A Concise Synthesis of (±)-, (+)-, and (−)-6-Methyl-6-azabicyclo[3.2.1]octan-3α-ol

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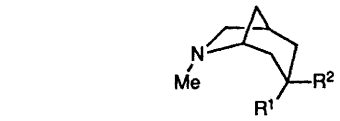
(±)-6-Methyl-6-azabicyclo[3.2.1]octan-3-one (**1c**) was prepared in three steps from 6-oxabicyclo[3.2.1]oct-3-en-7-one, and stereoselective reduction of (**1c**) provided (±)-6-methyl-6-azabicyclo[3.2.1]octan-3α-ol (**1a**); adaptation of the sequence provided the first synthesis of (+)- and (−)-(**1a**).

6-Methyl-6-azabicyclo[3.2.1]octan-3α-ol (**1a**) is the key intermediate for the synthesis of 6-methyl-6-azabicyclo[3.2.1]-octan-3α-ol 2,2-diphenylpropionate (**1b**, azaprophen), a novel, conformationally restricted, highly potent antimuscarinic analogue of atropine.[1] In order to prepare additional muscarinic agonists and antagonists as potential drugs for the treatment of Alzheimers disease,[2] a more convenient higher yield synthesis of (**1a**) was needed.

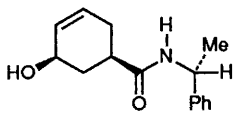
Initially, alcohol (**1a**) was prepared by lithium aluminium hydride reduction of 6-methyl-6-azabicyclo[3.2.1]octan-3-one (**1c**) which was prepared by a modification of the procedure reported by Furstoss and co-workers.[3] Even though the modifications offered a better synthesis of (**1c**), a simpler, higher yield method was needed. This need led us to investigate the sequence shown in Scheme 1, which starts with the readily available lactone 6-oxabicyclo[3.2.1]oct-3-en-7-one (**2**).[4,5] When lactone (**2**) was treated with a methanolic solution of methylamine at 100 °C, a nearly quantitative yield of the amide (**3**)† was obtained. Lithium aluminium hydride reduction of (**3**) afforded the hydroxy amine (**4**). Allylic oxidation of (**4**) using activated manganese dioxide in methylene chloride solution gave the α,β-unsaturated ketone (**5**) which spontaneously cyclized to give the desired azabicyclic ketone (**1c**) in 78% overall yield from (**2**). The ketone (**1c**) is conveniently stored as the hydrochloride salt, m.p. 157—158 °C. Since reduction of (**1c**) with lithium aluminium hydride gave a 60:40 mixture of (**1a**) and (**1d**),[1] we examined other methods for this conversion. When (**1c**) was reduced with L-Selectride ($LiBu^s_3BH$), an 85% yield of >97% pure (**1a**) was obtained.‡

When lactone (**2**) was treated with (*R*)-(+)-α-methylbenzylamine, an 81% yield of a 1:1 mixture of the diastereoisomers (**6**) and (**7**) was obtained. Flash chromatography on silica gel using a diethyl ether–ethyl acetate gradient was found to resolve the mixture of (**6**) and (**7**).§ The earlier eluting isomer (**6**) had m.p. 163—164 °C, $[\alpha]_D^{24}$ +98° (*c* 1, $CHCl_3$), whereas the other isomer (**7**) had m.p. 155.5—157 °C, $[\alpha]_D^{24}$ +81.6° (*c* 1, $CHCl_3$). The absolute stereochemistry of (**6**) and (**7**) was shown to be (1*R*,5*R*) and (1*S*,5*S*) respectively by establishing that (−)-(1*S*,5*S*)-6-oxabicyclo[3.2.1]oct-3-en-7-one[6]¶ gave (**7**) on treatment with (*R*)-(+)-α-methylbenzylamine.

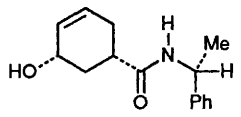


(**1**)

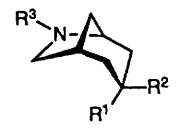
a; R^1 = OH, R^2 = H
b; R^1 = Ph_2CMeCO_2, R^2 = H
c; R^1, R^2 = O=
d; R^1 = H, R^2 = OH

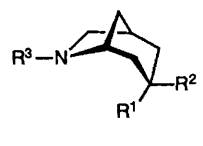


(**6**)

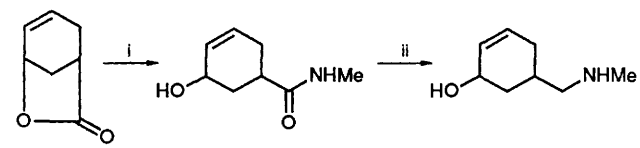


(**7**)





(**8**) R^1, R^2 = =O, R^3 = $PhCHMeNH_2$ (**9**)
(**10**) R^1 = OH, R^2 = H, R^3 = $PhCHMeNH_2$ (**11**)
(−)-(**1a**) R^1 = OH, R^2 = H, R^3 = Me (+)-(**1a**)
(−)-(**1e**) R^1 = $MeCO_2$, R^2 = H, R^3 = Me (+)-(**1e**)



(**2**) (**3**) (**4**) (**5**) (**1c**) (**1**)

a; R^1 = OH, R^2 = H
d; R^1 = H, R^2 = OH

Scheme 1. *Reagents and conditions*: i, $MeNH_2$, MeOH, 100 °C; ii, $LiAlH_4$, tetrahydrofuran (THF), reflux; iii, MnO_2, CH_2Cl_2, 25 °C; iv, L-Selectride, THF, −78 to 0 °C.

† All new compounds gave satisfactory analysis.

‡ None of the isomer (**1d**) could be detected by ^1H NMR (250 MHz) analysis of the reaction mixture.

§ HPLC analyses (ethyl acetate, Dynamax 60A silica column, 2 ml/min flow rate, 256 nm UV detection) indicated >98% diastereoisomeric purity.

¶ The absolute stereochemistry of (+)-(**2**) and (−)-(**2**) has been established (ref. 6).

Subjection of (**6**) and (**7**) to the reaction sequence shown for (**3**) in Scheme 1 provided the optically active azabicyclic ketones (**8**) {m.p. 65—66 °C, $[\alpha]_D^{24}$ +17.7° (*c* 1, $CHCl_3$)} and (**9**) {m.p. 60—61 °C, $[\alpha]_D^{24}$ +9.5° (*c* 1, $CHCl_3$)}, respectively. L-Selectride reduction of (**8**) and (**9**) gave 84% of (**10**) {m.p. 125—126 °C, $[\alpha]_D^{23}$ −4.4° (*c* 1, $CHCl_3$)} and 98% of (**11**) {m.p. 78.5—80 °C, $[\alpha]_D^{23}$ +20.3° (*c* 1, $CHCl_3$)}, respectively. Catalytic debenzylation (Pd/C, MeOH, H_2) followed by catalytic reductive amination [Pd/C, MeOH, H_2, $(CH_2O)_n$] of (**10**) gave 79% of (−)-(1*R*,5*S*,3*R*)-(**1a**) as an oil, which was characterized as the resorcylate salt of the 3-acetate {(−)-(**1e**)]; m.p. 165—167 °C, $[\alpha]_D^{24}$ −7.8° (*c* 0.75, MeOH)}. Similar treatment of (**11**) gave (+)-(1*S*,5*R*,3*S*)-(**1a**); also characterized as the resorcylate salt of the 3-acetate {(+)-(**1e**), m.p. 166—167 °C, $[\alpha]_D^{24}$ +8.0° (*c* 0.75, MeOH)}.

In summary, we have developed a short, efficient, high-yield synthesis of (±)-6-methyl-6-azabicyclo[3.2.1]octan-3-one (**1c**) and studied its stereoselective reduction to the corresponding α-alcohol (**1a**).

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