Organic Process Research & Development **2002**, *6*, 49–53

An Enantioselective Synthesis of (2*S*,3*R*)-3-(*N*-Benzyloxycarbonyl)amino-1-chloro-4-phenylthiobutan-2-ol, a Central Intermediate of Nelfinavir[1]

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Abstract:

(2*S*,3*R*)-3-(*N*-Benzyloxycarbonyl)amino-1-chloro-4-phenylthiobutan-2-ol 1 is a central intermediate of nelfinavir 2, which, being a potent HIV protease inhibitor, represents one of the most clinically efficacious anti AIDS drugs. Thus, a practical enantioselective synthesis of 1 has been devised which employs sodium erythorbate 9 as a chiral starting material. Consisting of the total 14-step functional group manipulations that proceed via methyl (2*S*,3*R*)-4-hydroxy-2,3-epoxybutyrate 8, the synthetic processes can dispense with chromatographic purification and provide architecturally complex 1 in 17% overall yield under a strict control of stereochemistry.

Introduction

Being a potent and efficacious inhibitor against an HIV protease, nelfinavir **2** is one of the most prescribed therapeutic agents to suppress the AIDS epidemic now. In its industrial manufacturing, there are two different processes operating. One was established early in the exploratory stage and has since employed (2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)-amino-1-chloro-4-phenylthiobutan-2-ol **1** as a key chiral building block[2] (Figure 1). The other was explored in parallel with the clinical development of **2** and has adopted the *threo* amino alcohol derivative, a (2*R*)-epimeric congener of **1**,[3] as a pivotal intermediate, because the *threo* stereochemistry is easier to build logically than the *erythro* stereochemistry as represented by **1**.

Its industrial practice extending almost a decade, the original synthetic approach to **1** has suffered the following drawbacks, which can be deduced from Scheme 1 outlining it: (i) starting with relatively costly L-serine; (ii) introducing a phenylthio group into *N*-Cbz L-serine **3** via the intramolecular Mitsunobu reaction using expensive reagents; (iii) employing hazardous explosive diazomethane for one carbon homologation of **5**; and (iv) incomplete stereocontrol over the *erythro*-selective reduction of α′-chloroketone **6** to **1**.

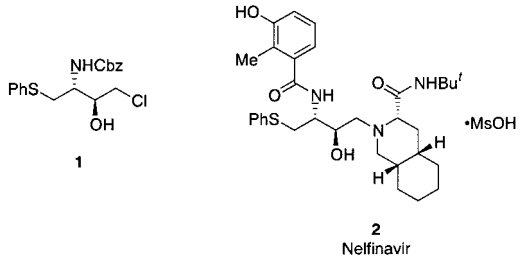
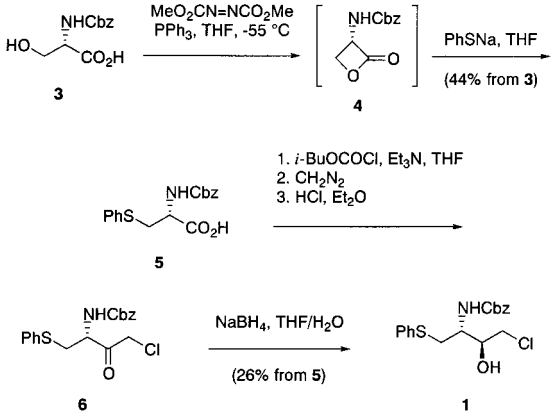


Figure 1. **Structures of nelfinavir 2 and its key intermidiate 1.**

Scheme 1. **Literature synthesis of 1**



Results and Discussion

Synthetic Plan. With its four-carbon skeleton functionalized all differently and its central amino alcohol moiety disposed as an *erythro* configuration, **1** has ever defied synthetic challenge. Keeping in mind not only those structural features inherent in **1** but also the pros and cons of its original synthesis (Scheme 1), we have defined the goals of our synthetic operations as follows: (i) to avoid carbon homologation and build the *erythro* (2*S*,3*R*)-amino alcohol motif with complete selectivity; (ii) to exploit only commodity materials; and (iii) to dispense with chromatographic purification.

To achieve these objectives, we conceived the chiral pool synthesis of **1** which would commence with sodium erythorbate **9**, a cheap fermentation product used widely as a

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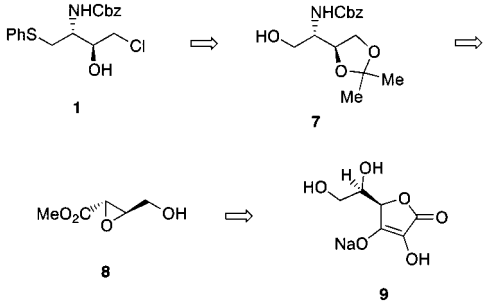
(1) This is a transcript of part of a lecture entitled "Stereoselective Synthesis of Chiral Pharmaceutical Intermediates" given at the Fourth International Conference on Organic Process Research and Development, Hong Kong, March 18−21, 2001. For another part of the lecture and other papers at this meeting contact Scientific Update, Wyvern Cottage, High Street, Mayfield, East Sussex, TN20 6AE, U.K.; telephone: +44 1435 873062; fax: +44 1435 872734; e-mail: sciup@scientificupdate.co.uk.

(2) (a) Kaldor, S. W.; Appelt, K.; Fritz, J. E.; Hammond, M.; Crowell, T. A.; Baxter, A. J.; Hatch, S. D.; Wiskerchen, M.; Muesing, M. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 715. (b) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. W.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

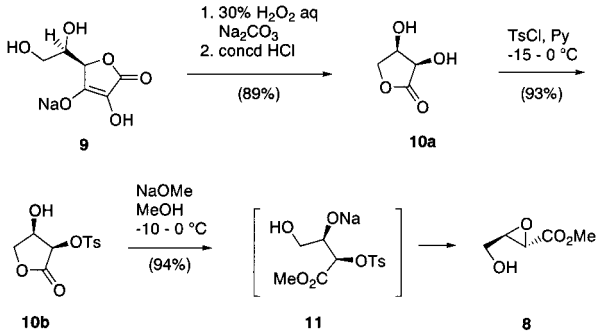
(3) (a) Inaba, T.; Birchler, A. G.; Yamada, Y.; Sagawa, S.; Yokota, K.; Ando, K.; Uchida, I. *J. Org. Chem.* **1998**, *63*, 7582. (b) Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem.* **2000**, *65*, 1623. (c) Zook, S. E.; Busse, J. K.; Borer, B. C. *Tetrahedron Lett.* **2000**, *41*, 7017.

10.1021/op010073i CCC: $22.00 © 2002 American Chemical Society and The Royal Society of Chemistry
Published on Web 01/04/2002

Scheme 2. **Synthetic plan**



Scheme 3. **Preparation of eopxy ester 8 by Weigel's method**

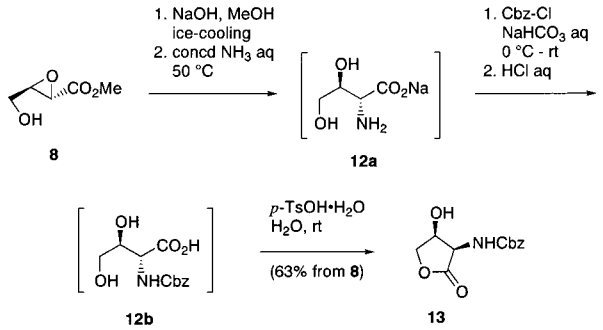


food preservative (Scheme 2). Its strategic features are itemized as follows: (i) excision of a four-carbon chiron,[4] methyl (2*S*,3*R*)-4-hydroxy-2,3-epoxybutyrate **8** from **9**; (ii) regio- and stereoselective introduction of amine function to **8**; (iii) differentiation between the molecular termini of **7** to allow for successive introduction of a phenylthio and chloride function; and (iv) good atom economy with respect to the stereogenic carbons.[5]

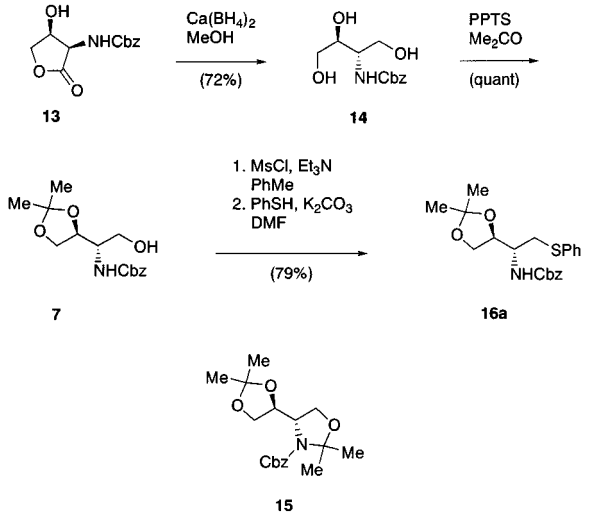
Excision of the C_4 Chiron. The early phase of the synthesis had recourse to Dunigan and Weigel's method, and it was reproduced uneventfully as summarized in Scheme 3.[6] Oxidative cleavage of **9** with alkaline hydrogen peroxide followed by acidic workup gave D-erythronolactone **10a** in 89% yield.[7] After its regioselective *O*-tosylation (93% yield), the resulting α-tosylate **10b** was treated with sodium methoxide to afford directly the key epoxyester **8** in 94% yield without isolating a hypothetical, but plausible intermediate **11**.[7]

Stereoselective Introduction of the Amine Function. After mild saponification of **8**, the resulting sodium carboxylate was treated directly with aqueous ammonia, according to the same procedures as reported by Manchand et al., to give the dihydroxy α-amino acid as its sodium salt **12a** in a reproducible way (Scheme 4).[8] It was then subjected

Scheme 4. **Preparation of lactone 13 after Manchand's method**



Scheme 5. **Regioselective introduction of the phenylthio group**



to the biphasic Schotten−Bauman conditions to form a benzyl carbamate. After liberating the free acid **12b** in the aqueous phase by acidification, *p*-toluenesulfonic acid (TsOH) was added to induce lactonization. Interestingly, the lactonization took place even in the aqueous phase to furnish more elaborate γ-lactone **13** in 63% overall yield from **8**.[9]

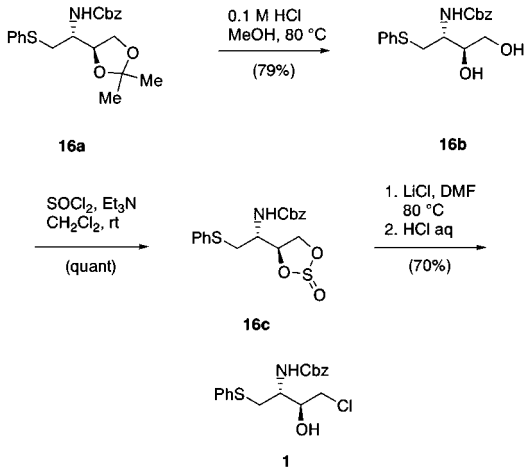
Heavily functionalized by polar groups, both **12a** and **12b** were difficult to isolate from the aqueous mixture by extraction. Thus, to skip their isolation, the telescopic processes from **8** to **13** were explored. As a result, the through operations that covered the four functional group manipulations were established, which led to such a high overall throughputness.

Regioselective Introduction of the Phenylthio Group. Having built the *erythro* (2*S*,3*R*)-amino alcohol framework on the basis of the literature precedents, we moved on to installing the phenylthio group in the terminus closer to the amine function (Scheme 5).

When **13** was treated with calcium borohydride prepared in situ in methanol,[10] triol **14** was obtained in 72% yield. The applied reaction conditions were so mild that no epimerization was detected at all, judging from the ^{1}H NMR spectroscopy of **14**.

(4) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983.
(5) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
(6) (a) Dunigan, J.; Weigel, L. O. *J. Org. Chem.* **1991**, *56*, 6225. (b) Astleford, B. A.; Weigel, L. O. Resolution Versus Stereoselective Synthesis in Drug Development: Some Case Histories. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. : John Wiley & Sons Ltd.: Chichester, 1997; pp 99−117.
(7) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Organic Syntheses*; Wiley & Sons: New York, 1985; *63*, pp 127−135.
(8) For the enantiomeric series see: Manchand, P. S.; Luk, K.-C.; Belica, P. S.; Choudhry, S. C.; Wei, C. C.; Soukup, M. *J. Org. Chem.* **1988**, *53*, 5507.
(9) For the enantiomer of **13** see: Sendai, M.; Hashiguchi, S.; Tomimoto, M.; Kishimoto, S.; Matsuo, T.; Ochiai, M. *Chem. Pharm. Bull.* **1985**, *33*, 3798.
(10) (a) Kollonitsch, J.; Fuchs, O.; Gábor, V. *Nature* **1955**, *175*, 346. (b) Brown, E.; Robin J. P.; Dahl, R. *Tetrahedron* **1982**, *38*, 2599; **1989**, *45*, 1141.

Scheme 6. **Regioselective introduction of the chloride group**



To differentiate the two primary hydroxy groups, we opted to take advantage of the 1,2-diol functionality embedded in **14**. However, when it was subjected to the 1,3-dioxolane formation catalyzed by TsOH, bisacetal **15** was generated as a major product instead of the desired monoacetal **7**. Thus, to suppress such an overreaction, the acid catalyst was substituted with much milder pyridinium *p*-toluenesulfonate (PPTS). In fact, when an acetone solution of **14** was treated with a catalytic amount of PPTS, selective, single acetalization took place, giving **7** quantitatively.

The primary hydroxy group left unaffected in **7** was then mesylated under the usual conditions (MsCl, Et_3N, PhMe), and finally displaced in DMF by thiophenoxide which was prepared in situ from thiophenol and potassium carbonate to give **16a** in 79% overall yield from **7**.

Regioselective Introduction of the Chloride Functionality. Now that the acetonide protection in **16a** had served its role, it was removed by the acid-catalyzed methanolysis to give diol **16b** in 79% yield.[11] The stage was now set for the last functionalization maneuver to introduce the primary chloride group to **16b** (Scheme 6).

At first, we thought that **16b** would undergo regioselective *O*-tosylation and that the resulting tosylate could be displaced by chloride, whether it was the one generated internally or the one added externally. However, the regioselective monotosylation turned out to be more difficult in itself than had been expected, as it was always accompanied by ditosylation, even if *p*-toluenesulfonyl chloride was employed in a limited amount.

To introduce the chloride function to **16b** regioselectively, its 1,2-diol setting was exploited again. Thus, **16b** was treated with thionyl chloride in the presence of triethylamine to afford cyclic sulfite **16c**,[12] which was allowed to react with lithium chloride in DMF without further oxidative activation. Under these conditions, **16c** underwent regioselective nucleophilic displacement smoothly to provide **1** after the hydrolytic workup. Single recrystallization gave the final product **1** as colorless crystals in 70% yield from **16b**.

(11) Rieger, D. L. *J. Org. Chem.* **1997**, *62*, 8546.
(12) Lohray, B. B. *Synthesis* **1992**, 1035.

Conclusions

In summary, we have achieved the enantioselective synthesis of **1**, which highlights the following pragmatic features: (i) **1** was synthesized in a total of 14 steps and 17% overall yield from inexpensive sodium erythorbate **9**;[13] (ii) complete regio- and enantioselectivity were both achieved; (iii) no recourse was made to chromatographic purification throughout the synthesis; (iv) neither exotic reagents nor special equipment was necessary; (v) the through processes were established to circumvent isolation of both the highly water-soluble intermediates **12a** and **12b**; and (vi) the chloride functionality could be installed regioselectively by nucleophilic displacement on the cyclic sulfite **16c** without its further oxidative activation to the corresponding cyclic sulfate.

The manufacturing processes thus developed for the enantioselective synthesis of **1** were indeed practical enough to be viable on an industrial scale. However, the recent outbreak of an AIDS epidemic in developing countries has put anti-HIV drugs under severe price pressure[14] and made launching their new manufacturing processes less attractive. In addition to this circumstance, the structural complexity of **1** has frustrated its further development and commercial production.

Experimental Section

^{1}H NMR spectra were recorded at 400 MHz on a Varian UNITY-400 spectrometer for solutions in $CDCl_3$, CD_3OD, or D_2O with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. Mass spectra were recorded on a Hitachi M-8000 mass spectrometer (ESI). Elemental analyses were performed on an Elementar vario EL analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. Melting points (mps) were measured on an Electrothermal 1A8104 melting point apparatus and recorded without correction.

(2*R*,3*S*)-2-(*N*-Benzyloxycarbonyl)amino-3-hydroxy-4-butanolide (13). To a stirred and ice−salt-cooled solution of **8** (17.4 g, 132 mmol) in MeOH (20.0 mL) was added a solution of NaOH (5.80 g, 145 mmol) in MeOH (40.0 mL) dropwise over 45 min, during which yellow−white solids precipitated as the addition proceeded. After the heterogeneous mixture was stirred with ice-cooling for 6 h, diisopropyl ether (IPE, 240 mL) was added. The mixture was left to stand at −12 °C overnight, and the precipitated solids were collected by filtration, washed with IPE, and dried in vacuo at an oven temperature of 40 °C for 4 h to give sodium (*2S*,*3R*)-4-hydroxy-2,3-epoxybutanoate as off-white powders (18.73 g, quantitative): ^{1}H NMR (D_2O) δ 3.84−3.80 (m, 1H), 3.51−3.47 (m, 1H), 3.24 (dd, J = 2.0, 4.0 Hz, 1H), 3.12−3.08 (m, 1H). To a portion of it (10.34 g, 73.8 mmol) was added 28% aqueous solution of NH_3 (90 mL). The homogeneous mixture was stirred and heated at a bath temperature between 48 and 50 °C for 10 h. After the mixture

(13) For another related synthesis starting with D-tartaric acid see: Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349.
(14) McCoy, M. *Chem. Eng. News* **2001**, *79* (11) 13.

was allowed to cool to ambient temperature, the dark-red mixture was concentrated in vacuo to give crude **12a** as a syrupy residue. After H_2O (50 mL) was added, the mixture was concentrated in vacuo again to remove the residual NH_3. To the dark-red syrup of crude **12a** was added a solution of $NaHCO_3$ (4.30 g, 51.1 mmol) in H_2O (100 mL). The homogeneous mixture was stirred and ice-cooled, and CbzCl (95%, 13.2 g, 73.8 mmol) was added dropwise. After stirring at a temperature between 5 and 10 °C for 5 h, the mixture was washed with IPE (20 mL × 3) and PhMe−AcOEt (1:1; 20 mL × 3) to remove less polar, nonbasic impurities. The aqueous phase was concentrated in vacuo to distill off the organic volatiles. The residue was acidified to pH 3 with 2.0 M aqueous solution of HCl. To the aqueous solution of free acid **12b** thus obtained was added *p*-TsOH·H_2O (7.02 g, 36.9 mmol) at an ambient temperature. After stirring at ambient temperature overnight, the mixture was extracted with AcOEt (100 mL × 1, 30 mL × 2). The combined AcOEt extracts were washed with saturated aqueous Na_2CO_3 solution, and saturated aqueous NaCl solution (20 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **13** as off-white powders (11.7 g, 63.1% yield from **8**): mp 126−129 °C {lit. mp 128−131 °C};[9] $[\alpha]^{20}_D$ −35.5 (*c* 0.49, AcOEt) {lit. for the enantiomer of **8**: $[\alpha]^{20}_D$ +36.9 (*c* 0.5, AcOEt)};[9] ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 5H), 5.50−5.40 (m, 1H), 5.14 (s, 2H), 4.70−4.60 (m, 1H), 4.53−4.45(m, 1H), 4.40−4.30 (m, 2H), 2.88−2.70 (m, 1H). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. found: C, 57.30; H, 5.20; N, 5.40.

(2*S*,3*S*)-2-(*N*-Benzyloxycarbonyl)amino-1,3,4-butanetriol (14). To a stirred and water-cooled mixture of **13** (6.50 g, 25.9 mmol), $NaBH_4$ (3.91 g, 103 mmol) and MeOH (130 mL) was added $CaCl_2$ (5.74 g, 51.7 mmol) portionwise, during which the inner temperature was kept around 30 °C with cooling. After stirring at ambient temperature for 4 h, the mixture was ice-cooled, and its pH was adjusted to 2 by adding a 10% solution of HCl in MeOH. The mixture was concentrated in vacuo to give a syrupy residue. To this was added saturated aqueous NaCl solution (100 mL), and the mixture was extracted with AcOEt (200 mL × 2, 100 mL × 1). The combined AcOEt extracts were washed with saturated aqueous NaCl solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a pale-yellow solid (5.85 g), which was dissolved in AcOEt (24 mL) with heating at reflux. To the solution was added IPE (24 mL), and the mixture was allowed to cool to 5 °C. The precipitated solids were collected by filtration, and washed with IPE (12 mL) to give **14** as colorless powders (4.78 g, 72.3% yield): mp 126−129 °C; $[\alpha]^{20}_D$ +12.2 (*c* 1.00, MeOH); ^{1}H NMR (CD_3OD) δ 7.40−7.20 (m, 5H), 5.08 (s, 2H), 3.74−3.61 (m, 5H), 3.56−3.53 (m, 2H); MS *m*/*z* 354 {$[M - H]^+$}.

(1*S*,1′*S*)-4-[1′-(*N*-Benzyloxycarbonyl)amino-2′-hydroxyethyl]-2,2-dimethyl-1,3-dioxolane (7). To a stirred solution of **14** (11.9 g, 46.4 mmol) in acetone (178 mL) was added PPTS (1.17 g, 4.64 mmol) in one portion. After stirring at ambient temperature for 24 h, the solvent was evaporated off in vacuo to give a syrupy residue. This was dissolved in PhMe (300 mL), and the PhMe solution was washed with saturated aqueous NaCl solution (100 mL), 1% aqueous HCl solution (100 mL), 10% aqueous $NaHCO_3$ solution (100 mL), and saturated aqueous NaCl solution (100 mL). The PhMe solution was then dried ($MgSO_4$) and concentrated in vacuo to give crude **7** as a colorless syrup (13.7 g, 99.9% yield): ^{1}H NMR ($CDCl_3$) δ 7.36−7.26 (m, 5H), 5.38 (br d, J = 4.0 Hz, 1H), 5.13−5.07 (m, 2H), 4.30−4.20 (m, 1H), 4.10−4.00 (m, 1H), 3.90−3.80 (m, 2H), 3.75−3.60 (m, 2H) 2.42 (br s, 1H), 1.42 (s, 3H), 1.34 (s, 3H). This was employed in the next step without further purification.

(1*S*,1′*R*)-4-[1′-(*N*-Benzyloxycarbonyl)amino-2′-phenylthioethyl]-2,2-dimethyl-1,3-dioxolane (16a). To a stirred and ice-cooled solution of **7** (11.2 g, 37.9 mmol) and Et_3N (7.92 mL, *d*0.728, 56.9 mmol) in PhMe (80 mL) was added MsCl (3.52 mL, *d*1.48, 45.5 mL) dropwise at a temperature between 5 and 10 °C. After stirring at ambient temperature for 2 h, the reaction mixture was diluted with PhMe (50 mL) and AcOEt (100 mL). The mixture was washed with H_2O (50 mL), an aqueous solution of 0.5 M citric acid (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and saturated aqueous NaCl solution (50 mL). The mixture was then dried ($MgSO_4$) and concentrated in vacuo to give a white solid (15.1 g). This was dissolved in DMF (100 mL), and K_2CO_3 (10.47 g, 75.8 mmol) was added. The resulting heterogeneous mixture was cooled to 10 °C, and PhSH (3.89 mL, *d*1.073, 37.9 mmol) was added dropwise. After the mixture was stirred at ambient temperature for 4 h, PhMe (200 mL) was added. The mixture was washed with H_2O (100 mL), saturated aqueous K_2CO_3 solution (50 mL), saturated aqueous NaCl solution (50 mL), an aqueous solution of 0.5 M citric acid (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and saturated aqueous NaCl solution (50 mL). The washed mixture was dried ($MgSO_4$) and concentrated in vacuo to give crude **16a** as a white solid (13.9 g, 94.6% yield): mp 115−118 °C; $[\alpha]^{20}_D$ −70.7 (*c* 1.00, MeOH); ^{1}H NMR δ ($CDCl_3$) 7.40−7.10(m, 10H), 5.13−5.05 (m, 2H), 5.03−4.97 (m, 1H) 4.20−4.10 (m, 1H), 4.10−4.00 (m,1H), 3.90−3.60 (m, 2H), 3.30−3.18 (m, 2H), 1.39 (s, 3H), 1.28 (s, 3H); MS *m*/*z* 386 {$[M - H]^+$}, 370 {$[M - H_2O + H]^+$}. This was employed in the next step without further purification.

(2*S*,3*R*)-3-(*N*-Benzyloxycarbonyl)amino-4-phenylthio-1,2-butanediol (16b). To a stirred solution of **16a** (15.2 g, 39.1 mmol) in MeOH (120 mL) was added an aqueous 0.1 M HCl solution (32 mL). After the stirring was continued with heating at 80 °C for 1.5 h, the mixture was concentrated in vacuo. To the residue were added saturated aqueous $NaHCO_3$ solution (100 mL) and H_2O (50 mL). The mixture was extracted with AcOEt (250 mL × 1, 100 mL × 1). The combined AcOEt extracts were washed with saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a solid residue (13.1 g). This was suspended in AcOEt (65 mL), and the stirred mixture was heated to a refluxing temperature, where part of the solids still remained not dissolved. The heterogeneous mixture was allowed to cool to ambient temperature, during which *n*-hexane (40 mL) was added. After the mixture was cooled to 5 °C, the precipitated solids were collected by filtration, washed with *n*-hexane (40 mL), air-dried at an oven

temperature of 50 °C overnight to give **16b** as white powders (10.7 g, 78.7% yield): mp 126−129 °C; $[\alpha]^{20}_{D}$ −81.4 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (m, 10H), 5.22−5.18 (m, 1H), 5.12−5.08 (m, 2H), 3.90−3.80 (m, 1H), 3.67−3.60 (m, 2H), 3.53−3.47 (m, 1H), 3.39−3.22 (m, 2H), 3.18−3.14 (m, 1H), 2.68 (d, J = 8.8 Hz, 1H); MS *m*/*z* 348 $\{[M + H]^+\}$.

(2*S*,3*R*)-3-(*N*-Benzyloxycarbonyl)amino-1-chloro-4-phenylthiobutan-2-ol (1). To a stirred and ice-cooled suspension of **16b** (0.50 g, 1.44 mmol) in CH_2Cl_2 (10.0 mL) were added dropwise $SOCl_2$ (0.27 mL, *d*1.66, 3.74 mmol) and Et_3N (0.80 mL, *d*0.728, 5.76 mmol) in sequence. The heterogeneous mixture was stirred at ambient temperature for 10 min, and concentrated in vacuo to give crude **16c** as a brown oil (0.58 g, quantitative): IR (film) ν 3325, 3013, 1718, 1702, 1542, 1522, 1508, 1210, 1020, 891, 743 cm^{-1}. This was dissolved in DMF (10 mL), and LiCl (244 mg, 5.76 mmol) was added in one portion. After the stirring was continued with heating at 80 °C for 1.5 h, the mixture was acidified with an aqueous 2.0 M HCl solution (40 mL), and extracted with AcOEt (30 mL). The AcOEt extract was washed with saturated aqueous NaCl solution (30 mL × 3), dried ($MgSO_4$), treated with activated charcoal, and concentrated in vacuo to give crude **1** (0.52 g) as a brown solid. To this was added AcOEt (5.0 mL), and the mixture was stirred and heated at reflux until it became homogeneous. The resulting solution was allowed to cool to ambient temperature, during which *n*-hexane (5.0 mL) was added to induce recrystallization. After the heterogeneous mixture was cooled to 5 °C, the precipitated solids were collected by filtration, washed with *n*-hexane (5.0 mL), and air-dried with heating at an oven temperature of 50 °C to give a first crop of **1** (0.24 g) as white powder. The combined filtrate and washing were concentrated in vacuo to give a solid residue, which was recrystallized from AcOEt (3.0 mL) and *n*-hexane (5.0 mL) in the same manner as described above to give a second crop of **1** (0.13 g) as white powder: a total yield of 0.37 g (70.3%); mp 113−114 °C; $[\alpha]^{20}_{D}$ −73.4 (*c* 0.96, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (m, 10H), 5.26−5.17 (m, 1H), 5.05 (br s, 2H), 3.98−3.88 (m, 2H), 3.70−3.54 (m, 2H), 3.28 (d, J = 4.0 Hz, 2H), 2.92 (m, 1H); MS *m*/*z* 330 $\{[M - Cl]^+\}$.

Acknowledgment

M.I. thanks Mr. Masafumi Moriwaki, Director of Research and Development Center, Nagase & Co., Ltd. for his consistent encouragement throughout this synthetic program.

Received for review September 5, 2001.

OP010073I