Total Synthesis of DL-Isoretronecanol and DL-Trachelanthamidine using Anodic Methoxylation in a Key Functionalizing Step *

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The title substances have been synthesized in six steps from simple starting materials. The key step involved anodic functionalization of the tertiary amide 9 followed by an intramolecular amidalkylation, thus creating the pyrrolidine ring system in 11. The two diastereomeric pairs of compounds 4a and 4b were then separated by column chromatography. These lactams were reduced cleanly with retained stereochemistry to the title substances 1a and 1b, respectively.

An attempt at an intramolecular amidalkylation of the monoester 3 resulted in the formation of an 0-alkylated product, the ketene acetal 6.

The ability of α-substituted amides to undergo acid-catalyzed nucleophilic substitution, shown in eqn. 1, is a well-established

\[
\begin{align*}
R-CO-N-C-X & \quad \text{Nu}^- \quad \xrightarrow{\text{acid}} \\
R-CO-N-C-Nu
\end{align*}
\]

\(X=\text{OH}, \text{OR, halide, etc.}\)

fact in organic chemistry. However, applications of this reaction, known as the amidalkylation reaction, to cyclic systems have been limited due to the inaccessibility of these types of amides. In 1966, Ross and co-workers discovered that

\[
\begin{align*}
R-CO-N-C-OCH_3 & \quad \xrightarrow{\text{acid}} \\
R-CO-N-C+ & \leftrightarrow R-CO-N+C
\end{align*}
\]

This stabilized cation can then be captured by a number of nucleophilic species, such as aromatic compounds, olefins, acetylenes and malonic ester derivatives. It is the purpose of this work to show the usefulness of the following sequence of reactions:

* See Ref. 1.
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Anodic alkoxylation of an amide followed by reaction with a nucleophile to form a new carbon-carbon bond, by its application to the synthesis of the pyrrolizidine ring system, as outlined in Scheme 1 (Z is an electron-withdrawing group). Alkaloids containing this ring system are widely distributed in nature both in the free form, and, more commonly, as esters of the necic acids in Senecio alkaloids. The biochemistry, synthesis and pharmacology of these alkaloids have been continuously reviewed. In this paper, we focus on the two simplest bases, i.e. the two diastereomers trachelanthamidine (1a) and isoretronecanol (1b). Similar approaches to the synthesis of the quinolizidine ring system were recently reported by several groups.

RESULTS

The synthesis of the necine bases 1a and 1b began with the acylation of pyrrolidine with succinic anhydride giving 2a in 83% yield (Scheme 2). This carboxylic acid was then esterified using a strongly acidic ion exchange resin as a catalyst to give 2b in almost quantitative yield. The anodic oxidation of 2b in methanol containing Bu₄NBF₄ as supporting electrolyte proceeded smoothly, and, after passage of 2.6 F/mol, a 95% yield of the methoxyolated compound 3 was isolated. When 3 was submitted to amidokyla- tion conditions (TiCl₄/CH₂Cl₂), the product isolated after column chromatography showed an MS with a molecular ion peak at 183, indicating loss of methanol from 3, which is consistent with the desired structure 4. The ¹H NMR spectrum, however, showed a multiplet at 5.6 ppm corresponding to one proton seemingly in a vinyllic position, implying that the enamide 5 had been formed. For comparison, 5 was prepared simply by distilling 3 at reduced pressure. It turned out that 5 had completely different spectral properties from the unknown product and was thus excluded from the possibilities. Further reaction of this unknown material with LiAlH₄ in THF, a reagent known to reduce the two stereoisomers 4a and 4b stereospecifically to 1a and 1b, respectively, gave a compound where MS gave a molecular ion of 143, which is inconsistent with 1a or 1b. ¹H NMR indicated that the structure of the reduced product corresponds to 7. This implies that if the product from amidokyla- tion of 3 is bicyclic, the new bond being formed must be a carbon-heteroatom bond, since carbon-carbon bonds are usually inert to LiAlH₄. The accumulated evidence leads us to suggest 6 as the tentative structure for the unknown product. Compound 6 is actually isomeric with 4, but instead of the desired C-alkylation a to the ester, O-alkylation has occurred creating a ketene acetal. We believe this is due to the inability of the ester 3 to enolize under the reaction conditions. The proposed structure also explains the unexpected instability of this material; in solution a rapid decomposition to enamide 5 and
several other, unidentified products, took place.

The results described hitherto are perhaps not unexpected, considering the fact that α-methoxylated amides have been reacted mostly with doubly activated nucleophiles such as malonic and acetooacetic esters and, in a few cases with simple ketones.5–8,11 There is no case of a successful amidoalkylation using a simple ester as nucleophile. What is surprising, however, is that a reaction actually occurs creating the unusual structure 6.

In view of the reactivity of α-methoxyamides discussed above, it was logical for us to try an intramolecular amidoalkylation on a malonic ester derivative such as 10. The synthesis of 10 is outlined in Scheme 2 and began with the acylation of pyrrolidine with bromoacetyl bromide at −78 °C giving 1-(1-bromoacetyl)-pyrrolidine (8) in 86 % yield. Alkylation of dimethyl malonate with 8 produced the diester 9 in 83 % yield. Anodic oxidation of 9 under similar conditions as for 2b gave 10, again in a high yield (90 %). Treatment of 10 with AlCl₃ gave the desired pyrrolizidine 11 in 90 % yield. In this case, AlCl₃ is much superior to TiCl₄; with 3, however, only enamine 5 was formed using AlCl₃ as catalyst. Conversion of 11 to 4 was achieved in one step, using the Krapcho dealkoxyacylation procedure.17 The yield of 4 was 85 %, the product consisting of a mixture of isomers, 4a and 4b in a ratio of 4:1, which could be separated on a silica column. Since the ethyl ester corresponding to 4b has been characterized15 and the minor isomer formed had almost identical spectral properties whereas the major differed substantially, the minor isomer was identified as 4b. Moreover, regardless of the reagent used to cause the demethoxyacylation (LiCl/DMF, NaCl/DMF, NaCN/DMF), the two isomers were formed in the same ratio, which might indicate that the reaction was subject to thermodynamic control. This was tested by heating pure 4a or 4b to 50 °C with potassium tert-butoxide in DMSO. Irrespective of starting material, a 4:1 ratio of 4a and 4b was formed which confirmed that this is the position of the equilibrium. This is in accord with earlier work on compounds 12a and 12b where 12a has been shown to be the thermodynamically most stable isomer, 12b being converted into 12a on treatment with base.18

A further test of the stereochemistry of 4a and 4b was provided by reduction of 4a with LiAlH₄ in THF which produced trachelanthamidine, 1a, in 88 % yield. The reduction of 4b to 1b is known to proceed with retention of the stereochemistry,15 and thus, the formal synthesis of isoroteneanol, 1b, is completed. The total yield of the described synthesis is 43 % which compares favourably with synthesis reported earlier.13

Note added in proof. In a recent publication, 1a and 1b were synthesized in seven steps via anodic methoxylation of the corresponding carbamate; Shono, T., Matsumura, Y., Uchida, K., Tsubata, K. and Makino, A. J. Org. Chem. 49 (1984) 300.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were recorded on a JEOL MH 100 or, where indicated, at 360 MHz using a Nicolet FT instrument. Carbon 13 nuclear magnetic resonance spectra were recorded on a JEOL FX 60 spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard using CDCl₃ as the solvent. IR spectra were recorded on a Perkin-Elmer 298 instrument. Mass spectral analyses were carried out on a Finnigan 4021 spectrometer at 70 eV using a direct inlet unless otherwise indicated. For analysis of crude reaction mixtures a Hewlett-Packard 5830A gas chromatograph fitted with 5 % NPGS column (2 m × 3 mm) or a 5 % OV 351 column (1 m × 3 mm) was used. Electrolyses were carried out in a water-cooled cell with an AMEL 552 potentiostat set for constant current electrolysis. In all chromatographic separations, the flash chromatography technique was used.19

Preparation of carboxylic acid (2a). To a stirred solution of succinic anhydride (20 g, 0.2 mol) in 250 ml CHCl₃ was added pyrrolidine (35 ml, 0.42 mol) dropwise. On completion of the

mildly exothermic reaction the reaction mixture was refluxed for 1 h and then allowed to stand overnight. After evaporation of the solvent and some unreacted pyrrolidine, the residue was acidified with 10% HCl, the organic phase separated, the aqueous phase extracted three times with CHCl₃. The combined organic extracts were washed with saturated NaCl, dried and evaporated. The product, 28.4 g (83%) of an off-white solid could be recrystallized from ethyl acetate, m.p. 109–111 °C (lit. 20 106.5–108 °C); IR (KBr): 2980, 2960, 1727, 1604 cm⁻¹. ¹H NMR: 1.55–2.03 (4H, m), 2.43 (4H, s), 3.15–3.49 (4H, m), 11.88 (1H, broad s), m/e (rel. int.) 171 (8), 98 (17), 97 (15), 70 (100).

Esterification of 2a. 2a (20.5 g, 0.12 mol) was dissolved in 200 mL abs. methanol and 5 g of the strongly acidic cation exchange resin Amberlyst 15 were added. After stirring for 15 h, the solution was filtered, evaporated and the residue distilled using a kugelrohr apparatus (bath temperature 80 °C at 0.1 mmHg). Yield: 21.3 g (96%). IR (film): 2960, 2880, 1738, 1640 cm⁻¹. ¹H NMR: 1.69–2.07 (4H, m), 2.41–2.75 (4H, m), 3.29–3.53 (4H, m), 3.65 (3H, s), m/e (rel. int.): 185 (5), 154 (10), 115 (23), 98 (12), 70 (100).

Methoxylation of 2b. A solution of 2b (6.1 g, 33 mmol) in 250 mL methanol containing Bu₄NF (0.05 M) as supporting electrolyte was oxidized at a Pt anode (8×10 cm) in an undivided cell at a constant current of 300 mA. The progress of the electrolysis was followed by TLC. After passage of 2.6 F/mol the electrolysis was discontinued, the solvent evaporated, the residual oil treated with 250 mL of ether which was separated. After two more ether extractions the white crystalline residue (containing almost pure Bu₄NF which can be re-used for electrolysis) was separated and the combined ether extracts evaporated. The residual oil was chromatographed on a 50×4 cm silica column using ether–ethyl acetate 1:1 (v/v) as eluent to yield 3 (6.7 g, 95%) as a colourless liquid. IR (film): 2950, 2870, 1738, 1640 cm⁻¹. ¹H NMR: 1.75–2.15 (4H, m), 2.54–2.78 (4H, m), 3.22–3.66 (6H, m), 3.71 (3H, s), m/e (rel. int.): 216 (10), 184 (48), 115 (24), 100 (10), 85 (11), 70 (100).

Enamide 5. The methoxylated amide 3 was distilled using a kugelrohr apparatus (bath temperature 80 °C at 0.1 mm Hg). Yield: 92%. IR (film): 3100, 2945, 2825, 1730, 1652, 1610 cm⁻¹. ¹H NMR (360 MHz): 2.55–2.82 (6H, m), 3.70 (3H, s), 3.81–3.88 (2H, m), 5.20–5.27 (1H, m), 6.53 (0.5 H, dt, J₉=4.4 Hz, Jₑ=2.1 Hz), 6.92 (0.5 H, dt, Jₑ=4.4 Hz, Jₑ=2.1 Hz), m/e (rel. int.): 183 (14), 152 (13), 115 (25), 69 (100), 59 (22), 55 (48), 41 (46).

**Attempted ring-closure of 3.** 3 (1.08 g, 5 mmol) was added to a solution of TiCl₄ (1.1 ml, 5 mmol) in 10 ml CH₂Cl₂ at 0 °C under argon atmosphere. The solution was stirred for 3 h. After an aqueous work-up, the crude product was purified by column chromatography on a silica column (25×2 cm) using ethyl acetate as an eluent. Yield: 0.43 g (43%) of an unstable colourless liquid. Because of this instability we were unable to obtain a good ³¹C NMR. IR (film): 2950, 2880, 1738, 1640 cm⁻¹. ¹H NMR (360 MHz): 1.88–2.20 (4H, m), 2.55–2.73 (4H, m), 3.25–3.72 (4H, m), 5.53–5.75 (1H, m), m/e (rel. int.): 183(4), 115(42), 86(30), 70(48), 69(68), 59(59), 55(78), 43(100).

**Reduction of 6.** This reduction was performed with LiAlH₄ in THF according to a literature procedure. The spectral properties of the product were in complete agreement with the proposed structure of the product, 7.

**Preparation of 1-((bromacetyl)-pyrrolidine (8).** A solution of pyrrolidine (71.2 g, 1.0 mol) in 100 ml CH₂Cl₂ was added dropwise to a solution of bromoacetyl bromide (47.6 ml, 0.55 mol) in 500 ml CH₂Cl₂ which was kept under argon atmosphere at −78 °C. The rate of the addition was adjusted so that the reaction temperature did not exceed −50 °C. After the addition, the temperature was kept at −78 °C for another 15 min, 15 ml abs. methanol were added and the dry ice bath removed. When the temperature had reached 0 °C, the reaction mixture was washed with 200 ml water and with 200 ml 10% HCl. The aqueous phases were extracted twice with CH₂Cl₂, and, finally the combined organic phases were washed with a saturated NaCl solution. After drying and evaporation of the solvent, the residue was distilled using a kugelrohr apparatus (bath temperature 90 °C at 0.1 mm Hg) giving 83 g (86%) of 8 as a colorless oil. IR (film): 2970, 2880, 1725, 1640 cm⁻¹. ¹H NMR: 1.69–2.18 (4H, m), 3.37 (4H, m), 3.84 (2H, s), m/e (rel. int.): 193 (3), 191 (3), 112 (62), 98 (60), 70 (50), 55 (100).

**Preparation of diester 9.** 9 was prepared according to the standard procedure for alkylation of malonic ester from 0.5 mol sodium dimethylmalonate, 0.4 mol 8 in 250 mL abs. methanol. The crude reaction mixture (containing more than 90% 8) was purified by flash filtering through a short (40×3 cm) silica column using ethyl acetate as eluent giving pure 9 (82.0 g, 83%) as a colourless liquid. IR (film): 2980, 2880, 1730, 1640 cm⁻¹. ¹H NMR: 1.75–2.11 (4H, m), 2.88 (2H, d, J=7.5 Hz), 3.31–3.56 (4H, m), 3.77 (6H, s), 3.98 (1H, t, J=7.5 Hz), m/e (rel. int.): 243 (3), 212 (2), 180 (8), 145 (12), 113 (26), 70 (100).

**Anodic methoxylation of 9.** The electrolysis

was carried out as described for 2b. In this case, however, a graphite anode (5×10 cm) was used which caused a somewhat higher current efficiency. The electrolysis was interrupted after passage of 2.2 F/mol and work-up was carried out as described for 3. The product was purified by recrystallization from ether at -20°C giving the α-methoxymethyl amide 10 (90 % material yield) as white crystals, m.p. 45-46°C, IR (KBr): 2980, 2960, 2880, 1733, 1659 cm⁻¹. ¹H NMR: 1.63-2.21 (4H, m), 2.99 (2H, dd, J₁=7.5 Hz, J₃=11.3 Hz), 3.29-3.66 (6H, m), 3.79 (6H, s), 4.02 (1H, t, J=7.5 Hz). ¹³C NMR: 169.9, 169.4, 88.71, 87.09, 56.41, 53.97, 52.76, 47.40, 46.02, 45.70, 33.93, 33.28, 31.49, 30.92, 22.89, 21.02, m/e (rel. int.): 274 (1), 210 (5), 145 (18), 113 (25), 70 (100).

Intramolecular amidokylation of 10. A solution of 10 (13.7 g, 50 mmol) in 50 ml CH₂Cl₂ was added dropwise to a stirred suspension of AlCl₃ (10.0 g, 75 mmol) in 100 ml CH₂Cl₂ during 30 min while cooling the reaction mixture with ice. Stirring was continued for 4 h. 100 ml water were added and the organic phase separated. The aqueous phase was extracted twice with CH₂Cl₂, the combined organic extracts were washed with saturated NaCl solution, dried and evaporated. The diester 11 was obtained (10.9 g, 90 %) as white crystals after recrystallization from ethyl acetate, m.p. 105-107°C, IR (KBr): 2960, 2905, 1735, 1685 cm⁻¹. ¹H NMR (360 MHz). 1.26-1.58 (1H, m), 1.96-2.11 (3H, m), 2.97 (1H, ddd, J₁=17.2 Hz, J₂=1.2 Hz, J₃=0.8 Hz), 3.06-3.14 (1H, m), 3.18 (1H, d, J=17.2 Hz), 3.53-3.61 (1H, m), 3.78 (3H, s), 3.80 (3H, s), 4.53 (1H, dd, J₁=5.9 Hz, J₂=10.2 Hz). ¹³C NMR: 171.2, 169.9, 169.0, 64.69, 57.14, 53.16, 52.84, 41.64, 41.39, 27.51, 26.05. m/e (rel. int.): 241 (1), 213 (8), 182 (20), 154 (11), 113 (14), 70 (100).

Demethoxycarbonylation of 11. A stirred mixture of 11 (1.21 g, 5 mmol), LiCl (212 mg, 5 mmol), water (90 mg, 5 mmol) and DMSO (10 ml) was slowly heated to the reflux temperature. Heating was continued until no further gas evolution took place. After cooling, the mixture was diluted with 50 ml water and extracted three times with CH₂Cl₂. The organic phase was washed with saturated NaCl solution, dried and evaporated. Gas chromatographic and mass spectral analyses indicated the presence of two isomers in a ratio of 4:1. These isomers could be separated by column chromatography on silica (40×2 cm) and ethyl acetate–ether (1:1, v/v) as eluent. The total yield of 4a and 4b was 0.78 g (85 %).

Spectral data (4a): IR (film): 2950, 2885, 1737, 1690 cm⁻¹. ¹H NMR (360 MHz): 1.40-1.55 (1H, m), 1.98-2.23 (3H, m), 2.65-2.73 (1H, m), 2.93-3.12 (3H, m), 3.57 (1H, dt, J=11.5 Hz, J=7.9 Hz), 3.75 (3H, s), 4.01-4.09 (1H, m). ¹³C NMR: 172.4, 172.1, 63.79, 52.27, 45.77, 41.23, 38.47, 31.65, 26.70. m/e GLC inlet (rel. int.): 183 (4), 168 (8), 155 (30), 96 (72), 70 (100).

Spectral data (4b): IR (film): 2955, 2890, 1733, 1690 cm⁻¹. ¹H NMR (360 MHz): 1.22-1.35 (1H, m), 1.82-2.14 (3H, m), 2.80-2.86 (2H, m), 3.02-3.11 (1H, m), 3.41 (1H, dt, J=5.5 Hz, J=8.1 Hz), 3.61 (1H, dt, J=11.5 Hz, J=8.1 Hz), 3.72 (3H, s), 4.07-4.16 (1H, m). ¹³C NMR: 173.6, 172.5, 62.98, 52.19, 42.04, 40.17, 36.37, 27.75, 26.29. m/e GLC inlet (rel. int.): 183 (12), 152 (6), 124 (7), 96 (7), 70 (100).

Equilibration of 4a or 4b (18.3 mg, 0.1 mmol), respectively, was dissolved in 5 ml DMSO and potassium t-butoxide (15 mg) was added. The solution was kept at 50°C for 20 min. After aqueous work-up, GLC analysis indicated the presence of 4a and 4b in a ratio of 4:1.

Reduction of 4a, synthesis of trachelanthamidine (1a). 4a was reduced with LiAlH₄ in THF according to the literature procedure. The product was distilled using a kugelrohr apparatus (bath temperature 120°C at 0.1 mmHg), yield of 1a: 88 %, m/e (rel. int.): 141 (15), 124 (10), 110 (8), 83 (100), 82 (57). Picrate, m.p. 177-178°C (lit. 174-175.5°C).

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