The preparation of (*S*)-3,4-dehydroproline from (2*S*,4*R*)-4-hydroxyproline

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(2*S*,4*R*)-*N*-Benzyloxycarbonyl-4-tosyloxyproline methyl ester, readily prepared from commercially available (2*S*,4*R*)-*N*-benzyloxycarbonyl-4-hydroxyproline, was converted to (*S*)-3,4-dehydroproline of high enantiomeric purity by a process which involved a highly regioselective phenylselenoxide elimination to introduce the olefinic function.

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On a transformé l'ester méthylique de la *N*-benzyloxycarbonyltosyloxy-4 proline (2*S*,4*R*), provenant de la *N*-benzyloxycarbonylhydroxy-4 proline disponible commercialement, en déhydro-3,4 proline (*S*) d'une grande pureté énantiométrique. On a introduit la fonction oléfinique en utilisant une méthode qui fait intervenir une élimination très régiosélective par le sélénate de phényle.

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Seventy years ago Fischer and Gerlach (1) reported that the reduction of pyrrole-2-carboxamide with phosphonium iodide and fuming hydriodic acid yielded a product which they thought to be (±)-3,4-dehydroproline. Fifty years then passed until Robertson and Witkop (2) proved that, under carefully controlled conditions, this imino acid is indeed a product of the reaction.

Robertson and Witkop (2) obtained (*S*)-3,4-dehydroproline (**1**) of good optical purity by the action of hog acylase on (±)-3,4-dehydroproline amide, and provided the first report of its biological properties: saying *inter alia* that colleagues had found **1** to be a potent antimetabolite for some microorganisms, apparently as a consequence of its ability to act as an antagonist for (*S*)-proline. Subsequently, it has been shown (3) that **1** inhibits collagen synthesis in some mammalian cells, and that its introduction into peptides in lieu of (*S*)-proline can result (4) in modified biological properties, though not necessarily so (5).

Interest in the biological properties of **1** seems to have stimulated efforts to improve its availability. Various improvements in the Fischer–Witkop approach have been reported (5*b*, 6), culminating in those of Scott *et al.* (7).

As an alternative to these approaches, which require the resolution of racemic products, we were interested in preparing **1** from (2*S*,4*R*)-4-hydroxyproline (**2**). Although Robertson and Witkop (2) had noted that extensive efforts to convert 4-hydroxyproline to 3,4-dehydroproline had met with little success, it appeared to us that recent developments in synthetic methodology were encouraging: we were particularly impressed by the reported high-yield conversion of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxyproline methyl ester via a Chugaev elimination (8), and thought that a selenoxide elimination might be even more regioselective in introducing the required 3-ene, i.e. we hoped that the sequence of reactions shown in Scheme 1 would provide a convenient route to (*S*)-3,4-dehydroproline.

We were guided in this plan by reports that selenoxide eliminations which could yield an olefin with or without oxygen (9) or sulphur (10) as a heteroatom substituent strongly favoured formation of the unsubstituted olefin. After we had completed our work, a publication describing the similar directive effects of amido groups appeared (11). We selected trimethylsilyl iodide for the final N-deblocking and ester cleavage reactions since it was known to effect these reactions under mild conditions (12), which an alkene survived (13).

As detailed in the Experimental section, these hopes were fulfilled: crystalline (*S*)-dehydroproline was obtained from the commercially available **3**, in 50% yield, with an optical rotation in accord with that reported for the enantiomerically pure amino acid.

Experimental

Melting points were determined on a Leitz microscope hotstage melting point apparatus, and are uncorrected. The nmr data were collected on a Varian XL 200 instrument and chemical shifts are reported in parts per million relative to tetramethylsilane. In the case of the ^{13}C nmr spectrum of **1** the shifts are reported using 1,4-dioxane as an internal standard (δ = 66.6 ppm from TMS). Infrared spectra were recorded on a Perkin–Elmer 467 grating infrared spectrophotometer. Mass spectra were measured on a Varian MAT CH-5 spectrometer (*m*/*z* (relative intensity)) at 70 eV. The cd spectra were recorded with a Jasco J-500A instrument, $[\alpha]_D$ values with a Durrum–Jasco SS-20 machine. Combustion analyses were performed on a Perkin–

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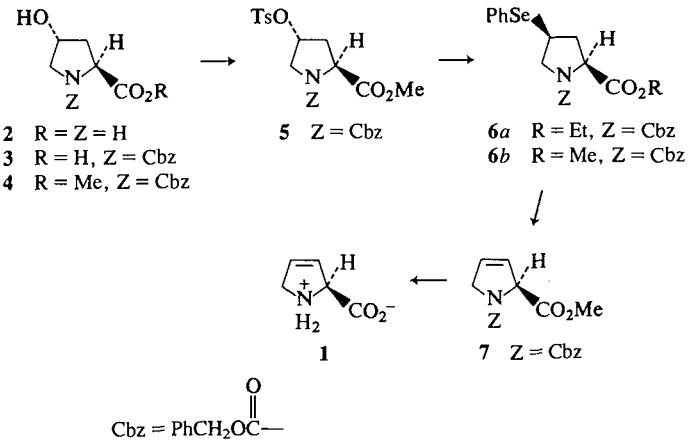

SCHEME 1

Elmer 240 elemental analyzer. All thin layer chromatography was performed using precoated Merck tlc plates: silica gel 60 F-254.

(2S,4R)-N-Benzyloxycarbonyl-4-hydroxyproline methyl ester (4)

To a stirred solution of (2*S*,4*R*)-*N*-carbobenzyloxy-4-hydroxyproline (Sigma) (99% pure by $[\alpha]_D$, homogeneous by tlc) (25 g, 94 mmol) in absolute EtOH (100 mL) was slowly added a cold solution of diazomethane (100 mmol) in Et_2O (200 mL), the temperature being kept below 5°C. After 15 min the slight excess of diazomethane was decomposed with glacial acetic acid. The colorless solution was dried ($MgSO_4$), filtered, and concentrated to provide 25.0 g (99%) of **4** as a colorless oil (lit. oil (14), mp 82°C (15)), which was homogeneous on tlc, R_f 0.57 (AcOEt/hexane 1:1); ir (film): 3450, 2960, 1745, 1700, 1495, 1425, 1360, 1210, 1170, 1125, 1090 cm^{-1}; nmr ($CDCl_3$) δ: 7.29 (5H, m), 5.10 (2H, m), 4.47 (2H, m), 3.74 + 3.54 (3H, s, two rotamers), 3.63 (2H, m), 2.62 (1H, br s), 2.28 (1H, m), 2.17 (1H, m); mass spectrum, *m/z*: 279 (M^+, 1.5), 220 (13), 176 (20), 92 (11), 91 (100), 65 (11), 44 (13).

(2S,4R)-N-Benzyloxycarbonyl-4-tosyloxyproline methyl ester (5)

To a solution of **4** (25.1 g, 90 mmol) in anhydrous pyridine (250 mL) was added *p*-toluenesulfonylchloride (18.9 g, 99 mmol) at 0–5°C, and the resulting mixture was refrigerated at that temperature for 1 week. The pyridine was removed under reduced pressure at 10–20°C, the residue dissolved in Et_2O (400 mL), and this solution was then extracted with cold aqueous 5% HCl (3 × 30 mL) and H_2O (5 × 30 mL). Evaporation of the dried Et_2O layer gave an oil (40.2 g), which crystallized from Et_2O/pentane to give **5** (35.4 g, 91%): mp 74–75°C (lit. (14) mp 74–77°C); $[\alpha]_D^{27}$ −34.0° (*c* 5.0, $CHCl_3$); tlc, R_f 0.51 (AcOEt/hexane 1:1); ir (KBr): 3060, 2990, 2950, 2870, 1735, 1690, 1425, 1355, 1275, 1180, 775, 765, 745, 710 695 cm^{-1}; nmr ($CDCl_3$) δ: 7.1–7.9 (9H, m), 5.10 (3H, m), 4.45 (1H, m), 3.73 + 3.51 (3H, s), 3.5–3.8 (2H, m), 2.45 + 2.43 (3H, s), 2.0–2.7 (2H, m); mass spectrum, *m/z*: 433 (M^+, 0.3), 158 (27), 91 (100), 65 (11). *Anal.* calcd. for $C_{21}H_{23}NO_7S$: C 58.18, H 5.35, N 3.23; found: C 58.41, H 5.39, N 3.30.

(2S,4S)-N-Benzyloxycarbonyl-4-phenylselenoproline methyl ester (6)

Diphenyldiselenide (8.58 g, 27.5 mmol) was dissolved in absolute EtOH (250 mL). $NaBH_4$ (2.08 g, 55 mmol) was then added in batches, while the reaction mixture was stirred under a N_2 atmosphere until the bright yellow solution turned colorless (9, 16). After addition of the tosylate **5** (19.1 g, 44 mmol) the reaction mixture was refluxed for 2.5 h. The solvent was removed *in vacuo*, the residue was diluted with Et_2O (300 mL) and the resulting solution was washed with H_2O (3 × 200 mL), then dried ($MgSO_4$), filtered, and concentrated to give a yellow oil (18.1 g). Thin-layer chromatography (AcOEt/hexane 1:2) revealed a single major product accompanied by two minor impurities. The mixture was purified by flash chromatography (17) on silica gel (300 g, 230–400 mesh, 30 × 5 cm). Petroleum ether/ethyl acetate 4:1 (500 mL), 3:1 (500 mL), and 2:1 (700 mL) eluted diphenyldiselenide (1.2 g), the ethyl ester[2] **6***a* (1.47 g, 8%), and the methyl ester **6***b* (14.97 g, 81%); **6***a* and **6***b* were homogeneous on tlc, R_f 0.40, 0.34 (hexane/AcOEt 2:1) respectively, and crystallized on storage at 0°C. Recrystallization from Et_2O/pentane gave **6***a*, mp 46–47°C, and **6***b*, mp 53°C. The physical properties of **6***b* were as follows: $[\alpha]_D^{27}$ −25.7° (*c* 2.5, $CHCl_3$); ir (KBr): 3060, 2950, 2870, 1730, 1690, 1425, 1350, 1295, 1275, 1180, 1120, 1030, 775, 765, 745, 705, 665 cm^{-1}; nmr ($CDCl_3$) δ: 7.2–7.6 (10H, m), 5.12 (2H, m), 4.34 (1H, m), 4.0 (1H, m), 3.4–3.8 (2H, m), 3.71 + 3.54 (3H, s), 2.5–2.8 (1H, m), 1.95–2.2 (1H, m): mass spectrum, *m/z*: 419 (M^+, 1.6), 316 (9), 158 (8), 81 (100), 68 (15), 65 (19). *Anal.* calcd. for $C_{20}H_{21}NO_7Se$: C 58.33, H 5.36, N 3.24; found: C 58.45, H 5.35, N 3.22.

(S)-N-Benzyloxycarbonyl-3,4-dehydroproline methyl ester (7)

To a stirred solution of selenide **6***b* (8.36 g, 20 mmol) and pyridine (2.37 g, 30 mmol) in CH_2Cl_2 (100 mL) was gradually added 30% H_2O_2 (5.6 g, 50 mmol), while the reaction vessel was cooled in an ice bath (18). The reaction mixture was stirred vigorously at 25°C for an additional 1.5 h, then diluted with CH_2Cl_2 (100 mL) and extracted successively with aqueous 5% HCl (2 × 50 mL), saturated aqueous Na_2CO_3 solution (50 mL), and H_2O (3 × 50 mL). The organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue purified by flash chromatography on silica gel (200 g, 230–400 mesh, 30 cm × 5 cm, AcOEt/petroleum ether 1:2), giving **7** as an oil (4.49 g, 87%); tlc, R_f 0.64 (AcOEt/hexane 1:1); ir (film): 3085, 3060, 3030, 2950, 2900, 2865, 1750, 1710, 1620, 1498, 1415, 1355, 1310, 1260, 1205, 1180, 1125, 1105, 1000, 780, 770, 760, 700 cm^{-1}; nmr ($CDCl_3$) δ: 7.30 (5H, m), 5.97 (1H, m), 5.74 (1H, m), 5.0–5.3 (3H, m), 4.31 (2H, m), 3.74 + 3.50 (3H, s); mass spectrum, *m/z*:

[2]Formation of the ethyl ester could presumably be prevented by running the reaction in MeOH–THF.

261 (M^+, 0.3), 202 (25), 158 (36), 92 (19), 91 (100), 65 (21). We found no trace of the corresponding 4,5-dehydroproline, by tlc or ^1H nmr analysis of the crude reaction product, i.e. the selenoxide elimination must be very regioselective.

(S)-Dehydroproline (1)

To a solution of **7** (0.8 g, 3 mmol) in anhydrous CH_3CN was added, via a syringe, trimethylsilyl iodide (1.3 mL, 9 mmol) under a nitrogen atmosphere (12, 13). The reaction mixture was then refluxed for 20 h. The mixture was then cooled to ca. 0°C and a mixture of EtOH/AcOH 1:1 (5 mL) was added quickly. After a further 20 min of stirring, the reaction mixture was further diluted with H_2O (20 mL) and then extracted with CH_2Cl_2 (5 × 15 mL). The H_2O layer was then poured onto a column of Dowex 50W-X8 (10 cm × 1.5 cm) cation exchange resin (100–200 mesh) (7). After washing the column with H_2O (150 mL) until the eluates were neutral, the product was eluted with 0.5 *M* aqueous pyridine acetate solution (200 mL). The ninhydrin positive fractions were combined, and concentrated at <25°C. To remove traces of pyridine, the white residue was dissolved in H_2O (20 mL) and reevaporated under the same conditions. This process was repeated once more. The wet solid residue (0.33 g) was dissolved in H_2O (0.3 mL) and EtOH (3 mL), seeded, AcOEt (10 mL) added, and the solution refrigerated at −5°C overnight. The crystals which separated were filtered, washed with cold EtOH, Et_2O, and dried at 20°C/0.1 Torr, thus affording (*S*)-3,4-dehydroproline (**1**) (0.275 g, 80%): tlc, R_f 0.22 (n-BuOH/AcOH/H_2O 3:1:1); mp 242–243°C (dec.), $[\alpha]_D^{27}$ −404.6° (*c* 1.1, H_2O); e.e. 99.8%, (lit. (7) mp 244°C (dec.), $[\alpha]_D^{27}$ −403.1° (*c* 1.0, H_2O)); cd (H_2O): $\Delta\varepsilon_{202} = -25.4°$; ir (KBr): 3280, 3080, 2100–3300, 1620, 1600, 1360, 1330, 1280, 1270, 1230, 1195, 1065, 1005, 930, 830, 775, 740, 695; ^1H nmr (CD_3COOD) δ: 6.05 (1H, dddd, J = 6.5, 2, 2, 2 Hz), 5.92 (1H, dddd, 6.5, 2.5, 2, 2 Hz), 5.15 (1H, m), 4.29 (2H, m) cf. lit. (19); ^{13}C nmr (D_2O, dioxane) δ: 172.2, 125.7, 125.4, 68.5, 52.4; mass spectrum, *m/z*: 111 (M − 2, 12), 95 (12), 94 (12), 93 (12), 69 (17), 68 (70), 67 (100), 66 (16), 44 (59), 41 (100), 40 (34), 39 (59). *Anal.* calcd. for $C_5H_7NO_2$: C 53.06, H 6.24, N 12.39; found: C 53.11, H 6.36, N 12.44.

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