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FACILE SYNTHESIS OF 1-SUBSTITUTED C-NORBENZOMORPHANS

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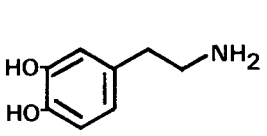
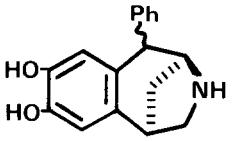
Abstract - The olefinic-nitrile (4) undergoes a bromonium ion-induced cyclisation to the tetrahydronaphthalene (5a) which on subsequent reduction and intramolecular nucleophilic displacement provides a facile route to 1-substituted C-norbenzomorphans.

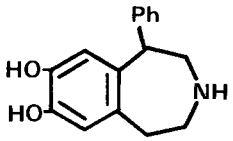
As part of a chemical programme designed to prepare conformationally rigid analogues of dopamine (1) the c-norbenzomorphan (2) was required. This is the 2,5-methano bridged analogue of the benzazepine (3), SKF 38393, a compound which has a unique profile of pharmacological activity at both central[1,2] and peripheral dopamine receptors.



(1)

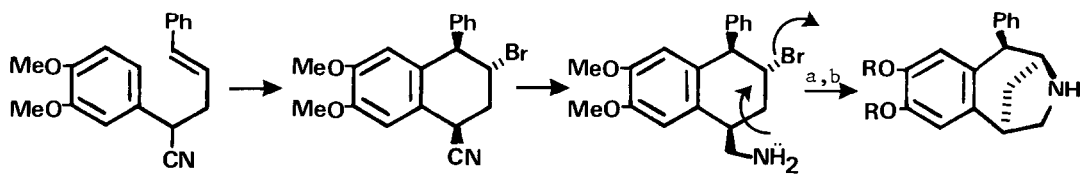


(2)



(3)

Since the reported[3,4] approaches to c-norbenzomorphans are lengthy and not applicable to compounds substituted at the 1-position an alternative strategy was adopted. This new strategy involved a bromonium ion-induced cyclisation of an alkene onto a proximate aromatic ring. Thus treatment of the olefinic-nitrile (4), readily prepared in one step from commercially available materials[5], with bromine gave the tetrahydronaphthalene (5a). Subsequent reduction of the nitrile function gave the c-norbenzomorphan (7), presumably *via* the corresponding amine (6) which has the requisite stereochemistry to undergo an *in situ* intramolecular nucleophilic displacement of the bromine substituent. Demethylation then gave the required diol (8).



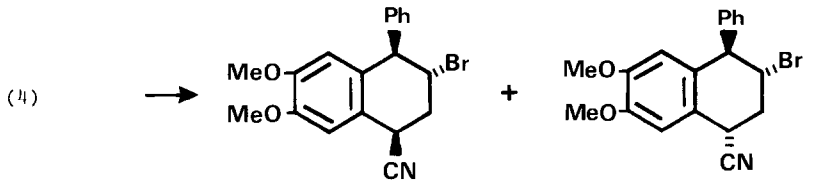
(4) (5a) (6) not isolated (7) R = Me (8) R = H

a. AlH_3, THF, basic work-up, 83%

b. BBr_3, CH_2Cl_2, 87%

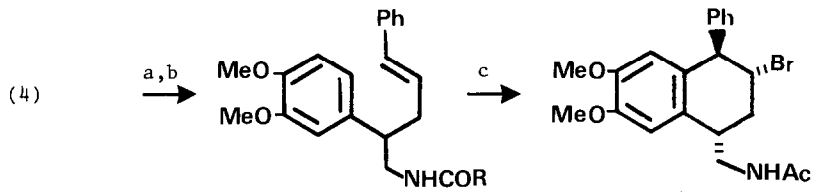
The brominative-cyclisation of the olefinic-nitrile (4) was studied briefly (Table 1). Use of bromine initially gives an approximately equal mixture of the tetrahydronaphthalenes (5a) and (5b) but equilibration occurs under the reaction conditions[6] to yield predominantly the former, i.e. the isomer with the bromine substituent trans to both the phenyl and cyano groups. In contrast N-bromoacetamide gave mainly the alternative product (5b). The generality of this cyclisation is demonstrated by the conversion of the analogous amide (9a) into the bromo compound (10) in excellent yield.

Table 1



(5a) (5b)

Conditions	Ratio - (5a):(5b)	Yield
Br_2; CH_2Cl_2; 5; 10 min.	1.3:1	100%
Br_2; CH_2Cl_2; RT; 30 min.	4 :1	100%
NBA; Acetone; RT; 30 min.	1 :3	84%

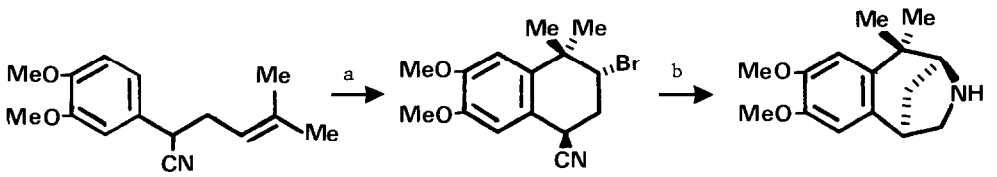


(9a) R = CH_3
(9b) R = CF_3

(10)

a. AlH_3/THF; 100% b. Ac_2O; 85% or $(CF_3CO)_2O$; 91% c. NBA, acetone; 90%

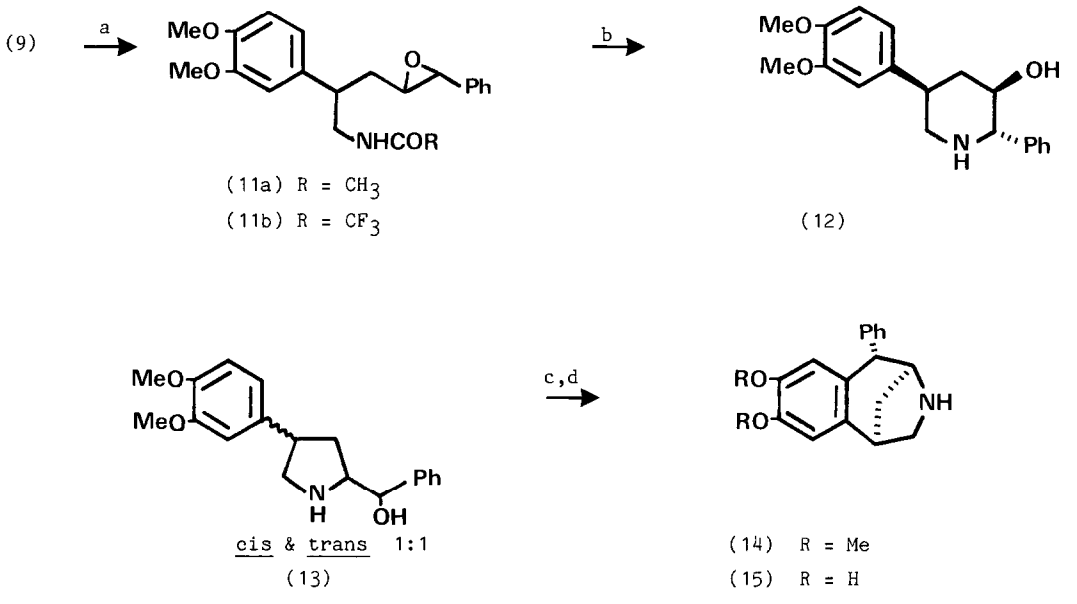
Furthermore this process also enables the preparation of 1,1-dialkyl c-norbenzomorphans and this is exemplified by the gem-dimethyl[8] example below;



a. Br_2/CH_2Cl_2; 30% + 30% cis isomer

b. BH_3/THF; basic work-up, reflux THF; 75%

Unfortunately the new methodology just described above provided only one of the required isomers of the 1-phenyl c-norbenzomorpan (2) and hence a different approach was used for the synthesis of the isomeric compound (15). The olefinic-nitrile (4) was converted into the acetamide (9a) by reduction and acetylation. Epoxidation and subsequent treatment with base gave the required pyrrolidine (13) (cis:trans, 1:1), together with the piperidine (12)[9,10]. As expected this hydrolysis-cyclisation process was effected much more readily from the corresponding trifluoroacetamide (11b). Treatment of the crude reaction product with trifluoroacetic acid/sulphuric acid provided the c-norbenzomorphan (14) as the only isolable pure product, albeit in low yield. The stereochemistry is that where the phenyl group is cis to the methano bridge and trans to the amino substituent. Demethylation then gave the diol (15).



(11a) R = CH_3
(11b) R = CF_3

(12)

cis & trans 1:1
(13)

(14) R = Me
(15) R = H

a. MCPBA, $NaHCO_3$, CH_2Cl_2; 91% for (11a); 100% for (11b). b. 2N NaOH, EtOH, reflux 48hr; 61% for (11a), 2N NaOH, MeOH, RT 8nr; 77% for (11b). c. CF_3CO_2H,H_2SO_4, reflux 45 min; 11%. d. BBr_3, CH_2Cl_2; 100%

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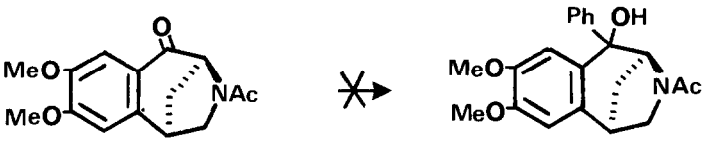
1. P. E. Setler, et. al., Eur. J. Pharmacol., 1978, 50, 419.

2. R. G. Pendleton, et. al., ibid., 1978, 51, 19.

3. K. Mitsubashi, et. al., Chem. Pharm. Bull., 1969, 17, 434.
T. Komatani and S. Shiotani, J. Med. Chem., 1978, 21, 1105.
F. B. Block and F. H. Clarke, Chem. Abs., 1971, 74, 99911k.

For an excellent review on the related benzomorphan analgetics see D. C. Palmer and M. J. Strauss, Chem. Rev., 1977, 1.

4. An earlier attempt to prepare these derivatives via the addition of phenylmagnesium bromide or phenyl lithium to the keto-acetamide[7](16) failed. (16) was synthesised in 10 steps (overall yield 2.3%) by the method of Komatani (ref. 3), H. Finch and S. Guntrip, unpublished work.



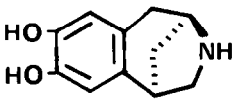
(16)

This approach has been used to prepare 1-aryl benzomorphans, A. Zeiring et. al., J. Med. Chem., 1970, 13, 9.

5. The olefinic-nitrile (4) was obtained by alkylation of (3,4-dimethoxyphenyl) acetonitrile with cinnamyl bromide (LDA, THF, -78°, 63%).

6. This isomerisation is assumed to occur via an acid-catalysed (N.B. HBr is produced) epimerisation of the nitrile group.

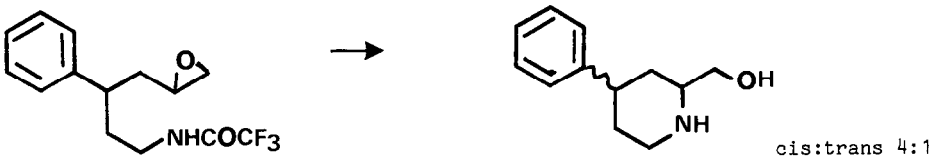
7. The keto-acetamide (16) (ref. 4) has been converted in 4 steps to the parent diol (17), H. Finch and S. Guntrip, unpublished work.



(17)

8. The starting material was obtained by alkylation of the (3,4-dimethoxyphenyl)aceto-nitrile with dimethylallyl bromide (C_6H_6, 50% NaOH, $PhCH_2Et_3N^+Cl^-$, reflux; 80%).

9. However, similar cyclisation of the epoxide (18) to the piperidine (19) gives a more favourable cis:trans ratio. L. Stella, et. al., Tetrahedron, 1981, 37, 2843.



(18) (19) cis:trans 4:1

10. For other examples of this type see E. J. Corey, et. al., J. Amer. Chem. Soc., 1970, 92, 2488 and J. W. Huffman, J. Heterocycl. Chem., 1973, 10, 463.

11. All compounds possessed satisfactory spectroscopic and/or analytical data.

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