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

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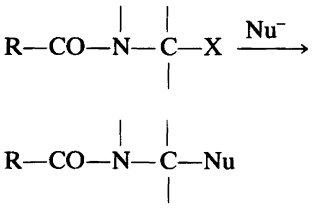
The title substances have been synthesized in six steps from simple starting materials. The key step involved anodic functionalization of the tertiary amide *9* followed by an intramolecular amidoalkylation, thus creating the pyrrolizidine ring system in *11*. The two diastereomeric pairs of compounds *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 amidoalkylation of the monoester *3* resulted in the formation of an *O*-alkylated product, the ketene acetal *6*.

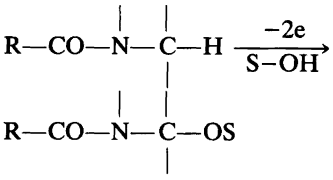
The ability of α-substituted amides to undergo acid-catalyzed nucleophilic substitution, shown in eqn. 1, is a well-established



(1)

X=OH, OR, halide, etc.

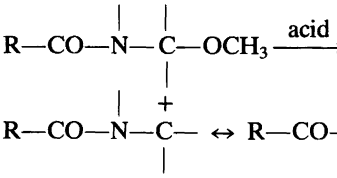
fact in organic chemistry[2]. However, applications of this reaction, known as the amidoalkylation reaction, to cyclic systems have been limited due to the inaccessibility of these types of amides. In 1966, Ross and co-workers discovered[3] that amides, containing a hydrogen on one of the α-carbons can be oxidized electrochemically in a nucleophilic solvent, usually methanol, to give α-substituted products in high yields:



(2)

The reaction is quite general for tertiary amides, both cyclic and acyclic, and can be run on a large scale using an undivided cell and constant current electrolysis,[4,5] making these types of compounds easily available.

Since their discovery by Ross, the chemistry of α-methoxylated amides, especially cyclic ones, has been studied extensively[5–10] and it has been shown that these compounds are excellent precursors to α-acyliminium ions:



(3)

This stabilized cation can then be captured by a number of nucleophilic species, such as aromatic compounds,[7] olefins,[10] acetylenes[10] and malonic ester derivatives.[8,11]

It is the purpose of this work to show the usefulness of the following sequence of reactions:

* See Ref. 1.

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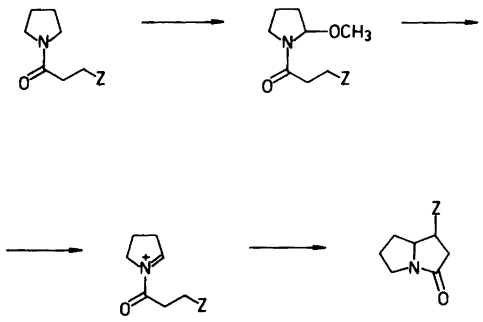


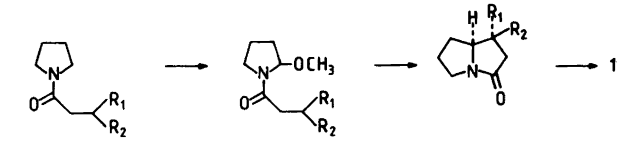
Anodic alkoxylation of an amide followed by reaction with a nucleophile to form a new carbon–carbon bond, by its application to the synthesis of the pyrrolizidine ring system, as outlined in Scheme 1 (Z is an electron-withdrawing group). Alkaloids containing this ring system are widely distributed in 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.[13] In this paper, we focus on the two simplest bases, *i.e.* the two diastereomers trachelanthamidine (*1a*) and

1a 1b

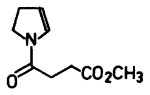
isoretronecanol (*1b*).[14] Similar approaches to the synthesis of the quinolizidine ring system were recently reported by several groups.[12]

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 Bu_4NBF_4 as supporting electrolyte proceeded smoothly, and, after passage of 2.6 F/mol, a 95 % yield of the methoxylated compound *3* was isolated. When *3* was submitted to amidoalkylation conditions[8] ($TiCl_4/CH_2Cl_2$), 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 vinylic 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 $LiAlH_4$ in THF, a reagent known to reduce the two stereoisomers *4a* and *4b* stereospecifically to *1a* and *1b*,[15] 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 amidoalkylation of *3* is bicyclic, the new bond being formed must be a carbon–heteroatom bond, since carbon–carbon bonds are usually inert to $LiAlH_4$. 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 *α* to the ester, *O*-alkylation has ocurred creating a ketene acetal.[16] 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 instabillity of this material; in solution a rapid decomposition to enamide *5* and



2a: R_1=CO_2H, R_2=H
2b: R_1=CO_2CH_3, R_2=H
9: R_1=R_2=CO_2CH_3
3: R_1=CO_2CH_3, R_2=H
10: R_1=R_2=CO_2CH_3
4a: R_1=CO_2CH_3, R_2=H
4b: R_1=H, R_2=CO_2CH_3
11: R_1=R_2=CO_2CH_3



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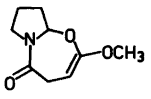

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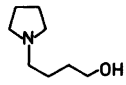

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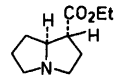
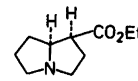
several other, unidentified products, took place.

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 acetoacetic esters and, in a few cases with simple ketones.[6–8,11] 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 $AlCl_3$ gave the desired pyrrolizidine *11* in 90 % yield.In this case, $AlCl_3$ is much superior to $TiCl_4$; with *3*, however, only enamide *5* was formed using $AlCl_3$ as catalyst. Conversion of *11* to *4* was achieved in one step, using the Krapcho dealkoxycarbonylation 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 characterized[15] 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 demethoxycarbonylation (LiCl/DMSO, NaCl/DMSO, 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 *t*-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]



12a



12b

A further test of the stereochemistry of *4a* and *4b* was provided by reduction of *4a* with $LiAlH_4$ 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 isoretronecanol, *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 $CDCl_3$ 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 $CHCl_3$ 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 $CHCl_3$. 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 Bu_4NBF_4 (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 Bu_4NBF_4 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, J_d=4.4 Hz, J_t=2.1 Hz), 6.92 (0.5 H, dt, J_d=4.4 Hz, J_t=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 $TiCl_4$ (1.1 ml, 5 mmol) in 10 ml CH_2Cl_2 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 ^{13}C 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 $LiAlH_4$ in THF according to a literature procedure.[15] The spectral properties of the product were in complete agreement with the proposed structure of the product, *7*.

Preparation of 1-(1-bromoacetyl)-pyrrolidine (*8*). A solution of pyrrolidine (71.2 g, 1.0 mol) in 100 ml CH_2Cl_2 was added dropwise to a solution of bromoacetyl bromide (47.6 ml, 0.55 mol) in 500 ml CH_2Cl_2 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 CH_2Cl_2, 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[21] 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-methoxylated 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, J_1=7.5 Hz, J_2=11.3 Hz), 3.29–3.66 (6H, m), 3.79 (6H, s), 4.02 (1H, t, J=7.5 Hz). ^{13}C 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 amidoalkylation of 10. A solution of *10* (13.7 g, 50 mmol) in 50 ml CH_2Cl_2 was added dropwise to a stirred suspension of $AlCl_3$ (10.0 g, 75 mmol) in 100 ml CH_2Cl_2 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 CH_2Cl_2, the combined organic extracts washed with saturated NaCl, dried and evaporated. The diester *11* was obtained (10.9 g, 90 %) as white crystals after one recrystallization from ethyl acetate, m.p. 105–107 °C. IR (KBr): 2960, 2905, 1735, 1685 cm^{-1}. ^1H NMR (360 MHz). 1.26–1.38 (1H,m), 1.96–2.11 (3H,m), 2.97 (1H, ddd, J_1=17.2 Hz, J_2=1.2 Hz, J_3=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, J_1=5.9 Hz, J_2=10.2 Hz). ^{13}C 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 CH_2Cl_2. The organic phase was washed with saturated NaCl, 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): 2955, 2885, 1737, 1690 cm^{-1}. ^1H NMR (360 MHz): 1.40–1.53 (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_d=11.5 Hz, J_t=7.9 Hz), 3.75 (3H, s), 4.01–4.09 (1H, m). ^{13}C 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_d=5.5 Hz, J_t=8.1 Hz), 3.61 (1H, dt, J_d=11.5 Hz, J_t=8.1 Hz), 3.72 (3H, s), 4.07–4.16 (1H, m). ^{13}C NMR: 174.3, 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 4. *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 $LiAlH_4$ in THF according to the literature procedure.[15] 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.[22] 174–175.5 °C).

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