Stereoselective Nucleophilic Substitution of 6-Methoxy-1-methoxycarbonylpipecolate: Enantioselective Synthesis of (+)-Sedamine from L-Lysine

K. Irie, K. Aoe, T. Tanaka,* and S. Saito

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., Toda, Saitama, Japan

Amidoalkylation 6-methoxy-1-methoxycarbonylpipecolate (**4**) with several nucleophiles gave the 2,6-*cis* 6-substituted pipecolates, stereoselectively.

We recently reported that electrochemical oxidation of the N^{α},N^{ε}-bis(methoxycarbonyl)-L-lysine ester (**1**) gave the 6-aminopipecolate derivative (**2**), which could be converted into (2*S*)-pipecolic acid (**3**), sustaining the chirality of the starting material.[1] We have now found that the condensations of the 6-methoxypipecolate (**4**),† obtainable from (**2**), with three nucleophiles (phenyl isocyanide,[2,3a] trimethylsilyl cyanide,[3b] and α-trimethylsilyloxystyrene[3c]), in the presence of titanium tetrachloride in CH_2Cl_2 at −50 °C gave the corresponding 2,6-*cis* 6-substituted pipecolates [(**5**), (**6**), and (**7a**)], stereoselectively (Scheme 1).[3d]‡

The structure of the 6-phenylcarbamoylpipecolate (**5**) {$[\alpha]_D^{20}$ + 15.6° (*c* 1.2, MeOH)} isolated as a single diastereoisomer was revealed by *X*-ray analysis: both substituents at C-2 and C-6 on the piperidine ring assuming a deformed chair conformation are in a *cis* relationship (Figure 1).§

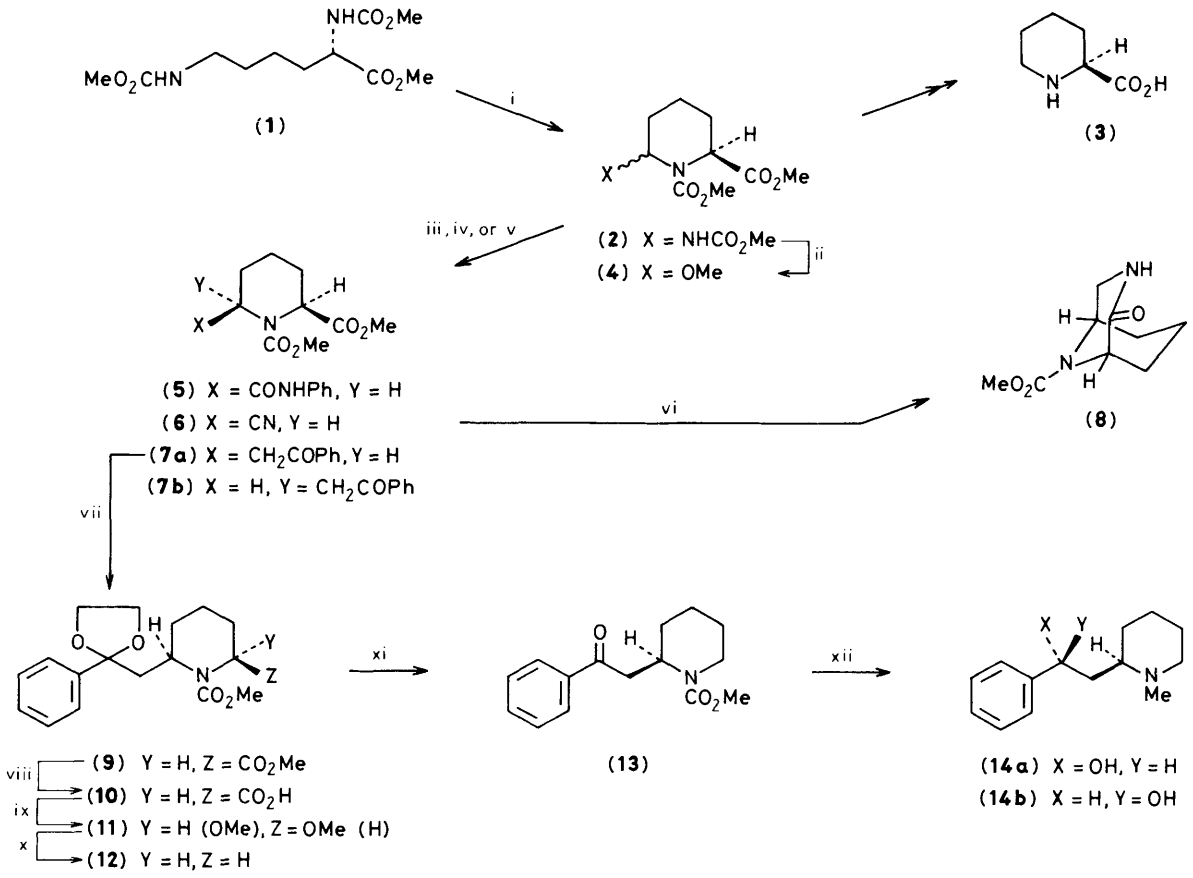
The 6-cyanopipecolate (**6**), was also obtained as one isomer {$[\alpha]_D^{20}$ + 15.8° (*c* 1.2, MeOH); δ ([$^2H_6$]Me_2SO) at 110 °C, 4.76 (1H, q, *J* 2.8, 6 Hz, H-6), 5.17 (1H, q, *J* 3.3, 6 Hz, H-2)} together with the 5,6-dehydropipecolate (14% yield). Compound (**6**) was reduced catalytically using Raney-nickel to give the aminomethylpipecolate, which spontaneously cyclised to the diazabicyclo[3.3.1]nonan-2-one (**8**) [ν(neat), 1680 cm^{-1}], proving the 2,6-diaxial relationship in (**6**).

The condensation of (**4**) with α-trimethylsilyloxystyrene afforded, after column chromatographic separation, two diastereoisomers, (**7a**) {$[\alpha]_D^{20}$ −36.9° (*c* 1.94, MeOH)} and

† This compound is labile and difficult to purify. A pure specimen of the 2,6-*cis* 6-methoxypipecolate (**4**) was obtained by careful alumina-column chromatography. The 400 MHz n.m.r. spectrum exhibited a *ca.* 1:1 mixture of the two rotamers, (A) and (B), about the N–CO bond δ ($CDCl_3$): (A) 3.362 (s, OMe), 3.724 (s, Me), 3.790 (s, Me), 4.718 (br. d, *J* 3.9 Hz, H-2), 5.450 (br. s, H-6); (B) 3.287 (s, OMe), 3.724 (s, Me), 3.764 (s, Me), 4.905 (br. d, *J* 3.3 Hz, H-2), 5.280 (br. s, H-6). We used the crude (**4**) (*ca.* 70% purity) in this work.

‡ Satisfactory microanalytical and spectral data were obtained for all new compounds referred to in this paper. Unless otherwise stated, ^1H n.m.r. spectra were recorded at 100 MHz.

§ *Crystal data* for (**5**): $C_{16}H_{20}N_2O_5$ (*M* 320.35), orthorhombic, space group $P2_12_12_1$, *a* = 9.8027(6), *b* = 17.2635(8), *c* = 9·7098(6) Å. *U* = 1643.2(2) Å^3, D_c = 1.295 g cm^{-3}, *Z* = 4, 1625 independent reflections. The structure was solved by the direct method using MULTAN and was refined by the block-diagonal least-squares procedure. The final *R* value was 0.061. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



Scheme 1. (i) −e (MeCN–H_2O 10:1, Et_4NClO_4, Pt anode, 4 F mol^{-1}), 50%; (ii) *p*-$MeC_6H_4SO_3H$, MeOH, room temp., 30 h, 70%; (iii) PhNC, $TiCl_4$, CH_2Cl_2, −50 °C, 58%; (iv) Me_3SiCN, $TiCl_4$, CH_2Cl_2, −50 °C, 53%; (v) α-trimethylsilyloxystyrene, $TiCl_4$, CH_2Cl_2, −50 °C, 60—68%; (vi) Raney-Ni, H_2, EtOH, 78%; (vii) ethylene glycol, *p*-$MeC_6H_4SO_3H$, benzene, reflux 21 h, 96%; (viii) NaOH, MeOH–H_2O, 5 °C—room temp., 3.5 h, 93%; (ix) −e (MeOH, MeONa, carbon anode, 2.6 F mol^{-1}), 84%; (x) NH_4Cl, toluene, reflux 2 h; H_2, Pd/C, AcOEt, 97%; (xi) pyridinium toluene-*p*-sulphonate, acetone, reflux 3 h, 81%; (xii) $LiAlH_4$, Et_2O, reflux 2.5 h, 95%.

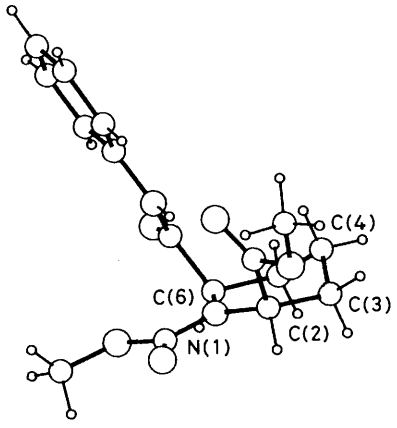


Figure 1. Molecular structure of compound (**5**).

(**7b**) {$[\alpha]_D^{20}$ −17.9° (*c* 2.0, MeOH)}, in a ratio of 10:1. Comparison of their n.m.r. spectra [δ($CDCl_3$) (**7a**) 4.7—5.0 (2H, m, H-2 and H-6); (**7b**) 4.42 (1H, t, *J* 6 Hz, H-2eq.), 4.50 —4.76 (1H, m, H-6)] suggested that both products should have an equatorial proton at C-2, and that they should be epimeric at C-6.[4] To resolve the ambiguity of the n.m.r. assignment, we transformed the major product (**7a**) into the piperidine alkaloids (sedamine family) whose absolute configurations have already been confirmed.[5]

Thus, a conventional acetalisation followed by alkaline hydrolysis of (**7a**) provided the pipecolic acid (**10**), which was subjected to decarboxylation by anodic oxidation[6] in MeOH using sodium methoxide as a supporting electrolyte to give the 2-methoxy-6-phenacylcarbamate (**11**) as a diastereoisomeric mixture. Subsequent elimination of MeOH and hydrogenation of the double bond produced afforded the acetal-carbamate (**12**) in 81.5% overall yield from (**10**). After removal of the acetal group from (**12**), the keto-carbamate (**13**) was reduced with $LiAlH_4$ to give two epimeric alcohols, (**14a**) and (**14b**), in a 49:51 ratio, quantitatively.[3c] Their physical data (n.m.r., i.r., mass spectroscopic, and the optical rotation) were in good accord, with those of natural (2*S*, 8*S*)-(−)-sedamine and (2*S*,8*R*)-(−)-allosedamine, respectively, except for the signs of the specific rotations {$[\alpha]_D^{20}$ −82.4° (*c* 5, MeOH) and −31.5° (*c* 4.9, MeOH) for sedamine and allosedamine:[5b] + 84.2° (*c* 0.66, MeOH) and +28.8° (*c* 0.16, MeOH) for (**14a**) and (**14b**), respectively}, indicating that our major product (**7a**) from the amidoalkylation[7] has, in turn, (2*S*,6*R*)-configuration, that is 2,6-*cis*.

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