# Triterpenoid total synthesis. Part 4.[1] Synthesis of (±)-hippospongic acid A, a triterpene isolated from the marine sponge *Hippospongia* sp.

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Hippospongic acid A (**1**), a triterpene metabolite of a marine sponge *Hippospongia* sp. with inhibitory activity against gastrulation of starfish embryos, was synthesized as its racemate by starting from (2*E*,6*E*)-farnesol (**2**).

## Introduction

In 1996 hippospongic acid A (**1**), a triterpene with inhibitory activity for gastrulation of starfish embryos, was isolated by Ohta and co-workers from a marine sponge *Hippospongia* sp.[2] In 1998 the planar structure of **1** was revised and the absolute stereochemistry was determined as shown in Scheme 1 by the syntheses achieved by the same group.[3] Due to gastrulation being a fundamental process for multicellular animals and there being only a few selective inhibitors of it, **1** is a remarkable and unique natural product. In addition, the structure of **1**, which possesses a tetrahydropyran ring and an α-methylene carboxylic acid moiety on a triterpenoid skeleton, is rather unusual. We therefore became interested in synthesizing **1** as a part of our synthetic work on marine natural products.[1,4] Herein we describe our synthesis of (±)-hippospongic acid A (**1**) in detail.

## Results and discussion

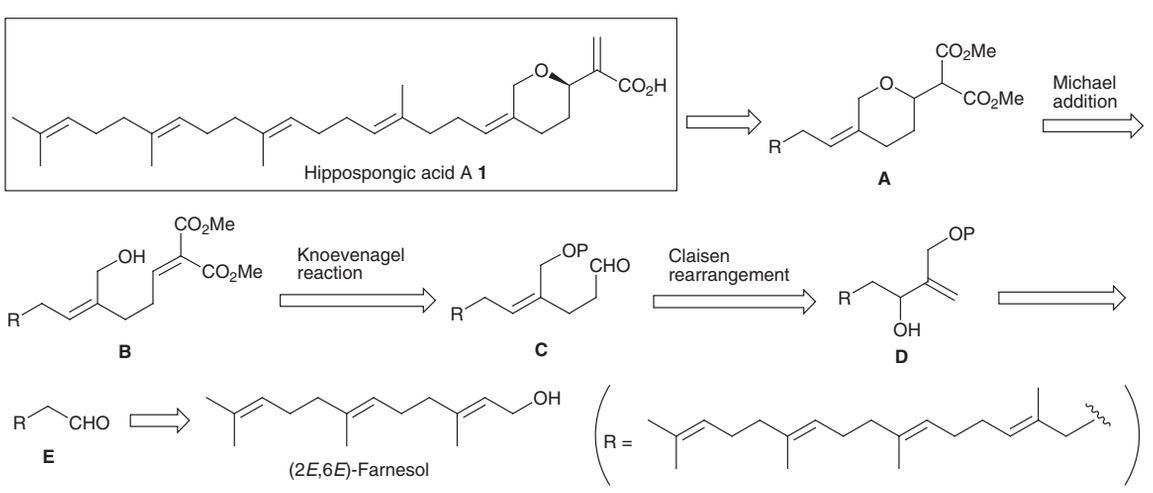
### Synthetic plan

Scheme 1 shows our synthetic plan for **1**. For preparation of the α-methylene carboxylic acid portion, the malonate derivative **A** was thought to be an appropriate intermediate. To construct the tetrahydropyran ring, we adopted an intramolecular Michael addition strategy employing **B** as the precursor. It was envisaged that the Michael acceptor **B** could be synthesized by Knoevenagel reaction of **C** with dimethyl malonate. It was hoped that the aldehyde **C** could be prepared by Claisen rearrangement of **D**, obtainable from the aldehyde **E**. The known aldehyde **E**, the starting material, is easily synthesized by starting from (2*E*,6*E*)-farnesol **F**.

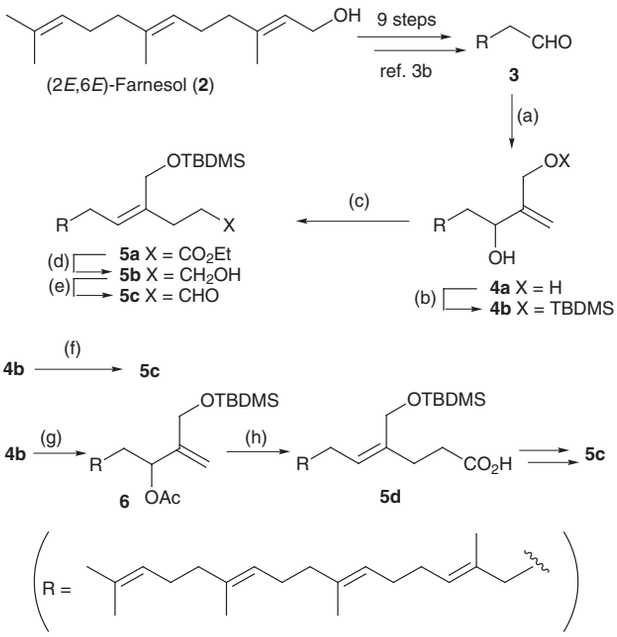
### Synthesis of hippospongic acid A

Our synthetic plan was realized as shown in Scheme 2. First we aimed at synthesizing the known aldehyde **3** (= **E**). Although several papers concerning the synthesis of **3** have been reported,[5,6] all of their methods seemed to be unsuitable for multi-gram scale synthesis. We therefore developed a new approach to **3**. However, our methodology turned out to be almost identical with that of Tokumasu *et al.*,[3b] which was reported very recently. Nevertheless, we could prepare **3** and continued our synthesis as shown in Scheme 2. The aldehyde **3** was treated with the *O*,2-dilithio derivative of allyl alcohol, $H_2C{=}C(Li)CH_2OLi$,[7] to afford **4a** (94%). The selective protection of the primary hydroxy group of **4a** as the TBDMS ether yielded **4b** (= **D**) in 91% yield. The allyl alcohol **4b** was subjected to Claisen rearrangement under Johnson's conditions[8] to give the ester **5a**, which was immediately reduced with DIBAL-H to afford **5b** in 69% yield (2 steps). The *Z*:*E* ratio was estimated to be 96:4 by $^1$H-NMR analysis. Oxidation of **5b** with Dess–Martin periodinane[9] gave **5c** (= **C**) in 78% yield. In this reaction sequence, replacement of the TBDMS protecting group with the TBDPS group provided no remarkable improvement.

We also examined other Claisen rearrangement conditions. An attempt to obtain **5c** directly from **4b** by the classical pro-




**Scheme 1** Structure and retrosynthetic analysis of hippospongic acid A.

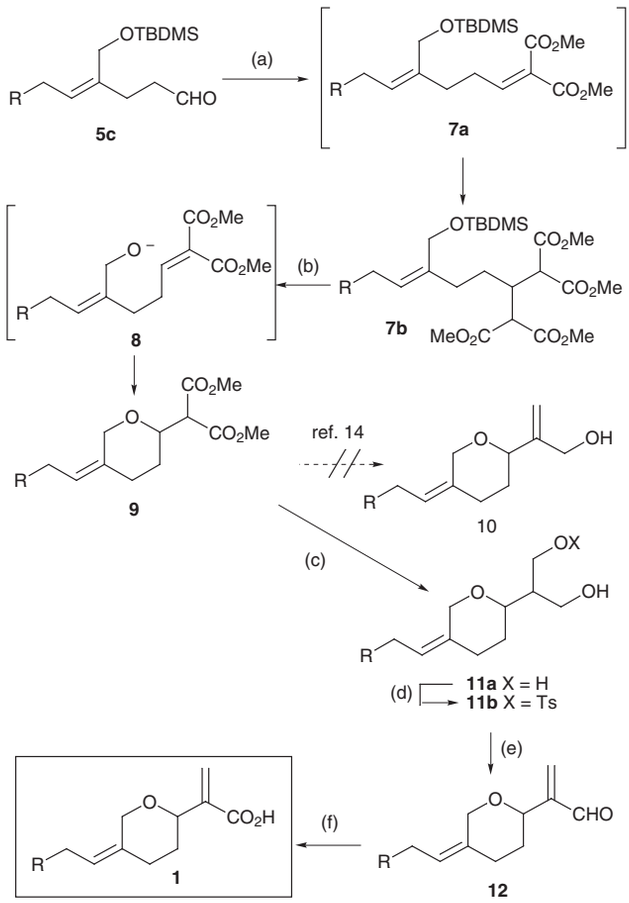



**Scheme 2** Synthesis of hippospongic acid A–(1). *Reagents*, *conditions and yields*: (a) 2-bromoallyl alcohol, Bu$^t$Li, $Et_2O$, (94%); (b) TBDMSCl, DMAP, $Et_3N$, $CH_2Cl_2$ (91%); (c) $CH_3C(OEt)_3$, propionic acid, 138 °C; (d) DIBAL-H, $CH_2Cl_2$ (69%, 2 steps); (e) Dess–Martin periodinane, $CH_2Cl_2$ (78%); (f) $Hg(OAc)_2$, ethyl vinyl ether, heat (52%); (g) $Ac_2O$, pyridine (89%); (h) LDA, TBDMSCl, HMPA, THF; aq. $K_2CO_3$, MeOH, THF (94%).

cedure[10] was not successful, because although the product was obtained, the $Z:E$ ratio was *ca*. 2:1. We then tried to utilize the Ireland enol ester Claisen rearrangement.[11] The alcohol **4b** was converted into the corresponding acetate **6**, which was subjected to Ireland Claisen rearrangement conditions followed by hydrolysis[12] to give **5d**. Although the efficiency of rearrangement was better than former attempts ($Z:E = 98:2$; 94% yield), three additional steps were required to convert **5d** into **5c**. Judging from the view of overall efficiency, therefore, we chose the first procedure as the most appropriate one.

The resulting aldehyde **5c** was employed in the Knoevenagel reaction. To our surprise, treatment with 1.5 eq. of dimethyl malonate in the presence of piperidinium acetate[13] gave a mixture of **5c**, **7a** and **7b** as shown in Scheme 3, in which **7b** was the predominant product (~ 60%). The unexpected adduct **7b** was thought to be produced by Michael addition of dimethyl malonate to the usual Knoevenagel reaction product **7a**. At this stage, we decided to prepare **7b** preferentially, because the key intermediate **7a** or **8** (= **B**) was thought to be obtainable from **7b** by retro-Michael type elimination of one dimethyl malonate. By treatment with 2.5 eq. of dimethyl malonate, **5c** was converted into **7b** in 75% yield. Conversion of **7b** to **7a** or its equivalent was achieved by treatment with TBAF to afford the desired ring-closure adduct **9** (= **A**) in 88% yield. It was deduced easily that not only deprotection of the TBDMS group but also our expected elimination of one malonate took place and the resulting **8** underwent intramolecular Michael addition to construct the tetrahydropyran ring.

The remaining objective was to construct the α-methylene carboxylic acid moiety. We initially attempted to convert **9** into **10** by Marshall's methodology.[14] However, the desired allylic alcohol **10** could not be obtained. We therefore adopted a stepwise procedure as follows. The reduction of **9** with LAH followed by mono-tosylation[15] afforded the tosylate **11b** in 58% yield (2 steps). This was then oxidized with PCC, together with β-elimination of the tosyloxy group, to give aldehyde **12** in 63% overall yield. Finally, further oxidation of **12** with sodium chlorite[16] gave (±)-hippospongic acid A (**1**) as a colorless oil in quantitative yield. The overall yield of **1** was 13% based on **3** in




**Scheme 3** Synthesis of hippospongic acid A–(2). *Reagents*, *conditions and yields*: (a) dimethyl malonate, piperidinium acetate (75%); (b) TBAF, THF (88%); (c) LAH, $Et_2O$ (74%); (d) Bu$^n$Li, THF, TsCl (78%); (e) PCC, NaOAc, $CH_2Cl_2$ (63%); (f) $NaClO_2$, $NaH_2PO_4$ 2-methylbut-2-ene, aq. Bu$^t$OH (quant.).

11 steps. The $^1$H- and $^{13}$C-NMR as well as IR and MS spectra of (±)-**1** were in good accord with those previously reported.[2,3]

In conclusion, the synthesis of (±)-hippospongic acid A (**1**) was achieved by starting from the known aldehyde **3**, which was easily prepared from (2*E*,6*E*)-farnesol.

## Experimental

IR spectra were measured as films for oils on a JASCO A-102 spectrometer. $^1$H-NMR spectra were recorded at 90 MHz on a JEOL JNM-EX 90A spectrometer, at 400 MHz on a JEOL JNM-LA400 spectrometer and at 500 MHz on a JEOL JNM-LA500. The peak for TMS or $CHCl_3$ (at $\delta_H = 7.26$) was used for the internal standard. *J* Values are given in Hz. The $^{13}$C-NMR spectrum was recorded at 126 MHz on a JEOL JNM-LA500. The peak for $CDCl_3$ (at $\delta_C = 77.0$) was used as an internal standard. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

### (6*E*,10*E*,14*E*)-6,11,15,19-Tetramethyl-2-methyleneicosa-6,10,14,18-tetraene-1,3-diol 4a

To a solution of 2-bromoallyl alcohol (276 mg, 2.02 mmol) in diethyl ether (30 cm$^3$) was added slowly Bu$^t$Li (1.48 mol dm$^{-3}$ in pentane; 3.52 cm$^3$, 5.05 mmol) at −78 °C under Ar. This mixture was quickly warmed to 0 °C and stirred for 3.5 h. The *aldehyde* **3** (212 mg, 0.670 mmol) was added to the solution and stirring was continued at 0 °C for 1 h. The reaction mixture was quenched with methanol and water, and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure.

The residue was chromatographed on $SiO_2$ to give the *diol* **4a** (235 mg, 94%) as a colorless oil; $n_D^{25}$ 1.4992 (Found: C, 80.44; H, 11.00. $C_{25}H_{42}O_2$ requires 80.16; H, 11.30%); $\nu_{max}$(film)/cm$^{-1}$ 3350s (O–H); $\delta_H$(90 MHz; $CDCl_3$) 1.60 (12H, s, 6-, 11-, 15- and 19-$CH_3$), 1.68 (3H, s, 20-$H_3$), 1.60–2.20 (18H, m, 4-, 5-, 8-, 9-, 12-, 13-, 16- 17-$H_2$ and OH), 4.26 (3H, br s, 1-$H_2$ and 3-H), 5.09 (6H, br s, 2-C=$CH_2$, 7-, 10-, 14- and 18-H).

### (6*E*,10*E*,14*E*)-1-*tert*-Butyldimethylsilyloxy-6,11,15,19-tetramethyl-2-methyleneicosa-6,10,14,18-tetraen-3-ol 4b

To a solution of **4a** (1.54 g, 4.11 mmol) in $CH_2Cl_2$ (10 cm$^3$), DMAP (151 mg, 1.23 mmol), triethylamine (0.86 cm$^3$, 6.2 mmol) and TBDMSCl (723 mg, 4.93 mmol) were added successively at 0 °C under Ar. After stirring at room temperature for 6 h, the mixture was quenched with water and extracted with $CHCl_3$. The extract was washed with saturated aq. $NH_4Cl$, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *TBDMS ether* **4b** (1.83 g, 91%) as a colorless oil; $n_D^{25}$ 1.4869 (Found: C, 75.94; H, 11.60. $C_{31}H_{56}O_2Si$ requires C, 76.16; H, 11.55%); $\nu_{max}$(film)/cm$^{-1}$ 3450s (O–H), 1260m (Si–Me); $\delta_H$(90 MHz; $CDCl_3$) 0.09 (6H, s, SiMe), 0.92 (9H, s, Si$^t$Bu), 1.60 (12H, s, 6-, 11-, 15- and 19-$CH_3$), 1.68 (3H, s, 20-$H_3$), 1.60–2.20 (16H, m, 4-, 5-, 8-, 9-, 12-, 13-, 16- and 17-$H_2$), 2.42 (1H, d, *J* 5.3, OH), 4.11 (1H, m, 3-H), 4.24 (2H, br s, 1-$H_2$), 5.07 (6H, br s, C=$CH_2$, 7-, 10-, 14- and 18-H).

### Ethyl (4*Z*,8*E*,12*E*,16*E*)-4-*tert*-butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaenoate 5a

To a solution of **4b** (4.01 g, 8.18 mmol) in ethyl orthoacetate (10.5 cm$^3$, 57.3 mmol) was added propionic acid (*ca*. 0.04 g, 0.5 mmol). This mixture was heated at 138 °C for 2 h, and ethanol was removed by distillation. After cooling to room temperature, the mixture was concentrated under reduced pressure to give the *crude ester* **5a** (*ca*. 4.6 g) as an oil; $\delta_H$(90 MHz; $CDCl_3$) 0.02 (6H, s, SiMe), 0.92 (9H, s, Si$^t$Bu), 1.60 (12H, s, 8-, 13-, 17- and 21-$CH_3$), 1.68 (3H, s, 22-$H_3$), 2.00 (18H, m, 3-, 6-, 7-, 10-, 11-, 14-, 15-, 18- and 19-$H_2$), 2.42 (2H, m, 2-$H_2$), 4.19 (4H, m, OC$H_2$CH$_3$ and $CH_2$OSi), 5.14 (5H, br s, 5-, 9-, 12-, 16- and 20-H). This *ester* was employed in the next step without purification.

### (4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaen-1-ol 5b

DIBAL-H (0.94 mol dm$^{-3}$ in hexane; 20.1 cm$^3$, 18.9 mmol) was added dropwise to a solution of **5a** (*ca*. 4.6 g) in dry $CH_2Cl_2$ (50 cm$^3$) at −78 °C under Ar. The reaction mixture was slowly warmed to 0 °C and stirred for 5 h. The resulting solution was quenched with MeOH (50 cm$^3$), filtered through Celite and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the recovered **4b** (0.48 g, 12%) and the *alcohol* **5b** (2.56 g, 69% based on the consumed **4b**, 2 steps) as a colorless oil; (*E*:*Z* = 4:96; determined by $^1$H-NMR), $n_D^{26}$ 1.4891 (Found: C, 76.34; H, 11.46. $C_{33}H_{60}O_2Si$ requires C, 76.68; H, 11.70%); $\nu_{max}$(film)/cm$^{-1}$ 3350s (O–H), 1260m (Si–Me); $\delta_H$(500 MHz; $CDCl_3$) 0.07 (6H, s, SiMe), 0.91 (9H, s, Si$^t$Bu), 1.60 (12H, s, 8-, 13-, 17- and 21-$CH_3$), 1.68 (3H, s, 22-$H_3$), 1.68–1.74 (2H, m, 2-H), 1.95–2.19 (19H, m, OH, 3-, 6-, 7-, 10-, 11-, 14-, 15-, 18- and 19-$H_2$), 3.63 (2H, s, 1-$H_2$), 4.06 [~ 0.08H, s, $CH_2$OSi due to (*E*)-isomer], 4.17 (2H, s, $CH_2$OSi), 5.07–5.16 (4H, m, 9-, 12-, 16- and 20-H), 5.26 (1H, t, *J* 7.0, 5-H).

### (4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaenal 5c

To a solution of Dess–Martin periodinane (67.7 mg, 0.160 mmol) in $CH_2Cl_2$ (2 cm$^3$) was added **5b** (16.4 mg, 0.0317 mmol) in $CH_2Cl_2$ (0.5 cm$^3$) at room temperature under Ar. After stirring for 30 min, the reaction mixture was diluted with diethyl ether and quenched with aq. $Na_2SO_3$ (10%, 1 cm$^3$), saturated aq. $NaHCO_3$ (1 cm$^3$) and extracted with diethyl ether. The extract was washed with saturated aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *aldehyde* **5c** (12.8 mg, 78%) as a colorless oil; $n_D^{26}$ 1.4878 (Found: C, 76.62; H, 11.43. $C_{33}H_{58}O_2Si$ requires C, 76.98; H, 11.35%); $\nu_{max}$(film)/cm$^{-1}$ 2710w (CHO), 1730s (C=O), 1260m (Si–Me); $\delta_H$(500 MHz; $CDCl_3$) 0.06 (6H, s, SiMe), 0.90 (9H, s, Si$^t$Bu), 1.59 and 1.60 (3H and 9H, each s, 8-, 13-, 17- and 21-$CH_3$), 1.68 (3H, s, 22-$H_3$), 1.95–2.13 (16H, m, 6-, 7-, 10-, 11-, 14-, 15-, 18- and 19-$H_2$), 2.43 (2H, t, *J* 7.3, 3-$H_2$), 2.55 (2H, dt, *J* 1.8 and 7.3, 2-$H_2$), 4.17 (2H, s, $CH_2$OSi), 5.07–5.16 (4H, m, 9-, 12-, 16- and 20-H), 5.22 (1H, t, *J* 7.3, 5-H), 9.75 (1H, t, *J* 1.8, CHO).

### Direct conversion of 4b to 5c

A mixture of **4b** (21 mg, 0.043 mmol) and $Hg(OAc)_2$ (4.1 mg, 13 mmol) in ethyl vinyl ether (1 cm$^3$) was stirred and heated under reflux for 12 h. *o*-Xylene (3 cm$^3$) was added to the mixture, and it was heated with removal of ethyl vinyl ether at 145 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *aldehyde* **5c** (11.4 mg, 52%) as a colorless oil (*E*:*Z* = *ca*. 1:2; determined by $^1$H-NMR); $\delta_H$(400 MHz; $CDCl_3$) 0.05 and 0.065 (total 6H, each s, SiMe), 0.89 (9H, s, Si$^t$Bu), 1.58 and 1.60 (3H and 9H, each s, 8-, 13-, 17- and 21-$CH_3$), 1.68 (3H, s, 22-$H_3$), 1.95–2.16 (16H, m, 6-, 7-, 10-, 11-, 14-, 15-, 18- and 19-$H_2$), 2.35–2.47 (2H, m, 3-$H_2$), 2.52–2.59 (2H, m, 2-$H_2$), 4.04 [2/3H, s, $CH_2$OSi due to (*E*)-isomer], 4.17 [4/3H, s, $CH_2$OSi due to (*Z*)-isomer], 5.07–5.16 (4H, m, 9-, 12-, 16- and 20-H), 5.22 [2/3H, t, *J* 7.1, 5-H due to (*Z*)-isomer], 5.41 [1/3H, t, *J* 7.1, 5-H due to (*E*)-isomer], 9.75 [2/3H, t, *J* 1.8, CHO due to (*Z*)-isomer], 9.77 [1/3H, br s, CHO due to (*E*)-isomer].

### (6*E*,10*E*,14*E*)-1-*tert*-Butyldimethylsilyloxy-6,11,15,19-tetramethyl-2-methyleneicosa-6,10,14,18-tetraen-3-yl acetate 6

To a solution of **4b** (33.6 mg, 0.0687 mmol) in pyridine (1 cm$^3$) was added $Ac_2O$ (0.05 cm$^3$, 0.5 mmol) at 0 °C. After stirring at room temperature overnight, the reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed with saturated aq. $CuSO_4$, water, saturated aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *acetate* **6** (32.5 mg, 89%) as a colorless oil; $n_D^{24}$ 1.4799 [Found: (HREI-MS) $M^+$, 530.4178. $C_{33}H_{58}O_3Si$ requires *M*, 540.4155]; $\nu_{max}$($CCl_4$)/cm$^{-1}$ 1740 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.07 (6H, s, SiMe), 0.91 (9H, s, Si$^t$Bu), 1.60 (12H, s, 6-, 11-, 15- and 19-$CH_3$), 1.68 (3H, s, 20-$H_3$), 1.60–2.20 (16H, m, 4-, 5-, 8-, 9-, 12-, 13-, 16- and 17-$H_2$), 2.04 (3H, s, Ac), 4.16 (2H, m, 1-$H_2$), 5.00–5.23 (7H, br s, C=$CH_2$, 3-, 7-, 10-, 14- and 18-H).

### (4*Z*,8*E*,12*E*,16*E*)-4-*tert*-Butyldimethylsilyloxymethyl-8,13,17,21-tetramethyldocosa-4,8,12,16,20-pentaenoic acid 5d

A solution of LDA was prepared from Pr$^i_2$NH (0.026 cm$^3$, 0.19 mmol) and Bu$^n$Li (1.53 mol dm$^{-3}$ in hexane; 0.11 cm$^3$, 0.17 mmol) in THF (0.5 cm$^3$) at 0 °C under Ar. After cooling to −78 °C, HMPA (0.01 cm$^3$) was added. To the resulting solution, **6** (29.8 mg, 0.0561 mmol) and TBDMSCl (9.3 mg, 0.062 mmol) in THF (0.5 cm$^3$) was added at −78 °C. After stirring at room temperature for 24 h, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in methanol (3 cm$^3$) and THF (1 cm$^3$), and $K_2CO_3$ (50 mg, 0.36 mmol) in water (0.5 cm$^3$) was added. It was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue

was diluted with brine, acidified (pH 4–5) with aq. $KHSO_4$ (1 mol $dm^{-3}$) and extracted with diethyl ether. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *carboxylic acid* **5d** (27.9 mg, 94%) as a slightly yellow oil ($E:Z = 2:98$; determined by $^1$H-NMR); $n_D^{25}$ 1.4915; $\nu_{max}(CCl_4)$/$cm^{-1}$ 3200–2800br ($CO_2H$), 1710s (C=O), 1260m (Si–Me); $\delta_H$(400 MHz; $CDCl_3$) 0.07 (6H, s, SiMe), 0.90 (9H, s, Si′Bu), 1.59 and 1.60 (3H and 9H, each s, 8-, 13-, 17- and 21-$CH_3$), 1.68 (3H, s, 22-$H_3$), 1.95–2.18 (16H, m, 6-, 7-, 10-, 11-, 14-, 15-, 18- and 19-$H_2$), 2.42 (2H, br t, *J* 7.5, 3-$H_2$), 2.51 (2H, br t, *J* 7.5, 2-$H_2$), 4.06 [~ 0.04H, s, $CH_2OSi$ due to (*E*)-isomer], 4.18 (2H, s, $CH_2OSi$), 5.05–5.18 (4H, m, 9-, 12-, 16- and 20-H), 5.28 (1H, t, *J* 7.1, 5-H); the proton due to carboxylic acid could not be observed.

**Dimethyl (3′*Z*,7′*E*,11′*E*,15′*E*)-3-(3′-*tert*-butyldimethylsilyloxymethyl-7′,12′,16′,20′-tetramethylhenicosa-3′,7′,11′,15′,19′-pentaen-1-yl)-2,4-bis(methoxycarbonyl)glutarate 7b**

To a solution of **5c** (947 mg, 1.84 mmol) in dimethyl malonate (0.53 $cm^3$, 4.6 mmol) was added piperidinium acetate (267 mg, 1.84 mmol). After stirring at room temperature for 20 h, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *ester* **7b** (1.04 g, 75%) as a colorless oil; $n_D^{27}$ 1.4870 (Found: C, 67.88; H, 9.42. $C_{43}H_{72}O_9Si$ requires C, 67.95; H, 9.42%); $\nu_{max}$(film)/$cm^{-1}$ 1760s (C=O), 1740s (C=O), 1260m (Si–Me), 1150 (C–O); $\delta_H$(500 MHz; $CDCl_3$) 0.06 (6H, s, SiMe), 0.89 (9H, s, Si′Bu), 1.59 and 1.60 (3H and 9H, each s, 7′-, 12′-, 16′- and 20′-$CH_3$), 1.68 (3H, s, 21′-$H_3$), 1.65–1.70 (2H, m, 1′-$H_2$), 1.95–2.13 (18H, m, 2′-, 5′-, 6′-, 9′-, 10′-, 13′-, 14′-, 17′- and 18′-$H_2$), 2.91 (1H, dt, *J* 6.1 and 6.1, 3-H), 3.72 (12H, s, $CO_2CH_3$), 3.82 (2H, d, *J* 5.8, 2- and 4-H), 4.11 (2H, s, $CH_2OSi$), 5.07–5.16 (4H, m, 8′-, 11′-, 15′ and 19′-H), 5.19 (1H, t, *J* 7.0, 4′-H); EI-MS *m*/*z* 760 ($M^+$).

**Dimethyl (5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]-malonate 9**

To a solution of **7b** (1.04 g, 1.37 mmol) in dry THF (15 $cm^3$) was added dropwise TBAF (1.0 mol $dm^{-3}$ in THF; 3.49 $cm^3$, 3.49 mmol) at room temperature. After stirring at room temperature for 18 h, the reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *ester* **9** (618 mg, 88%) as a colorless oil; $n_D^{26}$ 1.4983 (Found: C, 74.35; H, 10.17. $C_{32}H_{50}O_5$ requires C, 74.68; H, 9.79%); $\nu_{max}$(film)/$cm^{-1}$ 1760s (C=O), 1740s (C=O), 1160s ($CO_2R$); $\delta_H$(400 MHz; $CDCl_3$) 1.38–1.50 (1H, m, 3′-H), 1.56 and 1.60 (3H and 9H, each s, 4″-, 9″-, 13″- and 17″-$CH_3$), 1.68 (3H, s, 18″-$H_3$), 1.86 (1H, m, 3′-H), 1.95–2.15 (16H, m, 2″-, 3″-, 6″-, 7″-, 10″-, 11″-, 14″- and 15″-$H_2$), 2.25–2.33 (2H, m, 4′-$H_2$), 3.48 (1H, d, *J* 9.3, 2-H), 3.73 (3H, s, $CO_2Me$), 3.76 (3H, s, $CO_2Me$), 3.80 (1H, d, *J* 12.8, 6′-H), 4.07 (1H, ddd, *J* 11.0, 9.3 and 1.9, 2′-H), 4.58 (1H, d, *J* 12.8, 6′-CH), 5.07–5.16 (4H, m, 5″-, 8″-, 12″- and 16″-H), 5.18 (1H, t, *J* 8.0, 1″-H).

**(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]propane-1,3-diol 11a**

To a suspension of LAH (67.6 mg, 1.78 mmol) in diethyl ether (20 $cm^3$) was slowly added **9** (457 mg, 0.889 mmol) in diethyl ether (5 $cm^3$) at 0 °C. The resulting mixture was allowed to warm to room temperature with stirring overnight. The reaction mixture was quenched with water (0.07 $cm^3$), aq. NaOH (15%, 0.07 $cm^3$) and water (0.2 $cm^3$). The mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *diol* **11a** (302 mg, 74%) as a colorless gum (Found: C, 78.99; H, 11.21. $C_{30}H_{50}O_3$ requires C, 78.55; H, 10.99%); $\nu_{max}$(film)/$cm^{-1}$ 3400s (O–H); $\delta_H$(400 MHz; $CDCl_3$) 1.55–1.64 (1H, m, 3′-H), 1.59 and 1.60 (3H and 9H, each s, 4″-, 9″-, 13″- and 17″-$CH_3$), 1.68 (3H, s, 18″-$H_3$), 1.71–1.77 (2H, m, 2- and 3′-H), 1.94–2.20 (18H, m, 2″-, 3″-, 6″-, 7″-, 10″-, 11″-, 14″-, 15″-$H_2$ and OH), 2.23–2.35 (2H, m, 4′-$H_2$), 3.69 (1H, ddd, *J* 11.3, 5.2 and 2.1, 2′-H), 3.75 (1H, d, *J* 12.8, 6′-H), 3.79–3.87 and 3.95 (3H and 1H, m and dd, *J* 11.0 and 4.6, 1- and 3-$H_2$), 4.60 (1H, d, *J* 12.8, 6′-H), 5.08–5.13 (4H, m, 5″-, 8″-, 12″- and 16″-H), 5.19 (1H, t, *J* 6.6, 1″-CH).

**(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]-3-tosyloxypropan-1-ol 11b**

To a solution of **11a** (57.8 mg, 0.126 mmol) in dry THF (3 $cm^3$) was added dropwise Bu$^n$Li (1.53 mol $dm^{-3}$ in hexane; 0.086 $cm^3$, 0.13 mmol) at −78 °C under Ar. After the solution was slowly warmed to −15 °C, TsCl (26.8 mg, 0.141 mmol) was added. After stirring at −15 °C for 2 h, the reaction mixture was quenched with water and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *monotosylate* **11b** (60.6 mg, 78%) as a colorless oil. This was a mixture of (2*R**,2′*R**)- and (2*R**,2′*S**)-isomers (*ca.* 1:1); $n_D^{26}$ 1.5169; $\nu_{max}$(film)/$cm^{-1}$ 3400m (O–H), 1600m (aromatic), 1180s (S=O); $\delta_H$(500 MHz; $CDCl_3$) 1.40–1.49 (0.5H, m, 3′-H), 1.55–1.74 (1H, m, 3′-H), 1.57 and 1.60 (3H and 9H, each s, 4″-, 9″-, 13″- and 17″-$CH_3$), 1.68 (3H, s, 18″-$H_3$), 1.84 (0.5H, m, 2-H), 1.91–2.15 [18H, m, 2-H (0.5H), 3′-H (0.5H), 2″-, 3″-, 6″-, 7″-, 10″-, 11″-, 14″-, 15″-$H_2$ and OH], 2.17–2.34 (2H, m, 4′-$H_2$), 2.45 (3H, s, Ar-$CH_3$), 3.57 (0.5H, ddd, *J* 11.3, 6.0 and 2.1, 2′-H), 3.62–3.69 [2.5H, m, 1-H, 2′-H (0.5H) and 6′-H], 3.76 (0.5H, dd, *J* 11.3 and 4.9, 1-H), 3.83 (0.5H, dd, *J* 11.6 and 3.7, 1-H), 4.16 and 4.19–4.27 (0.5H and 1.5H, dd, *J* 9.9 and 5.8 and m, 3-$H_2$), 4.48 (0.5H, d, *J* 12.8, 6′-H), 4.53 (0.5H, d, *J* 12.8, 6′-H), 5.08–5.21 (5H, m, 1″-, 5″-, 8″-, 12″- and 16″-CH), 7.35 (2H, dd like, *J* 8.2 and 2.6, Ar-H), 7.80 (2H, br d, *J* 8.2, Ar-H).

**(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]prop-2-enal 12**

To a solution of **11b** (60.6 mg, 0.0970 mmol) in $CH_2Cl_2$ (5 $cm^3$), sodium acetate (108 mg, 1.32 mmol) and PCC (34.1 mg, 0.158 mmol) were added at room temperature. After stirring at room temperature for 5 h, the reaction mixture was filtered through $SiO_2$ and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give the *aldehyde* **12** (27.5 mg, 63%) as a colorless oil; $n_D^{25}$ 1.5036 (Found: C, 82.07; H, 10.33. $C_{30}H_{46}O_2$ requires C, 82.14; H, 10.57%); $\nu_{max}$(film)/$cm^{-1}$ 1700s (C=O), 1630w (C=C); $\delta_H$(500 MHz; $CDCl_3$) 1.25–1.35 (1H, m, 3′-H), 1.60 (12H, s, 4″-, 9″-, 13″- and 17″-$CH_3$), 1.68 (3H, s, 18″-$H_3$), 1.95–2.21 (17H, m, 3′-H and 2″-, 3″-, 6″-, 7″-, 10″-, 11″-, 14″- and 15″-$H_2$), 2.30 (1H, br d, *J* 13.5, 4′-H), 2.38 (1H, d, *J* 13.5, 4′-H), 3.87 (1H, d, *J* 12.5, 6′-CH), 4.33 (1H, d, *J* 11.0, 2′-H), 4.69 (1H, d, *J* 12.5, 6′-H), 5.07–5.18 (4H, m, 5″-, 8″-, 12″- and 16″-H), 5.21 (1H, t, *J* 6.9, 1″-H), 6.06 (1H, s, 2-C=CH), 6.54 (1H, s, 2-C=CH), 9.54 (1H, s, CHO).

**(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]prop-2-enoic acid [(±)-hippospongic acid A] 1**

To a solution of **12** (42.0 mg, 0.0957 mmol) in Bu$^t$OH (15 $cm^3$) and 2-methylbut-2-ene (1 $cm^3$), a mixture of 79% sodium chlorite (112 mg, 0.957 mmol) and $NaH_2PO_4$ (0.12 mg, 0.77 mmol)

in water (2 $cm^3$) was added dropwise over 10 min. The pale yellow solution was stirred at room temperature overnight. After removal of volatile components under reduced pressure, the residue was diluted with diethyl ether, acidified with dil. HCl and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ to give hippospongic acid A **1** (43.7 mg, quant) as a colorless oil; $n_D^{26}$ 1.5079 [Found: (HREI-MS) $M^+$, 454.3451. $C_{30}H_{46}O_3$ requires *M*, 454.3437]; $\nu_{max}$(film)/$cm^{-1}$ 3600–2600s ($CO_2H$), 1700s (C=O), 1640m (C=C), 1430s, 1380m, 1310w, 1290m, 1170w, 1080s, 1050m, 970m, 900w; $\delta_H$(500 MHz; $CDCl_3$) 1.47 (1H, m, 3′-H), 1.60 (12H, s, 4″-, 9″-, 13″- and 17″-$CH_3$), 1.68 (3H, s, 18″-$H_3$), 1.95–2.20 (17H, m, 3′-H, 2″-, 3″-, 6″-, 7″-, 10″-, 11″-, 14″- and 15″-$H_2$), 2.32–2.42 (2H, m, 4′-$H_2$), 3.91 (1H, d, *J* 12.8, 6′-H), 4.32 (1H, d, *J* 11.3, 2′-H), 4.72 (1H, d, *J* 12.8, 6′-H), 5.08–5.17 (4H, m, 5″-, 8″-, 12″- and 16″-CH), 5.24 (1H, t, *J* 7.0, 1″-CH), 5.93 (1H, s, 2-C=CH), 6.38 (1H, s, 2-C=CH); the proton due to carboxylic acid could not be observed; $\delta_C$(126 MHz; $CDCl_3$) 16.0, 16.1, 17.7, 25.6, 25.7, 26.7, 26.8, 28.21, 28.25, 32.9, 33.7, 39.7, 67.1, 75.6, 124.21, 124.24, 124.4, 124.89, 124.93, 127.1, 131.2, 132.5, 134.4, 134.9, 135.2, 140.7, 170.0.

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