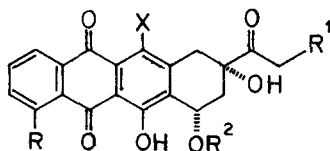


AN EFFICIENT AND FLEXIBLE APPROACH FOR THE SYNTHESIS OF 4-DEMETHOXY-
 DAUNOMYCINONE AND 4-DEMETHOXY-11-DEOXYDAUNOMYCINONE

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Abstract: A flexible and common approach for the synthesis of aglycones of the biologically active antitumor anthracyclines has been described.

Synthetic anthracycline antibiotics are likely to be an exception to the general concept that it is difficult to find a totally synthetic analogue of an antibiotic produced through the natural process of fermentation¹. Recent findings indicate that 4-demethoxydaunomycin (3) is eight times more effective compared to daunomycin (1) and adriamycin (2) and the results of its clinical trials are reported to be promising². Similar observations have also been made with 4-demethoxy-11-deoxydaunomycin (5) compared to the natural 11-deoxydaunomycin (4)³. As it is not possible to obtain 4-demethoxy analogues of both 1 and 4 by fermentation, numerous synthetic approaches in particular for the synthesis of 4-demethoxydaunomycinone 6, have been reported^{3,4}. We wish



- 1 R = OCH₃, R¹ = H, X = OH, R² = daunosaminyl
2 R = OCH₃, R¹ = X = OH, R² = daunosaminyl
3 R = R¹ = H, X = OH, R² = daunosaminyl
4 R = OCH₃, R¹ = X = H, R² = daunosaminyl
5 R = R¹ = X = H, R² = daunosaminyl
6 R = R¹ = R² = H, X = OH
7 R = R¹ = R² = X = H

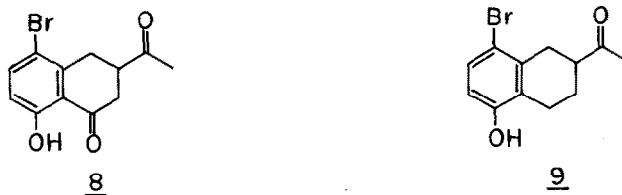
to report here an expeditious and flexible approach for both (+)4-demethoxydaunomycinone (6) and (+)4-demethoxy-11-deoxydaunomycinone (7) which is simple, conceptually different from previous approaches and totally free from expensive reagents and reactions which are difficult to scale up.

Our strategy is to make use of the key synthon (8) which was reported recently by us from *m*-cresol⁵ and building both 4-demethoxydaunomycinone and 4-demethoxy-11-deoxydaunomycinone as desired.

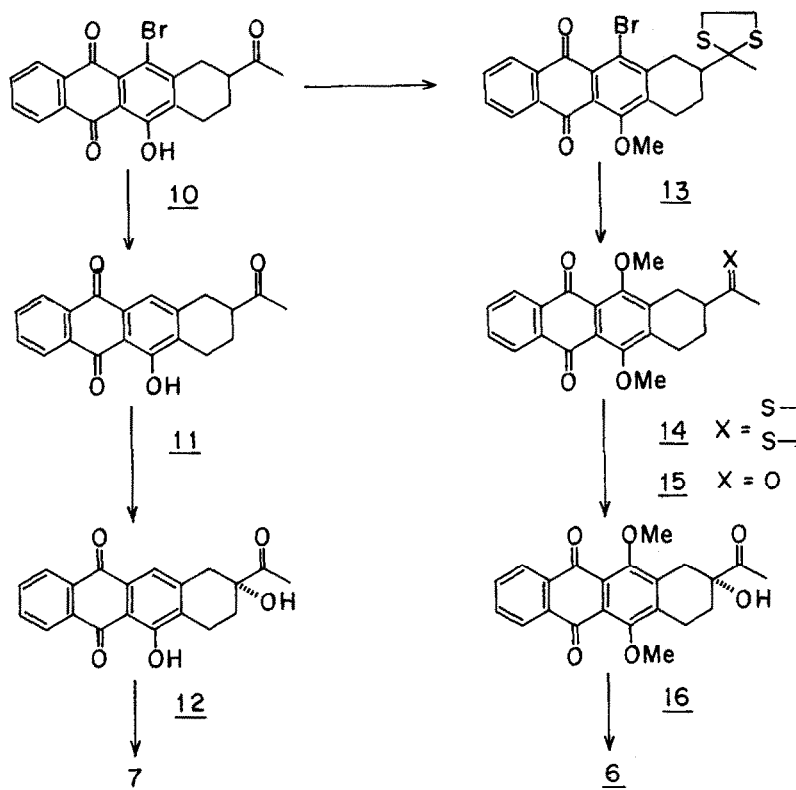
The requisite AB synthon 8, was converted to 2-acetyl-5-hydroxy-8-bromo-1,2,3,4-tetrahydronaphthalene, (9) (m.p. 131°, 90% yield) by first protecting the acetyl ketone (ethylene glycol, PTS acid, C₆H₆, reflux, 6 hr), followed by Wolf-Kishner reduction (H₂N NH₂H₂O, KOH, 160-65°, 4 hr. and acid work up). 9 was then converted directly to 2-acetyl-1,2,3,4-tetrahydro-12-bromonaphthalene-6,11-dione (10) by fusing an intimate mixture of phthalic anhydride (2.0 eq), AlCl₃-NaCl (5:1, ten fold excess) at 180° for 10 min. and treating the resultant mass with cold dil. HCl (5%) and followed by chromatographic purification⁶ (yield 50%) m.p. 221-2°; M⁺ 398, 400; ¹H NMR (CDCl₃) δ 1.73 (m, 2H), 2.26 (s, 3H), 2.57-3.24 (m, 5H), 7.77 (m, 2H), 8.26 (m, 2H), 13.68 (s, 1H, OH). The bromohydroxyquinone, 10 was then made use of for the synthesis of both 4-demethoxydaunomycinone (6) and 4-demethoxy-11-deoxydaunomycinone (7) (Scheme 1).

The bromo compound, (10) was dehalogenated by hydrogenation (Pd/C, 10% EtOAc, 1 drop HCl, 25°, 1 hr), to give (11) in 96% yield (m.p. 188-189°); M⁺ 320; ¹H NMR (CDCl₃) δ 1.56 (m, 2H) 2.26 (s, 3H), 2.73-3.03 (m, 5H), 7.36 (s, 1H), 7.63 (m, 2H) 8.13 (m, 2H), 12.83 (s, 1H, OH). Hydroxylation at tertiary carbon (C-9) was accomplished by preparing the enol acetate (PTS acid and AC₂O), followed by epoxidation and the resultant epoxy acetate was then treated successfully by base and acid to give (+)-4-demethoxy-7,11-dideoxydaunomycinone (12), which after chromatographic purification resulted in 50% overall yield from 11, m.p. 212-14° (dec) lit³ 208-14° (dec). The conversion of 12 to (+)-4-demethoxy-11-deoxydaunomycinone (7) was reported earlier³.

Conversion of 10 to (+)-4-demethoxydaunomycinone (6) was achieved by the following sequence of reactions. 10 was methylated (DMS, K₂CO₃, acetone) to give the methyl ether (95% yield, m.p. 145-6°), which on thioketalization (HSCH₂CH₂SH, BF₃-Et₂O, CHCl₃, RT, 1.5 hr) gave 13 (85%, m.p. 190-91°) ¹H NMR, (CDCl₃) δ 1.53 (m, 2H) 1.88 (s, 3H), 2.11-2.95 (m, 5H), 3.43 (s, 4H) 3.93 (s, 3H), 7.73 (m, 2H) 8.17 (m, 2H). The displacement of bromo in 13 with methoxyl group was achieved by treating 13 with sodium methoxide in pyridine using catalytic amount of cuprous chloride at room temperature for 6 hr to give 14 which was subjected directly to dethioketalization (HgCl₂-HgO, aq. CH₃CN 80%, 1 hr) and chromatographic purification to give 4-demethoxy-7,9-dideoxydaunomycinone dimethylether (15) (50% m.p. 145-146°, lit⁴ 147-9°) ¹H NMR δ (CDCl₃) 1.62 (m, 2H), 2.36 (s, 3H), 2.67-3.13 (m, 5H), 3.84 (s, 3H), 3.93 (s, 3H) 7.73 (m, 2H) 8.22 (m, 2H). The conversion of 15 to 4-demethoxy-7-deoxydaunomycinone dimethylether (16) was achieved by hydroxylation at the tertiary carbon (C-9) by a similar procedure adopted for the synthesis of 4-demethoxy-11-deoxydaunomycinone. As the method for the demethylation of 16 and introduction of hydroxyl function at C-7 have already been described⁴,



Scheme 1



this route formally constitutes a total synthesis of (+)-4-demethoxydaunomycinone (6).

Thus for the first time we have demonstrated a flexible and convenient approach for the synthesis of anthracyclines. This method is being extended for the regiospecific synthesis of both daunomycinone and 11-deoxydaunomycinone⁷.

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