Tetrahedron Letters,Vol.24,No.44,pp 4809-4812,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A Useful Extension of the Marschalk Reaction Directed Toward Synthesis of 11-Deoxydoxorubicin Antitumor Antibiotics.

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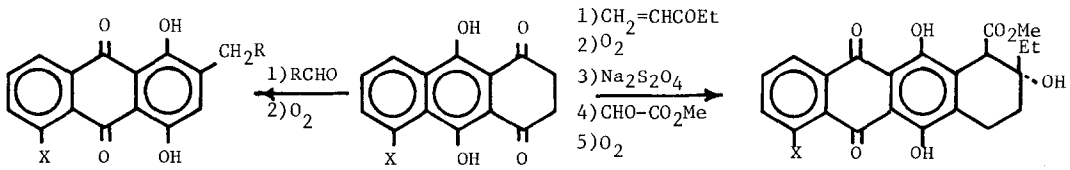
Summary: Diisopropylidine methylene dimalonate (8) has been developed as a useful reagent for the introduction of functionalized 3-carbon chains in otherwise deactivated monohydroxyanthraquinones and its utility is expanded to the synthesis of advanced intermediates of 11-deoxydoxorubicin analogues.

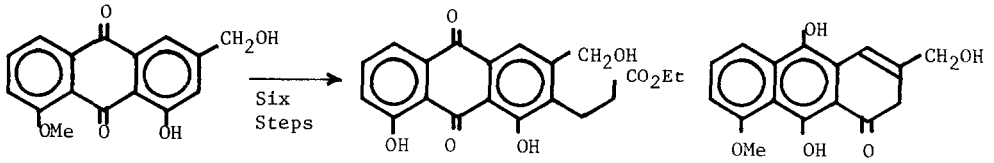
The Marschalk reaction (2 → 1), discovered in 1936, provides a useful means of adding carbon atoms and functionalized side-chains to certain otherwise highly deactivated anthraquinones.[1] It has recently been utilized effectively in preparation of synthons directed toward 4,6,11- and 6,11-hydroxylated anthracycline antibiotics (3).[2] With leucoquinizarin analogues (2, X=H) we, and others, have observed that two different side-chains can be added--if the side-chains are added in the appropriate sequence--to provide advanced functionalized tetracyclic intermediates (3). Whereas the original Marschalk reaction involved preferably highly reactive non-enolizable aldehydes, conjugate addition of acrylates and vinyl ketones can be accomplished within the scope of the common reaction conditions.[2c,3,6]



(1) X=H,OH,OMe (2) (3)

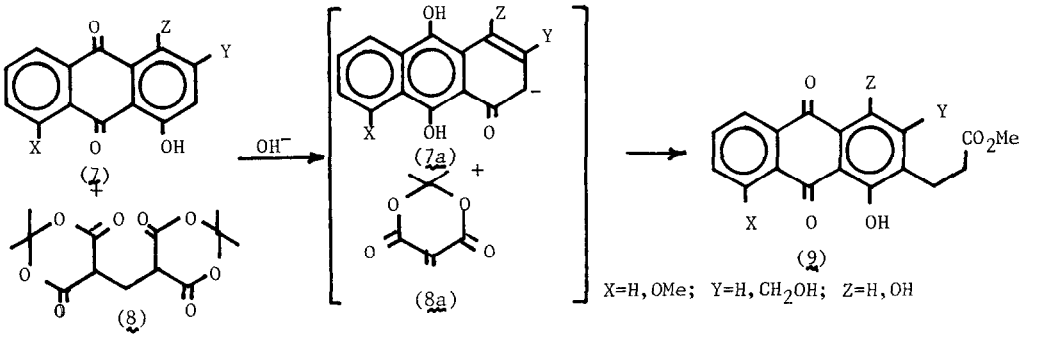
Recently a number of investigators have worked toward the synthesis of 11-deoxydoxorubicin analogues.[4] The original Marschalk reaction[1] demonstrated that 1-hydroxyanthraquinones were suitable substrates if highly reactive aldehydes were used as partners. We found, however, that unacceptable yields are obtained in the conjugate

addition modification with anthraquinones having a single peri OH group such as aloe-emodin monomethyl ether (4). Consequently, a rather longer procedure involving a Claisen-Cope rearrangement was required to reach 5[4a] needed for 11-deoxyanthracycline synthesis.



We reasoned that the failure of the shorter Marschalk-type reaction was due to the low steady-state concentration of essential intermediate 6 and its observed pronounced tendency to oxidize back to the non-reactive starting quinone (4). If this were correct, then the reaction might succeed if a more reactive Michael-acceptor were employed.

After several attempts, we found that diisopropylidene methylenedimalonate (8),[5] derived from Meldrum's acid, serves this purpose well. This finding not only considerably expands the scope of the Marschalk reaction but also enhances the practicality of routes to 11-deoxyanthracycline antibiotics from aloe-emodin. The reactive components in the process are believed to be 7a and 8a.



To illustrate: to a degassed and argon filled solution of 1-hydroxyanthraquinone (7a) (0.5 mM) in aqueous NaOH (200 ml, 0.2 M) at 60°, is added $Na_2S_2O_4$ (1.1 eq.). The temperature is raised to 90° and diisopropylidine methylenedimalonate (8) (1.1 eq.) is added. Up to 10-11 eq. of additional $Na_2S_2O_4$ and 8 are added over 14-16 hrs. The solution

should be kept alkaline by addition of added base as needed. The reaction is complete in about 24 hr. and is quenched with conc. HCl (35 ml) and refluxed for 7-8 hr. to complete decarboxylation. After cooling to room temperature, the reaction mixture is extracted with AcOEt, the organic layer is washed with H_2O, dried over Na_2SO_4 and evaporated. The residue is esterified by 12 hr. reflux with CH_3OH-H_2SO_4 and purified by flash chromatography over SiO_2 to give 9a in 47% overall yield. Yields and characterization data for several analogous reactions are set forth in the Table.

The methylene analogue of Meldrum's acid (8a) is not stable to the conditions of the reaction and it cannot be formed *in situ* because the leucobases of 7 (e.g., 2, X=H) intercept the formaldehyde component to produce varying contaminating amounts of the 2-methyl analogues (e.g., 1, R=X=H).

Quinizarin derivatives are much less reactive and best yields are obtained by heating with 8 (1.3 eq.) in dry DMF and KOH (85%, 4 eq.) at 65° for 75 min instead. After processing through to the ester, monoalkylated 9c is obtained in 23% yield accompanied by 5% of dialkylated 9d and 33% of recovered quinizarin (7c). Thus, the use of the new methodology with leucoquinizarin does not offer any perceptable advantages over the previously reported technique.[3,6]

Reaction with aloe-emodin monomethylether (4) gave 5 in 24% yield accompanied by 12% of its deoxygenerated analogue 9e formed, presumably, by the prototropic shifts indicated in formulae 10 → 12. Despite this complication, the convenience and directness (3 reactions vs. 6[4a] of this approach and the demonstrated utility of synthons 5 and the ethyl ketone analogue of 9c for 11-deoxyanthracycline synthesis provides an easy entry to advanced intermediates.[2a,2b,4a]

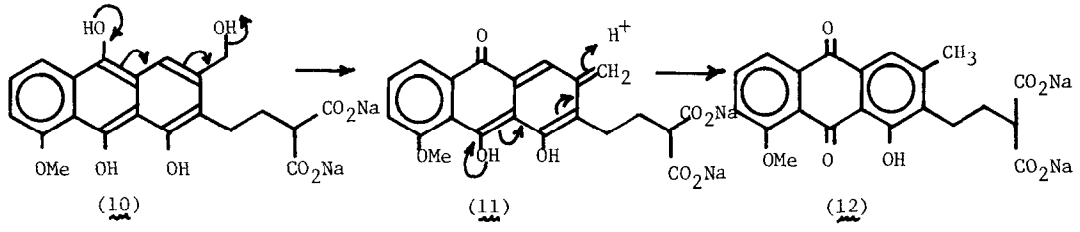


Table. Reaction of various leucoanthraquinones with diisopropylidene methylenedimalonate to produce β-anthraquinoylpropionate esters by a modified Marschalk-type procedure.

SUBSTRATE	PRODUCT*	YIELD	mp
7a (X=Y=Z=H)	9a (X=Y=Z=H)	47%	142-144°
7b (X=OCH_3,Y=Z=H)	9b (X=OCH_3, Y=Z=H)	52%	158-159°
7c (X=Y=H, Z=OH)	9c (X=Y=H, Z=OH)	23%	142-144°
	9d (X=H, Z=OH, Y=$CH_2CH_2CO_2CH_3$	5%	141-142°
4	5 (X=OCH_3, Y=CH_2OH, Z=H)	24%	170-172°
4	9e (X=OCH_3, Y=CH_3, Z=H)	12%	161-163°

*All compounds listed gave satisfactory microanalyses (C, H) and IR, UV-Vis, MS and pmr spectra in accord with the assigned structures.

Acknowledgement. The authors thank ADRIA Laboratories for financial support of this work.

References

1. (a) C. Marschalk, F. Koenig and N. Ouroussoff, Bull. Soc. Chim. Fr., 3, 1545 (1936); (b) C. Marschalk, Bull. Soc. Chim. Fr., 6, 655 (1939).
2. (a) K. Krohn, Angew Chem. Int. Edn. (Engl.), 20, 576 (1981); (b) K. Krohn, Liebigs. Ann. Chem., 2285 (1981); (c) K. Krohn and M. Radeloff, Chem. Ber., 111, 3823 (1978); (d) F. Suzuki, S. Trenbeath, R. D. Gleim and C. J. Sih, J. Org. Chem., 43, 4159(1978).
3. A. T. Kisaka-Kibudiama, M. S. Thesis, University of Kansas, U.S.A. (1980).
4. (a) J. Alexander, D. L. Flynn, L. A. Mitscher and T. Veysoglu, Tetrahedron Lett., 3711 (1981), (b) A. S. Kende and J. P. Rizzi, Tetrahedron Lett., 1779 (1981); (c) A. S. Kende and J. P. Rizzi, J. Am. Chem. Soc., 103, 4247 (1981); (d) P. N. Confalone and G. Pizzolato, J. Am. Chem. Soc., 103, 4251 (1981); (e) T.-T. Li and Y. L. Wu, J. Am. Chem. Soc., 103, 7007 (1981); (f) J. P. Gesson, J. C. Jacquesy and M. Mondon, Tetrahedron Lett., 3351 (1980); (g) J. G. Bauman, R. B. Barber, R. D. Gless and H. Rapoport, Tetrahedron Lett., 4777 (1980), (h) J. Yadav, P. Corey, C.-T. Hsu, K. Perlman and C. J. Sih, Tetrahedron Lett., 811 (1981); (i) A. V. R. Rao, V. H. Deshpande and N. L. Reddy, Tetrahedron Lett., 775 (1982); (j) B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyma, H. Sekizaki and Y. Kishi; J. Am. Chem. Soc., 103, 4248 (1981).
5. (a) J. A. Hedge, C. W. Kruse and H. R. Snyder, J. Org. Chem., 26, 3166 (1961); (b) y. Oikawa, H. Hirasawa and O. Yonemitsu, Tetrahedron Lett., 1759 (1978).
6. G. Arsenault, A. D. Broadbent and P. Hutten-Czapski, J. Chem. Soc., Chem. Commun., 437 (1983).

(Received in USA 11 July 1983)