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A SIMPLE APPROACH TO HOMOTROPANES AND HOMOTROP-7-ENES

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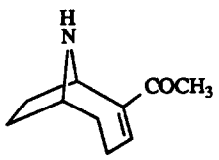
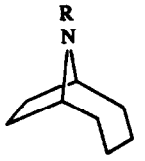
Abstract: 1,4-Functionalisation of cycloocta-1,3-diene using a nitroso-cycloaddition strategy is followed by intramolecular cyclisation to yield 9-azabicyclo[4.2.1]nonanes (homotropanes) and -non-7-enes (homotrop-7-enes); the approach can be adapted to allow access to 1-methylhomotropanes.

There has been considerable interest in the algal metabolite anatoxin-*a* (**1**) and a number of syntheses of this compound have been reported.[1] Routes to other derivatives of this ring system are rare.[2] We reported earlier[3] a high-yield route to tropane derivatives from cyclohepta-1,3-diene and we describe here the extension of this method to the synthesis of homotropanes (9-azabicyclo[4.2.1]nonanes) (**2**) and -7-enes (**3**) from cycloocta-1,3-diene together with an adaptation which yields 1-methyl derivatives (**4**).



(**1**)



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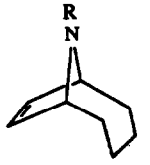
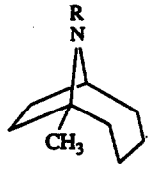


(**3**)

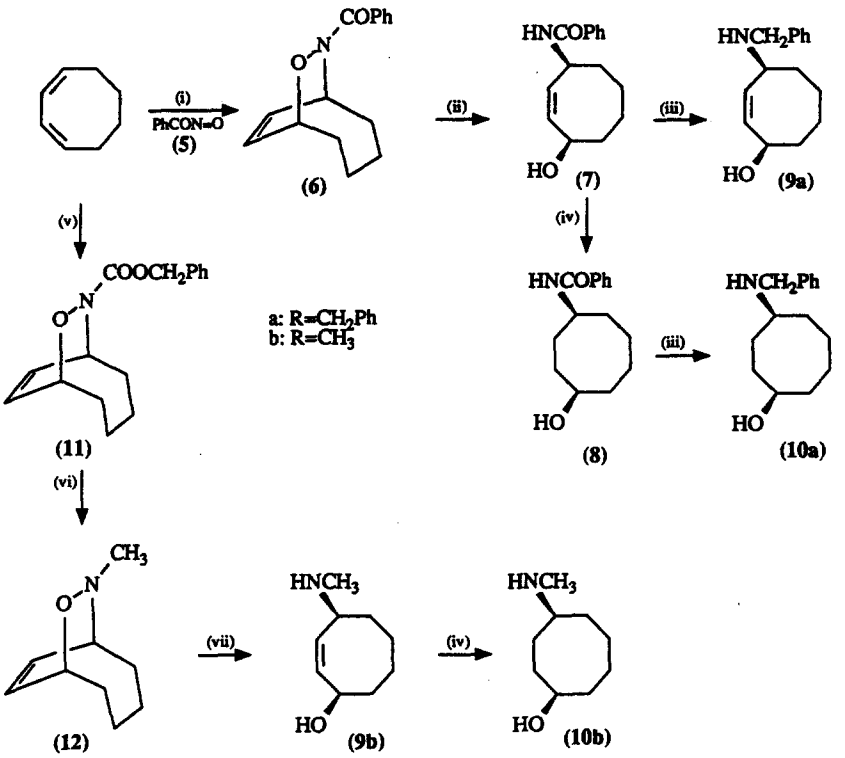


(**4**)

[R = CH_2Ph, CH_3, H]

The addition of nitroso-compound (**5**), generated *in situ* from benzohydroxamic acid and tetramethylammonium periodate,[4] gave reasonable yields of the cycloadduct (**6**) (Scheme 1). The yield of cycloadduct was lower than in the case of smaller cyclic dienes, presumably as a result of conformational restrictions on planarity of the diene; nevertheless, the overall process was amenable to large-scale preparation of (**6**) since cycloocta-1,3-diene is inexpensive. The benzyloxycarbonyl derivative (**11**) was prepared similarly.

The initial cycloadducts (**6**) and (**11**) were transformed efficiently into the *cis*-amino-alcohols (**9a,b**) and (**10a,b**) using standard methods (Scheme 1).

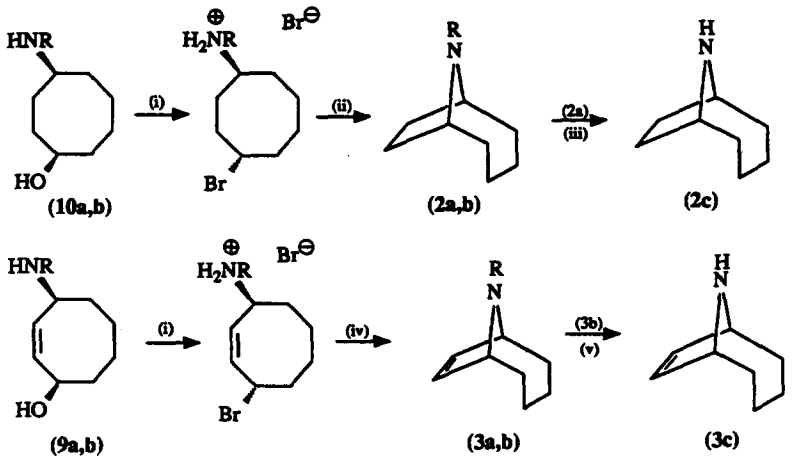


Scheme 1

(i)	$PhCONHOH/Me_4N^+IO_4^-/CH_2Cl_2$; 46%	(ii)	Al/Hg/THF/H_2O; 99%
(iii)	$LiAlH_4$/THF; 99%	(iv)	H_2/Pd/C/MeOH; 99%
(v)	$PhCH_2OCONHOH/Me_4N^+IO_4^-/CH_2Cl_2$; 77%	(vi)	$LiAlH_4$/THF; 82%
(vii)	Zn/HOAc; 92%		

Conversion of the amino-alcohols (**10a,b**) into the *trans*-bromoamines (as the hydrobromide salts) was achieved using thionyl bromide.[5] The amino- group acted as an intramolecular base, reacting with the HBr formed in the reaction and producing the bromide ion necessary for the inversion of configuration at carbon 4. Cyclisation occurred only on release of the free bromoamine (by basification with tetramethylpiperidine) giving N-benzylnorhomotropane (**2a**) and the parent homotropane (**2b**) respectively. The same approach, when applied to the unsaturated analogues (**9a,b**) led, in turn, to N-benzylnorhomotrop-7-ene (**3a**) and homotrop-7-ene (**3b**) (Scheme 2).[6]

Deprotection of the nitrogen in the case of (**2a**) was achieved simply by hydrogenolysis of (**2a:HCl**) to give the parent secondary amine, norhomotropane (9-azabicyclo[4.2.1]nonane) (**2c**). The corresponding 7-ene analogue (**3c**) was prepared by demethylation of (**3b**) using α-chloroethyl chloroformate.[8]



[a: R=CH_2Ph; b: R=CH_3; c: R=H]

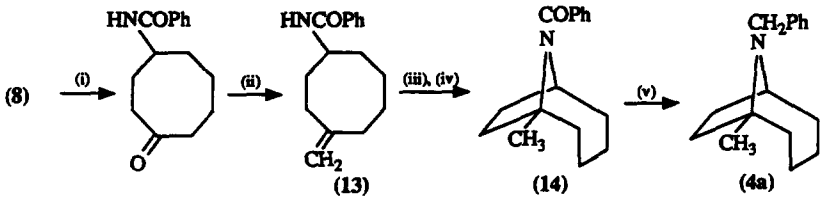
Scheme 2

(i) $SOBr_2/CH_2Cl_2$ (ii) TMP/CH_2Cl_2 (overall yield 54%)

(iii) $H_2/Pd/HCl$; 98% (iv) TMP/CH_2Cl_2 (overall yield 65%)

(v) α-chloroethyl chloroformate/$CDCl_3$; 78% (followed by NMR; not yet optimised)

The overall yields in the cyclisation steps were acceptable and the products were easily isolated in pure form by column chromatography. The bicyclic amines were uncontaminated by the aziridine isomers which might have been expected to have resulted from competitive 1,2- cyclisation (c.f. reference 3) although some elimination occurred during conversion of **(10)** into **(2)**. The cyclisation steps in Scheme 2 involve displacement at an sp^3 carbon; Scheme 3 summarises an adaptation of the approach which allows cyclisation on to an sp^2 carbon of an *exo*-methylene group.[9] Thus the amido-alcohol **(8)** was converted into **(13)** by Jones oxidation and Wittig methylenation. Mercury(II)-mediated amidocyclisation[10] followed by borohydride reduction gave **(14)**; reduction of the amide with $LiAlH_4$ gave **(4a)**,[7] the 1-methyl derivative of **(2a)**. Debenzylation with hydrogen and a palladium catalyst gave the secondary amine **(4c)**.



Scheme 3

(i) CrO_3/H_2SO_4; 93% (ii) $Ph_3P{=}CH_2$ (3 mol. eq.)/DMSO; 90%

(iii) $Hg(O_2CCF_3)_2$/ CH_3CN; (iv) $NaBH_4$/THF; (93% overall)[10]

(v) $LiAlH_4$/THF; 99%

These methods are clearly adaptable to the production of a wider range of substituted homotropanes/enes both by use of substituted cyclooctadienes and by further functionalisation of intermediates in the schemes shown above. Both approaches are currently being explored.[11]

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References.

1. W.W. Carmichael, D.F. Biggs, P.R. Gorham, *Science*, **1975**, *187*, 542; F.J. Sardina, M.H. Howard, M. Morningstar and H. Rapoport, *J.Org.Chem.*, **1990**, *55*, 5025 and references cited therein.

2. E.g. A.C. Cope, H.R. Nace and L.L. Estes Jr., *J.Amer.Chem.Soc.*, **1950**, *72*, 1123. (*via* ring expansion of tropinone followed by reduction of homotropinone).

3. A. Bathgate and J.R. Malpass, *Tetrahedron Lett.*, **1987**, *28*, 5937. Other reports of successful approaches to tropanes and derivatives based on intramolecular cyclisation reactions have been reported: H.E. Schink, H. Pettersson and Jan-E. Bäckvall, *J.Org.Chem.*, **1991**, *56*, 2769 and references to earlier work cited therein.

4. H. Iida, Y. Watanabe and C. Kibayashi, *J.Org.Chem.*, **1985**, *50*, 8516.

5. The cyclisation approach follows the general method described in reference 3. However, improved yields are generally obtained in both 7- and 8- membered ring systems using a better leaving group (bromide rather than chloride). A slight improvement in yield is possible when a more polar solvent is used for the cyclisation (dichloromethane is removed from the hydrobromide salt and replaced by dry acetone prior to treatment with base); these observations are entirely consistent with an S_N2 displacement mechanism.

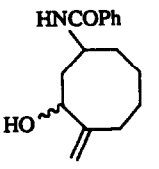
6. (2b) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 - 1.63 (m, 8H), 1.79 - 1.86 (m, 2H), 2.08 - 2.28 (m, 2H), 2.42 (s, 3H), 3.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6(t), 30.2(t), 35.5(t), 42.9(q), 64.6(d). (3b) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32-1.64 (m, 6H), 1.73-1.83 (m, 2H), 2.35 (s, 3H), 3.53 (ddd J = 6.3, 1.6, 1.0 Hz, 2H), 5.66 (d J = 1.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7(t), 32.6(t), 45.7(q), 71.9(d), 130.4(d); ^{m}/z calc. for $C_9H_{15}N$: 137.1204; found: 137.120.

7. (4a) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.33-1.88 (complex, 10H), 1.94-2.13 (m, 2H), 3.33 (m, 1H), 3.84 (AB J = 14.6 Hz, 2H), 7.10-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8(t), 25.2(t), 29.3(q), 29.8(t), 32.8(t), 38.5(t), 41.2(t), 47.3(t), 57.1(d), 62.9(s), 126.3(d), 128.0(d), 128.4(d), 141.8(s); ^{m}/z calc. for $C_{16}H_{23}N$: 229.1830; found: 229.183.

8. R.F. Olofson, J.T. Martz, J.-P. Senet, M. Piteau and T.J. Malfroot, *J.Org.Chem.*, **1984**, *49*, 2081.

9. See accompanying paper for examples of transannular 1,4- nucleophilic attack at sp^2 carbon of carbonyl groups.

10. The use of a 1:1 mixture of mercury (II) acetate and trifluoroacetate (c.f. J.M. Takacs, M.A. Helle and F. Takusagawa, *Tetrahedron Lett.*, **1989**, *30*, 7321) led to formation of **(14)** together with by-products including the interesting hydroxylated derivative **(15)**. In contrast, use of mercury (II) trifluoroacetate alone led to clean formation of **(14)** in 93% isolated yield.



(15)

11. D. Justice, J.R. Malpass and C. Smith, work in progress.

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