Synthesis of Anthracyclinones *via* *o*-Quinonoid Pyrones

David W. Jones* and Christopher J. Lock

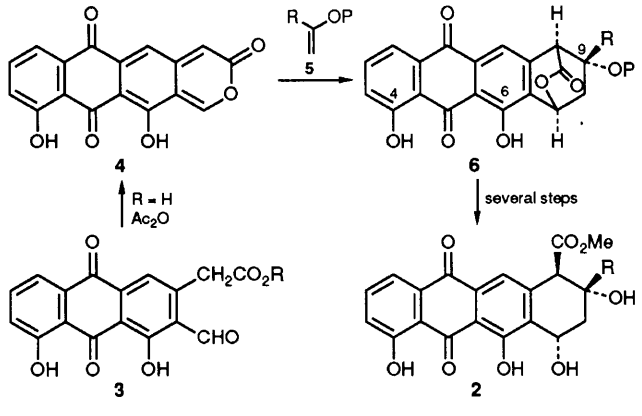
School of Chemistry, The University, Leeds LS2 9JT, UK

Dehydration of the acid **3** (R = H) with acetic anhydride at 80 °C generates the *o*-quinonoid pyrone **4** which can be trapped with several alkenes; the adduct **6** (R = Me, P = $SiEt_3$) and its 9-epimer from 2-triethylsilyloxypropene are readily transformed into (±)-auramycinone whilst those [(**6**; R = vinyl, P = $SiEt_3$) and its 9-epimer] from 2-triethylsilyloxybuta-1,3-diene are readily converted into the methyl ethers **12**, **13**, **14** and **15** of which **12**, **14** and **15** are known to be readily converted into (±)-aklavinone.

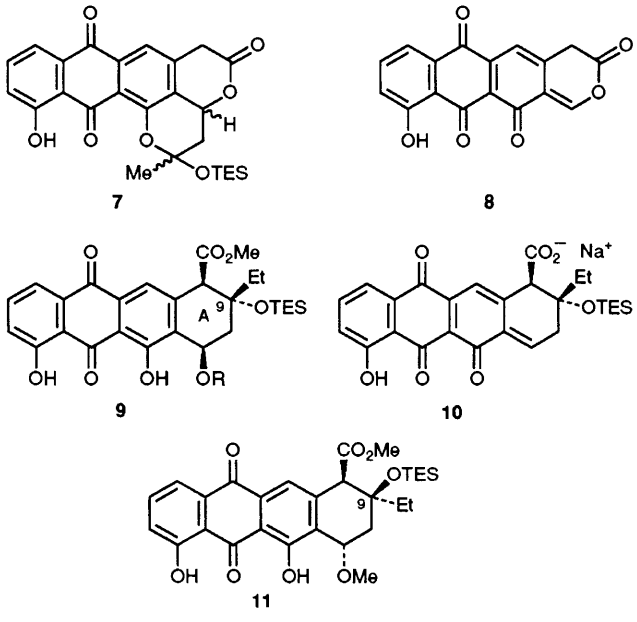
Derivatives of 2-benzopyran-3-one **1** are reactive Diels–Alder dienes which are useful building blocks for the assembly of aromatic steroids[1] and lignans like podophyllotoxin.[2] In addition the parent pyrone **1** has been used to prepare *AB*-ring analogues of anthracyclinones.[3] Like Jung and his collaborators[3] we have long cherished the view that anthracyclinones such as aklavinone **2** (R = Et) and auramycinone **2** (R = Me) could be prepared from the potentially tautomeric pyrone **4** along the lines outlined in Scheme 1. We now describe the reduction of this plan to practice.

The acid **3** (R = H) was prepared by acid-catalysed hydrolysis of the methyl ester **3** (R = Me), in turn available from 3-furoic acid and bromojuglone in six steps.[4] Attempts to generate and trap the pyrone **4** using our usual method (boiling acetic anhydride) were abortive but satisfactory yields of adducts could be secured by dehydration of **3** (R = H) in benzene–acetic anhydride at 80 °C in the presence of electron rich alkenes like norbornadiene and enol silyl ethers. Thus with **5** (R = Me, P = $SiEt_3$)† (17.4 mol equiv.) the *endo*-$OSiEt_3$ adduct **6** (R = Me, P = $SiEt_3$) and its *exo*-$OSiEt_3$ isomer were obtained in a ratio of 2:1 and in a yield of 52%. There was also obtained a *ca.* 1:1 mixture of the adducts **7** (18% yield); these are most simply regarded as arising from the quinone methide tautomer **8** of the pyrone **4**. Model experiments using the 4,6-dideoxy congener of **4**‡ and the ether **5** (R = Et, P = $SiMe_2Bu^t$) gave adducts derived from the *Z*- and *E*-forms of the double bond shift isomer of the starting alkene. Our planned route to aklavinone was therefore modified to involve adduction of **4** with the dienol ether **5** (R = vinyl, P = $SiEt_3$). Trapping **4** with this diene proceeded efficiently (75% yield) and without formation of adducts of the type **7**. The *endo*- and *exo*-adducts **6** (R = vinyl, P = $SiEt_3$) and its C-9 epimer (ratio 1:1) were separated by crystallisation and fully characterised.§ They were individually reduced (H_2/Wilkinson's catalyst) to give **6** (R = Et, P = $SiEt_3$) and its 9-epimer in high yield.

With a large excess of sodium methoxide (26 mol equiv.) in MeOH–CH_2Cl_2 **6** (R = Et, P = $SiEt_3$) gave, after a work-up involving brief treatment with diazomethane, a mixture of **9** (R = Me) (49%) and **9** (R = H) (9%) as well as 6% of the $\Delta^{7,8}$ alkene. Whilst the hydroxy ester arises *via* the usual acyl oxygen fission of the lactone the methoxy ester is most likely formed by elimination to the quinone methide carboxylate **10** which then adds methoxide to the less hindered β-face. Similar treatment of the C-9 epimer of **6** (R = Et, P = $SiEt_3$) gave the C-9 epimer of **9** (R = Me) (13%) as well as **11** (49%), and alkenic product (8%). In marked contrast to the related *tert*-butyldimethylsilyl ether which only loses the protecting group under conditions which also cause extensive aromatisation of ring-*A*, the $SiEt_3$ ether **9** (R = Me) was smoothly deprotected (6% HF–H_2O in 2:1 CH_3CN–CH_2Cl_2, 20 °C, 2 h) to give the alcohol **12** in quantitative yield. Replacement of the C-7 β-methoxy group in this product by an α-hydroxy group was accomplished using trifluoroacetic acid[4] to give (±)-aklavinone in 87% yield. For preparative purposes it is



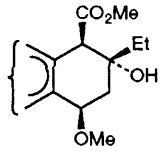
Scheme 1



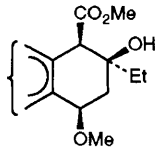
† The correct choice of silyl protecting group is crucial; the trimethylsilyl group fails to withstand NaOMe ring opening of the lactones **6** whilst the *tert*-butyldimethylsilyl group strongly resists removal in the final stages of the synthesis. The triethylsilyl group served admirably in both these steps.

‡ Anthracyclinone numbering.

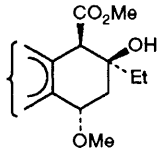
§ All new compounds have been characterised by IR, UV, 300 MHz ^1H NMR spectra, low resolution mass spectra and correct (±0.3%) C, H microanalysis.



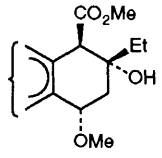
12



13



14



15

simplest to treat the mixture of hydrogenated adduct **6** (R = Et, P = $SiEt_3$) and its C-9 epimer with NaOMe to give four products separated by chromatography into two pairs; **9** (R = Me) and its C-9 epimer forming one pair (45%, ratio 6:1) and **11** and its C-9 epimer forming the second pair (26%, ratio 6:1). Desilylation of the first pair ($HF–H_2O–CH_3CN–CH_2Cl_2$) gave **12** (70%) and **13** (21%). Desilylation of the second pair gave **14** (86%) and **15** (12%). Since **12**, **14** and **15** are readily converted[4] into (±)-aklavinone **2** (R = Et) this route constitutes an efficient total synthesis of aklavinone. In essentially the same way the adducts **6** (R = Me, P = $SiEt_3$) are transformed into (±)-auramycinone **2** (R = Me). In summary we have shown that the novel pyrone **4** can be generated and trapped efficiently despite its possible tautomerism *e.g.* with **8**. Its additions to dienol silyl ethers are highly chemo- and regio-selective but there is little *endo*-preference shown between the silyloxy and vinyl (or alkyl) groups on the dienophile. The adducts **6** (R = alkyl) undergo smooth ring opening with sodium methoxide probably *via* quinone methide intermediates rather than by acyl-oxygen fission as originally conceived and investigated in model experiments.[3,5] This is important as the C-9 epimers of the adducts **6** lacking a C-6 hydroxy group fail to undergo clean lactone ring opening with sodium methoxide.[5] The availability of the quinone methide mechanism therefore allows utilisation of both the *endo* and the *exo*-$OSiEt_3$ compounds [(**6**; R = Et, P = $SiEt_3$) and its C-9 epimer].

Received, 24th July 1991; Com. 1/03796J

References

1 D. A. Bleasdale and D. W. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1683.
2 D. W. Jones and A. M. Thompson, *J. Chem. Soc., Chem. Commun.*, 1987, 1797; 1988, 1095; 1989, 1371.
3 M. E. Jung, R. W. Brown, J. E. Hagenah and C. E. Strouse, *Tetrahedron Lett.*, 1984, **25**, 3659.
4 B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki and Y. Kishi, *J. Am. Chem. Soc.*, 1981, **103**, 4248.
5 D. W. Jones and C. J. Lock, unpublished results.