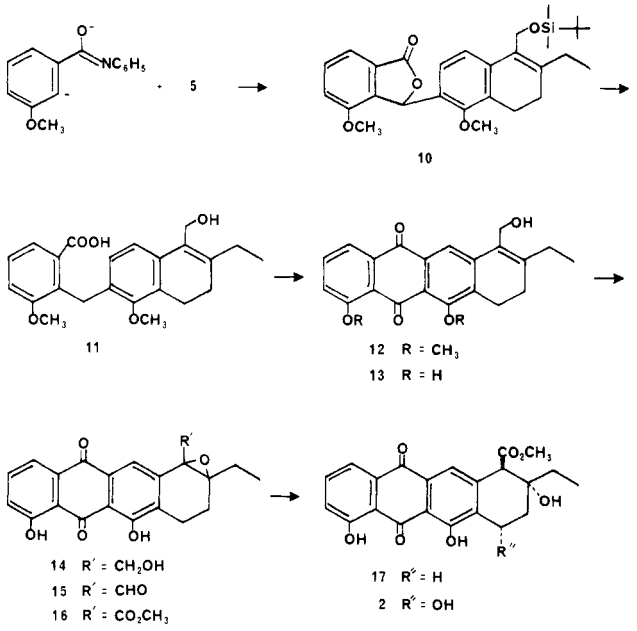
Scheme II



Epoxidation of triol **13** (*m*-chloroperbenzoic acid, CH_2Cl_2, aqueous $NaHCO_3$ buffer) gave the epoxide **14** (mp 185–187 °C) in 90% yield. Oxidation of the alcohol (PCC, CH_2Cl_2, room temperature, 24 h)[14] gave 79% of the epoxy aldehyde **15** (mp 210–212 °C),[15] which was separated from the aromatic impurity by preparative TLC. Sodium chlorite oxidation of aldehyde **15** (2 equiv of NH_2SO_3H, dioxane, room temperature, 15 min)[16] followed by brief treatment with diazomethane gave the epoxy ester **16** (mp 221–224 °C) in 98% yield. Stereospecific hydrogenolysis of the epoxide **16** ($Pd/BaSO_4$, 1:1 EtOH–$(HOCH_2CH_2)_3N$, H_2, 1 atm, room temperature, 2.5 h)[17] gave the single carbinol **17** (mp 220–222 °C)[18] in 76% yield.[19]

Finally, homolytic bromination of carbinol **17** with Br_2 in CCl_4 (2.0 equiv of Br_2, AIBN, CCl_4, reflux, 1 h) followed by solvolysis of the crude bromide with 1:1 H_2O–THF gave 88% of aklavinone (**2**) (mp 210–213 °C); ^1H NMR (400-MHz FT, $CDCl_3$) δ 12.73 (1 H, s), 11.96 (1 H, s), 7.83 (1 H, d, J = 8 Hz), 7.71 (1 H, s), 7.70 (1 H, t, J = 8 Hz), 7.31 (1 H, d, J = 8 Hz), 5.38 (1 H, br s, $\nu_{1/2}$ = 10), 4.09 (1 H, s); 3.85 (1 H, br s), 3.70 (3 H, s), 3.39 (1 H, br s); 2.54 (1 H, d of d, J = 12, 4 Hz), 2.27 (1 H, d, J = 12 Hz), 1.77–1.68 (1 H, m), 1.61–1.53 (1 H, m), 1.10 (3 H, t, J = 8 Hz).[20]

The remarkable kinetic stereospecificity (~10:1 cis) for introduction of C-7 hydroxyl is in contrast to the ratio (~5:2 trans) observed for 7-deoxydaunomycinone[21] but approaches that found in our laboratories for decarbomethoxyaklavinone (~5:1 cis)[7] and 10-*O*-acetyl-γ-rhodomycinone (~2:1 cis).[22] In the absence of C-13 carbonyl there appears to be a modest stereoelectronic preference for axial approach to the sp^2-hybridized C-7 (as quinone methide or carbocation), aided by possible hydrogen bonding of the entering nucleophile by the C-9 hydroxyl. In the daunomycinone series, participation by the C-13 carbonyl could favor the *trans*-diol.

It is of special interest that allylic alcohol **13** could be enantioselectively oxidized by the method of Sharpless.[23] Treatment of **13** with titanium(IV) isopropoxide (5 equiv), (−)diethyl *d*-tartrate (5 equiv) and *t*-BuOOH (10 equiv) in CH_2Cl_2 (−10 °C, 3 days) resulted in an 85% yield of the optically active epoxide **14**. An enantiomeric excess of 53 ± 2% was determined by ^1H NMR analysis of the corresponding MTPA ester[24] of **14**. This was confirmed by taking this epoxide on to aklavinone and comparing the specific rotation of our enantiomerically enriched produce ($[\alpha]_D$ +112° in dioxane)[25] with that reported for natural aklavinone ($[\alpha]_D$ +213° in dioxane).[26,27]

The above sequence comprises a stereospecific and enantioselective synthesis of aklavinone in 16 steps from 5-methoxy-1-tetralone with an overall yield of 6.5%.

Acknowledgment. We are grateful to Dr. P. Confalone (Hoffmann LaRoche Co.) for valuable discussions and reference samples. Partial support of this research by Grant CA-11326 awarded by the National Cancer Institute (USPHS) and Pharmacology Training Grant T-32-GM-07141 awarded by NIH to J.R. is gratefully acknowledged.

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(15) **15**: ^1H NMR (400 FT; $CDCl_3$) δ 12.40 (s, 1 H); 12.01 (s, 1 H), 10.00 (s, 1 H), 8.05 (s, 1 H), 7.84 (d, J = 8 Hz, 1 H), 7.70 (t, J = 8 Hz, 1 H), 7.31 (d, J = 8 Hz, 1 H), 3.41 (d of d, J = 17.4 Hz, 1 H), 2.55–2.46 (m, 1 H), 2.43–2.37 (m, 1 H), 2.03–1.92 (m, 2 H), 1.83–1.74 (m, 1 H), 1.10 (t, J = 8 Hz, 3 H).

(16) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

(17) For the hydrogenolysis of a related benzylic hydroxyl, see: Brockmann, H.; Niemeyer, J.; Brockmann, H., Jr.; Budzikiewicz, H. *Chem. Ber.* **1965**, *98*, 3785.

(18) **17**: ^1H NMR (400 FT, $CDCl_3$) δ 12.51 (s, 1 H), 12.10 (s, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.67 (t, J = 8 Hz, 1 H); 7.66 (s, 1 H), 7.29 (d, J = 8 Hz, 1 H), 3.94 (s, 1 H), 3.73 (s, 3 H), 3.10–3.03 (m, 1 H), 2.90–2.80 (m, 1 H), 2.37–2.27 (m, 1 H), 1.96–1.90 (m, 1 H), 1.77–1.67 (m, 1 H), 1.65–1.58 (m, 1 H), 1.51 (br s, 1 H); 1.09 (t, J = 8 Hz, 3 H).

(19) The complete stereospecificity observed in our hydrogenolysis (retention at benzylic position) is not typical of liquid-phase Pd-catalyzed hydrogenolysis of cyclohexene epoxides (cf. Accrombessi, G. C.; Geneste, P.; Olive, J.-L. *J. Org. Chem.* **1980**, *45*, 4139). This stereospecificity has been independently observed by P. Confalone (private communication). In the case of **17** the observed hydrogenolysis may be preceded by quinone reduction, elimination to a quinone methide, and hydrogenation of the latter.

(20) This was identical with natural aklavinone supplied by Dr. T. Oki (Sanraku Ocean Ltd.) and Dr. P. Confalone (Roche) and its identity independently confirmed by Professor Y. Kishi (Harvard University) through comparison with a sample of (±)-aklavinone recently synthesized in his laboratories. A total synthesis of aklavinone has also been completed by P. Confalone (Roche); see accompanying communications.

(21) Kende, A. S.; Tsay, Y.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967.

(22) Tsay, T., unpublished observations from this laboratory.

(23) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974 and references therein.

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(25) Recrystallization of intermediates and final product must be avoided due to preferential crystallization of the racemate.

(26) Thomson, R. H. "Naturally Occurring Quinones", 2nd ed.; Academic Press: New York, 1971; p 536.

(27) All new compounds showed NMR, IR, and CH or mass spectrometric analyses consistent with the assigned structures.

Practical Total Synthesis of (±)-Aklavinone and Total Synthesis of Aklavin

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The clinical efficacy of the anthracycline antibiotics adriamycin and daunomycin as agents for the treatment of human cancers has stimulated extensive synthetic work.[1] However, in spite of some promising aspects such as low cardiac toxicity, very little attention has been focused on the synthesis of aclacinomycin A (**1**).[2] In this communication we would like to report a practical

†National Institutes of Health Postdoctoral Fellow, 1976–1979.

‡National Institutes of Health Trainee at Harvard University, 1979–1981.

(1) For recent reviews on the anthracycline antibiotics, see: (a) Arcamone, F. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Halsted Press: New York; 1978; Vol. 2. (b) Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 125. (c) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: Somerset, NJ; 1979; Vol. 1. (d) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288.

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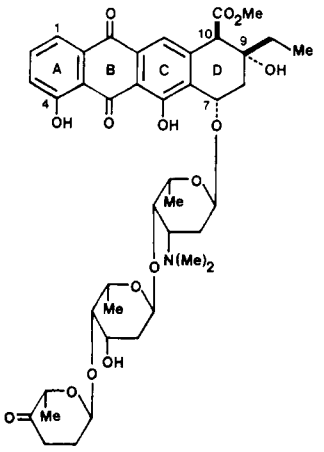
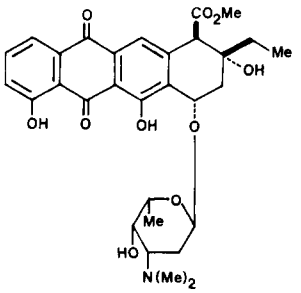


1 : aclacinomycin A



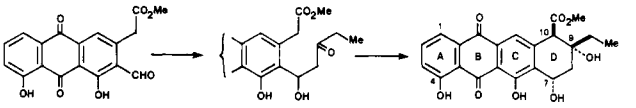
2 : aklavin

total synthesis of racemic aklavinone (**13**), the aglycon of aclacinomycins, and also report a total synthesis of aklavin (**2**),[3] the simplest member of the aclacinomycin group of anthracycline antibiotics.

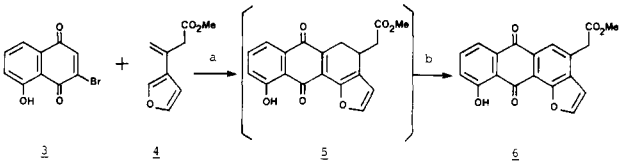
Our basic plan in controlling the functionalities on ring D[4] is outlined in Scheme I. An attractive aspect of this approach is that the C7 hydroxy group could be introduced without going through a C7 bromo compound, the synthesis of which is known to often cause technical problems in the adriamycin–daunomycin series.[5]

Among various possibilities examined, the sequence of reactions summarized in Scheme II provides the most practical route to an immediate precursor of the aldehyde requisite for this study.[6]

Scheme I



Scheme II[a]



3 4 5 6

[a] Reagents: (a) **3** + **4** (3 equiv)/C_6H_6/$SrCO_3$/4,4′-thiobis(6-*tert*-butyl-3-methylphenol)/reflux. (b) Air/(*i*-Pr)$_2$(Et)N/$CHCl_3$/room temperature.

There are several comments worth mentioning about this Diels–Alder reaction. First, under the conditions indicated there was no detectable amount of the regioisomer.[7] Second, addition of strontium carbonate was necessary to avoid substantial decomposition, probably due to hydrogen bromide produced, of the product and reactants. Third, addition of a radical scavenger [4,4′-thiobis(6-*tert*-butyl-3-methylphenol)][8] seemed to depress decomposition of the diene **4**.[9] Nonetheless, about 3 equiv of the diene were necessary to obtain the maximum yield. The crude adduct was directly oxidized to the benzofuran **6**[10] (mp 209–211 °C), which was best achieved by air in chloroform containing diisopropylethylamine. The overall yield of **6** from bromojuglone **3**[11] was 80–85%.

Ozonolysis of the benzofuran **6** in methylene chloride at −78 °C, followed by dimethyl sulfide workup, yielded the aldehyde **7**[10] (mp 205–209 °C) almost quantitatively. The crossed aldol reaction of **7** with 1-(trimethylsilyl)-2-butanone[12] was effected in methylene chloride containing titanium tetrachloride[13a] at −20 °C to give the expected aldol. However, this aldol was found not to behave as planned under basic conditions. Since one of the problems encountered was apparently the participation of the C7 hydroxy group to the carbomethoxy group,[14] the protected aldol

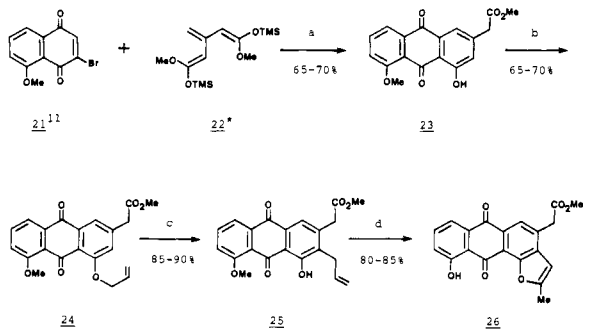
(2) (a) Isolation: Oki, T.; Kitamura, I.; Yoshimoto, A.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, T.; Inui, T.; Takamatsu, A.; Takeuchi, T.; Masuda, T.; Hamada, S.; Suda, H.; Ishizuka, M.; Sawa, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 791. (b) Structure elucidation: Oki, T.; Kitamura, I.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, Y.; Yoshimoto, A.; Inui, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 801. (c) Biological activity: Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Matsuzawa, Y.; Oki, T.; Inui, T. *J. Antibiot.* **1980**, *33*, 1323 and references cited therein.

(3) (a) Isolation: Strelitz, F.; Flon, H.; Weiss, U.; Asheshov, I. N.; *J. Bacteriol.* **1956**, *72*, 90. (b) Structure elucidation: Kumar, V.; Remers, W. A.; Grulich, R. *J. Antibiot.* **1977**, *30*, 881.

(4) Numbering in this paper corresponds to that used for the anthracycline antibiotics by Remers[1c] and also by Doyle.[21]

(5) For example, see the comments made by: Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, 3669. Jackson, D. K.; Narasimham, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. For routes *not* via bromination, see: Kelly, T. R.; Vaya, J.; Ananthasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5983. Krohn, K. *J. Chem. Res. Synop.* **1979**, 318, in addition to the two papers quoted above.

(6) We have developed four different routes to a benzofuran of type **6**. Among them, the following sequence of reactions also provided the benzofuran **26** in practical overall yield. For a similar Diels–Alder reaction, see: Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, 4911 and references cited therein. The benzofuran **26** proved to be as good a precursor as **6**.



21[11] 22* 23 24 25 26

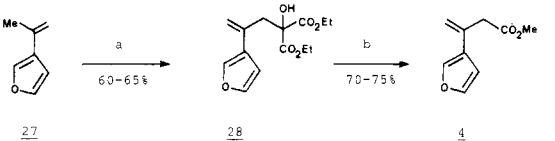
Reagents a. Diels-Alder reaction/Et_2O-CH_2Cl_2/-40°C, followed by silica gel workup. b. CH_2=$CHCH_2Br$/Ag_2O/C_6H_6/reflux. c. (o)-$C_6H_4Cl_2$/reflux. d. 1. $PdCl_2(C_6H_5CN)_2$/C_6H_6/reflux, 2. BCl_3/CH_2Cl_2/-78°C.

* The stereochemistry of the olefinic bonds is unknown.

(7) The signal of the phenol proton in the NMR spectrum of **5**, and also of the dimethyl acetal, i.e., X = $CH(OCH_3)_2$ in **7**, is very useful to determine the regioselectivity.

(8) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

(9) The diene **4** was prepared by the following sequence of reactions. For a similar sequence of reactions, see: Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2473.



27 28 4

Reagents a. EtO_2CCOCO_2Et/$CHCl_3$/160°C. b. 1. 10% KOH/RT, 2. $NaIO_4$/H_2O/RT, 3. CH_2N_2/Et_2O.

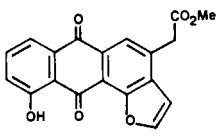
(10) This substance gave satisfactory elemental analysis and spectroscopic data.

(11) Wheeler, A. S.; Naiman, B. *J. Am. Chem. Soc.* **1922**, *44*, 2331. Thomson, R. H. *J. Org. Chem.* **1948**, *13*, 377. Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.

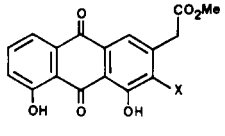
(12) This ketone was prepared by the reaction of $(CH_3)_3SiCH_2MgCl$–CuI and CH_3CH_2COCl in 80–90% yield, which seems to be more convenient and efficient than the known method (Musker, W. K.; Ashby, R. W. *J. Org. Chem.* **1966**, *31*, 4237. Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136).

(13) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887.

8[10] (mp 111–114 °C) was synthesized from **6** in 70–75% overall yield in 2 steps, i.e., acetalization (H_2SO_4/CH_3OH/reflux) and aldolization [$(CH_3)_3SiCH_2COCH_2CH_3$ (excess)/$SnCl_4$/CH_2Cl_2/−40 °C].[13b]

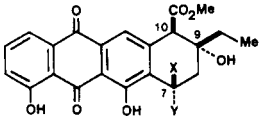


6



7 : X = CHO

8 : X = CH(OMe)CH_2COCH_2Me

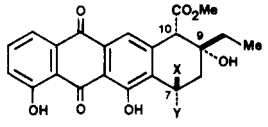


9 : X = H, Y = OMe

10 : X = OMe, Y = H

13 : X = H, Y = OH (aklavinone)

14 : X = OH, Y = H



11 : X = OMe, Y = H

12 : X = H, Y = OMe

15 : X = H, Y = OH

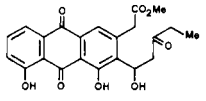
Potassium carbonate treatment of **8** (1.7 equiv of K_2CO_3/CH_3OH/room temperature/1.75 h) yielded an about 10:7:1 mixture of the cyclization products, which were isolated by silica gel chromatography: **11**[10,15] (~50% yield, mp 191–192 °C), **9**[10,16] (~36% yield, mp 193–199 °C), and **10**[10,17] (~5% yield, mp 205–207 °C).[18] Applying the NMR method used by Tresselt, Eckardt, and Tax[19] to this case, the relative stereochemistry at the C9 and C10 positions of **9** and **10** was tentatively assigned and later confirmed by the successful transformation of **9** and **10** to aklavinone (**13**), as the natural type,[20] and that of **11** as the unnatural.

The stereochemistry at the C7 position was concluded from the following equilibrium experiments. Upon 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) treatment (2 equiv/CH_2Cl_2/0 °C),[21] **11** yielded an about 6:1 equilibrium mixture[22] of **11** and **10**. Since the equilibrium was established via enolization of the C10 carbomethoxy group (compare with the K_2CO_3 experiment described in ref 26), this experiment concluded that **11** and **10** were stereoisomers at the C10 position. Structure **11** was assigned to the thermodynamically more stable isomer, since a conformation with *no* periinteractions involving the bulky C10 carbomethoxy or C7 methoxy groups is available for this.[23] The stereochemistry at the C7 position of **9** could be analyzed similarly. Upon DBN treatment, **9** yielded an about 3:1 equilibrium mixture[22] of **9** and **12** (mp 184–187 °C),[10,24] the C10 stereoisomer of **9**, which allowed assignment of the structure **9** to the thermodynamically more stable isomer.[25,26]

Hydrolysis of the C7 methoxy group of **9** and **10** was initially attempted under conditions known for epimerization of the C7 hydroxy group;[27] thus, trifluoroacetic acid treatment at room temperature, followed by aqueous workup, yielded an about 8:1 mixture of *dl*-aklavinone (**13**) and *dl*-7-*epi*-aklavinone (**14**) in about 60% yield from either **9** or **10**. However, hydrolysis by using boron trifluoride etherate (BF_3·Et_2O/CH_2Cl_2/room temperature), followed by aqueous workup, yielded exclusively *dl*-aklavinone (**13**)[10,28] [mp 203–206 and 223–228 °C (double melting points)] in 80–85% yield *from either* ***9*** or ***10***. The observed stereospecificity under the new conditions might be explained by considering a borate ester, involving the C7 and C9 hydroxy groups, as an intermediate. The synthetic substance was found to be identical with an authentic sample of natural aklavinone[29] by comparison of spectroscopic (NMR, UV, MS, IR) and TLC data.

The new hydrolysis conditions also allowed conversion of compound **11** to aklavinone (**13**) in high yield. Boron trifluoride treatment of **11** (BF_3·Et_2O/CH_2Cl_2/room temperature), followed by aqueous workup, yielded almost exclusively 10-*epi*-aklavinone (**15**)[30] in 85–90% yield. After protection of the C7 hydroxyl group as a tetrahydropyranyl (DHP/*p*-TSA·Py/CH_2Cl_2/room temperature), 10-*epi*-aklavinone was exposed to basic conditions (2 equiv of DBN/CH_2Cl_2/0 °C) to yield an about 3:1 mixture of 7-(tetrahydropyranyl)aklavinone and 7-(tetrahydropyranyl)-10-*epi*-aklavinone. With two recycles of 7-(tetrahydropyranyl)-10-*epi*-aklavinone, 7-(tetrahydropyranyl)aklavinone was obtained in 70–75% yield from 10-*epi*-aklavinone. Hydrolysis of 7-(tetrahydropyranyl)aklavinone (*p*-TSA·Py/MeOH/55 °C) yielded

(14) The major product isolated on base treatment (Et_3N/CH_3CN/70 °C) of the aldol **29** was the α,β-unsaturated ketone **31a** (the stereochemistry of the olefinic bond is unknown). The formation of **31a** seemed to be best explained by considering the lactone **30** as an intermediate, since potassium carbonate treatment of **8** yielded a small amount of the α,β-unsaturated ketone **31b** (the stereochemistry of the olefinic bond is unknown) in addition to **11**, **9**, and **10**.[26]



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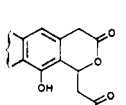
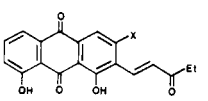


30



31a : X = Me

31b : X = CH_2CO_2Me

(15) NMR ($CDCl_3$): 0.99 (3 H, t, J = 7.2 Hz), 3.50 (3 H, s), 3.80 (3 H, s), 4.06 (1 H, s), 4.85 (1 H, dd, J = 5.0, 3.3 Hz), 11.99 (1 H, s), 12.55 (1 H, s) ppm.

(16) NMR ($CDCl_3$): 1.09 (3 H, t, J = 7.2 Hz), 3.62 (3 H, s), 3.68 (3 H, s), 4.14 (1 H, s), 4.89 (1 H, t, J = 3.0 Hz), 11.98 (1 H, s), 12.64 (1 H, s) ppm.

(17) NMR ($CDCl_3$): 1.04 (3 H, t, J = 7.2 Hz), 3.53 (3 H, s), 3.75 (3 H, s), 3.90 (1 H, s), 4.84 (1 H, t, J = 6.5 Hz), 12.03 (1 H, s), 12.65 (1 H, s) ppm.

(18) The choice of solvent seemed to be critical; cyclization of **8** with K_2CO_3, Et_3N, or DBN in aprotic solvents such as the THF or CH_2Cl_2 yielded exclusively **11**, while cyclization with Et_3N or DBN in alcoholic solvents gave results almost identical with those with K_2CO_3 in CH_3OH.

(19) Tresselt, D.; Eckardt, K.; Tax, J. *Tetrahedron* **1975**, *31*, 613.

(20) The term "natural type" is used to indicate the C9 and C10 relative stereochemistry found in aklavinone and aklavinone-II, while the term "unnatural type" is used to indicate that in aklavinone-I.[19]

(21) For epimerization of the C10 position under basic conditions, see: Doyle, T. W.; Nettleton, D. E.; Grulich, R. E.; Balitz, D. M.; Johnson, D. L.; Vulcano, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 7041. Essery, J. M.; Doyle, T. W. *Can. J. Chem.* **1980**, *58*, 1869 and also ref 2c.

(22) The equilibrium ratio was also confirmed in the reverse direction.

(23) For the conformation of aklavinones, see: Brockmann, H.; Brockmann, H., Jr.; Niemeyer, J. *Tetrahedron Lett.* **1968**, 4719 and also ref 1a and 21.

(24) NMR ($CDCl_3$): 1.00 (3 H, t, J = 7.2 Hz), 3.54 (3 H, s), 3.77 (3 H, s), 4.01 (1 H, s), 4.99 (1 H, t, J = 3.2 Hz), 12.01 (1 H, s), 12.64 (1 H, s) ppm.

(25) Details of the stereochemistry assignment based on conformational analysis and NMR data will be presented in a full paper.

(26) Potassium carbonate treatment of **11** (3.7 equiv of K_2CO_3/MeOH/1.75 h) *at 65 °C* resulted in a mixture of **11** (isolated yield 34%), **9** (21%), **10** (11%), and **12** (trace) along with two side products, i.e., the α,β-unsaturated ketone **31b** and the fully aromatized product known as bisanhydroaklavinone (for example, see a review by Brockmann, H. *Prog. Chem. Org. Nat. Prod.* **1963**, *20*, 122). This result strongly suggests that, contrary to the DBN equilibrium experiments, the protected aldol **8** was regenerated under these conditions. The reaction was also useful for converting **11**, which has the unnatural relative configuration at the C9 and C10 positions, to **9** and/or **10**, both of which have the natural configurations at these centers; thus, two recycles of **11** yielded **9** and **10** in about 60% combined yield.

(27) (a) Brockmann, H.; Niemeyer, J. *Chem. Ber.* **1967**, *100*, 3578. (b) Kende, A. S.; Tsay, Y.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967. (c) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969.

(28) NMR ($CDCl_3$): 1.10 (3 H, t, J = 7.2 Hz), 3.70 (3 H, s), 4.09 (1 H, s), 5.38 (1 H, br s), 11.94 (1 H, s), 12.72 (1 H, s) ppm.

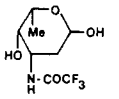
(29) (a) An authentic sample of aklavinone was prepared by hydrolysis of natural aclacinomycin A.[2b] We are indebted to Professor Umezawa, Institute of Microbial Chemistry, and Dr. Oki, Sanraku-Ocean, Inc., for a generous gift of a sample of aclacinomycin A. (b) We thank Dr. M. R. Uskokovic, Hoffmann-La Roche, Inc., for a generous gift of aklavinone, isolated from fermentation broths.

(30) This substance is known as aklavinone-I.[19]

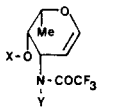
aklavinone nearly quantitatively.

The overall yield of aklavinone from bromojuglone was 34–41% counting two recycles of **11** and 18–22% not counting the recycles. Following the route exactly parallel with the one described for aklavinone, several aklavinone analogues have been synthesized. These results will be published elsewhere.[31]

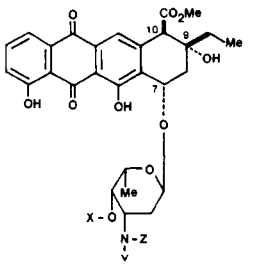
The glycosidation reaction of racemic aklavinone (**13**) and the *N*-methyl glycal **17**[10,32] (oil), prepared from *N*-(trifluoroacetyl)-



16

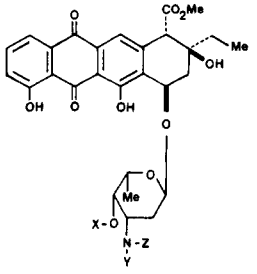


17 : X = $COC_6H_4NO_2$(p), Y = Me



18 : X = $COC_6H_4NO_2$(p), Y = Me, Z = $COCF_3$

20 : X = H, Y = Me, Z = H



19 : X = $COC_6H_4NO_2$(p), Y = Me, Z = $COCF_3$

daunosamine (**16**),[33-35] was smoothly effected in benzene containing a catalytic amount of *p*-toluenesulfonic acid monohydrate at 50 °C[36] to yield a mixture of mainly two products, chromatographic separation of which gave the glycosides **18**[10,37] (25–30% yield; mp 159–161 °C) and **19**[10,38] (25–30% yield; mp 158–161 °C). The NMR spectrum, in particular the spin–spin coupling constants and chemical shift of the anomeric proton, clearly indicated that both of the products were glycosides with the α-anomeric configuration. From the following experiments, the glycoside **18** was shown to be derived from aklavinone with the natural absolute configuration, while the glycoside **19** from aklavinone with the unnatural absolute configuration: (1) Acid hydrolysis of **18** (90% aqueous TFA/room temperature) yielded aklavinone with $[\alpha]_D$ +146°, whereas that of **19** yielded aklavinone with $[\alpha]_D$ −141°. The specific rotation of natural aklavinone[29] is known to be +158° in chloroform. (2) Glycosidation using aklavinone with the natural absolute configuration[29] gave only the glycoside **18** (mp, NMR, $[\alpha]_D$, TLC).

The stereoselectivity of the glycosidation was very high. This was most conclusively demonstrated by coupling aklavinone with the natural absolute configuration with the glycal **17**; NMR and TLC analysis of the reaction mixture indicated that several minor products were formed besides the desired glycoside **18** (80% isolated yield), but we were unable to isolate a large enough quantity of any one of the minor products to firmly assign a structure. However, the ratio of the α anomer to the β anomer, if any, was estimated to be better than 20:1.

Sodium methoxide treatment of **18** [$NaOCH_3$(excess)/CH_3OH/−20 °C/2 h] yielded *N*-demethylaklavin (**20**) along with a small amount (<5%, based on NMR analysis) of its C10 epimer; these conditions were crucial to the success of this transformation, since longer reaction time and/or higher reaction temperature led to the formation of as much as 35% of the C10 epimer (NMR and TLC analysis). The crude product was directly subjected to *N*-methylation by using the Borch procedure[39] (aqueous $CH_2O/NaBH_3CN$/AcOH/room temperature/1 h) to yield aklavin (**2**) in 70% overall yield from **18**. The synthetic substance was found to be identical with natural aklavin[40] on comparison of spectroscopic (NMR, IR, UV, $[\alpha]_D$) and TLC data.

Acknowledgment. Financial support from the National Cancer Institute, DHEW (Grant CA22215), is gratefully acknowledged.

(31) Sekizaki, H.; Hasan, I.; McNamara, J. M.; Kishi, Y., manuscript in preparation.

(32) Optically active *N*-trifluoroacetyldaunosamine (**16**)[33,34] was converted to the previously unknown glycal[10] [X = COC_6H_4-*p*-NO_2, Y = H in structure **17**; mp 152–153 °C] in 84% overall yield in 2 steps (i.e., (1) $ClCOC_6H_4$-*p*-NO_2/(dimethylamino)pyridine–pyridine/room temperature,[35] (2) 185 °C at 2.5 mmHg). N-methylation of this glycal under standard conditions (CH_3I/K_2CO_3/acetone/50 °C) afforded the *N*-methyl glycal **17**[10] [oil; NMR ($CDCl_3$): 1.29 (3 H, d, J = 6.6 Hz), 2.95 (3 H, q, J = 1.7 Hz), 4.67 (1 H, dt, J = 6.4, 2.0 Hz), 6.75 (1 H, dd, J = 6.4, 2.3 Hz) ppm; $[\alpha]_D$ −173° (*c* 1.12, $CHCl_3$)] in 92% yield.

(33) For the synthesis of daunosamine, see: (a) Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *Chem. Commun.* **1967**, 973. (b) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1976**, *46*, 227. (c) Wong, C. M.; Ho, T.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144. (d) Yamaguchi, T.; Kojima, M. *Carbohydr. Res.* **1977**, *59*, 343. (e) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1980**, 442. (f) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

(34) We are indebted to Dr. M. R. Uskokovic, Hoffmann-La Roche, Inc., for a sample of this substance.

(35) The product at this stage is a known substance (see: Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653).

(36) Arcamone, F.; Bargiotti, A.; Cassinelli, G.; Redaelli, S.; Hanessian, S.; DiMarco, A.; Casazza, A. M.; Dasdia, T.; Necco, A.; Reggiani, P.; Supino, R. *J. Med. Chem.* **1976**, *19*, 733. We thank Professor Hanessian, University of Montreal, for various procedures of the glycosidation.

(37) NMR ($CDCl_3$): 1.11 (3 H, t, J = 7.1 Hz), 1.22 (3 H, d, J = 6.2 Hz), 2.87 (3 H, br s), 3.70 (3 H, s), 5.32 (1 H, br s), 5.59 (1 H, br s), 5.75 (1 H, br s) ppm; $[\alpha]_D$ − 50° (*c* 0.328, $CHCl_3$).

(38) NMR ($CDCl_3$): 1.10 (3 H, t, J = 7.1 Hz), 1.24 (3 H, d, J = 6.5 Hz), 2.85 (3 H, br s), 3.73 (3 H, s), 5.60 (3 H, br s) ppm; $[\alpha]_D$ −336° (*c* 0.147, $CHCl_3$).

(39) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

(40) We are indebted to Dr. U. Weiss, National Institutes of Health, for a sample of natural aklavin.

Total Stereospecific Synthesis of (±)-Aklavinone

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The clinically important antitumor antibiotic aclacinomycin A (**1**), originally isolated from *Streptomyces galilaeus*,[1] exhibits inhibitory activity against leukemia L-1210 and P-388, sarcoma 180, 6C3HED lymphosarcoma, and other transplantable animal tumors.[2] Moreover, this anticancer agent shows less cardiotoxicity than either adriamycin or daunorubicin.[3] We wish to report the first total synthesis of (±)-aklavinone (**2**), the aglycon portion of aclacinomycin A, originally isolated by Ollis and co-workers as the naturally occurring (+) enantiomer.[4]

Reaction of 3-methoxyphthalic acid 1-methyl ester (**3**)[5] with 6-ethyl-5,6,7,8-tetrahydro-1-naphthol (**4**)[6] in the presence of

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(3) Yamaki, H.; Suzuki, H.; Mishimura, T.; Tanaka, N. *J. Antibiot.* **1978**, *31*, 1149–1154. Misumi, M.; Yamaki, H.; Akiyama, T.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 48–52.

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