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TOTAL SYNTHESIS OF (±)-7-DEOXYDAUNOMYCINONE AND (±)-7-DEOXYISODAUNOMYCINONE

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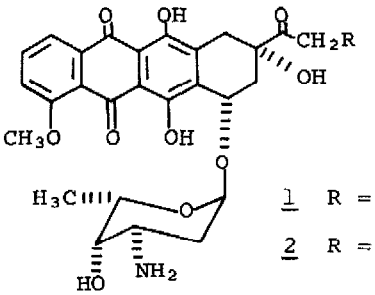
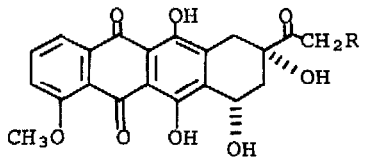
The anthracycline antibiotics, Daunorubicin[1], 1 and Adriamycin[2], 2 are established antineoplastic agents used for the clinical treatment of a broad spectrum of human cancers. The lack of an efficient biosynthetic process[3] coupled with their therapeutic importance have prompted the investigations of chemical synthesis to alleviate the scarcity of these drugs.[4,5,6] Recently, we described an effective route[7] to the tetracyclic anthracyclinone ring system based on an efficient one-step cyclization of the tetrahydronaphthyl esters of 3-methoxy-phthalic acid, catalyzed by BF_3-etherate. We now report the successful adaptation of this approach to allow the synthesis of (±)-7-deoxydaunomycinone, 16 and (±)-7-deoxyisodaunomycinone, 17.



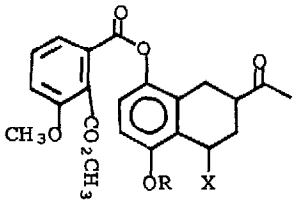
1 R = H
2 R = OH

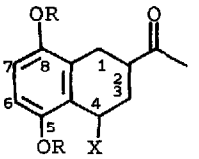


3 R = H
4 R = OH

The hydrogen bonded interaction between the C-4 carbonyl and the phenolic proton at C-5 in the dihydroxytetralone, 6, obtained by demethylation of the known dimethyl ether[8], 5 allowed us to prepare the key ester intermediate, 8 in 77% yield, m.p. 131-133°, NMR ($CDCl_3$) 12.20 (s, 1H), 7.76 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 7.50 (dd, $J_1 = J_2$ = 7.5 Hz, 1H), 7.32-7.1 (m, 2H), 6.83 (d, J = 9 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.33-2.7 (m, 5H), 2.22 (s, 1H), via regiospecific acylation[9] of 6 with 2-carbomethoxy-3-methoxy-benzoic acid, 7.

Efforts to catalyze an apparent Fries-rearrangement and subsequent dehydrative cyclization by treating 8 with BF_3-etherate[7] led to only a small quantity





8 X = =O; R = H 9 X = OH; R = H

10 X = H; R = H 11 X = H; R = CH_3

12 X = H; R = $-\overset{O}{\overset{\|}{C}}-O-iBu$

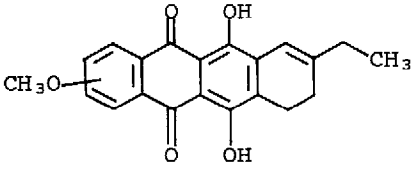
5 R = CH_3; X = =O

6 R = H; X = =O

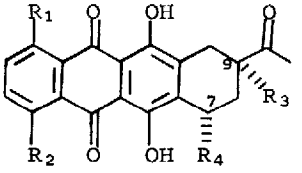
of tetracyclic compounds. Presumably, the electron withdrawing property of the C-4 carbonyl function deactivates the C-7 position of the dihydroxytetralone portion of the molecule. Similarly, reaction of 9, obtained by hydrogenation (5% Pd/C) of 8, with BF_3-etherate also gave very low yields of tetracyclic products. Therefore, 8 was hydrogenolyzed (Pd/C; HAc:H_2O:HCl; 50:5:1) to afford 10 in 70% yield, m.p. 168.5-170.5°, NMR 7.78 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.47 (dd, J_1 = J_2 = 7.8 Hz, 1H), 7.19 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.65 (AB, q, J = 8.7 Hz, νAB = 18 Hz, 2H), 3.86 (s, 3H), 2.18 (s, 3H), 1.3-3.00 (m, 7H). When 10 was heated with BF_3-etherate at 100° C for 75 minutes, two major components were obtained after chromatography over a silica gel column (chloroform eluent) (40% yield). The faster moving red band (3%) (R_f 0.59[11]) was assigned the structure 13 as an isomeric mixture, m.p. 121-125° C, NMR δ13.50, 13.30 (s, 1H each ArOH), 8.0-7.1 (m, 3H), 6.55 (s, 1H), 3.95 (s, 3H), 2.95-2.65 (m, 2H), 2.4-2.1 (m, 4H), m/e 350 (100); 321 (88); 306 (61); 303 (89). It is noteworthy that 13 may serve as an useful precursor to Rhodomycinone[12] and Aklavinone[13]. The second orange component (37%) (R_f 0.43) was further resolved into two compounds, the less polar 14, m.p. 243-245° C, NMR δ13.78, 13.43 (s, 1H each, ArOH), 8.1-7.2 (m, 3H), 4.08 (s, 3H, OCH_3), 3.2-2.5 (m, 4H), 2.27 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.15 (m, 1H); the more polar 15, m.p. 216-217° C, NMR δ13.77 (s, 1H), 13.32 (s, 1H), 8.0-7.2 (m, 3H), 4.10 (s, 3H), 3.2-2.5 (m, 4H), 2.27 (s, 3H), 2.17 (m, 1H), in a ratio of 60:40 via preparative tlc (ten developments in $CHCl_3$).

These results clearly show that this Lewis acid-catalyzed dehydrative cyclization did not proceed regiospecifically as we had hoped. In an attempt to improve the regioselectivity of this cyclization, we prepared 11 (reaction

of 10 with CH_3I/K_2CO_3) and 12 (treating 10 with isobutyl chloroformate) with a view to discriminating the electron densities at C-6 and C-7. Unfortunately, both 11 and 12 reacted slowly in BF_3-etherate resulting in a complex mixture of products in low yields. Thus, it appears that the phenolic function at C-5 in 10 must remain unprotected for facile cyclization to occur.



13



14 $R_2 = OCH_3$; R_1, R_3, R_4 = H

15 $R_1 = OCH_3$; R_2, R_3, R_4 = H

16 $R_2 = OCH_3$; R_3 = OH; R_1, R_4 = H

17 $R_1 = OCH_3$; R_3 = OH; R_2, R_4 = H

Introduction of the tertiary hydroxyl group into 14 at C-9 was accomplished via enol acetylation[14] (refluxing Ac_2O, TsOH, 16 hrs), epoxidation (m-chloroperbenzoic acid at 25°, 2 hr), followed by alkaline (0.3 N NaOH, EtOH:H_2O, 1:1, 1 hr 25°) and acid[15] (HOAc:H_2SO_4:H_2O) hydrolyses. After silica gel chromatography ($CHCl_3$ as eluent), (±)-7-deoxydaunomycinone, 16, m.p. 229-231°[16], NMR 13.78 (s, 1H), 13.38 (s, 1H), 8.1-7.2 (m, 3H), 4.08 (s, 3H), 2.98 (m, 4H), 2.37 (s, 3H), was obtained in 50% overall yield from 14. Using this same sequence of reactions, 15 was transformed into (±)-7-deoxyisodaunomycinone, 17, m.p. 223-224°, NMR 13.78 (s, 1H), 13.3 (s, 1H), 8.1-7.2 (m, 3H), 4.08 (s, 3H), 2.98 (m, 4H), 2.36 (s, 3H).

As the conversions of 16 into daunomycinone, 3 and adriamycinone, 4 via functionalization of the C-7 and C-14 positions have already been achieved[6,17], this synthetic route provides access to these anthracyclinones.

Acknowledgment

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References and Notes

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10. The yields reported are minimal and no efforts were expended in optimizing the reactions. All new compounds afforded satisfactory C, H analyses; mass spectra and nmr spectra are consistent with the assigned structures. IR and NMR (δ) spectra were taken in $CDCl_3$ solutions and melting points were uncorrected.

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16. All tetracyclic compounds were recrystallized from glacial acetic acid; (-)-7-deoxydaunomycinone melted at 246-248°; the infrared spectra of the triacetate derivatives of (±)-16, m.p. 204.5-205° (EtOAc-hexane) and (-)-16 are superimposable.

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