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A New Synthetic Route to Tropane Alkaloids Based on [4 + 2] Nitroso Cycloaddition to 1,3-Cycloheptadienes[1]

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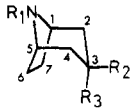
A facile synthesis of tropane, pseudotropine, and tropacocaine is described in which a key step is the Diels–Alder reaction of 1,3-cycloheptadienes with *C*-nitroso compounds to give the 8-oxa-9-azabicyclo[3.2.2]non-6-enes. Reductive treatment involving N–O bond fission of these materials followed by treatment with thionyl chloride gives the trans chlorides or dehydration products which are converted to the tropane alkaloids through intramolecular cyclization induced by a base or mercuric salt, respectively.

The tropane alkaloids occur as esters of relatively simple organic carboxylic acids with amino alcohols (alkamines) which are all hydroxylated derivatives of tropane (**1**), i.e.,

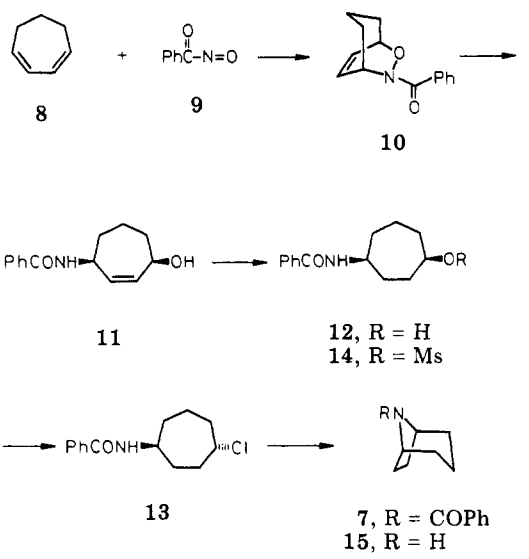


1, $R_1 = CH_3$; $R_2 = R_3 = H$
2, $R_1 = CH_3$; $R_2 = H$; $R_3 = OH$
3, $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$
4, $R_1 = R_2 = H$; $R_3 = OH$
5, $R_1 = CH_3$; R_2, $R_3 = O$
6, $R_1 = CH_3$; $R_2 = OCOPh$; $R_3 = H$
7, $R_1 = COPh$; $R_2 = R_3 = H$

tropine (**2**), pseudotropine (**3**), and nortropine (**4**) as monohydroxylated alkamines. Because of their pharmaceutical significance and the presence of an unusual ring system, this class of alkaloids have been the subject of intensive stereochemical, biogenetical, and synthetic activities.[2] In particular, a great deal of synthetic work on natural and nonnatural tropane bases has been carried out with the aim of investigating their pharmacological activity. The earliest synthetic approach to a tropane base was described by Willstätter.[2a] This approach to tropinone (**5**) in a multistage synthesis was followed by a more lucid and practical Robinson synthesis.[3] Since these classical syntheses of tropinone (**5**), a number of general synthetic methods for the preparation of some tropanes have been reported. However, except for two instances of new approach to tropane alkaloids via [3 + 2] nitrone cycloaddition[4] and [3 + 4] cyclocoupling,[5] efficient methods for the preparation of natural products are limited.

In this paper we describe a facile new route for the elaboration of the tropane ring system by utilizing a

Scheme I



Diels–Alder cycloaddition of nitroso compounds[6] with 1,3-cycloheptadienes and its application to the synthesis of the naturally occurring tropane alkaloids pseudotropine (**3**) and tropacocaine (**6**).

Results and Discussion

Synthesis of *N*-Benzoylnortropane. As our first model we chose *N*-benzoylnortropane (**7**) to investigate construction of the tropane ring system based on [4 + 2] nitroso cycloaddition. A search of the literature indicated that only one example of a Diels–Alder cycloaddition of a nitroso compounds with a seven-membered ring diene has been reported.[7] In view of this, the present study of tropane synthesis was initiated by the examination of the nitroso Diels–Alder reaction of 1,3-cycloheptadiene (**8**) (Scheme I). Thus reaction of **8** with the acylnitroso compound **9** generated in situ from benzohydroxamic acid

(1) A portion of this work has appeared in preliminary form: Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1984**, *25*, 5091.
(2) (a) Holmes, H. L. *Alkaloids (N.Y.)* **1950**, *1*; Chapter 6. (b) Fordor, G. *Ibid.* **1960**, *6*; Chapter 5. (c) Fordor, G. *Ibid.* **1967**, *9*; Chapter 7. (d) Fordor, G. *Ibid.* **1971**, *13*; Chapter 8. (e) Clarke, R. L. *Ibid.* **1977**, *16*; Chapter 2.
(3) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762.
(4) Tufariello, J. J.; Trybulski, E. J. *J. Chem. Soc., Chem. Commun.* **1973**, 720. Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Asrof Ali, Sk. *J. Am. Chem. Soc.* **1979**, *101*, 2435.
(5) Noyori, R.; Baba, Y.; Hayakawa, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3336. Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *Ibid.* **1978**, *100*, 1786.
(6) For recent entries into natural products utilizing nitroso Diels–Alder reaction, see: (a) Leonard, N. J.; Playtis, A. J. *J. Chem. Soc., Chem. Commun.* **1972**, 133. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem., Soc.* **1980**, *102*, 3632. (c) Keck, G. E.; Webb, R. R., II *J. Org. Chem.* **1982**, *47*, 1302. (d) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049.
(7) Hart, H.; Ramaswami, S. K.; Willer, R. *J. Org. Chem.* **1979**, *44*, 1.

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Table I. Reaction of Hydroxy Carbamates with $SOCl_2$

hydroxy carbamate	solvent	$SOCl_2$, equiv	base (equiv)	reaction conditions[b]	R	products, % yield: 25a,b[a]	26a,b[a]	27a,b[a]	28a,b[a]
24	$CHCl_3$	2.5	none	rt, 48 h	CO_2CH_2Ph	12		61	trace
24	ether	1.0	Py (1.3)	rt, 14 h	CO_2CH_2Ph	32		6	49
24	$CHCl_3$	1.6	Py (excess)	reflux, 5 h	CO_2CH_2Ph	55		4	18
20	$CHCl_3$	1.3	Py (1.9)	reflux, 3 h	$CO_2C_2H_5$	65		11	5

[a] (a), R = CO_2CH_2Ph; b, R = $CO_2C_2H_5$. [b] rt = room temperature.

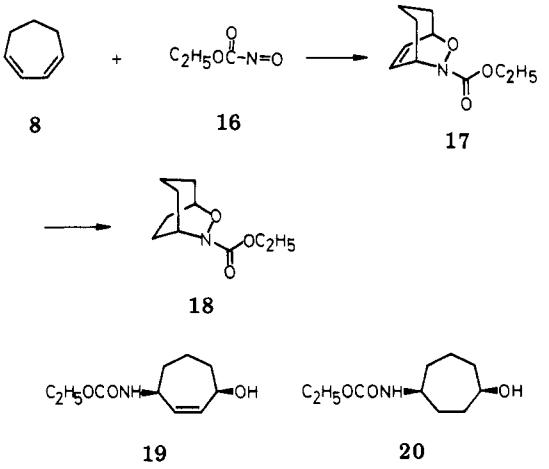
and tetrapropylammonium metaperiodate[8] was carried out at room temperature, affording the [4 + 2] cycloadduct **10** in 85% yield. Reductive N–O bond cleavage of **10** with 5% sodium amalgam[9] in ethanol gave **11** (77% yield), which was then hydrogenated over palladium on carbon to give the saturated alcohol **12** (84%). Treatment of **12** with thionyl chloride (1.0 equiv) and triethylamine (1.2 equiv) in chloroform at room temperature yielded the chloride **13** (76% yield).[10] Otherwise **12** was converted to the mesylate **14** by treatment with mesyl chloride and triethylamine at −20 °C for 5 min in 88% yield.

Although cyclization of the mesylate **14** to the tropane skeleton using various strong bases failed, the desired *N*-benzoylnortropane (**7**) was obtained in 87% yield when the chloride **13** was treated with potassium *tert*-butoxide in a 1:1 hexamethylphosphoric triamide (HMPA)–benzene solution at room temperature for 15 h. This transformation is suggested to involve an internal S_N2 process, and hence the cyclization may have occurred preferentially in the trans amide **13** rather than the cis amide **14** since only in the trans isomer is the benzoylamino group correctly disposed for a back-side displacement of the anionic leaving group.

In an attempt to lead to nortropane (**15**) [and tropane (**1**)], removal of the benzoyl group of **7** by hydrolysis was tried, but it failed.

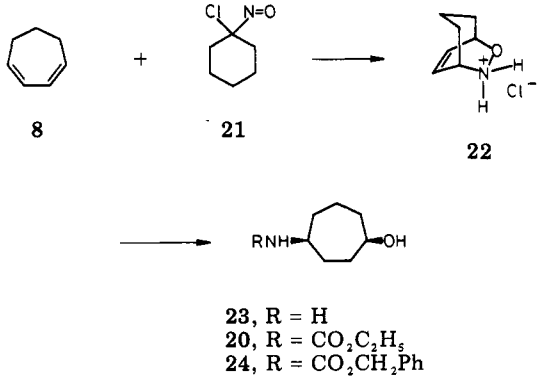
Synthesis of Tropane. The above preliminary experiments indicated that the amide alcohol **12** prepared via [4 + 2] nitroso cycloaddition can serve as a suitable intermediate for constructing the tropane framework. We thus attempted to prepare a carbamate derivative of the amino alcohol (i.e., **20**) as an intermediate for the synthesis of tropane (**1**).

1,3-Cycloheptadiene (**8**) was reacted with ethyl nitrosoformate **16**, formed by in situ generation from *N*-(ethoxycarbonyl) hydroxylamine and tetrapropylammonium metaperiodate, to afford the cycloadduct **17** (71%), which was hydrogenated to give **18** (98%). Attempts to cleave



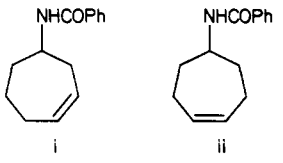
the N–O bonds of compounds **17** and **18** with sodium amalgam (Na_2HPO_4, ethanol) and thus to convert them to the respective amide alcohols **19** and **20** were unsuccessful, giving no reaction.

Attention was next turned to an alternative Diels–Alder reaction; thus the cyclic diene **8** was reacted with 1-chloro-1-nitrosocyclohexane (**21**)[11] in an ethanol–carbon tetrachloride solution at −20 °C for 10 h then at −10 °C for 48 h to yield the cycloadduct as its hydrochloride **22** in 68% yield. Catalytic hydrogenation of **22** afforded the amino alcohol **23** (isolated as its hydrochloride) which was



then subjected to selective acylation with ethyl or benzyl

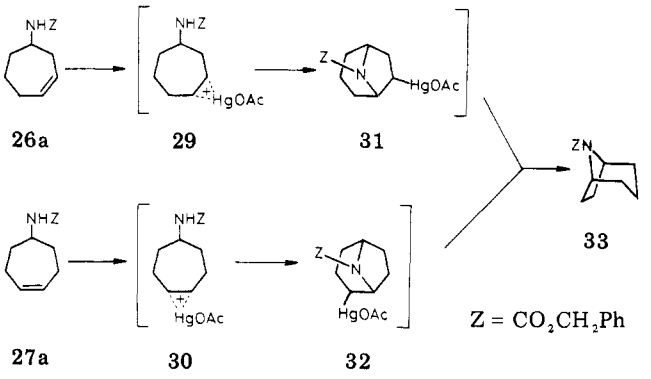
(8) Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, 4736.
(9) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(10) When the reaction was carried out in the absence of a base, the chloride **13** was contaminated with a tiny amount of a 1:1 mixture of the dehydration products i and ii: mp 139–140 °C (benzene–hexane); IR



(KBr) 3250, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.55 (series of m, 8 H), 4.23 (m, 1 H), 5.72 (m, 0.5 H), 5.82 (br s, 1 H), 6.01 (m, 0.5 H), 6.17 (br s, 0.5 H), 6.23 (br s, 0.5 H), 7.36–7.78 (m, 5 H); mass spectrum, *m/z* (relative intensity) 215 (M^+, 23), 122 (76), 105 (100), 94 (26), 79 (26), 77 (66). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.81; H, 7.93; N, 6.38.

(11) For recent studies on Diels–Alder cycloaddition with **21**, see: (a) Ranganathan, D.; Ranganathan, S.; Rao, C. B.; Raman, K. *Tetrahedron* **1981**, *37*, 629. (b) Horsewood, P.; Kirby, G. W. *J. Chem. Res., Synop.* **1980**, 401.

Scheme II



chloroformates to provide the desired carbamates **20** or **24** in 84% and 80% yields, respectively.

When the benzyl carbamate **24** was treated with thionyl chloride, the results varied widely depending upon the reaction conditions employed as shown in Table I. Thus treatment with thionyl chloride in the absence of a base gave a 1:1 mixture of the dehydration products **26a** and **27a** in 61% yield along with the chloride **25a** in 12% yield. When the reaction was carried out in the presence of 1.3 equiv of pyridine at room temperature the chloride **25a** was obtained in 32% yield along with the 1:1 olefin mixture of **26a** and **27a** (6%) and the dicycloheptyl sulfite **28a** (49%). On heating in the presence of excess pyridine, **25a** was obtained in improved yield (55%), together with the olefin mixture of **26a** and **27a** (4%) and **28a** (18%). Otherwise, the reaction of ethyl carbamate **20** with thionyl chloride and pyridine (1.9 equiv) in chloroform at reflux generated the chloride **25b** (65%) accompanied by the 1:1 mixture of olefins **26b** and **27b** (11%) and the dicycloheptyl sulfite **28b** (5%).

Recent studies have demonstrated[12-14] the potential synthetic utility of C–N bond formation via heteromercuration of carbamate derivatives of unsaturated amines. This prompted us to utilize the dehydration products **26a** and **27a** in the tropane synthesis via intramolecular heteromercuration. Thus the 1:1 mixture of **26a** and **27a** was treated with mercuric acetate in 10% aqueous tetrahydrofuran (THF), followed by reduction with $NaBH_4$, to furnish *N*-carbobenzoxynortropane (**33**) in 45% yield based on reacted starting material. The product **33** must result from reductive demercuration of both organomercurials **31** and **32** initially formed from the asymmetrical and symmetrical olefins **26a** and **27a**, respectively, via cationic intermediates **29** and **30** as depicted in Scheme II. Thus, separation of the olefin mixture is not necessary since both the olefins can equally be utilized as the reaction substrates in this cyclization.

Alternatively, the chloride **25a** was directly converted into *N*-carbobenzoxynortropane (**33**) in satisfactory yield (78%) when subjected to base-induced intramolecular "amidocyclization" with potassium *tert*-butoxide as described for the preparation of *N*-benzoylnortropane (**7**). In a similar reaction involving the chloride **25b** and potassium *tert*-butoxide, *N*-(ethoxycarbonyl)nortropane (**34**) was formed in 78% yield.

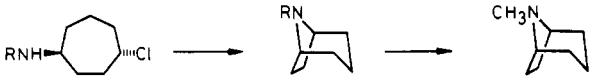
Finally, the synthesis of tropane (**1**) was achieved by $LiAlH_4$ reduction of the benzyl carbamate **33** in 72% yield.

Table II. ^{13}C NMR Data of Tropane Derivatives

					benzoyl carbons						
compd	C-1,5	C-2,4	C-6,7	C-3	ipso C	ortho C	meta C	para C	C=O	NCH_3	other carbons
1	61.5 (d)	31.1 (t)	25.9 (t)	16.1 (t)						40.6 (q)	
7	52.1 (d), 57.0 (d)[b]	30.9 (t), 32.6 (t)[b]	27.1 (t), 28.4 (t)[b]	16.9 (t)	136.8 (s)	128.3 (d)	127.0 (d)	129.6 (d)	167.6 (s)		
33	54.0 (d)	30.6 (t), 31.3 (t)[b]	27.6 (t), 28.3 (t)[b]	16.7 (t)							66.4 (t, CH_2), 127.7, 128.4 (d each, ortho, meta, para C),[c] 137.2 (s, ipso C), 153.5 (s, C=O)
34	53.9 (d)	30.5 (t), 31.1 (t)[b]	27.7 (t,), 28.3 (t)[b]	16.8 (t)							14.8 (q, CH_3), 60.6 (t, CH_2), 153.9 (s, C=O)
3	60.4 (d)	39.8 (t)[d]	26.8 (t)	63.8 (d)						38.7 (q)[d]	
6	60.3 (d)	35.8 (t)	26.6 (t)	67.9 (d)	130.7 (s)	129.5 (d)	128.3 (d)	132.7 (d)	166.0 (s)	38.8 (q)	
45	52.9 (d)	36.3–37.0 (br)	27.0–28.5 (br)	67.4 (d)	130.3 (s)	129.5 (d)	128.3 (d)	132.9 (d)	165.8 (s)		14.8 (q, CH_3), 61.0 (t, CH_2), 153.7 (s, C=O)
46	53.0 (d)	36.4 (t), 37.1 (t)[b]	27.8 (t), 28.5 (t)[b]	67.3 (d)	130.3 (s)	129.6 (d)	128.3 (d)	132.9 (d)	165.9 (s)		66.8 (t, CH_2), 127.9, 128.0, 128.5 (d each, ortho, meta, para C), 136.8 (s, ipso C), 153.5 (s, C=O)

[a] Signal multiplicity is given in parentheses. [b] Both signals are attributed to indivisual carbon atoms which are nonequivalent on account of the restricted rotation abut the C–N bond of the amide moiety. [c] Either of these signals overlaps. [d] For C-2,4 and NCH_3, δ values 38.3 and 39.2, respectively, have been reported in ref 15. However, considering multiplisities obtained by off-resonance decoupling experiments, these assignments should be interchanged as shown.

(12) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120.
(13) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. (b) Harding, K. E.; Burks, S. R. *Ibid.* **1984**, *49*, 40.
(14) Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11.



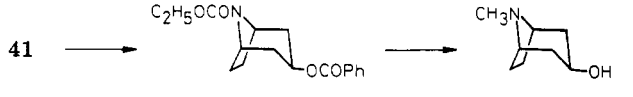
25a R = CO_2CH_2Ph 33, R = CO_2CH_2Ph 1
25b, R = $CO_2C_2H_5$ 34, R = $CO_2C_2H_5$

Similarly, the ethyl carbamate **34** was converted to tropane (**1**) in 71% yield. Physical data (see Experimental Section) and spectroscopic (^{13}C NMR) data (Table II) of synthetic tropane were in good agreement with those reported in the literature.[15]

Synthesis of Pseudotropine and Tropacocaine. Having developed the method for the preparation of the tropanes based on a nitroso Diels–Alder approach, we sought to apply this to the synthesis of the naturally occurring tropane alkaloids pseudotropine (**3**) and tropacocaine (**6**),[16] which exhibit marked local anesthetic action. From the above results, the most reliable approach to these alkaloids seemed to be the one involving cycloaddition with 1-chloro-1-nitrosocyclohexane (**21**) followed by base-induced amidocyclization. Thus the reaction of 3,5-cycloheptadienyl benzoate (**35**), prepared in three steps from cycloheptatriene,[17] with **21** generated a 4:1 mixture (estimated by 270-MHz ^1H NMR spectrum) of the oxazabicyclononene hydrochlorides favoring exo form **36** over endo form **37**. The stereochemistry of these cycloadducts was verified with their free bases separated by preparative TLC on the basis of their ^1H NMR spectra. The signal attributed to the 3-endo proton in the spectrum of the major adduct (free base of **36**) occurs significantly higher field (δ 4.95) than usual, indicating that it must lie within the shielding cone of the C-6–C-7 double bond, while the 3-exo proton signal (δ 5.57) suffers much less of a shielding effect of the double bond.

The major cycloadduct **36**, which was readily separable (57% yield) from **37** by recrystallization, can be utilized for the synthesis of the pseudotropine series of alkaloids (pseudotropines). Thus the synthesis of pseudotropine (**3**) was conducted as below.

Catalytic hydrogenation of **36** gave the amino alcohol hydrochloride **38** which in turn underwent selective N-acylation with ethyl chloroformate affording the carbamate **39** in 84% overall yield. Chlorination of **39** with thionyl chloride and excess pyridine at reflux yielded **41** (55% yield) along with a byproduct assigned the dicycloheptyl sulfite **43** (28% yield). The consequent tropane ring elaboration was pursued via amidocyclization of **41** with potassium *tert*-butoxide in the similar manner described above, resulting in the formation of **45** in 46% yield. Reduction with $LiAlH_4$ converted **45** to pseudotropine (**3**)

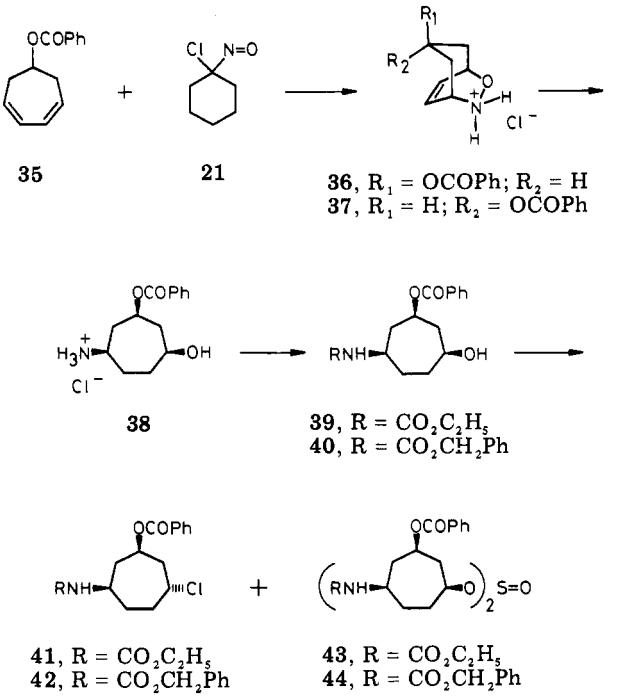


45 3

in 67% yield, the ^{13}C NMR data (Table II) and physical data (see Experimental Section) for which were identical with those reported in the literature.[15]

Furthermore, with **38** in hand, we employed the above sequence (Scheme III) for the synthesis of tropacocaine (**6**). The carbamate **40** derived from carbobenzoxylation

Scheme III

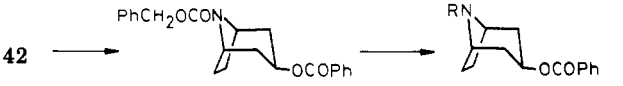


35 21 36, R_1 = OCOPh; R_2 = H
37, R_1 = H; R_2 = OCOPh

38 39, R = $CO_2C_2H_5$
40, R = CO_2CH_2Ph

41, R = $CO_2C_2H_5$ 43, R = $CO_2C_2H_5$
42, R = CO_2CH_2Ph 44, R = CO_2CH_2Ph

of **38** was treated with thionyl chloride and pyridine under the conditions employed with **39** to produce the chloride **42** and the sulfite **44** in 36% and 38% yield, respectively. The base-induced amidocyclization of **42** under the previously described conditions was effected to form **46** in 75% yield. Deprotection by catalytic hydrogenation converted **46** into *N*-nortropacocaine (**47**), which subsequently underwent the Eschweiler–Clarke reaction with formic acid and formaldehyde to provide desired tropacocaine (**6**) in



46 47, R = H
6, R = CH_3

71% yield from **46**. Synthetic **6** had identical physical data (see Experimental Section) and spectroscopic data (Table II) with those reported in the literature.[18]

Experimental Section

Melting points were determined in a Yanagimoto micro apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured at 270 and 67.8 MHz, respectively, with tetramethylsilane as an internal standard and deuteriochloroform as solvent unless otherwise stated. Mass spectra were obtained at an ionizing potential of 70 eV unless otherwise noted. TLC was run on Merck precoated silica gel 60-F 254 plates. Merck silica gel 60 (230–400 mesh) and Woelm activated alumina (neutral, activity I) were used for column chromatography.

***N*-Benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (10).** Tetrapropylammonium metaperiodate (20.0 g, 53 mmol) was dissolved in chloroform (500 mL) by warming; then **8** (3.6 g, 38 mmol) was added to this solution. To this mixture was added dropwise a solution of benzohydroxamic acid[19] (7.4 g, 54 mmol) in dimethylformamide (40 mL) and chloroform (100 mL) with stirring at room temperature over 30 min and stirring was continued for 3 h. The reaction mixture was washed with water, dried (Na_2SO_4),

(15) For ^{13}C NMR spectral assignment of tropane (**1**), see: Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Schell, F. M. *Acc. Chem. Res.* **1974**, *7*, 46.
(16) Johns, S. R.; Lamberton, J. A.; Sioumis, A. A. *Aus. J. Chem.* **1971**, *24*, 2399.
(17) Agosta, W. C., personal communication (cf.: Takakis, I. M.; Agosta, W. C. *J. Org. Chem.* **1978**, *43*, 1952).
(18) For ^{13}C NMR spectral assignment of tropacocaine (**6**), see: Hanisch, P.; Jones, A. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1202.
(19) Hauser, C. R.; Renfrow, W. B., Jr. "Organic Synthesis"; Wiley: New York, 1950; Collect. Vol. 2, p 67.

and concentrated at reduced pressure to leave a dark gum which was dissolved in hot benzene and treated with activated carbon. The benzene solution was evaporated at reduced pressure to give pale yellow crystals which were recrystallized from acetone–hexane to afford **10** (7.4 g, 85%) as colorless prisms: mp 101–102 °C; IR ($CHCl_3$) 1640, 1610 cm^{-1}; ^1H NMR δ 1.35–2.05 (series of m, 6 H), 4.70 (br s, 1 H), 5.44 (br s, 1 H), 6.30 (br s, 2 H), 7.30–7.80 (m, 5 H); ^{13}C NMR (CD_3OD)[20] δ 19.5 (t), 29.6 (t), 30.4 (t), 52.7 (d), 78.4 (d), 127.9 (d), 128.8 (d), 129.5 (d), 131.3 (d), 131.5 (d), 135.7 (s), 166.9 (s); mass spectrum, m/z (relative intensity) 229 (M^+, 14), 213 (7), 106 (13), 105 (100), 77 (49).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.57; N, 5.99.

***cis*-4-(Benzoylamino)-2-cycloheptenol (11).** To a solution of **10** (2.7 g, 11.8 mmol) in ethanol (100 mL) was added Na_2HPO_4 (7.6 g). To this suspension was added 5% sodium amalgam (35 g) in small portions over 30 min with stirring in an ice–water bath and the mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. The residue was dissolved in chloroform, washed with water, and dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by recrystallization from benzene gave **11** (2.1 g, 77%) as a colorless bulky solid: mp 157–159 °C; IR (KBr) 3350, 3260, 1620 cm^{-1}; ^1H NMR (CD_3OD) δ 1.43–2.11 (series of m, 6 H), 4.37 (br d, J = 10.5 Hz, 1 H), 4.63 (br d, J = 10.5 Hz, 1 H), 5.66 (br d, J = 11.9 Hz, 1 H), 5.79 (br d, J = 11.9 Hz, 1 H), 7.40–7.86 (m, 5 H); ^{13}C NMR (CD_3OD) δ 26.4 (t), 34.7 (t), 36.9 (t), 52.3 (d), 72.4 (d), 128.2 (d), 129.4 (d), 132.5 (d), 133.5 (d), 135.7 (s), 138.9 (d), 169.1 (s); mass spectrum, m/z (relative intensity) 231 (M^+, 16), 214 (28), 213 (99), 122 (100), 110 (48), 105 (50), 77 (74).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.94; H, 7.39; N, 5.98.

***cis*-4-(Benzoylamino)cycloheptanol (12).** A solution of **11** (1.0 g, 4.3 mmol) in methanol (100 mL) in the presence of 5% palladium on carbon (400 mg) was hydrogenated at 1 atm. After 7 h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to give a solid which was recrystallized from benzene to yield **12** (850 mg, 84%) as colorless needles: mp 143.5–145 °C; IR (KBr) 3600–3150 including 3340 (sharp), 1630 cm^{-1}; ^1H NMR δ 1.35–2.1 (series of m, 10 H), 4.07 (br m, 1 H), 4.27 (br m, 1 H), 6.59 (br s, 1 H), 7.33–7.82 (m, 5 H); ^{13}C NMR δ 19.6 (t), 28.5 (t), 32.4 (t), 35.3 (t), 36.9 (t), 42.4 (d), 70.6 (d), 126.9 (d), 128.5 (d), 131.2 (d), 135.0 (s), 166.5 (s); mass spectrum, m/z (relative intensity) 233 (M^+, 23), 215 (7), 176 (7), 161 (16), 128 (10), 122 (100), 105 (74).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.08; N, 6.27.

***trans*-1-(Benzoylamino)-4-chlorocycloheptane (13).** To a stirred ice-cold solution of **12** (230 mg, 0.99 mmol) and triethylamine (120 mg, 1.19 mmol) in chloroform (15 mL) was slowly added a solution of thionyl chloride (120 mg, 1.01 mmol) in chloroform (5 mL). The mixture was stirred at room temperature for 14 h and poured into ice–water (30 mL). After separation of the organic layer, the aqueous layer was extracted with chloroform and the combined organic extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated at reduced pressure and the residue was recrystallized from benzene–hexane to give **13** (188 mg, 76%) as colorless needles: mp 157–159 °C; IR (KBr) 3320, 1635 cm^{-1}; ^1H NMR δ 1.40–2.34 (series of m, 10 H), 4.19 (m, 2 H), 6.02 (br s, 1 H), 7.36–7.80 (m, 5 H); ^{13}C NMR δ 20.3 (t), 31.1 (t), 34.6 (t), 34.7 (t), 38.7 (t), 50.3 (d), 61.7 (d), 126.8 (d), 128.5 (d), 131.4 (d), 134.8 (s), 166.5 (s); mass spectrum, m/z (relative intensity) 251 (M^+, 8), 216 (22), 160 (10), 122 (79), 105 (100), 94 (23), 77 (36).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.79; H, 7.21; Cl, 14.08, N, 5.56. Found: C, 66.80; H, 7.08; Cl, 13.97; N, 5.46.

***cis*-4-(Benzoylamino)-1-[(methylsulfonyl)oxy]cycloheptane (14).** A solution of mesyl chloride (330 mg, 3.1 mmol) in chloroform (5 mL) was added dropwise to a stirred solution of **12** (360 mg, 1.55 mmol) and triethylamine (330 mg, 3.3 mmol) in chloroform (25 mL) at –20 °C (ice–acetone). After 5 min, the reaction mixture was poured into ice–water (40 mL) and the layers were separated. The organic layer was washed with water and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue recrystallized from chloroform–benzene to give **14** (420 mg, 88%) as colorless needles: mp 124–126 °C; IR ($CHCl_3$) 1665, 1360, 1340, 1180 cm^{-1}; ^1H NMR δ 1.3–2.2 (series of m, 10 H), 3.00 (s, 3 H), 4.18 (m, 1 H), 4.96 (m, 1 H), 6.30 (br s, 1 H), 7.38–7.80 (m, 5 H); ^{13}C NMR δ 19.4 (t), 27.9 (t), 30.4 (t), 34.8 (t), 35.1 (t), 38.6 (q), 50.3 (d), 82.4 (d), 127.0 (d), 128.6 (d), 131.6 (d), 134.3 (s), 167.0 (s); mass spectrum, m/z (relative intensity) 311 (M^+, 1.6), 216 (6), 215 (15), 160 (6), 122 (51), 106 (11), 105 (100), 94 (16), 79 (16), 77 (51).

Anal. Calcd for $C_{15}H_{21}NO_4S \cdot {}^1/_4H_2O$: C, 57.03; H, 6.70; N, 4.43. Found: C, 56.94; H, 6.67; N, 4.34.

***N*-Benzoylnortropane (7).** To a stirred cold (0 °C) solution of **13** (330 mg, 1.3 mmol) in 1:1 benzene–HMPA (5 mL) was added potassium *tert*-butoxide (160 mg) under N_2. The reaction mixture was allowed to come to room temperature, stirred for 15 h, and poured into ice–water (50 mL) containing 1 mL of concentrated HCl. The organic layer was separated and the aqueous layer was taken up in benzene. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel with chloroform–benzene (4:6). Recrystallization of the eluted product from hexane gave **7** (245 mg, 87%) as colorless plates: mp 93.5–95 °C (lit.[21] mp 94–95 °C); IR (KBr) 1620 cm^{-1}; ^1H NMR δ 1.4–2.15 (series of m, 10 H), 4.03 (br s, 1 H), 4.82 (br s, 1 H), 7.32–7.53 (m, 5 H); ^{13}C NMR, Table II; mass spectrum, m/z (relative intensity) 215 (M^+, 32), 186 (6), 172 (10), 110 (7), 106 (8), 105 (100), 77 (35).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.16; H, 8.01; N, 6.81.

***N*-(Ethoxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (17).** A solution of *N*-(ethoxycarbonyl)hydroxylamine (850 mg, 8.1 mmol) in chloroform (20 mL) was added dropwise to a mixture of tetrapropylammonium metaperiodate (3.05 g, 8.1 mmol) and **8** (740 mg, 7.9 mmol) in chloroform (50 mL) with stirring and cooling (0 °C) over 20 min. After being stirred at room temperature for 3 h, the mixture was washed with water and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure followed by chromatography on silica gel with benzene gave **17** (1.1 g, 71%) as a colorless oil: IR ($CHCl_3$) 1695 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.0 Hz, 3 H), 1.35–1.90 (series of m, 6 H), 4.22 (q, J = 7.0 Hz, 2 H), 4.77 (br s, 1 H), 4.87 (br s, 1 H), 6.20 (ddd, J = 9.0, 6.0, 1.0 Hz, 1 H), 6.36 (ddd, J = 9.0, 6.0, 1.0 Hz, 1 H); ^{13}C NMR δ 14.6 (q), 18.5 (t), 28.1 (t), 30.5 (t), 53.9 (d), 62.0 (t), 75.5 (d), 128.1 (d), 129.0 (d), 156.3 (s); mass spectrum, m/z (relative intensity) 197 (M^+, 27), 125 (8), 124 (10), 108 (16), 106 (16), 96 (27), 94 (70), 79 (100); exact mass calcd for $C_{10}H_{15}NO_3$, m/z 197.1051, found 197.1064.

***N*-(Ethoxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]nonane (18).** A mixture of **17** (390 mg, 2.0 mmol) and 5% palladium on carbon (150 mg) in methanol (70 mL) was hydrogenated at 1 atm. After filtration the solution was concentrated at reduced pressure and the residue was chromatographed on silica gel with benzene to give **18** (385 mg, 98%) as a colorless oil: IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR δ 1.31 (t, J = 7.0 Hz, 3 H), 1.64–2.18 (series of m, 10 H), 4.23 (q, J = 7.0 Hz, 2 H), 4.43 (br s, 1 H), 4.55 (br s, 1 H); ^{13}C δ NMR 14.8 (q), 19.4 (t), 21.3 (t), 21.8 (t), 32.4 (t), 32.9 (t), 51.2 (d), 61.5 (t), 76.3 (d), 154.6 (s); mass spectrum, m/z (relative intensity) 199 (M^+, 100), 126 (50), 110 (30), 95 (84), 59 (59); exact mass calcd for $C_{10}H_{17}NO_3$, m/z 199.1207, found 199.1228.

8-Oxa-9-azabicyclo[3.2.2]non-6-ene (22). The diene **8** (3.0 g, 32 mmol) was added dropwise to a solution of **21** (5.0 g, 34 mmol) in a mixture of ethanol (10 mL) and carbon tetrachloride (15 mL) with stirring at –20 °C (ice–methanol). The resulting solution was allowed to stand at –10 °C in a freezer for 48 h, and the separated crystals were collected by filtration and washed with ether until the blue color of the nitroso compound disappeared. The product was recrystallized from ethanol–ether to give **22** (3.5 g, 68%) as colorless needles: mp 179–181 °C dec; IR (KBr) 2950–2300, 1055, 960, 940 cm^{-1}; ^1H NMR (CD_3OD) δ 1.35–2.2 (series of m, 6 H), 4.54 (t, J = 6.5 Hz, 1 H), 4.96 (br t, 1 H), 6.42 (ddd, J = 9.5, 6.5, 1.0 Hz, 1 H), 6.60 (ddd, J = 9.5, 6.5, 1.5 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 18.7 (t), 27.5 (t), 31.6 (t), 55.8 (d), 79.2

(20) In a deuteriochloroform solution some signals overlap.

(21) von Braun, J.; Weissbach, K. *Chem. Ber.* **1930**, *63*, 489.

(d), 125.9 (d), 132.2 (d); mass spectrum, m/z (relative intensity) 125 (M^+ – HCl, 39), 108 (25), 96 (40), 94 (35), 91 (30), 80 (22), 79 (100), 77 (30).

Anal. Calcd for $C_7H_{11}NO\cdot HCl$: C, 52.02; H, 7.48; N, 8.67. Found: C, 51.99; H, 7.47; N, 8.80.

***cis*-4-Aminocycloheptanol (23).** A mixture of **22** (3.0 g, 18.6 mmol) and 5% palladium on carbon (1.0 g) in methanol (250 mL) was hydrogenated at 1 atm for 7 h. After filtration the solvent was removed at reduced pressure and the residue was recrystallized from ethanol–ether to give **23** hydrochloride (3.0 g, 98%) as a crystalline solid: mp 171–173 °C; IR (KBr) 3300, 2900–2300 cm^{-1}; ^1H NMR (CD_3OD) δ 1.35–2.15 (series of m, 10 H), 3.90 (m, 1 H), 4.82 (br s, 1 H); ^{13}C NMR (CD_3OD) δ 20.4 (t), 27.2 (t), 32.6 (t), 34.4 (t), 37.5 (t), 53.3 (d), 70.9 (d); mass spectrum, m/z (relative intensity) 129 (M^+ – HCl, 7), 112 (11), 86 (11), 83 (15), 82 (27), 72 (13), 70 (14), 57 (61), 56 (100).

Anal. Calcd for $C_7H_{15}NO\cdot HCl$: C, 50.75; H, 9.76; N, 8.46. Found: C, 50.46; H, 9.61; N, 8.56.

***cis*-4-[(Ethoxycarbonyl)amino]cycloheptanol (20).** A solution of **23** hydrochloride (1.6 g, 9.7 mmol) in water (20 mL) was suspended in chloroform (30 mL) and then Na_2CO_3 (2.0 g, 19 mmol) was added to this in one portion with stirring at 0 °C. After 30 min, a solution of ethyl chloroformate (1.1 g, 10 mmol) in chloroform (30 mL) was added dropwise to the suspension with vigourous stirring over 30 min at 0 °C and the resulting mixture was allowed to stir at room temperature for further 2 h. After the organic layer was separated, the aqueous layer was extracted with chloroform. The combined organic layers were successively washed with water and 5% HCl, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by chromatography on silica gel with 1:1 benzene–chloroform to give **20** (1.64 g, 84%) as a colorless oil: IR ($CHCl_3$) 3600, 3450, 1710 cm^{-1}; ^1H NMR δ 1.23 (t, J = 7.5 Hz, 3 H), 1.3–2.0 (series of m, 10 H), 2.45 (br s, 1 H), 3.69 (br s, 1 H), 3.93 (br s, 1 H), 4.10 (q, J = 7.5 Hz, 2 H), 5.00 (br s, 1 H); ^{13}C NMR δ 14.5 (q), 19.6 (t), 28.3 (t), 31.9 (t), 35.4 (t), 37.1 (t), 50.9 (d), 60.3 (t), 70.6 (d), 155.8 (s); mass spectrum, m/z (relative intensity) 201 (M^+, 8), 183 ($M^+ - H_2O$, 6), 155 (24), 154 (29), 130 (24), 129 (100), 128 (91), 100 (63), 95 (58), 90 (63), 84 (51), 62 (49), 56 (85); exact mass calcd for $C_{10}H_{19}NO_3$, m/z 201.1364, found 201.1365.

***cis*-4-([(Benzyloxy)carbonyl]amino)cycloheptanol (24).** The reaction of **23** hydrochloride with benzyl chloroformate was carried out in a similar manner as described above for **20**. After workup and chromatography as described for **20**, recrystallization from benzene–hexane afforded **24** (2.03 g, 80%) as colorless needles: mp 72–74 °C; IR ($CHCl_3$) 3460, 1720 cm^{-1}; ^1H NMR δ 1.25–1.55 (m, 3 H), 1.69 (br s, 5 H), 1.90 (br s, 2 H), 2.20 (br s, 1 H, exchanges with D_2O), 3.70 (br s, 1 H), 3.89 (br s, 1 H), 4.95–5.15 (br s, 1 H with s, 2 H at δ 5.06), 7.34 (s, 5 H); ^{13}C NMR δ 19.7 (t), 28.4 (t), 32.0 (t), 35.6 (t), 37.3 (d), 51.2 (d), 66.5 (t), 70.7 (d), 128.0 (d), 128.5 (d), 136.6 (s), 155.5 (s); mass spectrum, m/z (relative intensity) 263 (M^+, 1.3), 172 (3), 154 (4), 146 (10), 108 (43), 107 (23), 100 (15), 91 (100), 84 (22), 79 (28).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.37; H, 8.27; N, 5.18.

Reaction of 24 with Thionyl Chloride. (a) Without Base. To a stirred cold (0 °C) solution of **24** (1.52 g, 5.78 mmol) in chloroform (40 mL) was slowly added a solution of thionyl chloride (1.75 g, 14.7 mmol) in chloroform (20 mL) and the reaction allowed to stir at room temperature for 48 h. The reaction mixtue was then poured into ice–water (100 mL) and the aqueous layer was extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated at reduced pressure, and the residue was chromatographed on silica gel. The first fraction, eluted with benzene–hexane (1:1), afforded 860 mg (61%) of a mixture of 1-([(benzyloxy)carbonyl]amino)-3- and -4-cycloheptene (**26a** and **27a**, respectively) in a ratio of 1:1 (by ^1H NMR) as a colorless solid: IR ($CHCl_3$) 3450, 1720 cm^{-1}; ^1H NMR δ 1.25–2.4 (series of m, 8 H), 3.76 (m, 1 H), 4.86 (m, 1 H), 5.08 (s, 2 H), 5.62 (m, 0.5 H, olefinic proton of **26a**), 5.77 (br s, 1 H, olefinic protons of **27a**), 5.93 (m, 0.5 H, olefinic proton of 26a), 7.35 (s, 5 H); ^{13}C NMR δ, for cycloheptene ring carbons of **26a**, 23.1 (t), 28.5 (t), 34.3 (t), 37.9 (t), 48.4 (d), 126.9 (d), 134.8 (d), for cycloheptene ring carbons of **27a**, 24.3 (t), 33.5 (t), 53.7 (d), 131.8 (d), for benzyloxycarbonyl carbons of **26a** and **27a**, 66.5 (t), 128.1 (d), 128.5 (d), 136.7 (s), 155.3 (s); mass spectrum (20 eV), m/z (relative intensity) 245 (M^+, 1.6), 184 (3), 154 (3), 137 (6), 108 (97), 95 (39), 79 (100).

The second fraction eluted with benzene–hexane (1:1) gave 190 mg (12%) of *trans*-1-([(benzyloxy)carbonyl]amino)-4-chlorocycloheptane (**25a**) as colorless needles: mp 56–57 °C (hexane); IR ($CHCl_3$) 3445, 1715 cm^{-1}; ^1H NMR δ 1.25–2.25 (series of m, 10 H), 3.74 (br s, 1 H), 4.12 (br m, 1 H), 4.93 (br s, 1 H), 5.07 (s, 2 H), 7.33 (s, 5 H); ^{13}C NMR δ 20.0 (t), 31.1 (t), 34.3 (t), 34.9 (t), 38.7 (t), 51.6 (d), 61.7 (d), 66.6 (t), 128.1 (d), 128.5 (d), 136.5 (s), 155.4 (s); mass spectrum, m/z (relative intensity) 281 (M^+, 2.4), 245 (M^+ – HCl, 3.9), 202 (11), 190 (13), 146 (33), 108 (83), 91 (100), 79 (18).

Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.98; H, 7.11; N, 5.25.

The third fraction eluted with chloroform contained a trace amount of bis(*cis*-4-([(benzyloxy)carbonyl]amino)cycloheptyl) sulfite (**28a**) identical in all respects with that obtained in section b below.

(b) With Pyridine at Room Temperature. A stirred cold (0 °C) solution of **24** (526 mg, 2.00 mmol) and pyridine (200 mg, 2.53 mmol) in ether (20 mL) was added dropwise a solution of thionyl chloride (240 mg, 2.02 mmol) in ether (10 mL). During this procedure white precipitates separated immediately. The reaction mixture was allowed to stand at room temperature for 14 h and worked up as described above in (a) to give a 1:1 mixture of **26a** and **27a** (30 mg, 6%), **25a** (180 mg, 32%), and **28a** (280 mg, 49%).

28a: mp 102–103 °C (benzene–hexane); IR ($CHCl_3$) 3450, 1720, 1320, 1120 cm^{-1}; ^1H NMR δ 1.35 (m, 4 H), 1.6–2.05 (series of m, 8 H), 3.68 (br s or m, 2 H), 4.70 (br s, 2 H), 5.07 (s, 4 H, containing a 2 H signal at δ ca. 5.0), 7.35 (s, 10 H); ^{13}C NMR δ 19.3 (t), 28.1 (t), 30.4 (t), 35.2 (2 × t), 51.2 (d), 66.2 (t), 73.9 (d), 127.8 (d), 128.2 (d), 136.4 (s), 155.3 (s). No molecular ion peak appeared in the mass spectrum.

Anal. Calcd for $C_{30}H_{40}N_2O_7S$: C, 62.91; H, 7.04; N, 4.89. Found: C, 62.78; H, 6.97; N, 4.93.

(c) With Excess Pyridine at Reflux. To a stirred cold (0 °C) solution of **24** (1.10 g, 4.18 mmol) and pyridine (2.5 mL) in chloroform (40 mL) was added dropwise a solution of thionyl chloride (0.82 g, 6.89 mmol) in chloroform (15 mL). When the addition was complete the mixture was heated at reflux for 5 h and worked up as in (a), affording a 1:1 mixture of **26a** and **27a** (40 mg, 4%), **25a** (640 mg, 55%), and **28a** (220 mg, 18%).

Reaction of 20 with Thionyl Chloride. To a stirred cold (0 °C) solution of **20** (3.20 g, 15.9 mmol) and pyridine (2.40 g, 30.4 mmol) in chloroform (80 mL) was added dropwise a solution of thionyl chloride (2.50 g, 21.0 mmol) and then the mixture was refluxed for 3 h. Standard workup followed by chromatography as described for the reaction of **24** with thionyl chloride provided 0.31 g (11%) of a 1:1 mixture of 1-[(ethoxycarbonyl)amino]-3- and -4-cycloheptene (**26b** and **27b**, respectively), 2.27 g (65%) of *trans*-4-chloro-1-[(ethoxycarbonyl)amino]cycloheptane (**25b**), and 0.19 g (5%) of bis(*cis*-4-[(ethoxycarbonyl)amino]cycloheptyl) sulfite (**28b**).

The 1:1 mixture of **26b** and **27b**: colorless oil; ^1H NMR δ 1.23 (t, J = 7.6 Hz, 3 H), 1.30–2.45 (series of m, 8 H), 3.74 (br s, 1 H), 4.10 (q, J = 7.6 Hz, 2 H), 4.80 (br s, 1 H), 5.65 (m, 0.5 H, olefinic proton of **26b**), 5.77 (br s, 1 H, olefinic protons of **27b**), 5.94 (m, 0.5 H, olefinic proton of **26b**); ^{13}C NMR δ, for cycloheptene ring carbons of **26b**, 23.2 (t), 28.5 (t), 34.5 (t), 38.0 (t), 48.2 or 53.5 (d), 127.0 (d), 134.7 (d), for cycloheptene ring carbons of **27b**, 24.4 (t), 35.5 (t), 48.2 or 53.5 (d), 131.8 (d), for ethoxycarbonyl carbons, 14.6 (q), 60.5 (t), 155.7 (s); mass spectrum, m/z (relative intensity) 184 (M^+ + 1, 11), 183 (M^+, 8.5), 128 (100), 115 (39).

25b: mp 49–51 °C (hexane); IR ($CHCl_3$) 3460, 1720 cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.6 Hz, 3 H), 1.3–2.3 (series of m, 10 H), 3.74 (br s, 1 H), 4.11 (m, 3 H), 4.55 (br s, 1 H); ^{13}C NMR δ 14.6 (q), 20.0 (t), 31.2 (t), 34.4 (t), 34.9 (t), 38.7 (t), 51.4 (d), 60.7 (t), 61.7 (d), 155.7 (s); mass spectrum, m/z (relative intensity) 219 (M^+, 9.2), 184 (36), 128 (100), 115 (24), 95 (43), 90 (31), 84 (18).

Anal. Calcd for $C_{10}H_{18}ClNO_2$: C, 54.66; H, 8.26; N, 6.38. Found: C, 54.63; H, 8.21; N, 6.35.

28b: colorless oil; IR ($CHCl_3$) 3470, 1720, 1320, 1120 cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.5 Hz, 6 H), 1.40 (m, 4 H), 1.55–2.1 (m, 16 H), 3.68 (br s, 2 H), 4.09 (q, J = 7.5 Hz, 4 H), 4.72 (m, 4 H); ^{13}C NMR δ 14.6 (q), 19.6 (t), 28.5 (t), 30.6 (t), 35.5 (t), 35.6 (t), 51.3

(d), 60.6 (t), 74.1 (d), 155.7 (s); mass spectrum, *m/z* (relative intensity) 449 (M^+ + 1, 0.1), 399 (0.2), 366 (1.0), 312 (1.2), 248 (3.0), 200 (4.0), 184 (100), 129 (22), 95 (72).

***N*-[(Benzoyloxy)carbonyl]nortropane (33). (a) From Olefins 26a and 27a.** To a stirred solution of the 1:1 mixture of **26a** and **27a** (120 mg, 0.49 mmol) in 10% aqueous THF (40 mL) was added mercuric acetate (600 mg, 1.9 mmol) in one portion and the mixture was continued to stir at room temperature. After 48 h, a solution of $NaBH_4$ (160 mg, 4.2 mmol) in 10% aqueous NaOH solution (2.5 mL) was added to the stirred reaction mixture and then the resulting mixture was allowed to stir at room temperature for another 24 h. The resulting Hg was removed by decantation and the solution was concentrated at reduced pressure to leave a syrup which was dissolved in chloroform, washed with water, and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue was chromatographed on silica gel eluting with benzene–hexane (2:3) to afford 64 mg (53%) of starting material followed by **33** (25 mg, 21% or 45% based on recovered starting material) as a colorless oil: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR δ 1.4–2.05 (series of m, 10 H), 4.27 (br s, 2 H), 5.14 (s, 2 H), 7.35 (m, 5 H); ^{13}C NMR, Table II; mass spectrum, *m/z* (relative intensity) 245 (M^+, 86), 172 (32), 158 (74), 138 (25), 110 (38), 95 (21), 92 (46), 91 (100), 82 (21); exact mass calcd for $C_{15}H_{19}NO_2$, *m/z* 245.1414; found, 245.1428.

(b) From Chloride 25a. To a stirred cold (0 °C) solution of **25a** (620 mg, 2.21 mmol) in 1:1 benzene–HMPA (15 mL) added in small portions potassium *tert*-butoxide (260 mg, 2.32 mmol) under N_2. The mixture was allowed to stir at room temperature for 2 h and worked up as described for **7**. The crude product was purified by chromatography on silica gel with benzene–hexane (2:3) to give **33** (420 mg, 78%) identical in all respects with the product obtained in section a.

***N*-(Ethoxycarbonyl)nortropane (34).** As for **33** the amidocyclization was performed by using **25b** (190 mg, 0.87 mmol), 1:1 benzene–HMPA (10 mL), and potassium *tert*-butoxide (100 mg). Workup as for **33** gave **34** (124 mg, 78%) as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.6 Hz, 3 H), 1.3–2.0 (series of m, 10 H), 4.13 (q, J = 7.6 Hz, 2 H), 4.23 (br s, 2 H); ^{13}C NMR, Table II; mass spectrum, *m/z* (relative intensity) 183 (M^+, 43), 154 (40), 140 (100), 128 (36), 110 (47), 95 (36), 82 (57), 79 (57), 68 (85); exact mass calcd for $C_{10}H_{17}NO_2$, *m/z* 183.1258, found 183.1276.

Tropane (1). A solution of **33** (300 mg, 1.22 mmol) in THF (30 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (200 mg) in THF (50 mL) at 0 °C. The mixture was heated at reflux for 24 h and cooled at 0 °C, and 10% NaOH solution (0.3 mL) was added. The resulting slurry was filtered through a Celite pad and the filtrate was dried (Na_2SO_4). After removal of the solvent, the residual oil was distilled to give **1** (110 mg, 72%): bp 165–167 °C [lit.[22] bp 163–165 °C (corr), lit.[23] bp 166–169 °C]; ^1H NMR δ 1.3–2.5 (series of m, 10 H), 2.26 (s, 3 H), 3.10 (m, 2 H); ^{13}C NMR, Table II.

The free base was converted to the picrate which was recrystallized from ethanol to give yellow prisms: mp 284–285 °C (288 °C dec) (lit.[24] mp 280–288 °C dec).

Anal. Calcd for $C_8H_{15}N{\cdot}C_6H_3N_3O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.43; H, 5.10; N, 15.81.

***exo*- and *endo*-3-(Benzoyloxy)-8-oxa-9-azabicyclo[3.2.2]non-6-ene Hydrochloride (36 and 37).** To a solution of **35** (15.5 g, 72.4 mmol) in 3:2 ethanol–carbon tetrachloride (80 mL) was added dropwise **21** (11.8 g, 80.1 mmol) at −20 °C (ice–methanol). After stirring at the same temperature for 5 h, the mixture was allowed to stand at −10 °C in a freezer for 14 days. At this stage the product was shown to be a diastereomeric mixture of **36** and **37** in a ratio of 4:1 from the ^1H NMR signals corresponding to the olefinic protons (see below). The white crystals thus separated by standing were collected, washed with ether, and recrystallized from ethanol to give **36** (11.60 g, 57%) as colorless prisms: mp 187–188 °C dec; IR (KBr) 2850–2300, 1730 (sh), 1720 cm^{-1}; ^1H NMR (CD_3OD) δ 2.16–2.32 (m, 2 H), 2.61–2.83 (m, 2 H), 4.75 (t, J = 7.6 Hz, 1 H), 4.80–5.17 (m, 3 H), 6.56 (dd, J = 8.9, 7.6 Hz, 1 H), 6.73 (dd, J = 8.3, 7.6 Hz, 1 H), 7.45–8.02 (m, 5 H); ^{13}C NMR (CD_3OD) δ 32.5 (t), 37.3 (t), 52.1 (d), 68.6 (d), 75.1 (d), 126.6 (d), 129.6 (d), 130.5 (d), 131.1 (s), 133.0 (d), 134.5 (d), 166.9 (s); mass spectrum, *m/z* (relative intensity) 245 (M^+ − HCl, 5.9), 123 (18), 106 (19), 105 (100), 91 (41), 77 (59).

Anal. Calcd for $C_{14}H_{15}NO_3{\cdot}HCl$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.71; H, 5.57; N, 4.92.

The combined filtrates and washings were concentrated at reduced pressure and the residue was separated into two components by preparative TLC with chloroform–methanol (20:1) as developer. The faster moving one was isolated as the free base of **36**: mp 95–97 °C; ^1H NMR (CD_3OD) δ 1.93–2.08 (m, 2 H), 2.35–2.57 (m, 2 H), 3.77 (t, J = 7.6 Hz, 1 H), 4.61 (m, 1 H), 4.95 (m, 1 H), 6.29 (dd, J = 8.4, 6.4 Hz, 1 H), 6.60 (dd, J = 7.6, 6.4 Hz, 1 H), 7.44–8.00 (m, 5 H).

The second one was the free base of **37**: mp 52–54 °C; ^1H NMR (CD_3OD) δ 2.04 (br d, J = 15.4 Hz, 1 H), 2.20 (m, 1 H), 2.46 (m, 2 H), 3.72 (m, 1 H), 4.59 (br s, 1 H), 5.57 (m, 1 H), 6.43 (dd, J = 8.3, 6.7 Hz, 1 H), 6.70 (dd, J = 8.1, 6.7 Hz, 1 H), 7.43–7.99 (m, 5 H). This material was converted to the hydrochloride **37** which was recrystallized from acetone–hexane to give colorless prisms: mp 165–168 °C dec; IR (KBr) 2800–2300, 1720 cm^{-1}; ^1H NMR (CD_3OD) δ 2.44 (br d, J = 16.2 Hz, 1 H), 2.65 (m, 3 H), 4.63 (m, 1 H), 5.05 (m, 1 H), 5.49 (m, 1 H), 6.68 (dd, J = 9.3, 7.1 Hz, 1 H), 6.85 (dd, J = 9.6, 7.1 Hz, 1 H), 7.45–8.00 (m, 5 H); ^{13}C NMR δ 34.6 (t), 39.4 (t), 53.9 (d), 69.0 (d), 77.1 (d), 128.6 (d), 129.7 (d), 130.6 (d), 131.4 (s), 134.4 (d), 134.8 (d), 166.8 (s); mass spectrum, *m/z* (relative intensity) 245 (M^+ − HCl, 2.9), 123 (25), 105 (100), 92 (42), 91 (34), 77 (54).

Anal. Calcd for $C_{14}H_{15}NO_3{\cdot}HCl$: C, 59.68; H, 5.73; N, 4.97. Found: C, 59.54; H, 5.73; N, 4.87.

***all-cis*-5-Amino-3-(benzoyloxy)cycloheptanol Hydrochloride (38).** A solution of **36** (5.3 g, 18.8 mmol) in methanol (400 mL) was hydrogenated in the presence of 5% palladium on carbon (4.5 g) for 7 h. After removal of the catalyst by filtration, the filtrate was concentrated at reduced pressure, and the residue was recrystallized from ethanol–ether to give **38** (5.25 g, 98%) as colorless crystals: mp 212–214 °C dec; IR (KBr) 3320, 2900–2400, 1720 cm^{-1}; ^1H NMR (CD_3OD) δ 1.84–2.20 (m, 6 H), 2.48 (m, 2 H), 3.50 (m, 1 H), 4.06 (m, 1 H), 4.60–5.20 (br s, 3 H with br t, J = 11.5 Hz, 1 H at δ 5.09), 7.45–8.02 (m, 5 H); ^{13}C NMR (CD_3OD) δ 27.4 (t), 32.4 (t), 40.3 (t), 43.8 (t), 50.0 (d), 67.4 (d), 70.0 (d), 129.6 (d), 130.4 (d), 131.3 (s), 134.3 (d), 166.9 (s); mass spectrum, *m/z* (relative intensity) 249 (M^+ − HCl, 0.2), 193 (8), 144 (12), 128 (41), 105 (100), 77 (69).

Anal. Calcd for $C_{14}H_{19}NO_3{\cdot}HCl{\cdot}^1/_3H_2O$: C, 57.50; H, 7.12; N, 4.79. Found: C, 57.64; H, 7.40; N, 4.76.

***all-cis*-3-(Benzoyloxy)-5-[(ethoxycarbonyl)amino]cycloheptanol (39).** Ethoxycarbonylation was run similar to that of **20** by using **38** (1.22 g, 4.27 mmol), Na_2CO_3 (1.20 g, 11.3 mmol), and ethyl chloroformate (540 mg, 4.98 mmol). After workup the crude material, which was solidified by standing, was recrystallized from benzene–hexane to give **39** (1.15 g, 84%) as colorless needles: mp 120–122 °C; IR (KBr) 3360, 1725, 1690 cm^{-1}; ^1H NMR δ 1.20 (t, J = 7.4 Hz, 3 H), 1.70–2.01 (m, 6 H), 2.40 (m, 2 H), 3.28 (br s, 1 H), 3.81 (br s, 1 H), 3.95–4.17 (m, 1 H with q, J = 7.4 Hz, 2 H at δ 4.08), 5.05 (br t, J = 11.7 Hz, 1 H), 5.28 (br s, 1 H), 7.46–8.08 (m, 5 H); ^{13}C NMR δ 14.6 (q), 28.8 (t), 32.2 (t), 41.5 (t), 43.4 (t), 48.4 (d), 60.7 (t), 67.3 (d), 69.4 (d), 128.4 (d), 129.5 (d), 130.3 (s), 133.0 (d), 155.9 (s), 165.7 (s); mass spectrum, *m/z* (relative intensity) 321 (M^+, 0.06), 303 ($M^+ - H_2O$, 0.15), 216 (10), 158 (23), 110 (29), 105 (100), 77 (65).

Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.65; H, 7.20; N, 4.35.

***all-cis*-3-(Benzoyloxy)-5-([(benzyloxy)carbonyl]amino)cycloheptanol (40).** Benzyloxycarbonylation was performed in a similar manner described for **20** by using **38** (4.50 g, 15.8 mmol), Na_2CO_3 (4.4 g, 41.5 mmol), and benzyl chloroformate (2.74 g, 16.1 mmol). Standard workup followed by recrystallization from benzene–hexane gave **40** (5.80 g, 96%) as colorless crystals: mp 114–116 °C; IR (KBr) 3420 (sh), 3360, 1720, 1685 cm^{-1}; ^1H NMR δ 1.63–1.94 (m, 6 H), 2.36 (m, 2 H), 3.30 (s, 1 H), 3.80 (br s, 1 H), 3.97 (br s, 1 H), 4.95–5.13 (br s, 1 H with s, 2 H at δ 5.04), 5.49 (br d, J = 8.3 Hz, 1 H), 7.25–8.00 (m, 10 H); ^{13}C NMR δ 28.4 (t), 31.8 (t), 41.1 (t), 43.1 (t), 48.2 (d), 66.3 (t), 67.0 (d), 69.1 (d), 127.7

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(d), 127.8 (d), 128.1 (d), 128.2 (d), 129.2 (d), 130.0 (s), 132.7 (d), 136.3 (s), 155.3 (s), 165.4 (s); mass spectrum, m/z (relative intensity) 383 (M^+, 0.6), 276 (9), 170 (25), 123 (35), 108 (78), 105 (100), 91 (89).

Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.06; H, 6.59; N, 3.59.

Treatment of 39 with Thionyl Chloride. To a stirred cold (0 °C) solution of **39** (925 mg, 2.88 mmol) and pyridine (750 mg, 9.49 mmol) in chloroform (50 mL) was added dropwise a solution of thionyl chloride (440 mg, 3.70 mmol) in chloroform (10 mL) over 20 min. After being refluxed for 1 h, the mixture was poured into ice–water and aqueous layer extracted with chloroform. The combined extracts were washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel. The first fraction eluted with benzene–chloroform (9:1) gave 535 mg (55%) of 3β-(benzoyloxy)-5α-chloro-1β-[(ethoxycarbonyl)amino]cycloheptane (**41**) as a colorless oil: IR ($CHCl_3$) 3450, 1730 (sh), 1720 cm^{-1}; ^1H NMR δ 1.23 (t, J = 7.5 Hz, 3 H), 1.58–2.60 (series of m, 8 H), 3.90 (br s, 1 H), 4.08 (q, J = 7.5 Hz, 2 H), 4.34 (m, 1 H), 4.87 (br s, 1 H), 5.42 (m, 1 H), 7.43–8.02 (m, 5 H); ^{13}C NMR δ 14.6 (q), 31.9 (t), 35.0 (t), 40.1 (t), 43.4 (t), 48.4 (d), 57.0 (d), 60.8 (t), 69.3 (d), 128.5 (d), 129.5 (d), 130.1 (s), 133.2 (d), 155.6 (s), 165.3 (s); mass spectrum, m/z (relative intensity) 339 (M^+, 0.2), 304 (M^+ – Cl, 0.8), 234 (52), 182 (45), 141 (40), 105 (100), 77 (67); exact mass calcd for $C_{17}H_{22}ClNO_4$, m/z 339.1235, found 339.1232.

The second fraction contained 264 mg (28%) of bis(*all-cis*-3-(benzoyloxy)-5-[(ethoxycarbonyl)amino]cycloheptyl) sulfite (**43**) as a colorless vitreous substance: mp 50–54 °C; IR (KBr) 1720, 1710 (sh), 1690 (sh), 1315, 1115 cm^{-1}; ^1H NMR δ 1.21 (t, J = 7.4 Hz, 6 H), 1.76–2.53 (series of m, 16 H), 3.81 (br s, 2 H), 4.09 (q, J = 7.4 Hz, 4 H), 4.73–5.20 (series of m, 6 H), 7.20–8.00 (m, 10 H); mass spectrum, m/z (relative intensity) 410 (1.0), 368 (0.2), 304 (1.2), 258 (8.0), 181 (7.5), 105 (100), 77 (18).

Anal. Calcd for $C_{34}H_{44}N_2O_{11}S$: C, 59.28; H, 6.44; N, 4.07. Found: C, 59.51; H, 6.39; N, 3.98.

***N*-(Ethoxycarbonyl)nortropacocaine (45).** In the same manner for the cyclization of **25a**, **41** (1.26 g, 3.71 mmol) was treated with potassium *tert*-butoxide (460 mg, 4.11 mmol). Workup followed by chromatography on silica gel with benzene gave **45** (520 mg, 46%) as colorless oil: IR ($CHCl_3$) 1715 (sh), 1695 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.1 Hz, 3 H), 1.70–1.93 (m, 4 H), 1.98–2.17 (m, 4 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.39 (br s, 2 H), 5.45 (m, 1 H), 7.42–8.02 (m, 5 H); ^{13}C NMR, Table II; mass spectrum, m/z (relative intensity) 303 (M^+, 4.6), 230 (3.9), 214 (1.7), 198 (7.0), 182 (35), 181 (28), 152 (23), 139 (100), 105 (57), 77 (37); exact mass calcd for $C_{17}H_{21}NO_4$, m/z 303.1470, found 303.1497.

Pseudotropine (3). To a stirred cold (0 °C) slurry of $LiAlH_4$ (400 mg) in THF (80 mL) was added dropwise a solution of **45** (320 mg, 1.06 mmol) in THF (40 mL) over 30 min. After heating at reflux for 6 h, the mixture was cooled to 0 °C and 10% aqueous NaOH (2 mL) was added dropwise to this with stirring. The resulting slurry was filtered through a Celite pad, and the filtrate was dried (Na_2CO_3) and concentrated at reduced pressure. Chromatography of the residue on neutral alumina with chloroform followed by recrystallization from benzene–hexane gave **3** (100 mg, 67%) as colorless long needles: mp 108–109 °C (lit.[25] mp 108–109.5 °C); ^1H NMR δ 1.52–1.70 (m, 4 H), 1.76–1.87 (m, 2 H), 1.97–2.05 (m, 2 H), 2.30 (s, 3 H), 2.68 (br s, 1 H), 3.17 (br s, 2 H), 3.88 (m, 1 H); ^{13}C NMR, Table II.

The free base **3** was converted to the picrate which was recrystallized from ethanol to give yellow needles: mp 258–259 °C dec (lit.[26] mp 258–259 °C dec).

Treatment of 40 with Thionyl Chloride. Treatment of **40** with thionyl chloride in a similar manner to that described for treatment of **39** provided 195 mg (36%) of 3β-(benzoyloxy)-1β-([(benzyloxy)carbonyl]amino)-5α-chlorocycloheptane (**42**) and 210 mg (38%) of bis(*all-cis*-3-(benzoyloxy)-5-([(benzyloxy)carbonyl]amino)cycloheptyl) sulfite (**44**), after chromatography on silica gel with chloroform–benzene (7:3) followed by chloroform.

42: colorless oil; IR ($CHCl_3$) 3460, 1720 cm^{-1}; ^1H NMR δ 1.55–2.58 (series of m, 8 H), 3.90 (br s, 1 H), 4.31 (m, 1 H), 4.95–5.10 (br s, 1 H with s, 2 H at δ 5.06), 5.39 (m, 1 H), 7.30–8.02 (m, 10 H); ^{13}C NMR δ 31.9 (t), 34.9 (t), 40.0 (t), 43.4 (t), 48.6 (d), 56.9 (d), 66.6 (t), 69.4 (d), 128.0 (d), 128.1 (d), 128.4 (d), 128.5 (d), 129.5 (d), 130.0 (s), 133.1 (d), 136.4 (s), 155.3 (s), 165.2 (s); mass spectrum, m/z (relative intensity) 401 (M^+, 0.4), 365 (M^+ – HCl, 0.4), 294 (3.5), 243 (3.4), 190 (5.6), 123 (100), 105 (84), 91 (100); exact mass calcd for $C_{22}H_{24}ClNO_4$, m/z 401.1391, found 401.1391.

44: colorless prisms; mp 122–125 °C (benzene–hexane); IR (KBr) 1730, 1690, 1320, 1120 cm^{-1}; ^1H NMR δ 1.76–2.51 (series of m, 16 H), 3.82 (br s, 2 H), 4.83 (br m, 2 H), 4.97–5.20 (m, 4 H with s, 4 H at δ 5.08), 7.28–8.01 (m, 20 H); mass spectrum, m/z (relative intensity) 365 (0.4), 276 (2.0), 258 (2.4), 243 (5.2), 152 (7.0), 105 (99), 91 (100), 79 (62).

Anal. Calcd for $C_{44}H_{48}N_2O_{11}S$: C, 65.01; H, 5.95; N, 3.45. Found: C, 65.12; H, 5.99; N, 3.30.

***N*-[(Benzyloxy)carbonyl]nortropacocaine (46).** As for **25a** the cyclization was performed by using **42** (1.40 g, 3.49 mmol) and potassium *tert*-butoxide (450 mg, 4.02 mmol). Workup as for **25a** followed by purification by chromatography on silica gel with benzene–hexane (4:1) gave **46** (950 mg, 75%) as a colorless oil: IR ($CHCl_3$) 1715 (sh), 1695 cm^{-1}; ^1H NMR δ 1.70–1.89 (m, 4 H), 1.99–2.17 (m, 4 H), 4.41 (br s, 2 H), 5.18 (s, 2 H), 5.44 (m, 1 H), 7.34–8.01 (m, 10 H); ^{13}C NMR, Table II; mass spectrum, m/z (relative intensity) 365 (M^+, 4.4), 202 (12), 137 (15), 105 (28), 91 (100); exact mass calcd for $C_{22}H_{23}NO_4$, m/z 365.1626, found 365.1639.

Tropacocaine (6). A solution of **46** (270 mg, 0.74 mmol) in methanol (40 mL) was hydrogenated at 1 atm in the presence of 5% palladium on carbon (200 mg) for 8 h. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure. To the residual oil was added 90% aqueous formic acid (300 mg) and 37% aqueous formaldehyde (300 mg) and the mixture was heated at reflux. After 5 h, to this mixture was added again 90% aqueous formic acid (300 mg) and 37% aqueous formaldehyde (300 mg) and the mixture was refluxed for another 5 h. After addition of concentrated HCl (0.1 mL), the reaction mixture was concentrated at reduced pressure to leave the crude product as the hydrochloride, which was dissolved in minimum water. The resulting aqueous solution was basified with concentrated aqueous ammonia, saturated with NaCl, taken up in chloroform, and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the residue was chromatographed on neutral alumina with benzene–chloroform (1:1) to afford **6** (128 mg, 71%) as a colorless oil which was solidified by standing in a refrigerator: ^1H NMR δ 1.71 (m, 2 H), 1.83–2.12 (series of m, 6 H), 2.34 (s, 3 H), 3.24 (br s, 2 H), 5.25 (m, 1 H), 7.38–8.02 (m, 5 H); ^{13}C NMR, Table II; mass spectrum, m/z (relative intensity) 245 (M^+, 20), 124 (100), 105 (16), 94 (29), 83 (81), 82 (59), 77 (25).

The picrate prepared was purified by recrystallization from ethanol–water, yielding yellow needles: mp 238–241 °C dec (lit.[27] mp 240–242 °C).

Registry No. **1**, 529-17-9; **3**, 135-97-7; **6**, 537-26-8; **7**, 95687-85-7; **8**, 4054-38-0; **9**, 58696-10-9; **10**, 95687-88-0; **11**, 95687-90-4; **12**, 95687-91-5; **13**, 95687-93-7; **14**, 95687-92-6; **16**, 95799-05-6; **17**, 95798-87-1; **18**, 95798-88-2; **20**, 95798-91-7; **21**, 695-64-7; **22**, 95798-89-3; **23**, 95798-90-6; **24**, 95798-92-8; **25a**, 95798-95-1; **25b**, 95798-98-4; **26a**, 95798-93-9; **26b**, 95798-97-3; **27a**, 95798-94-0; **27b**, 38288-77-6; **28a**, 95798-96-2; **28b**, 95798-99-5; **33**, 95799-01-2; **34**, 6760-98-1; **35**, 59171-91-4; **36**, 95799-00-1; **36** (base), 95909-07-2; **37**, 95909-08-3; **37** (base), 95975-20-5; **38**, 95687-94-8; **39**, 95687-95-9; **40**, 95687-98-2; **41**, 95687-96-0; **42**, 95687-97-1; **43**, 95799-02-3; **44**, 95687-99-3; **45**, 95687-86-8; **46**, 95687-87-9; i, 95799-03-4; ii, 95799-04-5; PhCONHOH, 495-18-1; $C_2H_5OCONHOH$, 589-41-3; C_2H_5OCOCl, 541-41-3; $PhCH_2OCOCl$, 501-53-1.

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