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Total Synthesis of 1-Hydroxytropacocaine and Analogues

John R. Malpass,* and Anna L. Wallis

Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK.

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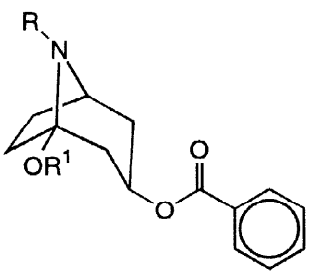
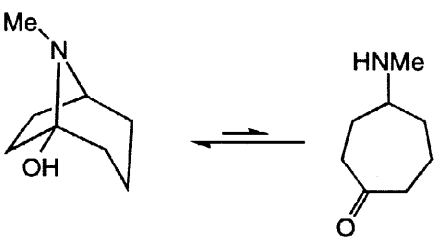
Abstract The first synthesis of the title alkaloid **(1)** (± 3-β-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octan-1-ol) is described from cyclohepta-3,5-dienol. The approach is extended to novel variants including the unknown nor-analogue **(3)** and a derivative of the 6,7-dehydro- system. Detailed NMR data are presented. VT NMR studies show that **(1)** is effectively bicyclic, although there is evidence confirming the occurrence of tautomerism involving the monocyclic amino-ketone; in contrast, N-benzyloxycarbonyl derivatives are monocyclic.

Introduction

The isolation of a new tropane alkaloid, 1-hydroxytropacocaine **(1)** in small quantities from *Erythroxylum coca* and in abundant quantities from a number of *Erythroxylum novogranatense* variants was described very recently.[1] As a 1-hydroxytropane, compound **(1)** joins a small, but growing, group of more highly hydroxylated natural 1-hydroxynortropane derivatives, collectively known as the calystegines, which have been extracted and identified only in the last decade despite the fact that they occur in well-known (and already well-studied) species.[2] The calystegines have multiple functions in rhizosphere ecology including glycosidase inhibitory activity. 1-Hydroxytropanes are also of interest in view of the occurrence of tautomerism involving the bicyclic hemi-aminal and monocyclic amino-ketone forms. This was first established in physoperuvine **(4 ⇌ 5)**, the first 1-hydroxytropane to be isolated from natural sources.[3,4] However, in the original report on 1-hydroxytropacocaine,[1] **(1)** was characterised not as the free amino-alcohol but as the O-heptafluorobutanoyl (HFB) derivative **(2)** in view of its apparent tendency to degrade readily in methanol. Clearly, this precluded any detailed study of **(1)** or of the tautomeric equilibrium in this case.



(1) R = Me, R^1 = H
(2) R = Me, R^1 = $COCF_2CF_2CF_3$
(3) R = R^1 = H



(4) **(5)**

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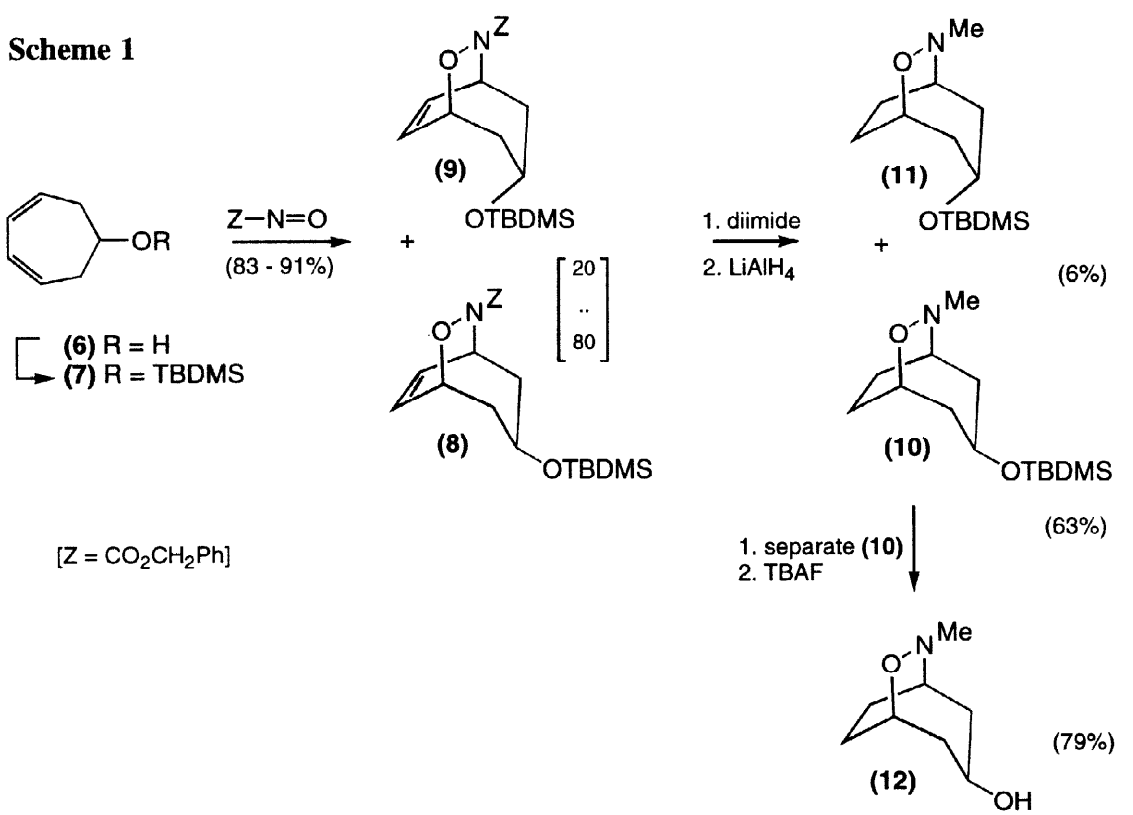
1-Hydroxy-derivatives of tropane are not available using the major conventional routes based on cycloaddition chemistry. We have developed an effective route to tropanes from 7-ring dienes which has been adapted successfully to the production of 6,7-dehydro-, 6,7-epoxy-, and 3-hydroxytropanes, as well as nor-systems, and higher homologues.[5] Significantly, the key monocyclic 4-hydroxycycloheptylamine intermediates which are central to our tropane strategy can be oxidised readily to the corresponding amino-ketones which are actually 1-hydroxytropanes. Our synthesis of physoperuvine (**4** ⇌ **5**) in high overall yield from cycloheptadiene[4] illustrates this and prompted us to extend our studies to 1,3-dihydroxytropanes and, in particular, to (**1**).

We report here the first synthesis of (±)-(**1**) in an overall yield of 33% from (**7**). Further, we feel that it is significant that all of the calystegines identified to date are based on the 1-hydroxy-*nor*-tropane skeleton (i.e. with a secondary bridging nitrogen) and it may well be that nor- derivatives of compounds such as 1-hydroxy-tropacocaine will be isolated from plant sources in due course. In anticipation of this possibility, we have modified our approach to produce the nor- compound (**3**). 6,7-Dehydro- analogues are also of interest as potentially useful precursors of 6-/7- mono- or di-hydroxylated 1-hydroxytropanes. VT NMR studies of the tautomeric equilibria are also described.

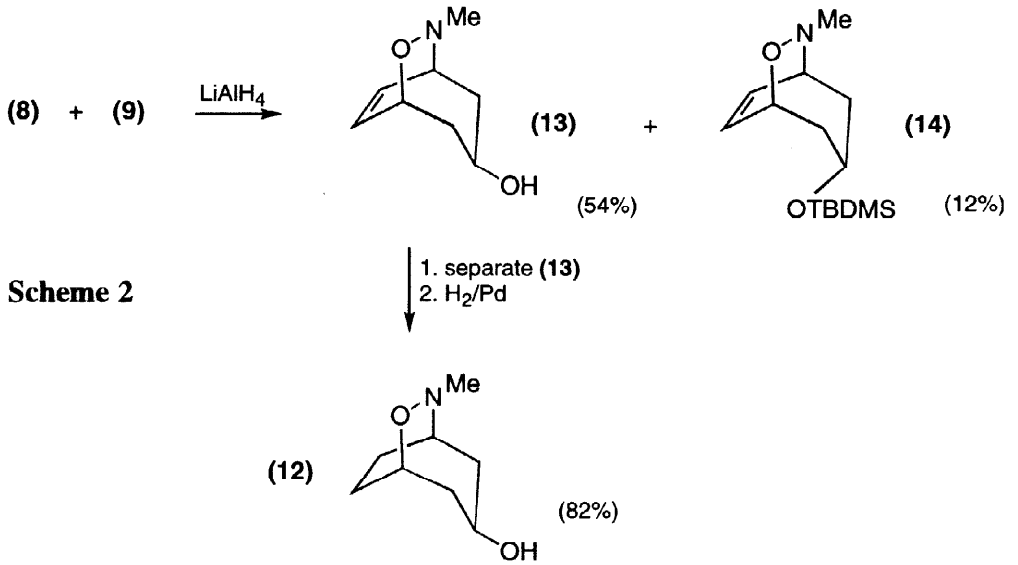
Discussion

The direct route to (**1**) began with the TBDMS derivative (**8**) formed by cycloaddition of benzyl nitrosoformate to the TBDMS derivative (**7**) [rather than to cyclohepta-3,5-dienol (**6**) itself] since the presence of the TBDMS group leads to facially selective addition giving a product containing 80% of the β-3-silyloxy isomer (**8**)[6] (Scheme 1). Treatment of the mixture of (**8**) and (**9**) with diimide followed by hydride reduction gave (**10**) and (**11**); the required β-isomer (**10**) was separated chromatographically in 63% overall yield. Desilylation of (**10**) with TBAF then gave (**12**) in good yield.

Scheme 1

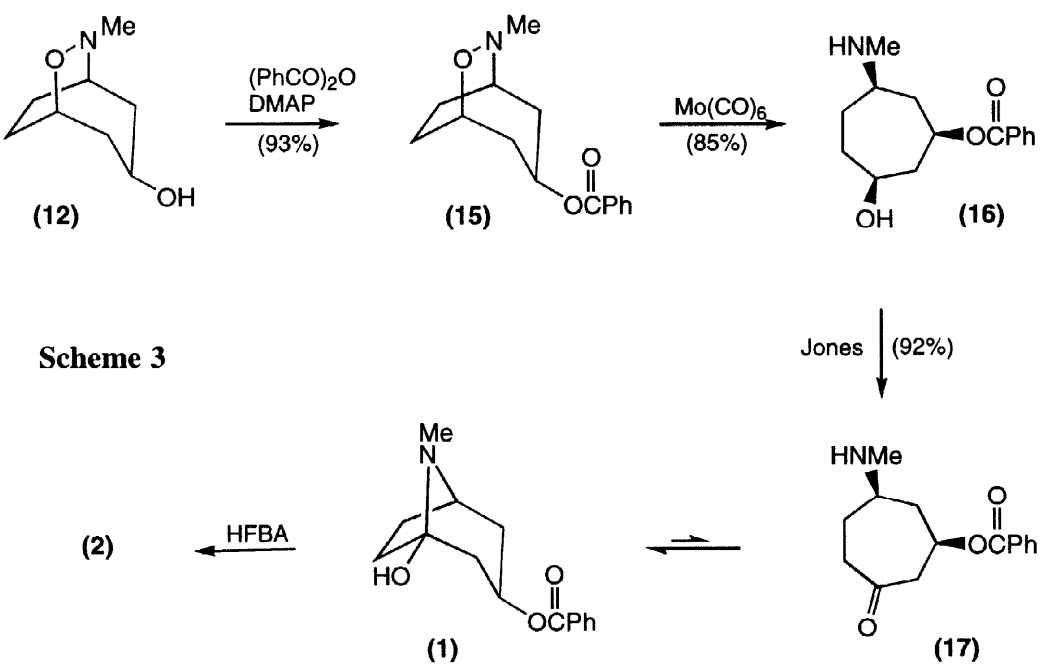


Treatment of the mixture of (**8**) and (**9**) with lithium aluminium hydride in THF at reflux reduced the N-protecting group in both cases but also led to selective deprotection of the 3-hydroxyl of (**8**) (Scheme 2). Conveniently, the small amount of the 3α-isomer (**14**) retained the TBDMS group under these conditions and the β-3-ol (**13**) was therefore easily separated by chromatography on silica. Catalytic hydrogenation of (**13**) gave (**12**). Unfortunately, the optimum conditions for selective deprotection of the 3-hydroxyl of (**8**) were not easy to reproduce cleanly; mixtures containing small but variable quantities of the TBDMS derivative of (**13**) were sometimes obtained and the approach shown in Scheme 1 was generally more reliable and efficient.



Scheme 2

Esterification of (**12**) with benzoic anhydride and 4-dimethylaminopyridine (DMAP), gave the bicyclic oxazine (**15**) (Scheme 3). Cleavage of the NO bond with $Mo(CO)_6$[8] furnished the all *cis*- compound (**16**) which was then oxidised efficiently to the ketone (**17**) using standard Jones conditions. The product was actually isolated as 1-hydroxytropacocaine (**1**), the bicyclic tautomer.



Scheme 3

Table 1. NMR chemical shift and multiplicity data for 1-hydroxytropacocaine (1), 1-OHFB derivative (2), and 1-hydroxynortropacocaine (3).

proton/carbon	(1) ^{1}H (223K)[b]	(2)[a] ^{1}H	(3) ^{1}H	(1) ^{13}C (223K)	(1) ^{13}C (300K)	(2)[a] ^{13}C	(3) ^{13}C (223K)	(3) ^{13}C (300K)
1				88.8	*c*	99.8	90.6	*c*
2β (axial)	~1.93 m	2.09 d^3	1.92 bd^3	33.9	35.2*d*	31.7	43.8	44.8
2α (equatorial)	~1.93 m	2.71 d^3	2.53 d^3					
3α (axial)	5.30 d^4	5.32 d^4	5.38 d^4	68.4	68.2	67.2	68.1	68.4
4β (axial)	2.02 m	2.00 d^4	1.65 d^4	27.4	29.0*d*	28.8	36.8	38.0
4α (equatorial)	1.75 d^3	1.85 d^3	2.15 m					
5	3.43 d^4	3.52 d^4	3.68 bd^3	56.3	57.2	56.5	52.0	52.3
6β (exo-)	2.08 m	2.18 d^4	~2.10 m	25.2	25.0	25.0	27.1	27.8
6α (endo-)	1.69 bd^3	1.67 d^4	1.75 bd^3					
7β (exo-)	1.82 bd^3	2.03 d^4	~1.90 m	36.0	36.1	33.5	34.5	35.4
7α (endo-)	2.05 m	2.61 d^3	2.05 d^3					
Me	2.42 s	2.53 s		29.2	29.7	29.9		
1'				130.4*e*	130.4*e*	130.0	130.3*e*	130.8*e*
2', 6'	8.05 d^2	8.01 d^2	8.04 d^2	129.8*e*	129.6*e*	129.6	129.9*e*	129.8*e*
3', 5'	7.48 d^2	7.44 d^2	7.48 brt	128.8*e*	128.4*e*	128.4	129.0*e*	128.7*e*
4'	7.62 t^2	7.56 t^2	7.61 t^2	133.5*e*	133.0*e*	133.2	133.7*e*	133.3*e*
PhC=O				166.0	166.0	165.7	166.1	166.1
NH/OH	*b*		5.04 brs					

Spectra for (1) and (3) were measured in CD_2Cl_2 (223 and 300K); d^3 = ddd; d^4 = dddd; t^2 = tt etc.

a Data from reference 1; the NMR solvent was not quoted.[7]

b Parts of the ^{1}H NMR spectra of (1) and (3) were second-order at 400MHz but were analysed as far as possible on a 'pseudo-first-order' basis with the help of ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra and selective spin-decoupling experiments in each case.[9] Some signals in the 1.6 - 2.1δ regions which overlapped at 300 K were separated at 223K. The OH/NH protons were broad and varied in position according to temperature, concentration and moisture content.

c Signal not visible at this magnetic field and temp. owing to rapid tautomerism.

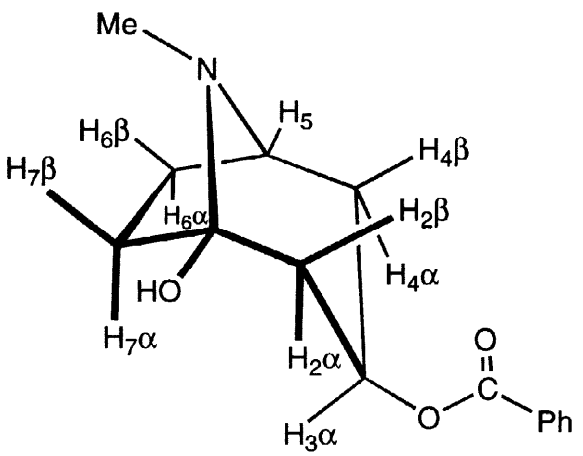
d Broad signal (see *c*).

e Aryl signals assigned with the aid of a CH COSY spectrum and by analogy with values quoted for (2).[1]

Careful examination of the ^{13}C NMR spectrum of (1) at 300K allowed identification of all of the carbon signals except that for C_1 although some of the visible signals (most notably those for C_2 and C_4) were broadened at this temperature. Lowering the temperature led to peak sharpening and revealed all of the signals expected of (1). Notably, the C_1 signal (which exchanges with the ring carbonyl carbon of (17) and coalesced at ambient temperature) became visible at 88.8 δ, which compares well with precedent.[4] This behaviour parallels that of physoperuvine and confirms that tautomerism is occurring despite the fact that the proportion of the monocyclic tautomer is too small to allow confident identification of signals from (17). Detailed spectroscopic data for compound (1) are summarised for the first time in Tables 1 and 2. Despite substantial overlap in the range 1.6 - 2.1 δ, the chemical shift for each proton was identified with the aid of ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra and selective spin-decoupling experiments. The upfield signals due to H_{4_α}, H_{6_α}, and H_{7_β}

overlapped at ambient temperature but were separated at 223K. Almost all of the coupling constants in the bicyclic portion of (**1**) could be estimated (Table 2) and these compared well with expectations based on compound (**2**) and other tropanes. The 3α proton was identified by its downfield position; the multiplicity and J values left no doubt that it was axial and that the ester substituent was therefore equatorial (β).

Table 2. $J_{H,H}$ values for 1-hydroxytropacocaine (1), 1-OHFB drivative (2), and 1-hydroxy-nortropacocaine (3) (values in Hz)



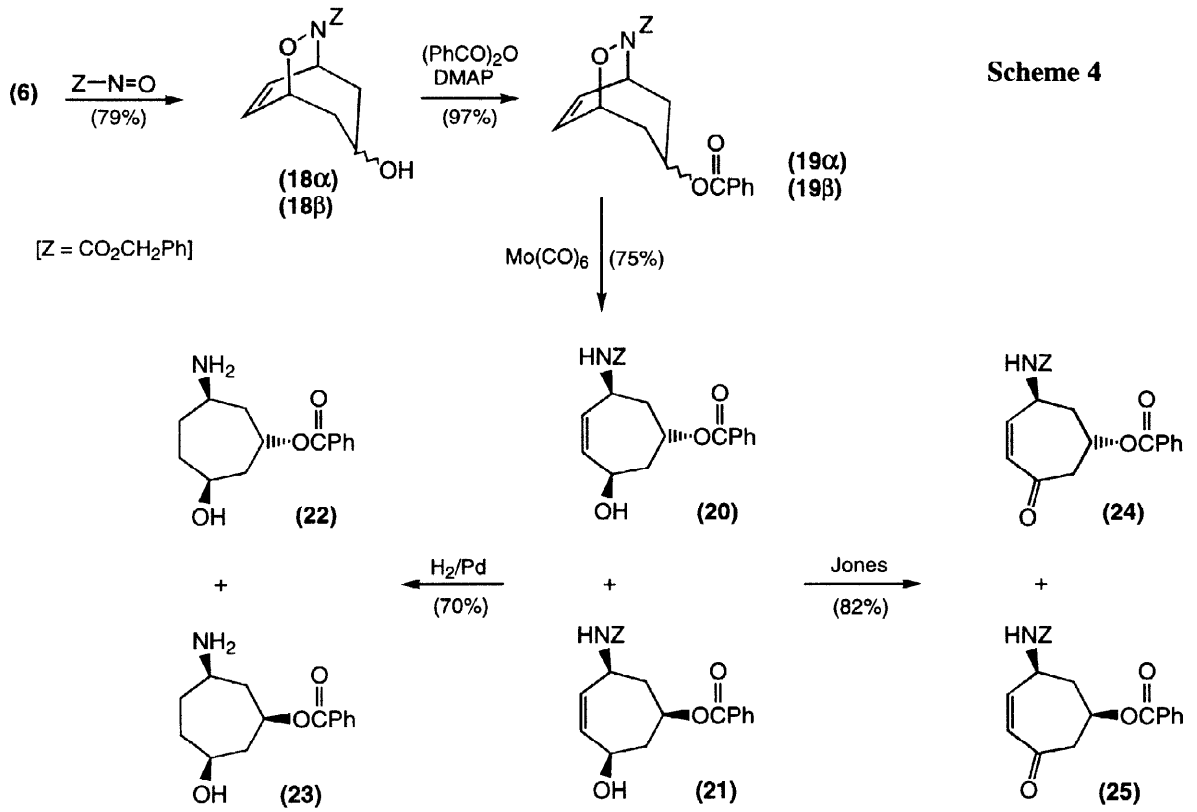
$J_{H,H}$	(1)	(3)	(2)[1]
$J_{2,2}$	*	12.4	11.9
$J_{2\alpha,3\alpha}$	6.5	6.1	6.5
$J_{2\beta,3\alpha}$	10.5	10.5	10.7
$J_{2\alpha,4\alpha}$	< 1	< 1	ca. 0.6
$J_{2\beta,7\beta}$	*	ca. 2	2.4
$J_{3\alpha,4\alpha}$	6.5	6.5	6.5
$J_{3\alpha,4\beta}$	10.5	10.7	10.7
$J_{4,4}$	12.5	13.3	13.3
$J_{4\alpha,5}$	2.5	2.5	2.2
$J_{4\beta,5}$	3.0	3.6	3.4
$J_{4\beta,6\beta}$	*	ca. 1	1.3
$J_{5,6\beta}$	7.0	7.3	7.2
$J_{5,6\alpha}$	< 1	< 1	ca. 0.6
$J_{6,6}$	13	13.3	12.7
$J_{6\alpha,7\alpha}$	10	9.0	9.8
$J_{6\alpha,7\beta}$	4.0	ca. 5	4.3
$J_{6\beta,7\alpha}$	*	ca. 5	4.8
$J_{6\beta,7\beta}$	13.5	*	12.7
$J_{7,7}$	13.5	13.3	13.3

J values (Hz) were determined on the basis of 'pseudo-first-order' analysis with the aid of selective spin-decoupling experiments from spectra measured at 400 MHz at 223K in CD_2Cl_2 (**1**) and 300K ($CDCl_3$) (**3**); values are considered accurate to ca. ± 0.2 Hz. * These J values were not measured because of peak overlap.

We found (**1**) to be stable to chromatography on silica (EtOAc/MeOH/NH_3 solvent) and to be stable over a period of months in the refrigerator. In the original report,[1] 1-hydroxytropacocaine was characterised as the 1-OHFB derivative (**2**). We therefore converted our sample into (**2**) to produce material which showed identical ^{1}H NMR characteristics to the literature sample.[7]

In an attempt to provide convenient access to both the 3β- and unknown 3α- derivatives, the procedures were carried through on the mixture of adducts (**18α,β**) formed from the dienol (**6**), in the hope of an easy separation at a later stage. Schemes 4 and 5 cover the N-protected and nor- compounds; conversion of the mixture (**18α,β**) into (**19α,β**) and hence into the cycloheptene derivatives (**20**) and (**21**) was straightforward; their separation was not easy but this was subsequently found to be the preferred point at which to separate the α- and β- series. Treatment of (**20, 21**) with hydrogen and a palladium-on-carbon catalyst removed the N-protecting group and the double bond to provide the mixture (**22, 23**); small samples of these compounds were separated chromatographically but the procedure was not practical. Oxidation of the mixture (**20, 21**) using standard Jones conditions produced the ketones (**24, 25**) in good yield but these were not separable.

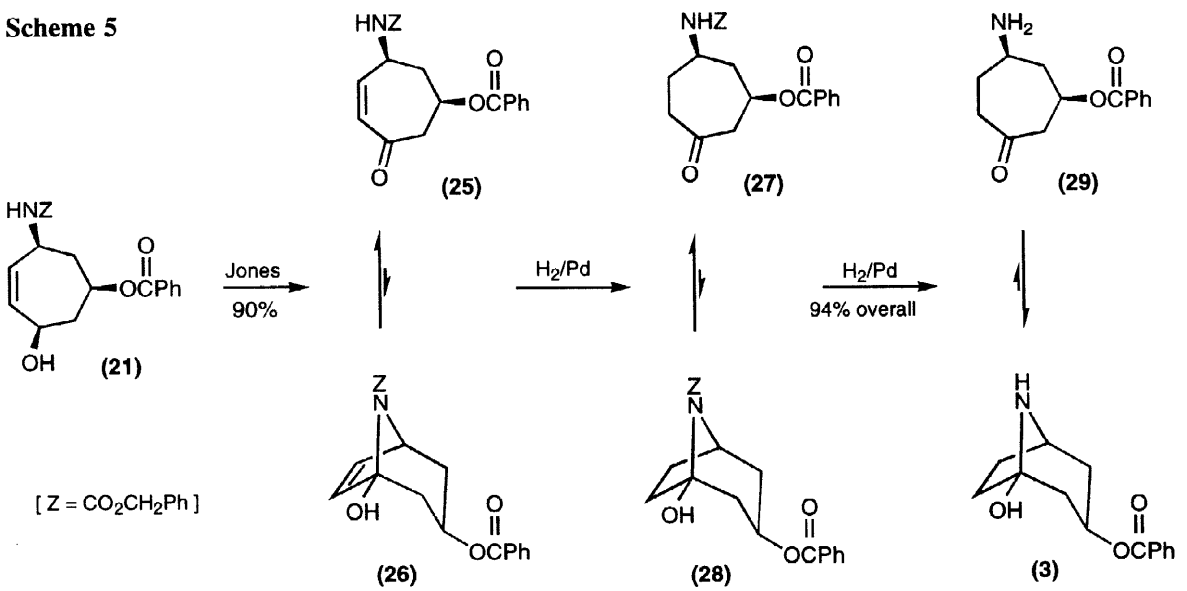
Careful chromatography separated a pure sample of (**21**) from the mixture of (**20**) and (**21**). Further work was confined to the 'β' series at this stage; we expect to report extension to the non-natural α-analogues of (**1**) and (**3**) in due course. Oxidation of (**21**) to the compound (**25**) (Scheme 5) proceeded in good yield from (**21**); the tautomeric equilibrium favoured the monocyclic (**25**) rather than the bicyclic tautomer (**26**).



Scheme 4

Treatment with hydrogen on palladium/carbon over a period of three hours converted (**25**) directly into the nor-compound (**3**) in an overall yield of 94%. Careful hydrogenation over a shorter period actually allowed isolation of the intermediate (**27**) (Scheme 5) although it was difficult to purify. The alternative sequence (**21**) → (**23**) → (**3**) was not as attractive since the unprotected amino-alcohols were more polar and difficult to handle. The secondary amino-compound (**3**) was easily hydrated but showed ^{1}H NMR characteristics which were very similar to those of (**1**). NMR data are shown in Tables 1and 2; J values for $H_{3\alpha}$ again confirmed the configuration at C_3 and the ^{13}C signal for C_1 was only detectable at low temperature. The change to a secondary bridging N led to substantial downfield shifts for C_2 and C_4 in comparison with values for (**1**).

Scheme 5



Tautomerism

Quite apart from any theoretical interest, tautomerism in 1-hydroxytropanes has practical consequences since the presence of reactive minor tautomers is easily neglected but may lead to unexpected products. The appearance of signals in the NMR spectra is naturally temperature- and field-dependent; some signals may be broadened to the point of invisibility, leading to potential misinterpretation of spectra. Table 3 summarises measurements for the compounds in this study together with comparison data for physoperuvine and derivatives.

Table 3. Tautomer ratios for 1,3-dihydroxytropane / 3-hydroxy-5-aminocycloheptanone derivatives[a]

Compound		Ratio (monocyclic : bicyclic)
1-hydroxytropacocaine	(17 ⇌ **1**)	ca. 0 : 100
1-hydroxynortropacocaine	(29 ⇌ **3**)	ca. 0 : 100
physoperuvine[4]	(5 ⇌ **4**)	2 : 98
norphysoperuvine[4]		ca. 0 : 100
N-benzyloxycarbonyl-1-hydroxy-nortropacocaine	(**27** ⇌ 28)	ca. 100 : 0
N-benzyloxycarbonyl-norphysoperuvine[4]		ca. 100 : 0
N-benzyloxycarbonyl-6,7-dehydro-1-hydroxynortropacocaine	(**25** ⇌ 26)	ca. 100 : 0
6,7-dehydrophysoperuvine[4]		major : minor

a These ratios were estimated by ^{13}C NMR in $CDCl_3$ at 223 K; the major tautomer is shown in **bold** in each case. Signals from possible minor tautomers were very difficult to assign with confidence in the heavily weighted examples so that ratios are approximate.

The heavy preference for the bicyclic tautomer (**4**) in both physoperuvine (**4** ⇌ 5) and norphysoperuvine is established.[4] The results of low-temperature ^1H and ^{13}C NMR studies (Table 3) show that the bicyclic preference is maintained for 1-hydroxytropacocaine (**1**) and the corresponding nor- compound (**3**). In contrast, data for 6,7-dehydrophysoperuvine suggested a preference for the monocycle.[4] In the case of the 6,7-dehydro-compound (**25** ⇌ 26), the shorter π-bond is expected to lead to increased strain in the bicyclic tautomer, and this, together with the stabilisation of the monocyclic tautomer (**25**) by resonance in the α,β-unsaturated ketone unit, presumably does play a part in the observed preference for the monocycle. However, this preference is likely to be due not only to the 'unsaturation' effect but also to the fact that the bridging nitrogen is sp^2-hybridised in this case. The additional, overriding destabilisation of the bicyclic urethane (26) stems from the need to achieve a 120° CNC bond angle [in contrast to (**1**) and (**3**) for which a nominal CNC bond angle of ~109.5° would be the ideal]. This also explains the contrast between the preference for the monocyclic (**27** ⇌ 28) and the bicyclic (29 ⇌ **3**). These results consolidate the earlier observations where the bicyclic preference in physoperuvine and norphysoperuvine is totally reversed in favour of the monocyclic tautomer when the bridging nitrogen bears a conjugating group.[4,10]

We are grateful to the EPSRC for the award of a studentship to AW.

Experimental

Routine ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 250 spectrometer (250 and 63 MHz). Higher field and variable temperature ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 spectrometer (400 and 101 MHz). Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), d^2 (doublet of doublets), d^3 (doublet of doublet of doublets) etc., t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad) and v (very); protons identified as NH or OH were shown to be exchangeable with D_2O. In some circumstances, signals that appear in a more simplified form than the molecule allows are given the prefix ~. For example, a d^4 which appears as a quintet is quoted as ~quin. Where data are quoted for two isomers or rotamers, overlapping signals are shown in italics but may be quoted separately for reasons of clarity even though they are not fully resolved or assigned. In the ^{13}C spectra, C, CH, CH_2, CH_3 are used to indicate quaternary, methine, methylene and methyl carbons respectively, as shown by off-resonance decoupling or DEPT experiments.

IR spectra were recorded on a PE 298 IR spectrometer as solutions in CH_2Cl_2 unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very). Mass spectra were measured on a Kratos Concept spectrometer using ionisation by electron impact except where fast atom bombardment (FAB) was used; intensities are given as percentages of the base peak.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected. Combustion Analyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex.

Reactions were performed under dry nitrogen using solvents dried by standard methods. Diethyl ether was distilled from $LiAlH_4$. Dichloromethane was distilled from calcium hydride. Petroleum ether was distilled prior to use. Methanol and ethanol were purified with magnesium and iodine.[11] Tetrahydrofuran was distilled from sodium- benzophenone and pyridine was distilled from calcium hydride. All other solvents were dried and purified as described by Perrin.[12] Flash chromatography was carried out using Silica gel 60 (35 - 70μm) supplied by Fluka. Separations using the Chromatotron were carried out using plates coated with a 4mm layer of silica. Analytical thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel 60.

Cyclohepta-3,5-dienol (**6**) and 6-[(t-Butyldimethylsilyl)oxy]cyclohepta-1,3-diene (**7**) were obtained using the procedures described in reference 6.

N-Benzyloxycarbonyl-3β-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]non-8-ene (8) and N-Benzyloxycarbonyl-3α-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]non-8-ene (9)

Tetramethylammonium periodate (4.13 g, 15.6 mmol) and (**7**) (3.0 g, 13.0 mmol) in dichloromethane (65 ml) were stirred at -78°C. A solution of benzyl-N-hydroxycarbamate (2.61 g, 15.6 mmol) in dichloromethane (10 ml) was dripped in over 10 min and the solution was then warmed to ambient temperature and stirred for 1.5h. The solution was filtered, washed with sodium thiosulphate solution (2 x 30 ml) and water (30 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residual dark yellow oil was purified by flash chromatography using 1:3 diethyl ether:petroleum ether (b.p. 40-60°C) to afford (**8**) (containing *ca.* 20% of the 3α-isomer (**9**), as calculated from ^1H NMR signal integrations) as a yellow oil (4.22 g, 83%). The NMR spectra were identical to those of a sample prepared by Justice (in 91% yield),[6] e.g., δ_H (250 MHz, $CDCl_3$): 0.01 [s, 6H, $(CH_3)_2Si$], 0.85 [s, 9H, $(CH_3)_3CSi$], 1.88 - 2.14 (series of m, 4H), 3.68 (~t^2, J = 10.3, 6.3 Hz, 1H, α-OSi), 4.70 (brt, J ≈ 5 Hz, 1H, α-N), 4.84 (brt, J ≈ 7 Hz, 1H, α-O), 5.15 (s, 2H, CH_2Ph), 6.18 (d^3, J = 9.1, 6.2, 1.3 Hz, 1H), 6.31 (d^3, J = 9.1, 6.8, 0.8 Hz, 1H), 7.32 (m, 5H). Small signals from the 3α- isomer (**9**) were visible.

N-Methyl-3β-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]nonane (10) N-Methyl-3α-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]nonane (11)

To a stirred solution of potassium azodicarboxylate (6.67g, 34.4 mmol) and a mixture of (**8**) and (**9**) (ratio 80:20, 1.34 g, 3.44 mmol) was added glacial ethanoic acid (3.9 ml, 68.2 mmol) over 10 min. The mixture was warmed to ambient temperature and stirred for a further 17 h. The mixture was quenched with water (3 ml), filtered, and the bulk of the solvent removed under reduced pressure. The residual oil was taken into dichloromethane, washed with saturated sodium bicarbonate solution (2 x 15 ml), and with water

(15 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered, and the solvent removed under reduced pressure to leave the mixture of N-benzyloxycarbonyl-3-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]nonanes as an oil (1.25 g). δ_H (250 MHz, $CDCl_3$): 0.06 [s, 6H, $(CH_3)_2Si$], 0.88 [s, 9H, $(CH_3)_3CSi$], 1.6 - 2.25 (series of m, 8H), 4.20 (m, 1H, α-OSi), 4.36 (brm, 1H, α-N), 4.40 (brm, 1H, α-O), 5.25 (s, 2H, CH_2Ph), 7.35 (m, 5H); δ_c (63 MHz, $CDCl_3$; some signals were broadened and not all were visible at this temperature owing to slow rotation about the N-CO bond): -4.7 [$(CH_3)_2Si$], 18.1 [$(CH_3)_3CSi$], 21.4 and 22.1 (2 x CH_2), 25.8 [$(CH_3)_3CSi$], 42.4 (br, CH_2), 48.6 (br, NCH), 66.3 (CHOSi), 67.3 (CH_2Ph), 73.3 (OCH), 128.1 (2 x Aryl CH), 128.5 (Aryl CH), 136.5 (Aryl C), 154.3 (C=O); ν_{max} (CH_2Cl_2): 2960s, 2930s, 2890m, 2860m, 1720s, 1690s, 1450brm, 1365m, 1345m, 1330m, 1310m, 1090brs, 1005m, 905m, 855m, 840s, 740bm cm^{-1}; $^m/z$ (FAB): 414 (MNa^+), 392 (MH^+); $C_{21}H_{34}NO_4Si$ [MH^+] requires 392.2258; observed 392.2258.

This mixture was partially purified by column chromatography using 1:4 diethyl ether:petroleum ether (b.p. 40-60°C) to yield a yellow oil (993 mg) which was dissolved in diethyl ether (70 ml), dried with anhydrous magnesium sulphate, and evaporated under reduced pressure. A sample of this mixture (544 mg, 1.39 mmol) in dry diethyl ether (25 ml) was added dropwise to $LiAlH_4$ (0.211 g, 5.5 mmol) with stirring at 0°C and allowed to warm to ambient temperature over 1h. The reaction was quenched by dropwise addition of water-saturated diethyl ether and the resulting suspension was dried with anhydrous magnesium sulphate. After filtration through celite, the filter cake was washed thoroughly with ethyl acetate and the combined extracts were evaporated under reduced pressure to give an oil which was chromatographed over silica using diethyl ether:petroleum ether in ratios ranging from 2:3 up to 3:2. A sample of the minor N-methyl compound (**11**) was eluted first (22 mg, 6% overall yield; this sample contained a small amount of the major isomer); a pure sample of the major isomer (**10**) was then eluted (237 mg, 63% overall).

(**10**): δ_H (250 MHz, $CDCl_3$): 0.06 [s, 6H, $(CH_3)_2Si$], 0.88 [s, 9H, $(CH_3)_3CSi$], 1.58 (m, 2H), 1.80 - 2.20 (series of m, 6H), 2.60 (s, 3H, NCH_3), 2.90 (brt, J ≈ 6 Hz, 1H, α-N), 4.00 (brm, 1H, α-O), 4.12 (m, 1H, α-OSi); δ_c (63MHz, $CDCl_3$): -4.9 [$(CH_3)_2Si$], 18.1 [$(CH_3)_3CSi$], 21.2 (br, CH_2), 22.3 (CH_2), 25.9 [$(CH_3)_3CSi$], 38.0 (br, CH_2), 44.7 (CH_3), 46.2 (CH_2), 55.6 (NCH), 66.7 (CHOSi), 69.9 (OCH); ν_{max} ($CDCl_3$): 2960s, 2948s, 2890m, 2860s, 1470m, 1462m, 1445w, 1435w, 1410w, 1390w, 1372w, 1362w, 1350w, 1325w, 1280w, 1260s, 1205w, 1165w, 1090s, 1005w, 995w, 965w, 855s, 840s, 815w, 805w cm^{-1}; $^m/z$ (FAB): 272 (MH^+); $C_{14}H_{30}NO_2Si$ [MH^+] requires: $^m/z$ 272.2046; observed: 272.2046.

(**11**): δ_H (400 MHz, $CDCl_3$): 0.08 [s, 6H, $(CH_3)_2Si$], 0.91 [s, 9H, $(CH_3)_3CSi$], 1.60 - 2.20 (series of m, 6H), 2.30 (m, 1H), 2.48 (m, 1H), 2.70 (s, 3H, NCH_3), 3.05 (brm, 1H, α-N), 4.15 (brm, 2H, 2 x α-O); δ_c (101MHz, $CDCl_3$): -4.5 [$(CH_3)_2Si$], 18.4 [$(CH_3)_3CSi$], 22.7 and 23.8 (2 x CH_2), 26.2 [$(CH_3)_3CSi$], 44.3 and 46.6 (2 x CH_2), 53.2 (CH_3), 57.1 (NCH), 67.3 (CHOSi), 70.2 (OCH); ν_{max} ($CDCl_3$): 2960s, 2945s, 2890m, 2860s, 1470m, 1260s, 855s, 840s cm^{-1}.

N-Methyl-3β-hydroxy-6-oxa-7azabicyclo[3.2.2]non-8-ene (13) and N-Methyl-3α-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]non-8-ene (14)

A flame-dried 2-necked flask, fitted with a septum cap and reflux condenser, was charged with $LiAlH_4$ (1 g, 26.5 mmol). Dry THF (10 ml) was injected and the system was alternately evacuated and purged with nitrogen gas. The slurry was cooled with stirring to 0°C and a solution of (**8**) and (**9**) (2.58 g, 6.63 mmol) in dry THF (40 ml) was introduced. The mixture was heated under reflux for 3h, after which time no starting material remained. The solution was cooled to 0°C and the minimum amount of water-saturated diethyl ether was added carefully to destroy the excess hydride. The suspension was dried with anhydrous sodium sulphate, filtered though celite and the inorganic residues washed with ethyl acetate (3 x 20 ml). The combined organic extracts were evaporated under reduced pressure to leave a yellow oil (1.4 g). Further washing with methanol yielded a yellow solid (524 mg). These extracts were combined and purified by flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40-60°C), to yield (**14**) (225mg, 12%) (the sample still contained a small amount of benzyl alcohol which was difficult to separate chromatographically): δ_H (250 MHz, $CDCl_3$): 0.12 [s, 6H, $(CH_3)_2Si$], 0.91 [s, 9H, $(CH_3)_3CSi$], 1.46 (m, 2H), 2.36 (m, 2H), 2.61 (s, 3H, NCH_3), 3.46 (brt, J ≈ 6 Hz, 1H, α-N), 4.36 (brm, 1H, α-O), 4.56 (m, 1H, α-OSi), 6.26 (brdd, J ≈ 9.1, 6.4 Hz, 1H, =CH), 6.46 (brdd, J ≈ 9.1, 6.6 Hz, 1H, =CH).

Futher elution with methanol:diethyl ether (1:9) afforded the desired compound (**13**) as a single stereoisomer (486mg, 54%). δ_H (250 MHz, $CDCl_3$): 1.46 (brd^2, J = 13.2, 10.5 Hz, 1H), 1.68 (m, 1H), 1.88 (m, 1H), 2.02 (m, 1H), 2.24 (s, 3H, NCH_3), 3.20 (brt, J ≈ 7 Hz, 1H, α-N), 3.35 ($\sim t^2$, J = 10.2, 4.8 Hz, 1H, α-O), 4.18 (m, 2H, α-O and OH), 5.89 (brd^2, J = 9.1, 6.1 Hz, 1H), 6.05 (brd^2, J = 9.1, 5.9 Hz, 1H); δ_c (63MHz, $CDCl_3$): 38.7 (br, CH_2), 41.1 (CH_2), 45.5 (CH_3), 58.0 (NCH), 65.5 (COH), 69.5 (OCH), 127.6 HC=), 128.8

(HC=); ν_{max} (CH_2Cl_2): 3600m, 3400br, 3040m, 2940s, 2880m, 2855m, 1600m, 1145w, 1075w, 935m, 910m, 830w, 800w cm^{-1}; $C_8H_{13}NO_2$ requires: $^m/z$ 155.0946; found: 155.0946.

N-Methyl-3β-hydroxy-6-oxa-7-azabicyclo[3.2.2]nonane (12) from (10)

Tetrabutyl ammonium fluoride (1M in THF, 2.2 ml, 2.2 mmol) was injected into a solution of **(10)** (0.2 g, 0.738 mmol) under a nitrogen atmosphere at 0°C. The solution was stirred as it was allowed to warm to ambient temperature. After a further 22 h, the bulk of the solvent was distilled off under reduced pressure. The residual oil was dissolved in chloroform (20 ml) and washed with potassium carbonate solution (5 ml, 10% by weight) and brine (5 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered, and the solvent removed under reduced pressure. The oily product was chromatographed on silica using ethyl acetate/ammonia and then 5% methanol in ethyl acetate/ammonia to yield **(12)** as a pale yellow oil (92 mg, 79%). δ_H (250MHz, $CDCl_3$): 1.58 (d J = 9 Hz, 2H), 1.93 - 2.27 (series of m, 6H), 2.63 (s, 3H, NCH_3), 3.02 (m, 1H, α-N), 3.45 (brs, 1H, OH, exch.), 4.13 (m, 2H, 2 x α-O); δ_c (63MHz, $CDCl_3$, signals in italics were broadened owing to VT effects): *19.8*, 23.4, *39.00* (3 x CH_2), 44.5 (CH_3), 45.7 (CH_2), 56.6 (NCH), 66.6 (COH), 70.7 (OCH); ν_{max} ($CDCl_3$): 3610w, 3340vbrw, 2995w, 2960s, 2955s, 2950s, 2935s, 2920s, 2890m, 2870m, 2850w, 1110m, 1058s, 1055s, 1048s, 1040s, 1030s, 1025m, 960m, 910brm, 900m, 890m. $^m/z$ (FAB): 158 (MH^+); $C_8H_{16}NO_2$ [MH^+] requires 158.1181; observed 158.1181.

N-Methyl-3β-hydroxy-6-oxa-7-azabicyclo[3.2.2]nonane (12) from (13)

A solution of **(13)** (486 mg, 3.14 mmol) in absolute ethanol (25 ml) was hydrogenated using a catalytic amount of 10% palladium on charcoal at 1 atmosphere pressure. After 20 h the solution was basified with gaseous ammonia, filtered through celite, dried over anhydrous magnesium sulphate, and the solvent distilled under reduced pressure to yield **(12)** as a yellow oil (408 mg, 82%) which showed identical spectroscopic properties to the sample prepared from **(10)**.

N-Methyl-3β-[(benzoyl)oxy]-6-oxa-7-azabicyclo[3.2.2]nonane (15)

To a solution of **(12)** (170 mg, 1.08 mmol) in dry pyridine (5 ml) was added benzoic anhydride (741 mg, 3.28 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred for 4 h. A ^1H NMR spectrum of a small sample showed that no starting material remained and the bulk of the solvent was removed under reduced pressure. The off-white solid residue was purified by flash chromatography eluting with diethyl ether : petroleum ether (4:1) to yield **(15)** as a pale yellow oil (261 mg, 93%). δ_H (250MHz, $CDCl_3$): 1.81(m, 2H), 2.15 - 2.42 (series of m, 6H), 2.72 (s, 3H, NCH_3), 3.11 (brt, J ≈ 6 Hz, 1H, αN), 4.22 (brm, 1H, αO), 5.53 (t^2, J = 10.6, 6.6 Hz, 1H, αOCOPh), 7.44 (m, 2H, $H_{3',5'}$), 7.56 (brt^2, J = 7.3, 1.3 Hz, 1H, $H_{4'}$), 8.05, (brm, 2H, $H_{2',6'}$); δ_C (63MHz, $CDCl_3$): 22.4 (CH_2), 42.1 (CH_2), 44.3 (NCH_3), 55.8 (NCH), 69.7 (COCOPh), 70.1 (OCH), 128.7 ($C_{3',5'}$), 130.2 ($C_{2',6'}$), 130.8 ($C_{1'}$), 133.3 ($C_{4'}$), 166.6 (COPh), some signals were too broad at this temperature due to be assigned with confidence; ν_{max} (CH_2Cl_2): 3060w, 3050w, 3040w, 2960m, 2940m, 2910m, 2885w, 2860w, 2850w, 2835w, 1715brs, 1605w, 1585w, 1285s, 1275s, 1262s, 1255s, 1120s, 1115s, 1110s, 978m, 974m, 970m cm^{-1}; $^m/z$ (FAB): 262 (MH^+), $C_{15}H_{20}NO_3$ [MH^+] requires 262.1443; observed 262.1443.

All-cis-1-Hydroxy-3-benzoyloxy-5[methylamino]-cycloheptane (16)

The oxazine **(15)** (46 mg; 0.176 mmol) was dissolved in acetonitrile (10 ml) and water (2.5 ml) and molybdenum hexacarbonyl (50.6 mg, 0.192 mmol) was added. The mixture was heated at reflux for 7 h under a nitrogen atmosphere. After cooling, the suspension was filtered through a plug of silica gel which was then washed thoroughly with dichloromethane. Further filtration through celite followed by evaporation of solvent under reduced pressure yielded the crude product as a brown solid which was chromatographed on silica using 2% methanol in ethyl acetate to yield **(16)** as a yellow oil (39.1 mg, 85%). δ_H (250MHz; $CDCl_3$): 1.68 - 1.86 (series of m, 7H), 2.25 (m, 1H), 2.35 (brs, 1H, OH exch), 2.39 (s, 3H, NMe), 2.68 (m, 1H, α-N), 3.98 (m, 1H, α-O), 5.04 (t^2, J = 10.4, 2.8 Hz), 1H, α-OCOPh), 7.42 (brt, J = 7.5 Hz, 2H, $H_{3',5'}$), 7.55 (brt^2, J = 7.5, 1.3 Hz, 1H, $H_{4'}$), 8.01 (brd^2, J = 7.5, 1.3 Hz, $H_{2',6'}$); δ_c (63MHz; $CDCl_3$): 28.4, 32.7 (2 x CH_2), 34.3 (CH_3), 41.5, 44.2 (2 x CH_2), 56.8 (NCH), 68.0 (HCOCOPh), 70.5 (OCH), 128.7 ($C_{3',5'}$), 129.9 ($C_{2',6'}$), 130.8 ($C_{1'}$), 133.3 ($C_{4'}$), 166.2 (COPh); ν_{max} (CH_2Cl_2): 3610w, 3415w, 3050w, 2920m, 2860w, 2795w, 1715brs, 1290s, 1280s, 1268s, 1258s, 1115m, 1025m, 910m cm^{-1}; $^m/z$ (%): 263 (M^+, 3), 243 (1), 206 (4), 190 (6), 175 (1), 158 (20), 142 (100), 124 (22), 105 (72), 96 (15), 84 (45), 77 (51), 70 (72), 57 (39); $C_{15}H_{21}NO_3$ [M^+] requires 263.1521; observed 263.1521.

8-Methyl-3β-benzoyloxy-8-azabicyclo[3.2.1]octan-1-ol (1-hydroxytropacocaine) (1)

A stirred solution of **(16)** (8.2 mg, 0.03 mmol) in propanone (3 ml) was cooled to 0°C and titrated with Jones reagent[6] until the green solution had a permanent orange tinge. After 1 minute, the remaining oxidant was reduced by the dropwise addition of isopropanol. The green solution was basified to pH 9 with a solution of $NaHCO_3$ and the bulk of the solvent removed under reduced pressure. The residual aqueous layer was extracted with dichloromethane (3 x 10 ml). The organic extracts were combined and dried over anhydrous sodium sulphate. Filtration and evaporation afforded the crude product as an off-white solid. Purification by flash chromatography eluting with ethyl acetate : methanol (95:5) saturated with ammonia yielded **(1)** as a white crystalline solid (7.2 mg, 92%). A sample was recrystallised from petroleum ether (b.p. 60 - 80°C) and had m.p. 116 - 118°C. δ_H (400MHz) 298K, CD_2Cl_2): see Tables 1 and 2; δ_c (100MHz, 298K and 223K, CD_2Cl_2): see Table 1; ν_{max} (CH_2Cl_2): 3580brw, 2950m, 2930m, 2920m, 2910m, 2895w, 2875w, 2850w, 1715s, 1605w, 1450m, 1315m, 1295m, 1280s, 1270s, 1255s, 1250s, 1120m, 1095m, 1070m, 1025m, 1010m, 970m; $^m/_z$ (%): 261 (M^+, 10), 156 (19), 140 (100), 122 (30), 110 (38), 105 (66), 98 (43), 84 (16), 77 (61), 70 (38), 57 (40), 51 (20). $C_{15}H_{19}NO_3$ [M^+] requires $^m/_z$ 261.1365; observed 261.1365. Figures from combustion analysis determinations were variable, probably as a result of hydrate formation: e.g. found: C, 64.31; H, 7.64; N, 4.80%. $C_{15}H_{19}NO_3 : H_2O$ requires C, 64.50; H, 7.58; N, 5.01%. However, a sample of **(1)** which had been dried over P_2O_5 under vacuum for 24 h at 30°C analysed correctly: found: C, 68.66; H, 7.07; N, 5.26%. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%.

Heptafluorobutanoyl ester of 1-hydroxytropacocaine (2)

To a stirred solution of **(1)** (7 mg, 0.027 mmol) in dry acetonitrile (2 ml) at 0°C was injected heptafluorobutyric anhydride (20 µl, 0.027 mmol) using a micro-syringe. The solution was allowed to warm to ambient temperature and stirred for 2h. After dilution with diethyl ether, washing with saturated $NaHCO_3$ (2 x 1 ml), water (1 ml), drying with anhydrous magnesium sulphate, and evaporation, the crude product was purified by chromatography on silica using 5% methanol in ethyl acetate. **(2)** was isolated as a colourless oil (3.6 mg, 30%). ^{1}H NMR data were in agreement with the literature data[1] summarised in table 1.[7]

N-Benzyloxycarbonyl-3α-hydroxy-6-aza-7oxabicyclo[3.2.2]non-8-ene (18α) and N-Benzyloxycarbonyl-3β-hydroxy-6-aza-7oxabicyclo[3.2.2]non-8-ene (18β)

Tetramethylammonium periodate (5.4 g, 20.4 mmol) and **(6)** (3.81 g, 17.0 mmol) in dichloromethane (70ml) were stirred at -78°C under nitrogen. A solution of benzyl-N-hydroxycarbamate (3.41g, 20.4 mmol) in dichloromethane (20 ml) was dripped in over 10 min and the solution was then warmed to ambient temperature and stirred overnight. The solution was filtered, washed with sodium thiosulphate solution (2 x 30 ml) and water (30 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. The residual dark yellow oil was purified by flash chromatography using diethyl ether, to afford an inseparable mixture of stereoisomers **(18α)** and **(18β)** in a 30:70 ratio (from ^{1}H NMR signal integrations), as a yellow oil (3.69g, 79%). The 250 MHz NMR spectrum was identical to that of a sample prepared by Justice;[6] partial analysis was possible: δ_H (250MHz, $CDCl_3$): *1.78 - 2.07 (series of m, 5H, inc OH), 2.20 - 2.67 (series of m, 5H inc OH), 3.67 (~t², J = 6.2, 4.4 Hz, 1H, α-OSi,* **(18β)**), 4.24 (~ quin, J = 5.5 Hz, 1H, α-OSi, **(18α)**), *4.74 (m, 1H, α-N), 4.90 (m, 1H, α-O),* 5.15 (s, 2H, CH_2Ph, **(18β)**), 5.17 (s, 2H, CH_2Ph, **(18α)**), 6.17 (d³, J = 9.1, 6.2, 1.2 Hz, 1H, HC=, **(18β)**, 6.32, (d³, J = 9.1, 6.8, 0.6 Hz, 1H, HC=, **(18β)**), 6.39 (d³, J = 9.1, 6.4, 1.3 Hz, 1H, HC=, **(18α)**), 6.50 (d³, J = 9.1, 6.4, 1.1 Hz, 1H, HC=, **(18α)**), *7.33 (m, 5H).*

N-Benzyloxycarbonyl-3α-[(benzoyl)oxy]-6-aza-7oxabicyclo[3.2.2]non-8-ene (19α) and N-Benzyloxycarbonyl-3β-[(benzoyl)oxy]-6-aza-7oxabicyclo[3.2.2]non-8-ene (19β)

To a 30:70 mixture of **(18α)** and **(18β)** (131 mg, 0.48 mmol) in dry pyridine (2 ml) was added benzoic anhydride (163 mg, 0.72 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 18h, then diluted with diethyl ether (20 ml). The organic layer was washed with saturated copper sulphate solution (3 x 25 ml), dried over anhydrous magnesium sulphate, filtered and the solvent evaporated under reduced pressure to afford **(19α)** and **(19β)** as a pale yellow oil (177 mg, 97%), in unchanged ratio after chromatography on silica using diethyl ether : petroleum ether (b.p. 40 - 60°C) in a 2:3 ratio. Spectroscopic data for the 3α-ester **(19α)** are derived from the mixture: δ_H (250MHz, $CDCl_3$) (signals common to both isomers are quoted in italics): *2.2 - 2.4 (m, 2H,), 2.4 - 2.6 (m, 2H), 4.8 - 5.2 (m, , 2H, α-N, α-O), 5.20 (s, 2H, CH_2Ph),* 5.51 (~t², J ≈ 5.3, 3.6 Hz, 1H, αOCOPh), *6.42 (m, 1H, HC=),* 6.58 (d³, J = 9.2, 6.9, 1.0 Hz, 1H,

HC=), *7.3 - 7.5 (series of m, 8H, ArH), 8.0 (m, 2H, ArH)*; δ_C (63MHz, $CDCl_3$): 35.4 & 38.2 (2 x CH_2), *51.0 (NCH), 67.8 (CH_2Ph), 68.7 (HCOCOPh),* 73.0 (OCH), 128.2 (Ar CH), 128 .6 ($C_{3'}$, $C_{5'}$), 129.5 ($C_{2'}$, $C_{6'}$), 130.0 (Ar CH), 130.3 ($C_{1'}$), 131.6 (2 x HC=), 132.9 ($C_{4'}$), 135.9 (Ar C), 156.4, (CO_2CH_2Ph), 165.3 (COPh); ν_{max} (CH_2Cl_2), mixture of **(19α)** and **(19β)**: 1715s, 1605w (Ar); $^m/z$ (%): 379 (M^+, 3), 335 (11), 213 (2), 183 (1), 122 (2), 105 (26), 91 (100), 77 (13), 65 (4); $C_{22}H_{21}NO_5$ requires $^m/z$ 379.1420; observed 379.1420.

A pure sample of the 3β-ester **(19β)**, m.p. 105-106°C, was obtained by recrystallisation from 1:1 diethyl ether : petrol (b.p. 60 - 80°C) and showed: δ_H (250MHz, $CDCl_3$; assignments made with the help of an HH COSY spectrum): 2.10 (d^3, J ≈ 13, 11, 1.0 Hz, 1H, $H_{2\beta}$), 2.15 (d^3, J ≈ 13, 11, 1.7 Hz, 1H, $H_{4\beta}$), 2.48 (m, 2H, $H_{2\alpha}$ $H_{2\beta}$), 4.84 [brd^2 (~brt) J ≈ 6.3, 4.5 Hz, 1H, H_5], 4.97 [brd^2 (~brt) J ≈ 6.6, 5.0 Hz, 1H, H_1], 5.03 (~t^2, J = 11.0, 6.4 Hz, 1H, $H_{3\alpha}$), 5.20 (s, 2H, CH_2Ph), 6.31 (d^3, J = 9.2, 6.3, 1.2 Hz, 1H, H_6), 6.45 (d^3, J = 9.2, 6.4, 1.3 Hz, 1H, H_5), 7.3 - 7.5 (series of m, 7H, ArH), 7.56 (t^2, J = 7.6, 1.5 Hz), 8.01 (brd, J=8.4 Hz, 2H, ArH); δ_C (63MHz, $CDCl_3$), 33.4 & 36.2 (2 x CH_2) *51.0 (NCH), 67.8 (CH_2Ph), 68.7 (HCOCOPh),* 72.0 (OCH), 128.1 (Ar CH), 128.3 (HC=), 128.4 ($C_{3'}$,$C_{5'}$), 129.4 (HC=), 129.9 (Ar CH), 130.4 ($C_{1'}$), 133.0 ($C_{4'}$), 135.9 (Ar C), 156.3 (CO_2CH_2Ph), 165.7 (COPh); δ_C (63MHz, $CDCl_3$): 33.9 & 36.7 (2 x CH_2), 51.4 (NCH), 68.3 (CH_2Ph), 69.2 (HCOCOPh), 72.4 (OCH), 128.5, 128.7, 128.8, 128.9, 129.1, 130.0, 130.4, 130.5, 133.5, 136.4, (aryl and alkenyl C), 156.8, (CO_2CH_2Ph), 166.2 (COPh); **(19β)**: found: C, 69.50; H, 5.29; N, 3.71%. $C_{22}H_{21}NO_5$ requires C, 69.64; H, 5.58. N, 3.69%.

1β-Hydroxy-4β[(benzyloxycarbonyl)amino]-6α-benzoyloxy-cyclohept-2-ene (20)
1β-Hydroxy-4β[(benzyloxycarbonyl)amino]-6β-benzoyloxy-cyclohept-2-ene (21)[13]

To a solution of **(19α)** and **(19β)** (26:74, 4.6 g, 0.012 mol) in acetonitrile:water (4:1, 125 ml) was added molybdenum hexacarbonyl (3.5 g, 0.013 mol). The mixture was heated under reflux for 24 h and then filtered through a silica plug which was washed thoroughly with ether:methanol (95:5). The solvent was removed under reduced pressure and the dark brown residue dissolved in dichloromethane. This solution was filtered again through celite to yield a crude brown solid which was partially purified by flash chromatography eluting with diethyl ether : petroleum ether (b.p. 40 - 60°C) in a ratio ranging from 3:2 to 4:1. Some remaining material was washed off the column using ethyl acetate and the combined fractions were evaporated to give **(20)** and **(21)** (3.46g, 75%) as a white solid. δ_H (250MHz, $CDCl_3$) (signals are quoted in italics where they overlap or where they are common to both isomers): **(20)**: *1.80 - 2.45 (series of m, 5H)*, 4.77 (brm, 2H, α-O and α-N), *5.08 (brs, CH_2Ph and NH, 3H,)*, 5.56 (m, 1H, α-OCOPh), 5.69 (d^2 J = 12.9, 3.0 Hz, 1H, HC=), *5.85 (m, 1H, HC=)*, 7.2 - 7.5 (m, 8H), 8.1 (brd^2, J ≈ 7.5 , 1.2 Hz, $H_{2',6'}$); **(21)** *1.80 - 2.45 (series of m, 5H)*, 4.31 (brm, 1H, α-N), 4.47 (brm, 1H, α-O) *5.08 (brs, CH_2Ph and NH, 3H,)*, 5.53 (m, 1H, α-OCOPh), 5.56 (m, 1H, HC=), *5.85 (m, 1H, HC=)*, 7.2 - 7.5 (m, 8H), 8.01 (brd^2, J ≈ 7.5 , 1.2 Hz, $H_{2',6'}$); ν_{max} (CH_2Cl_2): 3440w, 3055m, 3035m, 2950m, 2920m, 1720s, 1715s, 1510m, 1505m, 1500m, 1450m, 1425m, 1420m, 1415m, 1315w, 1277s, 1270s, 1260s, 1252s, 1248s, 1210m, 1200m, 1175w, 1115w, 1070w, 1035m, 1025s; $^m/z$ (FAB %): 404 (MNa^+, 25), 382 (MH^+, 49), 364 ((MH^+ - H_2O, 100). A sample of the mixture was recrystallised from 1:1 diethyl ether/petrol (b.p. 60 - 80°C) to give a mixed sample (m.p. 132 - 145 °C): found: C, 69.13; H, 6.20. N, 3.70%. $C_{22}H_{23}NO_5$ requires C, 69.28; H, 6.08. N, 3.67%.

A pure sample of **(21)** (1.0 g) was separated on silica (chromatotron) eluting with diethyl ether : petroleum ether (b.p. 40 - 60°C) (ratio ranging from 1:1 to 3:2). Early fractions contained pure **(21)** (0.46 g), a sample of which was recrystallised from 1:1 diethyl ether/petrol (b.p. 60 - 80°C) to give a white crystalline solid, m.p. 145 - 147°C. δ_H (250MHz, $CDCl_3$): 1.8 - 2.0 (brm, 3H, inc. OH), 2.2 - 2.4 (m, 2H), 4.34 (brm, 1H, α-N), 4.50 (brd J = 10 Hz, 1H, α-OH), 5.05 (brm, 1H, NH), 5.10 (brs, 2H, CH_2Ph), 5.33 (t^2, J = 10.7, 3.7 Hz, 1H, α-OCOPh), 5.59 (d^3 J ≈ 11.5, 3.4, 2.2 Hz, 1H, HC=), 5.84 (brd J = 11.5 Hz, 1H, HC=), 7.35 (m, 5H),), 7.41 (brt J ≈ 7.5 Hz, 2H, $H_{3',5'}$), 7.56 (brt^2, J = 7.5, 1.2 Hz, 1H, $H_{4'}$), 8.01 (brd^2, J ≈ 7.5, 1.2 Hz, $H_{2',6'}$); δ_c (63MHz, $CDCl_3$): 39.6, 42.4 (2 x CH_2), 48.0 (NCH), 66.9 (HCOCOPh), 67.3 (CH_2Ph), 71.4 (HCOH), 128.5, 128.6, 128.7 (3 x Aryl CH;benzyl), 129.0 ($C_{3',5'}$), 130.0 ($C_{2',6'}$), 130.6 ($C_{1'}$), 132.3 (HC=), 133.5 ($C_{4'}$), 136.7 (Aryl C; benzyl), 137.5 (HC=), 155.9 (NCO), 165.8 (COPh). Found: C, 69.15; H, 6.05. N, 3.71%. $C_{22}H_{23}NO_5$ requires C, 69.28; H, 6.08. N, 3.67%.

Later fractions, together with ethyl acetate washings, contained a mixture of **(20)** and **(21)** (0.395 g).

β-1-Hydroxy-3α-benzoyloxy-5β-aminocycloheptane (22)[13] and all-cis-(all-β-)-1-hydroxy-3-benzoyloxy-5-aminocycloheptane (23)

A 30:70 mixture of **(20)** and **(21)** (45 mg, 0.118 mmol) in dry methanol (7 ml) was hydrogenolysed using a catalytic amount of 10% palladium on charcoal at atmospheric pressure. After 1.5 h, gaseous ammonia was bubbled through the mixture which was filtered though celite and the solvent evaporated to

yield the mixture of (**22**) and (**23**) in quantitative yield (30 mg). Spectroscopic data are quoted separately but signals common to both isomers are shown in italics. (**22**): δ_H (250MHz, $CDCl_3$) : *1.6 - 2.4 (series of m. 9H)*, 3.45 (brm, 1H, α-N), 4.15 (brm, 1H, α-OH), 5.58 (m, 1H, $H_{3\beta}$), *7.43 (m, 2H, $H_{3',5'}$), 7.56 (m, 1H, $H_{4'}$), 8.02 (m, 2H, $H_{2',6'}$).* δ_c (63MHz, $CDCl_3$): 46.7 (NCH), 66.7 (HCOCOPh), 69.4 (HCOH), *128.8 ($C_{3',5'}$)*, 129.91 ($C_{2',6'}$), 130.8 ($C_{1'}$), 133.27 ($C_{4'}$), 166.20 (CO); additional minor peaks were observed in the ^{13}C NMR spectrum of the mixture but these could not be assigned with confidence to the ring CH_2 signals of the minor isomer. (**23**) δ_H (250MHz, $CDCl_3$) : *1.6 - 2.4 (series of m. 9H)*, 3.10 (brm, 1H, α-N), 4.05 (brm, 1H, α-OH), 5.04 (t^2, J = 10.7, 2.2 Hz, 1H, $H_{3\alpha}$), *7.43 (m, 2H, $H_{3',5'}$), 7.56 (m, 1H, $H_{4'}$), 8.02 (m, 2H, $H_{2',6'}$).* δ_c (63MHz, $CDCl_3$): 31.9, 32.6, 42.0, 43.9 (4 x CH_2), 49.0 (NCH), 68.1 (HCOCOPh), 70.0 (HCOH), *128.8 ($C_{3',5'}$)*, 129.94 ($C_{2',6'}$), 131.0 ($C_{1'}$), 133.35 ($C_{4'}$), 166.26 (CO); (**22**) + (**23**): ν_{max} (CH_2Cl_2): 3600m, 2860m, 1710s, 1605w, 1585w, 1560w, 1545w, 1465w, 1450w, 1317m, 1270brs, 1260brs, 1178w, 1115s, 1070w, 1025m.

The compounds could not be separated completely. Partial separation of the two stereoisomers was achieved using preparative thin layer chromatography (5% ethanol in diethyl ether). This yielded, firstly, a sample containing ca. 80% of the 3α-ester (**22**) as a pale yellow oil (1.2 mg, 5%). δ_H (250MHz, $CDCl_3$): 1.7 - 2.4 (series of m. 9H), 3.40 (m, 1H, α-N), 4.18 (brm, 1H, α-O), 5.70 (m, 1H, $H_{3\beta}$), 7.48 (m, 2H, $H_{3',5'}$), 7.58 (m, 1H, $H_{4'}$), 8.02 (m, 2H, $H_{2',6'}$).

Mixed fractions were then eluted and finally the 3β-ester (**23**) followed, also as a pale yellow oil (2.8 mg, 11%). δ_H (250MHz, $CDCl_3$): 1.70 - 2.45 (series of m. 9H), 2.90 (m, 1H, α-N), 4.05 (brm, 1H, α-O), 5.10 (t^2, J = 10.7, 2.2 Hz, 1H, $H_{3\alpha}$), 7.45 (m, 2H, $H_{3',5'}$), 7.55 (m, 1H, $H_{4'}$), 8.04 (m, 2H, $H_{2',6'}$). $^m/z$ (FAB): 272 (MNa^+), 250 (MH^+), $C_{14}H_{20}NO_3$ requires 250.1444, observed: 250.1443.

4β[(Benzyloxycarbonyl)amino]-6α-benzoyloxycyclohept-2-enone (24) and 4β[(benzyloxycarbonyl)amino]-6β-benzoyloxycyclohept-2-enone (25)[13]

To a stirred solution of (**20**) and (**21**) (50 mg, 0.13 mmol) in acetone was added chromic acid following the procedure used for compound (**1**) to afford (**24**) and (**25**) as a pale yellow oil (40mg, 82%). δ_H (250MHz, $CDCl_3$): 2.0 - 2.2 (brm, 2H), 2.5 and 2.65 (2 x m, 2H), 3.0 (m, 4H, α-CO), 4.78 (brm, 2H, 2 x α-N), 5.10 (s, 4H, CH_2Ph), 5.3 - 5.6 (brm, 4H, 2 x α-OCOPh + 2 x NH), 6.0 (m, 2H), 6.6 (m, 2H), 7.2 - 7.6 (series of m, 16H), 7.9 and 8.0 (2 x d, J = 7.8 Hz, 2H); δ_c (63 MHz): 39.2, 40.0, 47.9 (3 x CH_2), 48.3 (NCH), 48.8 (CH_2), 48.9 (NCH), 66.3 and 66.9 (2 x **C**HOCOPh), 67.1 (2 x **C**H_2Ph), [aryl and alkene CH signals were observed at 128.2, 128.29, 128.33, 128.45, 128.5, 128.6, 129.6, 129.7, 131.3, 132.0, 133.3, 133.4 together with aryl C signals at 136.0 and 136.1 but there was signal overlap and these were not assigned], 155.5 (2 x NCO), 165.5 and 165.6 (2 x COPh), 197.4 and 197.6 (2 x C=O); ν_{max} (CH_2Cl_2, film): 1715s, 1665m, 1605w, 1585w, 1510m; $^m/z$ (FAB): 380 (MH^+); $C_{22}H_{22}NO_5$ [MH^+] requires $^m/z$ 380.1498; observed 380.1498.

Conversion of (21) into (25)

Conversion of (**21**) (95 mg, 0.249 mmol) into (**25**) followed the general procedure used for the preparation of (**24**) and (**25**) above. The oily product was chromatographed using diethyl ether : petrol (7 : 3) to give (**25**) (85 mg, 90%) as a yellow oil. δ_H (400MHz, CD_2Cl_2, 300K): 2.13 (m, 1H) and 2.64 (m, 1H), 3.0 (m, 2H, α-CO), 4.71 (brm, 1H, α-N), 5.10 (s, 2H, CH_2Ph), 5.41 (brd, J ≈ 6 Hz, NH), 5.54 (~quintet, J ≈ 5.7 ± 1Hz, 1H, α-OCOPh), 6.08 (d^2, J = 12.3, 2.4 Hz, 1H), 6.58 (d^2, J = 12.3, 2.9 Hz, 1H), 7.32 - 7.37 (m, 5H), 7.41 (brt, J = 7.3 Hz, 2H, $H_{3',5'}$), 7.56 (t^2, J = 7.3, 1.2 Hz, 1H, $H_{4'}$), 7.94 (m, 2H, $H_{2',6'}$); δ_c (101MHz, CD_2Cl_2): 40.3, 48.2 (2 x CH_2), 49.3 (NCH), 67.3 (**C**H_2Ph), 67.5 (HCOCOPh), [aryl and alkene CH signals were observed at 128.4, 128.6, 128.85, 128.9, 129.9, 132.3, 133.6 together with aryl C signals at 130.3 and 136.9 but there was overlap and these were not assigned], 155.8 (**N**CO), 165.7 (**C**OPh), 197.7 (C=O). Measurements at 223 K showed no evidence of the bicyclic tautomer. ν_{max} (CH_2Cl_2): 3430m, 3050w, 2960w, 2870w, 1725s, 1680m, 1620w, 1605w, 1510w, 1450m, 1400w, 1315w, 1265brs, 1175m, 1110s, 1100m, 1070m, 1040m, 1025s cm^{-1}; $^m/z$ (FAB) 402 (MNa^+), 380 (MH^+); $C_{22}H_{22}NO_5$ (MH^+) requires 380.1498, observed: 380.1498.

Hydrogenation of (25) to 3β-benzoyloxy-5β[(benzyloxycarbonyl)amino]cycloheptanone (27)[13]

The hydrogenation of the double bond in (**25**) was performed at atmospheric pressure in methanol using standard conditions. The product (**27**) was shown by ^1H NMR spectroscopy to have lost the double bond but to have retained the N-benzyloxycarbonyl group; it was not purified.

Direct hydrogenolysis/hydrogenation of (25) to 1-hydroxynortropacocaine (3)

A solution of the ketone (25) in dry methanol was hydrogenolysed over a catalytic amount of 10% palladium on charcoal at atmospheric pressure. The progress of the reaction was monitored by TLC and after 3 hours, there remained no trace of either (25) or the intermediate (27). The reaction mixture was filtered through a pad of celite which was subsequently washed thoroughly with ethanol. The combined solutions were evaporated to yield (3) as a yellow oil, (ca. 85 mg). Chromatography on a small silica column using ethyl acetate/ammonia/5-10% methanol gave pure (3) as a crystalline solid (82 mg; 94%). A sample was recrystallised from ethyl acetate to give a sample which melted with decomposition at 103-105°C. NMR chemical shift data are listed in tables 1 and 2. $^{m}/_{z}$ (%): 247 (M^+, 4), 229 (4), 203 (1), 188 (2), 158 (2), 143 (12), 126 (64), 105 (100), 96 (35), 84 (28), 77 (67), 69 (16), 56 (32); $C_{14}H_{17}NO_3$ requires $^{m}/_{z}$ 247.1208; observed 247.1208; ν_{max} (CH_2Cl_2): 3045w, 2945w, 1720s, 1605w, 1540w, 1455w, 1385s, 1318w, 1265s, 1180w, 1150w, 1115m, 1070w, 1030w cm^{-1}.

References and Notes

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7. NMR solvents were not quoted in reference 1 and we find small differences in chemical shift with solvent. It was necessary to dry the NMR solution with anhydrous potassium carbonate (to ensure the absence of acid and moisture) before ^{1}H NMR data agreed with the earlier data. Neither the enantiomeric purity nor the absolute configuration of natural 1-hydroxytropacocaine from various sources have been reported as yet. We describe only work with racemic material.
8. In our earlier work,[4,5] we used various amalgams to cleave oxazine NO bonds efficiently. Molybdenum hexacarbonyl has been used more recently [Soulié, J.; Faitg, T.; Betzer, J.-F.; Lallemand, J.-Y. *Tetrahedron*, **1996**, *52*, 15137] and we also find this to be satisfactory.
9. We thank Dr. G.A. Griffith for assistance with these experiments.
10. We are grateful to Professor John B. Bremner for useful discussions concerning tautomerism in cyclic amino-ketones.
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13. For simplicity, and in keeping with the nomenclature used for the bicyclic systems in this paper, we have used the α- β- nomenclature to indicate relative configurations in the 7-ring compounds.

Note added following acceptance: We have been informed by Dr. Peter Bachmann, Institut für Pharmazeutische Biologie, T.U. Braunschweig that he has actually isolated the novel nor-derivative of 1-hydroxytropacocaine [our compound (3)] from extracts of *E. coca*. We are grateful to Dr. Bachmann for offering this information prior to publication, and quote it with his permission.