Tetrahedron Letters No. 48, pp 4807 - 4810. Pergamon Press. Printed in Great Britain.

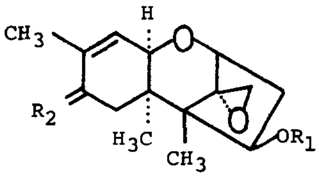
BICYCLIC INTERMEDIATES FOR TRICHOTHECANE SYNTHESIS. EXPLOITATION OF AN ENOLATE AS A PROTECTING GROUP.

David J. Goldsmith*, Arthur J. Lewis and W. Clark Still, Jr.
Department of Chemistry, Emory University, Atlanta, Georgia 30322, U.S.A.

(Received in USA 13 September 1973; received in UK for publication 16 October 1973)

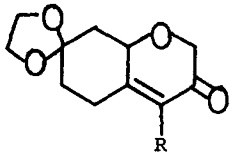
In the course of studies directed towards the total synthesis of trichodermin 1 and trichothecolone 2 we required the α,β-unsaturated ketones 3 and 4,and the *cis*-ketol 1 5. We wish to report, first,the preparation of the diketo-ethers 6 and 7 and their cyclization to give 3 and 4, respectively. Both the diketo-ethers and the heterocyclic enones are examples of relatively unknown systems. Second, the desired stereoselective introduction of a *cis*-angular methyl into diketone 8 can be accomplished using lithium dimethylcuprate(I), and the resulting enolate may then be exploited as a protecting group while methyl lithium is added 1,2 to the saturated carbonyl at C-7. A similar approach using a metal enolate as a protecting group has been used by Barton[1].

Alkylation of the allylic alcohol 9[2] using either methallyl chloride or ethallyl bromide afforded the olefinic ethers 10[4] (98% yield; nmr: δ 4.97, broad, 2H, $C{=}CH_2$; 4.83, broad, 2H, $C{=}CH_2$; 3.94, multiplet, 6H, $-O-CH_2CH_2-O-$ and $CH-O-\underline{CH_2}-$; 3.85, multiplet, 1H, $C\underline{H}-O-CH_2-$; 1.75, singlet, 3H, $-CH_3$) and 11 (98% yield; nmr: δ 4.95, broad, 2H, $C{=}CH_2$; 4.78, broad, 2H, $C{=}CH_2$; 3.87, multiplet, 6H, $-O-CH_2CH_2-O-$ and $CH-O-C\underline{H}_2-$; 2.05, quartet, J=7.2 Hz, 2H, $-C\underline{H}_2-CH_3$; 1.02, triplet, J=7.2 Hz, 3H, $-CH_2-C\underline{H}_3$) respectively. Ozonolysis converted 10 to 6 (m.p. 63-65; 79%;yield; nmr: δ 4.21, AB quartet, J_{AB} = 16.9, $\Delta\nu_{AB}$ = 30.4 Hz, 2H, $CH-O-C\underline{H}_2-$; 4.18, quartet, J = 12.1, J = 6.5 Hz, 1H, $C\underline{H}-O-CH_2-$, 4.04, singlet, 4H, $-O-CH_2CH_2-O-$; 2.19, singlet, 3H, $-CH_3$) and 11 to 7 (m.p. 64-65; 49% yield; nmr: δ 4.22, AB quartet, J_{AB} = 16.9, $\Delta\nu_{AB}$ = 29.8 Hz, 2H, $CH-O-C\underline{H}_2-$; 4.18, quartet, J = 12.5, J = 6.5 Hz, 1H, $C\underline{H}-O-CH_2-$; 4.04, singlet,



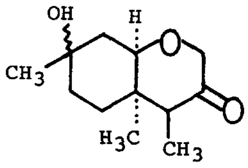
1 R_1= Ac, R_2= H,H

2 R_1= H, R_2= O

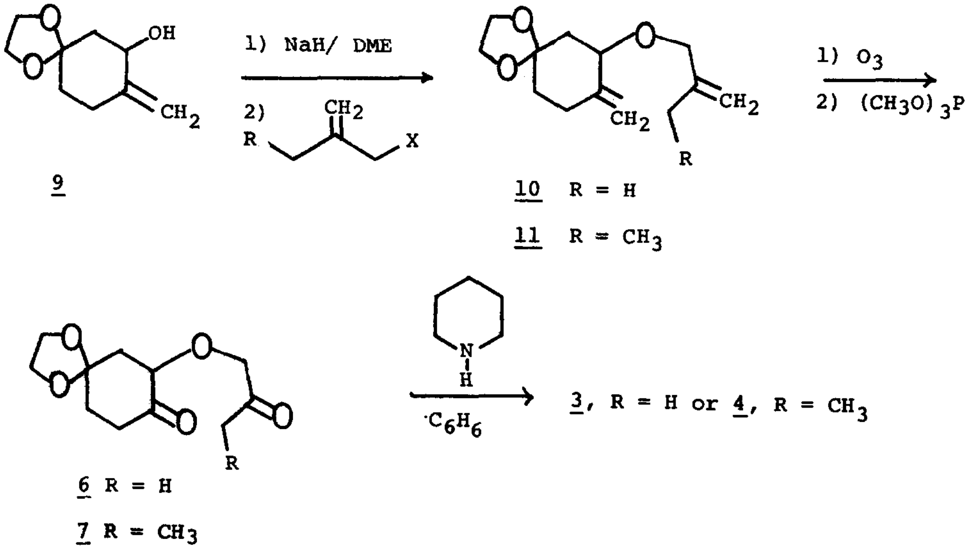


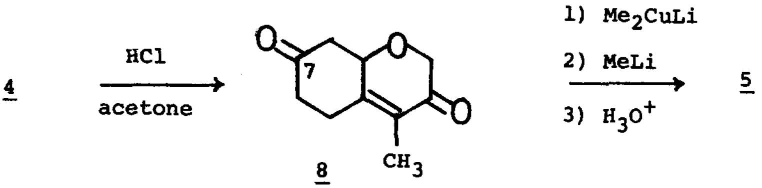
3 R= H

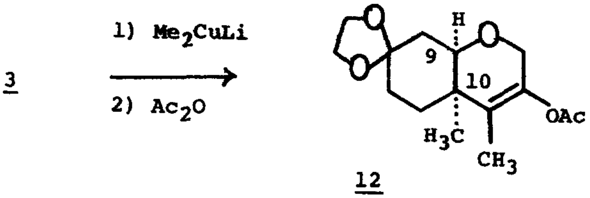
4 R= CH_3



5







4H, $-O-CH_2CH_2-O-$; 2.51, quartet, J = 7.5 Hz, 2H, $-C\underline{H}_2-CH_3$; 1.07, triplet, J = 7.5 Hz, 3H, $-CH_2-C\underline{H}_3$). With the exception of diglycolaldehyde, and diglycololic acid and its derivatives, diketo-ethers similar to 6 and 7 do not appear to have been reported previously.

Cyclization of 6 in the presence of piperidine yielded 3 (m.p. 70.5-71.5; 52% yield; nmr: δ 5.97, multiplet, 1H, $C=CH-$; 4.42, quartet, J = 11.5, J = 6.3 Hz, 1H, $C\underline{H}-O-CH_2-$; 4.17, doublet, J_{AB} = 15.9 Hz, 1H and 4.01, quartet, J_{AB} = 15.9, J = 1.8 Hz, 1H, $CH-O-C\underline{H}_2-$) and similar treatment of 7 afforded 4 (m.p. 85.5-86.5; 98% yield; nmr: δ 4.44, quartet, J = 6.2, J = 5.8 Hz, 1H, $C\underline{H}-O-CH_2-$; 4.21, doublet, J_{AB} = 11.8 Hz, 1H and 3.97, quartet, J_{AB} = 11.8, J = 1.9 Hz, 1H, $CH-O-C\underline{H}_2-$; 2.38, quartet, J = 5.9, J = 2.3 Hz, 1H and 2.15, quartet, J = 6.2, J = 2.3 Hz, 1H, $-C\underline{H}_2-CH-O-CH_2-$; 1.58, multiplet, 3H, $-CH_3$). A number of dihydropyran-3-ones derived from sugars have been recorded^4, all of which contain the usual carbohydrate anomeric center. Only one example of a non-oxygenated compound (2,2,6,6-tetramethyl-2,3-dihydro[6H]pyran-3-one) appears to have been prepared previously^5.

The diketone intermediate 8 (m.p. 65-66.5; nmr: δ 4.70, quartet, J = 10.9, J = 6.0 Hz, 1H, $-C\underline{H}-O-CH_2-$; 4.33, doublet, J_{AB} = 16.1 Hz, 1H and 4.14, J_{AB} = 16.1, J = 1.9 Hz, 1H, $-CH-O-C\underline{H}_2-$; 2.94, quartet, J_{AB} = 16.9, J = 6.6 Hz, 1H and 2.59, quartet, J_{AB} = 16.9, J = 10.9 Hz, 1H, $-C\underline{H}_2-CH-O-CH_2-$; 1.88, doublet, J = 1.8 Hz, 3H, $-CH_3$) used to prepare the ketol 5 was obtained by deketalization of 4 in 1:1 acetone: 10% hydrochloric acid in 93% yield.

Reaction of 8 with lithium dimethylcuprate(I) for 15 min at 0° was followed by the addition of excess methyl lithium. Hydrolysis after 15 min, by slowly pouring the reaction mixture into rapidly stirred hydrochloric acid^6, gave ketol 5 after isolation by column chromatography on silica-gel.

The ketol 5 (m.p. 79.5-80.5; 35% yield; nmr: δ 4.03, quartet, J_{AB} = 14.3, $\Delta\nu_{AB}$ = 15.7 Hz, 2H, $-CH-O-C\underline{H}_2-$; 4.01, broad singlet, wh/2 = 14.3 Hz, 1H, $-OH$; 3.82, multiplet, wh/2 = 7.8 Hz, 1H, $-C\underline{H}-O-CH_2-$; 2.33, quartet, J = 6.9 Hz; 1.18, singlet, 3H, $C-7CH_3$; 1.08, doublet, J = 6.9 Hz, 3H, $C-4CH_3$; 1.07, singlet, 3H, $C-10CH_3$) was assigned a *cis*-ring junction by analogy to reported examples of conjugate addition using lithium dimethylcuprate(I) or methylmagnesium halides in the presence of cuprous salts[6a,b].

Further support for the *cis*-ring junction was obtained from the spectral properties of the enol-acetate **12** (nmr: δ 3.94, quartet, J = 1.9 Hz, 1H, $-C\underline{H}-O-C\underline{H}_2-$; 3.91, 3.89, 3.87, 3.86, multiplet, 2H, $-O-CH_2CH_2-O-$; 3.56, quartet, J = 8.1, J = 4.5 Hz, 1H, $-C\underline{H}-O-CH_2-$; 2.08, singlet, 3H, $-O-CO-CH_3$; 1.47, triplet, J = 1.9 Hz, 3H, C-4CH_3; 1.10, singlet, 3H, C-10CH_3). The latter was prepared by treatment of the enolate produced by lithium dimethylcuprate(I) addition to **3** with Ac_2O (48% yield). The NMR spectra of **12** exhibited an nOe enhancement[7] of the C-9H (13.1 ± 1.5%) upon irradiation of the angular methyl at C-10 indicative of a *cis*-ring junction.

The formation of the ketol **5** is indicative of the differential reactivities of α,β-unsaturated ketones and saturated ketones to lithium dimethycuprate(I) confirmed by Posner[8] in a recent communication.

A full account of this and related work will be published later.

Acknowledgment: This work was supported in part by a Research Grant, GP-9542, from the National Science Foundation.

References

1. D. H. R. Barton, R. H. Hesse, M. M. Pechet and C. Wiltshire, *Chem. Comm.* **1972**, 1017.
2. W. C. Still, Jr., A. J. Lewis and D. J. Goldsmith, *Tetrahedron Lett.*, **1971**, 1421.
3. Combustion analyses of all new compounds reported are in agreement with the molecular formulas. Infrared, nmr and mass spectra of all new compounds are compatible with the indicated structures.
4. B. Fraser-Reid, A. McLean, E. W. Usherwood and M. Yunker, *Can. J. Chem.*, **48**, 2877 (1970).
5. I. K. Korobitsyna, K. K. Pivniitskii and Y. K. Yur'ev, *Zhur. Obschchei. Khim.*, **29**, 691 (1959).
6. (a) E. Piers and R. J. Keziere, *Can. J. Chem.*, **47**, 137 (1969) and references cited therein. (b) G. H. Posner, "Organic Reactions", Vol. 19, John Wiley and Sons, Inc., New York, 1972, p. 1.
7. G. E. Bachers and T. Schaefer, *Chem. Rev.*, **71**, 617 (1971).
8. G. H. Posner, C. E. Whitten and P. E. McFarland, *J. Amer. Chem. Soc.*, **94**, 5106 (1972).