A New Sequence for the Synthesis of 3-(Poly)enoyltetramic Acids

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The synthesis of 3-(poly)enoyltetramic acids from 2,2,6-trimethyl-1,3-dioxen-4-one *via* *N*-(3-oxo-4-alkenoyl)-α-amino-acids is described.

To extend our interest in the 3-acyltetramic acids **1**[1] and encompass the polyenoyl subclass of metabolites, such as the highly toxic pigment erythroskyrine **2**,[2] we require methods for the assembly of polyenoyltetramic acids. A popular strategy has been chain extension of 3-acetyl **1** (R^3 = Me)[3] and 3-phosphonacetyl **1** [$R^3 = CH_2P(O)(OEt)_2$] derivatives,[4] but the acidic and highly polar enolic nature of the heterocycle make it advantageous to form the heterocycle after assembly of the polyenoyl chromophore. We report herein a simple sequence to accomplish this goal using non-polar intermediates.[5,6]

2,2,6-Trimethyl-1,3-dioxen-4-one ('acetone-diketene adduct' **3a**) was converted *via* the chloride **3b** into the 6-diethylphosphonomethyl derivative **3c** [i, $LiNPr^i_2$, THF, −70 °C; C_2Cl_6, −50 °C; 59%; ii, $(EtO)_2P(O)H$, Bu^tOK, DMF, 0 °C; 60%].[7] The anion derived from the phosphonate **3c** was condensed with saturated and unsaturated aldehydes (Table 1) to give the (poly)enes **4a–e**† [$LiN(SiMe_3)_2$, THF, −78 °C for **4a**, **c–e**; BuLi, THF, 0 °C for **4b**]. In an alternative but less generally useful approach, the phosphonium salt **3e**[4a] was prepared from **3a** *via* the 6-bromomethyldioxenone **3d** (i, $LiNPr^i_2$, THF, −70 °C; $BrCl_2CCCl_2Br$, −55 °C; 78%; ii, Ph_3P, C_6H_6, reflux; 93%)‡ and underwent Wittig reactions in moderate yield, *e.g.* with hexa-2,4-dienal (BuLi, THF) to generate **4d** (30%). Direct deprotonation of **3a** and aldol condensation with aldehydes was examined, but gave only limited success, especially in the dehydration step.[8] Acid-

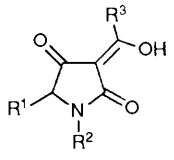
† All new compounds gave spectral data (IR, UV, NMR and MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

‡ Attempts to prepare bromide **3d** by radical bromination (*N*-bromosuccinimide, benzoyl peroxide, CCl_4, reflux), *cf.* ref. 4*a*, led to an inseparable mixture of **3a**, **3d** and the 6-dibromomethyl compound (1:5:1).

Table 1 Synthesis of 3-acyltetramic acids **6**

Aldehyde	6-Alkenyldioxenone **3a** or **4** (yield %)	β-Ketoamide **5** (yield %)	3-Acyltetramic acid **6** (yield %)
	3a	**5a** (73)	**6a** (65)
MeCHO	**4a** (61)	**5b** (69)	**6b** (45)
$Me[CH_2]_4CHO$	**4b** (71)		
(*E*)-MeCH=CHCHO	**4c** (20)[a]	**5c** (83)	**6c** (65)
(*E*,*E*)-$Me[CH{=}CH]_2CHO$	**4d** (70)	**5d** (75)	**6d** (52)
(all-*E*)-$Me[CH{=}CH]_4CHO$	**4e** (28)[a]		

[a] Isolated yield; difficulties in purification.



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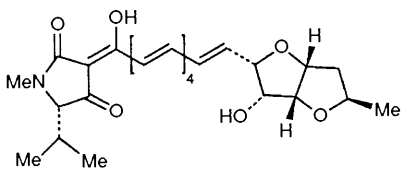

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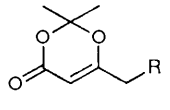
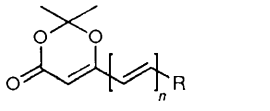
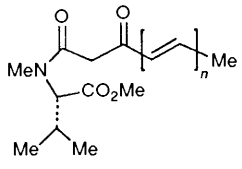


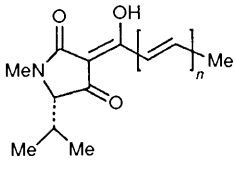
3 a; R = H
b; R = Cl
c; R = $P(O)(OEt)_2$
d; R = Br
e; R = $P^+Ph_3\ Br^-$



4 a; *n* = 1, R = Me
b; *n* = 1, R = $(CH_2)_4Me$
c; *n* = 2, R = Me
d; *n* = 3, R = Me
e; *n* = 5, R = Me



5 a; *n* = 0
b; *n* = 1
c; *n* = 2
d; *n* = 3



6 a; *n* = 0
b; *n* = 1
c; *n* = 2
d; *n* = 3

mediated thermolysis[9] of the 6-methyl **3a** and 6-alkenyldioxenones **4** with an α-amino ester afforded the corresponding β-ketoamides in good yield. Thus *N*-methyl-L-valine methyl ester, prepared *in situ* from the hydrochloride salt (Et_3N, CH_2Cl_2) was reacted with dioxenones **3a** and **4a**, **c**, **d** [pyridinium toluene-*p*-sulphonate (1 mol equiv.), toluene; reflux 3–4 h] to generate the amides **5a–d**, respectively (Table 1). Finally, Dieckmann cyclisation of the β-ketoamides proceeded efficiently using potassium t-butoxide in t-butyl alcohol at 20 °C within 45 min * to afford the 3-acyltetramic acids **6a–d** (Table 1).

We have thus demonstrated a mild methodology for accessing (poly)enoyltetramic acids that generates the polar heterocycle as a final step.

* Extended reaction times lead to racemisation, *cf.* ref. 5.

Acknowledgements

We thank SERC for a studentship (M. T.).

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Paper 0/04564K
Received 10*th October* 1990
Accepted 23*rd October* 1990