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Synthesis of Pyrrolizidines via Copper(I) Catalyzed Radical Atom Transfer Cyclization

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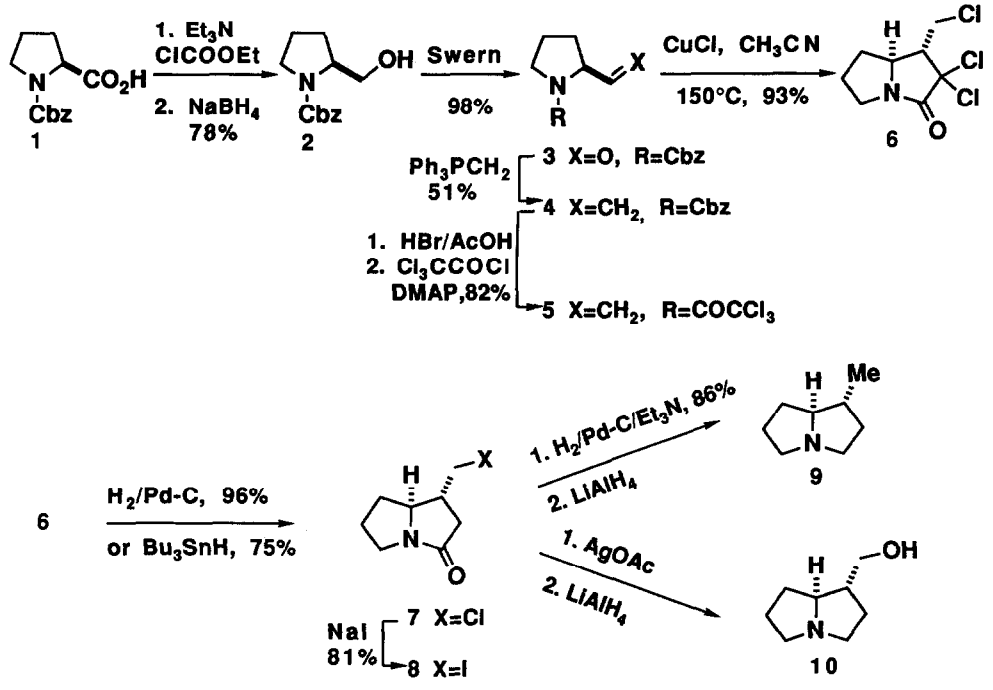
Trachelanthamidine and pseudoheliotridane are synthesized from (2S)-N-trichloroacetyl-2-vinylpyrrolidine (5) by a 5-exo-trig radical cyclization. The intermediate radical is generated heating 5 in a sealed tube (CH3CN/ 160°C) using CuCl as catalyst and the cyclization occurs in very good yield (93%). Cyclized product 6 is transformed either into (-)-trachelanthamidine (55% yield from 5) or into (-)-pseudoheliotridane (42% yield from 5).

Pyrrolidine ring is present in a wide variety of complex natural products. This fact has raised a great number of studies concerning to the development of useful synthetic methods for constructing this ring. Thus, the 3-aza-5-hexenyl radicals have been extensively investigated as a very useful synthetic approach[1] being successfully applied to the synthesis of bioactive substances presenting this type of ring system, among these, the pyrrolizidine alkaloids are remarkable, since they are known to exhibit an incredible range of biological activities, including antitumor, hypotensive, hepatotoxic actions, insect attraction, etc.,[2] and a lot of effort has been dedicated to develop new syntheses for them.[3]

In the last years, most of the synthetic routes via radical cyclization of heteroatom-containing substrates are based in generating an alkyl radical by treatment of haloalkanes with a radical initiator such as, AIBN or by photochemical methods.[1] Tributyltin hydride is usually added in order to transfer an hydrogen atom to the cyclized radical product. However the cyclizations reported till now, either via radical[1] or via palladium,[4] always are reported with poor or moderate yields of pyrrolizidines. Following with our interest in developing synthetic methods for pyrrolizidine alkaloids,[5] we thought that instead of using the usual tin hydride cyclization for the closure of a pyrrolidine ring we could generate a suitable radical by homolysis of a trihaloalkane by heating it in the presence of a catalytic ammount of Cu(I).[6] This radical adds to carbon-carbon multiple bonds intramolecularly affording a cyclized trihaloacetamide (scheme I). One of the advantages of this methodology compared with the tin hydride one is the lack of the secondary product arising from just the reduction of the halogen atom.

Scheme I

In this communication we focus on construction of the C1-C2 bond of the pyrrolizidine alkaloids pseudoheliotridane (9) and trachelantamidine (10) via cyclization of a radical derived from homolysis of C-Cl bond in a N-allyl-α-trichloroacetamide by a copper(I)-catalyzed cyclization. In this case the radical is generated from a trihaloalkane when heated in the presence of copper (I) chloride.



Scheme II

The required precursor for performing the radical cyclization was (S)-2-vinyl-N-(trichloroacetyl)pyrrolidine (5). This compound was prepared from L-proline following the synthetic scheme II. It was necessary to carry out a two step protection-deprotection of L-proline since trichloroacetamide group is not compatible with sodium borohydride reductive conditions. Thus, (S)-2-vinyl-N-(tert-benzyloxycarbonyl)pyrrolidine (4) was transformed into the trichloroacetamide 5 by deprotection of the benzyloxycarbonyl group with HBr-HOAc followed by treatment with Cl_3CCOCl/DMAP in 82% yield. The cyclization of 5 to give 6 was achieved by heating in acetonitrile with CuCl in a sealed tube, the use of pressure shown to be necessary since when we tried another sets of conditions (table I) yields were poorer and the reactions less clean, although in all cases over 70%. This key cyclization provide a diastereoface selection in an atom-transfer annulation, which induces the quirality present at C2 affording only one diastereoisomer, due to the steric hinderance of the pyrrolidine nucleus.

Table I: Cyclization of compound (5) to afford compound (6).

Solvent	Temperature	Reaction time	Yield (%)
CH_3CN	160°C (pressure)	2 h	93
CH_3CN	reflux	20 h	75
Toluene/Py (95:5)	reflux	12 h	71

The two geminal chlorine atoms present in lactam 6 were reduced by hydrogenolysis[7] or by treatment with Bu_3SnH affording 7 in 99 and 75% yield respectively. Filkenstein reaction of 7 with NaI in butanone under reflux gave iodide 8, this compound can be converted into (-)-pseudoheliotridane (9) by reduction of the iodide and the amide groups (1.H_2/Pd-C/Et_3N 86%, 2.$LiAlH_4$ 68%[4]) or its conversion to (-)-trachelantamidine (10) by replacing first the iodine atom by an acetoxy group[4] and reduction of the lactam and acetoxy group with lithium aluminum hydride.

Experimental Section

General Methods. Melting points were determined using a Büchi apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker WP-250 operating at 250 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. Low-resolution electron-impact mass spectra were recorded on a Hewlett-Packard mass spectrometer HP-59970MS Chem Station with direct sample insertion. Infrared spectra were measured on a Mattson instrument FT-IR Galaxy 2020 (cm^{-1}). Optical rotations were measured at room temperature at the sodium D line with a Perkin-Elmer 141 polarimeter and have been converted to specific rotations. Concentrations of the specific rotations are given as g/100 ml. Flash chromatography was performed using silica gel. Acetonitrile was distilled from calcium hydride under argon atmosphere.

N-benzyloxycarbonyl-L-prolinol (2). To a solution of N-benzyloxycarbonyl-L-proline (1) (8.75 g, 35.1 mmol) in THF (90 ml) at 0°C was added triethylamine (6.7 ml, 45.63 mmol). After the solution was stirred for 35 min at 0°C ethyl chloroformate was added (3.9 ml, 42.1 mmol) dropwise and left with stirring at room temperature for 45 min. Then the reaction mixture was cooled again at 0°C and a cool solution of $NaBH_4$ (2.68 g, 71 mmol) in water (60 ml) was added. The mixture was allowed to warm to room temperature and stirred at this temperature overnight. The reaction mixture was then cooled to 0°C, acidified with aq. 5% HCl till pH 5-6 and the THF solvent concentrated. The aqueous layer was extracted with ethyl acetate, organic extracts washed with aq. 10% NaOH, brine, dried (Na_2SO_4) and evaporated. Column chromatography (1:1 EtOAc/petroleum ether 60-80) of the crude material afforded N-benzyloxycarbonyl-L-prolinol (2) (6.47 g, 78%) as a pale yellow oil. [α] -40 (c 1.05, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.36 (br s, 5H, ArH), 5.14 (br s, 2H, CH_2Ph), 4.00 (br s, 1H), 3.66-3.34 (m, 4H), 2.06-1.60 (m, 4H). MS, m/z (relative intensity) 235 (M^+, 4), 204 (48), 160 (31), 138 (10), 91 (100).

(2S)-N-benzyloxycarbonyl-2-formyl-pyrrolidine (3). To a solution of oxalyl chloride (5.06 ml, 57.97 mmol) in dichloromethane (115 ml) at -60°C under argon was added DMSO (4.04 ml) in dichloromethane (50 ml). After 10 min a solution of N-benzyloxycarbonyl-L-prolinol (2) (12.94 g, 55.01 mmol) in dichloromethane (100 ml) was added and the solution was stirred for 15 min. Triethylamine (40.9 ml, 294 mmol) was added and the reaction mixture was allowed to reach room

temperature. Water (250 ml) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane, and the combined organic extracts washed with aqueous 1% HCl, aqueous 4% sodium carbonate and brine, dried with sodium sulfate and concentrated to afford the crude product 3 (12.7 g, 98%), (IR (film, NaCl) ν 1730, 1700) which was used in the next step without additional purification.

(2S)-N-benzyloxycarbonyl-2-vinylpyrrolidine (4). Sodium hydride (80% in parafin, 180 mg, 6 mmol) was added to DMSO (5 ml) at 0°C, and the resulting suspension was heated at 55°C under argon for 1 h. Methyltriphenylphosphonium bromide in DMSO (8 ml) was added to the above solution by syringe and heated to 55°C another 45 min. To a solution of (2S)-N-benzyloxycarbonyl-2-formyl-pyrrolidine (3) (1.3 g, 5.6 mmol) in DMSO (15 ml) was added the above solution of Wittig reagent by syringe using a water bath to refrigerate and the mixture was stirred at room temperature overnight. The reaction mixture was added over ice-water (30 ml) and extracted with CH_2Cl_2 (5 x 25 ml). The organic layer was washed with water (25 ml), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (1:4) to afford the oily product N-benzyloxycarbonyl-2-vinylpyrrolidine (4) (0.650 g, 51%). [α] -9 (c 1.6, CH_2Cl_2). IR (film, NaCl) ν 1705, 1410, 1354, 1112. ^{1}H NMR ($CDCl_3$) δ 7.34 (br s, 5H, ArH), 5.77 (m, 1H, $\underline{CH}$=CH_2), 5.12-5.00 (m, 4H, CH=$\underline{CH_2}$, CH_2Ph), 4.40 (br s, 1H, H-2), 3.47 (br s, 2H, H-5), 2.05-1.72 (m, 4H, H-3, H-4).MS m/z 231 (0.3), 204 (9), 91 (100).

(2S)-N-trichloroacetyl-2-vinylpyrrolidine (5). A solution of HBr-HOAc (33%, 9.6 ml, 53.8 mmol) was added to N-benzyloxycarbonyl-2-vinylpyrrolidine (4) (2.1 g, 9.1 mmol) under ice-cooling and the solution was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (24 ml) under ice-cooling and DMAP (3.7 g, 30.49 mmol) and trichloracetyl chloride (3.13 ml, 28.5 mmol) were added and the solution was stirred at room temperature overnight. Dichloromethane (65 ml) was added to the reaction mixture and the organic layer was washed with water (20 ml), 10% HCl (20 ml), brine, dried over sodium sulfate and concentrated. The residue was purified by column cromatography on silicagel eluted with ethyl acetate-hexane (1:9) to afford a solid product of N-trichloroacetyl-2-vinylpyrrolidine (5) (1.8 g, 82%). Mp 36-38°C (hexane/Et_2O). [α] -18 (c 0.75, CH_2Cl_2). IR (KBr) ν 2980, 1678, 1384, 841, 810. ^{1}H NMR ($CDCl_3$) δ 5.77 (ddd, 1H, J= 17.1, 10.3 and 5.6 Hz, $\underline{CH}$=CH_2), 5.17 (d, 1H, J= 17.2 Hz, CH=$\underline{CH_2}$), 5.15 (d, 1H, J= 10.2 Hz, CH=$\underline{CH_2}$), 4.68 (m, 1H, H-2), 3.95 (m, 2H, H-5), 2.00 (m, 3H, CH_2CH_2), and 1.78 (m, 1H, CH_2CH_2). MS, m/z (relative intensity) 247 (0.2), 245 (1.7), 243 (54), 241 (5.6), 124 (98), and 81 (100). Anal. cald. for C_8 H_{10} Cl_3 N O: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.75; H, 4.39; N, 6.02.

(1R,8S)-1-chloromethyl-2-dichloro-3-oxo-hexahydropyrrolizidine (6). A suspension of 5 (500 mg, 2.06 mmol) and recently recrystallized copper (I) chloride (194 mg,1.96 mmol) in deoxygenated acetonitrile (14 ml) is heated in a sealed tube with a teflon tap at 160°C for 2 h. After cooling, solvent was removed under reduced pressure and the residue purified by flash column on silicagel eluted with hexane-ethyl acetate (4:1) to afford 6 as a white solid (467 mg, 93%). Mp 60-62°C (hexane/Et_2O). [α] -24 (c 1.0, CH_2Cl_2), IR ν 2972, 1918, 1413, 843. ^{1}H NMR ($CDCl_3$) δ 3.98 (dd, 1H, J= 11.3, 4.2 Hz, CHCl), 3.86 (dd, 1H, J=11.3 and 10.3 Hz, CHCl), 3.68 (m, 1H, CHN), 3.55 (m, 1H, CH_2N), 3.28 (ddd, 1H, J= 12.1, 8.9 and 3.2 Hz, CHN), 2.76 (m, 1H, CH_2CH_2), 2.17 (m, 2H, CH_2CH_2), 1.60 (m, 1H, CH_2CH_2). MS, m/z (relative intensity) 247 (13), 245 (12), 243 (4), 241 (0.4), 206 (100). Anal. cald. for C_8 H_{10} Cl_3 N O: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.67; H, 3.98; N, 5.53.

(1R, 8S)-1-cloromethyl-3-oxo-hexahydropyrrolizidine (7). Method (a): A solution of 6 (500 mg, 2.06 mmol) in abs. ethanol containing NaOAc (500 mg, 6.1 mmol) was stirred under an atmosphere of hydrogen in the presence of a catalytic amount of 10% Pd-C for 1 d. The solution was filtered through celite and the filtrate evaporated and purified by column chromatography on silica gel eluted with dichloromethane:methanol (98:2) to afford an oily product of 7 (345 mg, 96%), as an oil.

Method (b): To a solution of 6 (50 mg, 0.21 mmol) in dry toluene (7 ml) under argon atmosphere were added tributyltin hydride (0.19 ml, 0.73 mmol) and a catalytic amount of AIBN, and refluxed 1 d. The reaction mixture was concentrated and purified by flash chromatography on silica gel eluted with EtOAc:hexane (1:1 -> 7:3) to afford 7 (27 mg, 76%).

[α] -19.3 (c 0.3, CH_2Cl_2). IR (film, NaCl) ν 2926, 1690, 1420. ^1H NMR ($CDCl_3$) δ 3.76-3.49 (m, 4H, CH_2Cl, CHN), 3.05 (ddd, 1H, J= 12.1, 8.9 and 3.7 Hz, CHN), 2.62-2.46 (m, 3H, $\underline{CH}CH_2Cl$, CH_2CON), 2.21-2.00 (m, 3H, CH_2CH_2), 1.44 (m, 1H, CH_2CH_2). MS m/z 175 (18), 173 (54), 138 (43), 70 (100). Anal. cald. for C_8 H_{12} Cl N O: C, 55.34; H, 6.96; N, 8.07. Found: C, 55.75; H, 6.81; N, 8.00.

(1R,8S)-1-Iodomethyl-3-oxo-hexahydropyrrolizidine (8). A suspension of 1-chloromethyl-3-oxo-hexahydropyrrolizidine (7) (400 mg, 2.34 mmol) and sodium iodide (1.8 g, 12 mmol) in butanone (60 ml) was stirred at reflux under argon overnight. The reaction mixture was evaporated and diluted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, evaporated and purified by flash column on silica gel eluted with diclorometha ne:methanol (95:5) to afford 8 (504 mg, 81%), as an oil. [α] -17.4 (c 1.2, CH_2Cl_2), IR (film, NaCl) ν 2970, 1680, 1415, 1188. ^1H NMR ($CDCl_3$) δ 3.65-3.48 (m, 2H, CHN), 3.31 (dd, 1H, J= 10.1 and 5.4 Hz, CH_2I), 3.22 (dd, 1H, J= 10.1 and 7.6 Hz, CH_2I), 3.06 (ddd, 1H, J= 11.6, 8.5 and 4.1 Hz, CHN), 2.67-2.35 (m, 3H, CH_2CON, $\underline{CH}CH_2I$), 2.32-2.10 (m, 1H, CH_2CH_2), 2.08-1.96 (m, 2H, CH_2CH_2), 1.52-1.36 (m, 1H, CH_2CH_2). MS, m/z (relative intensity) 265 (M^+, 8), 138 (71), 70 (100).

(-)Pseudoheliotridane (9). A solution of idodide 8 (214 mg, 0.82 mmol) in dry methanol (15 ml) and freshly distilled triethylamine was stirred under an atmosphere of hydrogen in the presence of a catalytic amount of 10% Pd-C for 1 d. The solution was filtered through celite and the filtrate evaporated. The residue was purified by column chromatography on silica gel eluted with dichloromethane:methanol (95:5) to afford (1R, 8S)-1-methyl-3-oxo-hexahydropyrrolizidine (97 mg, 86%) as an oil. [α] -47.1 (c 0.55 $CHCl_3$). IR (film, ClNa) ν 2959, 1687, 1422. ^1H NMR ($CDCl_3$) δ 3.59-3.45 (m, 2H, CHN), 3.06 (m, 1H, CHN), 2.55 (dd, 1H, J= 16.0 and 8.4 Hz, CHCON), 2.40 (dd, 1H, J= 16.0 and 10.9 Hz, CHCON), 2.20-1.97 (m, 4H, CH_2CH_2, CHMe), 1.38 (m, 1H, CH_2CH_2), 1.15 (d, 3H, J= 6.6 Hz, Me). MS m/z (relative intensity) 139 (M^+, 53), 138 (70), 124 (14), 111 (65), 96 (100).

(1R, 8S)-1-Methyl-3-oxo-hexahydropyrrolizidine was reduced with $LiAlH_4$ following the procedure described in ref. 4 to give (-)pseudoheliotridane in 68% yield. [α] -5.2 (c 1.15, $CHCl_3$) (lit.[8] d-isomer [α] +6.94, l-isomer [α] -8.25).

(-)Trachelantamidine (10). (1R, 8S)-1-iodomethyl-3-oxo-hexahydropyrrolizine was transformed through (1R, 8S)-1-acetoxymethyl-3-oxo-hexahydropyrrolizine in (-)-trachelantamidine (77% yield) following de procedure described in ref. 4. [α] -13.5 (c 1.9, $CHCl_3$) (lit.[9] [α] -13.8 (c 1.28 in EtOH).

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