Tetrahedron Letters,Vol.24,No.5,pp 519-522,1983 0040-4039/83/050519-04$03.00/0
Printed in Great Britain

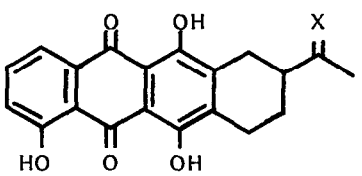
A SECOND SYNTHESIS OF 7,9-BISDEOXYCARMINOMYCINONE FROM 5-HYDROXYQUINIZARIN

David T. Davies, Philip S. Jones and James K. Sutherland*

Chemistry Department, The Victoria University of Manchester, Manchester M13 9PL, U.K.

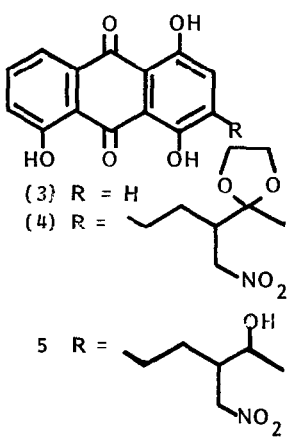
Abstract. *By reversing the order of bond formation to 5-hydroxyquinizarin, 7,9-bisdeoxycarminomycinone has been synthesised from ethyl laevulinate in seven steps, two fewer than the previous synthesis.*

We have previously described[1] an efficient synthesis of (1) from 5-hydroxyquinizarin (3) in which the initial C-C bond was formed by regiospecific nitronate addition[2] to C-2 of (3) and the second by Marschalk[3] (aldol) condensation. We now show that this strategy can be reversed using the regioselective[4] piperidinium acetate catalysed Marschalk-Lewis condensation[5] to form the first C-C bond followed by nitronate cyclisation.



(1) X = O

(2) X = $(OCH_2)_2$



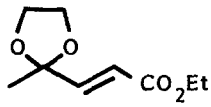
(3) R = H

(4) R =

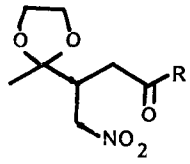
5 R =

The requisite C_6 unit (8) was prepared from ethyl 4-oxopent-2-enoate which was first converted to the acetal[§] (6) (90%) using Hase's conditions.[6] Michael addition of nitromethane

[§] All new compounds were fully characterised spectroscopically and by combustion analyses except for (9) which gave a correct accurate mass measurement.

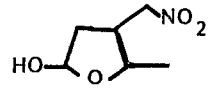


(6)



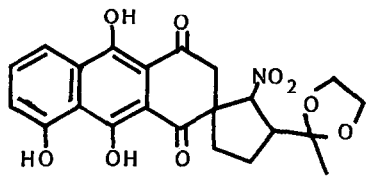
(7) R = OEt

(8) R = H



(10)

to (6) in Bu^tOH-EtOH (20 : 1) containing a catalytic amount of NaOEt gave the ester (7) (65%) which was reduced with Bu^i_2AlH-hexane-toluene at -78° to the aldehyde (8) (90%) [ν_{max} 2880, 1725 cm^{-1}; τ0.22 (1H, bs), 5.39 (1H, dd, J13 and 6 Hz), 5.66 (1H, dd, J13 and 7 Hz), 6.04 (4H, m), 6.74 (1H, m), 7.30 (1H, dd, J18 and 3 Hz), 7.49 (1H, dd, J18 and 7 Hz), 8.70 (3H, s)]. Condensation of the aldehyde (8)† with *leuco*-5-hydroxyquinizarin in refluxing Pr^iOH containing piperidinium acetate gave what is probably a 5 : 1 mixture (66%) of (4) and the C-2 alkylated isomer§; recrystallisation from Me_2CO gave pure (4) (40%). Reaction of (4) with NaOMe-MeOH partially converted it to a yellow isomer, the u.v.-visible and n.m.r. (below τ 4.0) spectra of which were identical to those of *leuco*-5-hydroxyquinizarin.



(9)

---

†The ethylene acetal of (8) did not add to (3) under the usual conditions, presumably due to steric hindrance to addition.

§In the course of this and previous work we have observed that the best criterion for establishing purity or mixture composition is to examine the 300MHz ^1H n.m.r. spectra of products in $CDCl_3$ in the τ0 to -6 region where the hydrogen bonded hydroxyl groups appear as sharp singlets which are extremely sensitive to structural change.

In addition, the ^{1}H n.m.r. spectrum showed absorptions at τ 4.08 (1H, d, J7 Hz), 5.96 (4H, m) 6.58 (1H, q, J7 Hz), 7.08 (2H, s), 7.90 (2H, m), 8.16 (2H, m), and 8.62 (3H, s); from these data and the inertness to mild oxidation the isomer was assigned the *spiro*-structure (9).[‡] When (4) was refluxed with NaOMe - MeOH it was converted into the tetracycle (2) (85%) which on hydrolysis (CF_3CO_2H - H_2O) gave the ketone (1) (95%) identical to the compound prepared previously.[1] When the mixture of alkylation products is cyclised and then hydrolysed a 5 : 1 mixture of (1) and its regioisomer is obtained (42% overall); a single crystallisation improves the material to a 12 : 1 mixture. Similar material (49%)[#] can be obtained in a one-pot process by carrying out the alkylation as before and then adding four equivalents of piperidine and refluxing for 18 h.

Piperidinium acetate catalysed condensation of the lactol[1] (10) with *leuco*-5-hydroxyquinizarin gave the alkylation product (5) and the C-2 isomer (23%) (4 : 1). Cyclisation of the mixture with NaOMe - MeOH followed by pyridinium chlorochromate oxidation gave the ketone (1) together with its regioisomer (53%) (5 : 1).

These results demonstrate the flexibility of the double alkylation approaches. The synthesis using an initial nitronate condensation has the advantage that this reaction is regiospecific but the disadvantage that this route is two stages longer. The approach using the initial Marschalk-Lewis alkylation is two steps shorter but is only regioselective and thus requires the ready removal of an isomer at some stage for it to be efficient.

Acknowledgement.

We thank the S.E.R.C. for financial support (DTD and PSJ) and I.C.I. PLC (Organics Division) for gifts of chemicals.

[‡]On treatment with NaOMe-MeOH the pure *spiro*-compound (9) partially reverted to (4), suggesting that there is an equilibrium process.

[#]The naphthacene corresponding to (2) was isolated as a by-product in this reaction (*ca.* 5%)

References.

1. A. E. Ashcroft and J. K. Sutherland, J. Chem. Soc., Chem.Commun., 1981, 1075.
2. C. W. Greenhalgh, J. K. Sutherland, and P. Towers, J.Chem.Soc., Chem.Commun., 1981, 740.
3. C. Marschalk, F. Koenig, and N. Ouroussoff, Bull. soc. chim. France, 1936, 1545.
4. L. M. Harwood, L. C. Hodgkinson, and J. K. Sutherland, J. Chem. Soc., Chem. Commun. 1978, 712.
5. C. E. Lewis, J. Org. Chem., 1970, 35, 2938.
6. T. A. Hase, A. Ourila, and C. Holmberg, J. Org. Chem., 1981, 46, 3137.

(Received in UK 22 November 1982)