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REGIO-SPECIFIC TOTAL SYNTHESIS OF (±)-2-HYDROXYAKLAVINONE

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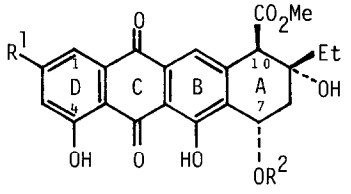
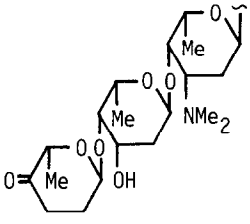
Summary: The tricyclic quinone 8 was successfully synthesized from naphthazalin, and the total synthesis of (±)-2-hydroxyaklavinone via 8 was accomplished in an overall yield of about 18% through the regio-controlled route.

As do many aclacinomycin-type anthracyclines[1], 2-hydroxyaclacinomycin A (1)[2] (which was produced from naturally occurring 2-hydroxyaklavinone (2)[3] by microbial glycosidation) has a potent anticancer activity against L1210 leukemia in mice. Our attention has, therefore, been focused on the chemical synthesis of this and related antibiotics. Recently, the total synthesis of aklavinone (4)[4] (an aglycone of the clinically important antitumor agent aclacinomycin A (3)[5]) has been achieved by several efficient process[6], but no synthesis of 2 has been reported yet. We now describe the total synthesis of racemic 2 in 14 steps starting from naphthazalin.



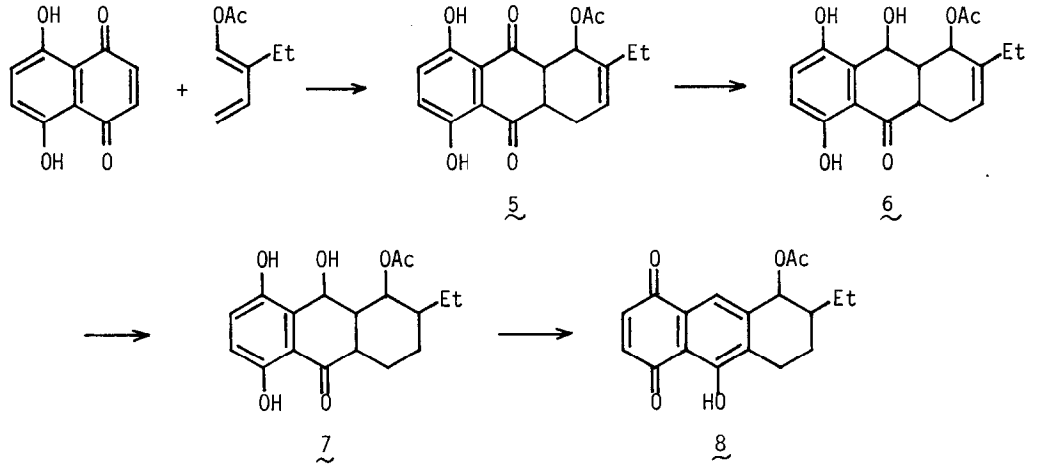


= RDC

1: R^1=OH, R^2=RDC
2: R^1=OH, R^2=H
3: R^1=H, R^2=RDC
4: R^1=R^2=H

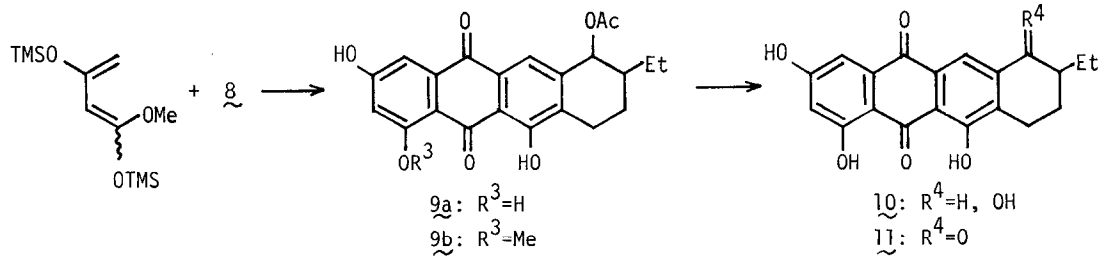
In order to construct 11-deoxy anthracyclinone, we made the versatile synthon (8), an ABC-ring unit, as described below. Diels-Alder reaction between naphthazalin and 1-acetoxy-2-ethyl-1,3-butadiene[7] in refluxing CH_2Cl_2 for 3 hr gave the adduct 5 (mp 144 ~ 145°C, 99%). Successive reduction of 5 (2 equiv. of $NaBH_4$, THF, 0°C) proceeded regioselectively to afford

the olefinic triol 6 (mp 158 ~159°C, 95%). The olefinic bond of 6 was readily hydrogenated over PtO_2 in EtOAc at atmospheric pressure, giving 7 (mp 148 ~149°C, 95%). Conversion of 7 into 8 was the key step, involving both dehydration and oxidation. Attempts to dehydrate the benzylic alcohol of 7 by treatment with acid or base failed, but trifluoroacetylation (i. 5 equiv. of $(CF_3CO)_2O$, pyr., 0°C, 0.5 hr. ii. addition of 10 equiv. of triethylenediamine, 50°C, 0.5 hr) gave an aromatized intermediate. This material was dissolved in benzene and subjected to air-oxidation in the presence of triethylamine to provide the tricyclic quinone 8[8] (mp 141 ~142°C) in 85% yield.



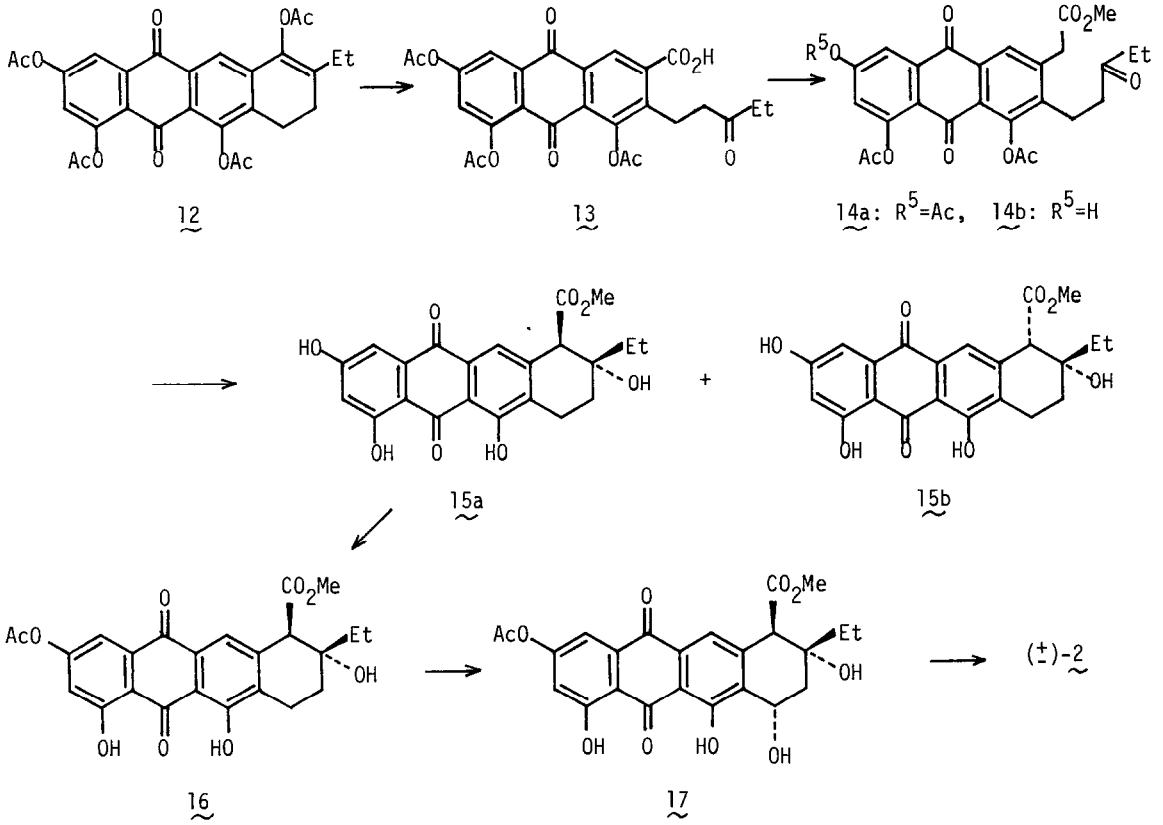
The quinone 8 having only one peri-hydroxy group was expected to be a regio-controlled dienophile on Diels-Alder reaction as described previously by Kelly[9] and others[10]. Indeed, the coupling between 8 and 1-methoxy-1,3-bis(trimethylsiloxy)butadiene[11] in CH_2Cl_2, followed by acid treatment (0.1N HCl/MeOH) gave a 79:21 mixture of the desired tetracyclic compounds 9a and 9b in 92% combined yield. Crystallization of the mixture from $CHCl_3$ afforded pure 9a (mp 278~280°C) and it was deacetylated with 5 equiv. of NaOMe in THF/MeOH into tetraol 10 (mp 256 ~ 259 °C, 100%). The tetraol 10 was oxidized with Jones reagent in Me_2CO to the key intermediate ketone 11[12] (mp 274 ~277°C, 96%).

Acetylation of 11 (i. Ac_2O/catalytic 60% $HClO_4$, CH_2Cl_2. ii. addition of pyr.) provided the tetraacetate 12 (mp 205 ~207°C, 96%). After ozonolysis of 12, 13 was subjected to Arndt-Eistert reaction (i. excess $SOCl_2$, CH_2Cl_2, reflux, 5 hr. ii. CH_2N_2, Et_2O, 0°C, 0.5 hr. iii. MeOH/Ag_2O, 60°C, 1 hr. under N_2 in all reactions. iv. chromatographic separation) to afford 14a (mp 159 ~165°C, 8.3%) and 14b (mp 204 ~ 208°C, 46%).



9a: R^3=H
9b: R^3=Me
10: R^4=H, OH
11: R^4=O

The compound 14a (or 14b) was cyclized and deacetylated with 5 equiv. of Triton B(OH)[6e] in MeOH at -20°C for 3 days, to provide a 72:28 mixture of (±)-7-deoxy-2-hydroxyaklavinone 15a[13] (mp 244 ~246°C) and its C-10 epimer 15b in 94.6% combined yield. The diastereomeric mixture could be separated on silica gel plates (15a: Rf=0.66, 15b: Rf=0.50) using Et_2O as an eluant. Base treatment of 15b (3.5 equiv. of DBU, CH_2Cl_2, 23°C, 18 hr) gave a 2:3 equilibrium mixture (by NMR analysis) of 15a and 15b. The yield of 15a was enhanced to 77% after one such equilibration.



As direct hydroxylation of 15a at the C-7 position resulted in poor yield, 15a was selectively protected as the monoacetate 16 (i. 2 equiv. of $B(OH)_3$/excess Ac_2O, THF, rt, 4 hr. ii. addition of pyr., 0.25 hr, 98%). Subsequent homolytic bromination of 16 (2 equiv. of Br_2/AIBN, reflux, 1 hr) followed by solvolysis (1:1 H_2O/THF, rt, 1 hr)[6a] provided (±)-2-O-acetyl-2-hydroxyaklavinone 17 (mp 229 ~232°C, 90%) in 100% stereospecific yield.

Finally, deacetylation of 17 (1.5 equiv. of NaOMe/MeOH, 0°C, 0.2 hr, under N_2, 100%) afforded (±)-2-hydroxyaklavinone[14] (mp ~220°C) which was identical with natural 2-hydroxy-aklavinone (2)[15] by mp, IR, UV, NMR and TLC.

The regio- and stereo-selective glycosidation of 2-hydroxyaklavinone with the tri-saccharide RDC has been reported[16]. Since we have described the synthesis of the aglycone moiety in this communication, a total synthesis of 2-hydroxyaclacinomycin A has been accomplished.

References and notes

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7. Prepared by enol-acetylation of 2-ethylcrotonaldehyde with isopropenylacetate and catalytic TsOH, bp 42°C/8mm, 82% yield.
8. 8: ν_{max}^{KBr} 1720, 1660, 1630 cm^{-1}; NMR($CDCl_3$) δ2.07(s, 3H), 6.90(s, 2H), 7.62(s, 1H), 12.34(s, 1H).
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12. 11: ν_{max}^{KBr} 1695, 1610 cm^{-1}; NMR($CDCl_3$) δ6.56(d, J=2, 1H), 7.19(d, J=2, 1H), 8.22(s, 1H).
13. 15a: λ_{max}, 90%MeOH 228, 276, 440 nm; ν_{max}^{KBr} 1720, 1665, 1615 cm^{-1}; NMR(1:1 $CDCl_3/CD_3OD$) δ1.08(t, J=7, 3H), 1.3~3.2(m, 6H), 3.73(s, 3H), 3.95(bs, 1H), 6.55(d, J=2, 1H), 7.18(d, J=2, 1H), 7.56(s, 1H).
14. (±)-2: λ_{max}, 90%MeOH 226, 256, 270, 292, 440 nm; ν_{max}^{KBr} 1730, 1725(sho), 1675, 1620 cm^{-1} (authentic 2: 1725, 1675, 1620 cm^{-1}); NMR(1:1 $CDCl_3/CD_3OD$) δ1.10(t, J=7, 3H), 1.65(m, 2H), 2.22(bd, J=15, 1H), 2.50(dd, J=4.5, 15, 1H), 3.72(s, 3H), 4.10(s, 1H), 5.31(dd, J=1.5, 4.5, 1H), 6.60(d, J=2, 1H), 7.22(d, J=2, 1H), 7.60(s, 1H).
15. Recrystallized from MeOH/$CHCl_3$ (mp ~220°C, dec.) and the spectral data were obtained for the identification.
16. H. Tanaka, T. Yoshioka, A. Yoshimoto, Y. Shimauchi, T. Ishikura, T. Takeuchi, H. Umezawa, J. Antibiotics, 36, 601 (1983).

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