Synthesis of 4-Substituted 2-Methyltetronic Acid Derivatives

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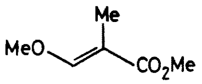
Summary Condensation of the carbanion derived from methyl (*E*)-3-methoxy-2-methylprop-2-enoate with aldehydes provides a one step synthesis of 4-substituted methyl 2-methyltetronates, which are transformed into the free acids and 4-alkylidene derivatives.

Recently, there has been a surge of interest in the synthesis of tetronic acid derivatives,[1] because of their wide distribution in nature. In connection with synthetic studies using specifically functionalised acrylate derivatives,[2] we found that methyl (*E*)-3-methoxy-2-methylprop-2-enoate (**1**) was a useful reagent for the synthesis of 4-substituted 2-methyltetronic acid derivatives.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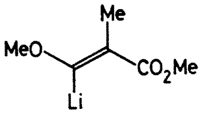
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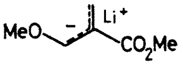
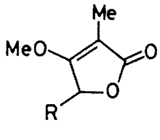

(3)

The configurationally pure 3-methoxy-2-enoate (**1**)† was obtained by potassium hydrogen sulphate-catalysed pyrolysis of methyl 2-(dimethoxymethyl)propionate[3] and the (*E*)-geometry was apparent from the actual formation of tetronates. Upon treatment with 1·2 mol. equiv. of lithium di-isopropylamide (LDA) at −80 °C in tetrahydrofuran (THF), compound (**1**) selectively produced the vinylic carbanion species (**2**), which was stable below −40 °C as indicated by a quenching experiment with deuterium oxide; there was no indication of the formation of an allylic carbanion (**3**), analogous to the case of the phenylthio analogue.[2b] Reactions of the carbanion (**2**) with a slight excess of propionaldehyde, isobutyraldehyde, n-butyraldehyde, benzaldehyde, nonanal, or geranal at −80 to −25 °C, gave, after preparative t.l.c., the corresponding 4-substituted tetronates (**4a**) (11%), (**4b**) (35%), (**4c**) (46%), (**4d**) (18%), (**4e**) (57%), and (**4f**) (40%), respectively, accompanied by the 1 : 2 products (**5**) (7—18%).‡ In these reactions the normal addition procedure for compounds (**4a,b**) and inverse addition for (**4c**)—(**4f**) gave the best results; addition of hexamethylphosphoric triamide did not improve the yields. Compound (**5b**) was also obtained through lithiation (LDA/THF) of compound (**4b**) followed by reaction with isobutyraldehyde, and it reverted upon treatment with potassium carbonate in hot aqueous methanol, to compound (**4b**). Furthermore, compound (**5b**) afforded the olefinic (**8**) and ketonic (**9**) derivatives by dehydration (thionyl chloride–pyridine) and oxidation (Collins reagent), respectively. These results confirm the assigned structures for the minor products (**5**) as shown.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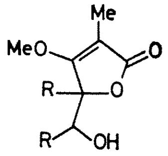
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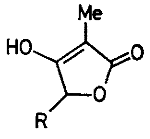
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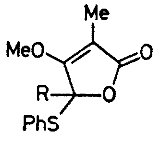
(7)

a; R = CH_2Me
b; R = $CHMe_2$
c; R = $[CH_2]_2Me$
d; R = Ph
e; R = $[CH_2]_6Me$
f; R = $Me_2C{=}CHCH_2CH_2C(Me){=}CH$

Hydrolysis of compounds (**4**) to the free tetronic acids (**6**) was accomplished by stirring the solution in 48% hydrobromic acid at room temperature. Thus, tetronic acids (**6b**) (after 41 h, 82%), (**6c**) (18 h, 85%), (**6d**) (24 h, 100%), and (**6e**) (140 h, 56%) were obtained.

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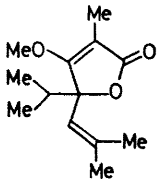
† Methyl 3-methoxy-2-methylprop-2-enoate (**1**) has been prepared from methyl methacrylate. However, the geometry was not reported. G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1958, 153.

‡ Yields are for the isolated pure products. All new compounds were characterized by combustion analysis as well as by i.r. and ^{1}H n.m.r. spectroscopy.



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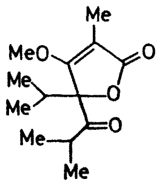
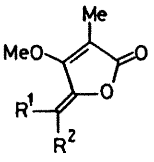


(9)

We then examined the transformation of compounds (**4**) into the 4-ylidene derivatives. According to the standard procedure,[4] lithiation of compounds (**4a**)—(**4c**) with LDA/THF at −60 °C followed by quenching with diphenyl disulphide gave the phenylthio derivatives (**7a**)—(**7c**), which, without purification, were oxidised with *m*-chloroperbenzoic acid and then pyrolysed in boiling carbon tetrachloride to give the 4-alkylidene compounds (**10a**)—(**10c**) in 32—40% yields.§ Each of the compounds (**10a**) and (**10c**) was found to be a single isomer and the (*Z*)-geometry for (**10a**) was established on the basis of the observed nuclear Overhauser effect enhancement (9%) between the olefinic proton and the methoxymethyl-group signals in the 100 MHz ^{1}H n.m.r. spectrum. Hydrolysis of the compounds (**10a,b**) in the same manner afforded (*Z*)-4-ethylidene- (**11a**) and 4-isopropylidene- (**11b**) 2-methyltetronic acids in 95 and 58% yields, respectively.



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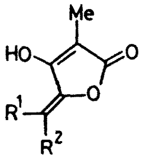

(11)

a; $R^1 = H, R^2 = Me$
b; $R^1 = R^2 = Me$
c; $R^1 = H, R^2 = MeCH_2$

Although the reported condensation results only in a low to modest yield, its simplicity and the ready availability of the reactants indicate that it should be a convenient alternative method for the synthesis of 4-substituted 2-methyltetronic acid derivatives.

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§ Dehydrogenation with dichlorodicyanoquinodimethane or bromination (*N*-bromosuccinimide)–dehydrobromination were unsatisfactory methods for achieving unsaturation.

[1] G. Pattenden, *Fortschr. Chem. Org. Naturst.*, 1978, **35**, 133; D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans.* 1, 1979, 62, 70, 84; S. C. M. Fell, J. Heaps, and J. S. E. Holker, *J. Chem. Soc., Chem. Commun.*, 1979, 81; H. Achenbach and J. Witzke, *Tetrahedron Lett.*, 1979, 1579; A. Pelter, M. T. Ayoub, J. Schultz, R. Hänsel, and D. Reinhardt, *ibid.*, 1979, 1627; P. J. Jerris, P. M. Wovkulich, and A. B. Smith, III, *ibid.*, 1979, 4517; J. Weinstock, J. E. Blank, H.-J. Oh, and B. M. Sutton, *J. Org. Chem.*, 1979, **44**, 673; R. R. Schmidt and J. Talbiersky, *Synthesis*, 1977, 869; *idem, Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 204; D. Caine and A. S. Frobese, *Tetrahedron Lett.*, 1978, 5167; C. D. Pourter, E. A. Mash, J. C. Argyle, O. J. Muscio, and H. C. Rilling, *J. Am. Chem. Soc.*, 1979, **101**, 762.

[2] (a) H. Hagiwara, K. Nakayama, and H. Uda, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3769; S. Yamagiwa, H. Sato, N. Hoshi, H. Kosugi, and H. Uda, *J. Chem. Soc., Perkin Trans.* 1, 1979, 570; H. Hagiwara, H. Uda, and T. Kodama, *ibid.*, 1980, 963; (b) K. Isobe, M. Fuse, H. Kosugi, H. Hagiwara, and H. Uda, *Chem. Lett.*, 1979, 785.

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[4] B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, 1976, **98**, 4887.