

# Total synthesis of a diastereomer of the marine natural product clavosolide A

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The first total synthesis of the reported structure of the sponge metabolite clavosolide A is described using a Prins cyclisation to assemble the tetrahydropyran core followed by manipulation of the side-chain, dimerisation and finally glycosidation.

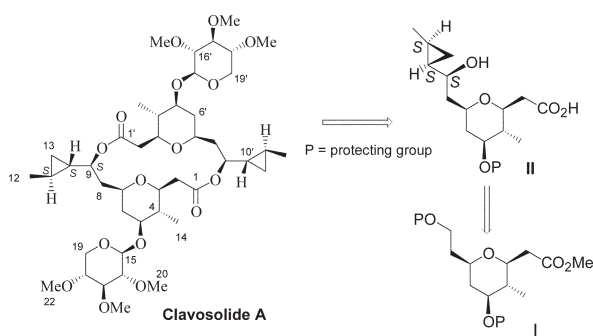
The clavosolides A–D are a family of unusual diolides which have been isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Phillipines.<sup>1</sup> The structure of clavosolide A was determined by use of extensive spectroscopic studies combined with molecular modelling. It is a symmetrical dimeric 16-membered ring dilactone assembled on a functionalised tetrahydropyran core with a permethylated D-xylose moiety. The macrocycle is further adorned by two cyclopropyl containing side-chains which were assigned 9*S*,9'*S*,10*S*,10'*S*,11*S*,11'*S*. Herein the first total synthesis of the reported structure of clavosolide A is described. The approach involved an efficient assembly of the tetrahydropyran core **I** via a Prins cyclisation followed by elaboration of the side-chain to **II**, then dimerisation and finally glycosidation (Scheme 1).

Clavosolide A shares a common tetrahydropyran core with the marine metabolite, polycavernoside A<sup>2</sup> and recently we have reported the enantioselective synthesis of tetrahydropyran **2** (Scheme 2).<sup>3</sup> The key steps were a stereoselective crotyl transfer reaction en route to the (*S*)-enol ether **1** followed by a TFA mediated cyclisation to create the 3 new asymmetric centres in the tetrahydropyran with complete stereocontrol in a single-pot process. This approach was adopted for the synthesis of the tetrahydropyran core of clavosolide A reported herein. The TIPS

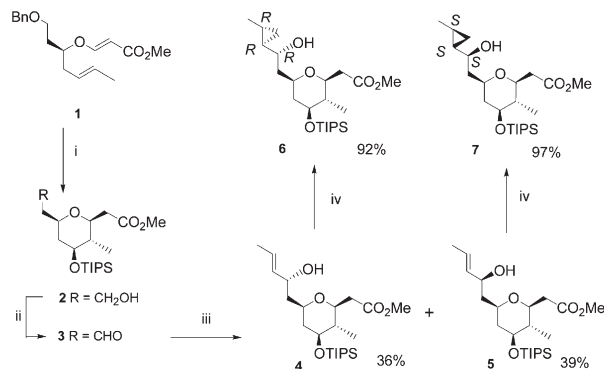
protecting group proved to be the best for later stages of the synthesis and alcohol **2** was prepared in 86% overall yield from enol ether **1**.

To install the required side chain which would become C-9 to C-13 of clavosolide A, a propenylation step to an (*E*)-allylic alcohol followed by a directed cyclopropanation were favoured. First alcohol **2** was oxidised to the known aldehyde **3**<sup>2b</sup> using Dess–Martin periodinane.<sup>4</sup> Nozaki–Hiyama–Kishi<sup>5</sup> coupling of **3** with *E*-1-bromo-1-propene in the presence of CrCl<sub>2</sub> and catalytic NiCl<sub>2</sub> gave a 1 : 1 mixture of allylic alcohols **4** and **5** which were separated by column chromatography. This approach gave exclusively the (*E*)-alkenes as apparent from the characteristic *trans* coupling constant (*J* 15 Hz) of the signals assigned to the olefinic protons in the <sup>1</sup>H-NMR spectrum of each. The lack of stereocontrol was advantageous as it gave access to both diastereomers required for confirmation of the structure of the target compound.

The final carbon–carbon bond forming reaction in the synthesis of clavosolide A required a stereoselective cyclopropanation. Charette reported that reaction of acyclic (*E*)-allylic alcohols with Et<sub>2</sub>Zn and CH<sub>2</sub>I<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> gives preferentially *syn*-directed cyclopropanation.<sup>6</sup> Thus allylic alcohols **4** and **5** were treated separately under Charette's conditions giving **6** and **7** in excellent yields and diastereoselectivities. However, since none of the compounds **4–7** or simple derivatives were crystalline, at this stage it was not possible to unequivocally assign the structures of the diastereomers **6** and **7**. Thus each was converted separately to the analogous dimeric lactones **11** and **15** respectively.



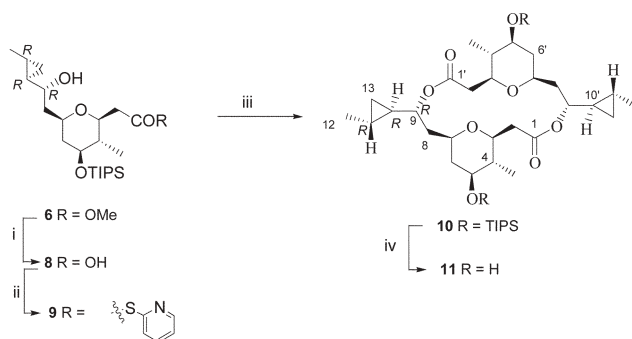
Scheme 1 Retrosynthesis of the reported structure of clavosolide A.



Scheme 2 Preparation of alcohols **6** and **7**.  
i, a, TFA, DCM; b, K<sub>2</sub>CO<sub>3</sub>, MeOH; c, TIPSCl, DMF, imid.; d, H<sub>2</sub>, Pd-C, EtOH (86%);<sup>3</sup> ii, Dess Martin periodinane (88%); iii, *E*-1-bromo-1-propene, CrCl<sub>2</sub>, NiCl<sub>2</sub>, DMF; iv, Et<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

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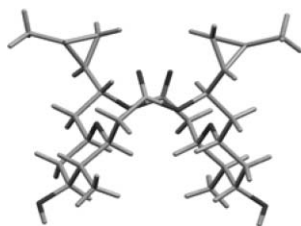


i, TMSONa, CH<sub>2</sub>Cl<sub>2</sub> then AcOH (87%); ii, 2,2'-bipyridyl disulfide, Ph<sub>3</sub>P, toluene (94%); iii, Δ, toluene (56%); iv, TBAF, THF (73%).

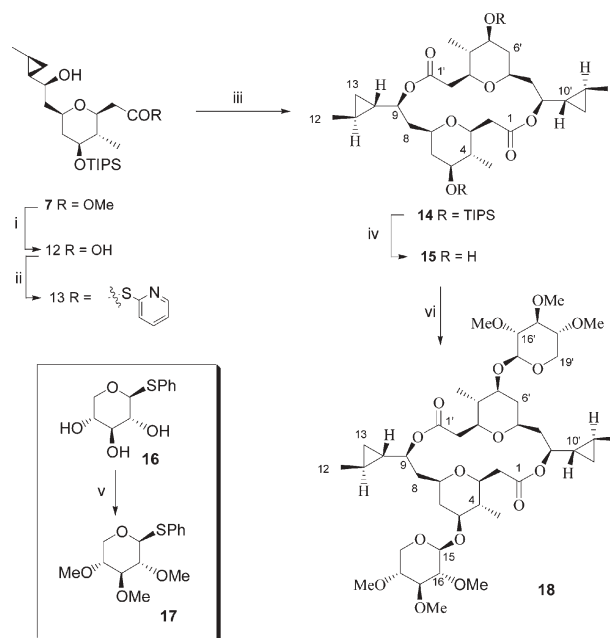
**Scheme 3** Synthesis of dimer **11**.

First methyl ester **6** was hydrolysed to hydroxy acid **8** in 87% yield under mild conditions using TMSONa (Scheme 3). It was then necessary to effect the dimerisation of **8** which we anticipated may be achieved without resorting to a multi-step strategy requiring protecting groups, as intramolecular lactonisation of **8** would not be favoured. Several macrolactonisation procedures were investigated and the Corey–Nicolaou protocol met with the greatest success.<sup>7</sup> Treatment of hydroxy acid **8** with 2,2'-bipyridyl disulfide and Ph<sub>3</sub>P gave 2-pyridine thiol ester **9** which, on refluxing in toluene, led to the required dimer **10** in 56% yield based upon recovered starting material **9**. High resolution electrospray MS confirmed that **10** was indeed a dimer. However none of compounds **8**, **9** and **10** were crystalline and so we were still faced with the issue of the unequivocal assignment of the stereochemistry at C-9(9'), C10(10') and C-11(11').

Deprotection of **10** using TBAF gave the required diol **11** as a crystalline solid in 73% yield. X-Ray analysis of **11** revealed a folded structure with the C<sub>2</sub> symmetric dimer adopting a conformation in which the cyclopropyl groups point towards each other (Fig. 1).<sup>8</sup> Thus this dimer is the 9*R*,9'*R*,10*R*,10'*R*,11*R*,11'*R* diastereomer confirming that the secondary alcohol **4** had the 9*R* configuration and that the stereoselective cyclopropanation of allylic alcohol **4** had indeed proceeded as expected with *syn*-stereocontrol giving cyclopropanol **6** (Scheme 2). The proposed structure of clavosolide A, with the 9*S*,9'*S*,10*S*,10'*S*,11*S*,11'*S* stereochemistry, had been assigned from spectroscopic studies alongside molecular modelling which revealed that the macrolide was relatively flat.<sup>1</sup> The <sup>1</sup>H-NMR spectrum of dimer **11** is significantly different from that of the natural product consistent with the distinct conformation of each macrodiolide.<sup>9</sup>



**Fig. 1** X-Ray structure of **11**.



i, TMSONa, CH<sub>2</sub>Cl<sub>2</sub> then AcOH (97%); ii, 2,2'-bipyridyl disulfide, Ph<sub>3</sub>P, toluene (97%); iii, Δ, toluene (57%); iv, TBAF, THF (85%); v, NaH, MeI, DMF (92%); vi, **17**, NBS, DCM (10%).

**Scheme 4** Synthesis of the reported structure of clavosolide A.

To complete the total synthesis of clavosolide A it was necessary to submit 9*S*-allylic alcohol **7** to the same sequence of reactions as used in the preparation of diolide **11**. Hydrolysis of ester **7** gave acid **12**, macrolactonisation followed by deprotection of the silyl ether **14** gave diolide **15** in 45% overall yield from **7** (Scheme 4). The stage was now set for the final transformation—the introduction of two permethylated D-xylose moieties. Due to concerns about the stability of the potentially labile cyclopropyl and ester functionalities, a mild method was selected involving thioglycoside trimethyl ether **17** as the glycosyl donor. Although this approach would give a mixture of [α,α], [α,β] and [β,β]-anomers, the target molecule **18** would be formed directly with no need for further manipulation of this highly functionalised dimer.

The known triol **16** was prepared from D-xylose following literature procedures.<sup>10</sup> Permethylation of **16** using NaH and MeI gave the novel thioglycoside **17** in 92% yield. Finally reaction of **17** with diol **15** using Nicolaou's NBS-mediated glycosylation protocol<sup>11</sup> gave the expected mixture of [α,α], [α,β] and [β,β]-anomers (17%, 26%, 10% respectively) which were separated by column chromatography and their structures assigned by <sup>1</sup>H-NMR spectroscopy. In the required [β,β]-anomer **18**, the signal assigned to 15-H (and 15'-H) appeared as a doublet (*J* 7.5 Hz) at δ 4.27 ppm consistent with an axial–axial relationship of 15-H and 16-H whereas in the [α,α]-anomer, the analogous signal appeared further downfield at δ 5.06 ppm as a doublet with the expected smaller coupling constant (*J* 3 Hz) in accord with an axial–equatorial coupling.

Synthetic dimer **18** was isolated as an oil and its <sup>13</sup>C-NMR spectrum correlated well with that of the natural product (Table 1). However whilst there was a very good correlation of the <sup>1</sup>H-NMR spectra of clavosolide A and **18** in the region δ 1.0–4.5 ppm, the signals assigned to the cyclopropyl protons were clearly different.

**Table 1** Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of synthetic dimer **18** and clavosolide A in  $\text{CDCl}_3$  (coupling constants reported to the nearest 0.5 Hz)

	$\delta_{\text{C}}$ (ppm)		$\delta_{\text{H}}$ (ppm)	
	Clav A <sup>1a</sup>	<b>18</b>	Clav A <sup>1a</sup>	<b>18</b>
<b>1</b>	170.7	171.0		
<b>2</b>	39.3	39.3	2.41 dd 17.5, 7 2.55 dd 17.5, 3	2.41 dd 17.5, 6.5 2.55 dd 17.5, 4
<b>3</b>	77.0 <sup>a</sup>	77.2	3.42 m	3.48 m
<b>4</b>	42.6	42.6	1.38 m	1.37 tq 10, 6.5
<b>5</b>	83.1	83.2	3.25 t 11.5	3.25 m
<b>6</b>	40.8	40.8	1.37 q 11.5 2.05 dd 11.5, 5	1.39 q 11.5 2.05 dd 11.5, 5
<b>7</b>	74.8	74.8	3.42 m	3.50 m
<b>8</b>	41.1	41.8	1.66 br d 15 1.87 dt 15, 9	1.71 br d, 15 1.92 dt 15, 9
<b>9</b>	77.1 <sup>a</sup>	77.0	4.41 br t 9	4.41 td 9, 1
<b>10</b>	24.8	24.9	0.72 tt 9, 5	0.70 tt 9, 4
<b>11</b>	12.0	11.0	0.83 m	0.60 m
<b>12</b>	18.6	18.4	0.96 d 6.5	1.00 d 5.5
<b>13</b>	11.0	12.4	0.22 dt 8, 5 0.33 dt 8, 5	0.21 dt 8, 4 0.60 m
<b>14</b>	12.7	12.6	0.96 d 6.5	0.96 d 6.5
<b>15</b>	105.4	105.5	4.27 d 8	4.27 d 7.5
<b>16</b>	83.8	83.8	2.96 t 8	2.96 dd 9, 7.5
<b>17</b>	85.6	85.6	3.12 t 8	3.10 t 9
<b>18</b>	79.4	79.4	3.25 td 8, 5	3.25 m
<b>19</b>	63.2	63.2	3.10 dd 11, 8 3.96 dd 11, 5	3.09 dd 11.5, 10 3.96 dd 11.5, 5
<b>20</b>	60.7	60.8	3.57 s	3.58 s
<b>21</b>	60.8	60.8	3.62 s	3.61 s
<b>22</b>	58.5	58.8	3.47 s	3.47 s

<sup>a</sup> Assignment may be reversed.

The chemical shifts of the signals ( $\delta$  0.22 and 0.33 ppm) assigned to 13(13')-H<sub>2</sub> of clavosolide A were much closer than in the case of the synthetic material ( $\delta$  0.21 and 0.60 ppm). In addition 11(11')-H in clavosolide A resonate 0.23 ppm downfield relative to the corresponding signal in **18**. Hence we propose that **18** is a diastereomer of the natural product.

The original structure elucidation of clavosolide A was conducted on a small quantity of material (extracted and purified from the sponge *M. clavosa*) and was a challenging problem considering the density of functionality within the molecule.<sup>1</sup> The *trans* stereochemistry about the cyclopropyl group was based on NOE data and coupling constants ( $J_{10,11}$  5 Hz); as expected the synthetic dimer **18** prepared from the *E*-allylic alcohol **5** gave a similar coupling constant,  $J_{10,11}$  4 Hz. The absolute stereochemistry of clavosolide A had been assigned on the assumption that the xylose moiety has the usual D-configuration. The close correlation of the  $^1\text{H}$ -NMR data of the natural product and **18** in the region  $\delta$  1.0–4.5 ppm as well as the  $^{13}\text{C}$ -NMR data are in accord with the proposed relative stereochemistry of the sugar moiety and macrocycle. Hence on the basis of the synthetic and spectroscopic studies reported herein combined with further analysis of molecular models, we propose that the structure of the tetrahydropyran core of clavosolide A is as reported<sup>1</sup> (*i.e.* 3*S*,3'*S*,4*R*,4'*R*,5*S*,5'*S*,7*S*,7'*S*) but the cyclopropyl side-chains

have the 9*S*,9'*S*,10*R*,10'*R*,11*R*,11'*R* configuration rather than the proposed<sup>1</sup> 9*S*,9'*S*,10*S*,10'*S*,11*S*,11'*S*.

In conclusion we have completed the first total synthesis of the reported structure for clavosolide A and found that it is in fact a diastereomer of the natural product. A revised structure of the natural product is proposed which awaits further verification by total synthesis.<sup>12</sup> This is currently under investigation.

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## Notes and references

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- Crystal data for 11*: C<sub>28</sub>H<sub>48</sub>O<sub>10</sub>,  $M = 544.66$ , monoclinic,  $a = 20.351(4)$ ,  $b = 8.8020(18)$ ,  $c = 8.8390(18)$  Å,  $\beta = 100.07(3)^\circ$ ,  $V = 1558.9(6)$  Å<sup>3</sup>,  $T = 100(2)$ , space group C2,  $Z = 2$ ,  $\mu = 0.087 \text{ mm}^{-1}$ ,  $R_{\text{int}} = 0.0249$  (for 12594 measured reflections),  $R_1 = 0.0589$  [for 1896 unique reflections with  $I > 2\sigma(I)$ ],  $wR_2 = 0.1447$  (for all 1919 unique 10 reflections). The absolute configuration of the molecule could not be determined from the X-ray. However, the absolute configuration of tetrahydropyran **2**, used for the synthesis of **11**, has been assigned previously<sup>3</sup> by comparison with the literature<sup>2b</sup>. CCDC 280355. See <http://dx.doi.org/10.1039/b509757f> for crystallographic data in CIF or other electronic format.
- Diolide **11**, mp: 175–177 °C;  $[\alpha]_{\text{D}} + 57.4$  ( $c$  1.5, CHCl<sub>3</sub>);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 0.23 (2H, dt,  $J$  8.5, 5, 13-HH and 13'-HH), 0.57 (2H, tt,  $J$  8.5, 5, 10-H and 10'-H), 0.67 (2H, m, 11-H and 11'-H), 0.88 (2H, dt,  $J$  8.5, 4.5, 13-HH and 13'-HH), 0.98 (6H, d,  $J$  6, 12-H<sub>3</sub> and 12'-H<sub>3</sub>), 1.03 (6H, d,  $J$  6.5, 14-H<sub>3</sub> and 14'-H<sub>3</sub>), 1.23 (2H, m, 4-H and 4'-H), 1.28 (2H, dt,  $J$  12, 11, 6-H<sub>ax</sub> and 6'-H<sub>ax</sub>), 1.48 (2H, d,  $J$  5.5, 2 × -OH), 1.65–1.78 (4H, m, 8-H<sub>2</sub> and 8'-H<sub>2</sub>), 1.95 (2H, ddd,  $J$  12.5, 4.5, 2, 6-H<sub>eq</sub> and 6'-H<sub>eq</sub>), 2.18 (2H, dd,  $J$  11.5, 0.5, 2-HH and 2'-HH), 2.62 (2H, dd,  $J$  12, 1.5, 2-HH and 2'-HH), 3.12 (2H, td,  $J$  11, 1.5, 3-H and 3'-H), 3.33–3.43 (4H, m, 5-H and 5'-H, 7-H and 7'-H), 4.45 (2H, ddd,  $J$  11.0, 8.5, 3, 9-H and 9'-H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 10.1 (C-11 and C-11'), 12.4 (C-13 and C-13'), 13.2 (C-14 and C-14'), 18.6 (C-12 and C-12'), 24.6 (C-10 and C-10'), 40.2 (C-2 and C-2'), 40.8 (C-8 and C-8'), 41.6 (C-6 and C-6'), 44.0 (C-4 and C-4'), 70.5 (C-5 and C-5'), 72.9 (C-9 and C-9'), 73.2 (C-7 and C-7'), 79.2 (C-3 and C-3'), 169.4 (C-1 and C-1');  $m/z$  (ESI): 531.2923 C<sub>28</sub>H<sub>44</sub>O<sub>8</sub> requires 531.2928.
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- Whilst clavosolide A is most likely derived from D-xylose and hence has the structure and absolute configuration proposed herein, at this stage it cannot be ruled out unequivocally that the natural product is the enantiomer of that proposed (*i.e.* derived from L-xylose). Once synthetic material is available, comparison of its optical rotation with that of the natural product,  $[\alpha]_{\text{D}} -48.5$  ( $c$  1, CHCl<sub>3</sub>),<sup>1a</sup> will verify the absolute configuration.