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

Abraham Philip,[a] J. Bruce Pitner,[a] Young J. Joo,[a] David J. Triggle,[b] and F. Ivy Carroll*[a]

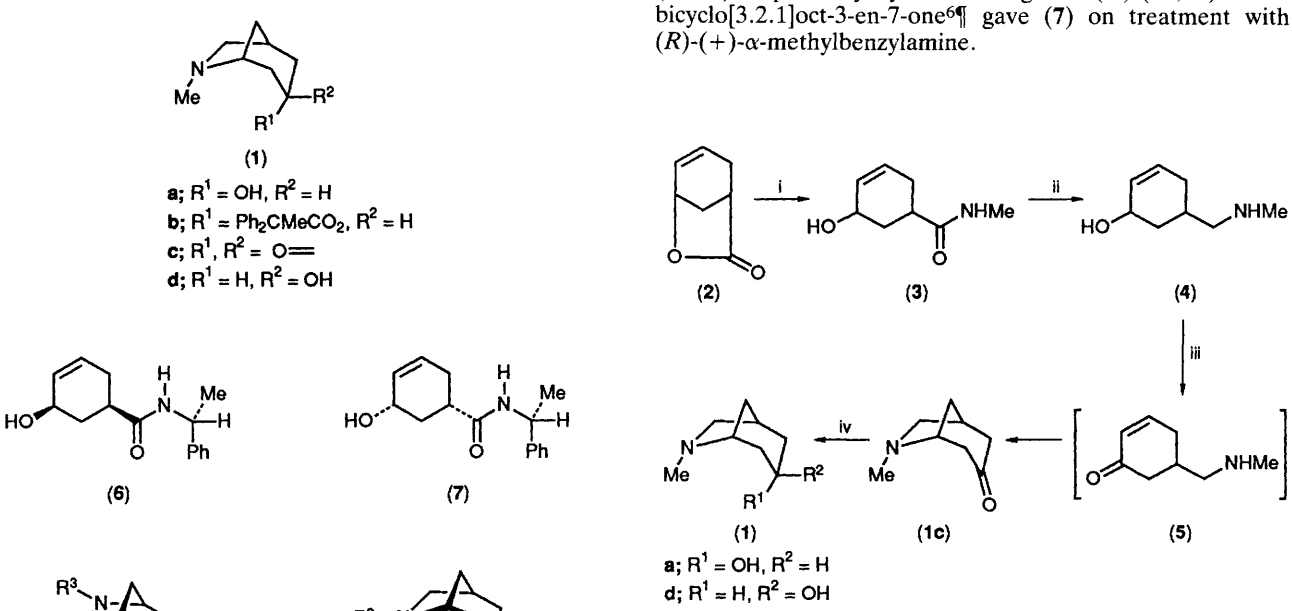
[a] *Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709, USA*
[b] *Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, USA*

(±)-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.



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**).

This research was supported by Grant AG-07418 from the National Institute on Aging.

Received, 12th March 1990; Com. 0/01089H

References

1 F. I. Carroll, P. Abraham, K. Parham, R. C. Griffith, A. Ahmad, M. M. Richard, F. N. Padilla, J. M. Witkin, and P. C. Chiang, *J. Med. Chem.*, 1987, **30**, 805.
2 For recent reviews on Alzheimers disease see: 'Current Research in Alzheimers Therapy,' eds. E. Giacobini and R. Becker, Taylor and Francis, New York, 1988; W. Armstrong, 'Recent Trends in Research on Alzheimers Disease,' PJB Publications, Ltd, Surrey, 1986.
3 R. Furstoss, P. Teissier, and B. Waegell, *Chem. Commun.*, 1970, 384; R. Furstoss, G. Esposito, P. Teissier, and B. Waegell, *Bull. Soc. Chim. Fr.*, 1974, 2485.
4 P. A. Bartlett and L. A. McQuaid, *J. Am. Chem. Soc.*, 1984, **106**, 7854.
5 T. Inukae and M. Kasai, *J. Org. Chem.*, 1965, **30**, 3567.
6 S. F. Martin, M. S. Dappen, B. Dupre, C. J. Murphy, and J. A. Colapret, *J. Org. Chem.*, 1989, **54**, 2209.