

# Total synthesis of the plasmoidal pigment physarorubinic acid, a polyenoyl tetramic acid

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The total synthesis of physarorubinic acid, a polyenoyltetramic acid plasmoidal pigment from *Physarum polycephalum*, is described in a series of steps from (*E*)-3-iodoacrylic acid **6** and employs aminolysis of the pentaene thioester **11** as a key synthetic step. Lacey–Dieckmann cyclisation and subsequent deprotection then affords physarorubinic acid **1** in high yield and purity.

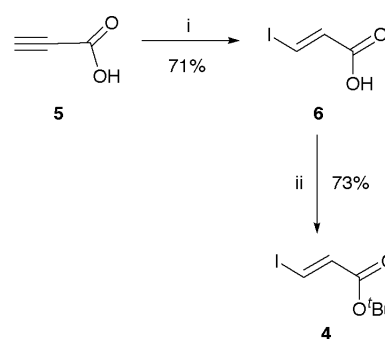
Naturally occurring tetramic acids (4-hydroxy-3-pyrrolin-2-ones) are of considerable interest to the synthetic organic chemist, not least because the majority of compounds isolated exhibit some biological function. The spectrum of biological activity displayed by the family is remarkable in its diversity and includes potent antibiotic, antiviral and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumours as well as fungicidal action.<sup>1</sup>

A notable member of this group of natural products is physarorubinic acid **1** which was first isolated and characterised by Nowak and Steffan in 1997.<sup>2</sup> As well as containing an *N*-methylserine derived acyltetramic acid terminus, physarorubinic acid contains a central fully conjugated all-(*E*)-pentaene chain attached to a terminal carboxylic acid. This kind of polyenoyltetramic acid framework has been studied previously by our group during the total syntheses of fuligorubin<sup>3</sup> and erythrosyrine.<sup>4</sup> Here we wish to report a further development of this chemistry in the first total synthesis of physarorubinic acid **1**.

Our analysis of the synthetic problem suggested a convergent approach involving three main fragments, namely the amino ester **2**, a  $\beta$ -keto thioester fragment **3** bearing a tributyltin group at its terminus and the vinyl iodide **4** (Fig. 1). Fragment **2** was readily available from (*S*)-*N*-methylserine while the middle tetraene portion was obtained from the phosphonate ester **9** and  $\beta$ -tributylstannylacrolein unit **10**. The remaining fragment **4** could be obtained using a literature route.<sup>5</sup>

Although high yielding, the existing literature conditions for preparation of the vinyl iodide used high pressures and temperatures, and long reaction times.<sup>5</sup> For this reason we developed a

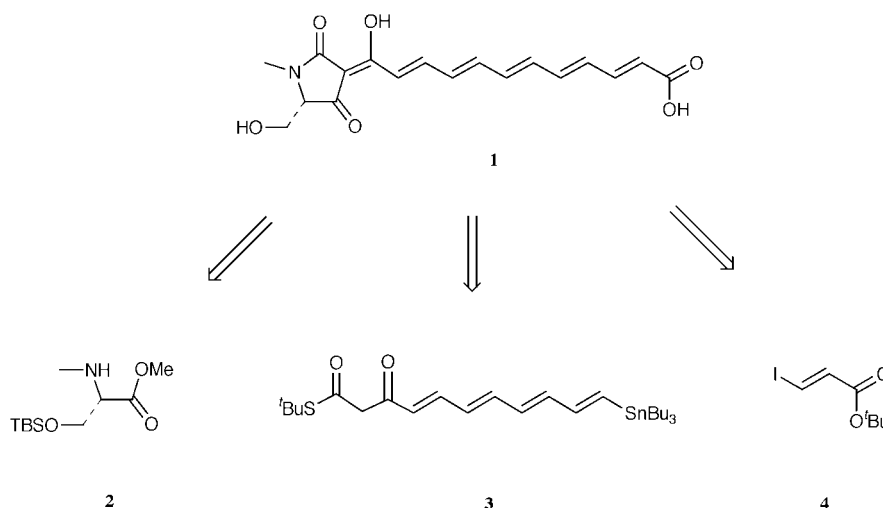
convenient and efficient method using copper(I) catalysis to facilitate the same transformation in good yield and purity. Propiolic acid was heated to reflux in an excess of aqueous hydrogen iodide with copper iodide catalyst for 30 minutes. Following cooling to room temperature, filtration, washing with water and drying, the vinyl iodide **6** was afforded in 71% yield directly from the reaction mixture (Scheme 1). Treatment of **6**



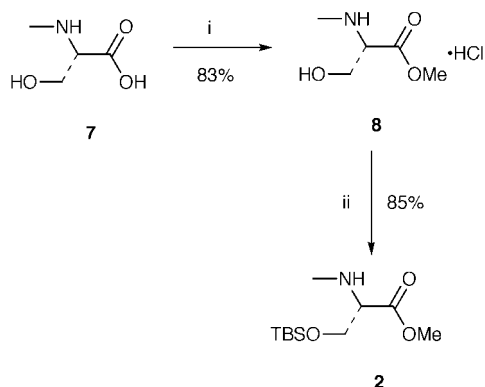
**Scheme 1** Reagents and conditions: i, CuI (0.6%), HI (57% aq.), 130 °C, 30 min; ii, <sup>t</sup>BuOAc (10 eq.), CF<sub>3</sub>SO<sub>3</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, RT, 60 min.

with *tert*-butyl acetate and a catalytic amount of triflic acid in dichloromethane at room temperature resulted in formation of the *tert*-butyl ester **4**, in 73% yield.

Synthesis of amino ester **2** was readily achieved starting from commercially available (*S*)-*N*-methylserine **7**, which was converted to the methyl ester hydrochloride salt by heating it to reflux in methanolic hydrochloric acid. Recrystallisation from acetone afforded **8** in 83% yield (Scheme 2). *tert*-Butyldimethylsilyl protection of the alcohol was then carried out in *N,N*-dimethylformamide. Imidazole (2.2 eq.) was added to a solution of the amino ester hydrochloride salt **8** at room temperature followed by *tert*-butyldimethylsilyl chloride and the reaction was stirred overnight. Following work-up, **2** was afforded in 85% yield.



**Fig. 1**



**Scheme 2** Reagents and conditions: i,  $\text{CH}_3\text{COCl}$  (10 eq.), MeOH, reflux, 12 h; ii, Imidazole (2.2 eq.), TBSCl (0.98 eq.), DMF, RT, 8 h.

Having gram quantities of both the vinyl iodide **4** and *tert*-butyldimethylsilyl protected (*S*)-*N*-methylserine methyl ester **2** in hand, the preparation of the polyene thioester fragment **3** was carried out following our previously established method.<sup>4</sup> Compound **3** was prepared as a mixture of keto and enol forms in the ratio 1 : 2.

The key Stille coupling of vinyl iodide **4** with the tributyl stannane **3** was next investigated.<sup>6</sup> Thus, treatment of stannane **3** with an excess of the iodide **4** (1.5 eq.) and bis(trifurylphosphine)palladium(II) chloride (0.15 eq.) in (*N,N*)-dimethylformamide at room temperature for one hour afforded isomerically pure all-(*E*)-pentaene **11**, existing mainly in the enol form in 67% yield as a golden powder (Scheme 3).

With the carbon framework intact, all that remained was the conversion of the thioester to tetramic acid and subsequent deprotection to physarorubinic acid **1**. Aminolysis of the *tert*-butyl thioester with *O*-protected (*S*)-*N*-methylserine methyl ester (3 eq.) occurred readily, mediated by silver trifluoroacetate (2 eq.) in tetrahydrofuran at 0 °C following a modification of our previously reported procedure to give  $\beta$ -keto amide **12** in 93% yield and high purity.<sup>7</sup> The Lacey–Dieckmann cyclisation of the ester **12** to acyltetramic acid **13** proceeded well under standard conditions.<sup>7</sup> The ester was dissolved in methanol and warmed to 25 °C at which point it was treated with sodium methoxide (0.5 M in methanol, 5 eq.). After 2 minutes saturated ammonium chloride was added to quench the reaction mixture and aqueous work up afforded essentially pure acyltetramic acid **13**. No further purification was attempted on this material.

The final deprotection to physarorubinic acid **1** was achieved using a 9:1 trifluoroacetic acid–water mixture. This was added at room temperature and immediately removed *in vacuo*. The process was repeated and was particularly useful due to the fact that all side products and excess reagents were volatile. Purification of the crude product by size exclusion chromatography on Sephadex LH-20 afforded pure physarorubinic acid **1** as a deep red–orange powder in 78% yield. The <sup>1</sup>H and <sup>13</sup>C NMR, IR, UV, negative APCI-MS and CD spectra were all in agreement with the reported data for the natural product.<sup>2</sup>

In summary, we have reported an efficient route to the polyenyltetramic acid physarorubinic acid **1** using chemistry previously developed in our laboratory in the synthesis of tetraene **3**. A new method has also been developed for a much more convenient and efficient synthesis of vinyl iodide **6** than those previously existing in the literature.

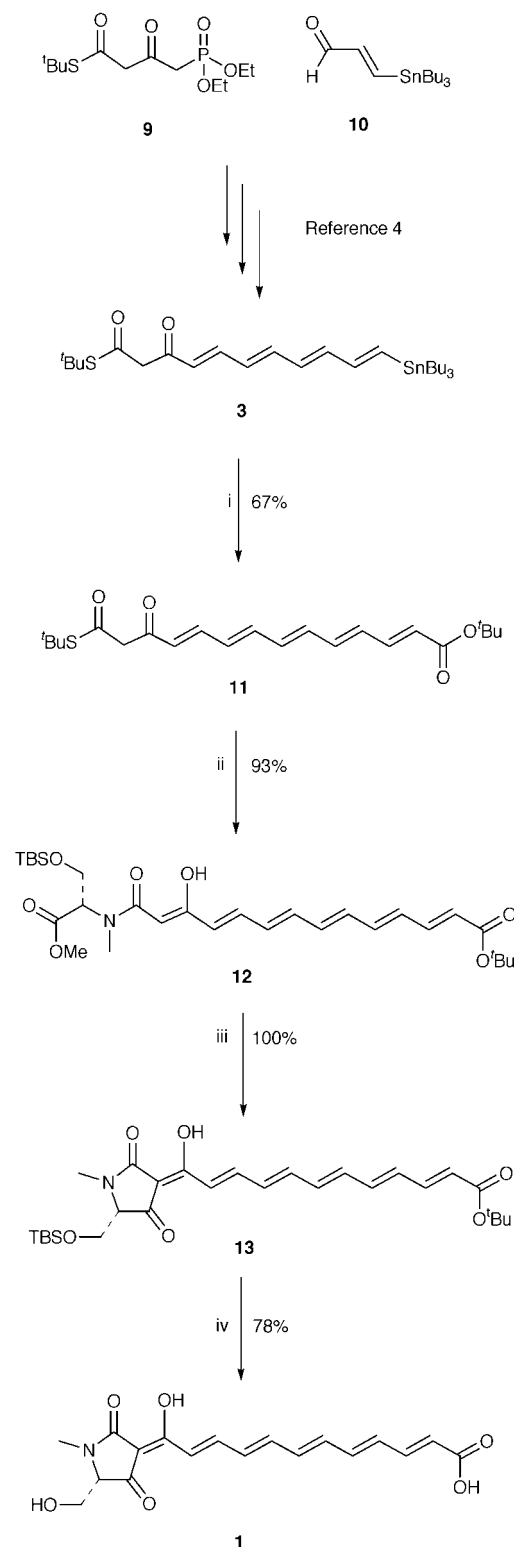
## Acknowledgements

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## Notes and references

1 For an excellent review, see B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981 and references cited therein.

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**Scheme 3** Reagents and conditions: i, **4** (1.5 eq.),  $[\text{P}(\text{Fur})_3]_2\text{PdCl}_2$  (0.15 eq.), DMF, RT, 60 min; ii, **2** (3 eq.),  $\text{Et}_3\text{N}$  (2 eq.),  $\text{CF}_3\text{COOAg}$  (2 eq.), THF, 0 °C, 30 min; iii, MeONa (5 eq.), MeOH, 25 °C, 120 s; iv,  $\text{CF}_3\text{CO}_2\text{H}:\text{H}_2\text{O}$  9 : 1, 10 min ( $\times 2$ –solvent removed *in vacuo*).

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