A Stereoconvergent Synthesis of (+)-4-Demethoxydaunomycin†

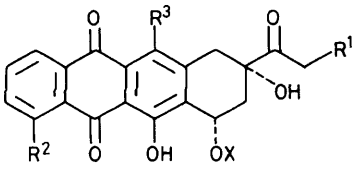
A. V. Rama Rao,* J. S. Yadav, K. Bal Reddy, and A. R. Mehendale

National Chemical Laboratory, Poona 411 008, India

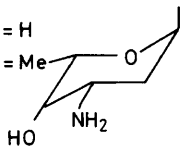
Sharpless kinetic asymmetric epoxidation on (±)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene [(**8**)] followed by $LiAlH_4$ reduction gave *R*-(−)-2-(*S*-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [(−)-(**10**)] and the undesired antipode: the former was converted into *R*-(−)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [*R*-(−)-(**3**)] while the latter was epimerized and recycled.

We have recently reported[1] a number of methods for the synthesis of racemic anthracyclinones (**1**), the aglycones of antitumour anthracyclines (**2**), such as daunomycinone (**1a**), 4-demethoxydaunomycinone (**1b**), 11-deoxydaunomycinone (**1c**), and 4-demethoxy-11-deoxydaunomycinone (**1d**). However, studies on the structure–activity relationships have indicated that 4-demethoxydaunomycin (**2b**), not available by fermentation methods, is *ca.* 10 times more effective than natural daunomycin (**2a**) or adriamycin (**2e**) and clinical trials

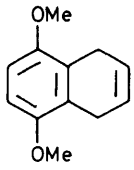
† This work forms part of the Ph.D. Dissertation of K. Bal Reddy, University of Poona, July 1983.



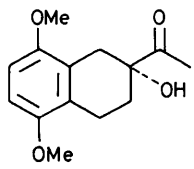
(1) X = H
(2) X = Me



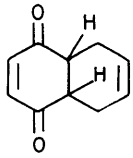
	R^1	R^2	R^3
a;	H	OMe	OH
b;	H	H	OH
c;	H	OMe	H
d;	H	H	H
e;	OH	OMe	OH



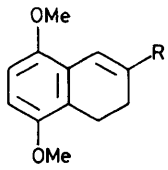
(5)



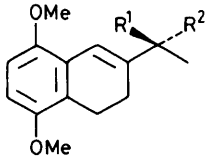
(3)



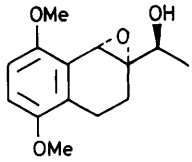
(4)



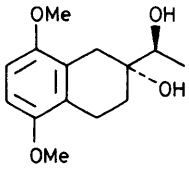
(6) R = H
(7) R = CHO
(8) R = CH(OH)Me



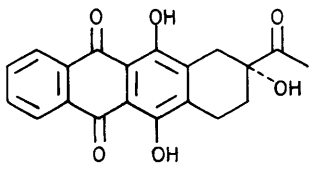
(8a) R^1 = OH, R^2 = H
(8b) R^1 = H, R^2 = OH



(9)



(-)-(10)



(-)-(11)

are reported to be promising.[2] Although numerous syntheses of anthracyclinones have been reported, the original assemblage of Wong *et al.*[3] for the tetracyclic system of AB + CD coupling, making use of the key intermediate, 2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (**3**), has proved to be the most practical approach for the synthesis of natural and synthetic anthracyclinones including (**1b**). Consequently, numerous approaches have been developed for the synthesis of (**3**) and this compound has been resolved to obtain optically pure *R*-(−)-(**3**).[4] We now wish to report a practical and convenient method of preparing *R*-(−)-(**3**) *via* Sharpless asymmetric epoxidation[5] (kinetic resolution method) of the racemic allylic alcohol (**8**) prepared from benzoquinone. The undesired antipode (**8b**) is then epimerized and recycled. Our present method is exceptionally simple and easy to operate for the synthesis of a variety of aglycones in optically active form.

Diels–Alder reaction of benzoquinone with butadiene in acetic acid at room temperature (r.t.) afforded the adduct (**4**) in 90% yield.[6] *O*-Methylation (Me_2SO_4, K_2CO_3, boiling acetone, 4 h) gave 5,8-dimethoxy-1,4-dihydronaphthalene[7] (**5**). Base catalysed isomerization of (**5**) (Bu^tOK, Me_2SO, r.t., N_2) resulted in the formation of 5,8-dimethoxy-3,4-dihydronaphthalene (**6**) in 100% yield.‡ [Colourless crystals, hexane, m.p. 70 °C, ^1H n.m.r. (CCl_4) δ 6.83 (m, 1H, H-1), 6.63 (s, 2H, ArH), 5.85 (m, 1H, H-2), 3.80 (s, 6H, OMe), 2.1—2.7 (m, 4H, H-3,4)]. Vilsmeier formylation of (**6**) ($POCl_3$, *N,N*-dimethylformamide, 80 °C, 4 h) gave the aldehyde (**7**) (m.p. 91—92 °C). Grignard reaction on (**7**) (MeMgI, Et_2O, r.t., 1 h, N_2) afforded the (±)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene[8] (**8**) (m.p. 78—79 °C; lit.[8] m.p. 78—79 °C).

Kinetic resolution of (±)-(**8**) was carried out at −55 to −50 °C by treating (**8**) (1 mol. equiv.) in CH_2Cl_2 sequentially with titanium tetraisopropoxide (TIP), (+)-di-isopropyltartrate [L-(+)-DIPT], and t-butylhydroperoxide (TBHP) in a 1:1:0.6 molar ratio. The progress of the reaction was monitored by titrating the concentration of TBHP. After completion of the reaction (10 h), the reaction was quenched with aqueous acetone maintained at −50 °C. Usual work up[5] gave a mixture of two products (**9**) and (**8b**) which was directly subjected to reduction [$LiAlH_4$, tetrahydrofuran (THF), r.t., 4 h] followed by chromatographic separation (silica gel, benzene–acetone) to give *R*-(+)-(**8b**) {38% yield, m.p. 88—89 °C, $[\alpha]_D^{20}$ + 20.3° (*c* 0.5, EtOH)} and *R*-(−)-2-(*S*-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (−)-(**10**) {40% yield, m.p. 154—155 °C, $[\alpha]_D^{20}$ −49.4° (*c* 0.5, EtOH); lit.[4c] m.p. 154—155 °C, $[\alpha]_D^{20}$ −49.7° (*c* 0.50, EtOH)}. The undesired antipode (+)-(**8b**) was inverted[9] by reacting with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid in THF to give the benzoate of (−)-(**8a**). Hydrolysis (NaOMe, MeOH, r.t., 5 h) followed by purification (silica gel, hexane–acetone) afforded (−)-(**8a**) {70% yield, m.p. 86—88 °C, $[\alpha]_D^{20}$ −18.6° (*c* 0.5, EtOH)}. Epoxidation of (−)-(**8a**) [CH_2Cl_2, −55 to −50 °C TIP, L-(+)-DIPT, TBHP, N_2] followed by reduction with $LiAlH_4$ gave (−)-(**10**) {83% yield, m.p. 152—154 °C, $[\alpha]_D^{20}$ −47.6° (*c* 0.5, EtOH)}.

Oxidation of (−)-(**10**) with Fetizon's reagent[10] ($AgCO_3$, celite) gave *R*-(−)-(**3**) {m.p. 128—129 °C, $[\alpha]_D^{20}$ −48.8° (*c* 1, $CHCl_3$); lit.[4b] m.p. 130—132 °C, $[\alpha]_D^{20}$ −50° (*c* 1, $CHCl_3$)}. Fusion of *R*-(−)-(**3**) with phthalic anhydride in an intimate mixture of $AlCl_3$–NaCl (5:1) at 180 °C (2 min) and usual work up gave (−)-4-demethoxy-7-deoxydaunomycinone (**11**) {m.p. 227—228 °C, $[\alpha]_D^{20}$ −84 °C (*c* 0.1, $CHCl_3$); lit.[11] m.p. 228—230 °C, $[\alpha]_D^{20}$ −87° (*c* 0.1, $CHCl_3$)}.

As the conversion of (**11**) into (**1b**)[12] and subsequently into (**2b**) by convenient methods[11] has already been described, we consider that our approach constitutes a practical total synthesis of optically active (**2b**).

‡ We are thankful to our colleagues, Jaweed and Sathaye for making available large amounts of this product. After completion of this work, a similar approach has been made use of by R. A. Russell, G. W. Collin, P. S. Gee, and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1983, 994.

All the new compounds gave satisfactory elemental and spectral analyses.

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

Received, 29th December 1983; Com. 1692

References

1 A. V. Rama Rao, K. Bal Reddy, and A. R. Mehendale, *J. Chem. Soc., Chem. Commun.*, 1983, 564; A. V. Rama Rao, G. Venkataswamy, V. H. Deshpande, M. Jaweed, and B. Ramanohan Rao, *J. Org. Chem.*, 1983, **48**, 1552; A. V. Rama Rao, A. R. Mehendale, and K. Bal Reddy, *Tetrahedron Lett.*, 1983, **24**, 1093; A. V. Rama Rao, V. H. Deshpande, and N. Laxma Reddy, *ibid.*, 1982, **23**, 4373; A. V. Rama Rao, B. M. Chanda, and H. B. Borate, *Tetrahedron*, 1982, **38**, 3555; A. V. Rama Rao, A. R. Mehendale, and K. Bal Reddy, *Tetrahedron Lett.*, 1982, **23**, 2415; A. V. Rama Rao, V. H. Deshpande, B. Ramamohan Rao, and K. Ravichandran, *ibid.*, 1982, **23**, 1115; A. V. Rama Rao, V. H. Deshpande, and N. Laxma Reddy, *ibid.*, 1982, **23**, 775; A. V. Rama Rao, V. H. Deshpande, and N. Laxma Reddy, *ibid.*, 1980, **21**, 2661.
2 S. Neidel, *Nature* (*London*), 1977, **268**, 195.
3 C. M. Wong, D. Popein, R. Schwenk, and J. TeRaa, *Can. J. Chem.*, 1971, **49**, 2712; C. M. Wong, R. Schwenk, D. Popien, and T. L. Ho, *ibid.*, 1973, **51**, 466.
4 (a) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, M. Cassazza, G. Prates, and P. Reggiari, *Cancer Treat. Rep.*, 1976, **60**, 829; (b) F. Arcamone, L. Bernardi, B. Patelli, and A. DiMarco, G. P. 2 601 785/1976; (c) for asymmetric synthesis see N. Tanno and S. Terashima, *Chem. Pharm. Bull.*, 1983, **31**, 821 and references cited therein.
5 V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.
6 O. Diels and K. Alder, *Chem. Ber*, 1929, **62**, 2337.
7 J. Alexander and L. A. Mitcher, *Tetrahedron Lett.*, 1978, 3408.
8 S. Tareshima, N. Tanno, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 2749; M. P. Reddy and G. S. Krishna Rao, *ibid.*, 1981, **22**, 3549.
9 O. Mitsunobu, *Synthesis*, 1981, 1.
10 M. Fetizon and M. Golfier, *C. R. Acad. Sci.*, 1968, **267**, 900.
11 F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. DiMarco, H. M. Casazza, C. Sarango, and G. Pratesi, *Experientia*, 1978, **34**, 1255; D. Dominguez and M. P. Cava, *J. Org. Chem.*, 1983, **48**, 2820.
12 D. Dominguez, R. Z. Ardecky, and M. P. Cava, *J. Am. Chem. Soc.*, 1983, **105**, 1608; T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wa, and D. W. Henry, *J. Org. Chem.*, 1977, **42**, 3653.