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TOTAL SYNTHESIS OF (±)-AKLAVINONE VIA BIOMIMETIC ROUTE. APPLICATION OF AN EFFICIENT "ZIPPER" REACTION——STEREO-CONTROLLED ONE-STEP BICYCLO-CYCLIZATION[1)]

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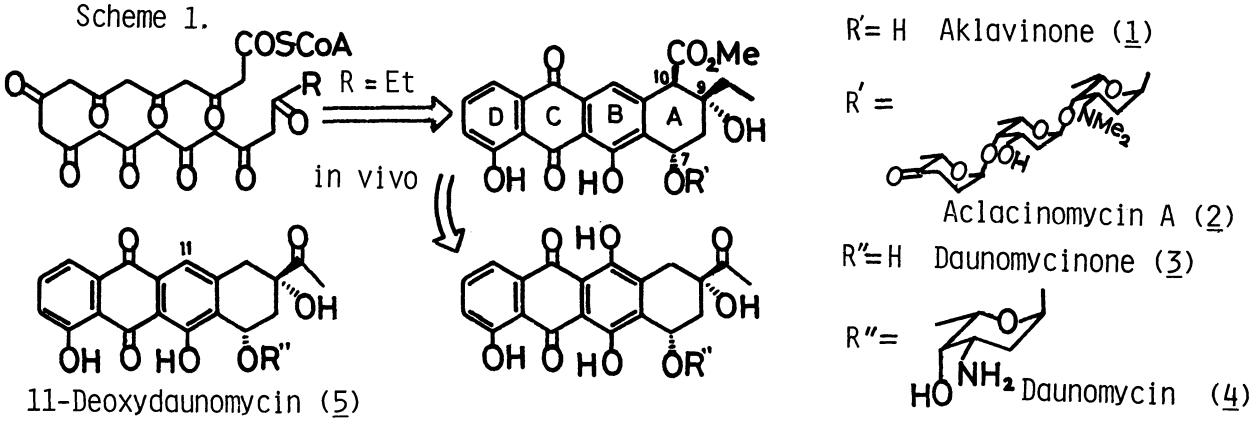
(±)-Aklavinone (1) was synthesized from tricarbonylnaphthalene derivative 6 by application of an efficient "zipper" reaction in a good yield. Using Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) in the key process of the reaction we attained a stereocontrolled one-step bicyclo-cyclization.

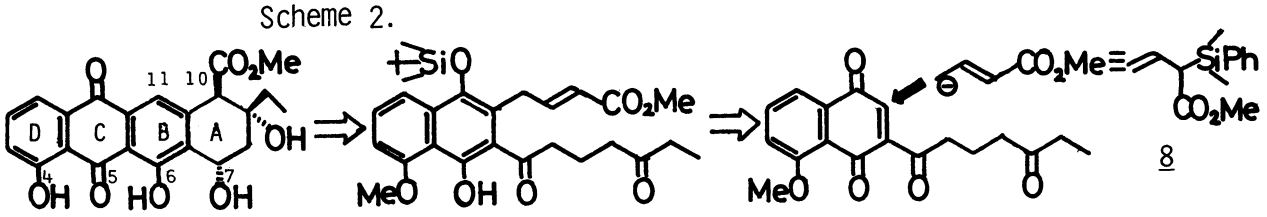
Although anthracyclines have attracted much attention for their antitumor activity, clinical use of them was of limited because of the dose-related cardiotoxic effects.[2)] However, anthracyclines which have no hydroxyl group at 11-position, aclacinomycin A (2)[3)] and 11-deoxydaunomycin (5),[4)] were reported to show higher antitumor activity and lower cardiotoxity. Therefore, a great interest of scientists in many fields has been focused on them. Especially organic chemists, who may modify the functional groups of compounds at will, have selected a new anthracycline group as a suitable target. Anthracyclinones, aglycons of anthracyclines, are likely to be synthesized *in vivo* from decaketides (Scheme 1), while the construction methods of tetracyclic skeleton reported so far consisted of combination of DC-rings and A-ring or of D-ring and BA-rings. We herein report a new synthetic route toward (±)-aklavinone (1)[5)] based upon biomimetic tricarbonyl cyclization as a key step of tetracyclic ring construction. Addition of an additive, Kryptofix 222, in the "zipper" reaction as a key step led us to a success in the stereocontrol.

Our retro-synthesis is shown in Scheme 2. The key intermediate 6[6,7)] was

Scheme 1.

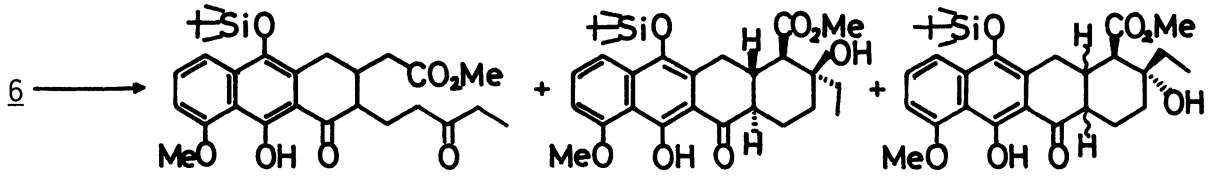


Scheme 2.



Aklavinone (1) 6 7 8

prepared from 3-acetyl-1,5-dimethoxy-4-naphthol (9)[8] in a 29% overall yield. Base promoted cyclization of the key intermediate 6 was examined under a variety of conditions. Results are summarized in Table 1. In methanol, intramolecular Michael addition simply occurred (Entries 1,2), while by treating with NaH in an aprotic solvent, tetracyclic compound 12,[6] whose stereochemistry was assigned to be cis in the relative configuration between 9-hydroxyl and 10-methoxycarbonyl groups, was obtained exclusively (Entries 3,4). The relative stereochemistry is opposite to the



11 12 13

Table 1.[a)]

Entry	Base	Conditions				Isolated yield/%[b)]			
		Additives	Solvent	Temperature	Time/h	11[c)]	12	13	6[d)]
1	K_2CO_3	none	MeOH	r.t.	2	62	-	-	-
2	NaOMe	none	MeOH	-78 °C→r.t.	2	97	-	-	-
3	KO^{t}Bu	none	THF	-78 °C→-50 °C	2	27	72	-	-
4	NaH	none	THF/DMF(1/1)	0 °C	2	-	89	-	-
5	DBU	none	THF	-78 °C→r.t.	4.5	(100)	-	-	-
6	Al_2O_3	none	THF	r.t.	19	(72)	(28)	-	-
7	KH	K222,[e)] HMPA	THF	-78 °C→-50 °C	3	-	25	53	-
8	KH	K222,[e)] HMPA	THF	-78 °C→-60 °C	3	26	25	17	trace
9	KH	K222,[e)] HMPA	THF	-78 °C→-60 °C	12	17(18)	16(24)	50(54)	-
10	KH	K222,[e)] HMPA	THF	-78 °C	9	(33)	-	-	(67)
11	NaH	K222,[e)] HMPA	THF	-78 °C→0 °C	4.5	-	(46)	(41)	-
12	NaH	K221,[f)] HMPA	THF	-78 °C→0 °C	2	-	(60)	(40)	-
13	LiH	K211,[g)] HMPA	THF	-78 °C→r.t.	7.5	-	(91)	(9)	-

a) A general procedure was performed as follows: a suspension of a base (excess) and additives, Kryptofix 222 (1 or 2 equiv. No difference could be observed in both cases.) and HMPA (1 equiv.), was stirred under a nitrogen atmosphere at room temperature. After one hour, a solution of 6 was added to the mixture and reacted as shown in Table. The mixture was quenched by aq-NH_4Cl solution and extracted by CH_2Cl_2 for several times. *b)* Yields in the parentheses are determined by NMR analyses of the reaction mixtures. *c)* Diastereomeric mixture (ca. 2:1). *d)* Recovered starting material. *e)* Kryptofix 222. *f)* Kryptofix 221. *g)* Kryptofix 211.

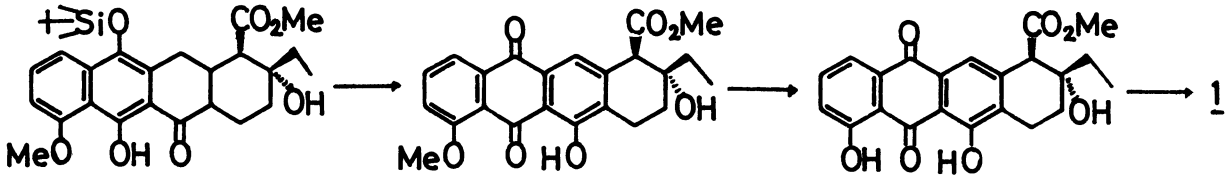
natural aklavinone. However, after several trials trans tetracyclic compounds 13[6] was obtained in a 53% yield when the [2.2.2]-KH cryptate was used as a base.

Trans tetracyclic compound 13 thus obtained was transformed to (±)-aklavinone (1) as follows (Scheme 3). After desilylative oxidation of 13 with CAN followed by reduction with $Na_2S_2O_4$, aromatization of B-ring (Br_2,AIBN,$CHCl_3$-CCl_4,ref.;Et_3N) accompanied with air oxidation gave anthraquinone 14[6] in a 76% yield. Demethylation of 14 with $AlCl_3$ followed by stereoselective introduction of 7-hydroxyl group (Br_2,AIBN,CCl_4ref.;THF/H_2O) afforded (±)-aklavinone (1)[9] in a 68% yield. In the similar way, (±)-10-epiaklavinone[10] was synthesized from cis tetracyclic compound 12 in a 45% yield.

In conclusion, we have achieved the total synthesis of (±)-aklavinone and (±)-epiaklavinone via biomimetic tricarbonyl cyclization in overall yields of 8.1% and 12% respectively from the starting naphthol 9.

We gratefully appreciate Prof. N. Tanaka and Dr. G. Lee(Institute of Peptides, Osaka University) for their X ray analysis of 12. This work was supported by funds from Yamada Science Foundation and by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

Scheme 3.



13 14 15

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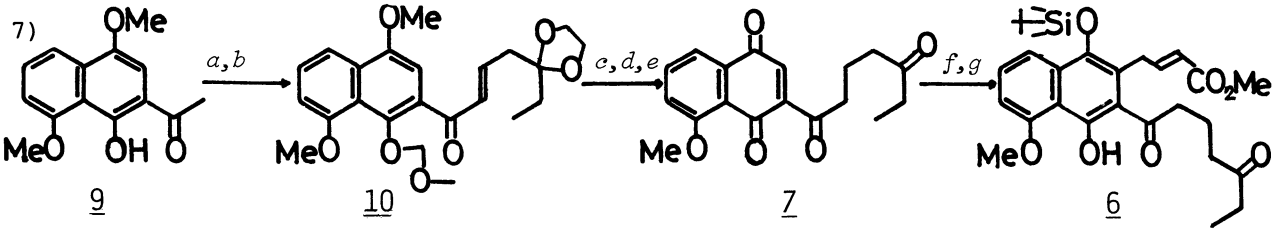
6) Physical and spectroscopic data of typical compounds are shown below; 6: pale yellow crystals, mp 109-111 °C; 100 MHz-^{1}H-NMR ($CDCl_3$) δ 0.13(6H,s), 1.06(9H,s; 3H,t,J=7 Hz), 1.96(2H,d,J=7 Hz), 2.44(2H,q,J=7 Hz), 2.52(2H,t,J=7 Hz), 2.94(2H,d,J=7 Hz), 3.67(3H,s;2H,d,J=6 Hz), 4.03(3H,s), 5.64(1H,d,J=16 Hz), 6.87(1H,d,J=8 Hz),

6.96(1H,dt,J=16, 6 Hz), 7.36(1H,t,J=8 Hz), 7.65(1H,d,J=8 Hz), 9.35(1H,s); IR (KBr) 3360, 1715, 1675, 1645, 1260, 1060 cm^{-1}; MS (20 eV) m/e 528(M^+,100%), 510(44%), 444(22%). 11: 2.1 diastereomeric mixture, orange yellow oil (yellow fluorescence); 100 MHz-^{1}H-NMR ($CDCl_3$) δ 0.14(6H), 1.0(3H), 1.08(9H) 2.25(2H), 1.6-3.4 (10H), 3.67(3H), 4.02(3H), 6.86(1H), 7.54(2H), 14.9(1H of minor diast.), 15.04 (1H of major diast.); IR (NaCl) 2920, 1715, 1705, 1605, 1255, 1050 cm^{-1}; MS (20 eV) m/e 528(M^+,100%), 526(51%), 510(8%), 456(8%). 12: yellow needles (yellow fluorescence), mp >185 °C(decomp.); 400 MHz-^{1}H-NMR ($CDCl_3$) δ 0.09(3H,s), 0.13 (3H,s), 0.95(3H,t,J=7.3 Hz), 1.08(9H,s), 1.35(1H,m,J=13.4, 10.0, 2.4 Hz), 1.42(1H, dq,J=15.3, 7.3 Hz), 1.48(1H,dq,J=15.3, 7.3 Hz), 1.82(1H,m,J=13.4, 11.0, 3.7 Hz), 1.97(1H,m,J=14.7, 3.7, 2.4 Hz), 2.24(1H,m,J=11.0, 3.7 Hz),2.32(1H,m,J=13.4, 2.4 Hz), 2.37-2.50(3H,m), 3.11(1H,d,J=12.2 Hz), 3.20(1H,s), 6.84(1H,m), 7.45-7.56(2H,m), 15.04(1H,s); IR (KBr) 3510, 2950, 1700, 1605, 1250, 1065 cm^{-1}; MS (20 eV) m/e 528 (M^+,100%). 13: orange yellow crystals (yellow fluorescence), mp 97-101 °C; 400 MHz-^{1}H-NMR ($CDCl_3$) δ 0.10(3H,s), 0.14(3H,s), 0.97(3H,t,J=7.3 Hz), 1.10(9H,s), 1.44(1H,dq,J=14.1, 7.3 Hz),1.52(1H,dq,J=14.1, 7.3 Hz), 1.58-1.69(2H,m). 2.13(1H, dt,J=13.6 Hz), 2.26(1H,dd,J=15.9, 13.5 Hz), 2.43(1H,m), 2.45(1H,m), 2.85(1H,d,J= 4.9 Hz), 2.98(1H,dt,J=12.8, 4.1 Hz), 3.2(1H,dd,J=16.4, 2.9 Hz), 3.71(3H,s), 4.01 (3H,s), 6.82(1H,d,J=7.8 Hz), 7.48(1H,t,J=8.0 Hz), 7.55(1H,d,J=8.3 Hz), 15.15 (1H,s); IR (KBr) 3460, 2900, 1720, 1600, 1240, 1060 cm^{-1}; MS (20 eV) m/e 528(M^+, 100%). 14: orange powder, mp >230 °C(decomp.); 400 MHz-^{1}H-NMR ($CDCl_3$) δ 1.07 (3H,t,J=7.5 Hz), 1.58(1H,s,OH), 1.60(1H,dq,J=14.9, 7.5 Hz), 1.68(1H,dq,J=14.9, 7.5 Hz), 1.91(1H,ddd,J=13.9, 7.0, 2.4 Hz), 2.29(1H,ddd,J=13.9, 10.3, 6.8 Hz), 2.83 (1H,ddd,J=19.3, 10.3, 7.0 Hz), 3.05(1H,ddd,J=19.3, 6.8, 2.4 Hz), 3.70(3H,s), 3.92 (1H,s), 4.06(3H,s), 7.33(1H,d,J=8.4 Hz), 7.56(1H,s), 7.71(1H,t,J=8.1 Hz), 7.92 (1H,d,J=7.7 Hz), 13.38(1H,s); IR (KBr) 3400, 1700, 1660, 1620 cm^{-1}; MS (70 eV) m/e 410(M^+,42%), 392(45%), 354(63%), 333(100%). 15: orange powder, mp >198 °C (decomp.); 100 MHz-^{1}H-NMR ($CDCl_3$) δ 1.08(3H,t,J=7 Hz), 1.2-3.3(7H,m), 3.73(3H,s), 3.93(1H,s), 7.25(1H,m), 7.5-7.9(3H,m), 12.02(1H,s), 12.40(1H,s); IR (KBr) 3400, 1720, 1660, 1610 cm^{-1}; MS (70 eV) m/e 396(M^+,36%), 388(46%), 367(25%), 364(33%), 340(57%), 320(33%), 319(94%), 307(75%), 278(100%).

7)



9 10 7 6

a; NaH, DMF, $ClCH_2OCH_3$, r.t. *b*; LDA, THF, 3-ethylenedioxypentanal, -78 °C→0 °C *c*; H_2, Pd/C, THF. *d*; p-toluenesulfonic acid, aq-acetone, ref. *e*; CAN, aq-CH_3CN, r.t. *f*; methyl 2-dimethylphenylsilyl-3-butenoate (8), $SnCl_4$, CH_2Cl_2, -78 °C→-30 °C 1 h. *g*; t-$BuMe_2SiCl$, imidazole, DMF, r.t., 4.5 h.

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9) Spectroscopic data (NMR, IR, MS) are identical with the natural one.

10) This substance is known as aklavinone-I; see D.Tresselt, K.Eckardt, and J.Tax, *Tetrahedron*, 31, 613 (1975).

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