Tetrahedron Letters No. 22, pp 1963 - 1966. 0040-4039/79/0522-1963$02.00/0

A NEW SYNTHESIS OF SUBSTITUTED α-METHYLENE-γ-LACTONES[1]

A. W. McCulloch* and A. G. McInnes
Atlantic Regional Laboratory, National Research Council
of Canada, Halifax, Nova Scotia, Canada, B3H 3Z1

Ene reactions of suitably substituted olefins with dimethyl acetylenedicarboxylate give substituted 1,4-pentadiene-1,2-dicarboxylates, which undergo acid-catalyzed cyclization to α-carbomethoxymethylene γ-lactones.

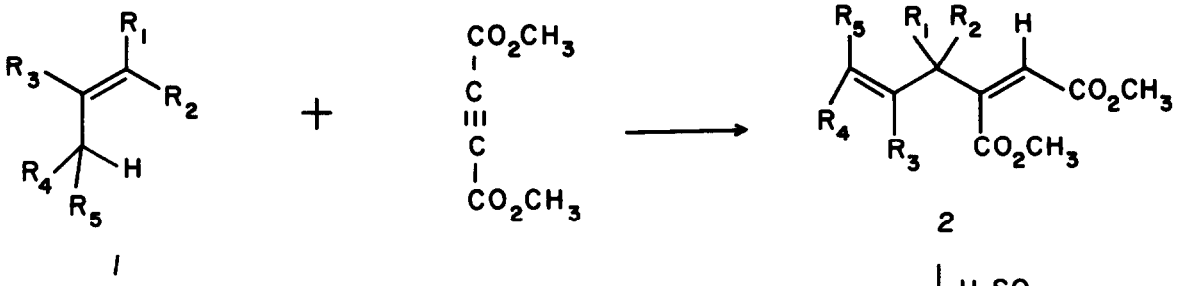
Many compounds of natural or synthetic origin having an α-methylene-γ-lactone moiety possess antitumor properties.[2,3] In this communication we describe a new synthesis of α-methylene-γ-lactones having a carbomethoxyl substituent at the methylene carbon. Since no antitumor testing had apparently been performed on such derivatives, and since conversion to the corresponding unsubstituted α-methylene compound is in principle quite facile, we were interested in developing this as a general method.

Our synthesis is comprised of two steps.

1. An initial ene reaction of a variable olefinic component 1 (or 4) with dimethyl acetylenedicarboxylate (DMAD);
2. Acid-promoted cyclization of the resulting adducts 2 (or 5) to give 3 (or 6).

Ene reacton. Considerable variation is possible in this step, subject only to the requirement of the ene reaction for the presence of an allylic proton.[4] In some cases (eg. methylenecyclohexane 1c, β-pinene 1d,[5] ethylidenecyclohexane 1f) the ene reaction with DMAD is most conveniently carried out thermally (120-140°; 8 hr), the adducts being obtained in 50-75% yield.[6] The corresponding reaction of vinylcyclohexane 1b is much slower and the adduct yield poor (ca. 10% in 60 hr). In the case of more volatile olefins (eg. 2-methyl-2-butene 1e, 2,3-dimethyl-2-butene 1g, 1-methylcyclohexene 4a, cyclohexene 4b) the reaction is best carried out in the presence of an equimolar amount of anhydrous $AlCl_3$ (CH_2Cl_2 as solvent; 1-3 hr at 25°, excess olefin).[7] Yields of adduct in these cases are of the order of 60%.[6] In the case of the acyclic 1,2-disubstituted olefins trans 2-hexene 1h or trans 3-hexene 1i, no ene reaction occurs and the predominant product (50-60%; 3 hr at 25°) of $AlCl_3$-promoted reaction with DMAD is the cyclobutene 7a or 7b.[7,8] With 1-hexene 1a, a mixture of 2a and 7c (~ 3:2) is obtained.

Cyclization. The reagent of choice to effect the lactonization of 2 (or 5) is 80% sulfuric acid and in successful cases (see below) the reaction is normally complete at 25° in a few minutes. Isolated yields of 3 (or 6) produced in this step are of the order of 80-85%.[6] All of the products possess (Z)-stereochemistry.[9] The cyclization step has been successfully carried out in the case of adducts 2c, 2e, 2f, 5a, and 2g, which are derived from 1,1-disubstituted (1c), trisubstituted (1e, 1f, 4a), and tetrasubstituted (1g) olefins. In all these adducts protonation of the double bond not substituted by ester groups will lead to a carbonium ion center stabilized by an attached alkyl substituent (R_3 in 2; R in 5) and suitably located for participation by the ester carbonyl. Where there is no such stabilization, as in the case of adducts derived from either monosubstituted or 1,2-disubstituted olefins (eg. 2a, 2b, 5b), cyclization does not occur



1

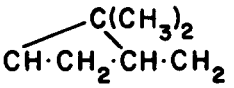
2

3

a. $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = {}^{n}Pr$

b. $R_1 = R_2 = R_3 = H$; $R_4 + R_5 = (CH_2)_5$

c. $R_1 = R_2 = R_5 = H$; $R_3 + R_4 = (CH_2)_4$

d. $R_1 = R_2 = R_5 = H$; $R_3 + R_4 =$ 

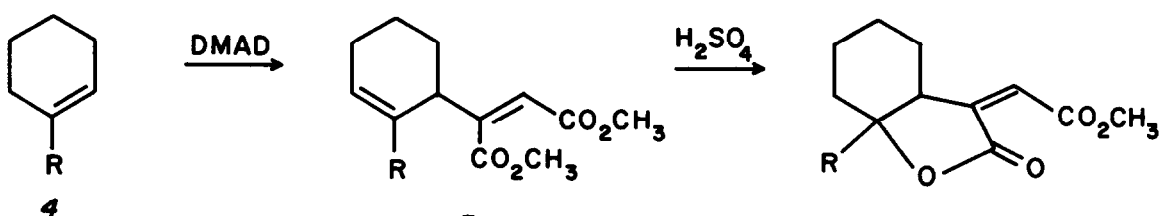
e. $R_1 = R_3 = CH_3$; $R_2 = R_4 = R_5 = H$

f. $R_1 = CH_3$; $R_2 = R_5 = H$; $R_3 + R_4 = (CH_2)_4$

g $R_1 = R_2 = R_3 = CH_3$; $R_4 = R_5 = H$

h. $R_1 = {}^{n}Pr$; $R_2 = R_3 = R_4 = R_5 = H$

i. $R_1 = Et$; $R_2 = R_3 = R_4 = H$; $R_5 = CH_3$



4

5

6

a. $R = CH_3$

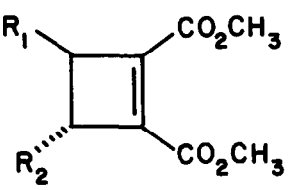
b. $R = H$

under the same conditions. Adduct 2d, moreover, being an α-pinene derivative, is as expected acid-sensitive and is not converted to 3d in the presence of 80% H_2SO_4.

The type of acid medium used for the cyclization step has a profound effect on the product composition and stereochemistry. For example, reaction of 2e or 2g with anhydrous HCl in CH_2Cl_2 (48 hr at 25°) affords chiefly the (E)-lactones 8a (37%) and 8b (60%),[9] while in the case of 5a the HCl-promoted reaction yields mainly the δ-lactone 9 (36%).[6]

Compounds 3e, 3g, 6a, and 8a have been shown to be inactive against P388 lymphocytic leukemia.[10] Antitumor activity appears to be enhanced by the presence of an unsubstituted methylene grouping.[11] Access to the desired unsubstituted α-methylene-γ-lactone system is provided in some cases by hydrolysis and decarboxylation. Compound 11, for example, can be prepared in 75-80% yield from 3g by saponification to 10 followed by decarboxylation using copper/quinoline at 200° (6 hr).[12]

Procedures for the lactonization of compounds such as 2a, 2b, 2d, and 5b are being actively studied, as are alternative approaches to the removal of the carbomethoxyl grouping.

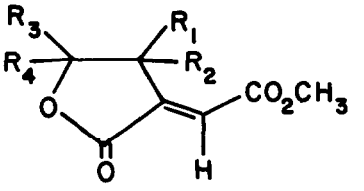


7

a. $R_1 = CH_3$; $R_2 = {}^nPr$

b. $R_1 = R_2 = Et$

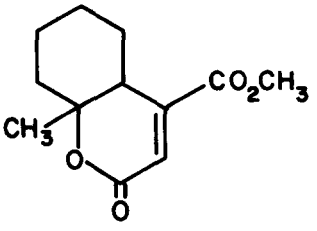
c. $R_1 = H$; $R_2 = {}^nBu$



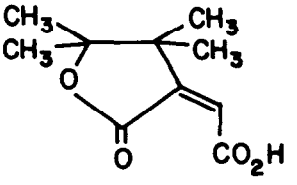
8

a. $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$

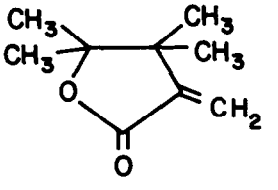
b. $R_1 = R_2 = R_3 = R_4 = CH_3$



9



10



11

References

1. Issued as NRCC No. 17159.
2. (a) K-H. LEE, T. IBUKA, S-H. KIM, B. R. VESTAL, I. H. HALL, and E-S. HUANG. J. Med. Chem. 18, 812 (1975); (b) A. ROSOWSKY, N. PAPATHANASOPOULOS, H. LAZARUS, G. E. FOLEY, and E. J. MODEST. ibid, 17, 672 (1974); (c) S. M. KUPCHAN, M. A. EAKIN, and A. M. THOMAS. ibid, 14, 1147 (1971); (d) G. A. HOWIE, P. E. MANNI, and J. M. CASSADY. ibid, 17, 840 (1974); (e) K-H. LEE, E-S. HUANG, C. PIANTADOSI, J. S. PAGANO, and T. A. GEISSMAN. Cancer Res. 31, 1649 (1971).
3. Widespread interest in such compounds has resulted in the development of a number of synthetic procedures. P. A. GRIECO. Synth. 67 (1975); R. B. GAMMILL, C. A. WILSON, and T. A. BRYSON. Synth. Comm. 5, 245 (1975).
4. H. M. R. HOFMANN. Angew. Chem. int. Edit. 8, 556 (1969).
5. R. K. HILL, J. W. MORGAN, R. V. SHETTY, and M. E. SYNERHOLM. J. Amer. Chem. Soc. 96, 4201 (1974).
6. All new compounds prepared in this work have been characterized by a combination of accurate mass determination, infrared and mass spectra, and high-resolution ^{1}H and ^{13}C magnetic resonance spectra.
7. During the course of this investigation a report appeared of $AlCl_3$ promotion of similar reactions utilizing propiolate esters: B. B. SNIDER. J. Org. Chem. 41, 3061 (1976).
8. Our 1,2-dicarbomethoxycyclobutene derivatives 7a,b ring-cleave surprisingly readily (as low as 40°) to give (Z,Z)-1,4-dialkyl-2,3-dicarbomethoxy-1,3-butadienes.
9. The magnitude of the coupling ($^{3}J_{CH}$) between the lactone carbonyl carbon and the olefinic hydrogen established their stereochemical relationship. cf. J. L. MARSHALL and R. SEIWELL. Org. Mag. Res. 8, 419 (1976); J. Magn. Reson. 15, 150 (1974).
10. We gratefully acknowledge the work of the Drug Evaluation Branch, National Cancer Institute, Bethesda, Maryland.
11. Introduction of alkyl substituents at the α-methylene grouping apparently also causes a reduction in activity (see ref. 2d above).
12. This procedure is at present limited to lactones having two substituents at C-4; in cases where there is a proton at this position these decarboxylation conditions lead to migration of the double bond into the ring.

(Received in USA 6 March 1979)