The Pictet-Spengler Reaction on L-Histidine. Preparation of Conformationally Restricted (+)-Pilocarpine Analogs

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The total regioselective synthesis of the rigid (+)-pilocarpine analogs **4**—**6** starting from L-histidine is described. The Pictet-Spengler condensation is used to prepare the tetrahydroimidazopyridine moiety present in the structure of these tricyclic derivatives.

Recently we reported the synthesis of the cyclic carbamate analogs of (+)-pilocarpine **1**—**3**[2] as a part of a novel series of muscarinic agonists containing the 2-oxazolidinone ring system.[3] In order to perform correlation analysis which would provide clues to the specific role of the structural features of the ligands acting at the corresponding muscarinic receptor,[4] we now wish to report our efforts to prepare the conformationally restricted derivatives **4**—**6**. It is of interest that no rigid analog of (+)-pilocarpine has been reported to have more than approximately 1% of the agonist activity of the naturally occurring alkaloid;[5] this is in contrast with the situation for other muscarinic receptors where active rigid congeners have been discovered.[6]

Results and Discussion

The Pictet-Spengler reaction has been used widely for the synthesis of a variety of alkaloids because of generally good yields and mild reaction conditions.[7,8] We first thought on this process for the key step to access to the tetrahydroimidazopyridine moiety present in the conformationally rigid analogs **4**, **5**, and **6** (Fig. 1).

The preparation of the two isomers **4** and **5** has been accomplished by a four-step synthetic sequence according to Scheme 1. The spinacine dihydrate **9**[9,10] was obtained by a variation of the reported procedures starting from L-histidine.[11]

Treatment of **9** with HCl in absolute metanol for 15 h at room temperature led to the methyl ester dihydrochloride **10·2HCl**, which after neutralization with ethanolic 1 M KOH led to the free base **10** by filtration of the KCl and evaporation of the solvent (Scheme 1).

Reaction of **10** with lithium aluminium hydride (LAH) in refluxing THF for 48 h afforded the hydroxy derivative **11** only after extraction of the worked up product in a Soxhlet with refluxing THF for 72 h.[12] The presence of a signal at $\delta=66.8$ (CH_2) in the ^{13}C NMR of **11** confirmed the structural change.

Treatment of **11** with dimethyl carbonate in methanol at room temperature using sodium methoxide as base afforded a crude material from which, it has been possible to isolate the 2-oxazolidinone **12** by flash chromatography on silica gel.

Treatment of **12** with NaH in DMF followed by addition of iodomethane at room temperature led to a mixture of products **4** : **5**=3 : 1, which was separated by flash chromatography on silica gel.[13] The regioselectivity observed in the alkylation step is due, in our opinion, to the evolution of the reaction through an aggregated transition state in which, the differentiation between the two faces of the substrate is possible, favoring the electrophilic attack at the N^{π} position.[14]

Though significant differeces are observed in the spectroscopic data of both isomers, structural assignment was possible by Eu(fod)$_3$-promoted paramagnetic shifts in unequal mixtures of both isomers. The reagent caused larger downfield shifts to the *N*-methyl signal of the less polar isomer **5**, thereby allowing us for this isomer to place the methyl on the nitrogen which is in the near vicinity of the carbonyl group where the shift reagent is most probably coordinated. Treatment of **12** under the same conditions as mentioned above using excess of alkylating reagent afforded the imidazolinium iodide **6**.

Semiempirical quantum mechanical (MNDO)[15,16] calculations of isolated **4** and **5** predicted global minimum energy conformations through the Broyden-Fletcher-Shanno algorithm for both isomers as shown in Fig. 2.

Both isomers show almost equal heat of formation. The tiny difference (0.1 kcal mol^{-1}) in favor of **5** is not significant, neither are the localized charges on nitrogens. The theoretical study of charge distribution on the intermediate anion obtained in the treatment of **12** with NaH makes no clear distinction between the two nitrogens as to justify the ratio **4** : **5** (3 : 1). We are led to accept that the interaction in an aggregated transition state determine the regioselectivity observed in the alkylation reaction. These interactions clearly should stabilize the isomer **4** in a polar solvent as DMF, since theoretical calculations predict for it much larger dipole moment than for the isomer **5** ($\mu=7.8$ and 4.2 D, respectively).

The regioselective synthesis of isomers **4** and **5** has

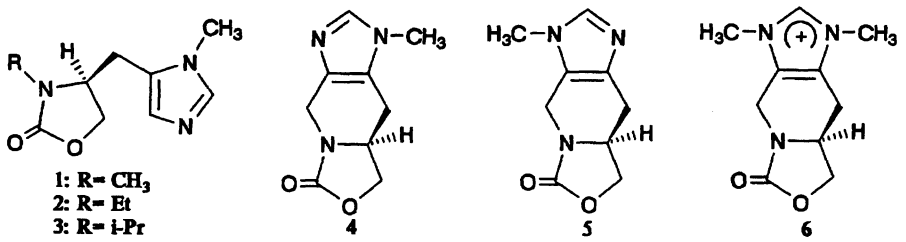
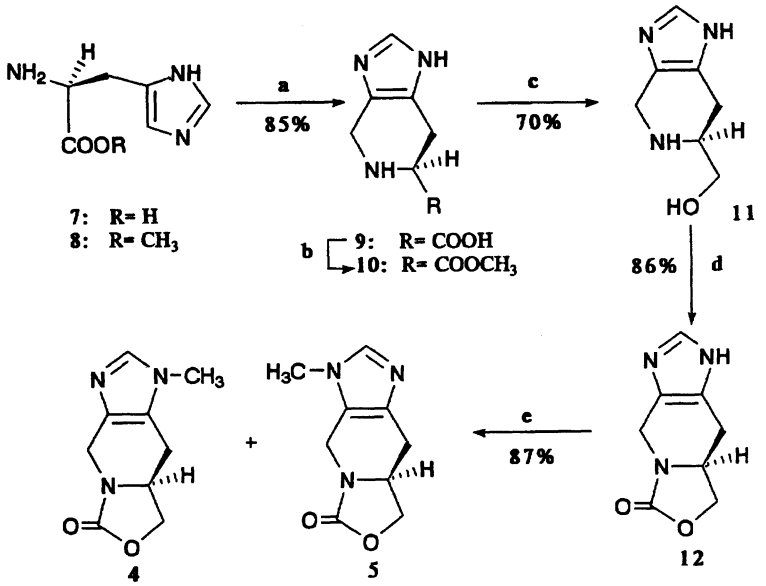


Fig. 1. (+)-Pilocarpine analogs.



a: HCHO (37%); pH= 7; 60 °C, 15h.; b: i) CH_3OH, HCl, r.t.; 15 h.; ii) 1M KOH (88%); c: LAH, THF, reflux; d: NaOH (1 equiv.), CH_3OH; $(MeO)_2CO$ (1.1 equiv.); e: NaH (1.1 equiv.), DMF, CH_3I (1.1 equiv.), r.t., 3h.

Scheme 1.

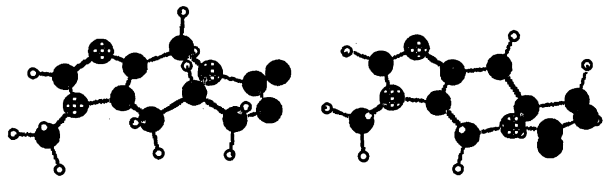


Fig. 2. Minimum energy conformations for tricyclic analogs 4 and 5 according to MNDO calculations.

been possible by application of identical synthetic sequence starting from two methylhistidines, **13** and **14**[17] (Scheme 2).

The Pictet-Spengler reaction of **13** and **14** followed by esterification and neutralization of the methyl ester dihydrochlorides afforded the piperidines **15** (82%) and **16** (75%). The reduction of **15** and **16** by LAH in refluxing THF afforded the amino alcohols **17** (76%) and **18** (78%) respectively.

Treatment of **17** with dimethyl carbonate in methanol at room temperature using sodium methoxide as base afforded a product identical to **4** (85%). Analogous treatment of **18** led to a tricyclic product with identical properties to those previously obtained for **5** (82%).

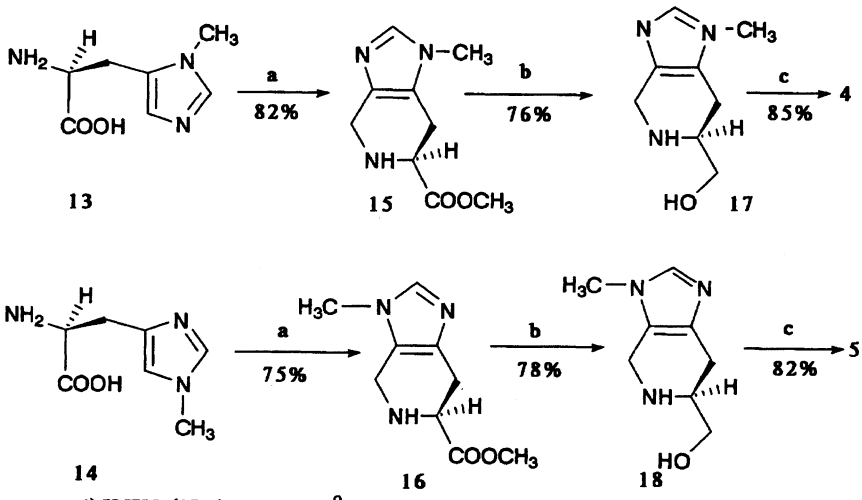
Biological results will be published elsewhere.

Conclusion

The transformation of L-histidine **7** into the tricyclic derivative **12** takes place in a four-step sequence with 51% overall yield. The tricyclic intermediate **12** undergoes a regioselective alkylation (**4** : **5** = 3 : 1) by treatment with NaH and iodomethane in DMF at room temperature. We assume that an aggregated transition state is required for this reaction in which, the electrophilic attack at the N^{π} position is favored because of the differentiation between the two faces of the substrate, which is acting as a ligand in the metal-complex transition state. Theoretical calculations provide the global minimum energy conformations for both isomers. The regioselective synthesis of the (+)-pilocarpine analogs **4** and **5** are also achieved starting from methylhistidines, **13** and **14** with 53 and 48% overall yield, respectively.

Experimental

Organic extracts were dried with commercially dried Na_2SO_4 and evaporated under reduced pressure below 40°C.



Scheme 2.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a digital Perkin-Elmer 241 polarimeter in a 1-dm cell. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 and 50.3 MHz respectively. The IR spectra were determined on a Beckman 33-IR spectrophotometer as indicated in each case. Mass spectra were recorded on a Kratos MS-25 instrument operating with EI (70 eV). Elemental analysis were carried out using a Perkin-Elmer 240 B Analyzer. All compounds discussed in this paper were obtained in a chromatographically homogeneous state.

The (6*S*)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid dihydrate **9**[9,10] was obtained by a variation of the reported procedure.[11] Thus, treatment of L-histidine (Aldrich) with excess of formaldehyde (37%) at pH=7 (0.1 M NaH_2PO_4, 1 M=1 mol dm^{-3}) for 15 h at 60°C afforded **9**[9] (85%) mp 262—265°C (lit,[11] mp 263—265°C).

Methyl (6*S*)-4,5,6,7-Tetrahydro-1*H*-imidazo[4,5-*c*]-pyridine-6-carboxylate Dihydrochloride (10·2HCl). Dry hydrogen chloride was introduced gently into a suspension of **9** (6.5 g, 32 mmol) in methanol at room temperature and the reaction mixture was stirred overnight at the same temperature. Distillation of the solvent afforded **10·2HCl** (7.7 g, 95%). $[\alpha]_D$ −119.8° (*c*1.6, CH_3OH). ^{1}H NMR (CD_3OD) δ=3.34 (1H, ddt, J_1=16.0 Hz, J_2=9.0 Hz, J_3=1.75 Hz, Ar$\underline{CH_2}$CH), 3.62 (1H, dd, J_1=16.0 Hz, J_2=5.5 Hz, Ar$\underline{CH_2}$CH), 3.93 (s, 3H, COO$\underline{CH_3}$), 4.72 (1H, dd, J_1=9.0 Hz, J_2=5.5 Hz, $\underline{CH}$COOCH$_3$), 4.75 (1H, d, J=1.75 Hz, Ar$\underline{CH_2}$N), 4.78 (t, J=1.75, Ar$\underline{CH_2}$N), 8.78 (1H, s, N$\underline{CH}$N), ^{13}C NMR (CD_3OD) δ=20.60 (t, Ar$\underline{CH_2}$CH), 40.03 (t, Ar$\underline{CH_2}$N), 54.43 (q, COO$\underline{CH_3}$), 54.97 (d, $\underline{CH}$COOCH$_3$), 121.94 (s, C7a), 125.41 (s, C3a), 136.52 (d, N$\underline{CH}$N), 168.50 (s, CO) MS *m/z* (%) 255 (M+1, 5), 236 (13), 195 (11), 181 (100), 122 (90), 95 (82), 69 (38), 57 (50). Found: C, 37.90; H, 5.20%. Calcd for $C_8H_{13}O_2N_3Cl_2$ (M.W. 254.11): C, 37.81; H, 5.15%.

Methyl (6*S*)-4,5,6,7-Tetrahydro-1*H*-imidazo[4,5-*c*]-pyridine-6-carboxylate (10). To a solution of **10·2HCl** (5 g, 19.7 mmol) in 5 ml of ethanol were added 39 cm^3 of ethanolic 1 M KOH. Stirring was maintained for 5 min. Then, filtration of the solid and evaporation of the solvent led to the free base **10** (3.56 g, 98%). $[\alpha]_D$ −61.12° (*c*1.5, CH_3OH). IR (film) ν=3420, 3090, 1740, 1650, 1410, 1120, 1085, 1070, 1020, 970, 950, 720 cm^{-1}. ^{1}H NMR (CD_3OD) δ=2.82 (1H, ddt, J_1=15.6 Hz, J_2=8.8 Hz, J_3=1.8 Hz, Ar$\underline{CH_2}$CH), 2.96 (1H, dd, J_1=15.6 Hz, J_2=5.4 Hz, Ar$\underline{CH_2}$CH), 3.34 (3H, s, COO$\underline{CH_3}$), 3.79 (1H, dd, J_1=8.8 Hz, J_2=5.4 Hz, $\underline{CH}$COOCH$_3$), 3.86 (1H, t, J=1.8 Hz, Ar$\underline{CH_2}$N), 3.90 (1H, d, J=1.8 Hz, Ar$\underline{CH_2}$N), 7.54 (1H, s, N$\underline{CH}$N), ^{13}C NMR (CD_3OD) δ=26.90 (t, Ar$\underline{CH_2}$CH), 42.50 (t, Ar$\underline{CH_2}$N), 52.69 (q, COO$\underline{CH_3}$), 56.66 (d, N$\underline{CH}$COOCH$_3$), 127.01 (s, C7a), 129.73 (s, C3a), 135.46 (d, N$\underline{CH}$N), 174.06 (s, CO), MS *m/z* (%) 181 (M, 5), 167 (5), 147 (70), 133 (75), 94 (100). Found: C, 53.11; H, 6.20%. Calcd for $C_8H_{11}O_2N_3$ (M.W. 181.19): C, 53.02; H, 6.12%.

Methyl (6*S*)-1-Methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate (15). Formaldehyde (37%, 10 ml) was added to a solution of a methyl-substituted L-histidine dihydrochloride **13·2HCl**[17] (10 g, 41.3 mmol) in 15 cm^3 of water at pH=7 (0.1 M NaH_2PO_4). Stirring of the reaction for 15 h at 60°C was followed by evaporation of the solvent to afford 12.5 g of crude product. Treatment of the crude with dry HCl in methanol for 15 h at room temperature led to the ester dihydrochloride **15·2HCl** (13.3 g) after the evaporation of the solvent. Neutralization on the dihydrochloride with ethanolic 1 M KOH led to the free base **15** (10 g) by filtration on the KCl and evaporation on the solvent. Flash chromatography of the crude product on silica gel, $CHCl_3$:CH_3OH (9:1), afforded **15** (6.6 g, 82%); $[\alpha]_D$ −80° (*c* 1.0, CH_3OH); IR (film) ν=3425, 3090, 1720, 1650, 1610, 1560, 1408, 1386, 1362, 1240, 1085, 1020, 720, 630 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.68 (1H, dt, J_1=15.8 Hz, J_2=8.7 Hz, J_3=1.6 Hz, Ar$\underline{CH_2}$CH), 2.82 (1H, dd, J_1=15.8 Hz, J_2=5.4 Hz, Ar$\underline{CH_2}$CH), 3.45 (3H, s, N$\underline{CH_3}$), 3.68 (1H, dd, J_1=8.7 Hz, J_2=5.4 Hz, $\underline{CH}$COOCH$_3$), 3.70 (3H, s, COO$\underline{CH_3}$), 3.84 (1H, t, J=1.6 Hz, Ar$\underline{CH_2}$N), 3.87 (1H, d, J=1.6 Hz, Ar$\underline{CH_2}$N), 7.23 (1H, s, N$\underline{CH}$N). ^{13}C NMR ($CDCl_3$) δ=24.27 (t, Ar$\underline{CH_2}$CH), 30.50 (q, N$\underline{CH_3}$), 43.21 (t, Ar$\underline{CH_2}$N), 51.94 (q, COO$\underline{CH_3}$), 55.45 (d, N$\underline{CH}$COOCH$_3$),

122.98 (s, C7a), 135.20 (s, C3a), 138.09 (d, NCHN) 172.85 (s, CO). MS *m/z* (%) 195 (M,15), 136 (85), 134 (40), 109 (80), 108 (100), 95 (35), 81 (60), 69 (80), 57 (80). Found: C, 55.45; H, 6.63%. Calcd for $C_9H_{13}O_2N_3$ (M.W. 195.21): C, 55.37; H, 6.71%.

Methyl (6*S*)-3-Methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-5-carboxylate (16). Prepared under the same conditions as described to prepare **15** from **13·2HCl**. From another methyl-substituted L-histidine dihydrochloride **14·2HCl**[17] (8 g). Flash chromatography on silica gel, $CHCl_3:CH_3OH$ (9:1), afforded **16** (4.8g, 75%); $[\alpha]_D$ −77.4° (*c* 1.6, CH_3OH). IR (film) ν=3280, 2980, 1720, 1520, 1450, 1240, 1210, 1150, 1020, 960, 760 cm^{-1}. ^1H NMR (CD_3OD) δ=2.70 (1H, ddt, J_1=15.8 Hz, J_2=8.8 Hz, J_3=1.7 Hz, ArCH$_2$CH), 2.85 (1H, dd, J_1=15.8 Hz, J_2=5.5 Hz, ArCH$_2$CH), 3.50 (3H, s, N–CH$_3$), 3.58 (1H, dd, J_1=8.8 Hz, J_2=5.5 Hz, CHCOOCH$_3$), 3.69 (3H, s, COOCH$_3$), 3.79 (1H, t, J=1.7 Hz, ArCH$_2$N), 3.88 (1H, d, J=1.7 Hz, ArCH$_2$N), 7.40 (1H, s, NCHN). ^{13}C NMR (CD_3OD) δ= 28.77 (t, ArCH$_2$CH), 31.50 (q, NCH$_3$), 40.22 (t, ArCH$_2$N), 52.72 (q, COOCH$_3$), 56.72 (d, NCHCOOCH$_3$), 126.09 (s, C7a), 133.90 (s, C3a), 137.88 (d, NCHN), 174.46 (s, CO). MS *m/z* (%) 195 (M, 75), 180 (5), 163 (10), 136 (100), 134 (40), 109 (70), 108 (60), 95 (20), 81 (20). Found: C, 55.47: H, 6.58%. Calcd for $C_9H_{13}O_2N_3$ (M.W. 195.21): C, 55.37; H, 6.71%.

(6*S*)- 6- Hydroxymethyl- 4, 5, 6, 7- tetrahydro- 1*H*-imidazo[4,5-*c*]pyridine (11). To a suspension of **10** (4.5 g, 24.8 mmol) in 250 cm^3 of dry THF was added $LiAlH_4$ (2.82 g, 74 mmol) in small portions. The reaction mixture was stirred under reflux for 48 h under nitrogen atmosphere. The reaction mixture was worked up as usually and the white solid residue was extracted in a Soxhlet with refluxing THF for 72 h.[12] Evaporation of the combined organic portions afforded **11** (2.66 g, 70%) mp 190—192°C; $[\alpha]_D$ −71.08° (*c* 1.8, CH_3OH). IR (KBr) ν=3310, 3110, 1605, 1445, 1385, 1240, 1070, 1040, 1012, 820, 790, 715 cm^{-1}. ^1H NMR (CD_3OD) δ=2.32 (1H, ddt, J_1=15.4 Hz, J_2=11.1 Hz, J_3=2.3 Hz, ArCH$_2$CH), 2.55 (1H, dd, J_1=15.4 Hz, J_2= 4.3 Hz, ArCH$_2$CH), 2.92 (1H, m, NCHCH$_2$OH), 3.50 (1H, dd, J_1=6.9 Hz, J_2=10.8 Hz, CH$_2$OH), 3.60 (1H, dd, J_1=10.8 Hz, J_2=5.3, CH$_2$OH, 3.75 (2H, m, ArCH$_2$N), 7.41 (1H, s, NCHN). ^{13}C NMR (CD_3OD), δ=26.25 (t, ArCH$_2$CH), 43.37 (t, ArCH$_2$N), 58.60 (d, CHCH$_2$OH), 68.83 (t, CH$_2$OH), 127.51 (s, C7a), 130.66 (s, C3a), 135.11 (d, NCHN). MS *m/z* (%) 153 (M, 5), 135 (12), 123 (10), 111 (20), 97 (30), 81 (45), 69 (90), 57 (100). Found: C, 54.93; H, 7.15%. Calcd for $C_7H_{11}N_3O$ (M.W. 153.18): C, 54.88; H, 7.23%.

(6*S*)-6-Hydroxymethyl-1-methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (17). Prepared under the same conditions as described to prepare **11** from **10**. From **15** (5 g), was obtained **17** (3.25 g, 76%); $[\alpha]_D$ −62.37° (*c* 1.1, CH_3OH); IR (KBr) ν=3386, 2924, 1656, 1612, 1585, 1510, 1439, 1385, 1224, 1078, 1024, 909, 842, 737, 675 cm^{-1}. ^1H NMR (CD_3OD) δ=2.32 (1H, ddt, J_1=15.3, J_2=11.0 Hz, J_3=2.5 Hz, ArCH$_2$CH) 2.61 (1H, dd, J_1=15.3 Hz, J_2=4.5 Hz, ArCH$_2$CH), 2.96 (1H, m, NCHCH$_2$OH), 3.53 (3H, s, NCH$_3$), 3.55 (1H, dd, J_1=6.8 Hz, J_2=10.7 Hz, CH$_2$OH), 3.68 (1H, dd, J_1=10.7, J_2=4.90, CH$_2$OH), 3.74 (2H, m, ArCH$_2$N), 7.40 (1H, s, NCHN). ^{13}C NMR (CD_3OD), δ= 24.24 (t, ArCH$_2$CH), 31.08 (q, NCH$_3$), 44.31 (t, ArCH$_2$N), 56.51 (d, CHCH$_2$OH), 65.75 (t, CH$_2$OH), 126.04 (s, C7a), 135.41 (s, C3a), 137.50 (d, NCHN). MS *m/z* (%) 167 (M, 30), 136 (80), 108 (100), 81 (50), 69 (60), 55 (85). Found: C, 57.51; H, 7.74%. Calcd for $C_8H_{13}N_3O$ (M.W. 167.20): C, 57.46; H, 7.83%.

(6*S*)-6-Hydroxymethyl-3-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine (18). Prepared under the same conditions mentioned above for the transformation of **15** into **17**. From **16** (4.5 g) was obtained **18** (3.0 g, 78%); $[\alpha]_D$ −61.2° (*c* 2.1, H_2O), IR (KBr); 3256, 2955, 1638, 1506, 1456, 1415, 1385, 1295, 1216, 1180, 1050, 1020, 950, 808, 735, 630 cm^{-1}. ^1H NMR (CD_3OD), δ=2.32 (1H, ddt, J_1=15.0 Hz, J_2=10.8 Hz, J_3=2.4 Hz, ArCH$_2$CH), 2.52 (1H, dd, J_1=15.0 Hz, J_2=4.6 Hz, ArCH$_2$CH), 2.9 (1H, m, NCHCH$_2$OH), 3.50 (3H, s, NCH$_3$), 3.55 (1H, dd, J_1=6.5 Hz, J_2=10.8 Hz, CH$_2$OH), 3.63 (1H, dd, J_1=10.8 Hz, J_2=4.9 Hz, CH$_2$OH), 3.80 (1H, t, J=2.0 Hz, ArCH$_2$N), 3.82 (1H, d, J=1.8 Hz, ArCH$_2$N), 7.38 (1H, s, NCHN). ^{13}C NMR (CD_3OD) δ=28.07 (t, CH$_2$Ar), 31.39 (q, NCH$_3$), 40.94 (t, ArCH$_2$N), 56.90 (d, CHCH$_2$OH), 65.93 (t, CH$_2$OH), 126.93 (s, C7a), 135.38 (s, C3a), 137.84 (d, NCHN). MS *m/z* (%) 167 (M, 20), 162 (25), 136 (100), 109 (50), 81 (20). Found: C, 57.53; H, 7.74%. Calcd for $C_8H_{13}N_3O$ (M.W. 167.20): C, 57.46; H, 7.83%.

(8a*S*)-4,8,8a,9-tetrahydro-1*H*,6*H*-imidazo[4,5-*d*]oxazolo[3,4-*a*]pyridin-6-one (12). Sodium hydride (70%) (1.2 g, 35.3 mmol) was added to a solution of **11** (2.70 g, 17.6 mmol) in 50 cm^3 of absolute methanol. The reaction mixture was stirred 30 min at room temperature under nitrogen atmosphere. Then, dimethyl carbonate (1.5 ml, 18 mmol) was added and stirring was maintained overnight. Evaporation of the solvent was followed by partition of the residue (4 g) by flash chromatography on silica gel. Elution with $CHCl_3:CH_3OH$=8:2 afforded **14** (2.75 g, 87%); mp 97°C (CH_3OH); $[\alpha]_D$ −158.6° (*c* 1.8, CH_3OH); IR (KBr) ν= 3490, 3055, 1746, 1650, 1620, 1470, 1450, 1422, 1400, 1350, 1280, 970, 770 cm^{-1}. ^1H NMR (CD_3OD) δ=2.64 (1H, ddt, J_1=15.1 Hz, J_2=9.9 Hz, J_3=2.1 Hz, ArCH$_2$CH), 2.88 (1H, ddd, J_1=15.1 Hz, J_2=4.6 Hz, J_3=1.2 Hz, ArCH$_2$CH), 4.09 (1H, m, CHCH$_2$OCO), 4.14 (1H, dt, J_1=15.5 Hz, J_2=1.8 Hz, ArCH$_2$N), 4.22 (1H, dd, J_1=8.4 Hz, J_2=5.6 Hz, CH$_2$OCO), 4.57 (1H, dd, J_1=15.5 Hz, J_2=1.8 Hz, ArCH$_2$N), 4.60 (1H, t, J=8.4 Hz, CH$_2$OCO), 7.59 (1H, s, NCHN). ^{13}C NMR (CD_3OD) δ=28.30 (t, ArCH$_2$CH), 40.30 (t, ArCH$_2$N), 53.64 (d, NCH$_2$OCO), 69.96 (t, CH$_2$OCO), 125.76 (s, C8a), 128.29 (C, 3a), 136.49 (d, NCHN), 159.77 (s, CO). MS *m/z* (%) 179 (M, 71), 134 (31), 118 (25), 94 (100). Found: C, 53.58; H, 5.11%. Calcd for $C_8H_9N_3O_2$ (M.W. 179.17): C, 53.62; H, 5.06%.

(8a*S*)- 1- Methyl- 4, 8, 8a, 9- tetrahydro- 1*H*, 6*H*- imidazo[4,5-*d*]oxazolo[3,4-*a*]pyridin-6-one (4) and (8a*S*)-3-Methyl-4,8,8a,9-tetrahydro-3*H*,6*H*-imidazo[4,5-*d*]-oxazolo[3,4- *a*]pyridin-6-one (5). Sodium hydride (70%) (0.17 g, 5 mmol) was added to a solution of **12** (0.89 g, 5 mmol) in 25 cm^3 of DMF under nitrogen atmosphere at 0°C. The reaction mixture was stirred 30 min at room temperature and iodomethane (0.7 g, 5 mmol) was added. The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent was followed by flash chromatography of the residue (0.83 g). Elution with $CHCl_3:CH_3OH$ (95:5) afforded **5** (0.62 g, 75%) mp 154—156°C (CH_3OH); $[\alpha]_D$ −80.4° (*c* 1.4, CH_3OH). IR (KBr) ν=3130, 3010, 1750, 1586, 1507, 1471, 1450, 1426, 1386,

1350, 1275, 1224, 1185, 1015, 967, 807, 770, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.62 (1H, ddt, J_1=15.0 Hz, J_2=10.2 Hz, J_3=1.8 Hz, ArC$\underline{H_2}$CH), 2.82 (1H, ddd, J_1=15.0 Hz, J_2=4.7 Hz, J_3=1.5 Hz, ArC$\underline{H_2}$CH), 3.54 (3H, s, NC$\underline{H_3}$), 4.02 (1H, m, C$\underline{H}$CH$_2$OCO), 4.14 (1H, dt, J_1=15.2 Hz, J_2=1.8 Hz, ArC$\underline{H_2}$N), 4.15 (1H, dd, J_1=8.2 Hz, J_2=5.8 Hz, C$\underline{H_2}$OCO), 4.57 (1H, t, J_1=8.2 Hz, C$\underline{H_2}$OCO), 4.68 (1H, dd, J_1=15.2 Hz, J_2=1.5 Hz, ArC$\underline{H_2}$N), 7.37 (NC$\underline{H}$N). ^{13}C NMR ($CDCl_3$) δ=29.65 (t, ArC$\underline{H_2}$CH), 31.10 (q, NC$\underline{H_3}$), 37.75 (t, ArC$\underline{H_2}$N), 52.35 (d, C$\underline{H}$CH$_2$OCO), 68.46 (t, C$\underline{H_2}$OCO), 121.49 (s, C8a), 132.89 (s, C3a), 137.35 (d, NC$\underline{H}$N), 157.34 (s, CO). MS *m/z* (%) 193 (M, 31), 178 (5), 148 (30), 132 (30), 121 (15), 108 (100), 81 (60). Found: C, 55.87; H, 5.82%. Calcd for $C_9H_{11}N_3O$ (M.W. 193.20): C, 55.94; H, 5.74%.

Elution with $CHCl_3$: CH_3OH (9:1) afforded **4** (0.21 g, 25%); $[\alpha]_D$ −84.0° (*c* 1.35, CH_3OH); IR (KBr) ν=3420, 1743, 1435, 1412, 1370, 1280, 1260, 1000, 900, 800, 735 cm^{-1}. ^1H NMR δ=2.65 (1H, ddt, J_1=14.5 Hz, J_2=9.6 Hz, J_3=2.4 Hz, ArC$\underline{H_2}$CH), 2.89 (1H, ddd, J_1=14.5 Hz, J_2=4.8 Hz, J_3=1.6 Hz, ArC$\underline{H_2}$CH), 3.53 (3H, s, NC$\underline{H_3}$), 4.00 (1H, m, C$\underline{H}$CH$_2$OCO), 4.15 (1H, dd, J_1=8.2 Hz, J_2=5.7 Hz, CH$_2$OCO), 4.17 (1H, dt, J_1=15.5 Hz, J_2=2.4 Hz, ArC$\underline{H_2}$N), 4.57 (1H, t, J=8.2 Hz, C$\underline{H_2}$OCO), 4.68 (1H, dd, J_1=15.5 Hz, J_2=1.6 Hz, ArC$\underline{H_2}$N), 7.37 (s, 1H, NC$\underline{H}$N). ^{13}C NMR ($CDCl_3$) δ=26.01 (t, ArC$\underline{H_2}$CH), 30.96 (q, NC$\underline{H_3}$), 41.00 (t, ArC$\underline{H_2}$N), 51.97 (d, NC$\underline{H}$CH$_2$O), 67.97 (t, C$\underline{H_2}$OCO), 121.88 (s, C8a), 133.09 (s, C3a), 137.64 (d, NC$\underline{H}$N), 171.75 (s, CO). MS *m/z* (%) 193 (M, 31), 148 (20), 134 (15), 121 (10), 108 (100), 81 (37), 42 (52). Found: C, 55.86; H, 5.82%. Calcd for $C_9H_{11}N_3O_2$: C, 55.94; H, 5.74%.

4(from **17**): Prepared under the same conditions as mentioned above for the preparation of **12** from **11**. **17** (2 g) afforded **4** (1.9 g, 85%) with identical spectroscopic properties to those mentioned above.

5(from **18**): Prepared under identical conditions as used in the transformation of **11** into **12**. From **18** (2.5 g) was obtained **5** (2.36 g, 82%) with identical spectroscopic properties to those mentioned above.

(8a*S*)-1,3-Dimethyl-5-oxo-4,8,8a,9-tetrahydro-3*H*, 6*H*-imidazo[4,5-*d*]oxazolo[3,4-*a*]pyridin-1-ium Iodide (6). Sodium hydride (70%) (0.14 g, 4 mmol) was added to a solution of **12** (0.7 g, 3.9 mmol) in 25 cm^3 of DMF at 0°C under nitrogen atmosphere. The reaction mixture was stirred for additional 30 min at room temperature. Then, iodomethane (1.1 g, 8 mmol) was dropwise added and the reaction mixture was stirred overnight at the same temperature. Evaporation of the solvent afforded **6** (1 g, 85%); mp 181—183°C (CH_3OH); $[\alpha]_D$ −98.96° (*c* 1.25, CH_3OH); IR (KBr) ν=3450, 3130, 2995, 1740, 1640, 1568, 1420, 1270, 1260, 1190, 1070, 767, 735, 702 cm^{-1}. ^1H NMR (CD_3OD) δ=2.75 (1H, ddt, J_1=15.5 Hz, J_2=9.7 Hz, J_3=2.2 Hz, ArC$\underline{H_2}$CH), 3.13 (1H, ddt, J_1=15.5, J_2=4.5 Hz, J_3=1.1 Hz, ArC$\underline{H_2}$CH), 3.82 (1H, s, NC$\underline{H_3}$), 3.84 (1H,s, NC$\underline{H_3}$), 4.22 (1H, m, C$\underline{H}$CH$_2$OCO), 4.32 (1H, dd, J_1=8.8 Hz, J_2=4.8 Hz, C$\underline{H_2}$OCO), 4.34 (1H, dt, J_1=15.8 Hz, J_2=2.2 Hz, ArC$\underline{H_2}$N), 4.68 (1H, t, J_1=8.8 Hz, C$\underline{H_2}$OCO), 4.82 (1H, dd, J_1=15.8 Hz, J_2=1.1 Hz, ArC$\underline{H_2}$N), 8.89 (1H, s, NC$\underline{H}$N). ^{13}C NMR (D_2O) δ=26.00 (t, ArC$\underline{H_2}$CH), 34.52 (q, NC$\underline{H_3}$), 34.99 (q, NC$\underline{H_3}$), 38.13 (t, ArC$\underline{H_2}$N), 52.25 (d, C$\underline{H}$CH$_2$OCO), 69.65 (t, C$\underline{H_2}$OCO), 127.19 (s, C8a), 128.78 (s, C3a), 137.43 (d, NC$\underline{H}$N), 158.85 (s,CO). MS (FAB) *m/z* (%) 207 (15), 193 (30), 147 (100). Found: C: 35.94; H, 4.30%. Calcd for $C_{10}H_{14}N_3O_2I$ (MW 335.13): C, 35.83; H, 4.21%.

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