Tetrahedron Letters,Vol.27,No.29,pp 3431-3434,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A New Route to 3-Hydroxyphthalides : Application to the Synthesis of Racemic [5-^{13}C] Daunomycinone.

Anna M. Becker, Robert W. Irvine, Alison S. McCormick,
*Richard A. Russell * and Ronald N. Warrener **

Chemistry Department, The Faculties,Australian National University, G.P.O. Box4, Canberra, A.C.T., 2601, Australia.

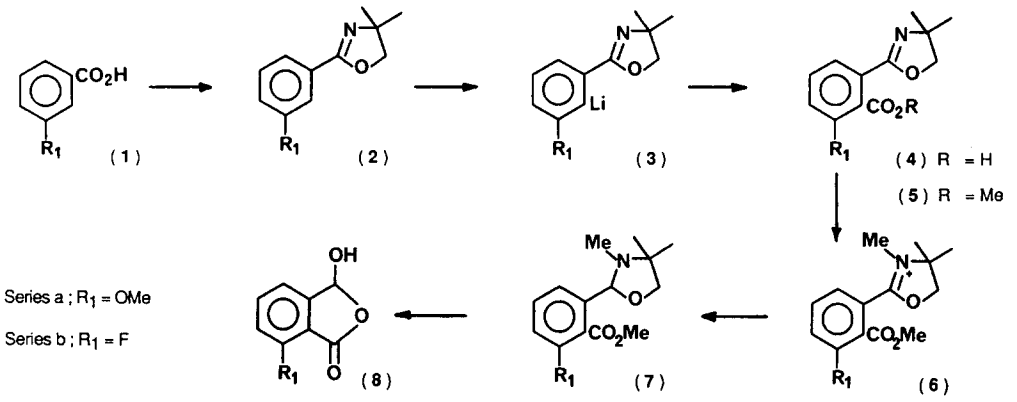
Abstract: Lithiation (n-BuLi) of the (3'-methoxyphenyl) oxazoline (**2a**) occurs specifically at C2' and, following carboxylation (CO_2/$^{13}CO_2$) and esterification, yields the phthalate derivative (e.g. **5a**). Elaboration of the oxazoline-ring furnishes the related aldehydes which spontaneously cyclise to form the 3-hydroxyphthalides (**8/10**). The title[5-^{13}C] anthracyclinone (**20**) is produced from 3-cyanophthalide (**11**) in good yield and with excellent isotopic efficiency.

3-Cyanophthalides, best prepared from 3-hydroxyphthalides,[1,2] are key reagents for the preparation of anthraquinones and anthracyclines via the phthalide anion annelation of quinone monoketals.[3] While several methods for the synthesis of precursor phthalides have been reported in the literature,[1,4] none is suitable for the efficient incorporation of isotopically labelled ^{13}C into the lactone ring of the phthalide. Consequently, we have developed a new method for the direct synthesis of 3-hydroxyphthalides (**8**) whereby high incorporation of ^{13}C can be achieved using labelled $^{13}CO_2$ as the isotopic component (see Scheme 1).

New metallation route to 3-hydroxyphthalides.

The first feature of this new approach to 3-hydroxyphthalides, exemplified by the preparation of the 7-methoxy derivative (**8a**), was to employ the oxazoline group to direct ortho-metallation. High selectivity was obtained in this step by treatment of oxazoline (**2a**)[5,6] with 0.95 eq. of n-butyl lithium at -40^{o}C in tetrahydrofuran. Subsequent reaction of anion (**3a**)with 0.77 eq. of carbon dioxide formed carboxylic acid (**4a**) in 71% yield, after crystallisation. These conditions were selected to ensure most efficient use of CO_2 ; unreacted (**2a**) was recovered

quantitatively. Conversion of acid (**4a**) to its ester (**5a**) was achieved in quantitative yield by reaction with *N,N*-dimethylformamide dimethyl ketal. These mild conditions, reported originally by Eschenmoser and his coworkers,[8] were entirely compatible with the oxazoline protecting group. The ester (**5a**) also could be formed directly from anion (**3a**) by reaction with methyl chloroformate at -40°C in tetrahydrofuran in 76% yield (based on **2a**). The two-step process described above was necessary only when producing labelled material (see later).



Scheme 1

The second feature of the the present method was to exploit the difference between the two individually protected carboxylic acid groups by selectively reducing the C2-carboxyl functionality of (**5a**) to the aldehyde level. This was achieved according to the method of Nordin [9] whereby oxazoline (**5a**) was converted to its *N*-methyl oxazolinium salt (**6a**) by reaction with methyl iodide, and subsequently reduced to the corresponding *N*-methyl oxazolidine (**7a**) by treatment with sodium borohydride. This reduction sequence could not be carried out on the related acid (**4a**) owing to intramolecular reaction occurring between the adjacent carboxyl and oxazolinium groups. Liberation of the aldehyde from (**7a**) was achieved by hydrolysis (6N HCl) as reported elsewhere,[10] conditions which also hydrolysed the ester group and yielded the 3-hydroxyphthalide (**8a**) directly on work up.

Applying these reactions in sequence starting from carboxylic acid (**1a**) but without purification of the any intermediates, yielded (**8a**) in 64% overall yield (based on CO_2 employed). The same procedure (methyl chloroformate route) was also used to prepare 7-fluoro-3-hydroxyphthalide (**8b**) in 59 % yield from 3-fluorobenzoic acid (**1b**), and provides a viable alternative to previously reported methods[1,2] to (**8b**).

Synthesis of the ^{13}C-labelled hydroxyphthalide (10).

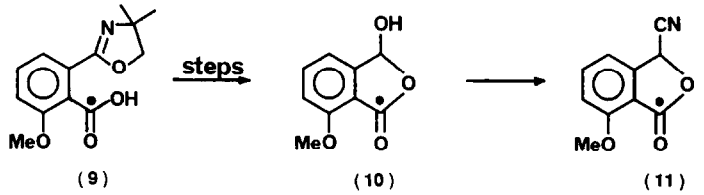
In applying the above reactions to the preparation of (**10**), anion (**3a**) was carboxylated using $^{13}CO_2$ (a cost effective ^{13}C isotopic label). This was carried out using conditions described by Dauben *et al.* [11] employing 91% $Ba^{13}CO_3$ as the isotopic ^{13}C-source. The

isotopically labelled acid (**9**) was formed in greater than 70% yield based on $Ba^{13}CO_3$. Conversion to the labelled ester and subsequent quaternisation, reduction and hydrolysis as described above, produced the ^{13}C labelled hydroxyphthalide (**10**) in 83% overall yield from carboxylic acid (**9**) (Scheme 2).

Conversion of the [1-^{13}C] 3-hydroxyphthalide (**10**) to the corresponding [1-^{13}C] - 3-cyanophthalide (**11**) was carried out by our previously described method.[2]

Scheme 2

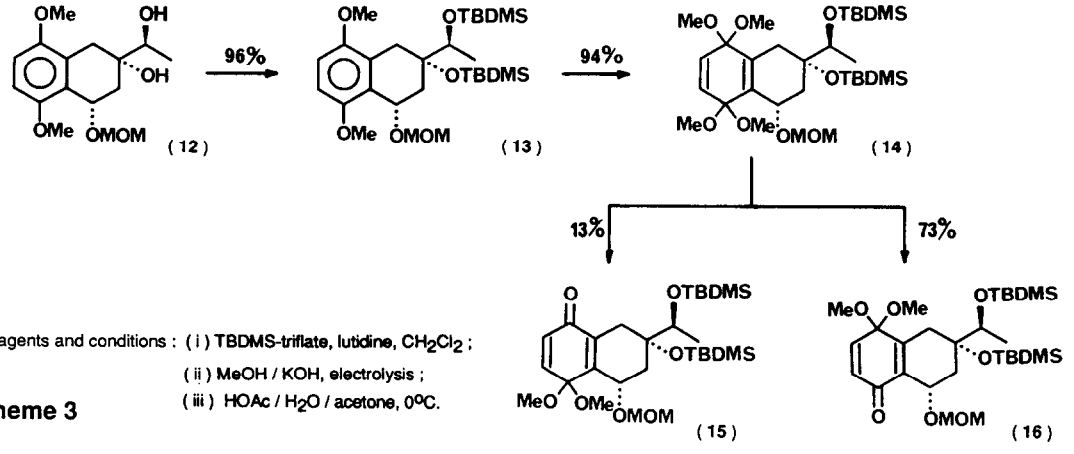
•= ^{13}C



(9) (10) (11)

Preparation of [5-^{13}C] Daunomycinone (20)

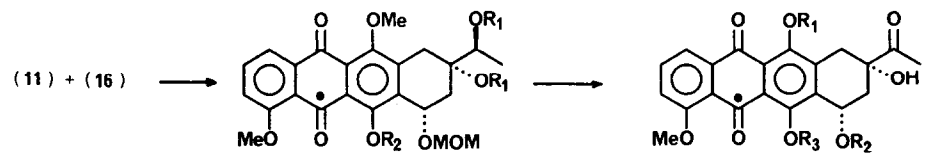
Condensation of the anion derived from the ^{13}C labelled cyanophthalide (**11**) with the dienone (**16**), prepared from our previously described diol (**12**)[12] as shown in Scheme 3, produced the protected anthracyclinone (**17**) in 95% yield (Scheme 4). The TBDMS protecting groups in (**17**) were difficult to remove, and the reaction was still incomplete after treatment with $Bu_4NF.3H_2O$ / THF / 10°C over a period of 7 days ; the 13-dihydrodauno-mycinone derivative (**18**) so formed was isolated in 40% yield, and 41% of starting material was recovered. Oxidation of this diol [$(nBu_3Sn)_2O$ / Br_2; 3 eq.] proved to be slow and in-efficient and produced the hydroxy ketone (**19**) (not isolated) which on treatment with BCl_3 in CH_2Cl_2 afforded [5-^{13}C] daunomycinone (**20**) ; the overall yield from (**17**) was 23%.



(12) (13) (14) (15) (16)

Reagents and conditions : (i) TBDMS-triflate, lutidine, CH_2Cl_2 ;
(ii) MeOH / KOH, electrolysis ;
(iii) HOAc / H_2O / acetone, 0°C.

Scheme 3



(17) R_1 = TBDMS, R_2 = H
(18) R_1 = R_2 = H
(21) R_1 = TBDMS, R_2 = Me
(22) R_1 = H, R_2 = Me

(19) R_1 = Me, R_2 = MOM, R_3 = H
(20) R_1 = R_2 = R_3 = H
(23) R_1 = R_3 = Me, R_2 = MOM

Scheme 4

A more satisfactory reaction sequence for the conversion of (**17**) to (**20**), while containing an extra step, could be achieved in 45% overall yield. This involved prior methylation of the phenolic group in (**17**) (Me_2SO_4 / K_2CO_3 / acetone) to afford the permethylated product (**21**), which was desilylated (above conditions for 16 hours) to form the diol (**22**) . Oxidation of (**22**) could now be carried out using Fetizon's reagent and cleanly afforded ketone (**23**) which, in turn, was transformed to the title product (**20**) by treatment with BCl_3 .

References and Footnotes.

1. Freskos, J.N., Morrow, G.W. and Swenton, J.S., *J. Org. Chem.*, 1985, **50**, 805.
2. Russell, R.A., Pilley, B.A. and Warrener, R.N., *Synthetic Commun.*, 1986, **16**, 425.
3. Russell, R.A. and Warrener, R.N., *J. Chem. Soc., Chem. Commun.*, **1981**, 108 ; Li, T., Wu, Y.L., and Walsgrove, T.C., *Tetrahedron*, 1984, **40**, 4701; Swenton, J.S., Freskos, J.N., Morrow, G.W., and Sercel, A.D., *Tetrahedron*, 1984, **40**, 4625; Keay, B.A. and Rodrigo, R., *Tetrahedron*, 1984, **40**, 4597; Russell, R.A., Pilley, B.A., Irvine, R.W. and Warrener, R.N., *Aust. J. Chem.*, in press.
4. Uemura, M., Tokuyama, S. and Sakan, T., *Chem. Lett.*, **1975**, 1195; Trost, B.M., Rivers, G.T. and Gold, J.M., *J. Org. Chem.*, 1980, **45**, 1835; Dodsworth, D.J., Calcagno, M.P., Ehrmann, E.U., Devadas, B. and Sammes, P.G., *J. Chem. Soc., Perkin 1*, **1981**, 2120; Hung, T.V., Mooney, B.A., Prager, R.H. and Tippett, J.M., *Aust. J. Chem.*, 1981, **34**, 383; Plaumann, H.P., Keay, B.A. and Rodrigo, R., *Tetrahedron Lett.*, **1979**, 4921.
5. Newman, M.S. and Kanakarajan, K., *J. Org. Chem.*, 1980, **45**, 2301; Meyers, A.I. and Avila, W.B., *J. Org. Chem.*, 1981, **46**, 3881; Edgar, K.J. and Bradsher, C.K., *J. Org. Chem.*, 1982, **47**, 1585.
6. All new compounds gave satisfactory combustion analyses and spectral data. Compound (m.p.^{o}C): **16** (122-3); **17** (160-1); **18** (188-9); **19** (163-4); **20** (283-5, lit 280); **21** (193-4); **22** (178-9); **23** (166-8).
7. Krohn, K. and Tolkiehn, K., *Chem. Ber.*, 1979, **112**, 3453.
8. Brechbuhler, H.v., Buchi, H., Hatz, E., Schreiber, J. and Eschenmoser, A., *Helv. Chim. Acta*, 1965, **48**, 1746.
9. Nordin, I.C., *J. Heterocyclic Chem.*, 1966, **3**, 531.
10. Goldberg, E.P. and Nace, H.R., *J. Am. Chem. Soc.*, 1955, **77**, 359.
11. Dauben, W.G., Reid, J.C. and Yankwich, P.E., *Anal. Chem.*, 1947, **19**, 828.
12. Irvine, R.W., Russell, R.A. and Warrener, R.N., *Tetrahedron Lett.*, 1985, **26**, 6117.

(Received in UK 2 May 1986)