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ENANTIOSPECIFIC SYNTHESIS OF (+)-(R)-1-PHENYL-3-METHYL-1,2,4,5-TETRAHYDROBENZ[d]AZEPINE FROM (+)-(S)-N-METHYL-1-PHENYL ETHANOLAMINE (HALOSTACHINE) via ARENE CHROMIUM TRICARBONYL METHODOLOGY

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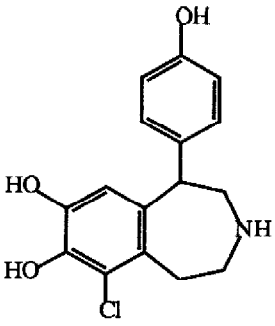
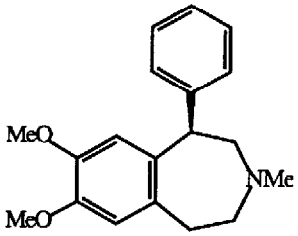
Summary: Acid promoted cyclisation of homochiral (R)-N-(3,4-dimethoxyphenethyl) halostachine chromium tricarbonyl is stereospecific, proceeding with retention of configuration, to afford, after decomplexation, homochiral (+)-(R)-1-phenyl-3-methyl-1,2,4,5-tetrahydrobenz[d]azepine.

The 1,2,4,5-tetrahydro-3H-benz[d]azepine† skeleton is found in nature and alkaloids possessing it are commonly referred to as the "benzazepine alkaloids".[1] In particular, 1-aryl-7,8-dioxygenated-tetrahydrobenzazepines exhibit potent pharmacological activity as D-1 receptor agonists[2,3] as exemplified by the renal vasodilator Fenoldopam **1**.[4,5] Moreover, the dopaminergic activity possessed by this class of compound resides almost exclusively in the (R)-enantiomer.[6,7] Although construction of 1-aryl-tetrahydrobenzazepines is readily accomplished by a variety of methods,[1] none of these permit the direct synthesis of homochiral material; a classical resolution procedure being necessary to allow the separation of the optical antipodes. We describe here the extension of arene chromium tricarbonyl chemistry to the synthesis of homochiral (+)-(R)-1-phenyl-3-methyl-tetrahydrobenzazepine **2**.[6]

†The descriptors 1,2,4,5 and [d] are omitted henceforth for clarity.

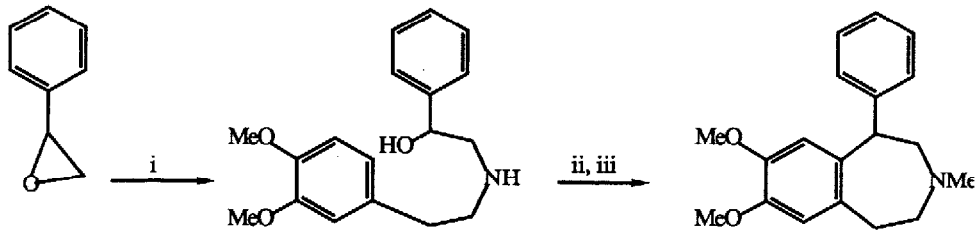


1



2

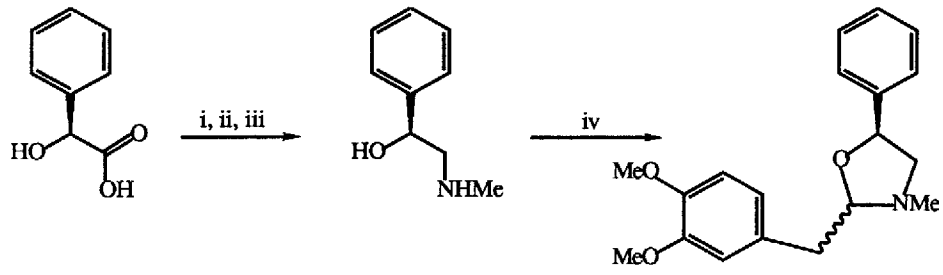
Acid treatment of racemic amino alcohol (R,S)-**3**, derived from (R,S)-styrene oxide and homoveratrylamine, afforded, after N-methylation of the cyclised product, (R,S)-1-phenyl-3-methyl-tetrahydrobenzazepine (**2**) as a white solid.[8] ^{1}H nmr analysis of (R,S)-**2** in the presence of the chiral shift reagent (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol[9] clearly distinguished the three methyl groups, the two aryl singlets and C-1 Proton corresponding to the two enantiomers.



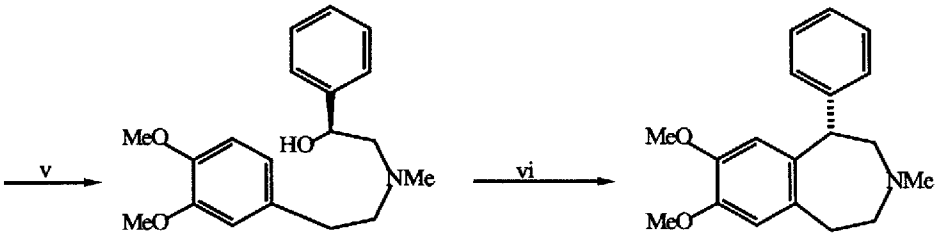
(±)-**3** (±)-**2**

i) 3,4-$(MeO)_2C_6H_3CH_2CH_2NH_2$, K_2CO_3, MeCN, 79%. ii) H_2SO_4, TFA, CH_2Cl_2, 51%. iii) HCOOH, CH_2O, 85%.

Homochiral (+)-(S)-halostachine (+)-(S)-**5** was synthesised as shown from (+)-(S)-mandelic acid **4**. Condensation of (+)-(S)-**5** with homoveratraldehyde (**6**)[10] yielded a mixture of diastereoisomeric oxazolidines **7**, which were reduced to (+)-(S)-**8** with methanolic sodium borohydride. Acid promoted cyclisation of the homochiral (+)-(S)-**8** below -20°C smoothly gave the expected benzazepine **2**. 300 MHz ^{1}H nmr analysis of this product in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol revealed an enantiomeric excess of 6% in favour of the (-) antipode. If the cyclisation reaction were to proceed through a free benzylic carbonium ion a completely racemic product would be expected. The small e.e. (6%) observed for the product (-)-**2** reflects a small amount of neighbouring group participation by the dimethoxybenzyl group in the ionisation process which would lead to inversion of configuration. The configuration of (-)-**2** is assigned as S on this basis.



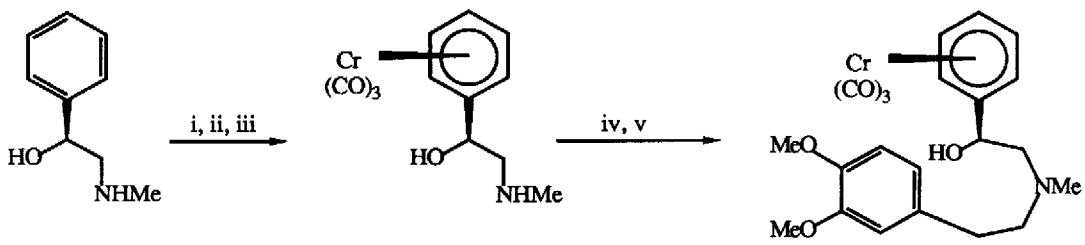
(+)-(S)-4 (+)-(S)-5 7



(+)-(S)-8 (-)-(S)-2 (e.e.=6%)

i) Me_2CO, H_2SO_4, 80%. ii) $MeNH_2$, EtOH, 97%. iii) $LiAlH_4$, THF, 94%.
iv) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**6**), CH_2Cl_2, pTsOH, sieves, 91%. v) $NaBH_4$, MeOH, 92%.
vi) $HBF_4.OMe_2$, CH_2Cl_2.

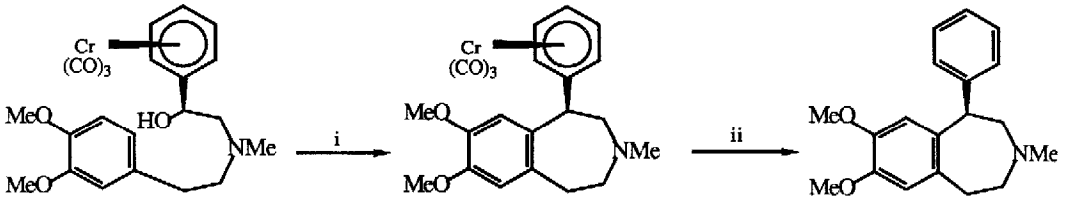
It was envisaged that coordination of the benzyl alcohol fragment of (+)-(S)-**8** to chromium tricarbonyl would render the cyclisation stereospecific.[11,12] It did not prove possible to complex halostachine directly. Therefore, (+)-(S)-halostachine **5** was first N-protected using Boc anhydride, after which heating with chromium hexacarbonyl under standard conditions[13] furnished the corresponding complex. N-Deprotection was effected upon exposure to formic acid, yielding (+)-(R)-halostachine chromium tricarbonyl **9** as yellow needles. Condensation of (+)-(R)-**9** with homoveratraldehyde (**6**) in the presence of molecular sieves followed by sodium borohydride reduction gave (R)-**10**, the chromium tricarbonyl complex of (+)-(S)-**8**.



(+)-(S)-5 (+)-(R)-9 (R)-10

i) $(Boc)_2O$, NEt_3, CH_2Cl_2, 89%. ii) $Cr(CO)_6$, Bu_2O, THF, 63%. iii) HCOOH, 95%.
iv) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**6**), CH_2Cl_2, pTsOH, sieves, 86%. v) $NaBH_4$, MeOH, 62%.

Exposure of a dichloromethane solution of (R)-**10** to tetrafluoroboric acid below -20°C resulted in smooth cyclisation to the benzazepine complex (-)-(R)-**11.** Decomplexation upon exposure to air and sunlight liberated (+)-(R)-1-phenyl-3-methyl-tetrahydrobenzazepine (+)-**2** {$[\alpha]_D^{18}$ +31.2° (c 0.99 MeOH), lit.[6] $[\alpha]_D^{25}$ +31.8° (c 1.0 MeOH)}. A chiral shift ^{1}H nmr analysis as described above confirmed that (+)-**2** was homochiral. The configuration of (+)-**2** was assigned as R, consistent with the expected mechanism involving participation with inversion by the chromium in the ionisation to generate a configurationally stable carbonium ion. Subsequent cyclisation would also occur with inversion of configuration making the overall process stereospecfic with retention of configuration.



(R)-10 **(-)-(R)-11** **(+)-(R)-2**

i) $HBF_4.OMe_2$, CH_2Cl_2, 76%. **ii)** Air, sunlight, Et_2O, 99%.

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References:

1. T.Kametani and K.Fukumoto, *Heterocycles,* 1975, **3**, 931.

2. N.Baindur, J.L.Neumeyer, H.B.Niznik, N.H.Bzowej, K.R.Jarvie, P.Seeman, R.K.Garlick and J.J.Miller, *J.Med.Chem.*, 1988, **31**, 2069.

3. S.T.Ross, R.G.Franz, G.Gallagher, M.Brenner, J.W.Wilson, R.M.DeMarinis, J.P.Hieble and H.M.Sarau, *J. Med. Chem.*, 1987, **30**, 35.

4. D.L.Ladd, J.Weinstock, M.Wise, G.W.Gessner, J.L.Sawyer and K.E.Flaim, *J. Med. Chem.*, 1986, **29**, 1904.

5. J.Weinstock, D.L.Ladd, J.W.Wilson, C.K.Brush, N.C.F.Yim, G.Gallagher, M.E.McCarthy, J.Silvestri, H.M.Sarau, K.E.Flaim, D.M.Ackerman, P.E.Setler, A.J.Tobia and R.A.Hahn, *J. Med. Chem.*, 1986, **29**, 2315.

6. C.Kaiser, P.A.Dandridge, E.Garvey, R.A.Hahn, H.M.Sarau, P.E.Setler, L.S.Bass and J.Clardy, *J. Med. Chem.*, 1982, **25**, 697.

7. J.Weinstock, H.Oh, C.W.DeBrosse, D.S.Eggleston, M.Wise, K.E.Flaim, G.W.Gessner, J.L.Sawyer and C.Kaiser, *J. Med. Chem.*, 1987, **30**, 1303.

8. *Chem Abstr.*, 1977 **86** 189747p, 1968 **69** 96507u, 1978 **88** 89536s.

9. W.H.Pirkle and C.W.Boeder, *J. Org. Chem.*, 1977, **42**, 3697.

10. Y.Ban and T.Oishi, *Chem and Pharm Bull.*, 1958, **6**, 574.

11. S.Top and G.Jaouen, *J. Org. Chem.*, 1981, **46**, 78.

12. S.J.Coote and S.G.Davies, *J. Chem. Soc., Chem. Commun.*, 1988, 648.

13. C.A.L.Mahaffy and P.L.Pauson, *Inorg. Synth.*, 1979, **19**, 154.

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