ORGANIC LETTERS

2004
Vol. 6, No. 19
3233−3235

Crystallization-Induced Chiral Inversion As the Key Step for Synthesis of (*S*)-2-Acetylthio-3-phenylpropanoic Acid from L-Phenylalanine

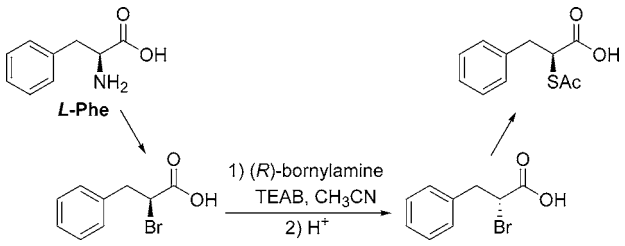
Jason G. Chen,[†] Jingyang Zhu,*[,†] Paul M. Skonezny,[†] Victor Rosso,[‡] and John J. Venit[‡]

Chemical, Fermentation and Biocatalysis Development Labs, Bristol-Myers Squibb Company, P.O. Box 4755, Syracuse, New York 13221, and Process Research and Development Department, Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, New Jersey 08903

jingyang.zhu@bms.com

Received June 2, 2004

ABSTRACT



A novel crystallization-induced chiral inversion of (*S*)-2-bromo-3-phenylpropanoic acid to its (*R*)-enantiomer with excellent enantiomeric excess (96−99%) is achieved. Optically pure (*S*)-2-acetylthio-3-phenylpropanoic acid can be prepared in good yield from inexpensive and commercially available L-phenylalanine via diazotization/bromination, chiral inversion, and thioacetate substitution reactions.

Omapatrilat and Gemopatrilat were developed as vasopeptidase inhibitors for treatment of hypertension, congestive heart failure, and renal disease.[1] During the course of developing these inhibitors, an efficient synthesis of the common intermediate, (*S*)-2-acetylthio-3-phenylropanoic acid (Figure 1, **1**), was needed.

An existing synthetic route in the literature for the acid starts from unnatural *D*-phenylalanine.[2] *D*-phenylalanine is first converted to (*R*)-2-bromo-3-phenylpropanoic acid through diazotization/bromination. The acid obtained is then subjected to nucleophilic substitution with potassium thioacetate to afford **1**. Although efficient, this approach is not desirable due to the high cost of *D*-phenylalanine.

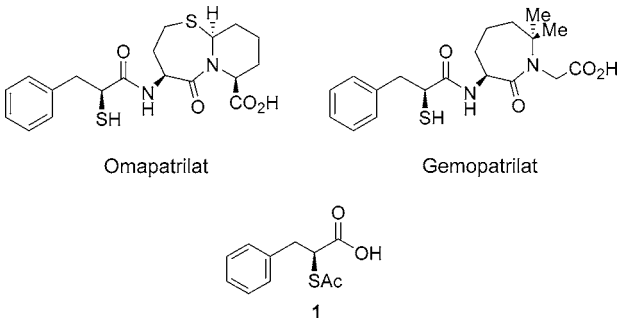


Figure 1.

Alternative synthetic routes were investigated in our laboratory, and we reported one approach to this intermediate

[†] Chemical, Fermentation and Biocatalysis Development Labs.
[‡] Process Research and Development Department.

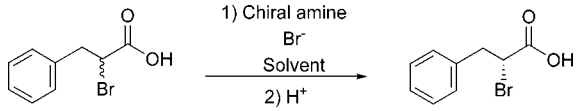
(1) Robl, J. A. U.S. Patent 5,508,272, 1996.
(2) Karanewsky, D. S.; Robl, J. A. U.S. Patent 5,552,397, 1996.

10.1021/ol0489806 CCC: $27.50
Published on Web 08/19/2004

via enzymatic resolution.[3] Here, we report a novel crystallization-induced chiral inversion approach to the acid using inexpensive L-phenylalanine as starting material.

The desired precursor to **1** is (*R*)-2-bromo-3-phenylpropanoic acid (Scheme 1, **3**). Recently, crystallization-induced dynamic resolution (CIDR) via a pair of salt diastereomers has gained popularity in asymmetric synthesis.[4] Preliminary lab studies indicated that some chiral amines were effective for dynamic kinetic resolution of the racemic 2-bromo-3-phenylpropanoic acid (**2**), which was available from our earlier work.[3] Among more than 40 chiral amines screened, (*R*)-bornylamine was found to be the most effective.

Scheme 1. Crystallization-Induced Dynamic Resolution of **2**



2 **3**

We further optimized the dynamic kinetic resolution conditions with various combinations of chiral amines, solvents, and halide sources. Selected combinations are compiled in Table 1. Excellent enantiomeric excess (~96%, Table 1, entry 13) could be obtained when (*R*)-bornylamine was used as the chiral amine, acetonitrile as the solvent, and tetraethylammonium bromide (TEAB) as a bromide ion source.

Table 1. Optimization of CIDR Conditions for **2**[6]

entry	bromide source[7]	solvent	yield(%)[a]	ee (%)[8]
1	TBAB	butyl acetate	40.00	87.0
2	TBAB	acetonitrile	45.49	93.5
3	TBAB	MTBE	78.93	85.1
4	TBAB	ethyl acetate	69.57	88.6
5	TBAB	THF	na[b]	na
6	TBAB	butanol	44.15	84.1
7	TBAB	isobutanol	56.19	78.1
8	TMAB	butyl acetate	77.19	74.3
9	TEAB	butyl acetate	77.59	89.4
10	THAB	butyl acetate	42.81	89.2
11	MTOAB	butyl acetate	40.00	84.5
12	TOAB	butyl acetate	64.75	87.6
13	**TEAB**	**acetonitrile**	**76.0**	**96.0**

[a] Yield was calculated on the basis of the chiral amine input and was not optimized. [b] No salt formation.

We then reasoned that under dynamic kinetic resolution conditions, the undesired (*S*)-enantiomer could be directly converted to its (*R*)-enantiomer. This concept can be described as a crystallization-induced chiral inversion, and this would ultimately allow us to start with the inexpensive L-phenylalanine.

It is known that diazotization/bromination of an amino acid results in retention of configuration. Converting L-phenylalanine via diazotization/bromination[5] leads to the (*S*)-enantiomer of the precursor (*S*)-2-bromo-3-phenylpropanoic acid **4**. Chiral inversion of **4** was then investigated using optimal reaction conditions identified for dynamic resolution of **2**: (*R*)-bornylamine as a chiral amine, acetonitrile as a solvent, and TEAB as the bromide ion source. Under these conditions, **4** was converted to **5**, the (*R*)-bornylamine salt of **4**, with high stereospecificity (>96% ee) and good yield (78%).

The enrichment of the desired bornylamine salt **5** is likely due to its lower solubility in acetonitrile. It was found that the undesired salt, the (*R*)-bornylamine salt of (*R*)-2-bromo-3-phenyl-propanoic acid, was almost three times more soluble than **5** (0.95 vs 0.35 mg/mL). Since the solubility for both salts in acetonitrile is low, a relatively long reaction time (~48 h) was needed to achieve the desired level of enantiomeric inversion. The bromide source also appeared to play an important role in achieving the optimal result. For example, under similar conditions TEAB gave a higher yield than TBAB (entries 13 and 2). The differences in isolation yields may primarily be attributed to the differences in solubility of the salt in different isolation medium, since there was no difference in reaction profiles. However, when no bromide was added, the reaction gave only ~40% ee under similar conditions.

(*R*)-2-bromo-3-phenylpropanoic acid (**3**) was obtained by dissolving **5** in water, acidifying with methanesulfonic acid, and extracting the product with MTBE. The ee of the acid obtained was usually between 96 and 98%. The (*R*)-bornylamine was also recovered by adjusting pH to 10−13 and then extracting the free amine into MTBE. The recovered bornylamine was ~97% pure, and the recovery was >92%.

The bromo acid **3** was subsequently converted to **1** by nucleophilic substitution with KSAc to furnish the desired common intermediate in ~87−90% yield. The ee of the acid obtained was between 92 and 95%. Recrystallization of the acid in MTBE/heptanes further increased the ee to ~99%.

(3) Zhu, J.; You, L.; Zhao, S.; White, B.; Chen, J. G.; Skonezny, P. M. *Tetrahedron Lett.* **2002**, *43*, 7585.

(4) (a) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. *J. Org. Chem.* **1987**, *52*, 955. (b) Moseley, J. D.; Williams, B. J.; Owen, S. N.; Verrier, H. M. *Tetrahedron: Asymmetry* **1996**, *7*, 3351. (c) Alabaster, R. J.; Gibson, A. W.; Johnson, S. A.; Edwards, J. S.; Cottrell, I. F. *Tetrahedron: Asymmetry* **1997**, *8*, 447. (d) Maryanoff, C.; Scott, A. L.; Shah, R. D.; Villani Jr, F. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3247. (e) Macdonald, S. J. F.; Clarke, G. D. E.; Dowle, M. D.;. Harrison, L. A.; Hodgson, S. T.; Inglis, G. G. A.; Johnson, M. R.; Shah, P.; Upton, R. J.; Walls, S. B. *J. Org. Chem.* **1999**, *64*, 5166. (f) Aelterman, W.; Lang, Y.; Willemsens, B.; Vervest, I.; Leurs, S.; de Knaep, F. *Org. Process. Res. Dev.* **2001**, *5*, 467.

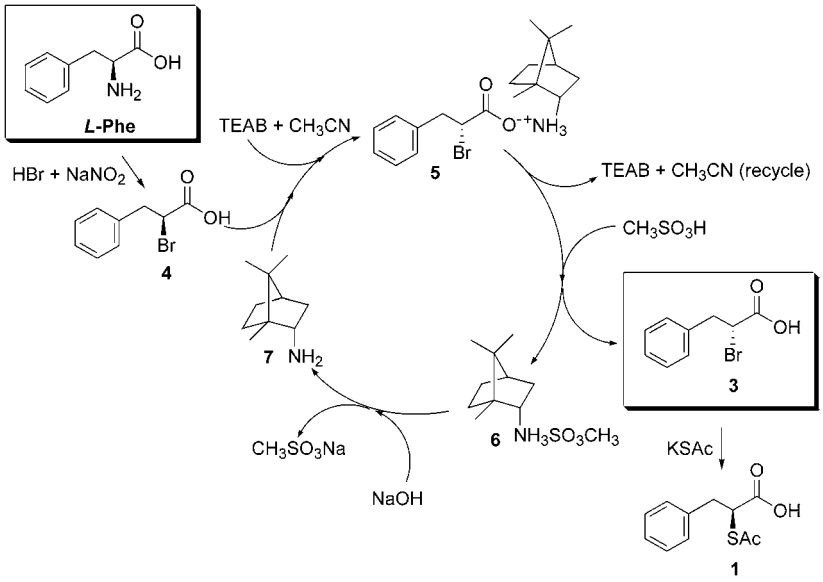
(5) Allegrini, P.; Soriato, G. WO Patent 99/42438, 1999.

(6) Typical reaction conditions: (*R*)-bornylamine (0.95−1 equiv) was slowly delivered over 24 h to a reaction mixture of **2** (1 equiv) and catalyst (0.1 equiv) in acetonitrile at 50−60 °C. The reaction mixture was continuously stirred for an additional 24 h. After cooling to room temperature, the slurry was filtered, and the solid was washed with acetonitrile and dried.

(7) Abbreviations for bromide sources: TBAB = tetrabutylammonium bromide; TMAB = tetramethylammonium bromide; TEAB = tetraethylammonium bromide; THAB = tetrahexylammonium bromide; MTOAB = methyltrioctylammonium bromide; TOAB = tetraoctylammonium bromide.

(8) Ee was determined by chiral HPLC using a Chiralcel AD column, 250 × 4.6 mm. Mobile phase: 97.9% hexane, 2% absolute ethanol, and 0.1% TFA. Flow rate: 1 mL/min. Detector: UV at 230 nm.

Scheme 2. Synthesis of **1** from L-Phenylalanine



The entire scheme, including the recycle of the bornylamine, is depicted in Scheme 2.

In conclusion, optically pure **3** can be obtained from the corresponding optically pure **4** via a crystallization-induced chiral inversion with an appropriate chiral amine, and a route to **1** utilizing inexpensive L-phenylalanine has been demonstrated. To the best of our knowledge, this is the first time that an α-substituted chiral carboxylic acid was synthesized by inverting its enantiomer through a crystallization-induced chiral inversion.

Acknowledgment. The authors thank Mr. Jun Qiu for preliminary chiral amine screening experiments.

Supporting Information Available: Experimental procedures and characterization data for compounds **1** and **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0489806