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SYNTHESIS OF 4,8-DIHYDROXY-3-METHYL-5,6-BENZO-2-OXABICYCLO[2.2.2]OCT-5-ENE

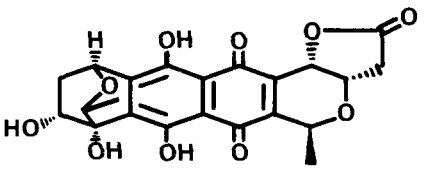
Mineichi Sudani, Yoshio Takeuchi, and Eiichi Yoshii*
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

and

Tadashi Kometani
Department of Chemistry, Toyama Technical College, Hongo 13, Toyama 930-11, Japan

Abstract : The title compound having the same relative configurations as granaticin(1) and U-58,431(2) was prepared either by dehydrogenative cyclization of the precursor 9a or by pinacol cyclization of the dicarbonyl compound 15.

Granaticin(1)[1] and antibiotic U-58,431(2)[2] both contain the 2-oxabicyclo[2.2.2]oct-5-ene ring system, a structural feature of which is apparently very unique to these compounds. As a part of our study on the total synthesis of granaticin[3] we initiated model experiments for the construction of this common structural unit ——— the title compound possessing the same stereochemistry as the antibiotics. Two approaches we considered for the key cyclization step are illustrated in the stereostructue 3 : (i) dehydrogenative C-O bond formation(*route a*) and (ii) reductive C-C bond formation by pinacol cyclization(*route b*). Successful results of both routes are described in the following separate sections.



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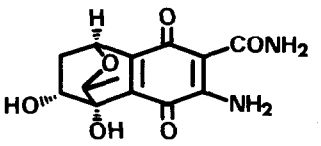

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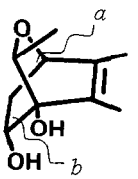

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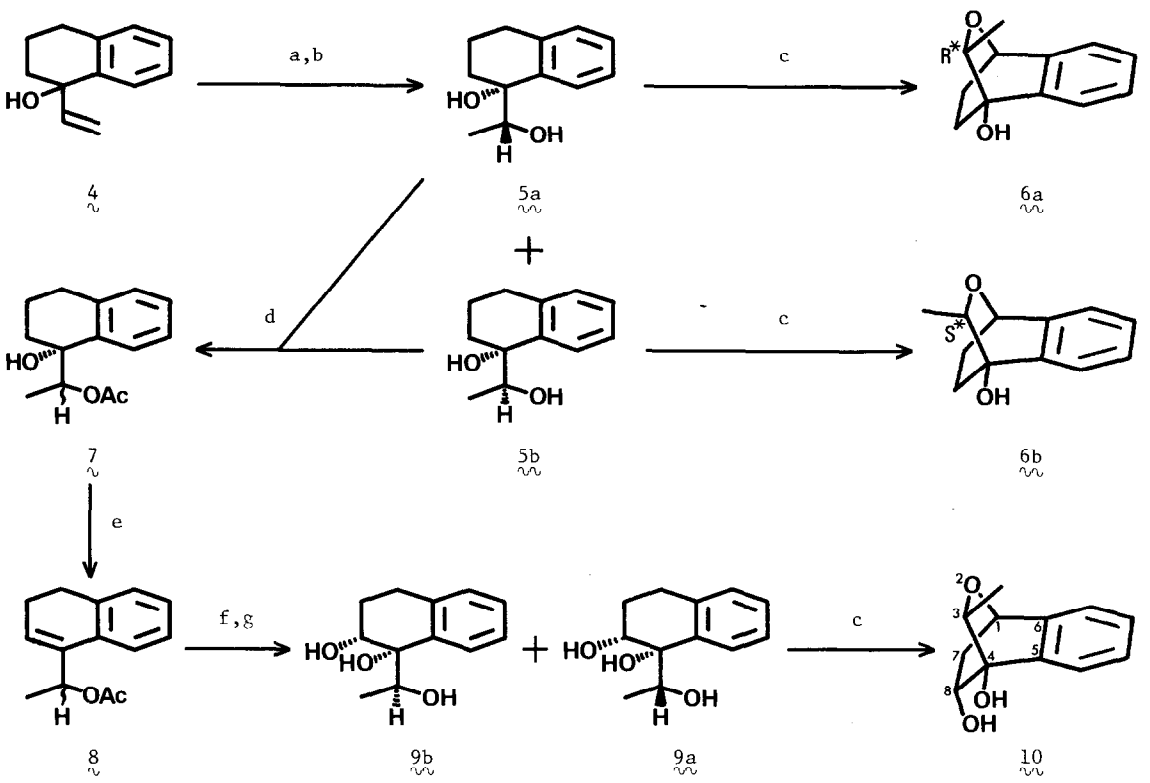
(i) Approach by *Route a* (Scheme I) As a preliminary experiment, the proposed dehydrogenative cyclization was examined with desoxy compound(5) as follows. Vinyl carbinol 4 prepared from α-tetralone and vinylmagnesium bromide was subjected to epoxidation according to the method of Sharpless.[4] The mixture of diastereomeric epoxides so obtained in excellent yield was then treated with $LiAlH_4$ to afford quantitatively oily diols, 5a(Rf=0.25[5]) and 5b(Rf=0.30[5]), in a ratio of 2 : 3 by nmr. These isomers were separated by silica gel column chromatography and exhibited the following spectral data : 5a, nmr($CDCl_3$,δ) 0.82(3H, d, J=6Hz, Me), 4.14(1H, q, J=6Hz, C<u>H</u>-Me), ir(neat) 3410cm^{-1}(OH), ms m/e 175(M^+-H_2O+1) ; 5b, nmr($CDCl_3$,δ) 1.03(3H, d, J=6Hz, Me), 3.85(1H, q, J=6Hz, C<u>H</u>-Me), ir(neat) 3410cm^{-1}(OH), ms m/e 175(M^+-H_2O+1).

With the expectation of benzylic bromination of the diols(5a,b), each isomer was treated with NBS in refluxing CCl_4 in the presence of cyclohexene oxide.[6] Actually realized by this

Scheme I



(a) t-BuOOH, $VO(acac)_2$, PhH, reflux, 5h(94%) ; (b) $LiAlH_4$, THF, room temperature, 30min(98%) ; (c) NBS, cyclohexene oxide, BPO, CCl_4, reflux, 30min(46% for 6a, 10% for 6b, 35% for 10) ; (d) Ac_2O/pyridine, room temperature, 15h(100%) ; (e) $SOCl_2$/pyridine, 0°C, 10min(97%) ; (f) $Me_3N{\rightarrow}O{\cdot}2H_2O$, OsO_4, aq t-BuOH, reflux, 3.5h(96%) ; (g) K_2CO_3, aq MeOH, room temperature, 2.5h(100%).

procedure was to our thanks the formation of the desired compounds[7] ; 6a, 46% yield, mp 143-145°C, nmr($CDCl_3$,δ) 0.71(3H, d, J=6Hz, C(3)-Me), 4.03(1H, q, J=6Hz, C(3)-H), 4.79(1H, dd, J=3,1Hz, C(1)-H), ir(KBr) 3310cm^{-1}(OH), ms m/e 146(M^+-MeCHO, base peak) ; 6b, 10% yield, mp 144-144.5°C, nmr($CDCl_3$,δ), 1.36(3H, d, J=6Hz, C(3)-Me), 3.42(1H, q, J=6Hz, C(3)-H), 4.78(1H, dd, J=3,1Hz, C(1)-H), ir(KBr) 3370cm^{-1}(OH), ms m/e 146(M^+-MeCHO, base peak). Stereochemistries at C(3) of 6a(R^*) and 6b(S^*), as depicted in Scheme I, were indicated by nmr data which showed remarkable differences in chemical shifts values of the C(3)-substituents due to anisotropic effects of benzene ring, *e.g.*, C(3)-Me of 6a which is syn to the benzene ring is more shielded than that of 6b.

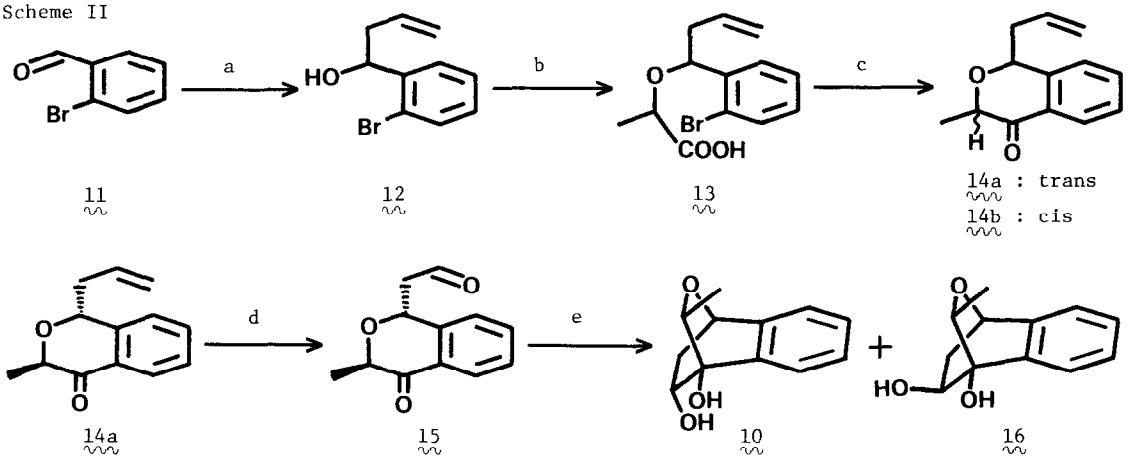
We next examined the validity of the above cyclization method for the synthesis of the title compound. The diastereomeric mixture(5a,b) was acetylated with Ac_2O/pyr to produce the acetate 7 quantitatively, ir(neat) 3470cm^{-1}(OH), 1730cm^{-1}(CO), ms m/e 234(M^+). Dehydration of the monoacetate 7 with $SOCl_2$/pyr afforded the allyl acetate 8 in 97% yield, ir(neat) 1740cm^{-1}(CO), nmr(CCl_4,δ) 1.44(3H, d, J=6Hz, CH-Me), 2.00(3H, s, OAc), 5.82(1H, q, J=6Hz, CH-Me), 6.07(1H, t, J=5Hz, -CH=), ms m/e 216(M^+). The allyl acetate(8) was then subjected to catalytic osmylation using amine oxide(N-oxide of either N-methylmorpholine[8] or trimethylamine[9]) and

the resulting triol monoacetate mixture was saponified to give in 96% yield a mixture of two isomeric triols separable by silica gel column chromatography[10] : 9a, Rf=0.35,[11] mp 94-95°C, nmr($CDCl_3$,δ) 0.91(3H, d, J=6Hz, Me), 4.1-4.5(5H, m, two C<u>H</u>-OH and three OH), ir(KBr) 3370cm^{-1} (OH), ms m/e 163(M^+-45), 145(M^+-45-H_2O, base peak) ; 9b, Rf=0.25,[11] mp 91-92°C, nmr($CDCl_3$,δ) 1.07(3H, d, J=6Hz, Me), 3.13(3H, br s, three OH), 3.87(1H, q, J=6Hz, C<u>H</u>-Me), 4.07(1H, dd, J=6,4Hz, C<u>H</u>-OH), ir(KBr) 3370cm^{-1}(OH), ms m/e 163(M^+-45), 145(M^+-45-H_2O, base peak).

The less polar isomer 9a, whose relative configuration at the asymmetric centers is that required for the synthesis of the title compound based on the nmr data,[12] was allowed to react with NBS as in the above model experiment. The bicyclic product 10 obtained in 35% yield was identified and its stereochemical structure was fully characterized by the following spectral and physical data, mp 161-162°C, 200MHz ^{1}H nmr($CDCl_3$,δ) 0.79(3H, d, J=6Hz, C(3)-Me), 1.48(1H, dt, J=14,2Hz, C(7)-H_{endo}), 2.88(1H, ddd, J=14,8,4Hz, C(7)-H_{exo}), 3.92(1H, q, J=6Hz, C(3)-H), 4.06(1H, dd, J=8,2Hz, C(8)-H), 4.82(1H, dd, J=4,2Hz, C(1)-H), 7.29 and 7.61(2H, each d, J=7Hz, Ar-H), 7.40 and 7.49(2H, each t, J=7Hz, Ar-H), ir(KBr) 3340cm^{-1}(OH), ms m/e 206.0965(M^+, calcd 206.0942), 162.0678(M^+-MeCHO, base peak, calcd 162.0680), anal. calcd for $C_{12}H_{14}O_3$ C, 69.88 ; H, 6.84, found C, 69.57 ; H, 6.79.

(ii) Approach by *Route b* (Scheme II) The dicarbonyl compound(15) required for the second route was prepared from 2-bromobenzaldehyde(11). Reaction of the aldehyde 11 with allylmagnesium bromide yielded the carbinol 12 quantitatively, ir(neat) 3400cm^{-1}(OH), 1640cm^{-1}(-CH=CH_2), ms m/e 228,226(M^+), 187,185(M^+- CH_2-CH=CH_2, base peak). O-Alkylation of the carbinol with ethyl 2-bromopropionate in the presence of NaH and saponification of the ester gave the acid 13 as a diastereomeric mixture in 95% yield, ir(neat) 1725cm^{-1}(CO), 1640cm^{-1}(-CH=CH_2), ms m/e 245,243 (M^+- CH_2-CH=CH_2, base peak). Lithium salt of the acid 13 was prepared by neutralization with LiOH and the dried salt was treated with n-BuLi in THF at -78°C, and then the temperature was allowed to rise to room temperature to give two isomeric cyclization products,[13] 14a,b, in 64% yield in a ratio of 1 : 1 based on nmr. They were separated by silica gel chromatography and

Scheme II



11 12 13 14a : trans 14b : cis

14a 15 10 16

(a) CH_2=CH-CH_2MgBr, Et_2O, reflux, 2h(100%) ; (b) i) NaH, $CH_3CH(Br)COOEt$, DMF, room temperature, 3.5h, ii) KOH, aq MeOH, room temperature, 20h(95%); (c) i) LiOH, MeOH, concentrated to dryness, ii)n-BuLi, THF, -78°C to room temperature, 1h(28% for 14a, 12% for 14b) ; (d) OsO_4, $NaIO_4$, aq DME, room temperature, 5h(56%) ; (e) Ti(0), THF, 0°C, 1h(5% for 10, 15% for 16).

their spectral data are as follows : trans isomer 14a, Rf=0.35,[14] nmr($CDCl_3$,δ) 1.48(3H, d, J=7 Hz, C(3)-Me), 4.63(1H, q, J=7Hz, C(3)-H), 5.06(1H, dd, J=8,5Hz, C(1)-H), ir(neat) 1700cm^{-1}(CO), 1640cm^{-1}(-CH=CH_2), ms m/e 161(M^+- CH_2-CH=CH_2, base peak) ; cis isomer 14b, Rf=0.40,[14] nmr($CDCl_3$, δ) 1.52(3H, d, J=7Hz, C(3)-Me), 4.27(1H, q, J=7Hz, C(3)-H), 4.94(1H, dd, J=7,4Hz, C(1)-H), ir (neat) 1700cm^{-1}(CO), 1640cm^{-1}(-CH=CH_2), ms m/e 161(M^+- CH_2-CH=CH_2, base peak). Oxidation of the trans isomer 14a with OsO_4-$NaIO_4$ gave the keto-aldehyde 15 in 56% yield, nmr($CDCl_3$,δ) 1.45 (3H, d, J=7Hz, C(3)-Me), 4.54(1H, q, J=7Hz, C(3)-H), 5.62(1H, dd, J=8,5Hz, C(1)-H), 9.91(1H, t, J=2Hz, CHO), ir(neat) 1725, 1700cm^{-1}(CO), ms m/e 204(M^+), 131(M^+-73, base peak).

The final key step, reductive cyclization of 15, was performed at 0°C by treatment with Ti(0) which was prepared from $TiCl_3$ and K in THF.[15] The bicyclic product obtained here in 40% yield was a C(8)-epimeric mixture of the title compound(ratio of formation, 16/10 = 3 by nmr). Each isomer was isolated by preparative TLC and the more polar one(Rf=0.30[16]) was identified to be the desired α-glycol, by comparison of its physical and spectral data with those of 10 obtained *via* the *route a*. The other was characterized to be the C(8)-epimeric α-glycol(16) by the 200MHz ^1H nmr, and showed the following data, Rf=0.40,[16] mp 147-150°C, ir(KBr) 3350cm^{-1} (OH), 200MHz ^1H nmr($CDCl_3$,δ) 0.76(3H, d, J=7Hz, C(3)-Me), 2.13(1H, ddd, J=14,4,3Hz, C(7)-H_{exo}), 2.25(1H, ddd, J=14,9,3Hz, C(7)-H_{endo}), 3.85(1H, m, C(8)-H), 4.50(1H, q, J=7Hz, C(3)-H), 4.77 (1H, t, J=3Hz, C(1)-H), 7.21 and 7.52(2H, each d, J=7Hz, Ar-H), 7.32 and 7.42(2H, each t, J=7 Hz, Ar-H), ms m/e 206(M^+), 162(M^+-MeCHO, base peak), anal. calcd for $C_{12}H_{14}O_3$ C, 69.88 ; H, 6.84, found C, 70.01 ; H, 6.64. Employment of the other metals for the pinacol cyclization, *e.g.*, Ti(II), Mg-Hg, and Al-Hg, did not result in the increased formation of 10. Attempt for conversion of 16 to 10, *i.e.*, oxidation of 16 to the corresponding ketone derivative followed by reduction to the α-glycol(10), is now under investigation.

Although the yields described in this paper have not been optimized yet, improvement will be expected during the course for the application of the present method to the total synthesis of the natural products 1 and 2, which is also in progress in our laboratory.

References and Notes

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3) For our previous papers entitled as "Pyranonaphthoquinone Antibiotics", see *J. Chem. Soc., Perkin I*, 1981, 1191, 1197.
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5) solvent system ; n-hexane : ethyl acetate = 3 : 1
6) Used as a HBr scavenger. V. Calo and L. Lopez, *J. Chem. Soc., Chem. Commun.*, 1975, 212.
7) By-products identified were the naphthalene and dihydronaphthalene derivatives.
8) V. VanRheenen, R.C. Kelly, and D.Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
9) R. Ray and D.S. Matteson, *Ibid.*, 1980, 449.
10) Ratio of 9a/9b varies with recipe and condition for the reaction within 1-2. The best ratio(9a/9b=2) was obtained by using trimethylamine N-oxide without pyridine additive.
11) solvent system ; chloroform : methanol = 20 : 1
12) From the experiments performed on 5a and 5b, it is apparent that the isomer 9a having more shielded methyl group is the desired one.
13) Procedure of R.J. Boatman, B.J. Whitelock, and H.W. Whitelock Jr., *J. Am. Chem. Soc.*, 1977, 99, 4822.
14) solvent system : benzene
15) E.J. Corey, R.L. Danheiser, S. Chandrasekaran, P. Siret, G.E. Keck, and J-L. Gras, *Ibid.*, 1978, 100, 8031.
16) solvent system ; ethyl acetate : chloroform = 3 : 1

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