Tetrahedron Letters No. 15, pp 1285 - 1288.
0040-4039/79/0408-1285$02.00/0

THE NAPHTHALENE ROUTE TO ANTHRACYCLINONES

Charles J. Sih*, David Massuda, Paul Corey, Robert D. Gleim and Fumio Suzuki
School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

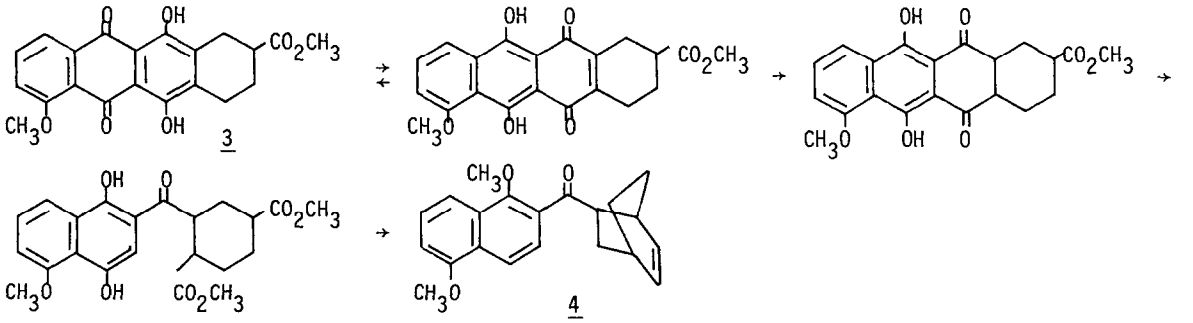
ABSTRACT. A regiospecific total synthesis of 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione-9-carboxylic acid methyl ester (3) was synthesized from the key intermediate (2).

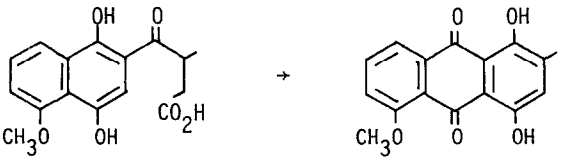
The anthracycline antibiotics daunorubicin (1) and especially adriamycin (2) have gained a firm place in chemotherapy for a wide range of human cancers.[1,2] In recent years, several different totally synthetic routes[3] to the aglycones (anthracyclinones) of 1 and 2 have been developed by different laboratories because of the lack of an efficient biosynthetic process[4] and that structural alterations in the aglycone[5] portion of these antibiotics can favorably change their therapeutic indices in experimental animals. However, anthracyclinone synthesis merits continuing attention, for each individual synthetic variant offers opportunities for unique structural modifications, which may lead to analogs with greater effectiveness and decreased cardiac toxicity[6].

Retrosynthetic analysis of 3 reveals that the naphthalene derivative 4 could serve as an useful intermediate, since the double bond of the norbornene system may be considered as a latent source of the two desired carbonyl functions. The feasibility of this synthetic approach was indicated by our earlier observation that acid-catalyzed cyclization[7] of 5 to 6 proceeded regiospecifically without Hayashi rearrangement[8].

Three approaches were used for the synthesis of 4. The first entails the Diels-Alder reaction between 1,3-cyclohexadiene and 1,5-dimethoxy-2-naphthyl vinyl ketone (9). The selenide, 8, m.p. 82-84°C, NMR[9] δ 6.7-8.1 (m, 10H), 4.95 (q, 1H, J = 7 Hz), 3.9 (s, 3H), 3.85 (s, 3H), 1.65 (d, 3H, J = 7 Hz), was prepared in 79% yield by the reaction of a solution of phenylselenyl bromide[10] with the lithium salt of 7 at -78°C for 10 min. Oxidation of 8 with H_2O_2 in pyridine at room temperature afforded 9, δ 6.7-8.1 (m, 6H), 6.3 (dd, 1H, J_1 = 18 Hz, J_2 = 1 Hz), 5.8 (dd, 1H, J_1 = 10 Hz, J_2 = 1 Hz), 3.90 (s, 3H), 3.87 (s, 3H), in 92% yield. Heating of 9 with an excess of 1,3-cyclohexadiene in a sealed tube at 140°C for 7 hrs afforded 4 (94%), as an isomeric (endo and exo) mixture, δ 8.0 (d, 1H, J = 8 Hz), 7.7 (d, 1H, J = 8 Hz), 7.5 (d, 1H, J = 8 Hz), 7.35 (t, 1H, J = 8 Hz), 6.9 (d, 1H, J = 8 Hz), 5.9-6.4 (m, 2H), 3.9 (s, 3H), 3.85 (s, 3H), 3.5-3.7 (m, 1H), 2.7-2.9 (m, 1H), 2.5-2.65 (m, 1H), 1.1-1.9 (m, 6H).

The second approach involves the reaction of the lithio salt of 1,5-dimethoxy naphthalene (10) with either the bicyclic methyl ester (11a)[11] or the acid chloride (11b)[12] at -78°C to give 4 as an isomeric mixture in 15-20% yield.

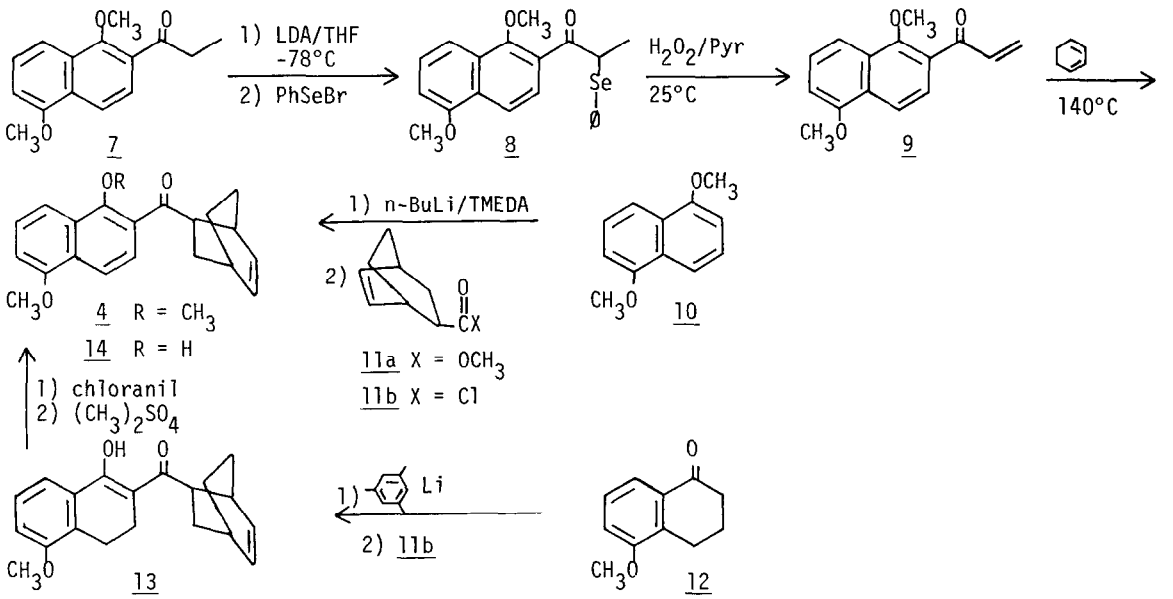




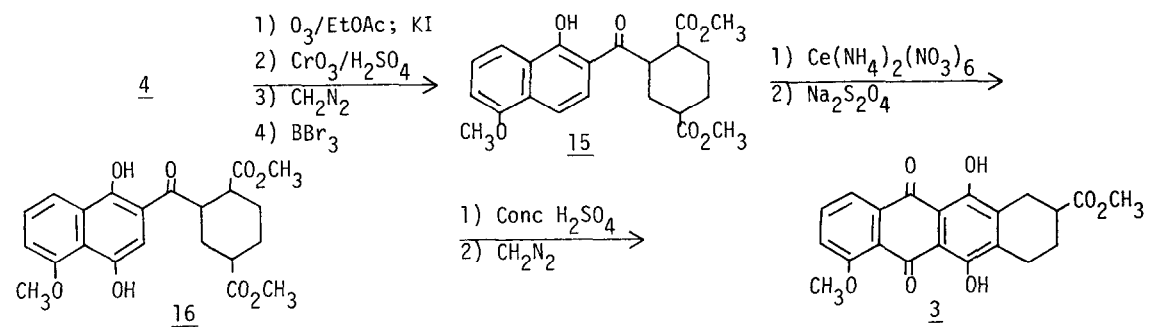
5 6

In turn, the lithio salt was prepared by reaction of 10 in TMEDA with n-butyllithium at 25°C for 3 hrs. The low yield of this acylation was attributed to the formation of the 2,6-dilithio salt of 10. Since attempts to suppress the formation of the dilithio species by varying temperatures, solvents and bases were unsuccessful, we turned to the use of 5-methoxytetralone (12) as the CD rings of 3 for the third approach to 4. The Li-enolate of 12, prepared by the use of mesitylene lithium[13] in pentane-ether, was condensed with 11b to furnish the 1,3-diketone 13 as an isomeric mixture consisting of a 3:1 ratio of endo and exo adducts in 51% yield. The major endo isomer was crystallized from isopropyl ether, m.p. 126.5-129.5°C, δ 16.3 (s, 1H), 7.5 (d, 1H, J = 7 Hz), 7.2 (t, 1H, J = 7 Hz), 6.85 (d, 1H, J = 7 Hz), 6.1-6.35 (m, 2H), 3.8 (s, 3H), 2.45-3.20 (m, 7H), 1.1-1.8 (m, 6H). Refluxing 13 in toluene for 24 hrs in the presence of chloranil gave 14 (83%), m.p. 152-154°C, which was quantitatively converted into 4 by methylation [$(CH_3)_2SO_4/K_2CO_3$/acetone].

Transformation of 4 into the diester 15 was achieved via a four step reaction sequence: ozonolysis to the dialdehyde (O_3/EtOAc at -78°C, KI); Jones oxidation to the diacid; esterification with diazomethane and demethylation (BBr_3 at -78°C). After silica gel chromatography, a 34% yield of 15, δ 13.7 (s, 1H), 8.05 (d, 1H, J = 8 Hz), 7.7 (d, 1H, J = 8 Hz), 7.5 (d, 1H, J = 8 Hz), 7.4 (t, 1H, J = 8 Hz), 7.0 (d, 1H, J = 8 Hz), 4.0 (s, 3H), 3.60 (s, 3H), 3.59 (s, 3H), 3.0-3.2 (m, 1H), 1.1-2.4 (m, 8H), was obtained. Oxidation of 15 with an excess of ceric ammonium nitrate[14] in a THF-H_2O (75:25) mixture for 4 min at 0°C furnished the quinone derivative, which without purification was reduced with sodium dithionite to yield 16 (45%). Finally, cyclization of 16 was accomplished using concentrated H_2SO_4 at 25°C for 16 hrs. Esterification with diazomethane gave 3 (41%), as red crystals, m.p. 261-262°C, δ 13.7 (s, 1H), 13.4 (s, 1H), 8.0 (dd, 1H, J_1 = 8 Hz,



J_2 = 1 Hz), 7.7 (t, 1H, J = 8 Hz), 7.3 (dd, 1H, J_1 = 8 Hz, J_2 = 1 Hz), 4.1 (s, 3H), 3.75 (s, 3H), 1.5-3.3 (m, 7H).



This convergent strategy provides a flexible framework suitable for the regiospecific elaboration of different classes of natural anthracyclinones by varying the substituents of the naphthyl and cyclohexyl synthons. More direct efficient routes to adriamycinone and especially alkavinone are currently under investigation.

Acknowledgment - This investigation was supported in part by Grant CA 21387 of the National Institutes of Health.

References and Notes

1. R. H. Blum and S. K. Carter, Ann. Intern. Med., 80, 249(1974).
2. D. W. Henry, "Adriamycin" in "Cancer Chemotherapy", Ed. A. C. Sartorelli, American Chemical Society, Washington, D.C., 1976.

3. C. M. Wong, R. Schwenk, D. Popein and T. L. Ho, Can. J. Chem., 51, 466(1973); A. S. Kende, J. Belletire, T. J. Bentley, E. Hume and J. Airey, J. Am. Chem. Soc., 97, 4425(1974); R. D. Gleim, S. Trenbeath, R. S. D. Mittal and C. J. Sih, Tetrahedron Lett., 3385(1976); A. S. Kende, Y. G. Tsay and J. E. Mills, J. Am. Chem. Soc., 98, 1967(1976); J. S. Swenton and P. W. Reynolds, J. Am. Chem. Soc., 100, 6188(1978); F. Suzuki, S. Trenbeath, R. D. Gleim and C. J. Sih, J. Am. Chem. Soc., 100, 2272(1978).
4. F. Arcamone, G. Cassinelli, G. Fantini, A. Grein, P. Orezzi, C. Poh and C. Spalla, Biotech. Bioeng., 11, 1109(1969).
5. F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi and P. Reggiani, Cancer Chemo. Rept., 60, 829(1976).
6. E. P. Cortes, G. Lutman, J. Wanka, J. J. Wang, J. Pickren, J. Wallace and J. F. Holland, ibid., 6, 215(1975).
7. R. D. Gleim, S. Trenbeath, F. Suzuki and C. J. Sih, Chem. Commun., 242(1978).
8. M. Hayashi, J. Chem. Soc., 2516(1927).
9. All intermediates gave C, H analyses and/or mass spectra, IR and NMR spectra consistent with the assigned structures. The yields reported are unoptimized and melting points were uncorrected. NMR spectra (δ) were taken in $CDCl_3$ solution.
10. H. J. Reich, J. M. Renga and I. L. Reich, J. Am. Chem. Soc., 97, 5434(1975).
11. R. Seka and O. Tramposch, Ber., 75, 1379(1942); R. Furstoss, R. Tadayoni and B. Waegell, J. Org. Chem., 42, 2844(1977). Both groups report the formation of the endo product only but no experimental data was presented to demonstrate the absence of the exo isomer. In our hands, a ratio of approximately 3:1 of endo vs. exo adducts was obtained when the reaction was carried out at 160-170°C for 12 hrs. This is indicated by the methyl ester signals at δ 3.60 (endo) and 3.67 (exo).
12. C. A. Grob, H. Kny and A. Gagneux, Helv. Chim. Acta, 40, 130(1957).
13. A. K. Beck, M. S. Hoekstra and D. Seebach, Tetrahedron Lett., 1187(1977).
14. T. L. Ho, T. W. Hall and C. M. Wong, Synthesis, 206, (1973).

(Received in USA 5 February 1979)