An Economical and Versatile Synthesis of 5,8-Dialkoxy-2-acetyl-3,4-dihydronaphthalenes: Key Precursors for the Synthesis of Chiral Anthracyclines

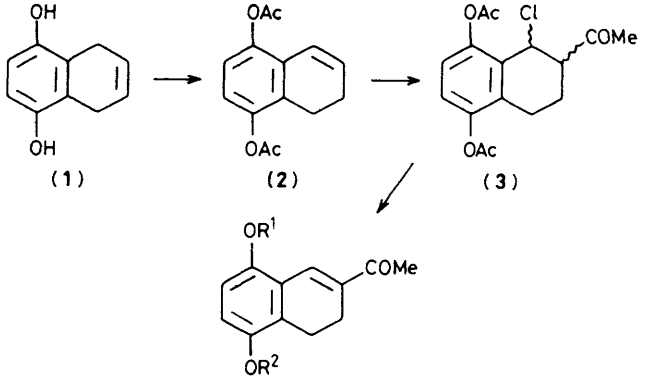
Richard A. Russell,*[a] Geoffrey J. Collin,[a] Paul S. Gee,[b] and Ronald N. Warrener*[b]

[a] *Department of Chemistry, Faculty of Military Studies, University of New South Wales, Duntroon, A.C.T.. 2600, Australia*

[b] *Department of Chemistry, The Faculties, Australian National University, G.P.O. Box 4, Canberra, A.C.T. 2601, Australia*

5,8-Diacetoxy-2-acetyl-3,4-dihydronaphthalene, prepared by a new route from the Diels–Alder adduct of buta-1,3-diene and *p*-benzoquinone, is selectively deacetylated (Cs_2CO_3 in tetrahydrofuran or K_2CO_3 in dimethyl sulphoxide) to intermediates suitable for use in chiral anthracycline synthesis.

No short, cheap synthesis of the daunomycin group of anthracycline antineoplastic agents is yet available despite the continuing efforts of synthetic chemists. We[1] and others[2] have demonstrated that 5,8-dialkoxy-2-acetyl-3,4-dihydronaphthalenes [*e.g.* (**5**), (**9**), and (**11**)] are versatile intermediates useful as AB-synthons for the enantiospecific synthesis of anthracyclines. 5,8-Dialkoxy-2-acetyl-3,4-dihydronaphthalenes are presently available only by tedious multi-step sequences,[3] which are unsuitable for large scale preparations. We now report a solution to this problem, which is short and uses simple reagents. Additionally, it allows discrimination between the C(5) and C(8) hydroxy groups of (**13**), a feature we have indicated previously,[4] can be exploited to control regiospecificity in anthracyclinone syntheses.



(**4**) $R^1 = R^2 =$ MeCO
(**5**) $R^1 = R^2 =$ Me
(**6**) $R^1 =$ H, $R^2 =$ MeCO
(**7**) $R^1 =$ Me, $R^2 =$ MeCO
(**8**) $R^1 =$ Me, $R^2 =$ H
(**9**) $R^1 =$ Me, $R^2 = CH_2Ph$
(**10**) $R^1 = CH_2Ph$, $R^2 =$ MeCO
(**11**) $R^1 = CH_2Ph$, $R^2 =$ Me
(**12**) $R^1 = CH_2Ph$, $R^2 =$ H
(**13**) $R^1 = R^2 =$ H

5,8-Dihydroxy-1,4-dihydronaphthalene (**1**) is readily available in one step from benzoquinone and buta-1,3-diene.[5] Under forcing conditions† the double bond can be conjugated and the product recovered as the bisacetate (**2**). The addition of acetyl chloride, catalysed by $AlCl_3$, forms a stereoisomeric mixture of the chloro-ketones (**3**) which, without purification, may be dehydrochlorinated by LiCl, to afford (**4**). Thus the basic skeleton is assembled in two operations, which is considerably shorter than any published route. Hydrolysis of (**4**),

Table 1

Starting compound	Product [a]	M.p./°C	Yield/%
(**1**)	(**2**)	137—138	53[b]
(**2**)	(**4**)	148—150	90[b]
(**4**)	(**5**)	103—104[c]	65
(**4**)	(**6**)	171—173	62
(**4**)	(**7**)	157—158	55
(**7**)	(**8**)	201—203	80[b]
(**8**)	(**9**)	111—112	65[b]
(**4**)	(**10**)	131—132	57
(**10**)	(**11**)	132—134	65

[a] All new compounds gave satisfactory combustion analyses and spectral data. [b] Optimised yields. [c] Lit.[2] m.p. 104—105 °C.

† Complete conjugation of (**1**) (50 g) can be achieved by heating it in a solution of sodium hydroxide (150 g) and water (120 ml) at reflux under argon for 4 h.

followed by *in situ* methylation yields (**5**), a well-publicised intermediate[3] in the enantiospecific and racemic synthesis of daunomycinone.

We examined next the mono-deacetylation of (**4**). Selective cleavage of the acetoxy group at C(8) occurred on treatment with caesium carbonate in tetrahydrofuran (THF)[6] to afford (**6**). Anhydrous potassium carbonate in dimethyl sulphoxide‡ was also successful and offered an economic advantage. Zinc catalysed methanolysis[7] was unsuccessful.

The phenol (**6**) was methylated *in situ* to yield (**7**) which, in a single step could be further hydrolysed to (**8**), and benzylated to yield the ketone (**9**). The successful conversion of (**4**) to (**9**) was thus achieved in four steps.

2-Acetyl-8-benzyloxy-3,4-dihydro-5-methoxynaphthalene (**11**), the regioisomer of (**9**), was prepared in a similar way by reversal of the methylation–benzylation sequence. Isolation of the acetate (**10**) was necessary, prior to its hydrolysis to the phenol (**12**) and subsequent methylation.

The availability of the ketones (**9**) and (**11**), each by a simple process, renders these compounds good candidates for a large scale synthesis of (+)-daunomycinone.

‡ Monodeacetylation with K_2CO_3 is slow if THF is used as a solvent.

The realisation of such a synthesis together with the preparation of a variety of other chiral anthracyclinones has been achieved[8] and will be reported elsewhere.

The financial support of the Australian Research Grants Scheme is gratefully acknowledged. We also thank Mr. R. Waring for technical assistance.

Received, 26th April 1983; Com. 526

References

1 R. N. Warrener, P. S. Gee, and R. A. Russell, *J. Chem. Soc., Chem. Commun.*, 1981, 1100.
2 S. S. Jew, S. Terashima, and K. Koga, *Chem. Pharm. Bull.*, 1979, **27**, 2351, and references therein.
3 M. Parameswara Reddy and G. S. Krishna Rao, *Tetrahedron Lett.*, 1981, **22**, 3549; A. V. Rama Rao, V. H. Deshpande, B. R. Rao, and K. Ravichandran, *Tetrahedron Lett.*, 1982, **23**, 1115; S. Del Nero, C. Gandolfi, P. Lombardi, and F. Arcamone, *Chem. Ind. (London)*, 1981, 810.
4 R. A. Russell and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1981, 108.
5 L. Fieser, *J. Am. Chem. Soc.*, 1948, **70**, 3151.
6 H. E. Zaugg, *J. Org. Chem.*, 1976, **41**, 3419.
7 A. G. Gonzalez, Z. D. Jorge, and H. L. Dorta, *Tetrahedron Lett.*, 1981, **22**, 335.
8 R. A. Russell, R. N. Warrener, and R. W. Irvine, unpublished results.