A SIMPLE ROUTE TO (±)- AND (+)-TRACHELANTHAMIDINE

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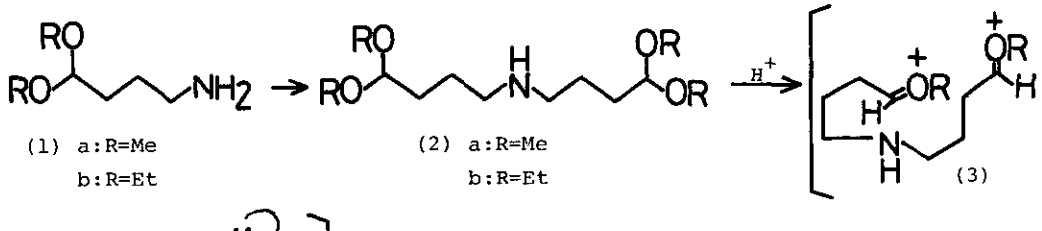
Abstract-----Starting from a single substrate(1a) (±)- and (+)-trachelanthamidine(6) has been synthesized in three steps.

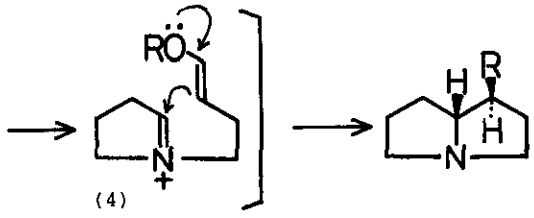
Owing to the production of certain industrial materials such as curing catalysts, 4-aminobutyral dimethyl acetal(1a) has now been available in large quantity[1]. Expecting to utilize this material as the functionalized four carbon building block for the construction of various natural products, we attempted to synthesize trachelanthamidine[2](6), a simple member of the pyrrolizidine alkaloids. Apparently, a naturally occuring trachelanthamidine(6) arises by Mannich reaction of the symmetric amine aldehyde(3, R=H) formed by decarboxylative deamination and coupling of two ornithine units in a plant. Actually the synthesis along this view has been achieved about two decades ago using the symmetric aminodiacetal(2b) obtained through alkylation of the primary amine(1b) with the four carbon halide[3]. Present report describes a convenient conversion of the primary amine(1a) into the symmetric aminodiacetal(2a) by deaminative coupling and its transformation to trachelanthamidine(6) in both racemic and enantioselective ways.



(1) a:R=Me b:R=Et

(2) a:R=Me b:R=Et

(3)



(4)

(5) R=CHO
(6) R=CH_2OH trachelanthamidine
(7) R=$CH(OMe)_2$

Treatment of the primary amine(1a) with freshly prepared Raney nickel catalyst (W-2) in boiling benzene resulted in the deaminative dimerization[4] to give the symmetric secondary amine(2a) in 71 % yield. When the reaction was carried out in toluene or xylene at reflux temperature, trimerization took place predominantly and the aminotriacetal[5] was obtained as a major product. The secondary amine(2a) upon reflux in a methanolic hydrochloric acid(c.HCl:MeOH=1:4) gave the crude Mannich base(5) which was directly reduced with sodium borohydride to furnish (±)-trachelanthamidine(6) stereoselectively in 40 % yield. The Mannich base(5) could be isolated as its methyl acetal(7) in 50 % yield when the less hydrolytic conditions (c.HCl:MeOH=1:15). The Mannich acetal(7) could also be isolated directly from the reaction mixture in 36 % yield as its picrate when the secondary amine(2a) was refluxed in methanol containing picric acid. The Mannich acetal(7) gave (±)-trachelanthamidine(6) in 44 % yield on hydrolysis, followed by reduction with sodium borohydride.

Treatment of the secondary amine(2a) with pyridinium (d)-camphor-10-sulfonate in aqueous media at 100 °C allowed an asymmetric cyclization to five (+)-trachelanthamidine(6)($[\alpha]_D$ +5.1°(EtOH)(optical yield 33.0 %) after reduction of the crude Mannich base(5) formed with sodium borohydride. This conversion consists the first asymmetric cyclization into the 1-substituted pyrrolizidine alkaloid[6] though it needs some improvements in terms of chemical and optical yields. Further synthetic studies of natural products using 4-aminobutyral dimethyl acetal(1a) and related compounds are now under investigations.

EXPERIMENTAL

All reactions were carried out under Ar atomosphere. Melting points are not corrected. IR spectra were measured with a Shimadzu IR 400 spectrometer. ^{1}H-NMR spectra were measured in deuteriochloroform solution with a JEOL-PMX 60 spectrometer. Mass spectra were measured with a JEOL-D 300 spectrometer. Optical rotation was measured with a JASCO-DIP automatic polarimeter.

γ-γ'-Imino-bis-butyraldehyde tetramethyl diacetal(2a): γ-Aminobutyraldehyde dimethyl acetal(1a)(22.0 g, 165 mmol) was suspended with freshly prepared Raney Ni (W-2)(ca. 24 g) in benzene(240 ml) and the suspension was refluxed for 24 hr with stirring. After the filtration using Celite, the organic layer was evaporated and distilled under vacuum to give the pure secondary amine(1a)(14.64 g; 71.1 %): Bp

88∿90 °C(0.06 mmHg); IR(neat) max 3300, 1130, 1055 cm^{-1}; NMR($CDCl_3$) δ 1.42∿1.78(8H, m), 1.88(1H, br.s, exchangeable with D_2O), 2.52∿2.84(4H, m), 3.35(6H, s), 4.32∿4.57 (2H, m); MS(m/e) 249(M^+), 85(100 %). $C_{12}H_{27}NO_4$ Calc. C, 57.80; H, 10.92; N, 5.62. Found. C, 57.53; H, 11.08; N, 5.89.

(±)-Trachelanthamidine(6) from the Diacetal(2a): Diacetal(2a)(3.73 g; 15.0 mmol) was refluxed with a mixture of c.HCl(20 ml) and MeOH(80 ml) for 3 hr and the reaction mixture evaporated to dryness to leave the crude aldehyde(5) hydrochloride which without purification was reduced with $NaBH_4$(2.0 g; 54 mmol) in MeOH(50 ml) at 0 °C. The reaction mixture was evaporated and extracted with $CHCl_3$. The extract was washed(sat.NaCl), dried(K_2CO_3), and evaporated to leave a pale brown oil(2.41 g) which was distilled under vacuum to give (±)-trachelanthamidine(6)(0.98 g; 40.7 %): Bp 135∿140 °C(0.1 mmHg), Kugelrohr)(lit.[6] Bp 97.5 °C(0.8 mmHg); IR(neat) max 3330, 1060 cm^{-1}; NMR($CDCl_3$) δ 1.33∿3.53(12H, m), 3.62(2H, d, J=6Hz), 4.90(1H, br.s, exchangeable with D_2O); MS(m/e) 141(M^+), 83(100 %). Picrate: mp 177∿178 °C(EtOH-n-hexane) (lit. 174∿175 °C[7]: 179 °C[8]).

Mannich base dimethyl acetal(7): Diacetal(2a)(3.73 g; 15 mmol) was refluxed with a mixture of c.HCl(1 ml) and MeOH(150 ml) for 5 hr. The reaction mixture was basified with sat.$NaHCO_3$ and extracted with $CHCl_3$. The extract was washed(sat.NaCl), dried(K_2CO_3), and evaporated. The oily residue was distilled under vacuum to give the Mannich base dimethyl acetal(7)(1.39 g; 50.1 %): Bp 75∿80 °C(0.2 mmHg); IR(neat) max 1130, 1050 cm^{-1}; NMR($CDCl_3$) δ 1.29∿3.48(12H, m), 3.36(6H, s), 4.25(1H, d, J≈7Hz), MS(m/e) 185(M^+), 83(100 %). Picrate: yellow needles (MeOH), mp 184.5∿186 °C, $C_{16}H_{22}N_4O_9$ Calc. C, 46.37; H, 5.35; N, 13.52. Found. C, 46.63; H, 5.15; N, 13.37.

Direct formation of the Mannich base acetal(7) picrate: Diacetal(2a)(250 mg; 1 mmol) was refluxed with picric acid(500 mg; 2.2 mmol) in MeOH(15 ml) for 12 hr. The reaction mixture was evaporated(ca. 3 ml) and cooled to give yellow needles which were collected to give the picrate as yellow needles after recrystallization from MeOH: yield 150 mg(36 %); mp 184.5∿186 °C.

(±)-Trachelanthamidine(6) from the Mannich base dimethyl acetal(7): Mannich base(7)(300 mg, 1.6 mmol) was dissolved in acetone(10 ml) and the mixture was refluxed with 10% H_2SO_4(10 ml) for 2.5 hr. After concentration of the mixture under reduced pressure, the residue containing the aldehyde(5) was dissolved in MeOH(10 ml) and reduced with $NaBH_4$(400 mg; 10.6 mmol) at 0 °C with stirring. The reaction mixture was concentrated and extracted with $CHCl_3$. The extract was washed(sat.NaCl), dried(K_2CO_3), and evaporated. The oily residue(140 mg) was distilled under vacuum

to give (±)-trachelanthamidine(6)(100 mg; 44.3 %): Bp 135∿140 °C(0.1 mmHg, Kugelrohr).

(+)-Trachelanthamidine(6): Diacetal(2a)(2.49 g; 10 mmol) was treated with pyridinium (d)-camphor-10-sulfonate(6.22 g; 20 mmol) in water(20 ml) at 100 °C for 2.5 hr. The reaction mixture was diluted with MeOH(30 ml) and reduced with $NaBH_4$ (1.0 g; 26 mmol) at 0 °C. The resulting mixture was extracted with $CHCl_3$ and the extract was washed(sat.NaCl), dried(K_2CO_3), and evaporated to leave a brown oil (1.24 g), which on vacuum distillation gave (+)-trachelanthamidine(6)(95 mg; 6.7 %): Bp 135∿140 °C(0.1 mmHg, Kugelrohr), $[\alpha]_D$ +5.1°(EtOH)(lit.[9] $[\alpha]_D$ +15.45(EtOH)).

Pyridinium (d)-camphor-10-sulfonate: (d)-Camphor-10-sulfonic acid(16.54 g; 70 mmol) was dissolved in pyridine and the mixture was stirred for 3 hr at room temperature. Removal of an excess pyridine under vacuum gave pale yellow crystallines which were crystallized from acetone to give the salt(17.67 g; 81.2 %) as colorless prisms: mp 152.5∿155 °C; IR(Nujol) max 3500, 3450 cm^{-1}; NMR($CDCl_3$) δ 0.88(3H, s), 1.14(3H, s), 1.29∿2.93(8H, m), 2.94(1H, d, J=15Hz), 3.46(1H, d, J=15Hz), 7.98∿8.39 (2H, m), 8.47∿8.82(1H, m), 9.09∿9.29(2H, m). $C_{15}H_{21}NO_4S$ Calc. C, 57.86; H, 6.80; N, 4.50; S, 10.30. Found. C, 57.57; H, 6.82; N, 4.42; S, 10.23.

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6. Enantioselective synthesis of (+)-trachelanthamidine(6) has been achieved by using (-)-4-hydroxy-L-proline as starting material: see, D.J. Robins and S.

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