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THE SYNTHESIS OF (±)-LAURENCIN[1]

Akio Murai, Hisashi Murase, Hajime Matsue, and Tadashi Masamune*
Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo, Japan 060

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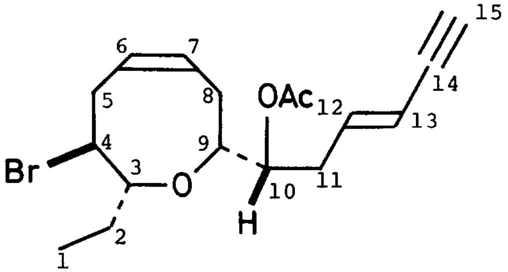
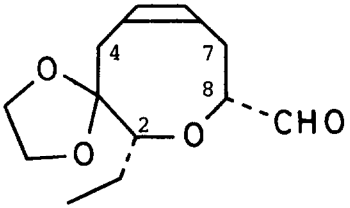
Laurencin[2] (1) and related compounds are a group of naturally occurring halogeno compounds with (a) medium-sized cyclic ether ring(s) as well as an enyne unit, and the structure and configuration have been well established.[3] We describe herein the conversion of cis-2-ethyl-8-formyl-7,8-dihydro-2$\underline{H}$-oxocin-3(4$\underline{H}$)-one 3-ethylene acetal[4] (2) into (±)-laurencin (1). Since compound 2 has recently been prepared,[4] the present work constitutes the first synthesis of a representative member of the group.

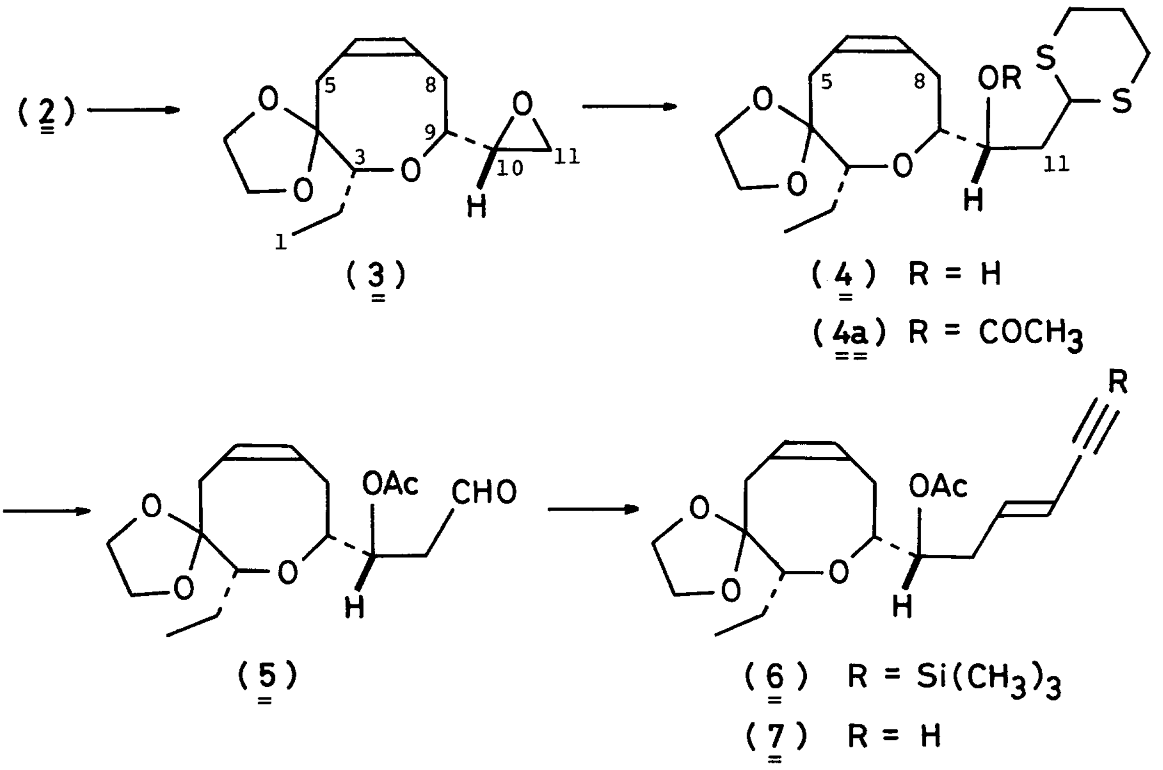


(1)

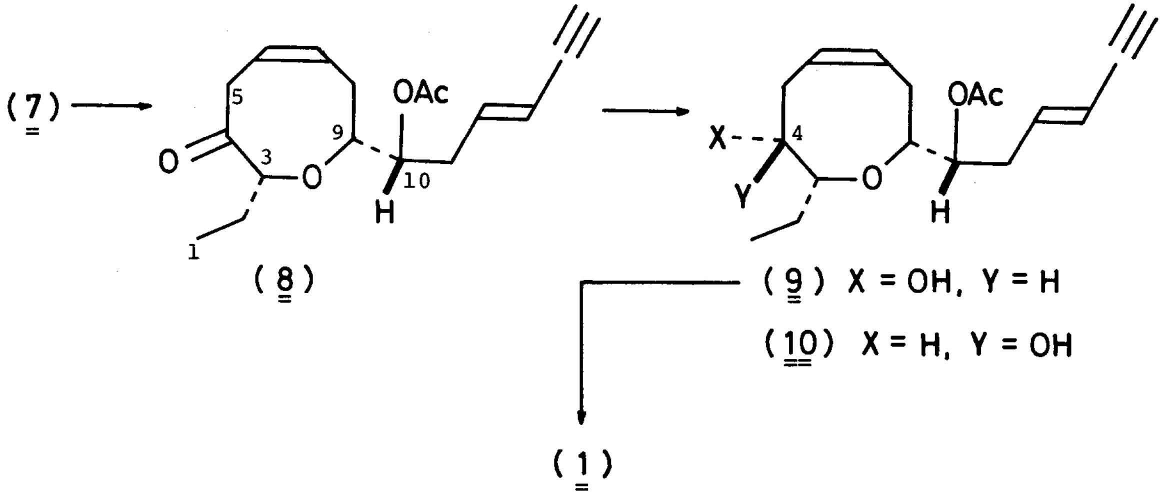


(2)

Treatment of the formylhydrooxocin (2) with dimethyloxosulfonium methylide (in DMSO, room temp, 1 h)[5] afforded epoxyethylhydrooxocin (3), mp 87-88°C, showing a single spot by GLPC (10% SE-30) and TLC (Wakogel B-5F), in a 66% yield, as a sole isolable epoxide: MS, m/e 240 (M^+); IR (Nujol), ν_{max} 1648, 1380, 1252, 1162, 1107, 1080, and 849 cm^{-1}; NMR,[6] δ 1.00 (3H, t J = 7 Hz, $CH_2C\underline{H}_3$), 1.44 (2H, m, $C\underline{H}_2CH_3$), 2.20 (3H, m, $\underline{H}$ at C_5 and 2$\underline{H}$ at C_8), 2.72 and 3.25 (each 2H, m, 4$\underline{H}$ at C_9, C_{10}, and C_{11}), 2.94 (1H, do d J = 13 and 8.5 Hz, $\underline{H}$ at C_5), 3.60 (1H, do d J = 7 and 6 Hz, $\underline{H}$ at C_3), 4.00 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), and 5.82 (2H, m, cis-C$\underline{H}$=C$\underline{H}$). The epoxide (3), when treated with 2-lithio-1,3-dithiane (in THF, -70°C ∿ -20°C, 6h and -20°C, 12 h),[7] was converted into 2-(2-hydroxyalkyl)-1,3-dithiane (4), which was isolated as its acetate (4a), mp 161-162°C, in an 80% yield from 3: MS, m/e 402 (M^+) and 342; IR (Nujol), ν_{max} 1740 and 1230 cm^{-1}; NMR, δ 2.03 (3H, s, $OCOC\underline{H}_3$), 2.10 (7H, m, $\underline{H}$ at C_5, 4$\underline{H}$ at C_8 and C_{11}, and $SCH_2C\underline{H}_2CH_2S$), 2.88 (5H, m, $\underline{H}$ at C_5 and $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.90 (5H, m, $OC\underline{H}_2C\underline{H}_2O$ and $SC\underline{H}S$), and 5.24 [1H, do t J = 9, 4, and 4 Hz, $C\underline{H}(OCOCH_3)$]. It is to be noted that the acetoxymethine proton at δ 5.24 appeared with the same splitting pattern as that (δ 4.98, do t J = 8, 5, and 5 Hz)[2] of laurencin (1). Treatment of dithiane 4a with mercury(II) oxide and boron trifluoride etherate (in 15% aq THF, room temp, 30 min)[7] effected only hydrolysis of the 1,3-dithiano group to yield β-hydroxyaldehyde (5), which was immediately submitted to the Wittig reaction with triphenyl-3-trimethylsilylpropynylidenephosphorane (in THF, -70°C ∿ 0°C, 1 h).[8] The reaction proceeded without elimination of acetic acid to give trimethylsilyl-*trans*-pentenyne (6), which on treatment with ammonium fluoride (in DMF, room temp, 4 h)[8,9] was converted readily into *trans*-pentenyne (7), oil, in a 94% yield: 6, MS, m/e 406 (M^+) and 346; IR (neat), ν_{max} 2160, 1740, 1248, and 960 cm^{-1}; NMR, δ 0.15 [9H, s, $Si(C\underline{H}_3)_3$], 2.05 (3H, s, $OCOC\underline{H}_3$), 5.02 [1H, do t J = 9, 4, and 4 Hz, $C\underline{H}(OCOCH_3)$], 5.54 and 6.08 (each 1H, br d J = 15 Hz and do t J = 15, 7, and 7 Hz, *trans*-$C\underline{H}=C\underline{H}$): 7, MS, m/e 334 ($M^+$) and 274; IR ($CHCl_3$), ν_{max} 3300, 2110, 1740, 1247, and 960 cm^{-1}; NMR, δ 2.03 (3H, s, $OCOC\underline{H}_3$), 2.80 (1H, d J = 2 Hz, $C\equiv C\underline{H}$), 5.01 [1H, do t J = 9, 4, and 4 Hz, $C\underline{H}(OCOCH_3)$], 5.50 and 6.14 (each 1H, br do d J = 15 and 2 Hz, and do t J = 15, 8, and 8 Hz, *trans*-$C\underline{H}=C\underline{H}$).



Deacetalization of the oxohydrooxocin ethylene acetal (7) with acid (p-TsOH in aq acetone, reflux, 16 h) proceeded smoothly to give ketone (8), oil, in a 74% yield: MS, m/e 290 (M^+) and 230; IR ($CHCl_3$), ν_{max} 3310, 2110, 1740, 1720, 1236, and 960 cm^{-1}; NMR, δ 2.06 (3H, s, $OCOC\underline{H}_3$), 2.81 (1H, d J = 2 Hz, $C{\equiv}C\underline{H}$), 3.72 (1H, t J = 7 Hz, $\underline{H}$ at C_3), 3.86 (1H, do d J = 11 and 8 Hz, $\underline{H}$ at C_5),[10] 5.00 [1H, do t J = 8, 5, and 5 Hz, $C\underline{H}(OCOCH_3)$], 5.52 and 6.14 (each 1H, br d J = 15 Hz and do t J = 15, 7, and 7 Hz, trans-$C\underline{H}{=}C\underline{H}$). Hydride reduction ($NaBH_4$ in CH_3OH, 0°C, 20 min) of the ketone (8) produced a mixture of 4-alcohols, from which a major alcohol (9), oil, with three cis-oriented substituents on the hydrooxocin ring, and a minor alcohol (10), oil, its 4-epimer, could be isolated in 50 and 30% yields. The configurations of hydroxyl groups at C_4 in the respective compounds (9 and 10) were deduced by analogy of the NMR data with those of the corresponding diethylhydrooxocins:[10] 9, MS, m/e 292 (M^+), 274, and 232; IR (neat), ν_{max} 3440, 3300, 2120, 1740, 1235, and 960 cm^{-1}; NMR, δ 1.86 (1H, br s, $O\underline{H}$), 2.05 (3H, s, $OCOC\underline{H}_3$), 2.82 (1H, d J = 2 Hz, $C{\equiv}C\underline{H}$), 3.64 [1H, br W_H = 20 Hz, $C\underline{H}(OH)$],[10] 4.98 [1H, do t J = 8, 5, and 5 Hz, $C\underline{H}(OCOCH_3)$], 5.52 and 6.16 (each 1H, br d J = 16 Hz and do t J = 16, 7, and 7 Hz, trans-$C\underline{H}{=}C\underline{H}$): 10, MS, m/e 292 ($M^+$), 274, and 232; IR (neat), ν_{max} 3440, 3300, 2110, 1740, 1235, and 960 cm^{-1}; NMR, δ 2.05 (3H, s. $OCOC\underline{H}_3$), 2.80 (1H, d J = 2 Hz, $C{\equiv}C\underline{H}$), 3.72 [1H, do t J = 9, 3, and 3 Hz, $C\underline{H}(OH)$],[10] 4.98 [1H, do t J = 8, 5, and 5 Hz, $C\underline{H}(OCOCH_3)$], 5.52 and 6.16 (each 1H, br d J = 15 Hz and do t J = 15, 7, and 7 Hz, trans-$C\underline{H}{=}C\underline{H}$). Contrary to the expectation,[10] the major alcohol (9), when treated with triphenylphosphine and carbon tetrabromide (in CH_2Cl_2, room temp, 12 h),[10,11] gave a complex mixture. However, an aimed bromo compound, mp 45-47°C, could be isolated after careful chromatography in a 14% yield along with the unreacted starting alcohol (9, 20%).



The bromo compound exhibited the following spectra: MS, m/e 356, 354 (M^+), 296, and 294; IR (neat), ν_{max} 3285, 2100, 1735, 1230, 1168, 1080, 1035, and 950 cm^{-1}; NMR, δ 0.98 (3H, t J = 7 Hz, $CH_2C\underline{H}_3$), 2.03 (3H, s, $OCOC\underline{H}_3$), 2.83 (1H, d J = 2 Hz, $C{\equiv}C\underline{H}$), 4.07 (1H, do t J = 9, 3, and 3 Hz, $C\underline{H}Br$), 4.98 [1H, do t J = 8, 5, and 5 Hz, $C\underline{H}(OCOCH_3)$], 5.52 and 6.15 (each 1H, br d J = 15 Hz and do t J = 15, 7, and 7 Hz, *trans*-$C\underline{H}{=}C\underline{H}$), and 5.90 (2H, m, *cis*-$C\underline{H}{=}C\underline{H}$). These spectra were completely identical with those of natural laurencin (**1**), indicating completion of the synthesis of (±)-laurencin. The overall yield amounted to 1.1% from the formylhydrooxocin (**2**).

References and Footnotes

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6) The NMR spectra were measured in chloroform-*d* at 100 MHz. The abbreviations "s, d, t, m, br, and do" denote "singlet, doublet, triplet, multiplet, broad, and double," respectively.

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