Biomimetic synthesis of marine sponge metabolite spiculoic acid A and establishment of the absolute configuration of the natural product†

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The synthesis of spiculoic acid A (1) using a biomimetic Diels–Alder reaction is described; comparison of the specific rotation of the natural and synthetic material revealed that the enantiomer of the natural product has been synthesized.

Spiculoic acid A (**1**) (Fig. 1) is a polyketide recently isolated from the extracts of the Caribbean marine sponge *Plakortis angulospiculatus* by Andersen *et al.*[1] Spiculoic acid A (**1**) was found to be optically active and its structure and relative stereochemistries were established based on a combination of NMR and mass spectrometry studies. Further activity assay showed that **1** is cytotoxic towards the human breast cancer MCF-7 cell line (IC_{50} 8 μg/mL).

At the time of its isolation and structure elucidation **1** was considered to be unprecedented due to its spiculane carbon skeleton. Six stereocentres reside within this relatively small bicyclic core, two of which are quaternary and adjacent to each other. A group of similar compounds were subsequently isolated from the marine sponge *Plakortis zyggompha*.[2]

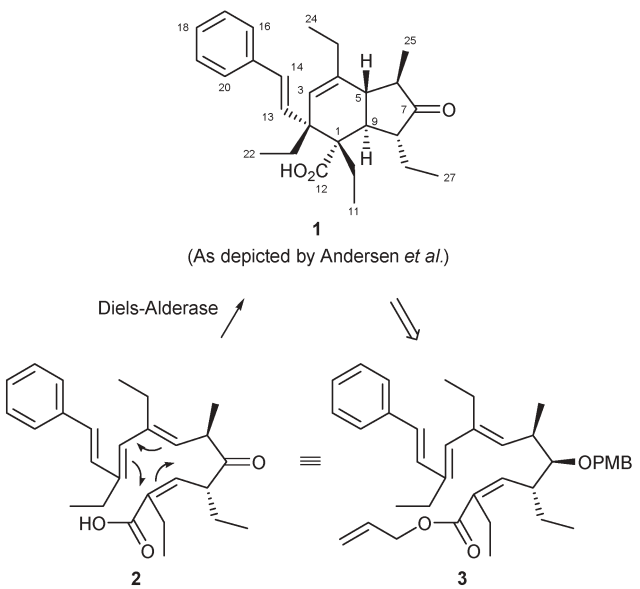
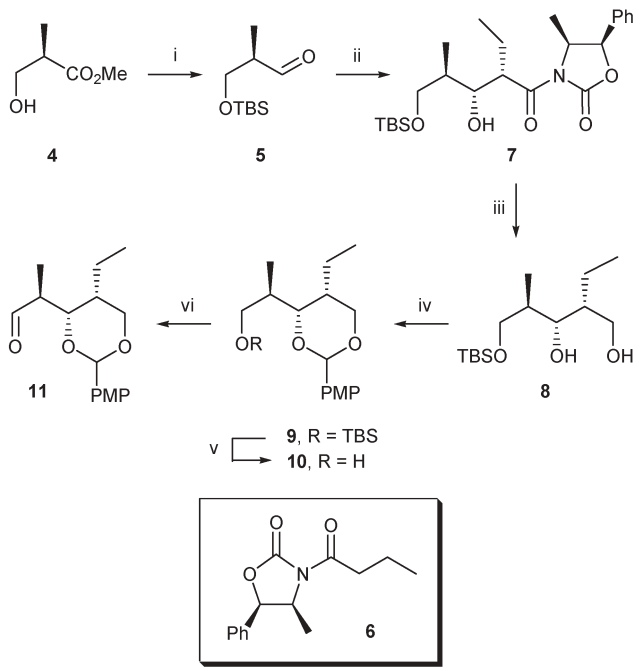


Fig. 1 Retrosynthetic analysis of spiculoic acid A (**1**).

Andersen *et al.* have proposed that **1** is biosynthesized from **2** through an enzyme catalysed Diels–Alder reaction (Fig. 1).[1,3] Our continued interest in biomimetic chemistry[4] prompted us to examine the application of this proposed intramolecular Diels–Alder reaction in the synthesis of **1**.[5] Herein we report the successful execution of our synthetic plan and the establishment of the absolute configuration of **1**. During the course of our investigation Mehta and Kundu disclosed a synthetic approach to **1** and prepared a highly truncated analogue of the natural product.[6]

Realizing the potential sensitivity of **2** we elected to use **3** as its surrogate. Since the absolute configuration of natural **1** was unknown, we decided to use the chiral structure of **1** depicted in Andersen's publication as our synthetic target. The synthesis of **3** commenced with the conversion of Roche ester **4** into aldehyde **5** in an overall yield of 98% by protection of the primary alcohol using imidazole and *tert*-butyldimethylsilyl chloride,[7] followed by reduction of the ester[8] to primary alcohol and oxidation to



Scheme 1 *Reagents and conditions*: (i) (a) TBSCl, imidazole, THF; (b) $LiBH_4$, THF, reflux; (c) DMSO, $(COCl)_2$, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 98% over three steps; (ii) **6**, $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 89%; (iii) $LiBH_4$, MeOH, H_2O, 73%; (iv) *para*-methoxybenzaldehyde dimethyl acetal, pyridinium tosylate, CH_2Cl_2, 96%; (v) TBAF, THF, 100%; (vi) IBX, THF, DMSO, 100%.

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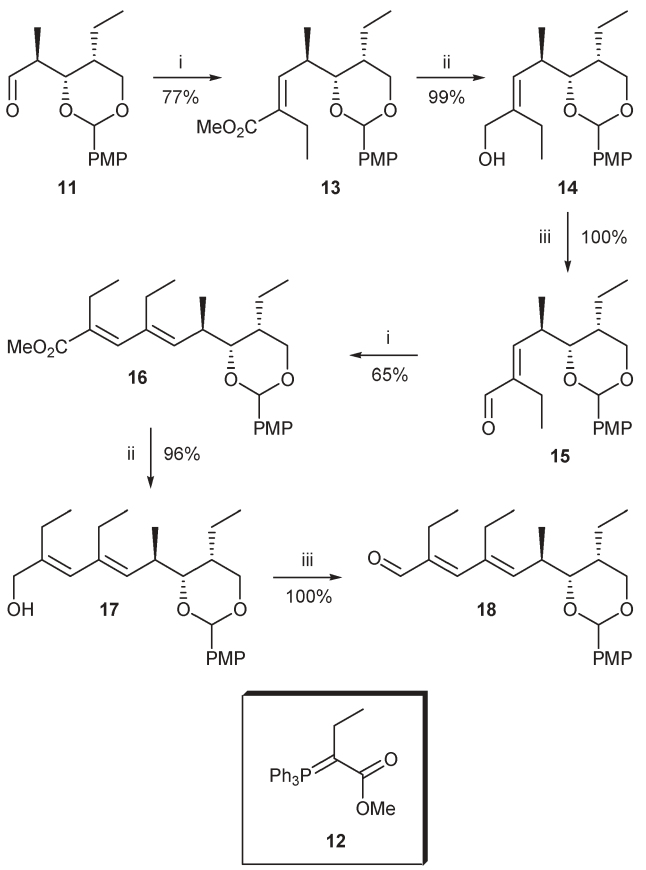
† Electronic supplementary information (ESI) available: ^1H, ^{13}C, DEPT, COSY, HSQC, NOESY and TOCSY NMR spectra for (−)-**1**. See DOI: 10.1039/b607035c

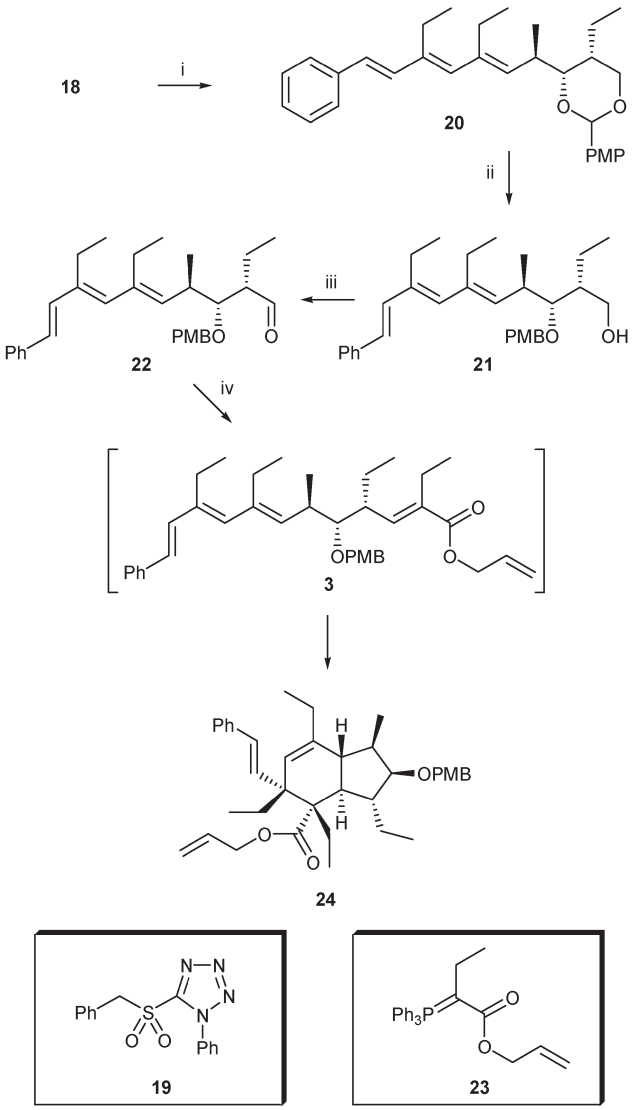
aldehyde **5** using Swern's conditions[9] (Scheme 1). Evans' aldol condensation[10] of **5** and oxazolidinone **6**[11] delivered secondary alcohol **7** in 89% yield. Reductive removal of the chiral auxiliary was effected with lithium borohydride in wet methanol[12] to afford diol **8** in 73% yield. Diol **8** was converted into *para*-methoxybenzylidene acetal **9** in 96% yield using *para*-methoxybenzaldehyde dimethyl acetal and a catalytic amount of pyridinium tosylate.[13] This was followed by removal of the TBS group with TBAF to afford primary alcohol **10** in quantitative yield, which was oxidized to aldehyde **11**, again in quantitative yield, using iodoxybenzoic acid (IBX).[14]

Wittig olefination of aldehyde **11** with stabilized ylide **12**[15] gave ester **13** in 77% yield (Scheme 2). The *E* stereochemistry of the double bond in **13** was confirmed by NOE studies. Ester **13** was reduced to alcohol **14** with lithium aluminium hydride[16] in 99% yield, which was oxidized to unsaturated aldehyde **15** by iodoxybenzoic acid (IBX) in quantitative yield. Treating aldehyde **15** with ylide **12** delivered the doubly conjugated ester **16** in 65% yield. Again, the geometry of the newly formed double bond was confirmed to be *E* by NOE experiment. Ester **16** was reduced to alcohol **17** in 96% yield, which was followed by oxidation to aldehyde **18** in 100% yield.

Aldehyde **18** was subjected to a Julia/Kocienski olefination[17] with benzylsulfone **19**[18] using lithium bis(trimethylsilyl)amide as base to give *E*,*E*,*E* triene **20** in 82% yield (Scheme 3). Reductive cleavage of the *para*-methoxybenzylidene acetal was effected with diisobutylaluminium hydride[13] to give primary alcohol **21** in 82%



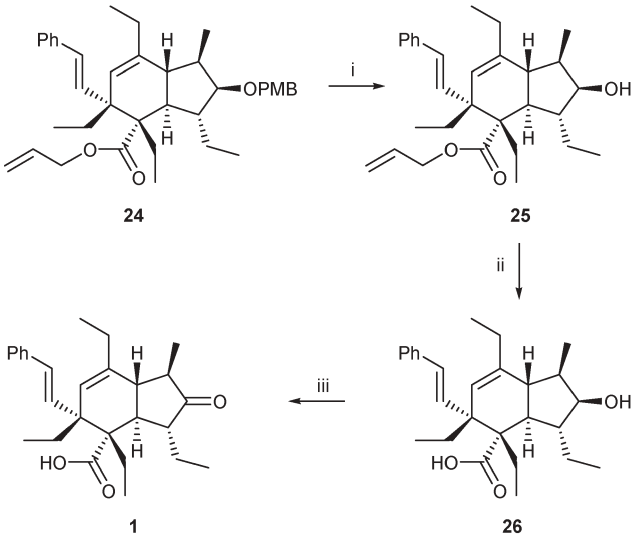
Scheme 2 *Reagents and conditions*: (i) **12**, toluene, 100 °C; (ii) $LiAlH_4$, THF, 0 °C; (iii) IBX, DMSO, THF.



Scheme 3 *Reagents and conditions*: (i) **19**, $LiN(TMS)_2$, THF, 82%; (ii) DIBAL, CH_2Cl_2, 82%; (iii) IBX, DMSO, THF, 80%; (iv) **23**, toluene, 100 °C, 25%.

yield, which was oxidized to aldehyde **22** in 80% yield with IBX. The final Wittig olefination in our synthesis was conducted by heating a mixture of aldehyde **22** with ylide **23**. Gratifyingly, this delivered bicyclic structure **24** directly in 25% yield. Presumably the desired Wittig reaction took place to afford **3**, which underwent a Diels–Alder reaction *in situ* to give **24**. We also isolated a 5–20% yield of an α,β-unsaturated aldehyde, which was formed by the E1cB elimination of *para*-methoxybenzyl alcohol from **22**.

The final stage of the synthesis of **1** began with removal of the *para*-methoxybenzyl protecting group from **24** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under buffered conditions[19] to afford secondary alcohol **25**, which was found to co-elute with the *para*-methoxybenzaldehyde formed in the DDQ deprotection during flash chromatography (Scheme 4). Therefore, this partially purified mixture was subjected to a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in the presence of excess morpholine[20] to remove the allyl ester. This delivered free acid **26** in a combined yield of 94% over two steps after chromatographic



Scheme 4 *Reagents and conditions*: (i) DDQ, CH_2Cl_2, pH 7 buffer; (ii) $(PPh_3)_4Pd$, morpholine, 94% over two steps; (iii) IBX, EtOAc, 70 °C, 45%.

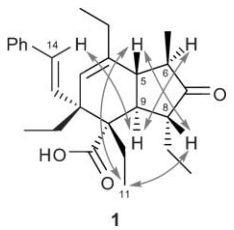


Fig. 2 Selected NOESY correlations of (−)-**1**.

purification. Finally, oxidation of **26** with IBX in hot ethyl acetate[21] gave spiculoic acid A (**1**) in 45% yield.

Extensive spectroscopic studies were conducted on compounds **24**, **25**, **26** and **1** to confirm their structures and relative stereochemistries. Analysis of the spectroscopic data for synthetic **1** gave an H-5/H-9 coupling constant of 11.8 Hz, indicating that both protons are axial and that the [4.3.0] bicycle is *trans*. NOESY studies indicated that the correct relative stereochemistry has been achieved *via* the Diels–Alder reaction (Fig. 2). The absolute stereochemistry of **1** was established through knowledge of the absolute configuration of the C-6 and C-8 stereocentres. The ^1H and ^{13}C NMR spectra of synthetic **1** were indistinguishable from those of the natural product.

The specific rotation of synthetic **1** ($[\alpha]_D^{22} = -97$, c = 0.16, CH_2Cl_2) is comparable in magnitude to that of natural **1** ($[\alpha]_D$ = +110, c = 0.1, CH_2Cl_2),[1] but of opposite sign. Therefore, we conclude that the absolute configuration of natural spiculoic acid A (**1**) is as depicted in Fig. 3.

In summary, we have demonstrated the application of a biomimetic strategy to the synthesis of spiculoic acid A (**1**) and through our synthesis have established the absolute configuration of the natural product. Analogues iso- (**27**), *nor*- (**28**) and *dinor*- (**29**) spiculoic acids A (Fig. 4), recently isolated from the marine sponge *Plakortis zyggompha*,[2] all possess specific rotations that are positive and large in value. Therefore, it is tempting to imply that the absolute configurations of these compounds are identical to that of (+)-**1**.

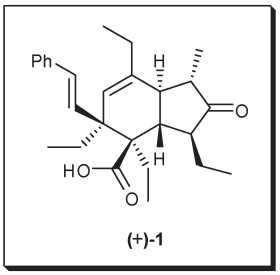
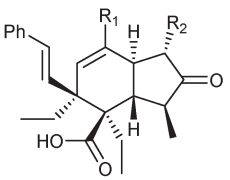


Fig. 3 Absolute configuration of natural spiculoic acid A (**1**).



Isospiculoic acid A (**27**) R_1 = Et, R_2 = Et
Nor-spiculoic acid A (**28**) R_1 = Et, R_2 = Me
Dinor-spiculoic acid A (**29**) R_1 = Me, R_2 = Me

Fig. 4 Speculated absolute configurations of iso- (**27**), *nor*- (**28**) and *dinor*-spiculoic acids A (**29**).

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