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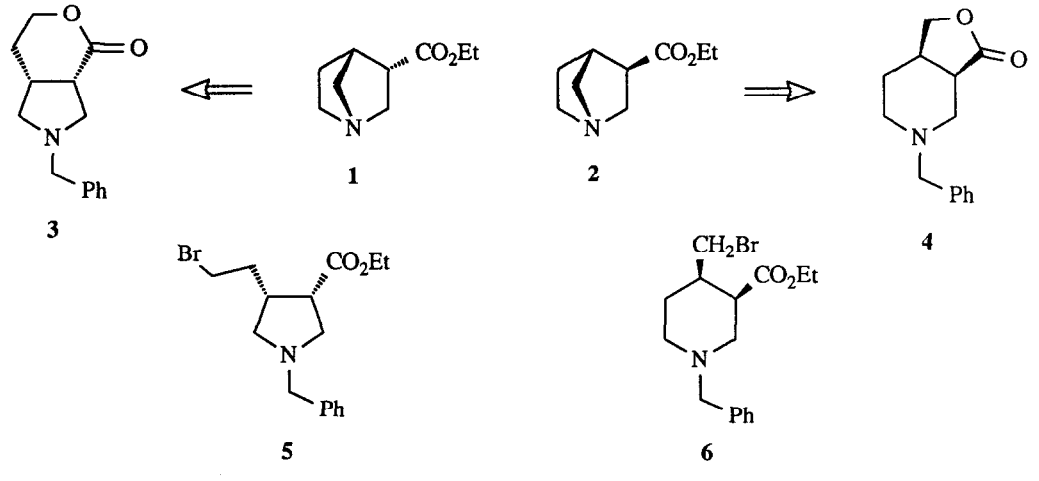
DIASTEREOSELECTIVE ROUTES TO endo AND exo ETHYL 1-AZABICYCLO[2.2.1] HEPT-3-YL CARBOXYLATES

Barry S. Orlek*, Harry Wadsworth, Paul Wyman and Michael S. Hadley
SmithKline Beecham Pharmaceuticals, Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD, UK.

Summary - Diastereoselective routes to endo and exo ethyl 1-azabicyclo[2.2.1]hept-3-yl carboxylates (1) and (2) based on the hydrogen bromide cleavage of the isomeric [4.3.0] bicyclic cis fused lactones (3) and (4) are described.

As part of a programme aimed at the synthesis of novel muscarinic agonists as potential therapeutic agents for Alzheimer type dementia, we required access to both the endo and exo azabicyclic esters (1) and (2). These intermediates can be converted into potent muscarinic agonists[1] with retention of configuration. Few methods are available for preparing 3-substituted 1-azabicyclo[2.2.1]heptanes. The synthesis of 1-azabicyclo[2.2.1]heptan-3-one was first described by Spry and Aaron[2], and more recently the conversion of this ketone into exo-methyl 1-azabicyclo[2.2.1]hept-3-yl carboxylate was reported[3]. In this letter we describe diastereoselective routes to the endo and exo esters (1) and (2) which are high yielding and capable of large scale synthesis.

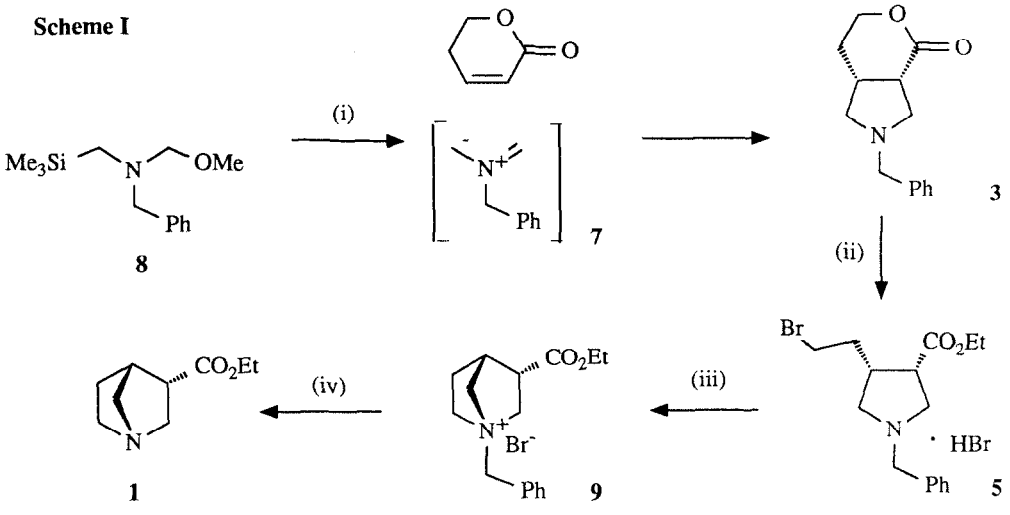
Retrosynthetic analysis suggested that the endo and exo isomers (1) and (2) could be accessed from suitably protected cis fused lactones (3) and (4). It is well established that lactones undergo ring opening upon treatment with HBr in ethanol to give ω-bromoalkyl esters.[4] In the case of (3) and (4) the intermediate cleavage products (5) and (6) are suitably arranged for subsequent cyclisation to give the required products.[5]



3 1 2 4

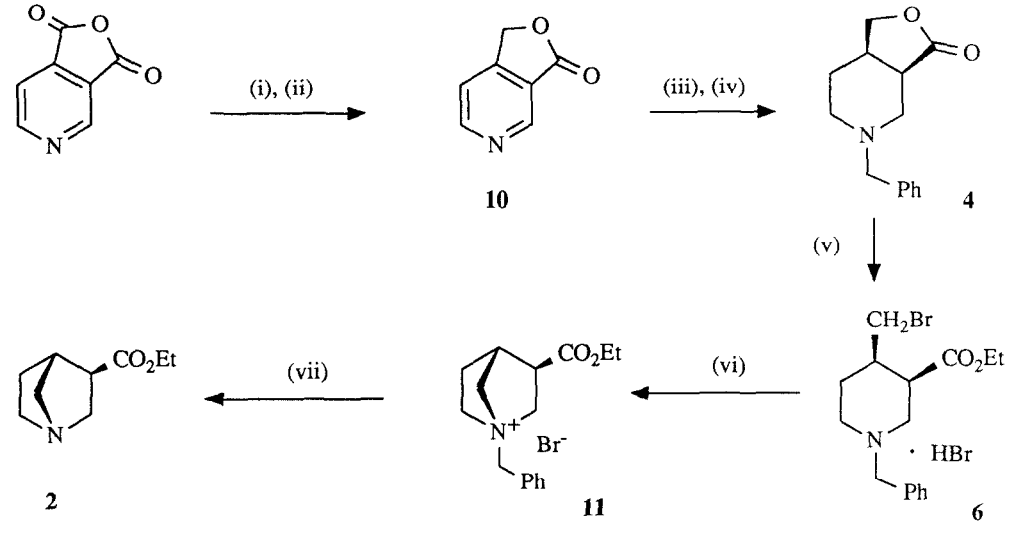
5 6

Scheme I



Reagents: (i) CF_3CO_2H, CH_2Cl_2, reflux (ii) EtOH saturated with HBr (iii) Aqueous K_2CO_3 (iv) H_2, Pd-C, EtOH

Scheme II



Reagents: (i) $NaBH_4$, DMF (ii) HCl, reflux (iii) H_2, Rh-C, 1000psi, EtOH (iv) $PhCH_2Br$, K_2CO_3, EtOH (v) EtOH saturated with HBr (vi) Aqueous K_2CO_3 (vii) H_2, Pd-C, EtOH

Lactone (3) was readily obtained in 58% yield by dipolar cycloaddition of the N-benzyl azomethine ylid (7) with 5,6-dihydro-2H-pyran-2-one[6] (Scheme I). The ylid (7) is available as a transient intermediate, prepared in situ by treatment of methoxymethyltrimethylsilylbenzylamine (8) with trifluoroacetic acid as described by Terao *et al*[7]. The precursor (8) was obtained by alkylation of benzylamine with chloromethyltrimethylsilane, followed by reaction with formaldehyde and methanol.[8] Saturation of a solution of (3) in ethanol with anhydrous hydrogen bromide resulted in lactone cleavage to afford the intermediate (5), which cyclised upon treatment with aqueous potassium carbonate to give the N-benzyl quaternary ammonium salt (9). Recovery of (9) by extraction into chloroform, followed by hydrogenation over a Pd-C catalyst and basification afforded (1)[9] as an oil (Bp 90-95°C at 0.5mm Hg) in 74% overall yield from (3).

The sequence of reactions leading to the isomeric lactone (4) is shown in Scheme II. Preferential reduction of pyridine-3,4-dicarboxylic acid anhydride at the more electrophilic carbonyl[10] at the 4-position of the pyridine ring provided a route to the lactone (10). The use of sodium borohydride in N,N-dimethylformamide[11] proved superior to an earlier procedure reported by Kuthan *et al*[12] which employs lithium aluminium hydride. The crude product, obtained after an acidic work up, was usually contaminated with 10-15% of the isomeric lactone resulting from reduction of the carbonyl at the 3-position of the pyridine ring. Crystallisation from toluene afforded pure (10) in yields of 30-50%. Hydrogenation under forcing conditions, followed by benzylation gave the expected cis fused lactone (4) in moderate yield (40%). Rearrangement of (4) as described above for the isomeric lactone (3) afforded the quaternary salt (11). Debenzylation under standard conditions completed the synthesis of the required exo ester (2)[13] (Bp 150°C at 0.1mm Hg in a kugelröhr) in 70% yield.

The development of diastereoselective routes to esters (1) and (2) has facilitated the synthesis of potent muscarinic agonists incorporating the 3-substituted 1-azabicyclo[2.2.1]heptane ring system. The biological activity of these compounds will be reported separately.

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References and Notes

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8. This route to (8) has been described by A. Padwa and W. Dent Org. Syn. 1989, 67, 133. In our experience the crude product, which is usually 75-80% pure by ^{1}H NMR, can be used without further purification.
9. Compound (1): ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.28 (3H, t, J=8Hz, CH_3), 1.3-1.45 (1H, m, H-5), 1.5-1.65 (1H, m, H-5), 2.5-2.7 (3H, m), 2.85-3.05 (5H, m), 4.15 (2H, q, J=8Hz, $\underline{CH_2}CH_3$); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 14.2 (CH_3), 25.3 (C-5), 40.9 and 46.3 (C-3 and C-4); 53.2, 55.7, 60.5, 61.2 (C-2, C-6, C-7, $\underline{CH_2}CH_3$), 173.2 (C=O).
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13. Compound (2): ^{1}H NMR ($CDCl_3$, 270MHz)(Assignments based on COSY experiment) δ: 1.08-1.20 (1H, m, H-5_{endo}), 1.26 (3H, t, J=8Hz, CH_3), 1.53-1.67 (1H, m, H-5_{exo}), 2.24 (1H, dd, J=4Hz, J=6Hz, H-3_{endo}), 2.36 (1H, d, J=9Hz, H-7_{anti}), 2.38-2.5 (1H, m, H-6_{endo}), 2.67 (1H, d, J=9Hz, H-7_{syn}), 2.79 (1H, m, H-2_{endo}), 2.82 (1H, m, H-4), 2.86 (1H, m, H-6_{exo}), 2.94 -3.04 (1H, m, H-2_{exo}), 4.13 (2H, q, J=8Hz, $\underline{CH_2}CH_3$). Stereochemistry was confirmed by irradiation of of H-5_{endo} which produced an NOE at H-3. In addition a "W" coupling was observed between H-3 and H-7_{anti}. ^{13}C NMR ($CDCl_3$, 67.8 MHz)(Assigned from C/H correlation experiment) δ: 14.2 (CH_3), 29.8 (C-5), 41.2 (C-4), 46.9 (C-3), 53.6 (C-6), 58.5 (C-2), 58.6 (C-7), 60.6 ($\underline{CH_2}CH_3$), 174.4 (C=O). The chemical shift of C-5 in the ^{13}C NMR spectra of the endo and exo isomers (1) and (2) is sensitive to the relative orientation of the ethoxycarbonyl group, and this is reflected in the chemical shift difference δC-5(exo)- δC-5(endo)= 4.5 ppm. Similar shift differences have been observed (H. Wadsworth, unpublished data) for 1-azabicyclo[2.2.1]heptanes bearing a range of substituents at the 3-position, and this trend is of considerable diagnostic value.

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