposes.

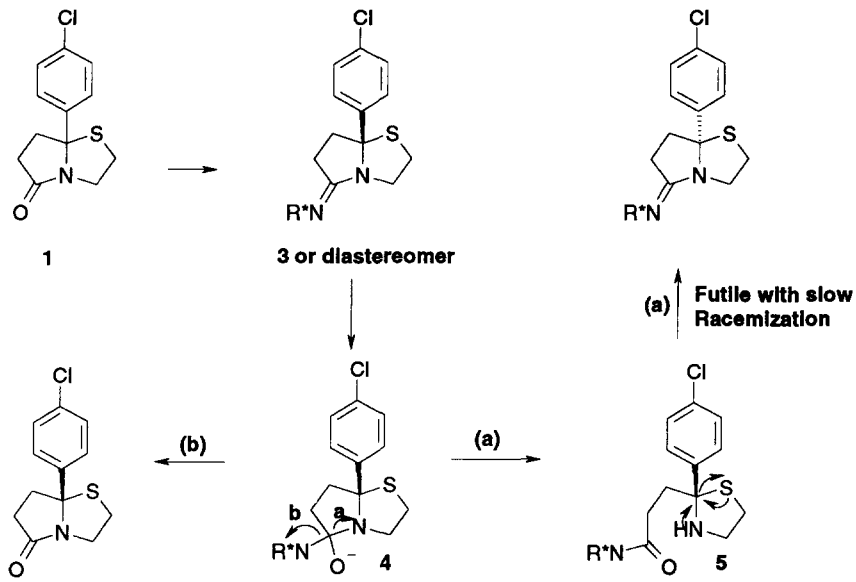


1 **2**

3a R = -(CHMePh)
3b R = H
3c R = (-)-menthylOC(=O)-
3d R = (1S)-(+)-10-camphorsulphonyl

We investigated whether formation, separation, and hydrolysis of diastereomeric amidines **3** would afford access to the chiral enantiomers of **1**. Although the two (E) amidines from (*R*)-(+)-α-methylbenzylamine were readily separable via chromatography, a problem arose upon the attempted basic hydrolysis of this amidine to **1**. From the transition state **4** of the hydrolysis, the reaction can proceed along

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01962-5



Optical Purity of the Hydrolysis of 3 is markedly improved where R = acyl, sulfonyl vs. alkyl since pathway (b) is favored over pathway (a).

two pathways. The desired pathway **(b)** leads to optically pure **1**. The alternative pathway **(a)** is futile, yielding **3** with significant racemization of the asymmetric center.

By changing *RN to a better leaving group via modification of **3b** (e.g. reaction with (1S)-(+)-10-camphorsulfonyl chloride, (-)-menthyl chloroformate, etc.), the diastereomeric amidines were still readily separable, and upon hydrolysis with dilute sodium hydroxide in methanol pathway **(b)** was favored. This allowed a practical synthesis of each enantiomer of **1** with high retention (> 99%) of optical purity.[4]

REFERENCES AND NOTES

1. Presented in part at the 214th American Chemical Society Meeting, Las Vegas, NV, 1997; Abstr. 214 ORGN 214.
2. Aicher, Thomas D.; Balkan, Bork; Bell, Phillip A.; Brand, Leonard J.; Cheon, Seung. H.; Deems, Rhonda O.; Fell, Jay B.; Fillers, William S.; Fraser, James D.; Gao, J.; Kahle, Gerald G.; Knorr, D. C.; Leone, Christina; Nadelson, Jeffrey; Simpson, Ronald J., Smith, Howard C. *J. Med. Chem.* In press.
3. a) Mertens, A.; Zilch, H.; Konig, B.; Shafer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H. *J. Med. Chem.* **1993**, *36*, 2526-2535. b) Shafer, W.; Friebe, W.-G.; Leinert, H.; Mertens, A.; Poll, T.; Saal, W.; Zilch, H.; Nuber, B.; Ziegler, M. L. *J. Med. Chem.* **1993**, *36*, 726-732.
4. Separation of the enantiomers of **1**: a) Et_3OBF_4, CH_2Cl_2, 20 °C b) sat. NH_3, CH_2Cl_2, 20 °C c) (-)-menthyl chloroformate, Et_3N, CH_2Cl_2; 60% (30 % of each diastereomer) for 3 steps d) aq. 2N NaOH, methanol, 81%.

Entry	Overall Chemical yield (1 to 3*)	Purity of 3	Yield of 1 from 3	%ee of 1
3a	68	99	70	40
3c	60	99	81	99
3d	56	99	85	99