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SYNTHESIS OF 3,5-DISUBSTITUTED 1-AZABICYCLIC SYSTEMS: INTERMEDIATES FOR NOVEL MUSCARINIC LIGANDS

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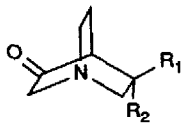
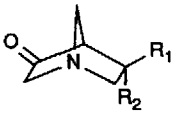
Summary - 3,5-disubstituted quinuclidines were obtained stereoselectively from 4-bromoacetylpiperidine (7) to give (1a) and (1b) (9:1) or by Dieckmann cyclisation of piperidine (9) to give ketals (13a) and (13b) (9:1). Pyrrolidine triester (14) gave exclusively the endo-1-azanorbornane ester (15a). Epimerisation of (13a) and (15a) gave (13b) and (15b) respectively as the thermodynamic products.

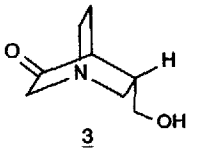
In the course of studies of novel cholinergic agents based on quinuclidine and 1-azanorbornanes[1] we required syntheses of the versatile keto ester intermediates (1) and (2). No examples of disubstituted 1-azanorbornanes have been reported previously, and the only case of quinuclidine with this substitution pattern gives an alcohol rather than the required ester[2]. For our purposes both diastereoisomers were needed. We report two syntheses of the novel intermediate (1) using either intramolecular alkylation or Dieckmann cyclisation. Application of the latter approach to (2), resulted in the stereoselective synthesis of both isomers in each case, providing the first examples of 3,5-disubstituted-1-azanorbornanes.



1a R_1=H, R_2=CO_2Me
1b R_1=CO_2Me, R_2=H



2a R_1=H, R_2=CO_2Me
2b R_1=CO_2Me, R_2=H



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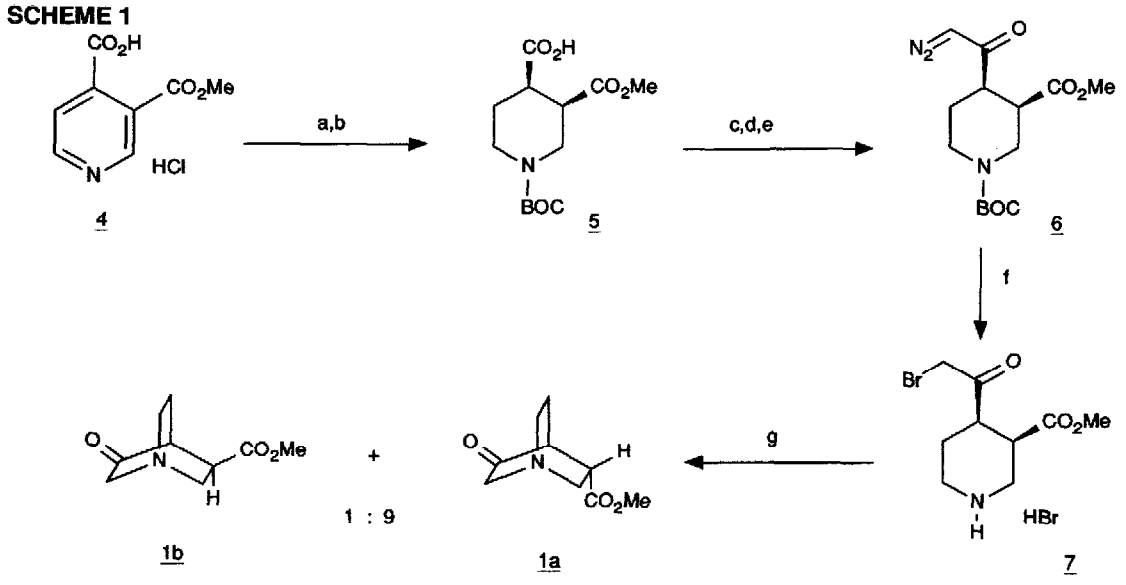
The only known 3,5-disubstituted quinuclidine is the alcohol (3)[2], formed by Dieckmann cyclisation of a bicyclic lactone, which would yield (1) on oxidation. However, in our hands the published route gave very poor yields and only traces of (3) were obtained. An alternative approach, which produces the ester directly, involving intramolecular alkylation of an amine by a bromoketone has been studied (Scheme 1). Hydrogenation of the pyridine monoester hydrochloride (4)[3] followed by BOC protection yielded mainly the cis-piperidine (5) (9:1 cis:trans, 82% yield, m.p. 130-136°C)[4]. The acid

chloride of (5), prepared via the sodium salt was treated with excess diazomethane to produce the diazoketone (6) in 71% yield after chromatography. Brief treatment of (6) with hydrogen bromide in acetic acid effected regiospecific introduction of the bromoketone and concomitant removal of the BOC group to give (7). Cyclisation of (7) was best carried out by slow addition (4h) of a solution of the salt in acetonitrile to a refluxing solution of Hunig's base in the same solvent under high dilution (1g in 300ml). Under these conditions (1) was obtained in 55% yield from (6) as a 9:1 mixture of (1a) and (1b), from which pure (1a) was obtained by mplc or by crystallisation of the hydrochloride (m.p. 171-172°C). Previously it was reported[5] that cyclisations of 4-bromoacetylpiperidines in aqueous alkali fail unless a geminal 4-substituent is present. No cyclisation of (7) was observed under aqueous conditions. The present method provides a short, stereoselective synthesis of (1a) in satisfactory yield, but the need to perform the cyclisation under high dilution coupled with the hazards of handling large quantities of diazomethane make it unsuitable for preparing (1) on a large scale.

We therefore turned our attention to the Dieckmann cyclisation, which is probably the most practical route to quinuclidinones[6]. Triester (8), the formal precursor to (1), cannot be used because of cyclisation to the 3 position. In the reported synthesis of (3), this problem was avoided by reduction of the ester, but we reasoned that the 3-carboxyl could be kept at the correct oxidation level by protection as the diethyl amide (9). The decreased reactivity and increased bulk should direct attack to the 4 position. Pyridine monoester (10)[3] was converted smoothly to amide salt (11) via the acid chloride. Hydrogenation over platinum at high pressure yielded (12) as mainly the cis-isomer (9:1, 92%), which was alkylated with methyl bromoacetate in the presence of potassium carbonate to form (9) in 89% yield. Cyclisation was achieved by adding (9) to a solution of potassium t-butoxide in refluxing toluene, followed by hydrolysis and reesterification, but instead of the expected ketone (1), the ketals (13) were obtained. The ratio of (13a) to (13b) was 9:1, in 65% overall yield. Formation of the ketal proved fortuitous, since not only could the separation of isomers now be achieved easily by flash chromatography to give pure (13a) (hydrochloride m.p. 163-166°C), but it also allowed epimerisation to a mixture in which (13b) predominated by 6:1 and was isolated in the same way (oxalate m.p. 88-91°C) (75% recovery). Deprotection of the separated ketals using perchloric acid gave pure (1a) and (1b) (hydrochloride m.p. 181-182°C) in 80-85% yield. This synthesis can be carried out conveniently on a multigram scale: typically 120g of (9) was used for the cyclisation, and either diastereoisomer can be obtained preferentially.

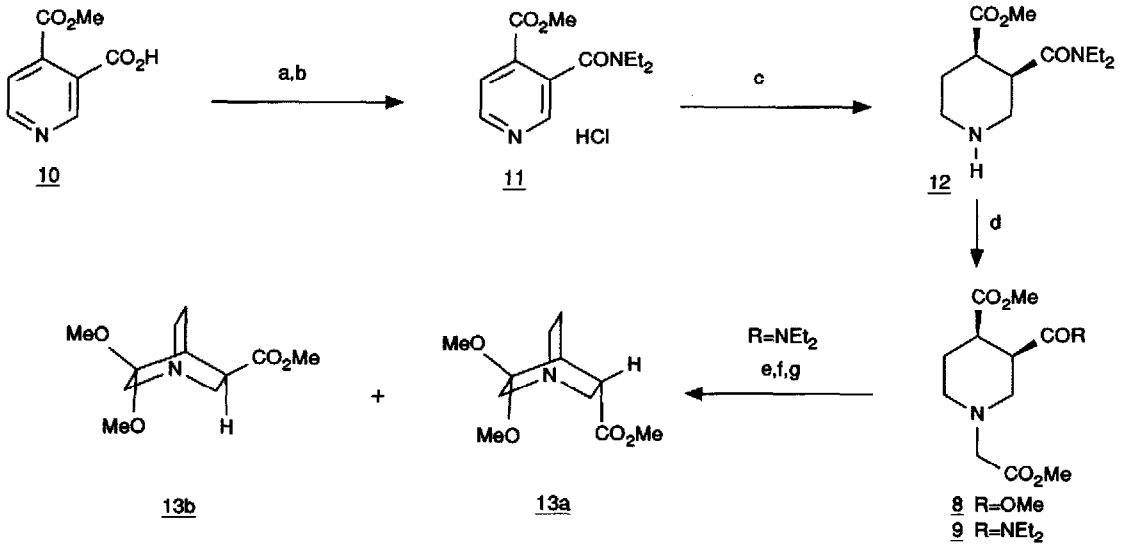
A similar Dieckmann cyclisation strategy was also employed for the synthesis of 3,5-disubstituted-1-azanorbornanes, which have greater affinity for the receptor[7]. (Scheme 3). In this case, with a symmetrical precursor, there is no regiochemical problem. The prerequisite pyrrolidine triester (14) was prepared by cyclisation of dimethyl fumarate with the azomethine ylid generated from N-benzyl glycine and

SCHEME 1



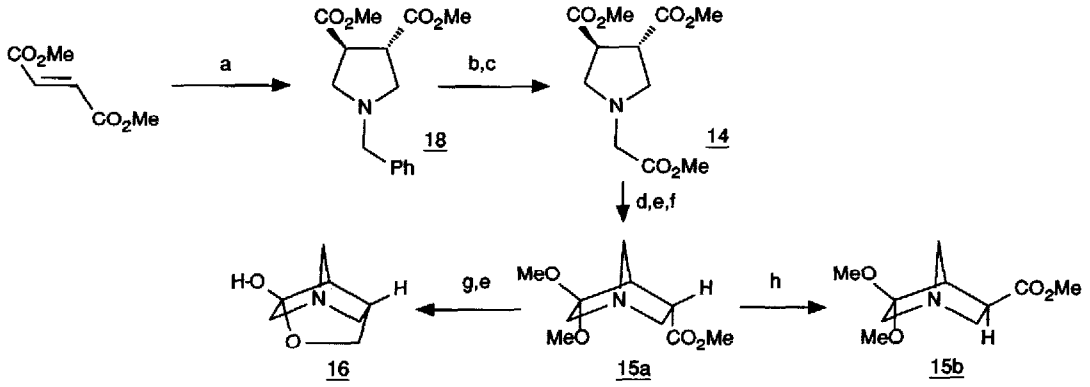
REAGENTS: a) H_2, PtO_2, MeOH; b) BOC_2O, Na_2CO_3, dioxan; c) NaH, THF,⇅; d) $SOCl_2$, THF,⇅; e) excess CH_2N_2; f) HBr, HOAc; g) iPr_2NEt, MeCN, high dilution, ⇅.

SCHEME 2



REAGENTS: a) $(COCl_2)$, CH_2Cl_2; b) Et_2NH; c) H_2, PtO_2, MeOH, 8bar; d) $BrCH_2CO_2Me$, K_2CO_3, PhMe, 60°; e) KOtBu, PhMe, ⇅; f) conc. HCl, ⇅; g) MeOH, HCl, $(MeO)_3CH$.

SCHEME 3



REAGENTS: a) $PhCH_2NHCH_2CO_2H$, $(CH_2O)_n$, PhMe, ⇅; b) H_2, $Pd(OH)_2$, MeOH; c) $BrCH_2CO_2Me$, K_2CO_3, PhMe,⇅; d) KOtBu, PhMe,⇅; e) conc. HCl,⇅; f) $SOCl_2$, MeOH; g) $LiAlH_4$, THF; h) NaOMe, MeOH,⇅.

paraformaldehyde[8,9]. Hydrogenation over Pearlman's catalyst followed by alkylation with methyl bromoacetate gave (14) in 71% yield. Dieckmann cyclisation with KOtBu in toluene, followed by hydrolysis, decarboxylation and reesterification with concomitant ketalisation surprisingly gave exclusively the endo-ketalester (15a) (25%, oxalate m.p. 135-137°C). The stereochemistry of (15a) was proved unequivocally by reduction with $LiAlH_4$ and formation of the cyclic hemiketal (16) (60%, m.p. 148-150°C) by refluxing in hydrochloric acid. Formation of (15a) requires isomerisation of the trans pyrrolidine (14); it is unclear when this occurs, but is probably prior to cyclisation. Epimerisation of (15a) with sodium methoxide resulted in complete conversion to the thermodynamic exo-ketalester (15b). Further elaboration of ketones (1) and (2) will be described elsewhere.

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