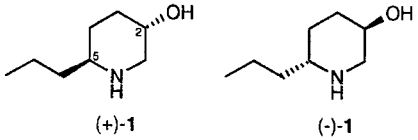
Synthesis of (-)-Pseudoconhydrine through Ring Enlargement of a L-Proline Derivative

Janine Cossy*, Cécile Dumas, Domingo Gomez Pardo*
Laboratoire de Chimie Organique, Associé au CNRS, ESPCI, 10 rue Vauquelin - 75231 Paris Cedex 05 France
Fax: 33.1.40.79.44.25; E-mail: janine.cossy@espci.fr
Received 12 May 1997

Abstract : A short synthesis of (-)-pseudoconhydrine is described from L-proline by using a ring enlargement reaction.

Alkaloids possessing the piperidin-3-ol system are abundant in nature and many of them have interesting biological properties.[1] Since its isolation from *Conium maculatum* L.[2] (Umbelliferae), the absolute configuration of (+)-**1** has been established to be (2*S*,5*S*) based on Hoffman degradation.[3] (+)-Pseudoconhydrine has been of special interest for many research groups. The synthesis of **1** has been reported several times in its racemic form[4] and enantiomerically enriched form[5] (+)-**1** as well as (-)-**1**.[6]

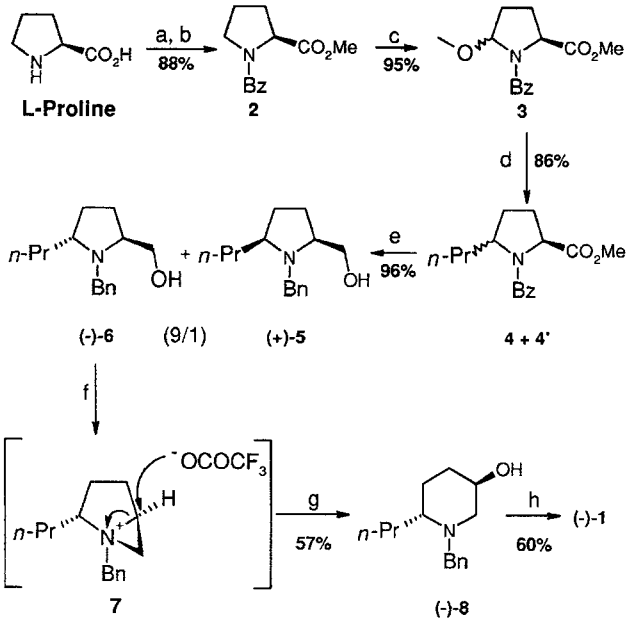


(+)-**1** (-)-**1**

In connection with our program directed towards the selective synthesis of 3-hydroxypiperidines through ring enlargement of prolinol[7], the synthesis of (-)-**1** has been achieved starting from the commercially available inexpensive L-proline.

N-Benzoyl L-proline (obtained by treatment of L-proline with benzoyl chloride in 1.25 M aqueous NaOH) reacted with K_2CO_3 and then with MeI to afford the methyl *N*-benzoylprolinate **2**[8] (88% overall yield). Anodic oxidation[9] of **2** (15.4 mmol) in methanol (15 mL) containing a catalytic amount of tetraethylammonium *p*-toluenesulfonate provided the methyl *N*-benzoyl-5-methoxyprolinate **3**[10] as a mixture of two separable stereoisomers in a 1:1 ratio (95%). Displacement of the methoxy group of **3** with a *n*-propyl group was achieved on treating **3** with one equivalent of *n*-PrMgBr, CuBr•Me_2S and BF_3•Et_2O in Et_2O.[11] This led to a 9:1 mixture of non-separable isomers **4** and **4'**. Reduction of this mixture with $LiAlH_4$ in THF produced the 1-benzyl-5-propylpyrrolidine-2-methanol (+)-**5** and (-)-**6** in a 1:9 ratio (96%) which were separated by flash chromatography on silica gel.[12] Treatment of 1-benzyl-5-propylpyrrolidine-2-methanol (-)-**6** with trifluoroacetic anhydride in THF followed by addition of NEt_3 and then addition of an aqueous solution of NaOH (2.5 M) gave piperidin-3-ol (-)-**8**[13,14] (57%) which has the pseudoconhydrine skeleton. The relative configuration of the hydroxy and the *n*-propyl groups was established by ^1H NMR spectrum and NOE experiments. Debenzylation was achieved by hydrogenolysis in the presence of $Pd(OH)_2$ (1 atm, H_2, 16 h, yield: 60%). This liberated (-)-pseudoconhydrine (-)-**1**, the structure of which was confirmed by addition of dry HCl and crystallisation of the hydrochloride salt from Et_2O which had spectral data, melting point (205 °C) and $[\alpha]_D^{20} = -6$ (*c* = 1.05, MeOH) similar to reported data in the literature.[5b]

In summary, we have realized a short synthesis of (-)-pseudoconhydrine [(-)-**1**] from L-proline based on a stereospecific prolinol/piperidin-3-ol rearrangement[7], a reaction which is consistent with the formation of a 1-azabicyclo[3.1.0]hexane intermediate **7** through S_Ni solvolysis of the primary alcohol of the prolinol (-)-**6** (participation of the amino moiety to the isomerization).



a) PhCOCl, NaOH; b) MeI, K_2CO_3; c) -2e$^-$, MeOH, Et_4NTs;
d) *n*-PrMgBr, CuBr.Me_2S, BF_3.Et_2O; e) $LiAlH_4$, THF;
f) i:$(CF_3CO)_2O$, ii:NEt_3; g) NaOH; h) H_2, $Pd(OH)_2$, MeOH.

Scheme 1

Acknowledgement

We thank Dr H. Dhimane for his help in anodic oxidation, C. Chassagnard for NOE experiments and Dr. J-L. Ranaivosata for providing the ^1H NMR spectra of compound (+)-**8**.

References and notes

(1) a) Strunz, G. M.; Findaly, J. A. *The Alkaloids*, Brossi, A. Ed. Academic Press: San Diego, **1986**, *26*, p 89-105. b) Plunkett, A.O. *Nat. Prod. Rep.* **1994**, *11*, 581-590.

(2) Ladenburg, A.; Adam, G. *Ber.* **1891**, *24*, 1671-1677.

(3) Sicher, J.; Tichý, M. *Collect. Czech., Chem. Commun.* **1958**, *23*, 2081-2093.

(4) a) Marion, L.; Cockburn, W. F. *J. Am. Chem. Soc.* **1949**, *71*, 3402-3404. b) Šorm, F.; Sicher, J. *Collect. Czech., Chem. Commun.* **1949**, *14*, 331-344. c) Gruber, W.; Schlögl, K. *Monatsh. Chem.* **1949**, *80*, 499-505. d) Gruber, W.; Schlögl, K. *Monatsh. Chem.* **1950**, *81*, 83-89. e) Govindachari, T. R.; Rajappa, S. *J. Chem. Soc.* **1958**, 1306-1307. f) Brown, E.; Dhal, R.; Lavoue, J. *Tetrahedron Lett.* **1971**, *12*, 2767-2770. g) Brown, E.; Dhal, R.; Lavoue, J. *Tetrahedron* **1973**, *29*, 455-461. h) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40-44. i) Plehiers, M.; Hootelé, C. *Tetrahedron Lett.* **1993**, *34*, 7509-7510. j) Fry, D. F.; Brown, M.; McDonald, J. C.; Dieter, R. K. *Tetrahedron Lett.* **1996**, *37*, 6227-6230.

(5) a) Tadano, K.; Iimura, Y.; Suami, T. *J. Carbohydr. Chem.* **1985**, *4*, 129-139. b) Takahata, H.; Inose, K.; Momose, T. *Heterocycles* **1994**, *38*, 269-272. c) Oppolzer, W.; Bochet, C. G. *Tetrahedron Lett.* **1995**, *36*, 2959-2962. d) Sakagami, H.; Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1433-1434. e) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746-748.

(6) Shono, T.; Matsmura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. *Chem. Lett.* **1984**, 1101-1104.

(7) Cossy, J.; Dumas, C.; Michel, P.; Gomez Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549-552. Our conditions were applied to bicyclic compounds cf.: Wilken, J.; Kossenjans, M.; Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Liebigs Ann.* **1997**, 573-579.

(8) Motonori, T.; Eiichi, K.; Tetsuya, S.; Morifusa, E. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 778-782.

(9) Shono, T. *Tetrahedron* **1984**, *40*, 811-850.

(10) Shono, T.; Yoshihiro, M.; Kenji, T.; Kenshi, U; Takenobu, K.; Kunio, T. *J. Org. Chem.* **1984**, *49*, 3711-3716.

(11) Wistrand, L. G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573-582.

(12) The flash chromatography eluent was CH_2Cl_2/MeOH/NH_3: 95/5/0.1.

(13) For compound (+)-**8** see Ref. 5c.

(14) Trifluoroacetic anhydride (56 µL, 0.40 mmol, 1.1 eq.) was added dropwise to a solution of (-)-**6** (85.2 mg, 0.36 mmol, 1 eq.) in THF (5 mL) cooled to -78 °C and under inert atmosphere. After 3 hours triethylamine (0.19 mL, 1.37 mmol, 3.8 eq.) was added dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C and then refluxed for 3 days. After addition of sodium hydroxide (2.5 M, 2 mL), the mixture was stirred for 1 hour then extracted by dichloromethane (3x5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The oil was purified by flash chromatography on alumina (Merk aluminium oxide 90, 0.063-0.200 mm) eluent (ethyl acetate/cyclohexane : 50/50).

(-)-**8**: oil; $[\alpha]_D^{20}$ = -43 (*c* = 2.06, EtOH). IR (NaCl): 3360, 2940, 1500, 1020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, ^3J=9.0 Hz, 3H), 1.10-1.63 (m, 6H), 1.67-1.83 (m, 2H), 1.97 (dd, ^2J=11.3 Hz, ^3J=8.1 Hz, 1H), 2.19-2.46 (m, 2H), 2.75 (dd, ^2J=11.3 Hz, ^3J=2.5 Hz, 1H), 3.34 (d, ^2J=13.3 Hz, 1H), 3.63-3.70 (m, 1H), 3.86 (d, ^2J=13.3 Hz, 1H), 7.07-7.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.4 (CH_3), 19.1 ($2CH_2$), 26.4 (CH_2), 30.8 (CH_2), 56.7 (CH_2), 57.7 (CH_2), 58.9 (CH), 66.3 (CH), 126.8 (CH), 128.1 (2CH), 128.8 (2CH), 139.0 (C). MS (CI, CH_4) *m/z*: 234 ($M+H^+$,100), 216 (60), 190 (92), 147 (16), 91 (16). HMRS calculated for $C_{15}H_{24}NO$: 234.1857, found : 234.1856.