Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 43–46

TETRAHEDRON: *ASYMMETRY*

A convenient method for synthesis of *trans*-4-cyclohexyl-L-proline

Xiao Chen, Da-Ming Du and Wen-Ting Hua*

The key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry & Molecular Engineering, Peking University, Beijing 100871, PR China

Received 19 December 2001; accepted 31 January 2002

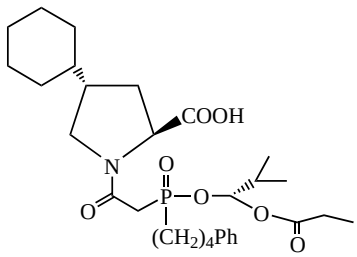
Abstract—A convenient method for the synthesis of the fosinopril precursor, *trans*-4-cyclohexyl-L-proline **1**, has been developed. A highly stereoselective alkylation of *N*-benzyl-pyroglutamic acid **2** with 3-bromocyclohexene at −10°C and subsequent hydrogenolysis afforded the *trans*-4-cyclohexyl-L-pyroglutamic acid **4**. The esterified **4** was sulfurized with Lawesson's reagent, desulfurized with Raney-Ni and hydrogenolytic cleavage of the benzyl protecting groups to afford **1** with 93% e.e.

1. Introduction

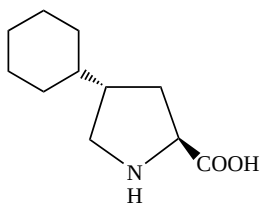
Various proline derivatives including 4-alkyl-substituted prolines are now widely used as chiral intermediates for the synthesis of drugs,[1–3] unnatural amino acids[4–7] and some proline-containing natural products.[8,9] For this reason, the study of synthetic methods and the stereochemistry of substituted L-prolines has attracted much attention in many fields. The target molecule we are studying is *trans*-4-cyclohexyl-L-proline **1**, which is a key structural moiety of fosinopril. The latter is a new inhibitor of angiotensin converting enzyme (ACE) for the treatment of hypertension and congestive heart failure. Although the structure of compound **1** is apparently simple, its synthesis is not trivial.

We report herein a practical route for the manufacture of **1** from an inexpensive raw material avoiding low temperature and high-pressure conditions, in a synthetic route which can be explored for large-scale throughput. This synthetic route is illustrated in Scheme 1.

In this synthesis, *N*-benzyl-L-pyroglutamic acid, prepared from L-glutamic acid according to the literature procedures,[10,11] was used as a chiral starting material. It was discovered that compound **2** having an unprotected carboxyl group could be stereoselectively alkylated at C(4) with 3-bromocyclohexene in the presence of two equivalents of LiHMDS without formation of the C(2)-alkylated product, whereas the esterified **2** gave the unwanted C(2)-alkylated side product, which was consistent with the result in the literature.[12] As a result, *trans*-4-cyclohexenyl-*N*-benzyl-L-proline was obtained successfully at −10°C as the major product. The stereochemistry of the *trans*-isomer at C(4) was determined by comparison of the specific rotation of compound **1** with that reported in the literature.[3] We assume that a



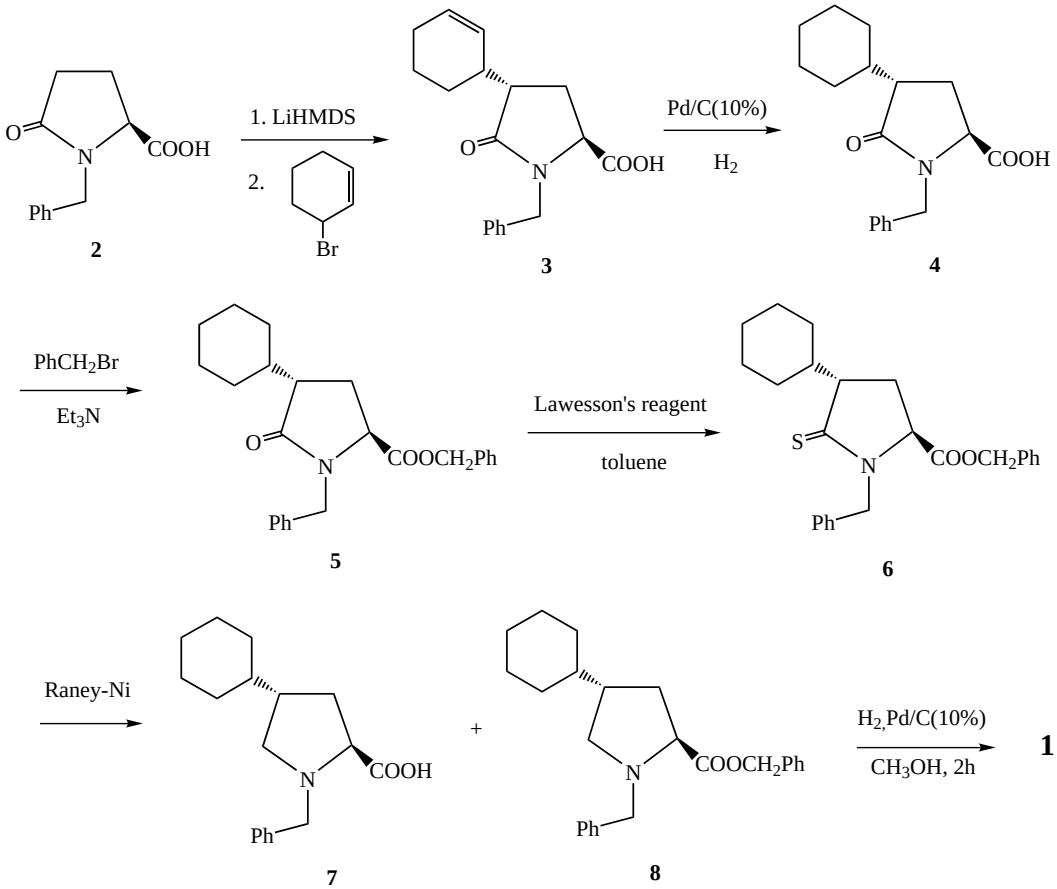
Fosinopril



1

* Corresponding author. Tel.: 86-10-62756568; fax: 86-10-62751708; e-mail: huawt@pku.edu.cn

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00052-6

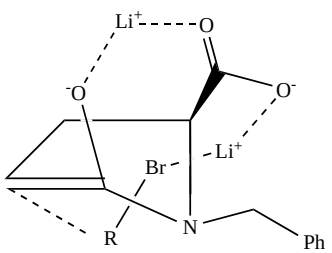


Scheme 1.

dilithium complex such as that shown in Scheme 2 is formed in the reaction.[4a]

Based on the structure of the lithium complex suggested above, approach of 3-bromohexene to the C(4) enolate can occur only from the direction opposite to the carboxyl group at C(2). Consequently, *trans*-**4** predominated heavily (*trans*:*cis* ratio of 18:1 by HPLC analysis).

Chemoselective reduction of the lactam group of **5** leaving the carboxyl group in place presents another difficulty in the synthesis of **1**. Several reducing agents have been used to reduce the lactam.[13] However, because the carboxylic acid is generally reduced more easily, most of them (e.g. BH_3, $NaBH_4$, $POCl_3$–$NaBH_4$ and $Et_3O^+BF_4^-$–$NaBH_4$) effect reduction of the carboxyl group while the lactam remains intact.[14] When $LiAlH_4$ was used to reduce both carboxylic acid and lactam groups, it was necessary to oxidize the resulting hydroxymethyl group back to the carboxyl group in a later step.[3]



Scheme 2.

In this study, the reduction was successfully achieved in two steps via *O*-sulfurization of the lactam using Lawesson's reagent and subsequent reductive desulfurization, a protocol which leaves the ester group intact. Reductive desulfurization of thiolactam **6** was effected by treatment with Raney-Ni in refluxing alcohol over 1.5 h to produce compounds **7** and **8** together in good yields. Raney-Ni (made from nickel–aluminium alloy treated with NaOH) is an inexpensive and readily available reducing agent which can be used for manufacture on a large scale.[15] The mixture of **7** and **8** could be successfully hydrogenated with Pd–C in the next step without further purification, thus *trans*-4-cyclohexyl-L-proline **1** was obtained in good yield from this straightforward synthesis.

2. Experimental

Generally, all melting points were determined on a XT-4 melting point apparatus and are uncorrected. IR spectra were recorded on a Vector 22 spectrometer. Mass spectra were determined on VG-ZAB-HS mass

spectrometer. ^{1}H NMR spectra were recorded on a Bruker ARX 400 NMR spectrometer. Chemical shifts are indicated in δ units (ppm) relative to TMS. Elemental analysis was carried out on Elementar Vario El. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. HPLC was performed on HP1100. THF was distilled under nitrogen from sodium. HMDS was dried with calcium hydroxide.

2.1. Synthesis of *trans*-4-cyclohexyl-*N*-benzyl-L-pyroglutamic acid 4

To a solution of hexamethyldisilazane (HMDS, 28 mL, 134 mmol) in dry THF (40 mL) was added *n*-butyllithium (69 mL, 134 mmol) dropwise under nitrogen at −10°C. After stirring the mixture for 30 min, *N*-benzyl-L-pyroglutamic acid **2** (14.2 g, 65 mmol) in THF (45 mL) was added and the stirring was continued for 1 h. 3-Bromocyclohexene (6.8 mL, 65 mmol) in THF (10 mL) was added and the mixture was stirred at −10°C for 2 h then stirred for a further 2 h at room temperature. The reaction mixture was quenched by addition of 2N aqueous HCl (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The crude product was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether = 1:1) to give viscous oil **3** (19 g).

The product **3** (19 g) was dissolved in ethyl acetate (120 mL) and hydrogenated in the presence of 10% Pd/C (1.9 g) at room temperature under 1 atm hydrogen pressure for 2 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate to afford **4** as a white solid (10.2 g, 52% from **2**): mp 167–168°C; $[\alpha]_D^{20} = +77.9$ ($c = 1$, $CHCl_3$); IR (KBr): 3452, 2913, 2848, 1733, 1652, 1441 cm^{-1}; ^{1}H NMR (CD_3OD): δ 1.20–2.32 (10H, m, CH_2), 1.71–1.75 (1H, d, $J = 8$ Hz, CH), 2.05–2.11 (2H, q, $J = 10.7$ Hz, CH_2), 2.65–2.67 (1H, m, CH), 3.86–4.18 (2H, m, $PhCH_2$), 5.17–5.25 (1H, d, $J = 15.2$ Hz, CH), 7.17–7.37 (5H, m, ArH), 9.8–10.3 (1H, s, COOH). FABMS: m/z 302 (M+1, 100), 219 (M–C_6H_{11}, 18); anal. calcd for $C_{18}H_{23}NO_3$: C, 71.76; H, 7.67; N, 4.65. Found: C, 71.61; H, 7.62; N, 4.54%.

The determination of the diastereomeric ratio of **4** was completed by HPLC (ZORBAX Extend-C18 column, elution with acetonitrile:water = 75:25, 1 mL/min, 220 nm).

2.2. Synthesis of the benzyl *trans*-4-cyclohexyl-5-thio-*N*-benzyl-L-pyroglutamate 6

To a solution of **4** (3.13 g, 10.4 mmol) in dry THF (45 mL) was added triethylamine (1.59 mL, 11.4 mmol) and benzyl bromide (1.31 mL, 10.86 mmol). After heating under reflux for 6 h, the mixture was cooled, filtered and then concentrated. The residue was extracted with chloroform (3×40 mL), washed successively with saturated aqueous sodium bicarbonate (30 mL) and brine (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **5** as a light yellow oil (4.1 g). The compound **5** obtained above was dissolved in dry toluene (10 mL) and reacted with Lawesson's reagent (2.1 g, 5.2 mmol) at 100°C for 5 h. The mixture was concentrated under vacuum, purified by silica gel column chromatography with methylene dichloride/petroleum ether (1:1) and recrystallized from ethanol to give **6** (2.96 g, 69% from **4**) as a light yellow solid: mp 46–47°C; $[\alpha]_D^{20} = +142.8$ ($c = 1.31$, chloroform); IR (KBr): 2925, 2852, 1743, 1645, 1476, 1423, 1191 cm^{-1}; FABMS: m/z 408 (M+1, 10); ^{1}H NMR (CD_3OD): δ 1.15–1.52 (10H, m, CH_2), 1.67–1.73 (2H, m, CH_2), 2.11–2.15 (1H, m, CH), 3.01 (1H, m, CH), 4.17–4.25 (2H, m, NCH_2Ph), 5.13 (2H, s, OCH_2Ph), 5.86–5.93 (1H, d, $J = 14.8$ Hz, CH), 7.14–7.43 (10H, m, ArH). Anal. calcd for $C_{25}H_{29}O_2SN$: C, 73.67; H, 7.17; N, 3.43; S, 7.86. Found: C, 73.53; H, 7.16; N, 3.54; S, 7.79%.

2.3. Synthesis of the *trans*-4-cyclohexyl-L-proline 1

To a solution of **6** (2.96 g, 7.25 mmol) in 95% ethanol (60 mL) was added Raney-Ni (6 g). After heating under reflux for 1.5 h, the reaction mixture was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure to obtain **7** and **8** (total 2.2 g), which was used in the next step without further separation.

The obtained intermediates **7** and **8** (2.2 g), 10% Pd/C (0.22 g), anhyd. methanol (45 mL) and glacial acetic acid (5 mL) were added to a high-pressure reactor. This mixture was hydrogenated under 20 atm hydrogen pressure at 50°C for 2 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure to obtain a white solid, which was recrystallized from methanol–ethyl acetate to afford pure **1** (0.5 g, 35% from **6**): mp 230°C; $[\alpha]_D^{20} = -33.8$ ($c = 0.42$, CH_3COOH), ee% = 93%; IR (KBr): 3422, 3111, 2926, 2849, 1623, 1448, 1384, 1288 cm^{-1}; FABMS: m/z 198 (M+1, 100), 152 (M−COOH); ^{1}H NMR (CD_3OD): δ 1.00–1.07 (2H, m, CH_2), 1.23–1.28 (4H, m, CH_2), 1.68–1.78 (6H, m, CH_2), 1.92–1.95 (2H, m, CH_2), 2.28–2.48 (1H, m, CH), 2.86 (1H, t, $J = 10.9$ Hz, CH), 3.55–3.58 (1H, m, CH), 4.02–4.05 (1H, t, NH). Anal. calcd for $C_{11}H_{19}O_2N$–$0.5H_2O$: C, 64.05; H, 9.77; N, 6.79. Found: C, 63.98; H, 9.74; N, 6.65%.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 20172001, 29872023).

References

1. Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; Deforrest, J. M.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148–1160.
2. Chen, Y. T.; Hua, W. T. *Chemistry* **1999**, *1*, 1–6.

3. Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140–3143.
4. (a) Charrier, J.-D.; Duffy, J. E. S.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1998**, *39*, 2199–2202; (b) Brana, M. F.; Garranz, M.; Perez-Castells, J. *Tetrahedron Lett.* **1998**, *39*, 6569–6572; (c) Dikshit, D. K.; Maheshwari, A. *Tetrahedron Lett.* **1999**, *40*, 4411–4412.
5. Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71–77.
6. Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwe, D. *Tetrahedron* **1998**, *54*, 1753–1762.
7. Bowler, A. N.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W. *Tetrahedron* **1997**, *53*, 10545–10548.
8. Langlois, N.; Rakotondradang, F. *Tetrahedron* **2000**, *56*, 2437–2448.
9. Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553–2556.
10. Quitt, Von P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327.
11. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.
12. (a) Baldwin, J. E.; Miranda, T.; Moloney, M. G.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459–7468; (b) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665–8678.
13. Chen, X.; Hua, W. T. *Chemistry* **2001**, *12*, 749–754.
14. (a) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061–4064; (b) Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920–1924; (c) Jabre, I.; Thuillir, A. *J. Chem. Res. (s)* **1990**, 106–107.
15. (a) Mozingo, R. *Org. Synth.* **1955**, Coll. Vol. 3, 181–183; (b) Petitt, G. R.; Tamelen, E. E. V. *Org. React.* **1962**, *12*, 356–529.