Synthetic Studies of Laurencin and Related Compounds. I. The Synthesis of *t*-3-Bromo-*r*-2,*c*-8-diethyl-3,4,7,8-tetrahydro-2*H*-oxocin

Tadashi MASAMUNE, Satoshi NUMATA, Hajime MATSUE, Akira MATSUYUKI, Takehiro SATO, and Hisashi MURASE

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

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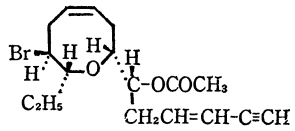
The synthesis of the titled bromohydrooxocin (**2**), one of model compounds for synthetic approaches to laurencin (**1**), is described. *trans*- and *cis*-2,5-Diethyl-2,5-dihydrofurans (**25**), prepared by treatment of furan with bromine and then with ethyl magnesium bromide, was submitted, after oxidation with ozone, to the Robinson-Schöpf condensation with methylamine to give *trans*- and *cis*-2,4-diethylbicyclononanones (**19a** and **19b**), whose configurations were discussed on the NMR spectra. These compounds were converted into *trans*- and *cis*-diethylhydrooxocinones (**38a** and **38b**), respectively, according to a six-step process analogous to the Paguette procedure. It is to be noted that (i) thermally induced, intramolecular dienyl 1,5-hydrogen transfer (**36** to **37**), one of the key reactions in the process, took place without difficulty with *cis*-aminodiene (**36b**), while the rearrangement did not proceed smoothly with *trans*-aminodiene (**36a**), and (ii) *trans*-ketone (**38a**) was isomerized readily into *cis*-ketone (**38b**). Further hydride reduction of *cis*-ketone (**38b**) followed by bromination with carbon tetrabromide and triphenylphosphine yielded the aimed bromohydrooxocin (**2**) as a major product, which possessed the same relative configuration concerning the ring substituents as laurencin (**1**).

One decade ago, we reported the isolation and structure elucidation of laurencin (**1**), a bromine-containing, acetylenic seaweed component.[1] Many related compounds have since been identified as constituents of marine algae,[2] and these natural halogenocyclic ethers have been attractive as a synthetic target owing to their unusual skeleton. We describe herein the preparation of *t*-3-bromo-*r*-2,*c*-8-diethyl-3,4,7,8-tetrahydro-2*H*-oxocin (**2**), which possesses the same relative configuration concerning the ring substituents as laurencin (**1**). In view of the fact that the synthetic process involved no complexity due to the side chain with an enyne grouping and gave information of conformational change or isomerization caused by introduction of substituents into oxocanes,[3] this hydrooxocin (**2**) was a most useful model compound for the natural cyclic ethers.



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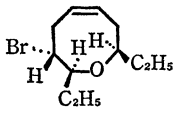

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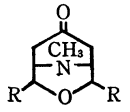
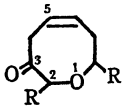
Although hydrooxocins are not readily accessible synthetically as compared with hydrooxoepine,[4,5] several methods for preparing the oxocins have been reported; namely, radical cyclization of olefinic alcohols,[6] dichlorocarbene homologation,[7] the Dieckmann condensation,[8] and so on.[9] In addition, Paquette and coworkers have recently published an elegant synthetic method,[10] which involves 9-methyl-9-aza-3-oxabicyclo-[3.3.1]nonan-7-one[11] (**3**) as an intermediate, prepared by the Robinson-Schöpf condensation, and leads to formation of 7,8-dihydro-2*H*-oxocin-3(4*H*)-one (**4**). While compound **4** possesses a most appropriate framework for the preparation of **2**, we first attempted to synthesize the compound in a manner analogous to the biogenesis, because "laurediols" (**5**), polyenyne glycols regarded as one of the precursors of the titled compounds, had been isolated from the seaweed.[12]





3 R=H
19a R=C_2H_5, *trans*
19b R=C_2H_5, *cis*

4 R=H
38a R=C_2H_5, *trans*
38b R=C_2H_5, *cis*

The preparation of undeca-5,8-dien-3-ol (**6**) a "laurediol" analog for **2**, was carried out as follows. The Grignard reagent from hex-1-yn-4-ol[13] (**7**) was coupled[14] with *trans*-pent-2-enyl bromide[15] (**8**) over cuprous bromide as catalyst to give *trans*-undec-8-en-5-yn-3-ol (**9**), oil, in 65% yield, which on hydrogenation over Lindler catalyst[16] afforded **6**, oil, in almost quantitative yield. Attempted cyclization reactions of **6** with lead tetraacetate or with hypobromous acid afforded complex tarry material, which resisted further purification. Compound **9** was then oxidized with

$C_2H_5CH^{t}{=}CHCH_2CH^{c}{=}CHCH_2CH(OH)R$

5 R=$CH(OH)CH_2CH{=}CH{-}C{\equiv}CH$

6 R=C_2H_5

$C_2H_5CH^{t}{=}CHCH_2C{\equiv}CCH_2CH(OH)C_2H_5$

9

$C_2H_5CH(\diagup O\diagdown)CHCH_2C{\equiv}CCH_2CH(OH)C_2H_5$

10

$C_2H_5CH(\diagup O\diagdown)CHCH_2CH^{c}{=}CHCH_2CH(OH)C_2H_5$

11

$C_2H_5{-}CH(OR){-}CHCH_2CH^{c}{=}CHCH_2CH(OH)C_2H_5$

15 R=CH_3

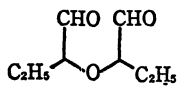
16 R=C_4H_9

17 R=$CH_3C_6H_4SO_2$

18 RO=Cl

perbenzoic acid to the 8,9-epoxide (**10**), which was converted by hydrogenation under the same conditions as **9** into 8,9-epoxyundec-5-en-3-ol (**11**) in 95% yield from **9**. This was further hydrogenated over Adams platinum to give 8,9-epoxyundecan-3-ol (**12**). Treatment of **11** with potassium hydroxide in refluxing aqueous DMSO resulted in no expected cyclization and produced undeca-4,6-diene-3,9-diol (**13**). The same treatment of saturated epoxide (**12**), however, led to simple cleavage of the epoxy ring, giving undecane-3,4,9-triol (**14**), mp 91—93 °C. Likewise, unsaturated epoxide (**11**), when treated with sodium methoxide in refluxing methanol or with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, afforded the corresponding unsaturated alkoxyglycols (**15** and **16**). Furthermore treatment of **11** with acids, *p*-toluenesulfonic acid in benzene or hydrogen chloride in methanol, also effected only the cleavage of the epoxy ring to give unsaturated triol monotosylates (**17**) or diol chlorides (**18**). Thus, all attempts to cyclize **11** to hydrooxocins under various conditions failed.

The synthesis of compound **2** was then undertaken by a modification of the Paquette procedure,[10] which required the preparation of 2,4-diethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-ones (**19**) as key intermediates. Attempted preparation of 2,4-diethyl-3-oxaglutaraldehydes (**20**), necessary as the starting substance for **19**, by the Williamson synthesis of methyl acetal[17] of 2-hydroxybutyraldehyde (**21**) and that[17] of 2-chlorobutyraldehyde (**22**) with bases (NaH) followed by acid treatment gave only tarry material. On the other hand, the Robinson-Schöpf condensation of **21** with methylamine and acetonedicarboxylic acid afforded a basic mixture, which was expected to contain piperidone derivatives (**23**) convertible into bicyclononanones **19** by ring closure. However, attempted formation of cyclic ethers **19** by tosylation of the basic mixture followed by base treatment[18] or by acid treatement[19] again failed; only a small amount of non-basic, undecane-3,6,9-trione (**24**), mp 78—80 °C, was isolated by chromatography of the tarry product.



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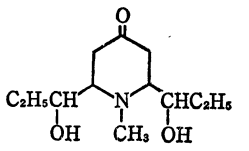

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25

The synthesis of bicyclononanones **19** was finally achieved as described below. Treatment of furan (1 mol) with bromine (1 mol) at −40——45 °C in ether produced 2,5-dibromofurans,[20] which were treated with ethyl magnesium bromide (2 mol) at −40——10 °C.[21] The resulting 2,5-diethyl-2,5-dihydrofurans (**25**), bp 51—54 °C/35 mmHg, obtained in 20% yield, were ozonized at −78 °C in ethyl acetate to give oxaglutaraldehydes **20** in 70% yield. This dialdehyde mixture (**20**) reacted with methylamine and acetonedicarboxylic acid in an aqueous buffered solution of pH 5.0 at room temperature for 43 hr[11] to give basic products, from which a mixture of *trans*- and *cis*-2,4-diethylbicyclononanones (**19a** and **19b**), showing the same R_f value on tlc, was separated after chromatography. While the *trans*-isomer (**19a**), mp 89—90 °C, could be isolated in 9.8% yield from furan by fractional recrystallizations of the mixture, the *cis*-isomer (**19b**), mp 86—88 °C, was obtained in 1.8% yield in pure state as follows. The mixture of **19a** and **19b**, freed from pure **19a** obtained by the recrystallizations, was reduced with lithium aluminum hydride (LAH) to give a mixture of alcohols, from which two alcohols could be isolated by preparative tlc. The more polar alcohol (**26b**) was converted into the *cis*-ketone (**19b**) with chromic anhydride–pyridine complex in dichloromethane,[22] and the less polar alcohol (**26a**) into the *trans*-ketone (**19a**) by the same treatment (15 min). Interestingly, the latter alcohol (**26a**), when treated for a long time (overnight) under the oxidation conditions, produced *N*-formyl ketone (**27a**) in good yield. This compound (**27a**) showed two singlets (1H in total) due to a formyl proton in the NMR spectrum, which would result from slow rotation of the bond between the carbonyl carbon and nitrogen atoms.[23]

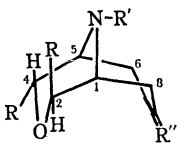
The *trans*- and *cis*-configurations of two ethyl groups in compounds **19a** and **19b** were deduced from the NMR spectra. These spectra, coupled with spin decoupling and/or contact shift [Eu(dpm)$_3$] studies, were interpreted by comparison with those of closely related compounds **28**,[24] **29**,[25] **30**[26] and **31**,[27] as well as by consideration of the influence of alkyl substituents on the chemical shifts of cyclohexane ring protons,[28] and the result is summarized in Table 1. As shown in Table 1, the signals due to equatorial and/or axial protons at C_1, C_2 and C_8 coincided with the corresponding protons at C_5, C_4 and C_6 in the spectrum of **19b**, indicating the existence of a plane of symmetry in the molecule. On the other hand, this equivalency was not observed in the spectrum of **19a**. Thus the two ethyl groups at C_2 and C_4 in question must be *cis*-oriented (β and β or α and α) in **19b**, and *trans*-oriented in **19a** (β and α or α and β). Since *cis*-2-acetoxy-4-ethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-one (**32**) exists in a double-chair conformation irrespective of the presence of the diaxial 2,4-substituents,[29] these and unsubstituted compounds (**19a**, **19b** and **3**) would undoubtedly adopt the double-chair conformation. The remaining problem was the conformation (and hence the configuration) of the two ethyl groups of **19b**. Judging from only the coupling constants, $J_{1,2}$ and $J_{4,5}$ (each 2 Hz) in **19b** and $J_{1,2}$ (0 Hz) and $J_{4,5}$ (2 Hz) in **19a**, it might not be unreasonable to assign equatorial conformations (α-configurations) to both the ethyl groups of the *cis*-isomer (**19b**). However, the constants in question depend delicately on the whole conformational change.[26] Furthermore, the ethyl methylene protons of **19b** (*cis*) appeared at remarkably low fields, as compared with those of **19a** (*trans*), the difference in δ-value being 0.20—0.35 ppm. In general, axial methyl protons at the α-carbon atom in oxacyclohexane systems absorb at lower fields than the corresponding equatorial protons[30] and are also deshielded when disposed 1,3-diaxially (*syn*-axially) to other methyl protons[31] and/or nitrogen lone pair electrons.[32] These facts strongly suggested that each of the relevant ethyl groups in **19b** would probably take an axial (and

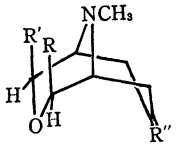
Table 1. The NMR spectra of 9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-ones[a)]

Protons	Chemical shift (δ) Compounds			J	Coupling constants[b,c)] (Hz) Compounds		
	3	**19a**	**19b**		**3**	**19a**	**19b**
H_1	3.00 br d,	2.76 br d,	2.82 br d,	$J_{1,2e}$	0.0	0.0	2.0
H_5	3.00 br d,	2.76 br d,	2.82 br d,	$J_{5,4e}$	0.0	—	2.0
H_{2e}	3.62 d,	3.36 do d,	3.00 do t,	$J_{1,2a}$	1.0	—	—
H_{4e}	3.62 d,	— —	3.00 do t,	$J_{5,4a}$	1.0	2.0	—
H_{2a}	3.71 br d,	— —	— —	$J_{1,8e}$	0.0	0.0	0.0
H_{4a}	3.71 br d,	3.57 do do d,	— —	$J_{5,6e}$	0.0	0.0	0.0
H_{6e}	2.12 d,	1.96 d,	1.92 d,	$J_{1,8a}$	6.0	6.0	6.0
H_{8e}	2.12 d,	2.04 d,	1.92 d,	$J_{5,6a}$	6.0	4.0	6.0
H_{6a}	2.61 do d,	2.55 do d,	2.51 do d,	$J_{2,H}$	—	8.0	6.5
H_{8a}	2.61 do d,	2.30 do d,	2.51 do d,			6.0	6.5
			1.62 qui,	$J_{4,H}$	—	9.0	6.5
$CH_3\underline{C}H_2$	— —	1.40 m,	1.60 qui,			5.0	6.5
$\underline{C}H_3CH_2$	— —	0.89 t,	0.89 t,	$J_{6a,6e}$	15.5	15.5	15.5
NCH_3	2.56 s,	2.48 s,	2.61 s,	$J_{8a,8e}$	15.5	15.5	15.5

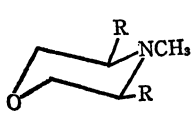
a) The spectra were measured in CCl_4 at 100 MHz, and the abbreviations "H_{2e} and $J_{1,2e}$" refer to "equatorial proton at C_2 and coupling constant between H_1 and H_{2e}," respectively. b) The coupling constants were estimated by first-order approximations. c) The coupling constant, $J_{2a,2e}$ and $J_{4a,4e}$, in compound **3** were 11.5 and 11.5 Hz.

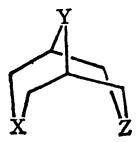
hence a β-configuration) rather than an equatorial conformation. The spectrum of the *trans*-isomer(**19a**) could be understood well on the same ground. This conformational assignment was consistent with that to the 7-deoxo derivatives (**33a** and **33b**) of **19a** and **19b**, which would also exist in a double-chair conformation; that is, the C_2- and C_4-proton signals were observed at δ 3.46 and 3.68 in the NMR spectrum of the *trans*-isomer (**33a**), while the corresponding signals coincided and appeared at higher field, δ 3.14, in that of *cis*-isomer (**33b**). The ethyl methylene protons in question of the *trans*-isomer (**33a**) were found by spin decoupling studies to be coupled to these C_2 and C_4 protons at higher field (near δ 1.35) than those of the *cis*-isomer **33b** (near δ 1.70).





19a R=C_2H_5, R'=CH_3, R''=O
19b R=R'=C_2H_5, R''=O
26a R=C_2H_5, R'=CH_3, R''=β-H, α-OH
26b R=R'=C_2H_5, R''=β-H, α-OH
27a R=C_2H_5, R'=CHO, R''=O
32b R=CH_2OCOCH_3, R'=C_2H_5, R''=O
33a R=C_2H_5, R'=CH_3, R''=H_2
33b R=R'=C_2H_5, R''=H_2

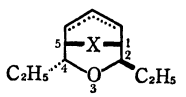


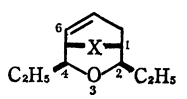


28 R=H
29 R=CH_3
30 X=O, Y=Z=CH_2
31 X=CH_2, Y=NCH_3, Z=O

Compound **19a** was reduced with lithium aluminum hydride in refluxing ether to give an epimeric alcohol mixture, consisting mainly of α-alcohol[11,26)] (**26a**). This alcohol mixture was dehydrated with sulfuric acid in acetic acid at 155 °C[33)] and produced a mixture of diastereoisomeric olefins (**34a**) in 95% yield from **19a**. This olefin mixture (**34a**) was converted quantitatively into the saturated *trans*-compound (**33a**) by hydrogenation over platinum in ethanol. Likewise, *cis*-ketone (**19b**) was convered into an epimeric alcohol mixture (main, **26b**) and then dehydrated under the comparable conditions to give an olefin (**34b**) in 90% yield, which on hydrogenation formed the *cis*-saturated compound (**33b**).

trans- and *cis*-Olefins (**34a** and **34b**) were converted into the corresponding methiodides, *trans*- (**35a**, a mixture of diastereoisomers), mp 179—182 °C, and *cis*-isomers (**35b**), mp 190—191 °C. These methiodides were submitted to the Hofmann degradation under the carefully controlled conditions to give *trans*- (**36a**, a mixture of diastereoisomers), oil, and *cis*-2,8-diethyl-3-dimethylamino-3,8-dihydro-2*H*-oxocins (**36b**), oil, in good yields, respectively.



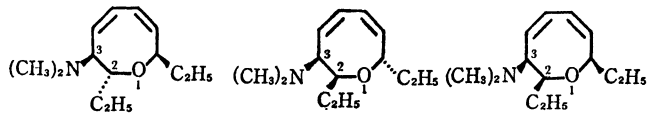


34a X=NCH_3
34b X=NCH_3
35a X=$\overset{+}{N}(CH_3)_2$ I^-
35b X=$\overset{+}{N}(CH_3)_2$ I^-

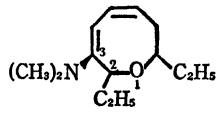
Heating of *cis*-aminodiene (**36b**), with 3-dimethylamino, and 2- and 8-ethyl groups all β-oriented, at 120—125 °C for 15 min resulted in facile intramolecular dienyl 1,5-hydrogen transfer, giving *cis*-dienamine (**37b**), oil, as a single product in almost quantitative yield. To the contrary, conversion of a mixture of *trans*-aminodienes (**36a**), one with the three groups β-, α- and β-oriented and the other with those β-, β- and

α-oriented, into the desired *trans*-dienamine (**37a**), oil, did not proceed smoothly as expected under the comparable conditions. The product was a multi-component mixture including **37a**, which was estimated to account for at most 60% of the total bases under the best conditions examined. The difference in reactivity between *trans*- and *cis*-aminodienes (**36a** and **36b**) indicated that this thermally induced, α-oriented-hydrogen shift from C_3 to C_7 in *trans*-isomer (**36a**), presumably concerted and suprafacial [1,5] sigmatropic rearrangement,[34] would be hindered by the presence of an α-oriented ethyl group either at C_2 or C_8.[35]

These *trans*- (without further purification) and *cis*-dienamines (**37a** and **37b**) were hydrolyzed in refluxing dil fluoroboric acid and produced *trans*- and *cis*-2,8-diethylhydrooxocinones (**38a** and **38b**), both oil, in 18 and 45% yields from bicyclononanones (**19a** and **19b**), respectively. In accordance with the assigned structures, both β,γ-unsaturated ketones (**38a** and **38b**) displayed absorption maxima near 310 nm (ε= 50—200) and near 1715 and 1650 cm^{-1} in the UV and IR spectra. Interestingly, the UV absorption intensity (ε 90—162) of the latter (**38b**) was about twice stronger than that (50—100) of the former (**38a**), indicative of larger overlap of π-electrons of the double bond and carbonyl group in *cis*-isomer (**38b**) as compared with that in *trans*-isomer (**38a**).

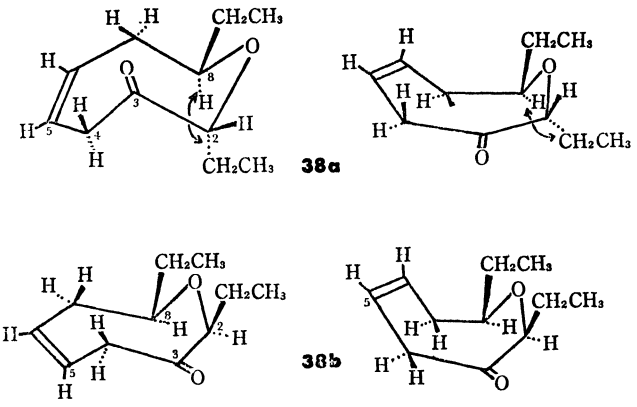


36a **36b**



37a *trans*
37b *cis*

The NMR spectra of these isomers (**38a** and **38b**) indicated a noteworthy difference concerning the C_4-protons. The protons of the latter (**38b**) appeared at δ 2.78 and 3.82 as two doublets with the same vicinal coupling constants of 6 Hz ($J_{4,5}$), while those of the former (**38a**) at δ 2.93 and 3.52 as two double doublets with different vicinal coupling constants ($J_{4,5}$) of 3 and 2 Hz. If the Karplus equation[36] held for the constants in question, the observed values suggested that the dihedral angles between the C_4- and C_5-protons would become about 30° and 150° in the *cis*-isomer (**38b**), and the corresponding angles about 65° and 55° in the *trans*-isomer (**38a**). These angles implied that the olefinic proton at C_5 in *cis*-isomer (**38b**) would be located in the outer side of two planes formed by the two carbon at C_4 and C_5 and each of two hydrogen atoms at C_4 and that in *trans*-isomer (**38a**) in the inner side of the planes. On the other hand, the two ethyl groups would reasonably be oriented towards the outer side of the ring in each of the isomers so as to decrease the possible serious steric interaction. Examination of



38a **38b**

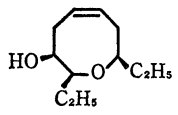
Fig. 1.

the Dreiding model, considering these dispositions as well as the UV intensities, indicated that only two forms as shown in Fig. 1 were possible as plausible conformations for each of the *trans*- and *cis*-hydrooxocinones (**38a** and **38b**). These conformations suggested that the *trans*-ketone (**38a**) would be less stable than the *cis*-ketone (**38b**), because the α-ethyl group in either one of **38a** (Fig. 1) would be disposed 1,3-*syn*-axially to the α-oriented α-hydrogen to the oxygen atom. As expected, the *trans*-ketone (**38a**) was readily epimerized to the *cis*-isomer (**38b**) by treatment with base (5% KOH in ethanol, room temperature, 20 min) almost quantitatively. This isomerization was most valuable for further investigations, because the two side chains at C_2 and C_8 of laurencin (**1**) possesses the *cis*-configuration.

Reduction of *cis*-diethylhydrooxocin (**38b**) with sodium borohydride produced a mixture of alcohols, from which epimeric alcohols (**39** and **40**) were isolated after chromatography in 50 and 15% yields, respectively. These alcohols (**39** and **40**) displayed characteristic peaks due to one of the C_4-protons and the C_3-proton in the NMR spectra; the major alcohol (**39**) showed a double doublet (J=8 and 12 Hz) and a multiplet at δ 2.63 and 3.68, and the minor alcohol (**40**) a double doublet (J=3, 7 and 13 Hz) and a double triplet (J= 3, 3 and 9 Hz) at δ 2.81 and 3.75, respectively. The observed signal patterns in the latter (**40**), apart from the chemical shifts, were completely superimposable over those of the corresponding protons (C_4- and C_3-protons) in laurencin (**1**), indicating that the minor alcohol (**40**) possessed the same relative configuration as to the three substituents as **1**, while the major alcohol (**39**) took the different configuration only at the carbon atom bearing the hydroxy group.

The major alcohol (**39**) was then treated with carbon tetrabromide and triphenylphospine to give bromohydrooxocin (**2**), oil, as an only isolable product in moderate yield, which showed a pair of molecular ion peaks at m/e 248 and 246 in the mass spectrum. Since this bromination usually proceeds in S_N2 manner,[37] the C_3-configuration of **2** was expected to be inverted. In fact, compound **2** revealed a clear, double triplet with coupling constants of 3, 3 and 9 Hz at δ 4.05 due to the C_3-proton, though the C_4-proton in question near δ 3.15 was not discernible as a separate peak owing to overlap with the C_2- and C_8-protons. Thus, bromodiethylhydrooxocin (**2**) took the same relative

configuration concerning the three substituents at C_2, C_3 and C_8 as the aimed natural compound, laurencin (**1**).



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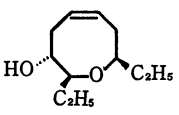

40

Experimental

All the mps and bps were uncorrected. The homogenity of each compound was always checked by tlc over silica gel (Wakogel B-5) and/or by glc (Hitachi K-53) over 10% SE-30. Column chromatographies were carried out over silicic acid (Merck, Kieselgel 60 or Mallinckrodt, silicic acid 100 Mesh). The UV and IR spectra were measured in ethanol and carbon tetrachloride, respectively, unless otherwise stated. The NMR spectra were obtained in carbon tetrachloride, unless otherwise stated, at 100 MHz, and the chemical shifts were given in δ-values, TMS being used as an internal standard. The abbreviations "s, d, t, q, qui, m, br, and do" in the NMR spectra denote "singlet, doublet, triplet, quartet, quintet, multiplet, broad, and double," respectively.

(E)-Undec-8-en-1-yn-3-ol (9). A stirred solution of hex-1-yn-4-ol[13] (**7**, 5.5 g) in anhydrous ether (50 ml) was mixed with ethyl magnesium bromide, prepared from ethyl bromide (13 g) and magnesium turnings (2.8 g) in ether (90 ml), and refluxed until evolution of ethane ceased. To the mixture cooled at 0 °C were added *trans*-pent-2-enyl bromide[15] (**8**) (9.4 g) and anhydrous cuprous chloride (0.6 g).[14] The whole mixture was refluxed for 2.5 hr, then stirred at room temperature for 14 hr and, after being cooled, treated with aqueous saturated ammonium chloride. After separation of the ether layer, the aqueous layer was extracted with ether repeatedly. All the ether solutions were combined, washed with 1 M hydrochloric acid, 5% aqueous sodium bicarbonate and water, dried over sodium sulfate, and evaporated to leave oil, which was distilled to give **9** (6.12 g), bp 111—114 °C/20 mmHg; IR, ν_{max} 3540, 2200, 1061, and 967 cm^{-1}; NMR (CCl_4 and D_2O), δ 0.93 and 0.98 (total 6H, each t J=7 Hz, $2CH_2C\underline{H}_3$), 1.49 and 2.02 (each 2H, qui J=7 Hz, $C\underline{H}_2$ at C_2 and C_{10}), 2.28 and 2.82 (each 2H, m, $C\underline{H}_2$ at C_4 and C_7), 3.55 [1H, qui J=6.5 Hz, $C\underline{H}$(OH)], 5.30 and 5.64 (each 1H, do t, J=14, 5, 5 and 14, 7, 7 Hz, $C\underline{H}$=$C\underline{H}$). Found: C, 79.35; H, 10.68%. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92%.

The acetate (**9a**) was prepared quantitatively by treatment of **9** (0.1 g) with acetic anhydride (1.0 ml) and pyridine (1.0 ml) at room temperature overnight; IR ($CHCl_3$), ν_{max} 1730, 1021, and 965 cm^{-1}; NMR, δ 1.97 (3H, s, $OCOC\underline{H}_3$), and 4.72 [1H, qui, J=6.5 Hz, $C\underline{H}$(OCOCH$_3$)].

(5Z,8E)-Undeca-5,8-dien-3-ol (6). Hydrogenation of **9** (1.0 g) was carried out over Lindlar catalyst[16] (1.5 g) at room temperature in ethanol and ceased after 1.5 hr, when 150 ml of hydrogen (1.0 mol) had been consumed. After removal of the catalyst and solvent, the residue was dissolved in dichloromethane, washed with saturated sodium chloride and water, dried and evaporated to dryness to give **6** (1.0 g); IR, ν_{max} 3570, 3470, 1015, and 968 cm^{-1}, NMR (CCl_4 and D_2O), δ 0.93 and 0.97 (total 6H, each t J=6.5 Hz, $2CH_2C\underline{H}_3$), 1.41 (2H, qui J=6.5 Hz, $C\underline{H}_2$ at C_2), 1.96 (2H, m, $C\underline{H}_2$ at C_{10}), 2.16 (2H, t J=6.5 Hz, $C\underline{H}_2$ at C_4), 2.73 (2H, br t J=4.5 Hz, $C\underline{H}_2$ at C_7), 3.45 [1H, qui J=6.5 Hz, $C\underline{H}$(OH)], and 5.38 [4H, m, 2($C\underline{H}$=$C\underline{H}$)]. Found: C, 78.78; H, 11.80%. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98%.

(Z)-8,9-Epoxyundec-5-en-3-ol (11). To a solution of **9** (2.5 g) in chloroform (60 ml) was added perbenzoic acid (3.0 g) at 0 °C, and the solution was allowed to stand in a refrigerator for 20 hr. The reaction mixture was worked up as usual to yield 8,9-epoxyundec-5-yn-3-ol (**10**, 2.7 g); IR ($CHCl_3$), ν_{max} 3420, 974, 939, 908, and 878 cm^{-1}; NMR ($CDCl_3$ and D_2O), δ 0.94 and 0.99 (total 6H, each t J=7 Hz, $2C\underline{H}_3CH_2$), 1.57 and 1.60 (total 4H, each qui J=6.5 Hz, $2CH_3C\underline{H}_2$), 2.40 (4H, m, $2C\underline{H}_2$ at C_4 and C_7), 2.84 (2H, m, 2C$\underline{H}$ at C_8 and C_9), 3.62 [1H, qui J=6.5 Hz, $C\underline{H}$(OH)]. Found: C, 71.35; H, 11.16%. Calcd for $C_{11}H_{20}O_2$: C, 71.59; H, 10.94%.

Compound **10** (1.4 g) was hydrogenated over Lindlar catalyst (2.3 g) in the same manner as **9** and afforded **11** (1.35 g); IR, ν_{max} 3440, 974, and 888 cm^{-1}; NMR (CCl_4 and D_2O), δ 0.92 and 0.96 (total 6H, each t J=6 Hz, $2C\underline{H}_3CH_2$), 1.42 (4H, m, $2CH_3C\underline{H}_2$), 2.22 (4H, m, $2CH_2$ at C_4 and C_7), 2.62 (2H, m, 2C$\underline{H}$ at C_8 and C_9), 3.43 [1H, qui J=6 Hz, $C\underline{H}$(OH)], and 5.48 (2H, m, $C\underline{H}$=$C\underline{H}$). Found: C, 70.68; H, 12.16%. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%.

8,9-Epoxyundecan-3-ol (12). Compound **11** (320 mg) in ethanol (10 ml) was hydrogenated over Adams platinum (105 mg as $PtO_2 \cdot H_2O$) at room temperature. The reaction was ceased after 1.5 hr, when 44 ml of hydrogen (1.0 mol) had been absorbed. After being worked up as usual, the reaction mixture gave **12** (330 mg); IR ($CHCl_3$), ν_{max} 3590, 3430, 960, and 893 cm^{-1}. Found: C, 69.88; H, 12.68%. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85%.

Undeca-4,6-diene-3,8-diol (13). A solution of **11** (60 mg) in a mixture of dimethyl sulfoxide (DMSO, 20 ml), potassium hydroxide (1 g) and water (10 ml) was heated at 155—160 °C for 3 hr. After being cooled, the reaction mixture was poured onto ice and extracted with chloroform repeatedly. The chloroform extracts were washed with 2 M hydrochloric acid, 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated to give **13** (53 mg); IR, ν_{max} 3530, 3370, 1055, 990, and 951 cm^{-1}, which was treated with acetic anhydride (0.6 ml) and pyridine (0.6 ml) at room temperature for 4.5 hr to yield the diacetate (**13a**, 56 mg); UV, λ_{max} 231 nm (ε 15600); IR, ν_{max} 1736, 1224, and 1007 cm^{-1}; NMR, δ 0.90 and 0.92 (total 6H, each t J=6.5 Hz, $2C\underline{H}_3CH_2$), 1.58 (4H, br m, $2CH_3C\underline{H}_2$), 1.97 and 2.01 (total 6H, each s, $2C\underline{H}_3COO$), 2.41 (2H, br t J=6.5 Hz, $C\underline{H}_2$ at C_4), 4.77 and 5.28 [each 1H, qui and q J=6.5 Hz, $2C\underline{H}$(OCOCH$_3$)], and 4.30 (4H, m, 2C$\underline{H}$=C$\underline{H}$). Found: C, 66.86; H, 9.11%. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

Undecane-3,4,9-triol (14). Compound **12** (200 mg) was treated with the afore-mentioned alkaline DMSO solution (45 ml) in the same manner as **11**. The reaction mixture was worked up as usual to leave oily residue, which showed a practically single spot on tlc and crystallized on trituration with ether. The crystalline material was recrystallized from ether-hexane to give **14** (45 mg), mp 91—93 °C; IR (Nujol), ν_{max} 3280, 1072, and 969 cm^{-1}. Found: C, 64.80; H, 11.68%. Calcd for $C_{11}H_{24}O_3$: C, 64.71; H, 11.76%.

The triacetate (**14a**) showed the following spectra; IR ($CHCl_3$), ν_{max} 1723 cm^{-1}; NMR, δ 0.88 and 0.90 (total 6H, each t J=7 Hz, $2C\underline{H}_3CH_2$), 1.45 (12H, br m, $6C\underline{H}_2$), 2.03 (9H, s, $3C\underline{H}_3COO$), and 4.85 [3H, br m, 3C$\underline{H}$(OCOCH$_3$)].

Treatment of 11 with Sodium Methoxide. Compound **11** (115 mg) was refluxed in a methanol solution containing sodium methoxide, prepared from sodium (345 mg) and methanol (15 ml), for 18 hr. The mixture was worked up as usual to give oil, which showed a single spot on tlc and

was identified as unsaturated methoxyglycols (**15**) on the spectral data; IR, ν_{max} 3420 and 1100 cm^{-1}; NMR (CCl_4 and D_2O), δ 0.93 (6H, t J=7 Hz, $2C\underline{H}_3CH_2$), 1.45 (4H, br m, $2CH_3C\underline{H}_2$), 2.18 (4H, br m, $2C\underline{H}_2CH{=}CH$), 3.33 (3H, s, $C\underline{H}_3O$), 3.52 (3H, br, 3C$\underline{H}$ at C_3, C_4 and C_9), and 5.48 (2H, m, C$\underline{H}$=C$\underline{H}$).

Treatment of ***11*** *with* p-*Toluenesulfonic Acid.* A solution of **11** (400 mg) in dry benzene (35 ml) containing *p*-toluenesulfonic acid (38 mg) was refluxed for 20 hr and, after being cooled, washed with a 5% sodium bicarbonate solution, dried and evaporated to leave oil (380 mg), which was found to consist of two components by tlc. The oil was separated into two fractions by chromatography over silicic acid (Mallinckrodt, 10 g) with a 3 : 1 mixture of benzene and ethyl acetate. The more polar fraction (197 mg) was identical with the unreacted starting epoxide **11**, and the less polar was identified as undecenetriol monotosylate(s) (**17**, 87 mg); IR, ν_{max} 3360, 1188, and 1176 cm^{-1}; NMR, δ 0.92 (6H, t J= 6.5 Hz, $2C\underline{H}_3CH_2$), 1.32 and 2.06 (4H and 2H, br, $3C\underline{H}_2$), 2.43 (3H, s, $C\underline{H}_3C_6H_4$), 3.50 [2H, m, $2C\underline{H}(OH)$], 4.40 [1H, m, $C\underline{H}(OSO_2)$], 4.61 (2H, br s, $2O\underline{H}$), 5.43 (2H, br, C$\underline{H}$=C$\underline{H}$), and 7.25 and 7.75 (each 2H, ABq J=8.5 Hz, $C_6\underline{H}_4$).

*The Robinson-Schöpf Condensation of 2-Hydroxybutyraldehyde (****21****) Followed by Acid Treatment.* The aldehyde (**21**) was prepared from the dimethyl acetal[17]; IR, ν_{max} 3600, 3490, 1079, 1062, and 970 cm^{-1}; NMR, δ 0.93 (3H, t J=7 Hz), 2.40 (1H, br s, disappeared on addition of D_2O), 3.32 and 3.37 (each 3H, s), and 4.03 (1H, d J=6 Hz), and was used for the next reaction without isolation. A solution of the acetal (13.5 g) in acetic acid (2.5 ml) and water (10 ml) was refluxed for 50 min and, after being cooled, poured into an aqueous solution (125 ml) containing anhydrous disodium phosphate (14.6 g) and citric acid (9.4 g). After addition of methylamine hydrochloride (6.1 g) and acetonedicarboxylic acid (14.6 g), the solution was adjusted to pH 5.0 by addition of aqueous sodium hydroxide, then diluted with water to 250 ml of the total volume, and stirred at room temperature for 48 hr. The solution was made acidic and shaken with dichloromethane to remove neutral and acidic substances. The acidic solution was made strongly basic and extracted with dichloromethane repeatedly. The dichloromethane solutions were combined and evaporated to leave dark brown oil, which was mixed with 20% sulfuric acid (20 ml). The mixture was refluxed for 2 hr, cooled, made basic, and again extracted with dichloromethane. The extracts were dried and evaporated to leave brown oil (3.9 g), which was chromatographed over silicic acid (Mallinckrodt, 100 g), using benzene–ethyl acetate (6 : 1). Several fractions gave crystalline material, which on recrystallization from hexane yielded undecane-3,6,9-trione (**24**) (0.34 g), mp 78—80 °C; IR ($CHCl_3$), ν_{max} 1714 cm^{-1}; NMR ($CDCl_3$), δ 1.05 (6H, t J= 7 Hz), 2.47 (4H, q J=7 Hz), and 2.70 (8H, s). Found: C, 66.62; H, 9.03%. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09%.

Compound **24** (55 mg) in dry methanol (10 ml) was reduced with sodium borohydride (100 mg) at 0 °C for 35 min and afforded oily alcohol (64 mg), which was treated with acetic anhydride (1.0 ml) and pyridine (1.5 ml) at room temperature overnight to give undecane-3,6,9-triol triacetate (88 mg), oil; IR, ν_{max} 1741, 1247, and 1018 cm^{-1}; NMR ($CDCl_3$), δ 0.88 (6H, t J=7 Hz), 2.02 (9H, s), and 4.81 (3H, m W_H=14 Hz). Found: C, 61.58; H, 9 02%. Calcd for $C_{17}H_{30}O_6$: C, 61.79; H, 9.15%. The triacetate (78 mg) was hydrolyzed with 5% potassium hydroxide in refluxing methanol (45 min) to give the triol (50 mg), which was reconverted into **24** (37 mg), mp 78—79 °C, by oxidation with Jones reagent (0.5 ml) in acetone (8 ml) at 0 °C for 1.75 hr.

trans- *and* cis-*2,5-Diethyl-2,5-dihydrofurans (****25****).* To a solution of freshly distilled furan (42 g) in ether (800 ml) cooled at −45 °C was dropwise added bromine (28 ml), and the solution was stirred at the temperature for 10 min. To the solution was added the Grignard reagent, prepared from ethyl bromide (210 g) and magnesium turnings (40.0 g) in ether (1000 ml), under stirring at such a rate that the temperature did not exceed −10 °C, and the whole mixture was kept at room temperature overnight. After careful addition of water under cooling to decompose excess of the Grignard reagent, the ether layer was separated, and the aqueous layer was extracted with ether. The ether solutions were combined, washed with water, dried and evaporated to leave oily residue, which was distilled to give **25** (25.0 g), bp 51—54 °C (35 mmHg); δ 0.88 (6H, t J=7 Hz), 1.50 (4H, m), 4.65 (2H, m), and 5.70 (2H, s). Found: C, 76.36; H, 11.02%. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18%.

trans- *and* cis-*2,4-Diethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]-nonan-7-ones (****19a*** *and* ***19b****).* Into a solution of **25** (11.0 g) in ethyl acetate (350 ml) cooled at −78 °C was bubbled ozone, until the solution became purplish. The solution was treated with potassium iodide and then with aqueous sodium thiosulfate at room temperature. The acetate solution was separated and the aqueous layer was extracted with ethyl acetate. The ethyl acetate solutions were combined, washed with water, dried and evaporated to leave crude 2,4-diethyl-3-oxaglutaraldehydes (**20**) (9.6 g), IR ($CHCl_3$), ν_{max} 1730 cm^{-1}, which were used for the next reaction without further purification.

To an aqueous solution (100 ml) containing anhydrous disodium phosphate (14.6 g) and citric acid (9.4 g) were added the crude aldehydes (**20**) (9.6 g), methylamine hydrochloride (6.1 g) and acetonedicarboxylic acid (14.6 g). The whole solution was adjusted to pH 5.0 by addition of conc sodium hydroxide solution, diluted with water to 250 ml of the total volume, and then stirred at room temperature for 43 hr. The reaction mixture, after being made acidic, was washed with ether, made basic and then extracted with chloroform repeatedly. The chloroform solutions afforded dark brown oil (8.4 g), which was separated by chromatography over alumina (Merck, 200 g), using benzene, benzene–ether (2 : 1, 1 : 1 and 1 : 2) and ether, successively. Fractions eluted with benzene and benzene–ether (2 : 1 and 1 : 1) gave oily (4.6 g) and crystalline bases (4.2 g), showing the same single spot on tlc. The latter was recrystallized twice from hexane to yield **19a** (2.5 g), mp 89—90 °C; Mass, *m/e* 211 (M^+) and 110 (base); IR (Nujol), ν_{max} 1705, 1164, 1059, 983, 908 and 843 cm^{-1}; NMR (Table 1). Found: C, 68.47; H, 10.29; N, 6.60%. Calcd for $C_{12}H_{21}O_2N$: C, 68.21; H, 10.02; N, 6.63%.

The remaining bases (1.7 g), obtained on the recrystallizations, were combined with the oily bases (4.6 g) and reduced with LAH (2.3 g) in ether (300 ml) at room temperature overnight and, after being worked up as usual, afforded a mixture of alcohols (6.3 g). These alcohols were separated into three fractions, more polar (0.5 g), middle (main **26b**, 1.8 g) and less polar fractions (main **26a**, 3.6 g), by preparative tlc (80 plates) over silica gel (Wakogel B-5), using ethanol as solvent; each plate was made of the gel (10 g) with area of 20×20 cm. The middle fractions (1.8 g) were oxidized with chromium trioxide (2.8 g), celite (4.5 g) and pyridine (4.5 ml) in dichloromethane (75 ml) at room temperature for 15 min. After removal of the celite by filtration, the dichloromethane solution was evaporated to leave oily residue, which was dissolved in chloroform and then extracted with dil hydrochloric acid. The acidic solution, after being

made basic, was extracted with chloroform repeatedly. The chloroform solution was washed with water, dried and evaporated to give crystalline substance, which on recrystallization from hexane yielded **19b** (1.0 g), mp 86—88 °C; Mass, *m/e* 211 (M^+) and 110 (base); IR (Nujol), ν_{max} 1714, 1167, 1026, 973, 917, and 853 cm^{-1}; NMR (Table 1). Found: C, 68.32; H, 10.20; N, 6.60%. Calcd for $C_{12}H_{21}O_2N$: C, 68.21; H, 10.02; N, 6.63%. The less polar fractions (3.6 g) were oxidized under the same conditions as mentioned above to give **19a** (1.9 g), mp 89—90 °C.

trans-*2,4-Diethyl-9-formyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-one* (***27a***). A solution of the crude *trans*-alcohol (main **26a**, 0.97 g) in pyridine (30 ml) was treated with chromium trioxide (3.0 g) at room temperature overnight and poured into ice-water. After being worked up as usual, the reaction mixture gave crude amide (0.88 g), which was purified by chromatography over silicic acid to yield **27a** (0.63 g), oil; Mass, *m/e* 225 (M^+); IR ($CHCl_3$), ν_{max} 1722 and 1663 cm^{-1}; NMR ($CDCl_3$), δ 8.12 and 8.26 (each s, total 1H).

trans-*2,4-Diethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]nonanes* (***34a***). A solution of **19a** (5.55 g) in ether (50 ml) was refluxed with LAH (2.0 g) for 16 hr. After addition of water, the resulting precipitate was removed by filtration and washed with ether. The filtrate was separated into aqueous and ether layers, and the aqueous layer was extracted with ether. All the ether solutions were combined, washed with water, dried and evaporated to give an epimeric alcohol mixture (main **26a**, 5.55 g), oil; Mass, *m/e* 213 (M^+) and 112 (base); IR, ν_{max} 3410, 1123, 1074, 1024, and 947 cm^{-1}; NMR, δ 0.92 (6H, t J=7 Hz, $2CH_2C\underline{H}_3$), 2.41 (3H, s, $NC\underline{H}_3$), 3.57, 3.71 and 3.64 (total 3H, do d J=6 and 9 Hz, do do d J=2, 5 and 8 Hz, and br, 3H at C_2, C_4 and C_7, respectively), 4.87 and 5.00 (total 1H, each s, O$\underline{H}$).

To the alcohol mixture (4.75 g) cooled in glacial acetic acid (1.87 g) was added dropwise conc sulfuric acid (6.11 g). The mixture was heated at 150 °C for 2.5 hr, cooled and poured into ice-water. The aqueous solution was made basic and filtered to remove a small amount of tarry substance. The filtrate was extracted with chloroform, and the chloroform solution gave **34a** (4.13 g), oil; Mass, *m/e* 195 (M^+) and 94 (base); IR, ν_{max} 1125, 1067, and 980 cm^{-1}; NMR, δ 0.87 (3H, t J=6 Hz, $2CH_2C\underline{H}_3$), 2.23 (3H, s, $NC\underline{H}_3$), 3.40 (2H, complex m, 2H at C_2 and C_4), 5.40 and 5.80 (each 1H, m, C$\underline{H}$=C$\underline{H}$). Found: C, 73.98; H, 10.55; N, 7.30%. Calcd for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17%.

cis-*2,4-Diethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]non-6-ene* (***34b***). A solution of **19b** (0.50 g) in ether (20 ml) was reduced with LAH (0.30 g) at room temperature for 17 hr. After being worked up as usual, the solution gave an epimeric alcohol mixture (main **26b**, 0.50 g), oil; Mass, *m/e* 213 (M^+) and 112 (base); IR, ν_{max} 3360, 1133, 1116, 1026, and 951 cm^{-1}; NMR, δ 0.91 (6H, t J=7 Hz, $2CH_2C\underline{H}_3$), 2.44 (3H, s, $NC\underline{H}_3$), 3.51 (2H, t J=7 Hz, 2H at C_2 and C_4), 3.30 and 3.75 (total 1H, each br, H at C_7), 4.92 and 5.04 (total 1H, each br s, O$\underline{H}$).

The alcohol mixture (0.50 g) was treated with conc sulfuric acid (0.60 g) and glacial acetic acid (0.20 g) at 160 °C for 2 hr. The mixture gave oily olefin (**34b**) (0.41 g); Mass, *m/e* 195 (M^+) and 94 (base); IR ($CHCl_3$), ν_{max} 1120, 1085, and 1050 cm^{-1}; NMR ($CDCl_3$), δ 0.94 (6H, t J=7 Hz, $2CH_2C\underline{H}_3$), 2.43 (3H, s, $NC\underline{H}_3$), 2.98 (1H, do d J=6 and 10 Hz, H at C_2 or C_4), 3.17 (1H, do t J=2, 7.5 and 7.5 Hz, H at C_4 or C_2), 5.64 and 5.72 (each 1H, ABq J=11 Hz, C$\underline{H}$=C$\underline{H}$). Found: C, 74.02; H, 10.83; N, 7.28%. Calcd for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17%.

trans- *and* cis-*2,4-Diethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]nonanes* (***33a and 33b***). A mixture of olefins (**34a**) (0.41 g) was hydrogenated over platinum (0.20 g as $PtO_2 \cdot H_2O$) in ethanol at room temperature for 1 hr, when 48 ml of hydrogen (1 mol) had been consumed. After removal of the catalyst, the mixture was evaporated, diluted with water, and extracted with chloroform. The chloroform solution was washed with water, dried and evaporated to give **33a** (0.40 g), oil; Mass, *m/e* 197 (M^+) and 96 (base); IR, ν_{max} 1180, 1066, and 862 cm^{-1}; NMR, δ 0.85 and 0.88 (total 6H, each t J=7 Hz, $2CH_2C\underline{H}_3$), 2.46 (3H, s, $NC\underline{H}_3$), 3.46 (1H, do d J=6 and 9 Hz, H at C_4 or C_2), and 3.68 (1H, do do d J=2.5, 6 and 8 Hz, H at C_2 or C_4).

Compound **34b** (60 mg) was hydrogenated over platinum (50 mg) in ethanol (10 ml) at room temperature for 17 hr, when 7 ml of hydrogen (1 mol) had been absorbed. The mixture afforded **33b** (43 mg), oil; Mass; *m/e* 197 (M^+) and 96 (base); IR, ν_{max} 1066 and 1036 cm^{-1}; NMR, δ 0.92 (6H, t J=7.5 Hz, $2CH_2C\underline{H}_3$), 2.57 (3H, s, $NC\underline{H}_3$), and 3.14 (2H, do t J=4, 7 and 7 Hz, 2H at C_2 and C_4).

trans- *and* cis-*2,4-Diethyl-9,9-dimethyl-9-azonia-3-oxabicyclo-[3.3.1]nonene Iodides* (***35a and 35b***). A *trans*-olefin mixture (**34a**, 3.64 g) was treated with methyl iodide (10 ml) in refluxing ethanol (40 ml) for 2 hr. The mixture was evaporated to leave crude methiodides (6.14 g), which crystallized on trituration with ether and were recrystallized from acetone-isopropyl ether to give **35a** (5.58 g) mp 179—182 °C; Mass, *m/e* 195 ($M^+ - CH_3I$), 142 (CH_3I), and 94; IR (Nujol), ν_{max} 1110, 1076, 998, and 914 cm^{-1}; NMR ($CDCl_3$), too complex to be interpreted. Found: C, 46.10; H, 7.28; N, 4.10%. Calcd for $C_{13}H_{24}ONI$: C, 46.26; H, 7.12; N, 4.15%.

A solution of *cis*-olefin (**34b**, 0.35 g) in ethanol (20 ml) was refluxed with methyl iodide (5 ml) to give crude methiodide (0.60 g), which crystallized on trituration with ether and was recrystallized from acetone-isopropyl ether to yield **35b** (0.52 g), mp 190—191 °C; Mass, *m/e* 195 (M^+—CH_3I), 142 (CH_3I), and 94 (base); IR (Nujol), ν_{max} 1135, 1112, 1078, 1030, and 993 cm^{-1}; NMR ($CDCl_3$), δ 1.00 and 1.04 (total 6H, each t J=7 Hz, $2CH_2C\underline{H}_3$); 3.50 and 3.73 (each 3H, s, $2NC\underline{H}_3$), 3.90 (1H, br t J=6 Hz, H at C_2 or C_4), 4.52 (1H, br s, W_H=7 Hz, H at C_4 or C_2), 5.90 and 5.93 (each 1H, ABq J=10 Hz, C$\underline{H}$=C$\underline{H}$). Found: C, 46.15; H, 7.26; N, 4.20%. Calcd for $C_{13}H_{24}ONI$: C, 46.26; H, 7.12; N, 4.15%.

trans- *and* cis-*2,8-Diethyl-3-dimethylamino-3,8-dihydro-2H-oxocins* (***36a and 36b***). An aqueous solution of **35a** (765 mg) was eluted through a column of Amberlite IRA-400 (hydroxide form). The alkaline eluate was evaporated below 45 °C under reduced pressure (below 15 mmHg) to leave the quarternary methoxide (**36a**), which was decomposed by heating at 45—50 °C under nitrogen (15 mmHg) for 10 min. The resulting liquid was extracted with ether, dried and evaporated to give **36a** (403 mg), oil; Mass, *m/e* 209 (M^+); IR, ν_{max} 1130, 1100, 1082, 1036, 1008, and 686 cm^{-1}; NMR δ 0.89 and 0.95 (total 6H, each t J=7 Hz, $2CH_2C\underline{H}_3$), 1.51 (4H, m, $2C\underline{H}_2CH_3$), 2.16 (6H, s, $2NC\underline{H}_3$), 3.31 (2H, m, 2H at C_2 and C_3), 4.18 (1H, br m, H at C_8), 5.22 (1H, do d J=3 and 12 Hz, H at C_4), 5.68 (2H, m, 2H at C_5 and C_6), and 6.06 (1H, do d J=5 and 12 Hz, H at C_7).

Compound **35b** (310 mg) was treated in the same manner as **35a** and afforded **35b** (159 mg), oil; Mass, *m/e* 209 (M^+); IR ($CHCl_3$), ν_{max} 1117, 1108, 1060, 1041, and 1016 cm^{-1}; NMR ($CDCl_3$), δ 0.99 and 1.02 (total 6H, each t J=7 Hz, $2CH_2C\underline{H}_3$), 1.54 (4H, m, $2C\underline{H}_2CH_3$), 2.20 (6H, s, $2NC\underline{H}_3$), 3.34 (1H, br do d J=5 and 7.5 Hz, H at C_3), 3.57 (1H, br do d J=2, 5 and 10 Hz, H at C_2), 4.03 (1H, br t J=7 Hz, H at C_8), 5.36 (1H, do d J=2 and 12 Hz, H at C_7), 5.46 (1H, do d J=7.5 and 12 Hz, H at C_4), 5.66 (1H, br do d J=5 and 12 Hz, H at C_5), and 6.04 (1H, br do d J=5 and 12 Hz,

H at C_6).

*trans- and cis-2,8-Diethyl-3-dimethylamino-7,8-dihydro-2H-oxocins (**37a** and **37b**).* Compounds **36a** (1.40 g) were heated at 120—125 °C (bath temperature) for 15 min under nitrogen to give a 4 : 6 mixture (1.40 g) of unidentified product(s) (**38**) and **37a**. The ratio was estimated by comparison of the signals due to dimethylamino groups in the NMR spectrum of the whole reaction product with that in the spectrum of **38**, which remained unchanged as basic component(s) in the next transformation of **37a** to **38a**. Treatment of **36a** under other conditions [heating at 105 °C for 2 hr, heating at 145 °C for 2 min, or distillation *in vacuo* (15 mmHg) at 110 °C (each bath temperature)] did not increase the yield of **37a**. Compound **37a** showed the following spectra; IR, ν_{max} 1603 and 1063 cm^{-1}; NMR, δ 0.82 and 0.90 (total 6H, each t J=7 Hz, $2CH_2CH_3$), 1.36 (4H, complex m, $2CH_2CH_3$), 2.30 (2H, m, 2H at C_7), 2.56 (6H, s, $2NCH_3$), 2.65 (1H, m, H at C_8), 4.36 (1H, t J=7 Hz, H at C_2), 4.98 (1H, d J=5 Hz, H at C_4), 5.38 (1H, do d J=5 and 12 Hz, H at C_5), and 5.82 (1H, do do d J=2, 4.5 and 12 Hz, H at C_6). The whole product was used in the next reaction without further purification.

Compound **36b** (750 mg) was heated at 70—80 °C (bath temperature) for 20 min under nitrogen to give a 1 : 1 mixture (750 mg) of **36a** and **37b**. However, **36b** (750 mg) when heated at 120—125 °C for 10 min, afforded **37b** (750 mg), as a sole product, as far as the product was examined by tlc and NMR. This dienamine (**37b**) was characterized by the following spectra and used for the next reaction without further purification: IR, ν_{max} 1603 and 1043 cm^{-1}; NMR ($CDCl_3$), δ 0.86 and 0.93 (total 6H, each t J=7 Hz, $2CH_2CH_3$), 1.60 (4H, complex m, $2CH_2CH_3$), 2.30 (2H, m, 2H at C7), 2.57 (6H, s, $2NCH_3$), 2.86 (1H, br do do d J=6, 6 and 8 Hz, H at C_8), 3.60 (1H, do d J=6.5 and 9 Hz, H at C_2), 5.02 (1H, d J=4.5 Hz, H at C_4), 5.76 (1H, m, H at C_6), and 6.13 (1H, br do d J=4.5 and 12 Hz, H at C_5).

*trans-2,8-Diethyl-7,8-dihydro-2H-oxocin-3(4H)-one (**38a**).* An aqueous solution (14 ml) containing **37a** (1.40 g) and 7% fluoroboric acid (2.8 ml) was refluxed for 15 min, cooled, neutralized with aqueous sodium carbonate, and extracted with ether (100 ml) and then with dichloromethane (2×100 ml). The organic solutions were combined, dried and evaporated to leave oil (860 mg), which was dissolved in ether. The ether solution was shaken with 1 M hydrochloric acid to separate neutral (540 mg) and basic components (**38**, 320 mg). A part (470 mg) of the neutral substance, showing a single spot on tlc, was purified by chromatography over silicic acid (Merck, 20 g) with a 25 : 1 mixture of benzene and ethyl acetate to yield **38a** (307 mg) in pure state, oil; Mass, *m/e* 182 (M^+), 153, 96, and 81 (base); UV (isooctane), λ_{max} 295 nm (ε 96) (sh), 305 (108), 313 (76), and 325 (50) (sh); IR (film), ν_{max} 1717, 1660, 1120, 1089, 1081, 1048, and 1005 cm^{-1}; NMR ($CDCl_3$), δ 0.96 and 1.00 (6H, each t J=7 Hz, $2CH_2CH_3$), 1.58 (2H, m, CH_2CH_3 at C_8), 1.64 (2H, qui J=7 Hz, CH_2CH_3 at C_2), 2.05 (2H, m, 2H at C_7), 2.93 and 3.52 (each 1H, do d J=16, 3 and 16 and 2 Hz, 2H at C_4), 3.70 (1H, m, H at C_8), 3.86 (1H, t J=7 Hz, H at C_2), and 5.63 (2H, m, 2H at C_5 and C_6). Found: C, 72.64; H, 9.95%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

*cis-2,8-Diethyl-7,8-dihydro-2H-oxocin-3(4H)-one (**38b**).* A solution of **37b** (700 mg) and 7% fluoroboric acid (1.5 ml) in water (7 ml) was refluxed for 15 min, cooled and then worked up as usual to leave oil (608 mg), showing a single spot. The oil was purified by chromatography in the same way as **37a**, giving **38b** (470 mg) in pure state, oil; Mass, *m/e* 182 (M^+), 153, 96, and 81 (base); UV (isooctane), λ_{max} 294 (ε 142) (sh), 303 (162), 313 (156), and 324 nm (90); IR (film), ν_{max} 1718, 1641, 1120, 1108, 1091, 1068, and 1013 cm^{-1}; NMR ($CDCl_3$), δ 0.99 (6H, t J=7 Hz, $2CH_2CH_3$), 1.62 (4H, m, $2CH_2CH_3$), 2.25 (2H, m, 2H, at C_7), 2.77 (1H, do d J=13 and 6 Hz, H at C_4), 3.36 (1H, m, H at C_8), 3.71 (1H, do d J=5 and 7 Hz, H at C_2), 3.82 (1H, do d J=13 and 6 Hz, H at C_4), 5.71 (2H, m, 2H at C_5 and C_6). Found: C, 72.23; H, 9.94%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

A solution of *trans*-ketone (**38a**, 10 mg) in methanol (4 ml) was stirred with base (5% KOH) at room temperature for 20 min, diluted with water (20 ml), and extracted with ether (2×30 ml). The ether solution, after being worked up as usual, gave oil (10 mg), which was identical with *cis*-ketone (**38b**) in all respects (tlc, IR, and NMR). Treatment of **38a** with acid (refluxing 7% HBF_4, 15 min, or *p*-TsOH in dichloromethane, room temperature, 20 hr) proved to give no **38b** by tlc.

*2,8-Diethyl-3,4,7,8-tetrahydro-2H-oxocin-3-ols (**39** and **40**).* Compound **38b** (60 mg) was reduced with sodium borohydride (40 mg) in methanol (10 ml) at 0 °C for 40 min. The reaction mixture was made acidic (pH 4—5) with 2 M hydrochloric acid, concentrated and extracted with ether (2×50 ml). The ether solution was washed with saturated brine, dried and evaporated to leave oil (65 mg), showing two spots on tlc. The oil was separated roughly into three fractions by column chromatography over silica gel (Merck, 2 g, benzene : methanol=9 : 1). Fractions (30 mg) eluted early showed a single spot and gave **39** (30 mg), oil; Mass, *m/e* 155 (M^+-C_2H_5), 137, and 108; IR (film), ν_{max} 3420, 1066, and 1010 cm^{-1}; NMR ($CDCl_3$), δ 0.94 and 0.97 (total 6H, each t J=7 Hz, $2CH_3CH_2$), 1.56 (4H, m, $2CH_3CH_2$), 2.30 (3H, m, 3H at C_4 and C_7), 2.63 (1H, do d J=8 and 12 Hz, H at C_4), 3.33 (2H, m, 2H at C_2 and C_8), 3.68 (1H, m, H at C_3), and 5.76 (2H, m, 2H at C_5 and C_6). Middle fractions (30 mg) consisted mainly of **39** (tlc). Fractions eluted later showed a single spot on tlc and gave **40** (5 mg), oil; Mass, *m/e* 155 (M^+—C_2H_5), 137, and 108, IR (film), ν_{max} 3400, 1066, and 1011 cm^{-1}; NMR ($CDCl_3$), δ 1.02 (6H, t J=7 Hz, $2CH_3CH_2$), 1.58 (4H, m, $2CH_3CH_2$), 1.62 (1H, s, OH), 2.30 (3H, m, 3H at C_4 and C_7), 2.82 (1H, do do d J=3, 7 and 13 Hz, H at C_4), 3.32 (2H, m, 2H at C_2 and C_8), 3.75 (1H, do t J=3, 3 and 9 Hz, H at C_3), and 5.88 (2H, m, 2H at C_5 and C_6).

*t-3-Bromo-r-2,c-8-diethyl-3,4,7,8-tetrahydro-2H-oxocin (**2**).* To a stirred solution of alcohol **39** (50 mg) and carbon tetrabromide (135.5 mg) in dichloromethane (4 ml, dried through molecular sieves) was added dropwise a solution of triphenylphosphine (71.3 mg) in dry dichloromethane (6 ml) at room temperature during 3 hr, and the whole mixture was stirred at the temperature overnight. After removal of the solvent under reduced pressure, the residue was extracted with pentane (total 30 ml) repeatedly. The pentane solution was evaporated carefully under atmospheric pressure to leave oily residue, which was passed through a column filled with silica gel (1 g), pentane being used as solvent. Early fractions gave a mixture (10 mg) of carbon tetrabromide and **2**, and the following fractions showed a single spot on tlc and afforded **2** (25 mg), oil; Mass, *m/e* 248 and 246 (M^+), 219 and 217 (M^+—C_2H_5), and 190 and 188 (M^+—$2C_2H_5$), and 109; IR (film), ν_{max} 1282, 1118, 1080, 1032, and 809 cm^{-1}; NMR ($CDCl_3$), δ 0.97 (6H, t J=7 Hz, $2CH_3CH_2$), 1.28 (2H, br s, CH_3CH_2), 1.57 (2H, m, CH_3CH_2), 2.20 (3H, m, 3H at C_4 and C_7), 4.30 (3H, m, 3H at C_2, C_4 and C_8), 4.05 (1H, do t J=3, 3 and 9 Hz, H at C_3), and 5.90 (2H, m, 2H at C_5 and C_6).

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