Asymmetric Synthesis of *N*-Substituted α-Aminobenzlactam via Crystallization-Induced Asymmetric Transformation of Covalent Diastereomer

Wen-Chung Shieh,* John A. Carlson, and Giedre M. Zaunius

Chemical & Analytical Development, Technical Research and Development, Novartis Pharmaceuticals Corporation, Summit, New Jersey 07901

Received June 11, 1997

Introduction

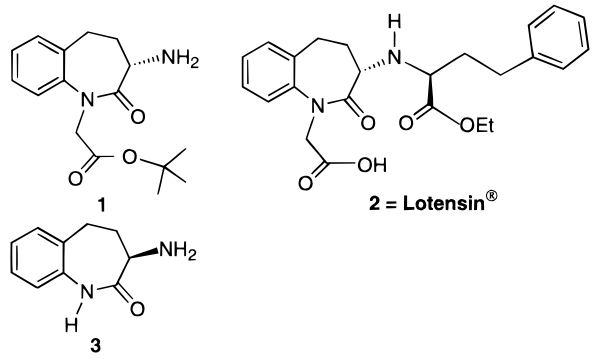
N-substituted α-aminobenzlactam **1** (Scheme 1) is a key intermediate in the total synthesis of Lotensin (**2**, CGS 14824A),[1] an angiotensin converting enzyme (ACE) inhibitor and one of the effective antihypertensive drugs on the market. Unsubstituted aminobenzlactam **3** is also an important precursor for a growth hormone secretagogue, L-692,429.[2] Asymmetric synthesis of **1** and subsequent transformation of it into **2** were demonstrated by Wetter.[3] Approaches to the asymmetric synthesis of **3** have been reported by a Merck group.[4] Herein, we describe a practical asymmetric synthesis of **1** utilizing a crystallization-induced asymmetric transformation of covalent diastereomer (a *thermal* epimerization−resolution methodology).

Results and Discussion

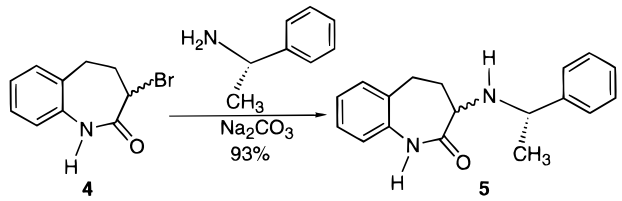
Our synthesis began with α-bromobenzlactam **4** (Scheme 2), which can be prepared from α-tetralone using a process described previously.[3] Formation of diastereomer **5** was accomplished in 93% yield by treating **4** with (*S*)-1-phenylethylamine and sodium carbonate in propylene glycol at 130 °C. The diasteromeric ratio of **5** was determined to be 60:40 by both HPLC and ^{1}H NMR, slightly enriched in (*S*,*S*)-isomer.

Asymmetric synthesis employing a crystallization-induced asymmetric transformation has been reported by our lab[5] and many others.[6] Conceptually, a pair of diastereomers can be completely converted into a single diastereomer if one diastereomer can be separated from the mixture while the other one is epimerized. A pair of enantiomers can also be transformed totally into a single enantiomer without making any diastereoisomeric derivatives, if and only if these enantiomers are racemic conglomerates and racemization of them in solution is facile.[5] In our case, **5** could be completely converted into (*S*,*S*)-**5** if (*S*,*S*)-**5** could be separated by direct crystallization under conditions which epimerize (*R*,*S*)-**5**. Since

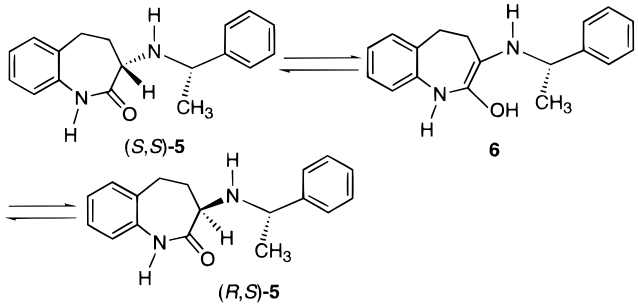
Scheme 1



Scheme 2



Scheme 3



diastereomer **5** has an enolizable chiral center, epimerization of (*R*,*S*)-**5** should be readily achieved (Scheme 3). After extensive screening of reaction conditions, diastereomerically pure (*S*,*S*)-**5** was produced by a total resolution process. Some of the most interesting results from the study are listed in Table 1.

In a typical experiment, diastereomer **5** was suspended in a nonpolar solvent (2× wt/vol) and heated at 140−160 °C for 5−16 h. The reaction mixture was cooled to 80 °C and diluted with cyclohexane (2× wt/vol) to increase the ease of handling of the slurry. The mixture was further cooled to room temperature and the product (*S*,*S*)-**5** was collected by filtration. An excellent diastereomeric ratio (99:1) and isolated yield (93%) for (*S*,*S*)-**5** was obtained when the reaction was carried out in mineral oil at 140 °C for 16 h (entry 1). Consistent diastereomeric ratios and yields for (*S*,*S*)-**5** were also achieved in either odorless mineral spirit (>99:1, 88%, entry 4) or decane (99:1, 80%, entry 6). It is noteworthy that both time and temperature are critical parameters to ensure high diastereomeric ratio and isolated yield. For example, raising the temperature to 160 °C increases the solubility of diastereomers and lowers the diastereomeric ratio to 94:6 (entry 5), while shortening the reaction time to 5 h leads to incompletion of epimerization and affords a lower diastereomeric ratio (96.5:3.5) and isolated yield (74%) (entry 2). Success in achieving both high diastereomeric ratio and chemical yield without any strong organic base suggests that the epimerization of (*R*,*S*)-**5** is probably temperature dependent. Indeed,

(1) (a) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 8, 1511. (b) Novartis Pharmaceuticals is the merged company of Ciba-Geigy and Sandoz corporations.

(2) Bhupathy, M.; Bergan, J. J.; McNamara, J. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 9445.

(3) Boyer, S. K.; Pfund, R. A.; Portman, R. E.; Sedelmeier, G. H.; Wetter, H. F. *Helv. Chim. Acta* **1988**, *71*, 337.

(4) Armstrong, J. D., III; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W., Jr.; Choi, W.-B.; Askin, D.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 3239.

(5) Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.

(6) (a) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. *J. Org. Chem.* **1987**, *52*, 955. (b) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolution*; Wiley-Interscience Publication: New York, 1981; pp 369−377.

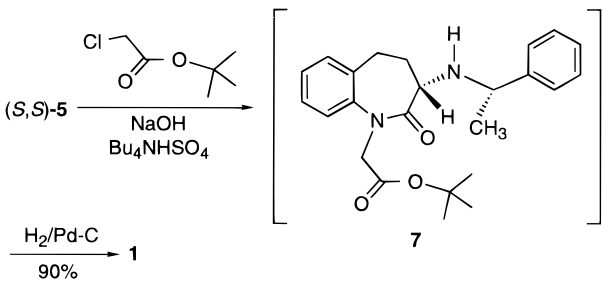
S0022-3263(97)01056-6 CCC: $14.00

Table 1. Epimerization−Resolution of Diastereomer 5 in Nonpolar Solvents

entry	solvent[a]	temperature/ time	(*S*,*S*)-**5**/(*R*.*S*)-**5** ratio[b]	% yield
1	A	140 °C/16 h	99:1	93
2	B	140 °C/5 h	96.5:3.5	74
3	B	140 °C/10 h	99:1	81
4	B	140 °C/16 h	>99:1	88
5	B	160 °C/16 h	94:6	81
6	C	140 °C/16 h	99:1	80

[a] A = mineral oil; B = odorless mineral spirit, bp 179−210 °C; C = decane, bp 174 °C. [b] The diastereomeric ratios were determined by HPLC: DuPont, Zorbax C-8, methanol/0.01 M KH_2PO_4 (pH 7) = 65/35, UV detector, 254 nm; (*S*,*S*)-**5**, t_r = 11.0 min; (*R*,*S*)-**5**, t_r = 13.1 min.

Scheme 4



epimerization of a single diasteromer (*S*,*S*)-**5** (99:1 ratio) in xylene solution at reflux (138 °C, 16 h) resulted in the formation of diastereomer **5** at an equilibrium ratio of 60:40. Having established a suitable laboratory procedure, we next examined its capability in our plant. The efficiency of this total resolution process was demonstrated on a 63 mole scale, employing a recycling loop for the mother liquors, to afford (*S*,*S*)-**5** (total of 52 kg) in 75% overall yield (99:1 diastereomeric ratio) from **4**.

The synthesis of **1** (Scheme 4) was completed by treating (*S*,*S*)-**5** first with aqueous sodium hydroxide in toluene in the presence of a catalytic amount of tetrabutylammonium hydrogen sulfate followed by *tert*-butyl chloroacetate to afford crude **7**. Subsequent hydrogenolysis of **7** with 5% palladium on charcoal at 60 °C generated compound **1** in 90% overall yield from (*S*,*S*)-**5**. The high chemical purity and (*S*)-configuration of **1** were confirmed by comparison of its optical rotation, NMR, and elemental analysis with an authentic sample. The enantiomeric purity of **1** was established to be 99% ee by chiral HPLC (Daicel Chiralcel OD).

In summary, a novel *thermal* epimerization−resolution methodology for the asymmetric synthesis of *N*-substituted α-amizobenzlactam has been presented. In principle, **3** can be prepared from **4** via reaction with (*R*)-1-phenylethylamine, followed by the thermal epimerization−resolution process and hydrogenolysis.

Experimental Section

Proton magnetic resonance spectra were recorded on an FT-NMR spectrometer (^{1}H at 270 MHz). ^{1}H NMR chemical shifts were reported in ppm referenced to the residual $CHCl_3$ (7.24 ppm), and *J* values were reported in hertz. Microanalysis was performed by Robertson Laboratory Inc. of Madison, NJ. The diastereomeric ratio of (*S*,*S*)-**5** was determined by high-performance liquid chromatography equipped with a DuPont Zorbax C-8 column, eluted (1 mL/min) with methanol−0.01 M KH_2PO_4 (pH = 7) 65:35 and detected by a UV lamp at λ = 254 nm: (*S*,*S*)-**5**, t_r = 11.0 min; (*R*,*S*)-**5**, t_r = 13.1 min. The enantiomeric excess of **1** was determined by high-performance liquid chromatography equipped with a Daicel Chiralcel OD column, 250 × 4.6 mm, eluted (0.75 mL/min) with hexane−2-propanol (with 2% diethylamine) = 80:20 and detected by a UV lamp at λ = 254 nm: (*S*)-**1**, t_r = 15.6 min; (*R*)-**1**, t_r = 11.8 min. Optical rotation was recorded at 25 °C. Concentration refers to removal of solvent under reduced pressure using a rotary evaporator.

3-[(1-(1*S*)-Phenylethyl)amino]-1,3,4,5-tetrahydro-2*H*-1-(3*RS*)-benzazepin-2-one (5). A mixture of 3-bromo-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepine (**4**) (144 g, 0.60 mol), (*S*)-1-phenylethylamine (76.8 g, 0.62 mol), sodium carbonate (31.8 g, 0.30 mol), and propylene glycol (144 mL) were heated to 130 °C for 3.5 h. The reaction mixture was cooled to 80 °C, and ethanol (60 mL) was added. The mixture was cooled to 40 °C, and water (180 mL) was added. The suspension was allowed to cooled to ambient temperature and stirred for 30 min. The solid was collected by filtration, rinsed with water (120 mL), and dried in a vacuum oven at 60 °C to a constant weight to obtain 156 g (93%) of diastereomer **5** (20% de) as a solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.50 (s, 1H), 6.72−7.18 (m, 9H), 3.47−3.62 (m, 1H), 3.15 (dd, *J* = 11.3, 7.8 Hz, 0.5H), 2.08−2.86 (m, 4.5H), 1.68−1.86 (m, 1H), 1.03−1.15 (dd, *J* = 6.5, 6.5 Hz, 3H, ratio of 60:40). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.10; N, 9.97.

3-[(1-(1*S*)-Phenylethyl)amino]-1,3,4,5-tetrahydro-2*H*-1-(3*S*)-benzazepin-2-one [(*S*,*S*)-5]. A mixture of 3-[(1-(1*S*)-phenylethyl)amino]-1,3,4,5-tetrahydro-2*H*-1-(3*S*,*R*)-benzazepin-2-one (**5**) (75 g) and odorless mineral spirits (75 mL) were heated at 140 °C for 16 h. The reaction mixture was cooled to 80 °C, and cyclohexane (150 mL) was added over a period of 30 min under stirring. The mixture was further cooled to ambient temperature. The product was isolated by filtration and rinsed with cyclohexane (75 mL) to offer 66 g (88%) of (*S*,*S*)-**5** (>98% de) as an off-white solid: mp 185−188 °C; $[\alpha]^{25}_D$ −364.1 (*c* = 1.0, methanol). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.92−7.30 (m, 9H), 3.75 (q, *J* = 6.5 Hz, 1H), 3.06 (dd, *J* = 11.3, 8.0 Hz, 1H), 2.76−2.93 (m, 1H), 2.55 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.26−2.44 (m, 1H), 2.20 (bs, 1H), 1.87−2.03 (m, 1H), 1.35 (d, *J* = 6.5 Hz, 3H). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.22; H, 7.31; N, 10.05.

***tert*-Butyl 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetate (1).** A mixture of 3-[(1-(1*S*)-phenylethyl)amino]-1,3,4,5-tetrahydro-2*H*-1-(3*S*)-benzazepin-2-one [(*S*,*S*)-**5**] (60 g, 0.21 mol), tetrabutylammonium hydrogen sulfate (0.60 g, 1.8 mmol), toluene (520 mL), and 50% sodium hydroxide (43 g, 0.54 mol) were heated at 35 °C and stirred for 1 h. The mixture was cooled to 20 °C and stirred for 16 h. A solution of *tert*-butyl chloroacetate (35.5 g, 0.23 mol) in toluene (100 mL) was added over a period of 30 min, and the mixture was stirred for additional 1 h. Water (130 mL) was added. The organic layer was separated, washed with water (130 mL), and concentrated. To the syrup were added ethanol (100 mL) and 5% Pd/C (4.2 g, 50% w/w) and hydrogenated in a Parr apparatus at 60 °C (55 psi) for 16 h. The mixture was filtered and concentrated to dryness. The residue was dissolved into ethyl acetate (210 mL) and washed sequentially with 1 M aqueous solution of sodium carbonate (30 mL) and water (30 mL). The organic layer was concentrated to dryness. A mixture of toluene (43 mL) and heptane (345 mL) was added, and the resulting slurry was heated to 75 °C for 30 min. The solution was cooled to −5 °C and stirred for additional 2 h. The product was isolated by filtration to obtain 54.5 g (90%) of **1** (99% ee) as a white solid: mp 110−111 °C; $[\alpha]^{25}_D$ −274.8 (*c* = 1.0, ethanol) (lit:[3] $[\alpha]^{25}_D$ −274, *c* = 2.0, ethanol). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10−7.27 (m, 4H), 4.55 (AB, *J* = 17.0 Hz, 1H), 4.35 (AB, *J* = 17.0 Hz, 1H), 3.42 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.25 (td, *J* = 13.2, 7.7 Hz, 1H), 2.58 (dd, *J* = 13.4, 6.9 Hz, 1H), 2.40 (m, 1H), 1.91 (m, 1H), 1.40 (s, 9H). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.26; H, 7.56; N, 9.65.

Acknowledgment. We are grateful to Drs. K. Gelotte and J. Brokatzky for helpful discussions and suggestions. We thank Mr. R. Winchurch for chiral HPLC assistance, and Mr. T. Tedesco and Mr. P. Prickett for a pilot plant demonstration.

JO971056N