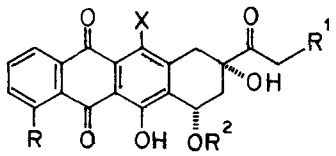
Tetrahedron Letters,Vol.24,No.10,pp 1093-1096,1983 0040-4039/83/101093-04$03.00/0
Printed in Great Britain ©1983 Pergamon Press Ltd.

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

A.V. Rama Rao*, A.R. Mehendale and K. Bal Reddy
National Chemical Laboratory, Poona - 411 008, India.

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 fermentation[1]. 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 promising[2]. Similar observations have also been made with 4-demethoxy-11-deoxydaunomycin (5) compared to the natural 11-deoxy-daunomycin (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 = OCH_3, R^1 = H , X = OH , R^2 = daunosaminyl

2 R = OCH_3, R^1 = X = OH , R^2 = daunosaminyl

3 R = R^1 = H , X = OH , R^2 = daunosaminyl

4 R = OCH_3 R^1 = X = H , R^2 = daunosaminyl

5 R = R^1 = X = H , R^2 = daunosaminyl

6 R = R^1 = R^2 = H, X = OH

7 R = R^1 = R^2 = X = H

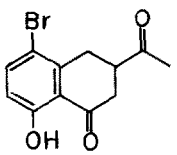
to report here an expeditious and flexible approach for both (±)4-demethoxy-daunomycinone (6) and (±)4-demethoxy-11-deoxydaunomycinone (7) which is simple, conceptually different from previous approaches and totally free from expensive reagents and reactions which are difficult to scale up.

Our strategy is to make use of the key synthon (8) which was reported recently by us from m-cresol[5] and building both 4-demethoxydaunomycinone and 4-demethoxy-11-deoxydaunomycinone as desired.

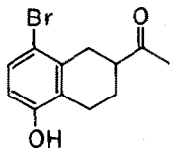
The requisite AB synthon 8, was converted to 2-acetyl-5-hydroxy-8-bromo-1,2,3,4-tetrahydronaphthalene, (9) (m.p. 131°, 90% yield) by first protecting the acetyl ketone (ethylene glycol, PTS acid, C_6H_6, reflux. 6 hr), followed by Wolf-Kishner reduction ($H_2N\ NH_2H_2O$, KOH, 160-65°, 4 hr. and acid work up). 9 was then converted directly to 2-acetyl-1,2,3,4-tetrahydro-12-bromonaphthacene-6,11-dione (10) by fusing an intimate mixutre of phthalic anhydride (2.0 eq), $AlCl_3$-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 purification[6] (yield 50%) m.p. 221-2°; M^+ 398, 400; ^1H NMR ($CDCl_3$) 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 ($CDCl_3$) 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 AC_2O), followed by epoxodation 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) lit[3] 208-14° (dec). The conversion of 12 to (±)-4-demethoxy-11-deoxydaunomycinone (7) was reported earlier[3].

Conversion of 10 to (±)-4-demethoxydaunomycinone (6) was achieved by the following sequence of reactions. 10 was methylated (DMS, K_2CO_3, acetone) to give the methyl ether (95% yield, m.p. 145-6°), which on thioketalization ($HSCH_2CH_2SH$, BF_3-Et_2O, $CHCl_3$, RT, 1.5 hr) gave 13 (85%, m.p. 190-91°) ^1H NMR, ($CDCl_3$) 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 ($HgCl_2$-HgO, aq. CH_3CN 80%, 1 hr) and chromatographic purification to give 4-demethoxy-7,9-dideoxydaunomycinone dimethylether (15) (50% m.p. 145-146°, lit[4b] 147-9°) ^1H NMR δ ($CDCl_3$) 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 described[4b],

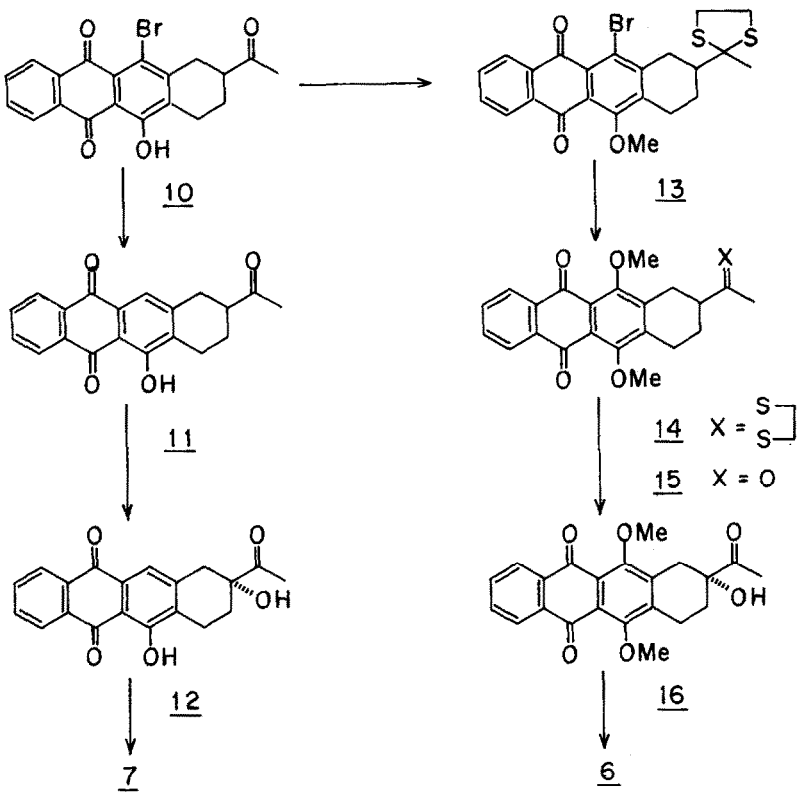


8



9

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 anthracyclinones. This method is being extended for the regiospecific synthesis of both daunomycinone and 11-deoxydaunomycinone[7].

References and Notes

1. For recent work on anthracyclines see:
(a) Arcamone, F. "Donorubicin-Anticancer Antibiotics" Medicinal Chemistry-A series of monographs, Vol.17, Academic Press, N.Y. 1981, (b) Arcamone, F. "Topics in Antibiotics Chemistry", Sammes, P.G., Ed. Halsted Press, N.Y. 1978. (c) Kelly, T.R. Annual Rep. Med. Chem. 1979, 14, 288. (d) Remers, W.A. "The Chemistry of Antitumor Antibiotics" Wiley interscience Somerset, N.J. 1979, VA.I.

2. S. Neidel, Nature (London) 268, 195 (1977).

3. H. Umezawa, Y. Takahashi, M. Kinoshita, N. Naganawa, K. Tatsuta and T. Takeuchi, Joun. of Antibiotics 33,(12) 1581 (1980).

4. (a) C.M. Wong, D. Popien, R. Schwenk and J. TeRaa, Can. J. Chem. 49, 2712 (1971). (b) F. Suzuki, R.D. Glein, S. Trenbeath and C.J. Sih, Tet. lett. 2303 (1977). (c) A.S. Kende, D.P. Curran, Y.G. Tsay and J.E. Mills, ibid 3537 (1977). (d) R.B. Garland, J.R. Palmer, J.A. Schulz, P.B. Sollman and R. Pappo, ibid 3669 (1978). (e) John R. Wiseman, Nadine iroff French, Richard K. Hallmark and Kaolin G. Chiong, ibid, 3765 (1978). (f) K. Krohn and K. Tolkichn, ibid, 4023 (1978). (g) T.R. Kelly and Wen-Ghih Tsang, ibid, 4457 (1978). (h) F.Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. Dimarco, A.M. Casazza, C. Soranzo and G. Pratesi, Experimentia, 34,1255 (1978). (i) Daniel K. Jackson, Lakshminarasimhan and J.S. Swenton, J. A. C.S. 101, 3989 (1979). (j) Frank, M, Hauser and Subbarao Prasanna, J. Org. Chem, 44, 2596 (1979). (k) Yvonne Bessiere and Pierre Vogel, Helv. Chim. Acta, 63, 232 (1980). (l) Francis, A.J. Kerdesky, R.J. Ardecky, M.V. Lakshmikantam and M.P. Cava, J. Am. Chem. Soc. 103, 1992 (1981). (m) J.S. Swenton, D.K. Anderson, D.K. Jackson and Lakshminarasimhan, J. Org. Chem. 46, 4825 (1981). (n) M.J. Broadhurst, C.H. Hassall and G.J. Thomas, J. Chem. Soc. Perk. Tran. I, 2239 (1982). (o) M.J. Broadhurst, C.H. Hassall and G.J. Thomas, ibid 2249 (1982). (p) A.V. Rama Rao, V.H. Deshpande and N. Laxma Reddy, Tet. lett. 23, 4373 (1982).

5. A.V. Rama Rao, A.R. Mehendale and K. Bal Reddy, Tet. lett.23, 2415 (1982).

6. A.V. Rama Rao, V.H. Deshpande and N. Laxma Reddy, Tet. lett. 21, 2661 (1980).

7. This work was assisted partly by a grant from the Science and Technology Cell, Education and Youth Services Department, Maharashtra State.

NCL Communication No. 3183

(Received in UK 9 December 1982)