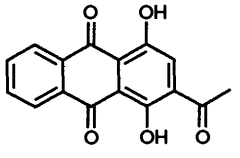
A Simple Synthesis of Anthracyclinones from 2-Acetylquinizarin

Khairuzzaman B. Mullah and James K. Sutherland*

Reaction of 2-acetyl-1,4-dihydroxyanthraquinone with a variety of β-keto esters in presence of tertiary amine in MeOH afforded anthracyclinone derivatives in a one-pot addition–oxidation–aldol sequence.

The present interest in the chemistry of anthracyclines arises from their established anticancer activity.[1] Lack of an efficient biosynthetic process has stimulated research on the total synthesis of these compounds and on new analogues with improved chemotherapeutic properties.[2] One of the challenges associated with the synthesis of anthracyclines is the preparation of the respective aglycones, the anthracyclinones, and a number of groups have devised elegant and ingenious strategies.[3–16] We postulated that the aromatic part of the anthracyclinones could be obtained from the readily available and cheap hydroxyanthraquinones, so our plan was to assemble suitably functionalised A ring components onto an electron deficient hydroxyanthraquinone moeity by nucleophilic aromatic substitution. In our laboratory we have developed methods for regioselective alkylation at C-2 and/or C-3 of hydroxyanthraquinones, and have shown that both 1,4-dihydroxy- and 1,4,5-trihydroxy-anthraquinones react with certain stabilised carbanions in Michael fashion.[17] We decided to use 2-acetylquinizarin **1** as the starting material in our

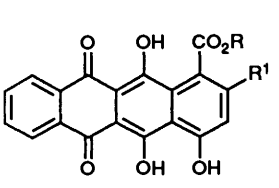


1

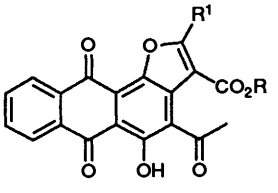
approach to the synthesis of anthracyclinones, expecting that an acyl group would facilitate addition to the anthraquinone system.

Compound **1** was prepared by Jones' oxidation of hydroxyethylquinizarin in 75% yield.[18] The reaction of ketone **1** with a variety of β-keto esters in MeOH in presence of tertiary amines was examined. Reaction of methyl acetoacetate with compound **1** in MeOH in presence of quinuclidine at room temperature gave four products; tetracene **2** (3%), furan **8** (13%), adduct **13** (14%) and a diastereoisomeric mixture of ketones **18a** and **18b** (20%). The diastereoisomeric ketones could not be separated and ^{1}H NMR spectroscopy showed the product to be a 2:1 mixture. At this stage it was not possible to assign stereochemistry to the ketones. The reaction of ethyl acetoacetate with **1** afforded aromatic tetracycle **3** (7%), furan **9** (19%), adduct **14** (17%) and a 2:1 inseparable mixture of ketones **19a** and **19b** (24%). The results of the reaction of methyl acetoacetate and ethyl acetoacetate with compound **1** were quite encouraging as the tetracyclic ketones were formed in a 'one pot' reaction. It was also observed from TLC scale experiments that adducts **13** and **14** could be cyclised to the respective tetracyclic ketones by treatment with Et_3N in MeOH at room temperature.

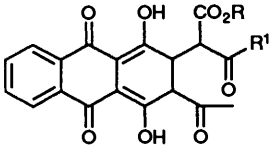
We then investigated the reaction of 2-acetylquinizarin **1** with methyl 3-oxovalerate because functional group manipulation of the cyclic ketones would give access to 4-deoxy-ε-rhodomycinone. Methyl 3-oxovalerate[6] was prepared



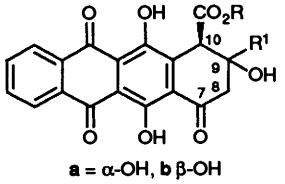
2 R = R^1 = Me
3 R = Et, R^1 = Me
4 R = Me, R^1 = Et
5 R = R^1 = Et
6 R = Bu^t, R^1 = Et
7 R = Me, R^1 = C(OMe)$_2$Me



8 R = R^1 = Me
9 R = Et, R^1 = Me
10 R = Me, R^1 = Et
11 R = R^1 = Et
12 R = Me, R^1 = C(OMe)$_2$Me



13 R = R^1 = Me
14 R = Et, R^1 = Me
15 R = Me, R^1 = Et
16 R = R^1 = Et
17 R = Me, R^1 = C(OMe)$_2$Me



a = α-OH, **b** β-OH

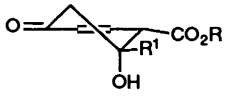
18 R = R^1 = Me
19 R = Et, R^1 = Me
20 R = Me, R^1 = Et
21 R = R^1 = Et
22 R = Bu^t, R^1 = Et
23 R = Me, R^1 = C(OMe)$_2$Me

from methyl acetoacetate in 80% yield. Reaction of **1** with methyl 3-oxovalerate in MeOH in presence of quinuclidine gave the aromatic tetracycle **4** (10%), the furan **10** (16%), the adduct **15** (20%) and a mixture of diastereoisomeric ketones **20a** and **20b**† (30%). The diastereoisomers could not be separated and the ^{1}H NMR spectrum showed a 4.5:1 ratio for the ketones. Treatment of the adduct **15** with Et_3N–MeOH afforded a mixture of ketones **20a** and **20b** (50%) along with **4** (10%) and **10** (17%). The ratio of the **20a** and **20b** from this reaction was also found to be 4.5:1. It is notable that the ketones were isolated in higher yield whereas the furan was obtained in lower yield than in the previous reactions. Thus, it was thought that substitution of the ester methyl for bulkier alkyl groups might improve the yield and the isomer ratio as well as cut down the amount of furan formation.

In the reaction of ethyl 3-oxovalerate with 2-acetylquinizarin aromatic tetracycle **5** (10%) was isolated as well as furan **11** (15%), the adduct **16** (20%) and a mixture of ketones **21a** and **21b** (35%). Although an increase in the yield of the ketones **21a** and **21b** was observed there was no change in the isomer ratio. Next we examined the reaction of *tert*-butyl 3-oxovalerate with 2-acetylquinizarin **1**. *tert*-Butyl 3-oxovalerate was prepared in

† All compounds described are racemates but only one enantiomer is used in formulae.

63% yield by Claisen reaction between *tert*-butyl acetate and ethyl propionate following the procedure of Danishefsky *et al.*[19] The reaction of compound **1** with *tert*-butyl 3-oxovalerate afforded the tetracycle **6** (25%), the furan **12** (10%) and the ketones **22a** (14%) and **22b** (26%). The C-10 methine proton (anthracyclinone numbering) of the major ketone appeared as a singlet at δ 4.38, while that in the minor isomer was at δ 4.48. NOE experiments provided information about the relative stereochemistry of C-9 and C-10 positions. A 13% increase in the intensity of the C-10 methine proton singlet of the major isomer was observed by irradiating the methylene protons of the ethyl group. This suggested that C-10 ester function and C-9 hydroxy group were *cis* orientated. No such intensity increase was observed in the minor isomer. Hence structure **22b** was assigned to the major isomer and structure **22a** was assigned to the minor. It was also noticed that the C-10 methine proton of the major ketone **22b** appeared at higher field than that of the minor ketone **22a**. This was also observed in the case of other diastereoisomeric mixtures. Thus, by analogy, structures **18b**, **19b**, **20b** and **21b** were assigned to the major isomers in the respective mixtures. These results are in accord with reaction to form conformation **24**, in which CO_2R is equatorial and the

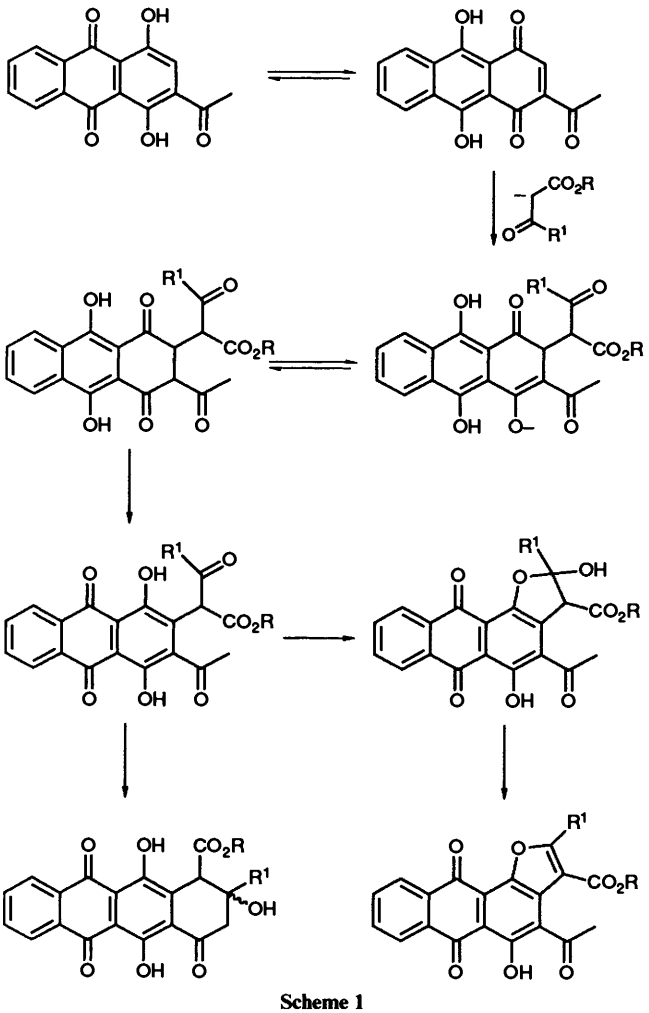


24

oxygen of the acceptor carbonyl axial as the favoured geometry for attack. This result is in agreement with the stereochemistry reported for the formation of β-hydroxycyclohexanones.[20] The mechanism for the formation of the various products is outlined in Scheme 1.

Next we examined the reaction of **1** with 4,4-dimethoxy-3-oxopentanoate in the hope that the diastereoselectivity of the reaction might improve. Methyl 4,4-dimethoxy-3-oxopentanoate was prepared, following the procedure of Danishefsky *et al.*[21] from the reaction of 3,3-dimethoxybutan-2-one[22] and dimethyl carbonate. Reaction of methyl 4,4-dimethoxy-3-oxopentanoate with compound **1** in presence of tetramethylethylenediamine (TMEDA) in MeOH afforded the aromatic tetracycle **7** (10%), the adduct **17** (20%), a tetracyclic ketone **23** (38%) and unchanged **1** (20%). No furan formation was observed possibly due to the steric hindrance induced by the side chain. The ^1H NMR spectrum of the adduct **17** indicated it to be a mixture of **17** and its enol form in 1.14:1 ratio. Surprisingly, the ^1H NMR spectrum of the tetracyclic ketone showed only one set of protons. From the results of other reactions it was expected that the product would be a mixture of two diastereoisomers **23a** and **23b**. Reaction of the adduct **17** with Et_3N in MeOH under nitrogen at room temperature gave a mixture of the ketones **23a** and **23b** (60%) along with the aromatic tetracycle **7** (10%) and unchanged **17** (12%).

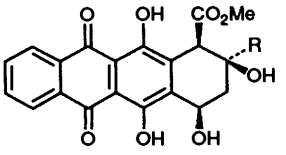
Reduction of the diastereoisomeric mixture of ketones **20a** and **20b** was next investigated because it would not only allow us to complete the synthesis of 4-deoxy-ε-rhodomycinone but also furnish further evidence regarding the stereochemistry of the tetracyclic ketones. Reaction of the mixture of ketones **20a** and **20b** with $NaBH_4$–$CeCl_3$–MeOH gave four diols which were separated by repetitive PTLC. The major diol (40%) in its ^1H NMR spectrum showed the following signals for the A ring protons: an unresolved quartet ($W_{\frac{1}{2}}$ 14.0 Hz) at δ 5.25 for 7-H, a doublet at δ 4.17 for the 7-OH, a singlet at δ 3.96 for 10-H, a singlet at δ 3.83 for the ester methyl protons, a singlet at δ 3.76 for the 9-OH, and two doublets of doublets at δ 2.45 (J 15.0 and 4.5 Hz) and δ 1.98 (J 15.0 and 5.5 Hz) for the 8-methylene protons. The assignments of the A-ring protons



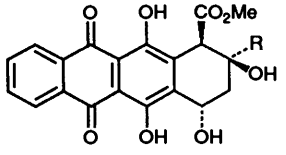
Scheme 1

were confirmed by decoupling experiments. No long range coupling was observed between 10-H and the 8-methylene protons. However, precedence exists for both the presence and absence of this type of long range coupling. A 1.3 Hz coupling was found between the C-10 and C-8 equatorial protons in 4-deoxyalkavinone[23] whereas no such coupling was observed in 4-deoxy-14-nor-ε-rhodomycinone.[24] Comparison of the coupling constants of the A ring protons of the product diol with literature[23,24] precedent indicated that the configurations at C-7 and C-9 in the product were different from those in the natural product. However, the coupling constant of 7-H and 8-H product showed similarity with those of 10-*epi*-4-deoxyauramycinone. Hence on the basis of the spectroscopic data the major product was assigned structure **25**. The *cis* orientation of 7-OH and 9-OH was confirmed by preparing[25] a phenyl boronate ester **33** (95%). The ambient temperature ^1H NMR spectrum of **33** unexpectedly showed a very broad singlet for the ester methyl protons at δ 3.53. At −47 °C the methyl signal split into two sharp singlets in 6:1 ratio establishing that at ambient temperature there was a conformational equilibrium slow on the NMR timescale.

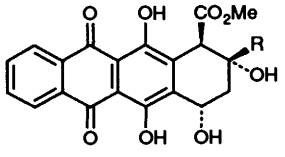
The second diol (20%) showed the following signals for the A-ring protons: an unresolved triplet ($W_{\frac{1}{2}}$ 14 Hz) at δ 5.44 for 7-H, a singlet at δ 3.78, and two doublets of doublets at δ 2.50 (J 15.0 and 7.5 Hz) and 2.03 (J 15.0 and 5.0 Hz) for the 8-methylene protons. The diol did not form a boronate and hence a *trans* orientation of the 7-OH and 9-OH was established. On this basis and comparison with a related compound reported by Krohn *et al.*[23] structure **27** was assigned. The third diol (10%) formed a phenylboronate. In the NMR spectrum 7-H appeared



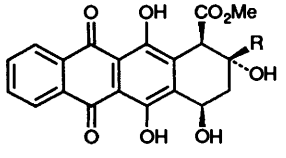
25 R = Et
26 R = Ac



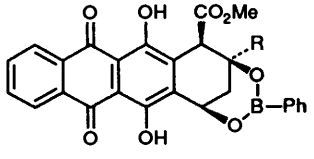
27 R = Et
28 R = Ac



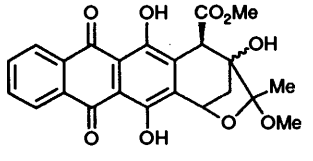
29 R = Et
30 R = Ac



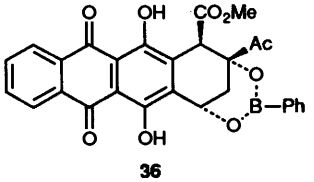
31 R = Et
32 R = Ac



33 R = Et
34 R = Ac



35



36

as an unresolved triplet ($W_{\frac{1}{2}}$ 8.0 Hz) at δ 5.42 and the 10-H singlet was found at δ 4.32. A 2 H distorted doublet at δ 2.30 was assigned to the 8-methylene protons. On the basis the diol was assigned the 4-deoxy-ε-rhodomycinone structure **29**. The fourth diol was obtained in meagre quantity.

Epimerisation of **25** at C-10 would give the enantiomer of **29** and provide further evidence for the structures assigned to these compounds.[26] To this end a solution of **25** in CH_2Cl_2 was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and gave a 2:1 mixture of **25** and **29**. This observation contrasts with the report[24] that the thermodynamically more stable isomer in the 11-deoxy series is that with methoxycarbonyl and hydroxy groups *trans*.

Reduction of the mixture of ketones **23a** and **23b** with $NaBH_4$–$CeCl_3$–MeOH gave a mixture from which only one product was isolated in 30% yield. The product, of composition $C_{23}H_{20}O_9$, showed δ_H 13.29 (1 H, s), 13.24 (1 H, s), 8.41 (2 H, m), 7.88 (2 H, m), 5.56 (1 H, t, *J* 3.0 Hz), 4.62 (1 H, s), 3.78 (3 H, s), 3.14 (3 H, s), 2.48 (2 H, d, *J* 3.0 Hz) and 1.44 (3 H, s), and was assigned structure **35**. If the crude mixture obtained from $NaBH_4$ reduction of ketones **23a** and **23b** was hydrolysed with CF_3CO_2H–H_2O then three main fractions were isolated by PTLC. The first product (38%), $C_{22}H_{18}O_9$, was a 3:1 mixture (which also gave an inseparable mixture of phenylboronates) showed δ_H(major) 5.43 (1 H, m), 4.60 (1 H, s), 2.46 (3 H, s) 2.43 (1 H, dd, *J* 15 and 3 Hz), 2.08 (1 H, dd, J 15 and 4.5 Hz) and δ_H(minor) 5.23 (1 H, m), 4.53 (1 H, s), 2.44 (3 H, s), 2.38 (1 H, dd, *J* 15 and 6 Hz), 2.02 (1 H, dd, *J* 15 and 4 Hz). On the basis of this evidence and by analogy the major diol was assigned structure **26** and the minor isomer postulated to be **30**. Hence structure **34** was assigned to the major boronate and structure **36** to the minor boronate.

The second diol (14%) did not form a boronate and showed δ_H 5.56 (1 H, m), 5.22 (1 H, s), 2.84 (2 H, m), and 2.62 (3 H, s). The third diol (6%) did not form boronate and showed δ_H 5.63 (1 H, m), 5.36 (1 H, s), 3.00 (1 H, dd, *J* 15 and 4 Hz), 2.92 (1 H, d, *J* 15 Hz), 2.62 (3 H, s). From the comparison of the chemical shifts of the 10-H and 8-H structure **28** was assigned to the more abundant diol and structure **32** to the minor one.

From these results it is clear that the major diastereoisomers formed in the intramolecular aldol condensations belong to the unnatural series with OH and CO_2Me *cis* and that these isomers are thermodynamically the more stable. We were also unable to decarbomethoxylate **30** to demethoxydaunomycinone.

Experimental

Melting points were recorded on a Kofler block and are uncorrected. NMR spectra were measured in $CDCl_3$ at 60 MHz on a Perkin Elmer R12B instrument, at 220 MHz on a Perkin-Elmer R34 instrument and at 300 MHz on a Varian SC300 instrument unless indicated to the contrary. *J* values are given in Hz. UV spectra were recorded in $CHCl_3$ on a Shimadzu UV-260 spectrometer, ε values are given in $dm^3\ mol^{-1}\ cm^{-1}$. IR spectra were recorded in $CHCl_3$ on either a Pye-Unicam SP3-200 or a Perkin-Elmer 1710 spectrometer. Mass spectra were recorded on AEI MS30 and Kratos MS25 instruments. TLC and PTLC were performed on Merck Silica gel 60F-254. Silica gel for column chromatography was Merck Kiesel gel 60 H.

2-Acetyl-1,4-dihydroxyanthraquinone **1**.—Jones' reagent (1.1 cm^3) was added dropwise to a stirred mixture of 1,4-dihydroxy-2-(1-hydroxyethyl)anthraquinone (500 mg) and Celite (1 g) in acetone (50 cm^3) at room temperature. After 1 h the mixture was filtered, diluted with CH_2Cl_2 (70 cm^3), washed with water (3 × 50 cm^3), dried ($MgSO_4$), passed through a plug of silica gel and the filtrate evaporated to give the *ketone* **1** as a red solid (372 mg), m.p. 200–202 °C; ν_{max}/cm^{-1} 1690, 1625 and 1590; λ_{max}/nm 252 (ε 15 600), 284 (5000) and 484 (4550); δ_H 13.84 (1 H, s), 12.62 (1 H, s), 8.42 (2 H, m), 7.91 (2 H, m), 7.76 (1 H, s), 2.75 (3 H, s) (Found: M^+, 282.0532. $C_{16}H_{10}O_5$ requires *M*, 282.0528).

Reaction of the Quinone **1** *with Methyl Acetoacetate*.—A suspension of the quinone **1** (160 mg) in MeOH (70 cm^3) was treated with quinuclidine (312 mg) and methyl acetoacetate (165 mg). The reaction mixture was stirred at room temperature for 2 h and then diluted with water (50 cm^3), acidified with 2 mol dm^{-3} HCl, and extracted with CH_2Cl_2 (2 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a red solid. Preparative TLC on silica gel eluting with CH_2Cl_2–AcOEt (19:1) afforded **2** (6.4 mg), **8** (28 mg), **13** (30 mg) and a mixture of **18a** and **18b** (45 mg). *4,5,12-Trihydroxy-2-methyl-1-methoxycarbonylnaphthacene-6,11-quinone* **2**: m.p. 233–235 °C; ν_{max}/cm^{-1} 3400–3100, 1730 and 1600; λ_{max}/nm 249 (ε 22 500), 272 (44 750), 467 (12 200), 498 (21 750) and 535 (21 550); δ 14.88 (1 H, s), 14.20 (1 H, s), 12.74 (1 H, s), 8.58 (2 H, m), 7.89 (2 H, m), 7.22 (1 H, s), 4.06 (3 H, s) and 2.44 (3 H, s) (Found: M^+ 378.0737. $C_{21}H_{14}O_7$ requires *M*, 378.0739). *4-Acetyl-5-hydroxy-2-methyl-3-methoxycarbonylfuro*[2,3-a]*anthraquinone* **8**: m.p. 194–195 °C; ν_{max}/cm^{-1} 1725, 1680, 1630 and 1590; λ_{max}/nm 258 (ε 21 250) and 426 (5800); δ 13.14 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 3.91 (3 H, s), 2.88 (3 H, s), 2.76 (3 H, s) and 2.76 (3 H, s); (Found: M^+, 378.0745. $C_{21}H_{14}O_7$ requires *M*, 378.0739). *3-Acetyl-2-*[*acetyl*(*methoxycarbonyl*)*methyl*]*-1,4-dihydroxyanthraquinone* **13**: m.p. 154–156 °C; ν_{max}/cm^{-1} 3500–2500, 1670, 1625 and 1590; λ_{max}/nm 252 (ε 66 200), 258 (65 050), 290 (19 650), 330 (5250), 485 (17 450) and 520 (10 500); δ 13.30 (1 H, s), 13.16 (1 H, s), 13.12 (1 H, s), 8.44 (2 H, m), 7.93 (2 H, m), 3.72 (3 H, s), 2.46 (3 H, s) and 1.90 (3 H, s) (Found: M^+, 396.0836. $C_{21}H_{16}O_8$ requires *M*, 396.0845).

1,2,3,4-*Tetrahydro*-2,5,12-*trihydroxy*-1-*methoxycarbonyl*-2-*methyl*-4-*oxonaphthacene*-6,11-*quinone* **18a** and **18b**: m.p. 202–204 °C; ν_{max}/cm^{-1} 3480–3100, 1730, 1700, 1628 and 1590; λ_{max}/nm 256 (ε 31 300), 289 (11 000) and 494 (10 000); δ (**18a**): 14.02 (1 H, s), 13.24 (1 H, s), 8.44 (2 H, m), 7.93 (2 H, m), 4.50 (1 H, s), 3.80 (3 H, s), 3.23 (1 H, d, *J* 16.5), 2.96 (1 H, s), 2.79 (1 H, d, *J* 16.5) and 1.54 (3 H, s); (**18b**): 14.02 (1 H, s), 13.32 (1 H, s), 8.44 (2 H, m), 7.93 (2 H, m), 4.44 (1 H, s), 3.82 (3 H, s), 3.23 (1 H, d, *J* 16.5), 2.96 (1 H, s), 2.83 (1 H, d, *J* 16.5) and 1.44 (3 H, s) (Found: M$^+$, 396.0844. $C_{21}H_{16}O_8$ requires *M*, 396.0845).

Reaction of the Quinone **1** *with Ethyl Acetoacetate*.—The same procedure was used as that described for methyl acetoacetate and **3** (7%), **9** (19%), **14** (17%) and a mixture of **19a** and **19b** (24%) were isolated after chromatography. *Compound* **3**: m.p. 229–230 °C; ν_{max}/cm^{-1} 1710 and 1600; λ_{max}/nm 245 (ε 11 750), 267 (23 200), 463 (4150), 496 (7650) and 529 (8250); δ 14.88 (1 H, s), 14.17 (1 H, s), 12.72 (1 H, s), 8.55 (2 H, m), 7.86 (2 H, m), 7.19 (1 H, s), 4.56 (2 H, q, *J* 7.5), 2.42 (3 H, s) and 1.41 (3 H, t, *J* 7.5) (Found: M$^+$, 392.0895. $C_{22}H_{16}O_7$ requires *M*, 392.0895). *Compound* **9**: m.p. 214–216 °C; ν_{max}/cm^{-1} 1700, 1670, 1630 and 1590; λ_{max}/nm 255, 275, 405, 425 and 445; δ 13.14 (1 H, s), 8.37 (2 H, m), 7.88 (2 H, m), 4.40 (2 H, q, *J* 7.5), 2.86 (3 H, s), 2.75 (3 H, s) and 1.38 (3 H, t, *J* 7.5); (Found: M$^+$, 392.0906. $C_{22}H_{16}O_7$ requires *M*, 392.0895). *Compound* **14**: m.p. 146–148 °C; ν_{max}/cm^{-1} 3600–3100, 1705, 1625 and 1590; λ_{max}/nm 252 (ε 16 200), 280 (5400), 482 (4000) and 520 (2700); δ 13.27 (1 H, s), 13.20 (1 H, s), 13.14 (1 H, s), 8.44 (2 H, m), 7.93 (2 H, m), 4.25 (2 H, q, *J* 7.5), 2.48 (3 H, s), 1.89 (3 H, s) and 1.22 (3 H, t, *J* 7.5); (M$^+$, 410.0995. $C_{22}H_{18}O_8$ requires *M*, 410.0994). *Compounds* **19a** and **19b**: m.p. 177–179 °C; ν_{max}/cm^{-1} 1730, 1710, 1625 and 1600; λ_{max}/nm 256 (ε 24 000), 290 (8300) and 496 (7600); δ (**19a**): 14.02 (1 H, s), 13.21 (1 H, s), 8.42 (2 H, m), 7.91 (2 H, m), 4.47 (1 H, s), 4.27 (2 H, q, *J* 7.0), 3.25 (1 H, d, *J* 16.5), 2.99 (1 H, s), 2.79 (1 H, d, *J* 16.5), 1.55 (3 H, s) and 1.31 (3 H, t, *J* 7.0); (**19b**): 14.02 (1 H, s), 13.28 (1 H, s), 8.42 (2 H, m), 7.91 (2 H, m), 4.41 (1 H, s,), 4.29 (q, *J* 7.0), 3.24 (1 H, d, *J* 16.5), 2.99 (1 H, s), 2.83 (1 H, d, *J* 16.5), 1.55 (3 H, s) and 1.29 (3 H, t, *J* 7.0) (M$^+$, 410.1006. $C_{22}H_{18}O_8$ requires *M*, 410.1002).

Methyl 3-*Oxovalerate*.—Sodium hydride (60% dispersion in mineral oil; 0.97 g) was placed in a flame dried three-necked flask under nitrogen and then washed three times with dry light petroleum (b.p. 40–60°). Dry tetrahydrofuran (THF) (50 cm^3) was added and the flask was placed in an ice bath. Methyl acetoacetate (2.5 g) was added dropwise and the solution was stirred for 20 min. A solution of butyllithium in hexane (1 mol dm^{-3}; 22.6 cm^3) was added dropwise and the orange solution was stirred at 0 °C for an additional 20 min. A solution of methyl iodide (3.36 g) in THF (5 cm^3) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with 10 mol dm^{-3} HCl (5 cm^3) and water (15 cm^3) and then diethyl ether (40 cm^3) added. The organic phase was washed with water until the aqueous extracts were neutral, then dried ($MgSO_4$) and evaporated to give crude product as a pale yellow liquid (2.68 g). Distillation at 69–71 °C/14 mmHg gave pure methyl 3-oxovalerate as a colourless liquid (2.24 g); ν_{max}/cm^{-1} (liquid film) 1740 and 1715; δ 3.70 (3 H, s), 3.40 (2 H, s), 2.55 (2 H, q, *J* 7.0) and 1.05 (3 H, t, *J* 7.0).

Reaction of the Quinone **1** *with Methyl* 3-*Oxovalerate*.—The reaction was carried out as described for methyl acetoacetate except that the reaction mixture was stirred for 3 h. Preparative TLC on silica gel eluting with CH_2Cl_2–AcOEt (19:1) gave *aromatic tetracycle* **4** (10%), *furan* **10** (16%), *adduct* **15** (20%) and a mixture of *ketones* **20a** and **20b** (30%). *Compound* **4**: m.p. 210–202 °C; ν_{max}/cm^{-1} 1725 and 1595; λ_{max}/nm 249 (ε 24 000), 272 (42 500), 467 (12 400), 498 (21 700) and 535 (20 900); δ 14.88 (1 H, s), 14.20 (1 H, s), 12.75 (1 H, s), 8.60 (2 H, m), 7.90 (2 H, m), 7.14 (1 H, s), 4.08 (3 H, s), 2.76 (2 H, q, *J* 7.5) and 1.34 (3 H, t, *J* 7.5) (Found: M$^+$, 392.0901. $C_{22}H_{16}O_7$ requires *M*, 392.0896). *Compound* **10**: m.p. 188–190 °C; ν_{max}/cm^{-1} 1710, 1670, 1630 and 1590; ν_{max}/nm 258 (ε 32 750) and 427 (9 050); δ 13.14 (1 H, s), 8.37 (2 H, m), 7.88 (2 H, m), 3.88 (3 H, s), 3.26 (2 H, q, *J* 7.5), 2.74 (3 H, s) and 1.45 (3 H, t, *J* 7.5) (Found: C, 67.6; H, 4.2. M$^+$, 292.0906. $C_{22}H_{16}O_7$ requires C, 67.4; H, 4.1%; *M*, 392.0896). *Compound* **15**: m.p. 148–150 °C; ν_{max}/cm^{-1} 1701, 1630 and 1590; λ_{max}/nm 253 (ε 35 450) and 494 (9650); δ 13.22 (1 H, s), 13.16 (1 H, s), 13.10 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 3.69 (3 H, s), 2.42 (3 H, s), 2.14 (2 H, q, *J* 7.5), 1.08 (3 H, t, *J* 7.5) (Found: M$^+$, 410.1005. $C_{22}H_{18}O_8$ requires *M*, 410.1002). *Compounds* **20a** and **20b**: m.p. 176–178 °C; ν_{max}/cm^{-1} 3600–3440, 1725, 1700, 1630 and 1590; λ_{max}/nm 256 (ε 24 300), 289 (8750) and 496 (8200); δ (**20a**): 14.00 (1 H, s), 13.23 (1 H, s), 8.41 (2 H, m), 7.91 (2 H, m), 4.56 (1 H, s), 3.78 (3 H, s), 3.15 (1 H, d, *J* 16.5), 2.92 (1 H, s), 2.80 (1 H, d, *J* 16.5), 1.64 (2 H, m) and 1.14 (3 H, t, *J* 7.5); (**20b**): 13.98 (1 H, s), 13.28 (1 H, s), 8.41 (2 H, m), 7.91 (2 H, m), 4.50 (1 H, s), 3.80 (3 H, s), 3.18 (1 H, d, *J* 16.5), 2.92 (1 H, s), 2.86 (1 H, d, *J* 16.5), 1.64 (2 H, m) and 1.00 (3 H, t, *J* 7.5) (Found: M$^+$, 410.1004. $C_{22}H_{18}O_8$ requires *M*, 410.1002).

Cyclisation of the Adduct **15**.—A solution of the adduct **15** (80 mg) in MeOH (40 cm^3) was treated with Et_3N (39 mg) at room temperature for 3 h. Work-up and chromatography gave **4** (7.6 mg), **10** (13.0 mg) and a mixture of **20a** and **20b** (40.0 mg).

Ethyl 3-*Oxovalerate*.—Ethyl 3-oxovalerate was prepared from ethyl acetoacetate and methyl iodide following the procedure described for methyl 3-oxovalerate. Distillation of the crude product at 78–80 °C/12 mmHg afforded pure product as a colourless liquid (2.27 g), ν_{max}/cm^{-1} (liquid film) 3400, 1740, 1715, 1640 and 1630; δ 4.15 (2 H, q, *J* 7.5), 3.40 (2 H, s), 2.55 (2 H, q, *J* 7.5), 1.30 (3 H, t, *J* 7.5) and 1.10 (3 H, t, *J* 7.5).

Reaction of the Quinone **1** *with Ethyl* 3-*Oxovalerate*.—The same procedure was used as that described for methyl 3-oxovalerate and the products were separated by preparative TLC. *Aromatic tetracycle* **5** (10%): m.p. 203–205 °C; ν_{max}/cm^{-1} 1730 and 1595; λ_{max}/nm 249 (ε 25 750), 272 (48 800), 467 (13 800), 498 (24 550) and 535 (24 100); δ 14.91 (1 H, s), 14.18 (1 H, s), 12.74 (1 H, s), 8.56 (2 H, m), 7.86 (2 H, m), 7.24 (1 H, s), 4.58 (2 H, q, *J* 7.5), 2.74 (2 H, q, *J* 7.5), 1.45 (3 H, t, *J* 7.5) and 1.32 (3 H, t, *J* 7.5) (Found: M$^+$, 406.1048. $C_{23}H_{18}O_7$ requires *M*, 406.1052). *Furan* **11** (15%): m.p. 168–170 °C; ν_{max}/cm^{-1} 1710, 1670, 1630 and 1590; λ_{max}/nm 258 (ε 28 450) and 427 (7900); δ 13.17 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 4.42 (2 H, q, *J* 7.5), 3.28 (2 H, q, *J* 7.5), 2.78 (3 H, s), 1.47 (3 H, t, *J* 7.5) and 1.42 (3 H, t, *J* 7.5) (Found: M$^+$, 406.1052. $C_{23}H_{18}O_7$ requires *M*, 406.1052). *Adduct* **16** (20%): m.p. 140–142 °C; ν_{max}/cm^{-1} 3480–2500, 1710, 1620 and 1590; λ_{max}/nm 253 (ε 37 400) and 486 (9650); δ 13.30 (1 H, s), 13.26 (1 H, s), 13.14 (1 H, s), 8.43 (2 H, m), 7.91 (2 H, m), 4.24 (2 H, q, *J* 7.5), 2.46 (3 H, s), 2.15 (2 H, q, *J* 7.5), 1.20 (3 H, t, *J* 7.5), 1.09 (3 H, t, *J* 7.5) (Found: M$^+$, 424.1150. $C_{23}H_{20}O_8$ requires *M*, 424.1158). *Ketones* **21a** and **21b** (35%): m.p. 167–169 °C; ν_{max}/cm^{-1} 1725, 1700, 1625 and 1590; λ_{max}/nm 256 (ε 41 900), 290 (14 300), 493 (13 750); δ (**21a**): 14.00 (1 H, s), 13.22 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 4.53 (1 H, s), 4.27 (2 H, q, *J* 7.5), 3.16 (1 H, d, *J* 16.0), 2.96 (1 H, s), 2.86 (1 H, d, *J* 16.0), 1.63 (2 H, m), 1.26 (3 H, t, *J* 7.5) and 1.14 (3 H, t, *J* 7.5); **21b**, 13.98 (1 H, s), 13.27 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 4.46 (1 H, s), 4.27 (2 H, q, *J* 7.5), 3.16 (1 H, d, *J* 16.0),

2.96 (1 H, s), 2.86 (1 H, d, *J* 16.0), 1.63 (2 H, m), 1.28 (3 H, t, *J* 7.5) and 1.00 (3 H, t, *J* 7.5) (Found: M^+, 424.1152. $C_{23}H_{20}O_8$ requires *M*, 424.1158).

tert-*Butyl* 3-*Oxovalerate*.—A solution of butyllithium in hexane (1 mol dm^{-3}; 11.53 cm^3) was added dropwise over a period of 5 min to a stirred solution of diisopropylamine (1.16 g) in THF (15 cm^3) at 0 °C under nitrogen and the solution was stirred for a further 10 min. The solution was cooled to −78 °C and *tert*-butyl acetate (1.16 g) was added dropwise over a period of 10 min. The solution was stirred at the same temperature for an additional 20 min. Ethyl propionate (1.07 g) was slowly added and the reaction mixture was warmed to room temperature over 5 h. The reaction was quenched by addition of water (20 cm^3) and then acidified with 2 mol dm^{-3} HCl. The mixture was extracted with diethyl ether (3 × 50 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated to give a pale yellow liquid (1.25 g). Chromatography on silica gel eluting with pentane–diethyl ether (6:1) afforded pure *tert*-butyl 3-oxovalerate as a colourless liquid (1.08 g), ν_{max}/cm^{-1} (liquid film) 3600–3360, 1735, 1720 and 1645; δ 3.30 (2 H, s), 2.55 (2 H, q, *J* 7.5), 1.46 (9 H, s) and 1.10 (3 H, t, *J* 7.5).

Reaction of the Quinone **1** *with* tert-*Butyl* 3-*Oxovalerate*.—The same procedure was carried out as that described for methyl 3-oxovalerate except that the reaction mixture was stirred for 9 h. The products were separated by preparative TLC. *Aromatic tetracycle* **6** (25%): m.p. 206–208 °C; ν_{max}/cm^{-1} 1710 and 1600; λ_{max}/nm 249 (ε 15 400), 272 (29 900), 467 (7900), 498 (14 200) and 535 (14 000); δ 15.00 (1 H, s), 14.15 (1 H, s), 12.66 (1 H, s), 8.52 (2 H, m), 7.85 (2 H, m), 7.22 (1 H, s), 2.75 (2 H, q, *J* 7.5), 1.64 (9 H, s) and 1.29 (3 H, t, *J* 7.5) (Found: M^+, 434.1365. $C_{25}H_{22}O_7$ requires *M*, 434.1365). *Furan* **12** (10%): m.p. 187–189 °C; ν_{max}/cm^{-1} 1720, 1670, 1630 and 1595; λ_{max}/nm 259 (ε 28 600) and 427 (8350); δ 13.17 (1 H, s), 8.36 (2 H, m), 7.87 (2 H, m), 3.19 (2 H, q, *J* 7.5), 2.76 (3 H, s), 1.60 (9 H, s) and 1.44 (3 H, t, *J* 7.5) (Found: M^+, 434.1359. $C_{25}H_{22}O_7$ requires *M*, 434.1365). *Ketone* **22a** (14%): m.p. 150–152 °C; ν_{max}/cm^{-1} 1715, 1700, 1630 and 1595; λ_{max}/nm 256 (ε 24 050), 291 (7750) and 496 (7700); δ 14.04 (1 H, s), 13.24 (1 H, s), 8.44 (2 H, m), 7.92 (2 H, m), 4.48 (1 H, s), 3.19 (1 H, d, *J* 16.5), 2.80 (1 H, d, *J* 16.5), 1.92 (1 H, m), 1.75 (1 H, m), 1.48 (9 H, s) and 1.19 (3 H, t, *J* 7.5) (Found: M^+, 452.1475. $C_{25}H_{24}O_8$ requires *M*, 452.1471). *Ketone* **22b** (26%): m.p. 152–154 °C; ν_{max}/cm^{-1} 1720, 1700, 1630 and 1590; λ_{max}/nm 256 (ε 25 000), 290 (7800) and 496 (7850); δ 14.02 (1 H, s), 13.32 (1 H, s), 8.40 (2 H, m), 7.90 (2 H, m), 4.38 (1 H, s), 3.26 (1 H, s), 3.11 (1 H, d, *J* 16.5), 2.87 (1 H, d, *J* 16.5), 1.63 (2 H, m), 1.48 (9 H, s) and 0.98 (3 H, t, *J* 7.5) (Found: M^+, 452.1468. $C_{25}H_{24}O_8$ requires *M*, 452.1471).

3,3-*Dimethoxybutan*-2-*one*.—A mixture of freshly distilled diacetyl (20 g) and anhydrous NH_4Cl (500 mg) in MeOH (100 cm^3) was heated under reflux for 1.5 h and then set aside overnight. The reaction mixture was made alkaline with $NaHCO_3$ solution. MeOH was removed by distillation and the ketal–water mixture was extracted with light petroleum (b.p. 40–60 °C) continuously for a week. The light petroleum layer was separated, concentrated and dried (Na_2SO_4). This was distilled initially at atmospheric pressure to remove light petroleum and then at water pump pressure to give pure 3,3-dimethoxybutan-2-one as a pale yellow liquid (15.34 g), b.p. 78–80 °C/90 mmHg; ν_{max}/cm^{-1} (liquid film) 1728; δ 3.23 (6 H, s), 2.23 (3 H, s) and 1.38 (3 H, s).

Methyl 4,4-*Dimethoxy*-3-*oxopentanoate*.—3,3-Dimethoxybutan-2-one (10 g) was added dropwise over a period of 2.5 h to a boiling suspension of NaH (4.66 g) in benzene (260 cm^3) and dimethyl carbonate (15.33 g). After 3 h of heating, the light green suspension was cooled in an ice bath and carefully quenched with acetic acid (12 cm^3) and diluted with diethyl ether (200 cm^3). The mixture was washed with water (3 × 100 cm^3), dried (Na_2SO_4) and evaporated to give a yellow liquid. Distillation at 80–82 °C/0.4 mmHg gave the ester as a colourless liquid (8.93 g), ν_{max}/cm^{-1} (liquid film) 1742, 1728, 1660 and 1630; δ 5.45 (1 H, s), 3.70 (3 H, s), 3.68 (3 H, s), 3.58 (2 H, s), 3.20 (6 H, s) 3.15 (6 H, s), 1.46 (3 H, s) and 1.38 (3 H, s).

Reaction of **1** *with Methyl* 4,4-*Dimethoxy*-3-*oxovalerate*.—A suspension of the quinone **1** (200 mg) in MeOH (300 cm^3) was treated with TMEDA (575 mg) and methyl 4,4-dimethoxy-3-oxopentanoate (1.35 g). The reaction mixture was stirred at room temperature for 72 h. Work-up and preparative TLC on silica gel eluting with CH_2Cl_2–AcOEt (9:1) afforded *aromatic tetracycle* **7** (32 mg), *adduct* **17** (66 mg), the *ketones* **23a** and **23b** (127 mg), and unchanged **1** (56 mg). *Compound* **7**: m.p. 142–144 °C; ν_{max}/cm^{-1} 1725 and 1595; λ_{max}/nm 253 (ε 16 950), 271 (32 050), 470 (8200), 501 (14 250) and 538 (13 600); δ 14.93 (1 H, s), 14.14 (1 H, s), 12.80 (1 H, s), 8.53 (2 H, m), 7.84 (2 H, m), 7.58 (1 H, s), 3.98 (3 H, s), 3.24 (3 H, s), 3.22 (3 H, s) and 1.65 (3 H, s) (Found: M^+, 452.1099. $C_{24}H_{20}O_9$ requires *M*, 452.1107). *Compound* **17**: m.p. 117–119 °C; ν_{max}/cm^{-1} 3600–3100, 1743, 1680, 1630 and 1585; λ_{max}/nm 251 (ε 31 500), 284 (10 150) and 475 (10 050); δ (keto form): 13.63 (1 H, s), 13.24 (1 H, s), 8.44 (2 H, m), 7.94 (2 H, m), 4.88 (1 H, s), 3.76 (3 H, s), 3.58 (3 H, s), 3.38 (3 H, s), 2.76 (3 H, s) and 1.49 (3 H, s); (enol form): 14.16 (2 H, s), 8.35 (2 H, m), 7.88 (2 H, m), 4.58 (1 H, s), 3.79 (3 H, s), 3.34 (3 H, s), 3.22 (3 H, s), 2.70 (3 H, s) and 1.52 (3 H, s); *m/z* 488 (M^+ + 18, CI) (Found: C, 61.0; H, 4.7. $C_{24}H_{22}O_{10}$ requires C, 61.3; H, 4.7%). *Compounds* **23a** and **23b**: m.p. 180–182 °C; ν_{max}/cm^{-1} 1730, 1705, 1630 and 1590; λ_{max}/nm 256 (ε 31 400), 290 (9550) and 497 (9400); δ 13.94 (1 H, s), 13.34 (1 H, s), 8.46 (2 H, m), 7.94 (2 H, m), 4.88 (1 H, s), 3.82 (3 H, s), 3.40 (3 H, s), 3.36 (1 H, d, *J* 15.5), 3.24 (3 H, s), 3.20 (3 H, s), 2.96 (1 H, d, *J* 15.5) and 1.46 (3 H, s); *m/z* 471 (M^+ + 1, CI) (Found: C, 61.4; H, 5.0; $C_{24}H_{22}O_{10}$ requires C, 61.3; H, 4.7%).

Cyclisation of the Adduct **17**.—The cyclization of the adduct **17** was carried out following the procedure described for adduct **15** and afforded a mixture of ketones **23a** and **23b** in 60% yield along with aromatic tetracycle **7** (10%) and unreacted **17**.

Reduction of the Mixture of Ketones **20a** *and* **20b**.—$CeCl_3$ (122 mg) was added to a solution of ketones **20a** and **20b** (120 mg) in isopropyl alcohol (40 cm^3). The solution was cooled in an ice bath and $NaBH_4$ (22 mg) was added. After 8 h of stirring another portion of $NaBH_4$ (16 mg) was added and the reaction mixture was stirred for another 24 h. The reaction mixture was diluted with water (50 cm^3), acidified with 2 mol dm^{-3} HCl and extracted with CH_2Cl_2 (2 × 30 cm^3). The extracts were dried ($MgSO_4$) and evaporated to give a red solid. Preparative TLC on silica gel eluting with CH_2Cl_2–AcOEt (9:1, 3 developments) gave four diols. *Compound* **25** (48 mg): m.p. 200–202 °C; ν_{max}/cm^{-1} 3500, 1730, 1625 and 1590; λ_{max}/nm 252 (ε 34 050), 289 (9500), 470 (9050) and 485 (9350); δ 13.63 (1 H, s), 13.59 (1 H, s), 8.41 (2 H, m), 7.89 (2 H, m), 5.25 (1 H, $W_{\frac{1}{2}}$ 14.0), 4.17 (1 H, d, *J* 6.0), 3.96 (1 H, s), 3.83 (3 H, s), 3.76 (1 H, s), 2.45 (1 H, dd, *J* 15.0 and 4.5), 1.98 (1 H, dd, *J* 15.0 and 5.5), 1.79 (1 H, m), 1.68 (1 H, m) and 1.05 (3 H, t, *J* 7.5), (Found: C, 64.5; H, 5.0. M^+ 412.1153. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.85%; *M*, 412.1158). *Compound* **27** (24 mg): m.p. 205–208 °C; ν_{max}/cm^{-1} 3540, 1730, 1625 and 1590; λ_{max}/nm 250 (ε 34 000), 288 (14 300), 469 (9050) and 484 (9350); δ 13.78 (1 H, s), 13.54 (1

H, s), 8.43 (2 H, m), 7.92 (2 H, m), 5.44 (1 H, $W_{\frac{1}{2}}$ 14.0), 4.14 (1 H, s), 3.82 (3 H, s), 3.78 (1 H, s), 2.62 (1 H, br s), 2.50 (1 H, dd, *J* 15.0 and 7.5), 2.03 (1 H, dd, *J* 15.0 and 5.0), 1.75 (2 H, m) and 1.07 (3 H, t, *J* 7.5) (Found: M^+, 412.1158. $C_{22}H_{20}O_8$ requires *M*, 412.1158). *Compound* **29** (12 mg): m.p. 174–176 °C; ν_{max}/cm^{-1} 3580–3200, 1729, 1625 and 1590; λ_{max}/nm 251, 257, 286 and 484; δ 13.64 (1 H, s), 13.38 (1 H, s), 8.43 (2 H, m), 7.91 (2 H, m), 5.42 (1 H, $W_{\frac{1}{2}}$ 8), 4.32 (1 H, s), 3.87 (1 H, br s), 3.74 (3 H, s), 3.50 (1 H, br s), 2.30 (2 H, m), 1.82 (2 H, m) and 1.16 (3 H, t, *J* 7.5) (Found: M^+, 412.1160. $C_{22}H_{20}O_8$ requires *M*, 412.1158). *Compound* **31** was isolated in meagre quantity and only a mass spectrum was recorded, (Found: M^+, 412.1158. $C_{22}H_{20}O_8$ requires *M*, 412.1158).

Conversion of the Diol **25** *into the Boronate* **33**.—The boronate was prepared following the procedure of Hassall *et al.*[25] A solution of the diol **25** (20 mg) in toluene (20 cm^3) was treated with phenylboronic acid (12 mg) and catalytic amount of camphorsulfonic acid. The reaction mixture was stirred at room temperature for 24 h and then washed successively with aqueous $NaHCO_3$ (5%, 2 × 15 cm^3) and water (3 × 15 cm^3). The organic phase was dried ($MgSO_4$), passed through a plug of silica gel and evaporated to give the *boronate* **33** as a red solid (23 mg), m.p. 255–257 °C; ν_{max}/cm^{-1} 1730, 1625 and 1585; λ_{max}/nm 252 (ε 33 600), 259 (32 850), 289 (8800) and 487 (8950); δ 13.54 (1 H, s), 13.40 (1 H, s), 8.42 (2 H, m), 7.90 (2 H, m), 7.81 (2 H, dd, *J* 8.0 and 1.5), 7.40 (3 H, m), 5.86 (1 H, $W_{\frac{1}{2}}$ 6.5), 4.17 (1 H, s), 3.53 (3 H, br s, 2.47 (1 H, dd, *J* 14.3 and 4.0), 2.36 (1 H, m), 2.14 (1 H, m), 1.96 (1 H, dd, *J* 14.3 and 2.3), 1.08 (3 H, t, *J* 7.5) (Found: M^+, 498.1490. $C_{28}H_{23}BO_8$ requires *M*, 498.1486).

Reduction of the Mixture of Ketones **23a** *and* **23b**.—To a solution of the tetracyclic ketones **23a** and **23b** (140 mg) in isopropyl alcohol (70 cm^3) at 0 °C was added $CeCl_3$ (166 mg) followed by $NaBH_4$ (17 mg). After 8 h of stirring at 0 °C a further portion of $NaBH_4$ (17 mg) was added and the stirring was continued for a further period of 26 h. The mixture was then diluted with water (50 cm^3), acidified with 2 mol dm^{-3} HCl and stirred for 10 min. The reaction mixture was extracted with CH_2Cl_2 (2 × 40 cm^3) and the organic extract was dried ($MgSO_4$) and evaporated to give a red solid. The red solid thus obtained was dissolved in trifluoroacetic acid (TFA) (15 cm^3), water (1 cm^3) was added and the solution was stirred at room temperature for 2 h. The solvent was removed, the residue was dissolved in CH_2Cl_2 (50 cm^3), washed with water (3 × 50 cm^3), brine (1 × 50 cm^3), dried ($MgSO_4$) and evaporated to give a red solid. The products were isolated by preparative TLC on silica gel eluting with CH_2Cl_2–AcOEt (9:1). *Compounds* **26** and **30** (48 mg): m.p. 214–216 °C; ν_{max}/cm^{-1} 3430, 1725, 1620 and 1590; λ_{max}/nm 246 (ε 52 000), 278 (14 100) and 470 (10 000); δ (**26**): 13.55 (1 H, s), 13.45 (1 H, s), 8.44 (2 H, m), 7.92 (2 H, m), 5.43 (1 H, br s, $W_{\frac{1}{2}}$ 10.0), 5.04 (1 H, s), 4.60 (1 H, s), 3.76 (3 H, s), 3.60 (1 H, br s), 2.46 (3 H, s), 2.43 (1 H, dd, *J* 15.0 and 3.0) and 2.08 (1 H, dd, *J* 15.0 and 4.5); δ (**30**): 13.68 (1 H, s), 13.45 (1 H, s), 8.44 (2 H, m), 7.92 (2 H, m), 5.23 (1 H, $W_{\frac{1}{2}}$ 11.0), 4.88 (1 H, s), 4.53 (1 H, s), 3.77 (3 H, s), 3.52 (1 H, br s), 2.44 (3 H, s), 2.38 (1 H, dd, *J* 15.0 and 6.0) and 2.02 (1 H, dd, *J* 15.0 and 4.0) (Found: C, 61.6; H, 4.1. M^+, 426.0952. $C_{22}H_{18}O_9$ requires C, 62.0; H, 4.2%. *M*, 426.0951). *Compound* **28** (18 mg): m.p. 221–223 °C; ν_{max}/cm^{-1} 3385, 1725, 1620 and 1590; λ_{max}/nm 245 (ε 47 100), 277 (12 800) and 466 (6000); $\delta(C_5D_5N)$ 13.74 (2 H, br s), 8.36 (2 H, m), 7.80 (2 H, m), 5.56 (1 H, $W_{\frac{1}{2}}$ 9.0), 5.22 (1 H, s), 3.70 (3 H, s), 2.84 (2 H, m) and 2.62 (3 H, s) (Found: C, 61.7; H, 4.2. M^+ 426.0956. $C_{22}H_{18}O_9$ requires C, 62.0; H, 4.2%; *M*, 426.0951). *Compound* **32** (8 mg): m.p. 235–237 °C; ν_{max}/cm^{-1} 3433, 1720, 1628 and 1580; λ_{max}/nm 246 (ε 48 100), 280 (13 200) and 470 (9250); $\delta(C_5D_5N)$ 13.64 (2 H, br s), 8.20 (2 H, m), 7.60 (2 H, m), 5.62 (1 H, $W_{\frac{1}{2}}$ 7.5 Hz), 5.36 (1 H, s), 3.67 (3 H, s), 3.00 (1 H, dd, *J* 15.0 and 4.0), 2.92 (1 H, d, *J* 15.0) and 2.62 (3 H, s) (Found: M^+, 426.0946. $C_{22}H_{18}O_9$ requires *M*, 426.0951).

Preparation of the Boronates **34** *and* **36**.—The boronates were prepared following the procedure described for **33** and an inseparable mixture of *boronates* **34** and **36** was obtained as a red solid (92%), m.p. 252–254 °C; ν_{max}/cm^{-1} 3300, 1744, 1730, 1626 and 1588; ν_{max}/nm 248 (ε 53 400), 258 (42 750), 280 (16 200), 475 (11 750) and 486 (11 800); δ (**34**): 1350 (1 H, s), 13.27 (1 H, s), 8.40 (2 H, m), 7.88 (2 H, m), 7.82 (2 H, d, *J* 8.0), 7.44 (1 H, d, *J* 8.0), 7.36 (2 H, t, *J* 8.0), 5.88 (1 H, $W_{\frac{1}{2}}$ 6.0), 4.86 (1 H, s), 3.66 (3 H, br s), 2.53 (3 H, s), 2.36 (1 H, dd, *J* 15.0 and 3.5) and 2.20 (1 H, dd, *J* 15.0 and 2.0); δ (**36**): 13.64 (1 H, s), 13.50 (1 H, s), 8.40 (2 H, m), 7.88 (2 H, m), 7.82 (2 H, d, *J* 8.0), 7.44 (1 H, d, *J* 8.0), 7.36 (2 H, t, *J* 8.0), 5.74 (1 H, $W_{\frac{1}{2}}$ 7.0), 4.79 (1 H, s), 3.66 (3 H, br s), 2.52 (3 H, s), 2.34 (1 H, dd, *J* 15.0 and 4.0) and 2.15 (1 H, dd, *J* 15.0 and 2.5) (Found: M^+, 512.1285. $C_{28}H_{21}BO_9$ requires *M*, 512.1278).

References

1 F. Arcamone, *The Development of New Antitumour Anthracyclines, Anticancer Agents based on Natural Products Models*, ed. J. M. Cassady and J. D. Dowes, Academic Press, New York, 1980, vol. 16, pp. 1–41.

2 J. R. Brown, *Prog. Med. Chem.*, 1978, **15**, 125; F. Arcamone, *Topics in Antibiotic Chemistry*, ed. P. G. Sammes, Halsted Press, New York, 1978; vol. 2, p. 102; W. A. Remers, *The Chemistry of Antitumour Antibiotics*, Wiley-Interscience, New York, 1979; vol. 1, p. 63; *Anthracyclines: Current Status and New Developments*, ed. S. T. Crooke and S. D. Reich, Academic Press, New York, 1980; F. Arcamone, *Doxorubicin*, Academic Press, New York, 1981; *Anthracycline Antibiotics*, ed. H. S. El Khadem, Academic Press, New York, 1982; T. R. Kelly, *Annu. Rep. Med. Chem.*, 1979, **14**, 228; for more recent developments, see *Recent Aspects of Anthracyclinone Chemistry, Tetrahedron Symposia-in-print*, No. 17, ed. T. R. Kelly, *Tetrahedron*, 1984, **40**, 4537; for recent reviews, see K. Krohn, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 790; K. Krohn, *Fortsch. Chem. Org. Naturst.*, 1989, **55**, 37; K. Krohn, *Tetrahedron*, 1990, **46**, 291.

3 A. S. Kende, J. A. Belltire, T. J. Bentley, E. Hume and J. Airey, *J. Am. Chem. Soc.*, 1975, **97**, 4425.

4 K. S. Kim, E. Vanotti, A. Surato and F. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 2483.

5 M. Braun, *Tetrahedron Lett.*, 1980, 3781.

6 A. V. Rama Rao, K. B. Reddy and A. R. Mehendale, *J. Chem. Soc., Chem. Commun.*, 1983, 564.

7 K. A. Parker and J. Kallmerton, *J. Am. Chem. Soc.*, 1980, **102**, 5881.

8 A. S. Kende, J. Rizzi and J. Reimer, *Tetrahedron Lett.*, 1979, 121.

9 F. M. Hauser and S. Prassana, *J. Am. Chem. Soc.*, 1981, **103**, 6378; F. M. Hauser and D. Mal, *J. Am. Chem. Soc.*, 1983, **105**, 5688.

10 M. G. Dolson, B. L. Chenard and J. S. Swenton, *J. Am. Chem. Soc.*, 1981, **103**, 5263.

11 B. A. Keay and R. Rodrigo, *Can. J. Chem.*, 1983, **61**, 637.

12 T. R. Kelly, J. Vaya and L. Ananthasubramanian, *J. Am. Chem. Soc.*, 1980, **102**, 5983.

13 H. Sekizaka, M. Jung, J. M. McNamara and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 7372.

14 J. P. Gesson and M. Mondon, *J. Chem. Soc., Chem. Commun.*, 1982, 421; R. K. Boeckmann and S. H. Cheon, *J. Am. Chem. Soc.*, 1983, **105**, 4112.

15 F. Suzuki, S. Trenbeath, R. D. Glein and C. H. Sih, *J. Am. Chem. Soc.*, 1978, **100**, 2272.

16 R. C. Gupta, P. A. Harland and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1983, 754.

17 L. M. Harwood, L. C. Hodgkinson, J. K. Sutherland and P. Towers, *Can. J. Chem.*, 1984, **62**, 1922; A. E. Ashcroft, D. T. Davies and J. K. Sutherland, *Tetrahedron*, 1984, **40**, 4579; K. Carr and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1987, 567; K. B. Mullah and J. K. Sutherland, *Tetrahedron Lett.*, 1987, 2065.

18 K. Krohn and C. Hemme, *Annalen.*, 1979, 19.

19 S. Danishefsky, K. Vaughan, R. Gadwood and K. Tsuzuki, *J. Am. Chem. Soc.*, 1981, **103**, 4136.

20 M. D. Turnbull, G. Hatter and D. E. Ledgerwood, *Tetrahedron Lett.*, 1984, 5449.

21 S. Danishefsky, R. Zamboni, M. Kahn and S. J. Etheredge, *J. Am. Chem. Soc.*, 1981, **103**, 3460.
22 E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 1953, 3131.
23 K. Krohn, M. Klimars, H.-J. Kohle and E. Ebeling, *Tetrahedron*, 1984, **40**, 3677.
24 K. Krohn and M. Radeloff, *Chem. Ber.*, 1978, **111**, 3823.
25 M. J. Broadhurst, C. H. Hassall and G. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2239.
26 T. W. Doyle, D. E. Nettleton, R. E. Grulich, D. M. Balitz, D. L. Johnson and A. L. Valcuno, *J. Am. Chem. Soc.*, 1979, **101**, 7041; J. M. Essery and T. W. Doyle, *Can. J. Chem.*, 1980, **58**, 1869.

Paper 2/00372D
Received 23*rd January* 1992
Accepted 18*th February* 1992