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An Improved Large Scale Synthesis of the Schöllkopf Chiral Auxiliaries: (2*R*)- and (2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine

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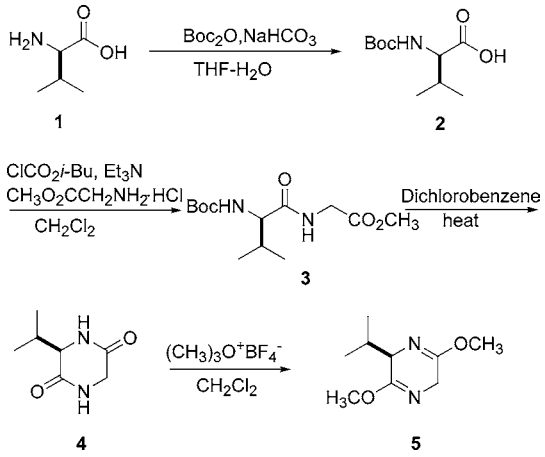
Abstract:

Syntheses of the Schöllkopf chiral auxiliaries have been carried out on large scale in high overall yields from D- and L-valine. This method avoids the use of highly toxic phosgene or triphosgene, low-temperature reactions, and unstable intermediates.

Introduction

Preparation of nonproteinogenic α-amino acids has received attention for decades[1] due to their importance in the medicinal and biotechnology fields.[2] Since the optical purity of α-amino acids is important for molecular recognition and biological activity, highly enantioselective methodologies for the preparation of α-amino acids have been sought. A variety of methods has been reported for the asymmetric preparation of nonproteinogenic α-amino acids.[1] Several methods have relied on diastereoselective alkylation of a masked glycine,[3,4] controlled by an attached homochiral fragment. Schöllkopf introduced his bis-lactim ether methodology in 1981,[3] and this protocol was demonstrated to be extremely successful for the preparation of α-amino acids.[5] Syntheses of the Schöllkopf ethers have been reported in the literature.[6] Although these synthetic procedures seem straightforward transformations, they have drawbacks on the large scale preparation: (1) the use of highly toxic phosgene or triphosgene; (2) requirement of the low temperature (≤−70 °C) reaction to minimize polymerization of the thermally unstable methyl *N*-valyl glycinate; (3) extensive purification of 3,6-piperazinedione; (4) requirement of freshly prepared alkylating reagent for the last step. We now report an improved synthesis for the large scale preparation of Schöllkopf chiral auxiliary, which avoids many of these problems.

Scheme 1



Results and Discussion

Our synthetic strategy is outlined in Scheme 1. D-Valine (**1**) was converted to Boc-D-valine (**2**)[7] in quantitative yield on kilogram scale. Intermediate **2** was treated with isobutyl chloroformate and triethylamine at 0−5 °C for 0.5 h followed by addition of a mixture of glycine methyl ester hydrochloride and triethylamine in dichloromethane, and the resulting mixture was stirred at room temperature for 16 h to afford the Boc-protected dipeptide **3**, isolated in excellent yield as a stable, crystalline solid at room temperature. Although cyclization of the unprotected dipeptide proceeding in toluene at reflux temperature has been reported by Davies and Cook,[6] preparation of the unprotected dipeptide was carried out at low temperature (≤−70 °C) to minimize polymerization, and purification of the cyclization product was tedious and its quality is crucial for the methylation. Cledera et al.[8] reported quantitative yield for the gram scale preparation of 3,6-piperazinedione **4** by heating dipeptide **3** neat at 200 °C. Under these conditions the yield decreased dramatically at a 40 g scale.[9] As a result, we decided to investigate the thermal cyclization of dipeptide **3** in the presence of an inert solvent (Table 1).

As illustrated in Table 1, when the reaction was carried out in toluene or xylene, the conversion of dipeptide **3** to

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(6) Bull, S. D.; Davies, S. G.; Moss, W. O. *Tetrahedron: Asymmetry* **1998**, *9*, 321 and references therein. Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu. S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.

(7) Both Boc-D-valine and Boc-L-valine are commercially available.

(8) Cledera, P.; Avendaño, C.; Menéndea, J. C.*Tetrahedron* **1998**, *54*, 12349.

(9) Intermediate **4** was obtained in 45% yield when the reaction was carried out on 40 g scale.

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Table 1. **Cyclization of dipeptide 3 to 4**

solvent	temp, °C	time, h	yield, %
toluene	110	16	37
xylene	138	20	37
ethylene glycol	200	2	48
diphenyl ether	210	2	32
1,2-dichlorobenzene	180	20	69

3,6-piperazinedione **4** was low. While no starting material remained after 2 h at 200 °C when the reaction was run in ethylene glycol or diphenyl ether, the isolated yields of 3,6-piperazinedione **4** were moderate. 1,2-Dichlorobenzene was found to be the best solvent for the cyclization as the product has low solubility in this solvent. It was essential to remove methanol formed during the reaction in order to achieve a high yield. When the reaction was complete, about two-thirds of the solvent was removed by distillation; *tert*-butyl methyl ether was carefully added at 50 °C to precipitate any 3,6-piperazinedione **4** remaining in solution. Solvent free **4** was easily obtained after filtration and drying under vacuum.

Davies[6] found that a high yield in the methylation of **4** could only be achieved by using freshly prepared trimethyloxonium tetrafluoroborate and completely solvent-free 3,6-piperazinedione **4**. When the methylation was carried out using **4** that was prepared as described above and commercial trimethyloxonium tetrafluoroborate in dichloromethane at ambient temperature, (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**5**) was isolated in 85% yield after vacuum distillation. The workup of this reaction was improved by the use of aqueous sodium hydroxide to adjust the pH to 8−9 rather than using sodium bicarbonate as in the original procedure; the latter requires such an excess of sodium bicarbonate that unstirrable mixtures resulted upon scale-up. The product by GC−MS analysis was typically >96% pure; the only impurities detected were the ethyl analogues, (2*R*)-2,5-dihydro-3-ethoxy-6-methoxy-2-isopropypiperazine and (2*R*)-2,5-dihydro-6-ethoxy-3-methoxy-2-isopropypiperazine, resulting from an impurity of triethyloxonium tetrafluoroborate present in the commercial trimethyloxonium tetrafluoroborate. However, the presence of these impurities has no detrimental effect on the use of **5** for the synthesis of chiral amino acids.

The suitability of this process to the synthesis of the Schöllkopf ether was confirmed by a similar synthesis of the enantiomer (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine in 46% overall yield from 200 g of L-valine.

Conclusions

The synthesis of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, one of the Schöllkopf bis-lactim ether chiral auxiliaries, was carried out successfully on 125 g scale in 53% yield over four steps. This method avoided using highly toxic phosgene or triphosgene. No exceptional purification was required for all intermediates and reagents. The cyclization product was easily isolated from 1,2-dichlorobenzene as the reaction solvent on a large scale. The commercial trimethyloxonium tetrafluoroborate was used in the alkylation without further purification. The workup on the last step was simplified by switching from sodium bicarbonate to sodium hydroxide to adjust the pH of the reaction mixture. The process is easy to execute and scale-up. The synthesis was also applied successfully to preparation of (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine.

Experimental Section

Reagents and solvents were used as received from commercial suppliers. D-Valine was purchased from Alfa Aesar (98%). Trimethyloxonium tetrafluoroborate was received from Aldrich. Thin-layer chromatography (TLC) was performed using Analtech silica gel plates 60 F_{254} and visualized by UV light at 254 nm or Hanessian stain. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance-300 spectrometer at 300 and 75 MHz, respectively. GC and GC/MS analyses were performed using a Hewlett-Packard G1800A-GCD gas chromatograph using HP-5MS column, 30 m × 0.25 mm × 0.25 μm. Carrier gas, He, 1 mL/min; injection temperature, 150 °C; column temperature, 100 °C (2 min) → 20 °C/min → 300 °C (5 min); detection, EID at 280 °C. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. Enantiomeric excess was determined by Agilent 100 series HPLC on a Chiralcel OD-H column, 250 mm × 4.6 mm. Solvents, 2:98 2-propanol/heptane; flow rate, 0.5 mL/min; wavelength, 210 nm; t_R 7.3 min for (*S*)-isomer and 7.9 min for (*R*)-isomer. GC and HPLC analyses are reported in area %.

Preparation of *N*-(*tert*-Butoxycarbonyl)-D-valine (2). $NaHCO_3$ (717 g, 8.53 mol) was added to a solution of D-valine (**1**) (500 g, 4.27 mol) in water (6.4 L) followed by a solution of di-*tert*-butyl dicarbonate (932 g) in THF (6.4 L). The mixture was stirred and heated under reflux for 16 h and then concentrated under vacuum to remove THF. EtOAc (4.5 L) was added, and the mixture was cooled to 10 °C and then adjusted to pH 3 with saturated aqueous $NaHSO_4$ (3.3 L). The layers were separated, and the aqueous layer was extracted with EtOAc (4 L). The combined EtOAc layers were washed with water (2 L) and brine (2 L), dried over $MgSO_4$, and concentrated under vacuum to give **2** (924 g, 99%). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.8 Hz), 1.41 (s, 9H), 2.18 (m, 1H), 5.04 (m, 1H), 6.28 (d, 1H, J = 7.4 Hz), 11.53 (br s, 1H).

Preparation of Methyl *N*-(*tert*-Butoxycarbonyl)-D-valyl Glycinate (3). Isobutyl chloroformate (580 g, 4.25 mol) was added over 30 min to a stirred mixture of **2** (924 g, 4.25 mol) and Et_3N (430 g, 4.25 mol) in CH_2Cl_2 (12.3 L) at 5 °C. When the addition was complete, the mixture was stirred at 0−5 °C for 30 min. In a separate flask, a mixture of glycine methyl ester hydrochloride (534 g, 4.25 mol), Et_3N (430 g, 4.25 mol), and CH_2Cl_2 (12.3 L) was stirred for 30 min and this mixture was then added to the flask containing **2** over 2 h. After the addition was complete, the mixture was stirred at room temperature for 16 h and then washed with water (3 × 15 L) and brine (5 L), dried, and concentrated under vacuum to give **3** (1118 g, 91%). ^{1}H NMR ($CDCl_3$): δ 0.94 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz), 1.40 (s, 9H), 2.18 (m, 1H), 3.75 (s, 3H), 3.94−4.07 (m, 3H), 5.09 (br s, 1H), 6.62 (br s, 1H).

Preparation of (2*R*)-Isopropylpiperazine-3,6-dione (4). A solution of **3** (999 g, 3.46 mol) in 1,2-dichlorobenzene (9 L) was heated at 175−180 °C for 18 h, allowing any MeOH formed to be removed by distillation. After removal of 6 L of the solvent by distillation at atmospheric pressure with the aid of a stream of nitrogen, the mixture was cooled to 50 °C and MTBE (5 L) was added cautiously. The mixture was cooled to room temperature and filtered. The resulting solid was washed with MTBE (200 mL) and dried under vacuum at 100 °C to give **4** (372 g, 69%). ^{1}H NMR (DMSO-d_6): δ 0.84 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz), 2.10 (m, 1H), 3.51 (m, 1H), 3.61 and 3.81 (AB, 2H, J = 17.7 Hz), 8.01 (s, 1H), 8.20 (s, 1H).

Preparation of (2*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine (5). To a mixture of **4** (135 g, 0.86 mol) and trimethyloxonium tetrafluoroborate (450 g, 3.07 mol) was added CH_2Cl_2 (2 L) at room temperature. The mixture was stirred at room temperature for 84 h. The resulting solid was collected by filtration under nitrogen and washed with CH_2Cl_2 (300 mL). The solid was added in portions to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (3 L) and CH_2Cl_2 (2 L) at 4 °C, while maintaining the pH between 8 and 9 by the simultaneous addition of 3 M aqueous NaOH as required. The mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic phases were washed with brine (500 mL), dried, and concentrated under vacuum. The pale yellow residual oil (93% pure by GC-MS) was purified by vacuum distillation (bp 72 °C/4.5 Torr) to give **5** (134.6 g, 85%, 96% ee) as a colorless oil. $[\alpha]^{25}_D = -106.6°$ (c = 1.0, EtOH), [lit.[10] $[\alpha]^{23}_D = -108 \pm 5°$ (c = 1.0, EtOH), lit.[3] $[\alpha]^{23}_D = +106.3°$ (c = 1.0, EtOH) for its enantiomer]. ^{1}H NMR ($CDCl_3$): δ 0.77 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz), 2.33 (m, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.90 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 17.25, 19.30, 32.70, 46.88, 52.66, 52.71, 61.34, 162.60, 165.09. MS: m/z 184 (M^+). The purity of the product was 98% by GC−MS, and the remaining 2% was the mixture of (2*R*)-2,5-dihydro-3-ethoxy-6-methoxy-2-isopropypiperazine and (2*R*)-2,5-dihydro-6-ethoxy-3-methoxy-2-isopropypiperazine.

(10) *Laboratory Chemicals and Analytical Reagents*; Fluka: 2001/2002; p 508.

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