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A Practical and Efficient Synthesis of (3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carboxylic acid via an Aziridinium Ion Intermediate

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Abstract:

A practical and efficient synthesis of (3*R*,4*S*)-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (1), a key chiral building block for synthesis of biologically active compounds was established by utilizing a stereospecific and regioselective chlorination of *in situ* generated aziridinium ion, followed by a nitrile anion cyclization. Starting from commercially available (*R*)-styrene oxide and 3-(benzylamino)propionitrile, the four-step synthesis features a through process without purification of intermediates until isolation of crystalline 1. The robust, chromatography-free and reproducible synthesis of 1 achieved an 84% overall yield from (*R*)-styrene oxide. This highly efficient process was successfully demonstrated at pilot scale with 17 kg output of 1.

Introduction

trans-3,4-Disubstituted pyrrolidines are key chiral building blocks for the synthesis of various biologically active compounds such as thrombin inhibitors,[1] coagulation factor Xa inhibitors[2] and CCR5 receptor antagonists.[3] There is often the requirement for such *trans*-pyrrolidines to be enantiopure.

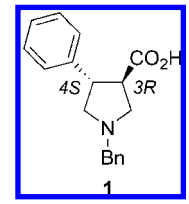

Figure 1. **(3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carboxylic acid (1).**

During an ongoing project, we required multikilogram quantities of (3*R*,4*S*)-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (**1**) for the synthesis of pharmaceutical candidates to support preclinical and clinical studies (Figure 1). Compound **1** is a trisubstituted *N*-benzyl pyrrolidine with a C3 carboxylic acid and a C4 phenyl moiety in the *trans*-3*R*,4*S* configuration. Unfortunately, this compound was unavailable from commercial sources in multikilogram quantities.

While a wide range of approaches to *trans*-3,4-disubstituted pyrrolidines are reported, there are far fewer examples for their preparation on a large scale. One of the most extensively studied and widely used methods involves an asymmetric 1,3-dipolar cycloaddition of nonstabilized azomethine ylides to olefinic dipolarophiles.[4a−e] However, this chiral auxiliary-based approach gave a mixture of diastereomeric 1,3,4-trisubstituted pyrrolidines with moderate diastereoselectivity (up to 48% de).[4b] As the medicinal chemistry group employed this approach for the preparation of screening/optimization samples, we first evaluated it for the multikilogram preparation of **1** by choosing commercially available and inexpensive (*S*)-4-phenyl-2-oxazolidinone as a chiral auxiliary (Scheme 1). As a result, the desired diastereomer **6a** was obtained as colorless oil from *trans*-cinnamoyl chloride (**2**) in 64% isolated yield (2 steps), and moderate diastereoselectivity was consistent with that of the literature. This strategy proved to have several drawbacks to overcome for multikilogram production: (1) silica gel chromatography was necessary for the separation of **6a** and **6b**; (2) the ylide **5** precursor, *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**4**), was not commercially available in multikilogram quantities. Therefore, this approach did not encourage further investigation, and the development of a new practical and efficient synthesis of **1** was desired.

We surveyed reported synthetic methods for *trans*-3,4-disubstituted pyrrolidines applicable to large-scale production.

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(1) Fevig, J. M.; Abelman, M. M.; Brittelli, D. R.; Kettner, C. A.; Knabb, R. M.; Weber, P. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 295.
(2) Fevig, J. M.; Buriak, J., Jr.; Stouten, P. F. W.; Knabb, R. M.; Lam, G. N.; Wong, P. C.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1195.
(3) Some examples: (a) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129. (b) Shen, D.-M.; Shu, M.; Mills, S. G.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 935. (c) Shen, D.-M.; Shu, M.; Mills, S. G.; Willoughby, C. A.; Shah, S.; Lynch, C. L.; Hale, J. J.; Mills, S. G.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Lyons, K.; Pivnichny, J. V.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 941. (d) Shu, M.; Loebach, J. L.; Parker, K. A.; Mills, S. G.; Chapman, K. T.; Shen, D.-M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Salvo, J. D.; Lyons, K.; Pivnichny, J. V.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 947. (e) Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Guthikonda, R. N.; MacCoss, M.; Mills, S. G.; Gould, S. L.; Malkowitz, L.; Siciliano, S. J.; Springer, M. S.; Carella, A.; Carver, G.; Hazuda, D.; Holmes, K.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A.; Schleif, W. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3419.
(4) For some applications of this reaction, see: (a) Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883. (b) Karlsson, S.; Han, F.; Högberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605. (c) Ling, R.; Ekhato, V.; Rubin, J. R.; Wustrow, D. J. *Tetrahedron* **2001**, *57*, 6579. (d) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977. (e) Kotian, P. L.; Lin, T.-H.; El-Kattan, Y.; Chand, P. *Org. Process Res. Dev.* **2005**, *9*, 193.

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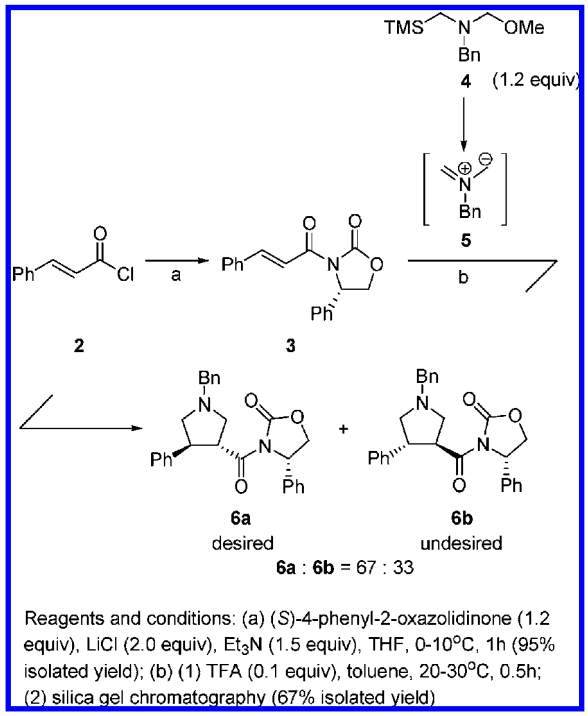
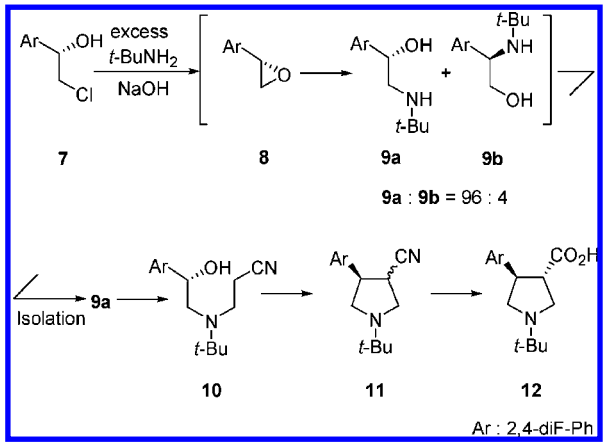
Scheme 1. **Asymmetric 1,3-dipolar cycloaddition approach to 1**



Scheme 2. **Synthesis of *trans*-pyrrolidine carboxylic acid 12 via a nitrile anion cyclization**



There were two other reported methods for the construction of *trans*-3,4-disubstituted pyrrolidines. One method involved the Rh-catalyzed asymmetric 1,4-arylation of aryl boronic acid to 3-pyrroline esters,[5] and the other is the enantioselective intramolecular cyclization of the acyclic hydroxynitriles.[6a,b] The former method gave the desired product in good enantioselectivity with bulky esters, but poor conversion. Better yields were obtained with smaller esters; however, the enantioselectivity was significantly lower. The latter method highlighted an intramolecular nitrile-anion cyclization which afforded an enantio-pure *trans*-pyrrolidine carboxylic acid **12** as a result of consecutive epimerization/saponification of a pyrrolidine nitrile **11** (Scheme 2).[6b] However, there were limitations in the application of this methodology to the synthesis of **1**. In particular, we needed to address the problems associated with the regioselective ring-opening of *in situ* generated epoxide **8**: (1) a bulky nucleophile such as *tert*-butylamine has a fundamental role in good regioselectivity; (2) excess *tert*-butylamine (5 volumes) is essential to improve the regioselectivity of the reaction, and the unreacted *tert*-butylamine was removed by evaporation; (3) crystallization to isolate the desired regioisomer **9a** was necessary for the separation from the undesired regioisomer **9b**.

Inspired by this strategy, we envisioned a synthetic route for **1** starting from commercially available (*R*)-styrene oxide (**13**) and 3-(benzylamino)propionitrile (**14**) (Scheme 3). The advantage of this synthetic plan did not rely upon stereocontrol at the C3 and C4 positions. On the other hand, a common problem associated with regioselective epoxide opening still existed. Furthermore, removal of **14** by a simple evaporation was impractical due to its high boiling point. With the above in mind, we investigated the ring-opening reaction of **13** with **14**. This reaction was completed in 42 h to afford an 89:11 mixture of the corresponding two isomeric amino alcohols **15a** and **15b** as an oil with the best selectivity.[7] However, separation of **15a** and **15b** was difficult with any practical purification methods. Furthermore, the excess **14** which was necessary to attain a practical reaction time posed an issue of removing **14** from the desired **15a**.

On the other hand, novel methods of hydroxyl group activation at the benzylic position have been reported. On the basis of these reports,[8a−d] we envisaged mesylation of the regioisomeric mixture of amino alcohols **15a** and **15b** using $MsCl/Et_3N$ should converge with a common aziridinium intermediate **18** which would afford an isomerically and enantiomerically pure β-chloroamine **19** as a result of spontaneous ring-opening (Scheme 4). If this sequence is realized, the epoxide-opening regioselectivity will be of no consequence.

The mesylation hypothesis was confirmed by successful transformation of isolated amino alcohols **15a** and **15b** to the single β-chloroamine **19** in good yield. Base treatment of **19** induced an S_N2-type intramolecular cyclization to afford the desired mixture of pyrrolidine nitriles **16a** and **16b** which were converted to a single isomeric pyrrolidine carboxylic acid **1** after the epimerization/saponification.[6b] We report here a practical and efficient synthesis of the single enantiomer of **1**, utilizing stereospecific and regioselective chlorination of the *in situ* generated aziridinium ion intermediate **18**.

Results and Discussion

We investigated the ring-opening reaction of (*R*)-styrene oxide (**13**) with 3-(benzylamino)propionitrile (**14**) (Table 1). The reaction in DMF did not occur at all (entry 1) and proceeded sluggishly in protic solvents such as EtOH, *i*-PrOH, and

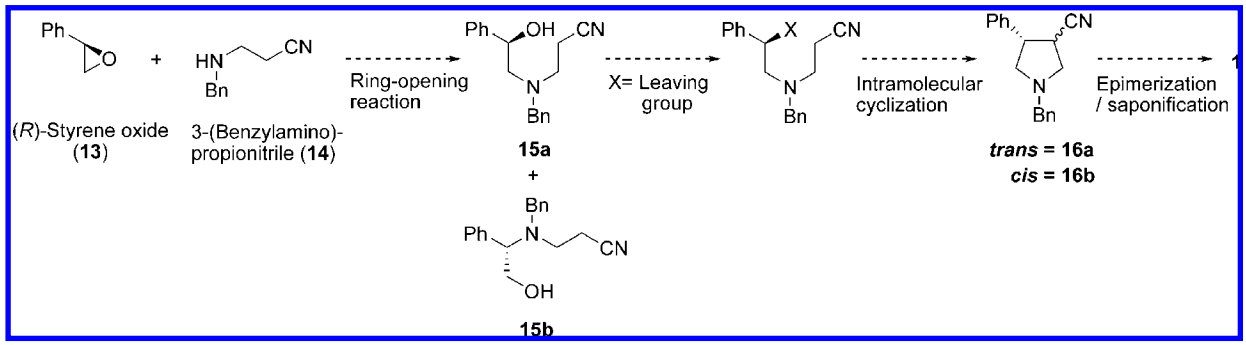
(5) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; DaSilva, J.; Askin, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265.

(6) (a) Achini, R. *Helv. Chim. Acta* **1981**, *64*, 2203. (b) Chung, J. Y. L.; Cvetovich, R.; Amato, J.; McWilliams, J. C.; Reamer, R.; DiMichele, L. *J. Org. Chem.* **2005**, *70*, 3592.

(7) The ring-opening of (*R*)-styrene oxide was conducted with 3-(benzylamino)propionitrile (2.0 equiv) in *i*-PrOH (1 volume) at 90 °C for 42 h.

(8) For some applications of this reaction, see: (a) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555. (b) Chuang, T.-H.; Sharpless, K. B. *Helv. Chim. Acta* **2000**, *83*, 1734. (c) Frizzle, M. J.; Caille, S.; Marshall, T. L.; McRae, K.; Nadeau, K.; Guo, G.; Wu, S.; Martinelli, M. J.; Moniz, G. A. *Org. Process Res. Dev.* **2007**, *11*, 215. (d) Anderson, S. R.; Ayers, J. T.; DeVries, K. M.; Ito, F.; Mendenhall, D.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1999**, *10*, 2655.

Scheme 3. **Synthetic strategy towards 1**



Scheme 4. **Regio- and stereoselective chlorination of the *in situ* generated aziridinium ion intermediate 18**

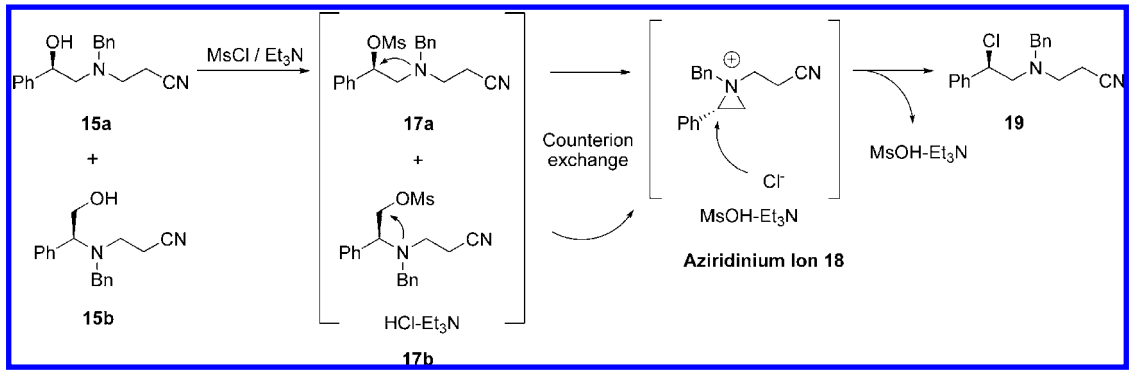


Table 1. **Effect of solvents and additives in the ring-opening of 13 with 14**

entry	**14** (equiv)	solvent[a]	additive[b]	temperature (°C)	time (h)	HPLC area % **15a** + **15b**	ratio[c] **15a**:**15b**
1	1.5	DMF	none	75	14	—[d]	
2	1.5	EtOH	none	75	15	92	82:18
3	1.5	*i*-PrOH	none	75	42	91	85:15
4	1.5	*n*-BuOH	none	100	21	88	82:18
5	1.2	60% EtOH	none	80	6	91[e]	76:24
6	1.2	EtOH	MsOH	85	2	—[f]	
7	1.2	EtOH	AcOH	85	2	78	57:43
8	1.2	EtOH	PhOH	85	6	95	68:32
9	1.2	toluene	ZnI_2	30	2	66	45:55

[a] 5 volumes in entries 1−5 and 1 volume in entries 6−9. [b] 1.0 equiv in entries 6−8 and 0.1 equiv in entry 9. [c] A ratio of each HPLC peak areas among **15a** and **15b**. [d] Not reacted. [e] Unacceptable amounts of impurities formed. [f] Decomposition of **13**.

n-BuOH to afford the mixture of regioisomers **15a** and **15b** (entries 2−4). The ring-opening reaction in aqueous 60% EtOH[9] proceeded very quickly but resulted in the formation of unacceptable amounts of byproducts (entry 5). Among the solvents tested, EtOH seemed to be the best from the viewpoints of reaction rate and product quality (entry 2).

The serious disadvantage of this reaction (entry 2) was that it required excess **14** and long reaction times. To address these issues, various additives such as MsOH, AcOH, PhOH, and ZnI_2 were investigated.[10a−e] The use of MsOH gave a disappointing result because of the decomposition of **13** (entry 6). Except for MsOH, the additives enhanced the reaction rates dramatically and reduced the amount of **14** required for the aminolysis of **13** (entries 7−9). On the other hand, these additives not only decreased the selectivity for **15a** but also tended to increase the amount of impurities. Since the reaction of the mixture with $MsCl/Et_3N$ converts both regioisomers **15a** and **15b** into a single β-chloroamine **19** via the common aziridinium ion intermediate **18**, the regioselectivity of ring-opening of **13** could be addressed. During the development of a drug candidate, we have encountered similar problems associated with the aminolysis of styrene oxide. Among many acidic additives, PhOH gave a best result in terms of reactivity and selectivity (unpublished results). Thus, we tried PhOH as an additive and obtained a best result using 1.0 equiv of PhOH in 1 volume of EtOH (entry 8). With this condition, 1.2 equiv of **14** was sufficient for reaction completion. As described above, when AcOH or ZnI_2 was used, the reaction proceeded very quickly but suffered from the formation of unacceptable amounts of byproducts (entries 7 and 9). After complete reaction (entry 8), toluene was added to the reaction mixture, and

(9) Azizi, N.; Saidi, M. *Org. Lett.* **2005**, *7*, 3649.
(10) For recent examples of various methods for activating epoxides, see: (a) Heydari, A.; Mehrdad, M.; Maleki, A.; Ahmadi, N. *Synthesis* **2004**, 1563. (b) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597. (c) Pachon, L. D.; Gamez, P.; van Brussel, J. J. M.; Reedijk, J. *Tetrahedron Lett.* **2003**, *44*, 6025. (d) Placzek, A. T.; Donelson, J. L.; Trivedi, R.; Gibbs, R. A.; De, S. K. *Tetrahedron Lett.* **2005**, *46*, 9026. (e) Shivani; Pujala, B.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 3713.

aqueous acid−base extractions were used to remove PhOH and the unreacted amine **14**. Thus, the oily mixture of **15a** and **15b** (68:32)[11] was obtained and used without further purification for the subsequent chlorination.

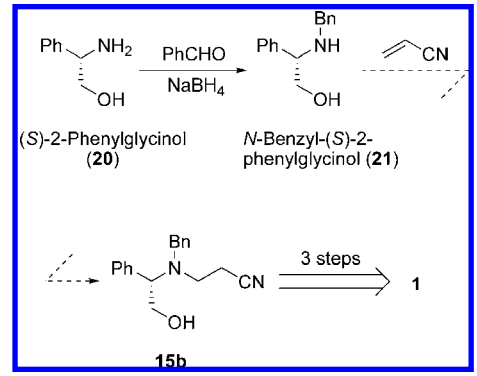
In the chlorination step, the mixture of regioisomers **15a** and **15b** was quantitatively converted via the aziridinium ion intermediate **18** into single β-chloroamine **19** by treatment with MsCl/Et_3N in toluene at room temperature. Although we did not isolate and identify **18**, the fact that a single regioisomer **19** was obtained from the mixture of **15a** and **15b** implies the existence of **18**. Interestingly, chlorination of the mixture of **15a** and **15b** with thionyl chloride instead of MsCl/Et_3N afforded only racemic **19** due to the participation of benzylic cation under highly acidic conditions. Therefore, the MsCl/Et_3N system is essential for the stereospecific chlorination. After completion, the reaction mixture was washed with water, aqueous sodium bicarbonate, and sodium chloride and concentrated under reduced pressure to give **19** as an oil. Fortunately, **19** was sufficiently stable under these conditions and was used without any further purification in the next cyclization step.

In the cyclization step, β-chloroamine **19** was treated with 1.1 equiv of sodium hexamethyldisilazide (NaHMDS) in toluene at −30 to −20 °C. The reaction was complete within 10 min, and after an aqueous workup yielded an 89/11 *trans*/*cis* mixture of pyrrolidine nitriles (**16a** and **16b**)[12] as an oil. The obtained mixture was used without further purification for the hydrolysis since the mixture of **16a** and **16b** was successfully converted into a single *trans*-pyrrolidine carboxylic acid **1** by hydrolysis, as described later. The attempts to combine the chlorination and cyclization steps in a one-pot fashion resulted in the large amount of unreacted **19**.

The final step in the synthesis involves a basic epimerization/saponification of *trans*-/*cis*-pyrrolidine nitriles **16a** and **16b** to *trans*-pyrrolidine carboxylic acid **1**. On the basis of Chung methodology,[6b] the hydrolysis of the mixture of **16a** and **16b** with NaOH in aqueous EtOH at reflux temperature was investigated. This reaction proceeded through an intermediate and was completed in 7 h. The intermediate was not identified, but it is likely to be the corresponding amide. Adjustment of the pH to around 4 by using 35% hydrochloric acid and subsequent addition of water afforded single **1** as a crystalline solid with an overall yield of 84% (four steps). These procedures produced **1** with an optical purity of 99.6% ee[13] starting from (*R*)-styrene oxide (**13**) with >99% ee. This observation indicates that there was no chirality leakage in the whole process. In addition, this highly efficient process was successfully demonstrated at pilot scale with 17 kg output of **1**.

Our attention then turned to the investigation of an alternative approach starting from a cheaper chiral starting material than (*R*)-styrene oxide (**13**). As amino alcohol **15b** was successfully converted into the isomerically and enantiomerically pure

Scheme 5. **Alternative synthetic route for 1 starting from (*S*)-2-phenylglycinol (20)**



β-chloroamine **19** via the *in situ* aziridinium ion intermediate **18**, we designed an alternative synthetic route for **1** starting from commercially available and cheaper (*S*)-2-phenylglycinol (**20**) (Scheme 5). We investigated the conjugate addition of *N*-benzyl-(*S*)-2-phenylglycinol (**21**) with acrylonitrile since the method for preparing **21** from **20** had been reported.[14a,b] Treatment of **21** with acrylonitrile and AcOH gave **15b** in 88% isolated yield (unoptimized). In the chlorination and cyclization steps, the same reaction conditions as above were employed. Amino alcohol **15b** was converted into the mixture of **16a** and **16b** via **19** in 67% yield (unoptimized). We think with further optimization this alternative route may be more useful for the synthesis of **1**.

Conclusions

In this contribution, a practical and efficient synthesis of (3*R*,4*S*)-1-benzyl-4-phenylpyrrolidine-3-carboxylic acid (**1**), a key intermediate for biologically active compounds, is described. The advantage over the original methods is as follows: (1) access to **1** from commercially available raw materials, (2) improvement of overall yield and cost-efficiency, (3) avoidance of column chromatographic purifications throughout the whole process. Furthermore, this synthesis has permitted the preparation of multikilogram quantities of **1**.

Experimental Section

^{1}H NMR spectra were recorded on a JEOL JNM-AL400 using TMS as an internal standard. IR spectra were recorded on a Horiba FT-720 Fourier transform infrared spectrometer. MS spectra were recorded on a Hewlett-Packard 1100LC/MSD mass spectrometer using API-ES ionization. HPLC was performed using Shimazu LC-10AT systems. All reagents and solvents were commercially available and used without further purification. All reactions were performed under an atmosphere of nitrogen.

Mixture of 3-{Benzyl[(2*R*)-2-hydroxy-2-phenylethyl]amino}propanenitrile (15a) and 3-{Benzyl[(1*S*)-2-hydroxy-1-phenylethyl]amino}propanenitrile (15b). (*R*)-(+)-Styrene oxide (**13**) (8.47 kg, >99% ee), 3-(benzylamino)propionitrile (**14**) (14.40 kg), PhOH (7.00 kg), and EtOH (1.8 L) were combined in a reaction vessel, and the mixture was stirred at 86−89 °C for 8 h. After cooling to 20−30 °C, toluene (32 L), and water (45 L) were added to the reaction mixture. The mixture was adjusted to pH 4.0 using 35% hydrochloric acid (1.6 L). The

(11) The ratio of each HPLC area % among **15a** and **15b**, see Experimental Section.
(12) The ratio of each HPLC area % among **16a** and **16b**, see Experimental Section.
(13) Enantiomeric purity of **1** was determined by chiral HPLC assay of the corresponding pyrrolidine methanol, see Experimental Section.
(14) (a) Monbaliu, J.-C.; Tinant, B.; Marchand-Brynaert, J. *Heterocycles* **2008**, *75*, 2459. (b) Blanchet, J.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 2935.

organic phase was separated and washed with water (18 L). To the organic phase was added water (45 L) and the mixture was adjusted to pH 12.0 using 24% aqueous sodium hydroxide solution (6.6 L), and then the organic phase was separated. To the organic phase was added water (45 L) and the mixture was adjusted to pH 12.1 using 24% aqueous sodium hydroxide solution (0.6 L). The organic phase was separated, and then washed with water (27 L) and aqueous sodium chloride solution [sodium chloride (5.4 kg) and water (22 L)] successively. The organic phase was concentrated under vacuum at 40−50 °C until approximately a 25 L of total volume was obtained. Toluene (17 L) was added, and the concentration was continued under vacuum at 40−50 °C to give a mixture of **15a** and **15b** (21.50 kg, overweight) as a yellow oil, and it was used without further purification for the next step. HPLC analysis of the mixture of regioisomers **15a** and **15b** (HPLC condition A, column: TSKgel ODS-80Tm 4.6 mm × 150 mm, eluent: 0.05 M KH_2PO_4 aq/MeCN, 40:60, flow rate: 1.0 mL/min, column temperature: 40 °C, wavelength: 210 nm) showed a 68:32 ratio of **15a**:**15b** with $t_R = 5.23$ min and $t_R = 4.70$ min, respectively.

Analytically pure **15a** and **15b** were obtained by silica gel chromatography. **3-{Benzyl[(2*R*)-2-hydroxy-2-phenylethyl]-amino}propanenitrile (15a)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 10H), 4.76−4.69 (m, 1H), 3.92 (d, J = 13.6 Hz, 1H), 3.62 (d, J = 13.6 Hz, 1H), 3.47 (d, J = 0.8 Hz, 1H), 3.02−2.95 (m, 1H), 2.85−2.75 (m, 2H), 2.66−2.60 (m, 1H), 2.47−2.43 (m, 2H); IR (ATR): 3417, 3030, 2834, 2243, 1603, 1492, 1451, 1375, 1342 cm^{-1}; MS (API-ES$^+$): 303 [M + Na]$^+$. **3-{Benzyl[(1*S*)-2-hydroxy-1-phenylethyl]amino}propanenitrile (15b)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.23 (m, 10H), 4.14−4.07 (m, 1H), 3.96−3.92 (m, 1H), 3.86 (d, J = 13.6 Hz, 1H), 3.75−3.69 (m, 1H), 3.38 (d, J = 13.6 Hz, 1H), 3.09−3.02 (m, 1H), 2.70 (dd, J = 2.0, 9.2 Hz, 1H), 2.63−2.57 (m, 1H), 2.46−2.23(m, 2H); IR (ATR): 3480, 3060, 3028, 2933, 2844, 2247, 1494, 1452 cm^{-1}; MS (API-ES$^+$): 303 [M + Na]$^+$.

3-{Benzyl[(2*R*)-2-chloro-2-phenylethyl]amino}propanenitrile (19). The mixture of **15a** and **15b** (21.50 kg), toluene (84 L), Et_3N (10.60 kg) were combined in a reaction vessel. After cooling to below 20 °C, MsCl (10.30 kg) was added dropwise at 8−20 °C, and the mixture was stirred at 20−27 °C for 2.5 h. To the reaction mixture was added water (63 L) slowly at below 30 °C. The organic phase was separated and washed with aqueous sodium bicarbonate solution [sodium bicarbonate (10.50 kg) and water (63 L)] and aqueous sodium chloride solution [sodium chloride (12.60 kg) and water (63 L)] successively. The organic phase was concentrated under vacuum at 35−45 °C until ∼40 L total volume was obtained. Toluene (42 L) was added, and the concentration was continued under vacuum at 35−45 °C to give **19** (41.14 kg, overweight) as an orange oil. It was used without further purification for the next step.

An analytical sample of **19** was purified by silica gel chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 10H), 4.80 (t, J = 6.8 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.21−3.08 (m, 2H), 2.85 (t, J = 6.8 Hz, 2H), 2.30−2.25 (m, 2H); IR (ATR): 3062, 3029, 2960, 2248, 1494, 1453 cm^{-1}; MS (API-ES$^+$): 263 [M − Cl]$^+$.

Mixture of (3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16a) and (3*S*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16b). Compound **19** (41.14 kg) and toluene (112 L) were combined in a reaction vessel. After cooling to −30 to −20 °C, 1 M NaHMDS in THF solution (75.17 kg) was added slowly to the mixture at this temperature. The mixture was stirred at −30 to −20 °C for 10 min and quenched with water (4.5 L) at −30 °C. After warming to 23 °C, water (85 L) was added to the mixture. The organic phase was separated and washed with aqueous sodium chloride solution [sodium chloride (13.40 kg) and water (67 L)]. The organic phase was concentrated under vacuum at 35−45 °C until HPLC analysis of the analytical sample showed residual toluene at 20−25 HPLC area % (HPLC condition A) to give a mixture of **16a** and **16b**. It was used without isolation for the next step. HPLC analysis of the mixture of diastereomers **16a** and **16b** (HPLC condition A) showed an 89:11 ratio of **16a**:**16b** with $t_R = 8.34$ min and $t_R = 6.79$ min, respectively.

Analytically pure **16a** and **16b** were obtained by silica gel chromatography. **(3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16a)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10H), 3.74 (d, J = 12.8 Hz, 1H), 3.69 (d, J = 12.8 Hz, 1H), 3.14−3.03 (m, 3H), 2.93 (dd, J = 8.8, 6.9 Hz, 1H), 2.91 (dd, J = 8.8, 6.9 Hz, 1H), 2.78 (dd, J = 9.6, 6.4 Hz, 1H); IR (ATR): 3062, 3029, 2961, 2918, 2239, 1603, 1494, 1453 cm^{-1}; MS (API-ES$^+$): 263 [M + H]$^+$. **(3*S*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16b)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 3.76 (s, 2H), 3.66 (dd, J = 8.6, 7.7 Hz, 1H), 3.47 (ddd, J = 9.6, 7.5, 6.2 Hz, 1H), 3.22−3.12 (m, 2H), 2.98 (dd, J = 9.5, 6.2 Hz, 1H), 2.89 (dd, J = 9.5, 8.0 Hz, 1H); IR (ATR): 3031, 2805, 2790, 2240, 1494, 1452, 1377, 1346 cm^{-1}; MS (API-ES$^+$): 263 [M + H]$^+$.

(3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carboxylic Acid (1). To the mixture of **16a** and **16b** in the reaction vessel was added EtOH (99 L). After cooling to 0 °C, aqueous sodium hydroxide solution [sodium hydroxide (9.00 kg) and water (20 L)] was added to the mixture at 0−13 °C. The mixture was heated to reflux at 77−80 °C for 7 h and then allowed to cool to 0 °C. The mixture was adjusted to pH 4.0 using 35% hydrochloric acid (23.5 L) at 26 °C for crystallization. Water (197 L) was added dropwise at 10−30 °C, and the mixture was adjusted to pH 4.0 using 24% aqueous sodium hydroxide solution (2.4 L) at 23 °C. The resulting slurry was cooled at 1 °C, filtered, and washed with aqueous EtOH solution [EtOH (20 L) and water (39 L)] and then toluene (59 L). The wet crystal was dried under vacuum at 43 °C to give 16.66 kg of **1** as a crystalline white solid [84% yield based on (*R*)-styrene oxide]. ^{1}H NMR (400 MHz, NaOD + D_2O) δ 7.16−7.02 (m, 10H), 3.48 (d, J = 12.4 Hz, 1H), 3.37 (d, J = 12.8 Hz, 1H), 3.30 (q, J = 8.4 Hz, 1H), 2.87 (t, J = 7.6 Hz, 1H), 2.77−2.66(m, 3H), 2.39 (t, J = 8.8 Hz, 1H); IR (ATR): 3440, 3396, 3306, 1673, 1602, 1580, 1496, 1451, 1398, 1377 cm^{-1}; MS (API-ES$^+$): 282 [M + H]$^+$.

Enantiomeric purity of **1** was determined by chiral HPLC assay of the corresponding pyrrolidine methanol, [(3*R*,4*S*)-1-benzyl-4-phenylpyrrolidin-3-yl]methanol, as follows: 70% Red-Al in toluene (8 equiv) was added slowly to **1** (1 equiv) in toluene (5 volumes) at 0−15 °C. The reaction mixture was

stirred at room temperature for 8 h. The mixture was slowly added to aqueous sodium hydroxide solution [sodium hydroxide (12 equiv) and water (7 volumes)] at 0−20 °C; subsequently, water (3 volumes) was slowly added at 10−30 °C. The organic phase was separated and then washed with water (3 volumes) and aqueous sodium chloride solution [sodium chloride (0.6 weight) and water (3 volumes)] successively. The organic phase was concentrated under vacuum to dryness to afford a white solid, identified as [(3*R*,4*S*)-1-benzyl-4-phenylpyrrolidin-3-yl]methanol by comparison to authentic samples.[15] The chiral assay (HPLC condition B, column: CHIRALCEL OD-H 4.6 mm × 250 mm, eluent: *n*-hexane/*i*-PrOH/diethyamine, 90:10:0.1, flow rate: 1.0 mL/min, column temperature: 40 °C, wavelength: 220 nm) gave a 99.8:0.2 ratio of (3*R*,4*S*):(3*S*,4*R*) enantiomers (99.6% ee) with t_R = 7.81 min and t_R = 6.28 min, respectively.

Mixture of (3*R*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16a) and (3*S*,4*S*)-1-Benzyl-4-phenylpyrrolidine-3-carbonitrile (16b) starting from *N*-Benzyl-(*S*)-2-phenylglycinol (21). Acetic acid (528 mg) was added to (*S*)-*N*-benzyl-2-phenylglycinol (**21**) (2.00 g) in acrylonitrile (8.40 g) at room temperature. The reaction mixture was refluxed for 41 h and then allowed to cool to room temperature. The mixture was concentrated under vacuum at 40 °C, and purification by silica gel chromatography (SiO_2: 20 g, elution: AcOEt/*n*-heptane, 1:4) gave 2.18 g of **15b** as a colorless oil (88% yield). It was identified as **15b** by comparison to an authentic sample. A crude mixture of **16a** and **16b** was obtained from **15b** (0.988 mg) using the experimental procedure as described above (690 mg, 68% yield). The yield was estimated from the peak area of the product on HPLC (HPLC condition A). HPLC analysis of the mixture of **16a** and **16b** (HPLC condition A) showed a 92:8 ratio of **16a**:**16b**.

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(15) The authentic samples of [(3*R*,4*S*)-1-benzyl-4-phenylpyrrolidin-3-yl]methanol and its enantiomer were synthesized respectively in our laboratories according to the literature 4b.