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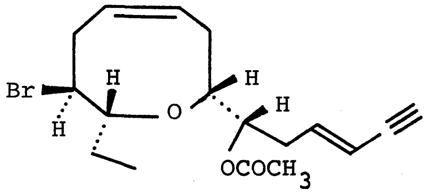
SYNTHETIC STUDIES OF LAURENCIN AND RELATED COMPOUNDS. II
THE SYNTHESIS OF *CIS*-2-ETHYL-8-FORMYL-7,8-DIHYDRO-2*H*-OXOCIN-3(4*H*)-ONE 3-ETHYLENE ACETAL[1]

Tadashi MASAMUNE and Hajime MATSUE
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

The synthesis of the titled hydrooxocinone (**2**) is described. Hydride reduction of a mixture of methyl 5-ethyl-2,5-dihydro-2-furoates (**3**) followed by ozonization afforded a dialdehyde mixture, which was submitted to the Robinson-Schöpf condensation to give, after acetylation, three 9-aza-3-oxabicyclo[3.3.1]nonanones (**5** ~ **7**). *cis*-Bicyclononanone (**5**) was further transformed by a modification of the Paquette procedure (**5** → **8** → **9** → **10a** → **11**) to give *cis*-2-ethyl-8-hydroxymethyl-7,8-dihydro-2*H*-oxocin-3(4*H*)-one (**11**), which was converted smoothly into the aldehyde (**2**), one of the most important intermediates for synthesis of laurencin (**1**).

Laurencin[2] (**1**) is a representative member of the titled naturally occurring halogeno-compounds,[3] and its structure is characterized by an eight-membered cyclic ether skeleton.[2] We describe herein the synthesis of *cis*-2-ethyl-8-formyl-7,8-dihydro-2*H*-oxocin-3(4*H*)-one 3-ethylene acetal (**2**), which offers promise in the synthesis of laurencin (**1**).



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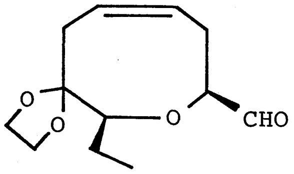
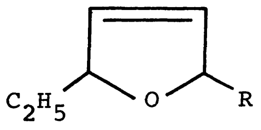
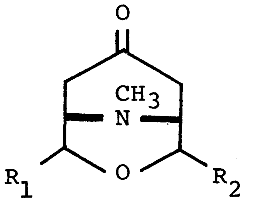


2

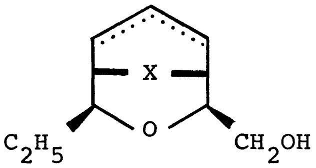
The Birch reduction of 5-ethyl-2-furoic acid followed by esterification produced a 1:1 mixture of methyl *cis*- and *trans*-5-ethyl-2,5-dihydro-2-furoates[4] (**3**), which were converted by hydride reduction into the corresponding alcohols[5] (**4**), bp 72-73°C (15 mmHg), m/e 128 and 99, ν_{max} 3410, 1075 and 1030 cm^{-1}, and δ 3.57 (2H, br s, $C\underline{H}_2OH$), in good yield. The alcohols (**4**) were ozonized at -70°C in methanol, and the resulting dialdehyde mixture was immediately treated with methylamine and acetonedicarboxylic acid under the Robinson-Schöpf conditions[6] (room temp, pH 5 and 2 days) to give a mixture of basic products, from which a 3:2:1 mixture of 2-acetoxymethyl-4-ethyl-9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-ones (**5** ~ **7**) was obtained in 7.8% yield after acetylation and column chromatography (CC). Further CC and preparative TLC effected isolation of each stereoisomer (5), mp 76-78°C, (6), oil, and (7), oil, in 2.2, 0.4 and 0.2% yields from 4, which showed the same fragmentation peaks (m/e 225, 196, 138, 111 and 110) and carbonyl absorption maxima (ν_{max} *ca.* 1735 and 1710 cm^{-1}) in the Mass and IR spectra. The NMR spectra and X-ray crystallographic analysis indicated the configurations of these compounds to be *cis*, *trans* and *trans*, respectively, concerning the two substituents, as had been reported previously.[7] These bicyclononanones were further transformed according to a modification of the Paquette procedure.[8]



3 R=$COOCH_3$
4 R=CH_2OH



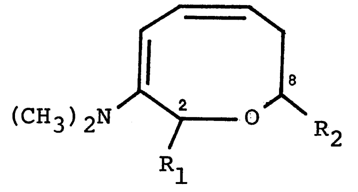
5 R_1=β-C_2H_5, R_2=β-CH_2OAc
6 R_1=α-C_2H_5, R_2=β-CH_2OAc
7 R_1=β-C_2H_5, R_2=α-CH_2OAc



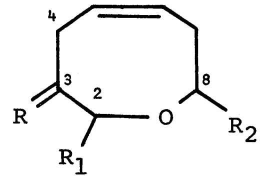
8 X=$N(CH_3)$
9 X=$N^+(CH_3)_2$ I^-

Treatment of *cis*-bicyclononanone (5) with tosylhydrazine in acidic (not neutral) THF under reflux and then with methyllithium in benzene and ether[9] produced olefinic alcohols (8), ν_{max} 3395 cm^{-1}, and δ 5.75 (2H, m), which were converted with methyl iodide into a crystalline mixture of methiodides (9) in good yield. Elution of the methiodide mixture (9) through Amberlite IRA-400 followed by heating at 60-80°C for 45 min resulted in the Hofmann degradation with concomitant 1,5-sigmatropic hydrogen transfer to yield a mixture of dienamines (10a and 10b), oil, ν_{max} 3420 and 1604 cm^{-1}, and δ 5.24 (1H, d J = 4 Hz), 5.76 (1H, complex m) and 6.16 (1H, do d J = 4 and 10 Hz). The mixture of dienamines 10 was hydrolyzed in refluxing 7% fluoroboric acid to a 3:2 mixture of β,γ-unsaturated ketones (11 and 12), which were isolated by CC in 32 and 13% yields from 9. While these ketones (11 and 12) exhibited essentially the same Mass, UV and IR spectra; e.g., 11, m/e 184, 155 and 125, λ_{max} 294 nm (ε 147) (sh), 303 (173), 312 (161) and 323 (84) (sh), and IR, ν_{max} 3480, 1720 and 1645 cm^{-1}, the NMR spectra, as coupled with the spin decoupling studies, provided definitive evidence for disposition of the respective carbonyl group in each compound; a double doublet [1H, J = 5 and 7 Hz, -C$\underline{H}$(O)-] at δ 3.82 in the spectrum of 11 was collapsed into a singlet on irradiation at δ 1.70 (2H, m, -$C\underline{H}_2CH_3$) but remained unchanged on that near δ 2.3 (2H, m, -$C\underline{H}_2$CH=CH-), while a double double doublet [1H, J = 2, 6 and 12 Hz, -C$\underline{H}$(O)-] at δ 3.40 in the spectrum of 12 was simplified to a broad doublet (J = 6 Hz) and to a double doublet (J = 6 and 12 Hz) on irradiation at δ 1.62 (2H, m, -$C\underline{H}_2CH_3$) and near δ 2.4 (2H, m, -$C\underline{H}_2$CH=CH-), respectively.

Repetition of the afore-mentioned sequence on the 2:2:1 mixture of bicyclononanones 5, 6 and 7, freed from pure 5, produced a mixture of ketones, from which a new ketone (13), oil, m/e 184, 155 and 125, λ_{max} 292 nm (ε 80), 303 (95), 313 (85) and 324 (40), ν_{max} 3360, 1715 and 1665 cm^{-1}, and δ 3.08 and 3.44 (each 1H, do d J = 15, 5 and 15, 3 Hz, 2H at C_4) and 3.96 (1H, do d J = 5 and 7 Hz), was isolated in 2% over-all yield besides ketones 11 (6%) and 12 (3%). The assigned structure (13) was consistent with these spectra and confirmed by facile isomerization of ketone 13 to cis-ketone 11 under mild conditions (5% aqueous KOH, room temp and 20 min). The low yields would result from difficult separation of products and also incomplete 1,5-hydrogen transfer in aminodienes (to dienamines) derived from the trans-bicyclononanones (6 and 7).$^{1)}$



10a R_1=β-C_2H_5, R_2=β-CH_2OH
10b R_1=α-CH_2OH, R_2=α-C_2H_5



11 R=O, R_1=β-C_2H_5, R_2=β-CH_2OH
12 R=O, R_1=α-CH_2OH, R_2=α-C_2H_5
13 R=O, R_1=α-C_2H_5, R_2=β-CH_2OH
14 R=O, R_1=β-C_2H_5, R_2=β-CH_2OAc
15 R=β-OH, α-H, R_1=β-C_2H_5, R_2=β-CH_2OAc
16 R=OCH_2CH_2O, R_1=β-C_2H_5, R_2=β-CH_2OH

Compound 11 was converted into the acetate (14), oil, ν_{max} 1750, 1725 and 1230 cm^{-1}, and δ 2.10 (3H, s), which on hydride reduction afforded hydroxyacetate (15), oil, m/e 170, 168, 125 and 116, ν_{max} 3400, 1745 and 1230 cm^{-1}, and δ 1.85 (1H, s, OH), 2.06 (3H, s), 2.62 (1H, do d J = 12 and 8 Hz, H at C_4) and 3.43 (1H, do do d J = 1.5, 5 and 8 Hz, H at C_2), as an isolable main product (60%). The NMR spectrum indicated that compound 15 would possess all cis-configurations (α, α and α) concerning the protons at C_2, C_3 and C_8.$^{1)}$ The predominant formation of all-cis-oriented compound was evidently convenient for conversion of the hydroxy group into a bromine atom with desirable configuration by bromination [$(C_6H_5)_3P$ and CBr_4], because the reaction usually proceeds in S_N2 manner.$^{1,10)}$ On the other hand, hydroxy-ketone 11 was converted into ethylene acetal (16), oil, m/e 228, 130 and 125, ν_{max} 3460, 1160, 1112 and 1022 cm^{-1}, δ 2.00 and 2.89 (each 1H, do d J = 13 and 8 Hz, 2H at C_4), which on oxidation (CrO_3 and Py in CH_2Cl_2)$^{11)}$ produced aldehyde (2), mp 73-74°C; m/e 197 and 168; ν_{max} 2820, 1735, 1160, 1110 and 1025 cm^{-1}, and δ 2.20 and 2.86 (each 1H, do d J = 13 and 6 Hz, 2H at C_4), 3.63 (1H, do d J = 8 and 5 Hz, H at C_2), 3.70 (1H, do d J = 7 and 4.5 Hz, H at C_8). This hydrooxocinone 2 would be one of the most appropriate intermediates convertible into laurencin (1).

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5) All numbered, new compounds gave elementary analyses in good accord with the assigned structures. The UV, IR and NMR (100 MHz) spectra were taken in isooctane, in liquid state and in $CDCl_3$, respectively, unless otherwise stated. The abbreviations "s, d, m, br, do, and sh" in the NMR spectra denote "singlet, doublet, multiplet, broad, double, and shoulder," resepctively.

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