A Stereospecific Total Synthesis of Aklavinone

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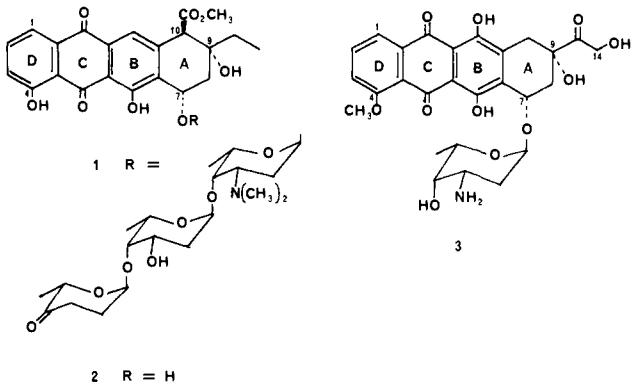
Aclacinomycin A (**1**) is a relatively new anthracycline isolated from *Streptomyces galilaeus* in 1975.[1] This antibiotic has been



1 R =

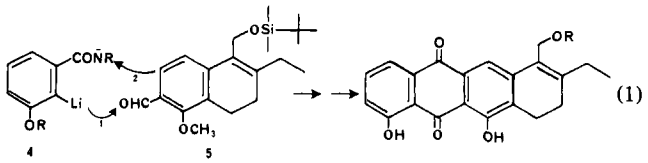
3

2 R = H

found to exhibit strong antineoplastic activity and substantially reduced toxicity relative to the clinically important agent adriamycin (**3**).[2] Current advances in the high-yield enzymatic glycosidation[3] of aklavinone (**2**) to the aclacinomycins has prompted vigorous activity toward the synthesis of aklavinone and its derivatives, although no total synthesis of **2** has yet been published. We now describe an efficient and stereospecific total synthesis of aklavinone (**2**) which provides practical access to this important anthracyclinone.

The two major challenges in the construction of aklavinone (**2**) are (a) the regiospecific connection of the D ring to an AB unit lacking C-11 oxygen and (b) timely and stereospecific introduction of the C-10 carbomethoxy group in a suitable form. The first of these challenges appears to preclude the various B-ring quinone strategies for daunomycinone successfully employed by Kelly and others.[4] The second appears to require early incorporation of the C-10 substituent, since strategies involving the late addition of a one carbon unit to a tetracyclic C-10 ketone are nonconvergent and can lead to severe tactical difficulties involving the hindered C-10 region.[5]

Regiospecific control in the connection of the D ring to the AB unit involves the condensation of a preformed bicyclic AB aldehyde (**5**) with a nucleophilic D-ring carboxamide (**4**), with stepwise bond formation as illustrated in eq 1.[6] The siloxymethyl aldehyde **5**



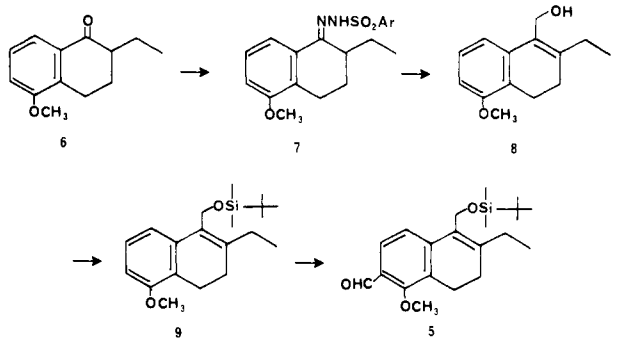
(1)

4 5

already contains the requisite C-10 carbon substituent and offers highly convergent access to the target aglycon **2**.

Construction of AB aldehyde **5** involved interesting modifications of the Shapiro reaction and heteroatom-facilitated *o*-lithiation. Tetralone **6**[7] was converted into its 2,4,6-triisopropylbenzenesulfonylhydrazone by the method of Bond (1.0 equiv of $ArSO_2NHNH_2$, MeOH/HCl, 0 °C, 24 h),[8] giving **7** (mp 161–163 °C) in 85% yield. Reaction of hydrazone **7** with *n*-BuLi (2.0 equiv of THF, −78 °C to room temperature) and trapping of the resulting vinyl anion[8] with paraformaldehyde gave 45% of the carbinol **8** (mp 87–89 °C) after silica gel chromatography. Alternatively, if the vinyl anion was trapped with DMF[8] followed by treatment with $NaBH_4$ directly after silica gel chromatography, carbinol **8** was obtained in 54% yield. Protection of the hydroxyl (1 equiv of *t*-$BuMe_2SiCl$, 2 equiv of imidazole, DMF, room temperature)[9] led quantitatively to the *tert*-butyldimethylsilyl (TBDMS) ether **9** which was used in the subsequent metalation step without further purification. Our choice of the bulky TBDMS group was critical, for smaller blocking groups (e.g., CH_3, $SiMe_3$, THP) directed competitive metalation to the B-ring position para to the methoxy. In contrast, reaction of TBDMS ether **9** with 1 equiv of *t*-BuLi–TMEDA complex in hexanes at 0 °C for 4 h, followed by inverse quench with DMF in THF at 0 °C gave the desired aldehyde **5** (mp 50–51 °C)[10] in 80% yield.

Scheme I



6 7 8

9 5

Generation of the nucleophilic carboxamide **4** was accomplished by reaction of 3-methoxybenzanilide with 2.0 equiv of *n*-BuLi–TMEDA (THF, from −78 to −20 °C, 5 h).[6a] Subsequent addition of aldehyde **5** (from −78 °C to room temperature, 16 h) followed by workup with cold aqueous oxalic acid gave phthalide **10** (mp 111–113 °C) in 80% yield. Reduction of **10** with zinc dust (1 N NaOH, reflux, 48 h)[11] gave the desilylated hydroxy acid **11** (mp 148–149 °C) in 95% yield. The latter was smoothly cyclized [$(CF_3CO)_2O$–CH_2Cl_2, 0 °C, 4 h] to the anthrone, which was immediately oxidized (O_2, CH_3OH, Triton B, room temperature) to the anthraquinone **12** (mp 233–234 °C)[12] in 60% overall yield. At this point we encountered major difficulties in O-demethylation of **12** to the dihydroxyanthraquinone system. Lewis acid reagents (e.g., BBr_3, $AlCl_3$) attacked the allylic hydroxyl, even when protected; nucleophilic demethylation (e.g., LiSMe, –CN, PhNMe) led to concomitant aromatization of the A ring. Selective demethylation was ultimately achieved by using LiI in the presence of $PhCO_2H$ (in 1:1 pyridine–collidine, 145 °C, 90 min).[13] Under these exact conditions quinone **12** was reproducibly converted to the triol **13** (mp 199–201 °C) in 92% yield, accompanied by ca. 3% of the corresponding aromatic A-ring derivative. Because of the difficulty in separating these compounds, they were carried through together for two more steps, where purification proved easier.

(1) Oki, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Maganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830.

(2) Hori, S.; Shirai, M.; Shinchi, H.; Oki, T.; Inui, T.; Tsukagoshi, S.; Ishizuka, M.; Takeuchi, T.; Umezawa, H. *Gann* **1977**, *68*, 685.

(3) Oki, T.; Yoshimoto, A.; Matsuzawa, Y.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1331.

(4) For a comprehensive review of previous synthetic studies, see: (a) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288. (b) Kelly, T. R.; Vaya, J.; Ananthasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5983.

(5) Unpublished observations from these laboratories.

(6) For the use of this reaction in the synthesis of simple anthraquinones, see: (a) Baldwin, J. E.; Blair, K. W. *Tetrahedron Lett.* **1978**, 2559. (b) Forbes, I.; Pratt, R. A.; Raphael, R. A. *Ibid.* **1978**, 3965. (c) Osmund de Silva, S.; Snieckus, V. *Ibid.* **1978**, 5103.

(7) Kende, A. S.; Rizzi, J. P. *Tetrahedron Lett.* **1981**, 1779.

(8) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(10) **10**: ^1H NMR (100 MHz; CH_2Cl_2, δ 5.25 as standard; $CDCl_3$) 10.29 (s, 1 H), 7.62 (d, *J* = 8 Hz, 1 H), 7.29 (d, *J* = 8 Hz, 1 H), 4.53 (s, 2 H), 3.80 (s, 3 H), 2.79–2.63 (m, 2 H), 2.40–2.11 (m, 4 H), 1.06 (t, *J* = 8 Hz, 3 H), 0.85 (s, 9 H), 0.07 (s, 6 H).

(11) Newman, M. S.; Sankoran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237.

(12) **12**: ^1H NMR (400 FT, $CDCl_3$) δ 8.12 (s, 1 H), 7.85 (d, *J* = 8 Hz, 1 H), 7.64 (t, *J* = 8 Hz, 1 H), 7.31 (d, *J* = 8 Hz, 1 H), 4.72 (s, 2 H), 4.03 (s, 3 H), 3.93 (s, 3 H), 2.92 (t, *J* = 8 Hz, 2 H); 2.43 (q, *J* = 8 Hz, 2 H), 2.33 (t, *J* = 8 Hz, 2 H), 1.70 (br s, 1 H), 1.15 (t, *J* = 8 Hz, 3 H).

(13) Harrison, I. T. *Chem. Commun.* **1969**, 616.

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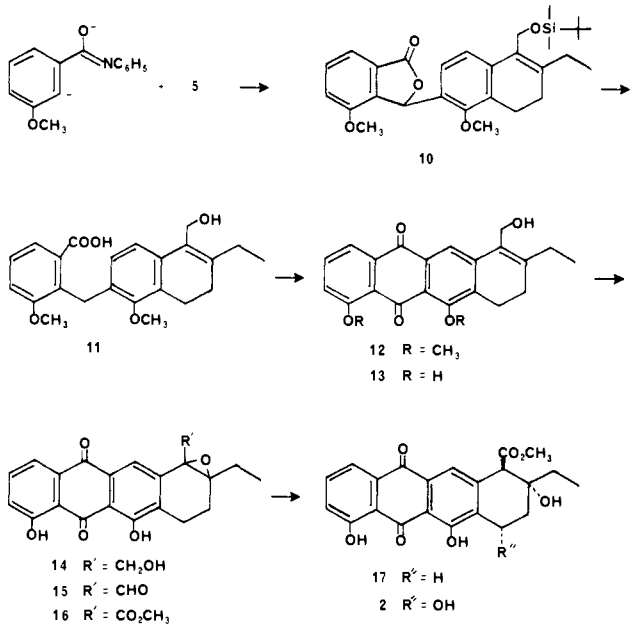
Scheme II



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.

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(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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