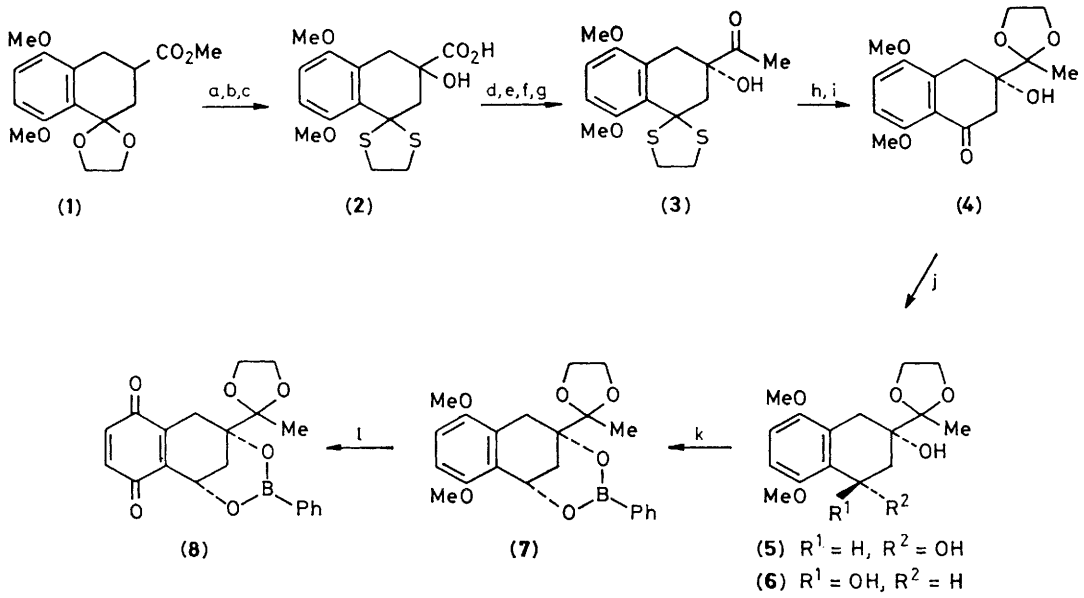
Total Synthesis of 4-Demethoxydaunomycin

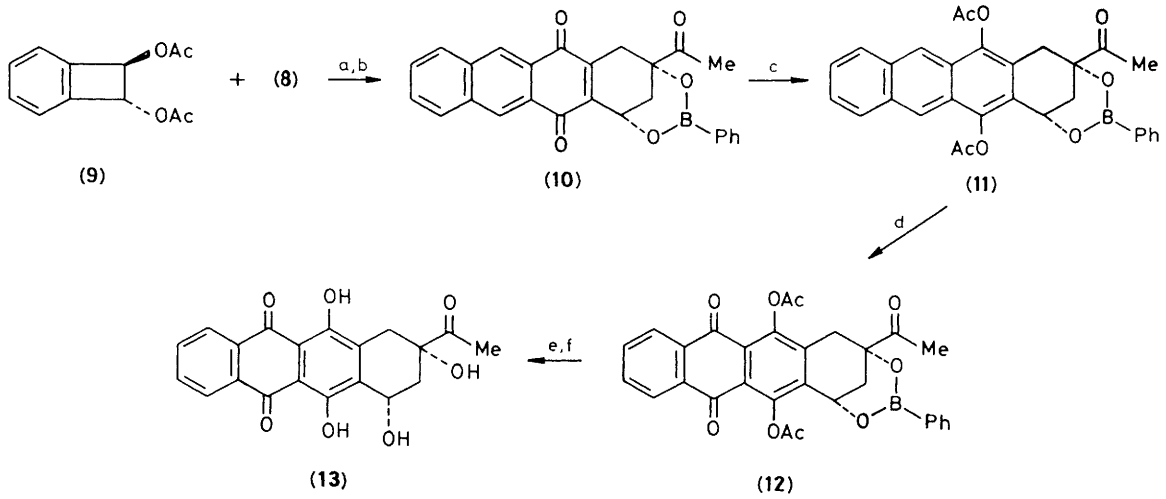
Michael J. Broadhurst, Cedric H. Hassall* and Gareth J. Thomas
Roche Products Limited, Welwyn Garden City, Herts. AL7 3AY, U.K.

The Diels–Alder adduct prepared from the optically active, fully functionalised bicyclic precursor (**8**) and *o*-benzoquinone dimethide has been converted in good yield into (+)-4-demethoxydaunomycinone (**13**), glycosidation of which with the daunosamine derivative (**14**) gives 4-demethoxydaunomycin.

The clinical efficacy of the anticancer agents daunomycin and adriamycin[1–4] has stimulated the study of new analogues with a view to identifying compounds with a broader spectrum of activity and reduced toxicity. The 4-demethoxyanthracyclines, which are not available from natural sources, are particularly promising.[5,6] Several syntheses of aglycones have been pub-



Scheme 1. Reagents and conditions: (a) $LiNPr^i_2$, O_2, $(EtO)_3P$, tetrahydrofuran (THF), —78 °C, 2 h, 85%; (b) $HSCH_2CH_2SH$, $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 15 min; (c) NaOH, H_2O, 25 °C, 1.5 h, 84% over 2 steps; (d) brucine, then 5M-HCl; (e) $BF_3(MeOH)_2$, MeOH, 25 °C, 4 h; (f) $Na^{+-}CH_2SOCH_3$, Me_2SO, THF, 0 °C, 15 min; (g) Al(Hg), THF, H_2O, 12 °C, 2 h, 61% over 3 steps; (h) $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_3H$, C_6H_6, reflux, 6 h, 88%; (i) HgO, $HgCl_2$, THF, MeOH, H_2O, 25 °C, 75 min, 86%; (j) $LiBH_4$, THF, 25 °C, 3 h; (k) $PhB(OH)_2$, toluene, *p*-$MeC_6H_4SO_3H$, 25 °C, 18 h, 93.5% over 2 steps; (l) $(NH_4)_2[Ce(NO_3)_6]$, MeCN, H_2O, 25 °C, 5 min, 97%.



Scheme 2. Synthesis of (+)-4-demethoxydaunomycinone. Reagents and conditions: (a) xylene, reflux, 3 h, 81%; (b) 6 M-HCl, dioxan, 25 °C, 4 h, 89%; (c) H_2, Pd–C, Ac_2O, pyridine, 25 °C, 40 min, 82.5%; (d) CrO_3, Ac_2O, AcOH, 25 °C, 20 h, 57%; (e) BCl_3, CH_2Cl_2, —70 → +10 °C, 1.5 h; (f) $Me_2C(OH)CH_2CH(OH)Me$, AcOH, CH_2Cl_2, 25 °C, 42 h, 81% over 2 steps.

lished.[7] Most of these involve preparation of 7-deoxy or 7,9-dideoxy tetracycles, with subsequent functionalisation, but some allow construction of a fully functionalised tetracycle,[8,9] or provide for the preparation of glycosides in sufficient quantity for biological evaluations.[5,10] We have developed a synthetic route which can be used for larger scale preparation of 4-demethoxyanthracyclines and illustrate this with the case of 4-demethoxydaunomycin (**17**).

Our synthesis utilises a fully functionalised bicyclic precursor (**8**) in which the *cis*-stereochemistry of 7- and 9-substituents of anthracyclines is determined. Chirality was defined at an early stage through resolution of the hydroxy-acid (**2**) [(±)-acid, m.p. 189.5—190.5 °C; (−)-acid, m.p. 145—148 °C, α_D^{20} −13.5° in dioxan] (Scheme 1),† prepared in excellent yield from the readily available ester (**1**) obtained by the procedure of Wong and his co-workers.[11] The absolute configurations of the hydroxy-ketones (**3**) [n.m.r. ($CDCl_3$) δ 2.33 (3H, s); i.r. (Nujol) ν_{max} 3460 and 1700 cm^{-1}; m.p. 178.5—179.5 °C; (*S*)-ketone α_D^{20} −24.4° in $CHCl_3$] derived from the enantiomeric acids (**2**) were determined by *X*-ray crystallography.‡ The mixture of *cis*- and *trans*-diols (**5**) and (**6**) prepared through the (*S*)-ketone (**3**) gave the *cis*-boronate (**7**) [n.m.r. ($CDCl_3$) δ 7.74 (2H, m), 7.23 (3H, m), and 5.6 (1H, t, *J* 3 Hz); m.p. 126—127 °C; α_D^{20} +35.8° in $CHCl_3$] exclusively when treated with benzeneboronic acid–toluene-*p*-sulphonic acid; the *trans*-diol (**6**) in the mixture was epimerised under the experimental conditions. This provided a novel method for achieving the *cis*-stereochemistry of the 7- and 9-hydroxy-functions and simultaneously introducing suitable

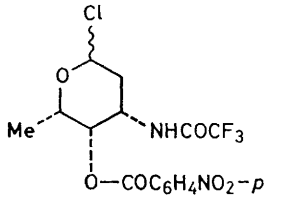
† All new compounds were fully characterised by spectroscopic means (n.m.r., i.r., m.s., u.v.) and gave satisfactory elemental analysis (crystalline compounds).

‡ We are indebted to Dr. J. Daly, Hoffman-La Roche, Basle for carrying out the *X*-ray analysis.

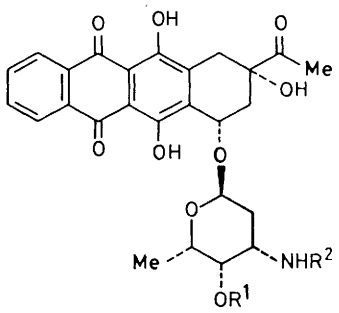
protection. Oxidation of the protected phenol (**7**) to the quinone (**8**) used ammonium cerium(IV) nitrate; this little-exploited procedure[12] gave a nearly quantitative yield. None of the alternative oxidising agents investigated were as specific or as effective.

The tetracyclic system was prepared by a Diels–Alder reaction between the quinone (**8**) and *o*-benzoquinone dimethide prepared *in situ* by heating *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene (**9**).[13] The diacetate (**11**) [n.m.r. ($CDCl_3$) δ 2.68 (3H, s), 2.57 (3H, s), and 2.55 (3H, s); i.r. (Nujol) ν_{max} 1760 and 1710 cm^{-1}; u.v. ($CHCl_3$) λ_{max} 258 sh., 265, 324, 338, 353, 372, and 392 nm; m.p. 271.5—272 °C; α_D^{20} +263° in dioxan], prepared from the Diels–Alder product, was oxidised with chromium(VI) oxide under strictly anhydrous conditions to give the diacetoxyquinone (**12**) [i.r. (Nujol) ν_{max} 1770, 1720, and 1670 cm^{-1}; u.v. ($CHCl_3$) λ_{max} 260 and 340 nm; m.p. 191—200 °C; α_D^{20} +171° in dioxan] which was deprotected to give (+)-4-demethoxydaunomycinone (**13**) [n.m.r. ($CDCl_3$–CD_3SOCD_3) δ 13.58 (1H, s), 13.33 (1H, s), 8.40—8.28 (2H, m), 7.91—7.79 (2H, m), 5.56 (1H, s), 5.26 (1H, m), 4.88 (1H, d, *J* 7 Hz), 3.20 (1H, dd, *J* 19.5 and 2 Hz), 2.98 (1H, d, *J* 19.5 Hz), 2.44 (3H, s), 2.36 (1H, dt, *J* 14 and 2 Hz), and 2.06 (1H, dd, *J* 14 and 5 Hz); u.v. ($CHCl_3$) λ_{max} 252, 259, 289, 330 sh., 475 sh., 486, and 518 sh. nm (log ε 4.61, 4.57, 4.02, 3.43, 3.98, 4.01, and 3.77); M^+, *m/z* 368; m.p. 182.5—183 °C (lit.[5] 184—186 °C); α_D^{20} +165° in dioxan (lit.[5] +170°, lit.[6] +140°)].

The α-glycoside (**15**) (m.p. 171—175 °C; α_D^{20} −89.8° in dioxan) was formed, specifically, in 84% yield by silver trifluoromethanesulphonate-catalysed glycosidation using the chloro sugar (**14**).[14]§ Stepwise hydrolysis gave *N*-trifluoroacetyl-4-demethoxydaunomycin (**16**) [m.p. 155—156 °C (lit.[6] 155—157 °C); α_D^{20} +190° in dioxan (lit.[6] +188°)] and 4-demethoxydaunomycin (**17**) [(hydrochloride) m.p. 172—174 °C (lit.[6] 183—185 °C); α_D^{20} +187° in methanol (lit.[6] +205°)] respectively.



(**14**)



(**15**) $R^1 = COC_6H_4NO_2$-*p*, $R^2 = COCF_3$
(**16**) $R^1 = H$, $R^2 = COCF_3$
(**17**) $R^1 = R^2 = H$

This synthetic route to 4-demethoxydaunomycin compares favourably with other procedures with respect to overall yield and convenience. Large-scale preparations are practicable and are facilitated by the avoidance of tedious chromatographic separations of intermediates in the synthesis of aglycones. The application of this synthetic route to the preparation of novel analogues of 4-demethoxyanthracyclines will be reported subsequently.

Received, 17th November 1981; Com. 1342

References

1 R. H. Blum, *Cancer Chemother. Rep.*, Part 3, 1975, **6**, 247.
2 F. Arcamone, 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood, Chichester, 1978, vol. 2, p. 102.
3 D. W. Henry, 'Cancer Chemotherapy,' ed. A. C. Sartorelli, Am. Chem. Soc., Washington D.C., 1976, p. 15.
4 J. R. Brown, *Prog. Med. Chem.*, 1978, **15**, 125.
5 F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. Di Marco, A. M. Casazza, C. Soranzo, and G. Pratesi, *Experientia*, 1978, **34**, 1255.
6 F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. Di Marco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, 1976, **60**, 829.
7 For a review see T. R. Kelly *Ann. Rep. Med. Chem.*, 1979, **14**, 288.
8 D. K. Jackson, L. Narasimhan, and J. S. Swenton, *J. Am. Chem. Soc.*, 1979, **101**, 3989.
9 K. Krohn and K. To'kiehn, *Chem. Ber.*, 1979, **112**, 3453.
10 D. W. Henry, *Cancer Treat. Rep.*, 1979, **63**, 845 and references therein.
11 C. M. Wong, R. Schwenk, D. Popien, and T. Ho, *Can. J. Chem.*, 1973, **51**, 466.
12 P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, 1976, **41**, 3627.
13 B. J. Arnold, P. G. Sammes, and T. W. Wallace, *J. Chem. Soc., Perkin Trans.* 1, 1974, 415.
14 T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, 1977, **42**, 3653.

§ We are grateful to Dr. M. R. Uskokovic, Hoffman-La Roche, Nutley, for supplying the intermediate methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxohexopyranoside, which was prepared from D-mannose by a procedure based on that of D. Horton and W. Weckerle, *Carbohydr. Res.*, 1975, **44**, 227.