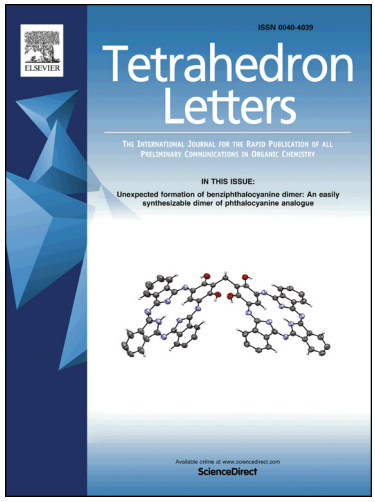

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Graphical Abstract

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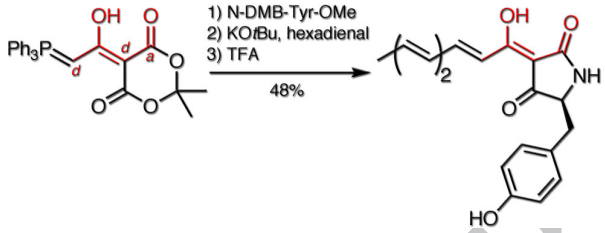

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A short synthesis of 3-enoyltetramic acids employing a new acyl ylide conjugate of Meldrum's acid

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ABSTRACT

2,2-Dimethyl-5-(triphenylphosphoranylidene)acetyl-1,3-dioxan-4,6-dione (**3**) is a new activated β-ketoacyl equivalent, readily prepared in quantitative yield by reaction of Meldrum's acid with the stable ylide Ph_3PCCO. Its reaction with α-amino esters affords the corresponding N-(β-ketoacyl)amino ester ylides which, when treated with aldehydes and KO*t*Bu, undergo a simultaneous Wittig olefination cum Dieckmann cyclisation to yield the respective 3-enoyltetramic acids.

Introduction

3-Acyltetramic acids occur as metabolites of bacteria, molds, fungi, and sponges.[1–4] Biosynthetically, they are comprised of polyketides and α-amino acids. 3-Enoyltetramic acids **1** constitute an interesting subclass, frequently associated with biological activity, and synthetically accessible on various routes.[5-9] In 1988 Boeckman reported the synthesis of 6-diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one (**2**) and its use as an activated β-ketoester equivalent in the synthesis of 3-enoyltetramic acids.[10] As an alternative, we developed a related acyl ylide **3** derived from Meldrum's acid which offers access to compounds **1** in only three steps (Fig. 1).

Results and discussion

2,2-Dimethyl-5-(triphenylphosphoranylidene)acetyl-1,3-dioxan-4,6-dione (**3**) was readily obtained as an airstable solid in virtually quantitative yield from heating THF solutions of Meldrum's acid (**4**) and ketenylidenetriphenylphosphorane, Ph_3PCCO (**5**). The latter is a stable ylide, not entering into olefinations with carbonyl compounds, but reacting instead with OH-, NH-, SH-, and CH-acidic compounds to give acyl ylides.[11] It was prepared in three steps from ethyl bromoacetate and Ph_3P.[12] The molecular structure of ylide **3**, as obtained from a single crystal X-ray diffraction analysis, revealed bond lengths and dihedral angles in line with its anticipated enol character (Fig. 2). ^1H, ^{13}C, and ^{31}P NMR spectra show the presence of a mixture of two tautomers, the ylide form depicted in Figure 1 and the corresponding phosphonium betaine form.

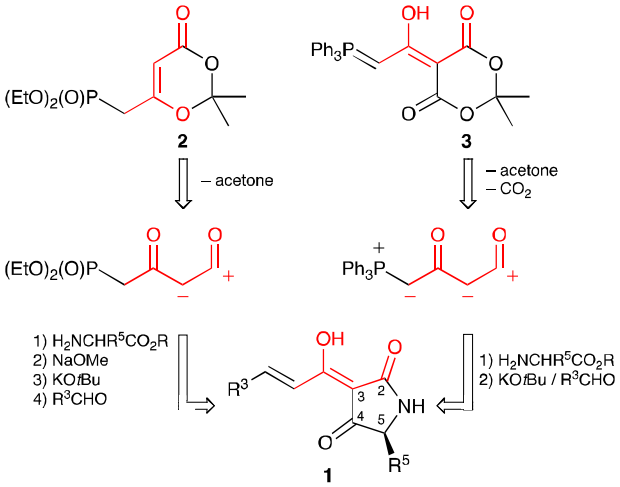

Figure 1. Synthesis of 3-enoyltetramic acids **1** with activated β-ketoacyl equivalents **2** and **3**.

Ylide **3** can be applied to the synthesis of 3-enoyltetramic acids in two ways differing in the number of steps and the order of olefination (a/e), amidation (b/d), and Dieckmann cyclisation (c/e) reactions. The olefination step attaches the 3-acyl side chain, the amidation step generates the *N*-(β-ketoacyl)amino ester, and the Dieckmann cyclisation closes the pyrrolidine ring (Scheme 1). Three 3-enoyltetramic acids **10a-c** derived from L-alanine and three different aldehydes, *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde and isobutyraldehyde were prepared on both routes. Route **A** begins by converting these aldehydes via olefination (a) with ylide **3** to the corresponding Wittig products **6a-c** in yields above 80%.

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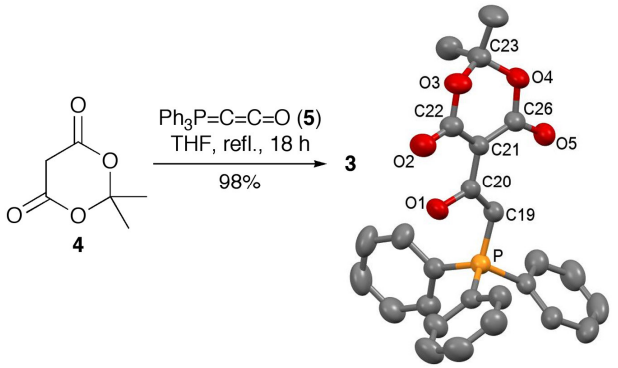
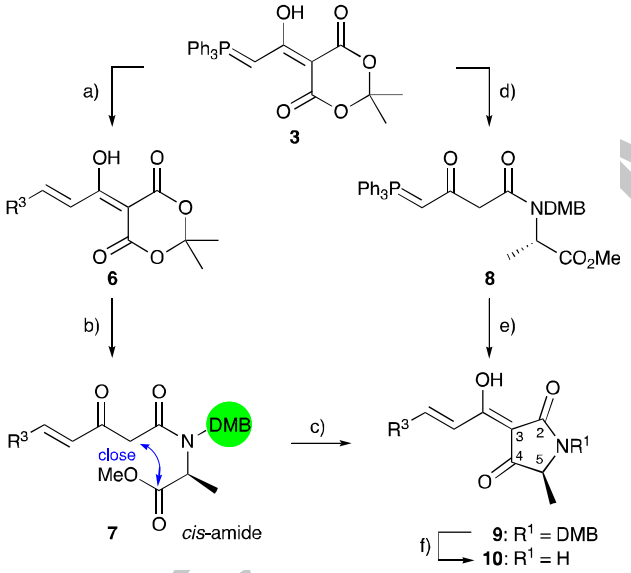


Figure 2. Synthesis and molecular structure of **3**, as thermal ellipsoid representation at 50% probability level showing the atomic numbering scheme (H-atoms omitted). CCDC 1564727. Selected bond lengths [Å] and angles [°]: P–C19 1.723(2), C19–C20 1.376(3), C20–O1 1.342(3), C20–C21 1.443(3), C21–C26 1.430(3), C21–C22 1.418(3), C22–O2 1.238(3), C26–O5 1.221(3), P–C19–C20–O1 1.7(3), O1–C20–C21–C22 –0.2(3), O1–C20–C21–C26 177.0(2), C20–C21–C22–O2 6.8(4), C20–C21–C22–O3 –176.0(2).



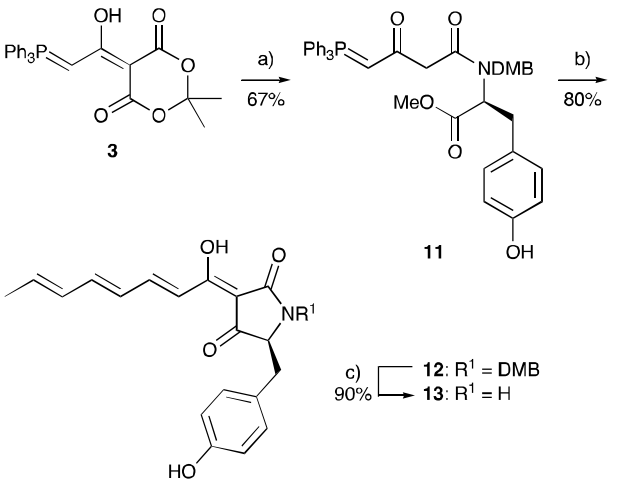
Scheme 1. Reagents and conditions: (a) KO*t*Bu, R^3CHO, THF, r.t., 18 h; (b) (DMB)NHCHR^5CO_2Me, DMAP, dioxane, reflux, 30 min; (c) NaOMe, MeOH, r.t., 20 min; (d) (DMB)NHCHR^5CO_2Me, DMAP, dioxane, reflux, 24 h; (e) KO*t*Bu, R^3CHO, THF, r.t., 24 h; (f) TFA, CH_2Cl_2, r.t., 1h.

The important point is that ylide **3** does not enter into Wittig olefinations with aldehydes and ketones but needs to get deprotonated by KO*t*Bu to an anionic Wittig-active species first. The following amidation (b) with methyl L-*N*-(2,4-dimethoxybenzyl)alaninate afforded three β-ketoamides **7a-c** in moderate yields. The 2,4-dimethoxybenzyl (DMB) group is necessary to orient the ester group of compounds **7** in a way favourable for the ensuing Dieckmann cyclisation step (c) under basic conditions, as indicated in scheme 1.[13] The product 3-enoyltetramic acids **9a-c** were obtained in good to excellent yields. The shorter route **B** starts with an aminolysis (d) of Meldrum's acid derivative **3** with methyl L-*N*-(2,4-dimethoxybenzyl)alaninate to give ylide **8** in almost 70% yield. This aminolysis reaction took distinctly longer than the aminolysis of Meldrum's acid derivatives **6** with the same amino ester. Ylide **8** was then treated with KO*t*Bu and the respective aldehyde to initiate both the olefination and Dieckmann cyclisation reactions in one step (e) to give the DMB-protected 3-enoyltetramic acids **9**. The overall yields of the shorter route **B** were on average slightly higher than those of **A** (40% *vs.* 35%). Deprotection of compounds **9** with TFA in CH_2Cl_2 (f) afforded the tetramic acids **10a-c**. Table 1 summarises the individual compounds and yields.

Table 1. Isolated compounds and yields.

Compound	R^1	R^3	Yield **A**/**B** [%]
3	–	–	98
6a	–	*p*-NO_2-Ph	98
6b	–	*p*-OMe-Ph	88
6c	–	Isobutyl	83
7a	DMB	*p*-NO_2-Ph	55
7b	DMB	*p*-OMe-Ph	40
7c	DMB	Isobutyl	34
8	DMB	–	68
9a	DMB	*p*-NO_2-Ph	93/80
9b	DMB	*p*-OMe-Ph	93/40
9c	DMB	Isobutyl	84/55
10a	H	*p*-NO_2-Ph	88
10b	H	*p*-OMe-Ph	90
10c	H	Isobutyl	80

The applicability of this approach to natural products was demonstrated by the synthesis of the tyrosine-derived 3-acyltetramic acid **13**, a bright yellow pigment responsible for the colour of the slime mould *Leocarpus fragilis*.[14,15] Ylide **3** was reacted with *N*-DMB-protected methyl tyrosinate to afford amino ester ylide **11** in 67% yield. Protection of the phenolic OH-group was not necessary. Reaction of ylide **11** with a mixture of KO*t*Bu and (*E,E*)-2,4-hexadienal gave tetramic acid **12** in 80% yield by a simultaneous Wittig olefination cum Dieckmann cyclisation. Deprotection with TFA afforded the natural product **13** in 48% overall yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) *N*-DMB-Tyr-OMe, toluene, reflux, 16 h; (b) (2*E*,4*E*)-hexadien-1-al, KO*t*Bu, MeOH, r.t., 24 h; (c) TFA, CH_2Cl_2, r.t., 1 h.

Conclusion

A new, easy to prepare, Meldrum's acid ylide conjugate was developed that acts as an activated β-ketoester equivalent allowing the synthesis of 3-enoyltetramic acids from α-amino esters in three steps and up to 50% yield. It is applicable to tetramic acids derived from amino acids with polar residues, and with alkyl, alkenyl, or aryl side chains at C-3.

Acknowledgements

We thank Dr. Ulrike Lacher (University Bayreuth) for in-depth MS analyses.

Supplementary data

Supplementary data associated with this article (experimental protocols, physical data, and NMR spectra of compounds **3** and **6**-**13**) can be found in the online version, at doi:xx.xxxx/j.tet.2017.xx.xxx

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Highlights:

- A new Meldrum's acid ylide conjugate acts as an activated β-ketoester equivalent
- It allows the synthesis of 3-enoyltetramic acids from α-amino esters in three steps
- It is compatible with unprotected polar residues
- A yellow pigment from the slime mould *Leocarpus fragilis* was prepared in 3 steps