Tetrahedron Letters,Vol.23,No.42,pp 4373-4374,1982 0040-4039/82/424373-02$03.00/0
Printed in Great Britain

A SHORT SYNTHESIS OF (±) 2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL - A KEY INTERMEDIATE FOR ANTHRACYCLINONE SYNTHESIS

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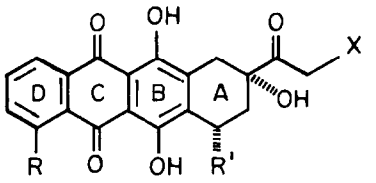
Metal ammonia reduction of 2-acetyl-5,8-dimethoxynaphthalene gave 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene which was converted to 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol, a key intermediate for the synthesis of many antitumor anthracyclinones.

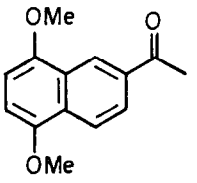
It is generally believed that synthetic anthracycline antibiotics may prove to be an exception to the general concept that it is difficult to find a better or totally synthetic analogue of an antibiotic produced through the natural process of fermentation.[1] Recent findings indicate that 4-demethoxydaunomycin (1) is four to eight times more effective compared to daunomycin (2) and adriamycin (3) and the result of its clinical trials are reported to be promising.[2] As there is no possibility of obtaining (1) by fermentation, numerous synthetic approaches for the synthesis of the aglycone, 4-demethoxydaunomycinone (4) have been reported.[3] The versatile method first employed by Wong et al[4] for the assemblage of the tetracyclic system of AB + CD coupling made use of the key intermediate 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (5) as the starting material for different unnatural anthracyclinones, including 4-demethoxydaunomycinone (4). Various methods have since been reported for the synthesis of 5 employing Friedel-Crafts acylation and Diels-Alder reaction involving multi-step operations.[3-5] We wish to report an efficient and totally different approach starting from an aromatic precursor such as 1,4-dimethoxy-naphthalene and obtaining 5 in a three-step synthesis.

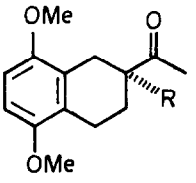
Acylation of 1,4-dimethoxynaphthalene with acetic anhydride (1.2 eq) using anhydrous aluminium chloride (2.2 eq) in ethylene dichloride at 60° (3 hr) gave on usual work up and chromatographic separation (silica gel, pet. ether-acetone mixture) 1-hydroxy-4-methoxy-2-acetylnaphthalene[6] (50%) and 2-acetyl-5,8-dimethoxynaphthalene (6) (30% yield, m.p. 111-112°); PMR : δ $CDCl_3$: 2.63 (s, 3H, $COCH_3$), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.46 (s, 2H, 6,7-H), 7.77 (dd, J=9 and 2Hz, 1H, 3-H), 8.00 (d,J=9Hz, 1H, 4-H), 8.60 (d, J=2Hz, 1H, 1-H).

Metal ammonia reduction[7] on 6 with potassium (8 g. atom eq.) in liquid ammonia (50 fold excess) at -33° followed by quenching the mixture in ethanol and usual work up gave 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (7) in 75% yield [m.p.81°-82°, lit.[4] m.p.81°-82°;

PMR δ CCl_4 2.20 (s, 3H, $COCH_3$), 2.2-3.2 (m, 7H, 3 X CH_2 and CH), 3.73 (s, 6H, 2 X OMe), 6.46 (s, 2H, Ar-H); M^+ 234]. Oxidation of 7 in t-butanol with potassium-t-butoxide and oxygen followed by reduction (Zn-AcOH) gave 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (5)[4] in 60% yield. The product is identical with the authentic sample.[3]







1 R = X = H , R' = O-daunosaminyl

2 R = OMe , X = H , R' = O-daunosaminyl

3 R = OMe , X = OH , R' = O-daunosaminyl

4 R = X = H , R' = OH

8 R = R' = X = H

6

5 R = OH

7 R = H

Earlier we have shown that 4-demethoxy-7-deoxydaunomycinone (8) can be made by fusion of 5 with an intimate mixture of phthalic anhydride, $AlCl_3$-NaCl (5:1)[3]. The conversion of 8 to 4-demethoxydaunomycin (1) has been well established.[8]

References and Notes

1. S. Neidle, Nature (London) 268, 195 (1977).

2. F. Arcamone "Doxorubicin - Anticancer antibiotics", Medicinal Chemistry (monographs), Vol. 17, Academic Press, N.Y. 1981; F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A.M. Casazza, G. Pratesi and P. Regiani, Cancer Treat. Rep. 60, 829 (1976).

3. A.V. Rama Rao, V.H. Deshpande, N. Laxma Reddy, Tetrahedron Lett. 21, 2661 (1980) and references cited therein.

4. C.M. Wong, D. Popien, R. Schwenk and J.T. Raa, Can. J. Chem. 49, 2712 (1971).

5. S.D. Nero, C. Gandolfi, P. Lombardi and F. Arcamone, Chemistry and Industry 810 (1981) and references 5-7 cited therein.

6. J. Hase and T. Nishimura, J.Pharm.Soc.Japan 75 203 (1955); C.A. 50, 1712 (1956). This compound has been made use of the synthesis of 4-demethoxy-11-deoxydaunomycinone. See A.V. Rama Rao, V.H. Deshpande, N. Laxma Reddy, Tetrahedron Lett. 23, 775 (1982).

7. G.S.R. Subba Rao and N. Shyamasundar, J. Chem. Soc. Perkin I, 875 (1982).

8. F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. DiMarco, A.M. Casazza, C. Soranzo and G. Pratesi, Experientia 34, 1255 (1978).

NCL Communication No. 3044
(Received in UK 4 August 1982)