Tetrahedron Letters,Vol.25,No.27,pp 2883-2886,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

NOVEL SYNTHETIC ROUTE γ-OXO-ACRYLATES
Application to the synthesis of Pyrenophorin antibiotic

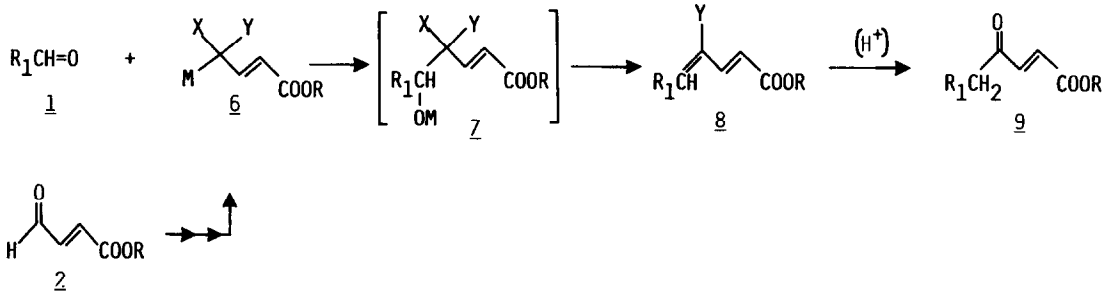
W. Dumont, C. Vermeyen and A. Krief*

Facultés Universitaires Notre-Dame de la Paix
Department of Chemistry
61, rue de Bruxelles, B-5000 Namur (Belgium)

We report a new method for the synthesis of γ-oxo-acrylates which allows the direct introduction of suitably functionalised four carbon skeleton.

The γ-oxo-α,β-unsaturated ester fragment is an important feature of several natural products particularly pyrenophorin[2] and vermiculin[3] natural antibiotic macrolides. Although several syntheses of such compounds have been described during the past ten years, there is still a need for short and efficient ones (i.e. ref. 4-10 for synthesis of pyrenophorin). We report in this letter original reactions which allow the synthesis of γ-oxo-acrylates from aldehydes 1 and 4-oxo-butenoates 2 in a straightforward way (Scheme I).

Scheme I

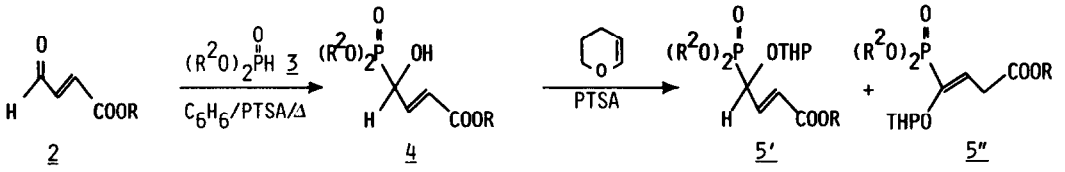


4-Oxo-butenoate 2[12] is a readily available material whose electrophilic properties have been successfully exploited in the synthesis of dienoic esters[13a] and chrysanthemic acids[13]. We now find that simple functional group manipulation on 2 permits its transformation to the valuable nucleophilic building blocks 6 .

Among the various combinations for X and Y in 6, we chose the phosphonato and the tetrahydropyranyloxy groups. The phosphonato group is known to stabilise an α-carbanion[14] and allows the synthesis of olefins when an alkoxy group is present on the β-carbon (Wadsworth-Emmons reaction). This reaction has been extended to the synthesis of heterosubstituted olefins including vinyl ethers[15]. In our case however, the over-stabilization of the carbanion in 6 and its ambident nature[16] may give rise to some problems.

The previously unknown functionalized phosphonato derivatives 6 were readily prepared in a two step one-pot process which involves the addition of dialkylphosphites 3 to 4-oxobutenoates 2 (C_6H_6, PTSA, Δ) and the protection of the resulting alcohol as a tetrahydropyranyl ether by subsequent addition of dihydropyran to the medium (Scheme II).

Scheme II



2 4 5' 5"

	R	R^2	conditions for 2 + 3 → 4	conditions for 4 → 5	Yield of 5 %
a	Me	i-Pr	60°, 15h	0°, 0.2h then 20°, 6h	52 (as 5')*
b	Me	Me	60°, 4h+	0°, 0.2h then 20°, 3h	61 (as 5")*
c	Et	Me	60°, 4h	0°, 0.2h then 20°, 4h	34 (as 5")*

+ lower yields of 5 are obtained if longer reaction times are used.

* this refers to the major isomer present in the mixture.

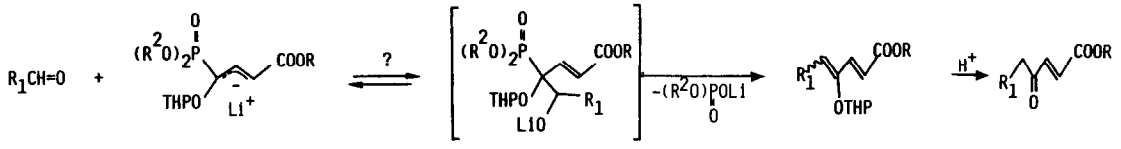
Metallation of 5 (5a' or 5a") to 6 is performed with lithium diisopropylamide in THF and is already complete after 0.1 h at -78°. Further addition of aldehydes to the medium (1 mol. eq., -78°, 0.2 h, then -78° to +20°, 2 h) leads to the expected products 8, isolated in fair to good yield (Scheme III) as a mixture of two stereoisomers 8 possessing the 4E and 4Z stereochemistry. Longer reaction times increase the yield in most cases, but not dramatically.

The substituents (R^2O) present on the phosphonato group play an important role in these reactions : the best results are observed with methoxy derivatives (6, R^2 = Me). This effect is particularly important when aliphatic aldehydes are involved (Scheme III). ^{31}P NMR monitoring of the reaction shows that the formation of the betaine 7 from 6 and aldehydes takes place at -78° and is complete after few minutes at that temperature. The elimination reaction leading to 8 is much more difficult and there is a big difference of reactivity between the betaines 7 (R^2 = i-Pr) derived from benzaldehyde and from 3-silyloxy butanal. In the first case the elimination does not occur in THF at -50°, is slow at -30° but is very fast at 0° or at -50° if 1 molar eq. of HMPT is added (see Scheme III for yields of 8). In the second one the reaction occurs around -20°, is not complete even after several hours at +20° and addition of HMPT on to the betaine does not favor the elimination to a large extent.

We have also tried to react 6 with aromatic and aliphatic ketones but we were unable to obtain the corresponding γ-pyranyloxy dienoic ester.

As expected, the dienes 8 are very good precursors of 4-oxo-butenoates 9. Removal of the tetrahydropyranyl group of 8 was achieved after 1 h at 20° in methanol CH_3OH-CH_2Cl_2(1-1 ; 5 M in 8) provided that p-toluene sulfonic acid (PTSA) (0.2 mol. eq.) was used as catalyst (Scheme III).

Scheme III



1 6 7 8 9

	R_1	R_2	R	Yield of 8 %	Yield of 9 %
a	C_6H_5	i-Pr	Me	72	
b	p-$MeOC_6H_4$	i-Pr	Me	52	
c	o-ClC_6H_4	i-Pr	Me	75	
d	n-Hex	i-Pr	Me	42	91
e	i-Pr	i-Pr	Me	55 (61)*	80
f	MeCH-CH_2 (OMe)	i-Pr	Me	25	70
g	C_6H_5	Me	Me	77 (85)*	94
h	n-Hex	Me	Me	51 (51)	
i	n-Hex	Me	Et	55	
j	MeCH-CH_2 (OTBMDS)	i-Pr	Me	15 (25)*	
k	"	Me	Me	47 - 57	
l	"	Me	Et	48	

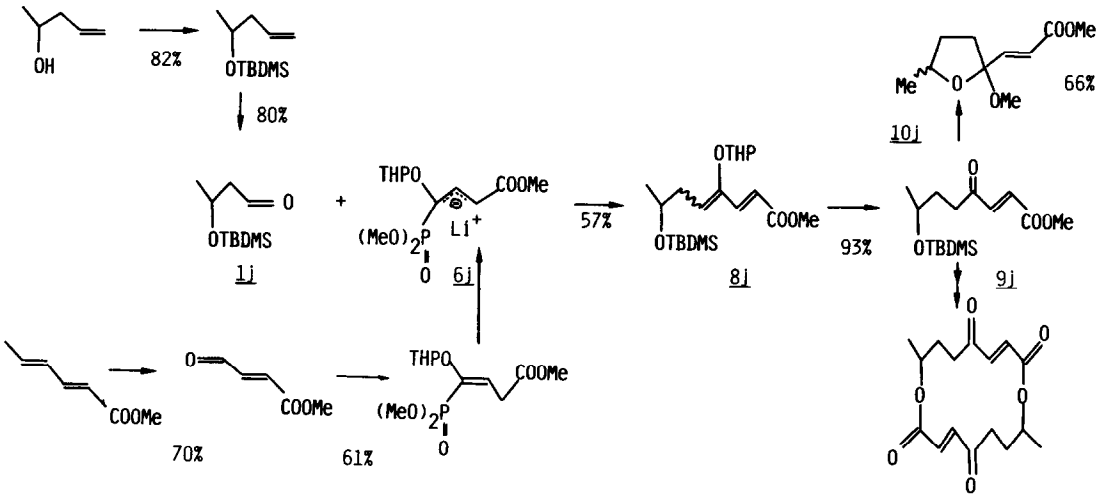
We have used (Scheme IV) the strategy presented in Scheme III for the synthesis of the γ-oxo-α,β-unsaturated ester 11 an important intermediate in the synthesis of pyrenophorin described by Gerlach[5] and Trost[8].

3-Silyloxybutanal (1j) needed as starting material for that synthesis was prepared in two steps (82 % and 80 %) from commercially available 1-pentene-4-ol by silylation of the hydroxyl group [t-$BuMe_2SiCl$ (1.4 mol. eq.), imidazole (2 mol. eq.), DMF, 20°C, 15 h] and subsequent ozonolysis [(i)O_3/CH_2Cl_2, 20°, ii)Me_2S (excess) 40°C, 10 h]. Reaction of 1j led to the diene 8 in 57 % yield as shown in Scheme III. Deprotection of 7 to 11 was not successful under the conditions we described above, and the methoxy tetrahydrofuran 10 is formed instead. This can be explained by the concomitant cleavage of the tetrahydropyranyl and the silyl groups followed by cyclization. The precursor 11 of pyrenophorin was however nearly quantitatively formed (93 % yield) if the reaction was performed with ethylene glycol (10 mol. eq.) and p-toluene sulfonic acid (0.2 mol. eq.) in benzene at reflux for 3 h.

It is interesting to note that the method described above should in principle allow the synthesis of optically active pyrenophorin from optically active 4-silyoxy butanal. We are applying the methodology reported herein for the synthesis of other macrolide antibiotics.

More direct routes to pyrenophorin from 8 and the original reactivity of compounds 4 and 5 are under investigation and will be reported in due course.

Scheme IV



Dr. M.J. De Vos-Pierreux obtained the preliminary results on this project. She is gratefully acknowledged.

REFERENCES

1) C. Vermeyen, Mémoire de Licence, Namur (September 1982)

2) S. Nozoe, K. Hirai, K. Tsuda, K. Ishibashi, M. Shiraska, J.F. Grove, Tet. Lett., 4675 (1965)

3) R.K. Boeckman, J. Fayos, J. Clardy, J. Amer. Chem. Soc., 96, 5954 (1974)

4) E.W. Colvin, T.A. Purcell, R.A. Raphael, JCS Chem. Comm., 1031, (1972) and JCS Perkin I, 1718 (1976)

5) H. Gerlach, K. Oertle, A. Thalmann, Helv. Chim. Acta, 60, 2860 (1977)

6) D. Seebach, B. Seuring, H.O. Kalinowski, W. Lubosch, B. Renger, Angew. Chem. Int. Ed., 16, 264 (1977) ; B. Seuring, D. Seebach, Justus Liebigs Ann. Chem., 2044 (1978)

7) P. Bakuzis, M.L.F. Bakuzis, T.F. Weingartner, Tet. Lett., 2371 (1978)

8) B.M. Trost, F.W. Gowland, J. Org. Chem., 44, 3449 (1979)

9) T.A. Hase, A. Ourila, C. Holmberg, J. Org. Chem., 46, 3137 (1981)

10) J.W. Labadie, J.K. Stille, Tet. Lett., 4283 (1983)

11) F.L.M. Smeets, Ph.D. Thesis, University of Nijmegen (Laboratory of Prof. Zwanenburg).

12) P.L. Slotter, J.B. Eppner, Tet. Lett., 2317 (1973)

13) M.J. De Vos, L. Hevesi, P. Bayet, A. Krief, Tet. Lett., 3911 (1976)
M.J. De Vos, A. Krief, Tet. Lett., 1515 (1979)

14) W.S. Wadsworth, Organic Reactions, 25, 73 (1972), John Wiley, N.Y. ISBN 0-471-01741-8

15) E. Nakamura, Tet. Lett., 663 (1981)

16) J.F. Biellman, J.B. Ducep, Organic Reactions, 27, 1 (1982), John Wiley N.Y. ISBN 0-471-09657

(Received in UK 9 February 1984)