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TETRAHEDRON

Diastereoselective Synthesis of Spongian Diterpenes.Total Synthesis of the Furanoditerpene (-)-spongia-13(16),14-diene.

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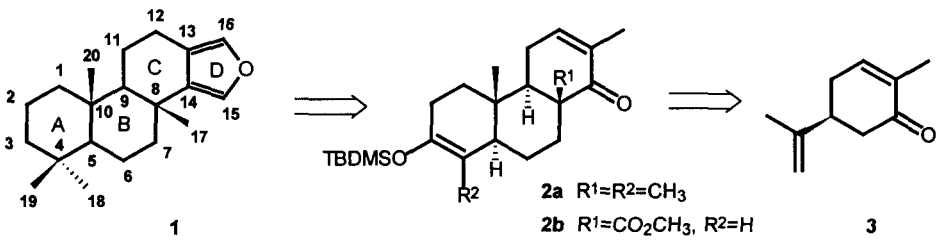
Abstract: An effective diastereoselective synthesis of the marine-sponge metabolite (-)-spongia-13(16),14-diene **1** is achieved starting from *S*-(+)-carvone *via* a homochiral phenanthrenone as the key intermediate for the construction of the furan ring system. *S*-(+)-Carvone was transformed into the phenanthrenone **2a** in six steps (53% overall yield), using an intramolecular Diels-Alder reaction as the key step. Conversion of the enone function in **2a** into an epoxyaldehyde function followed by cyclisation and aromatisation in acid conditions completed the construction of ring D.

Keywords: Marine metabolites; Synthesis; Furanoditerpenes; Sponges.

INTRODUCTION

An increasing number of diterpenes with the spongian carbon skeleton have been isolated from various marine organisms.[1] Several members of this family have shown many biological activities against a wide range of organisms, including microorganisms, invertebrates and vertebrates.[2] For the past few years our research group has developed several synthetic strategies towards the synthesis of some of these compounds.[3] As a starting material we have used (+)-podocarp-8(14)-en-13-one, which is easily obtained from natural sources.[4] Recently, we have developed a new synthetic approach which, starting from carvone, permits the synthesis of different enantiomerically pure phenanthrenone systems **2** (Scheme 1).[5]



1 3

Scheme 1

0040-4020/99/$ - see front matter
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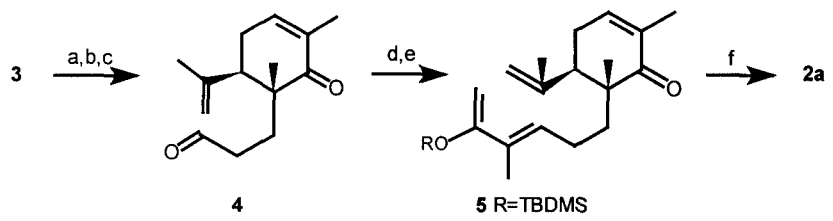
These compounds contain the tricyclic ABC-ring system characteristic of many spongian diterpenes, and a functionalisation which makes them useful as a starting material in the diastereoselective synthesis of spongian systems. They possess an enone group in the C-ring that can be used in the construction of the D-ring present in the spongian structure; in addition, the silyl enol ether in ring A can facilitate the introduction of an appropriate functionalisation in this ring.

In this paper we describe the diastereoselective total synthesis of the simplest member of the furanoditerpene spongian family, (-)-spongia-13(16)-14-diene **1**,[6] using as starting material the phenanthrenone **2a**. This tetracyclic diterpene, isolated from the sponges *Spongia officinalis*[7] and *Hyatella intestinalis*,[8] has been shown to have interesting antifungal activities.

RESULTS AND DISCUSSION

The synthesis of (-)-spongia-13(16),14-diene starts with the preparation, in which commercial *S*-(+)-carvone **3** is used, of the tricyclic intermediate **2a**,[9] which contains the two necessary methyl groups R^1,R^2 present in the target molecule (Scheme 2).

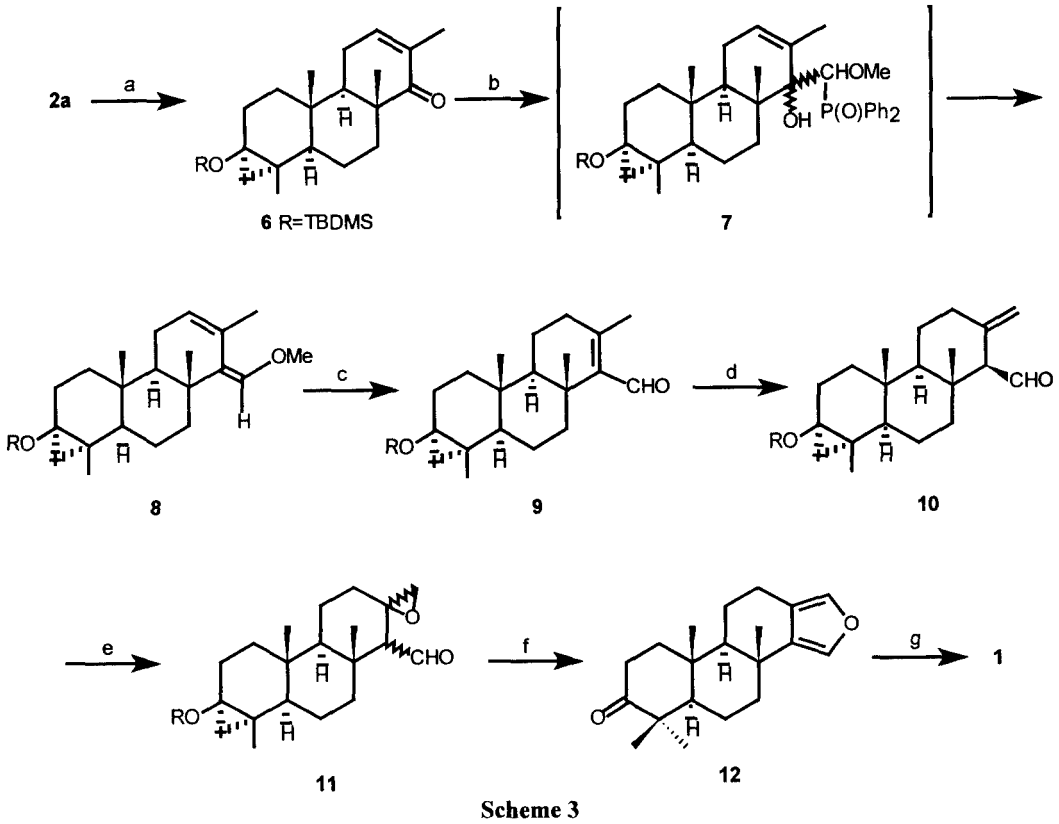


Scheme 2

Reagents and Conditions: a) LDA, THF, -10°C then MeI, 87%; b) LDA, THF, HMPA, -78°C then $ICH_2CH_2CH(OEt)_2$, 80%; c) PPTS, acetone-H_2O, reflux, 94%; d) $(EtO)_2P(O)C(Na)(Me)COMe$, THF, rt, 86%; e) Et_3N, TBDMSTf, CH_2Cl_2, -78°C, 98%; f) PhMe, propylene oxide, 190°C, 97%.

S-(+)-Carvone was transformed into the aldehyde **4** by double alkylation of its kinetic enolate, first with methyl iodide and then with 3-iodopropanaldehyde diethyl acetal. Subsequent removal of the acetal protecting group through PPTS in aqueous acetone yielded **4** diastereoselectively. Wittig reaction of aldehyde **4** with the α-phosphonate carbanion generated from diethyl 2-oxobutane-3-phosphonate and NaH in THF at room temperature gave an (*E*)-enone, which was then converted into the intramolecular Diels-Alder (IMDA) precursor **5** after undergoing treatment with TBDMS triflate and triethylamine in dichloromethane at -78°C. The IMDA reaction of **5** was carried out in toluene solution with a catalytic amount of propylene oxide at 190°C for seven days to give the *trans-anti-trans* fused adduct **2a**.

With the phenanthrenone **2a** in hand, the necessary structural changes for the functionalisation of ring A and the construction of the furan D-ring were made in order to complete the furanospongian skeleton. The synthetic route developed is presented in Scheme 3.



Scheme 3

Reagents and Conditions: a) CH_2I_2, $ZnEt_2$, toluene, rt, 92%; b) $Ph_2P(O)CH(Li)OCH_3$, THF, -78°C-rt, 90%; c) TMSCl, NaI, CH_3CN-CH_2Cl_2 2:3, rt, 90%; d) i). LDA, HMPA, THF, -78°C; ii). H_2O-THF 1:3, 50%; e) MCPBA, CH_2Cl_2, pH= 8, 5°C, 76%; f) PTSA anhydrous, DMSO-CH_2Cl_2 3:1, 50°C, 53%; g) Hydrazine, di(ethylene glycol), KOH, 120°C-220°C, 75%.

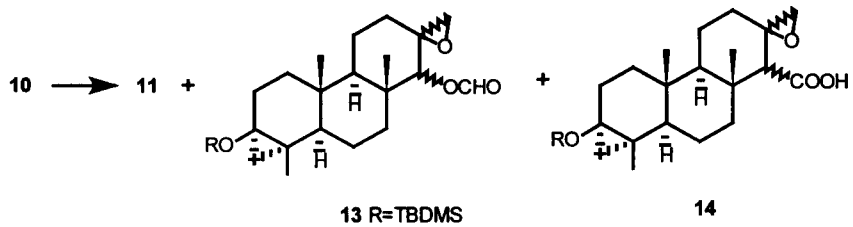
Preliminary attempts at homologation of the C-14 carbonyl group of the enone **2a** showed high instability for the *tert*-butyldimethylsilyl enol ether group present in ring A. For this reason, a cyclopropane ring was introduced stereoselectively and regioselectively into the 3,4-double bond of **2a** by means of cyclopropanation with diiodomethane and diethyl zinc.[10] This gave the enone **6** in 92% yield, as the only stereoisomer to be obtained. We thus obtained a more resistant functionalisation in ring A, which not only allowed us to work on the construction of ring D, but also facilitated the conversion of ring A into the spongian skeleton through cyclopropane ring opening. An NOE enhancement observed between the α hydrogen atom of the methylene

group of the cyclopropane ring at δ 0.21 ppm and the axial hydrogen atoms at C-5 and C-1 supported the stereochemistry assigned to the cyclopropane ring. A variety of methods were explored for the homologation of enone **6**, but we obtained the best results using the carbanion generated from methoxymethyldiphenylphosphine oxide and LDA/THF at –78°C.[11] This reaction led to a mixture of alcohols **7** in 88% yield. Subsequent standard treatment with NaH/DMF afforded the enol ether **8** in a poor 24% yield. We eventually determined that the yield of this homologation could be notably improved if the reaction was allowed to reach room temperature after the addition of the carbanion. This caused the diphenylphosphine oxide to be eliminated *in situ*, which gave the (*E*)-enol ether **8** as the sole identifiable product in an excellent 90% yield. The assigned stereochemistry at C-15 was supported by the NOE effect observed between the C-16 methyl and the methoxy group.

Once the introduction of the new carbon at C-14 had been accomplished, the functionalisation of C-16 had to be carried out. This proved to be the main difficulty in this synthesis. Treatment of **8** with *tert*-BuOOH and SeO_2 supported on silica gel in CH_2Cl_2[12] to obtain the allylic alcohol at C-16 led to a complex mixture of products. We eventually determined that the functionalisation at C-16 was only possible through the aldehyde **9** obtained from **8**. Initially, the conversion of the enol ether **8** into the aldehyde **9** was unsuccessful when acid conditions such as HCOOH/H_2O or HCl/ether at room temperature were used; this only yielded recovered starting material. When stronger conditions such as MeOH/HCl 9:1 or Acetone/HCl 9:1 at 60°C were used, the reaction led to mixtures arising from the hydrolysis of the enol ether functionalisation and the *tert*-butyldimethylsilyl group together with products from partial cyclopropane ring opening. We finally completed the synthesis of the aldehyde **9** using nucleophilic conditions; namely, by treatment with trimethylsilyl chloride and NaI[13] at room temperature, obtaining a 90% yield. For this result, however, a very strict control of the time and temperature of reaction was necessary. In all cases the conversion of enol ether **8** into the aldehyde **9** was accompanied by the isomerisation of the 12,13-double bond to 13-14 position, which is a more thermodynamically stable structure. After much experimentation, we were able to introduce a double bond between C-13 and C-16 isomerising **9** to the unconjugated aldehyde **10**.[14] This transformation was carried out through the addition of a mixture of cold water/THF 1:3 to the kinetic enolate of **9**, which had been generated with LDA/HMPA, at –78°C. This afforded **10** in 50% yield and 25% of the starting material. The stereochemistry of aldehyde **10** was confirmed by means of NOE experiments. Irradiation of the hydrogen in the aldehyde group at δ 9.86 ppm enhanced the signals assigned to the C-17 methyl at δ 1.17 ppm and H-16 at δ 4.45 ppm.

After having functionalized C-16, we thought that the epoxidation of the exocyclic double bond and subsequent acid treatment would probably lead to the furan D-ring. But when MCPBA in CH_2Cl_2,[15] $CHCl_3$,[16] or ether[17] was used at different temperatures, concentrations and times of reaction, a complex mixture of products was obtained. Among them we identified the epoxides **11**, and the formiates **13** and acids **14** which resulted

from Baeyer-Villiger oxidation (Scheme 4). The use of MCPBA in CH_2Cl_2 in a basic medium like 0.5 M $NaHCO_3$[18] decreased the amount of by-products from Baeyer-Villiger oxidation, but the epoxide yield barely reached 50%.



13 R=TBDMS 14

Scheme 4

Finally, epoxidation of **10** with MCPBA in CH_2Cl_2 at 5°C and pH= 8,[19] gave a mixture of four epoxides **11** in an approximate 55:23:16:6 ratio in 76% yield and with 16% of the starting material. For our purposes, the isolation of the isomeric epoxides was unnecessary since they could be directly transformed into the furan ring.

The next steps involved the cyclisation and aromatisation of the aldehyde and epoxy groups to obtain the furan ring D, followed by hydrolysis and opening of the silyl enol ether and cyclopropane rings, respectively, to complete the *gem*-dimethyl function in ring A. To reduce the number of steps in the sequence, the possibility of carrying out all the processes under the same conditions was explored. After testing various methods, we obtained the optimum yield for the completion of the target furanospongian skeleton by using dry PTSA in DMSO-CH_2Cl_2 3:1 at 50°C for 8 hours, which gave the furanoketone **12** in 53% yield. The spectroscopic data for this compound were identical to those previously reported for the racemic form of **12**.[6b]

We considered carrying out the final conversion of **12** into spongia-13(16)-14-diene **1** by following the procedure described by Kanematsu.[6b] In this process, **12** is first reduced with $LiAlH_4$ to produce an alcohol, which is then converted into the corresponding xanthate, followed by radical reduction with tristrimethylsilylsilane to afford the desired diterpene **1** in 50% overall yield for the three steps. Instead of this elaborate process, however, we chose to use a simple Wolff-Kishner reduction with hydrazine/KOH in di(ethylene) glycol to obtain the pure furanoditerpene **1** as a solid in 75% yield. The spectral and physical data of synthetic **1**, including its optical rotation, were in total agreement with those recorded for the natural product isolated from *Spongia officinalis*.[7]

In conclusion, we have accomplished a diastereoselective synthesis of (-)-spongia-13(16)-14-diene **1** in 9% total yield from *S*-(+)-carvone, using the phenanthrenone **2a**, which was obtained in 53% overall yield from *S*-(+)-carvone in six steps. The utility of the tricyclic intermediates **2** in natural product synthesis has also been well demonstrated. Studies involving the functionalisation of ring A and manipulation of ring D are currently in progress.

EXPERIMENTAL

General details

The melting points were measured with a Büchi 535 apparatus and are uncorrected. Optical rotations were determined on a Schmidt Haensch Polartronic D polarimeter using a 5-cm path-length cell. $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were measured as KBr pellets on a Perkin-Elmer 281 spectrophotometer. NMR spectra were measured on a Varian Unity VXR-300 at 299.95 MHz (^1H) and at 75.43 MHz (^{13}C), and a Varian Unity VXR-400 at 399.95 MHz (^1H). The signal of the deuteriated solvent ($CDCl_3$) was taken as the reference (the singlet at δ_H 7.24 for ^1H and the triplet centered at δ_C 77.00 for ^{13}C NMR data). Complete assignments of NMR data were made on the basis of a combination of DEPT, HMQC and NOE experiments. *J* values are given in Hz. In all compounds, NMR assignments are given with respect to the numbering scheme shown in structure **1**. Mass spectra (EI) were run on a VG AUTOSPEC SS mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on a silica gel plate (Merck Kieselgel 60 F_{254}) and flash chromatography was performed with Merck silica gel 60 (230-400mesh), although the purification by MPLC was carried out on a medium pressure apparatus with a Büchi 688 pump and a Knauer refractometer using Macherey Nagel silica gel 60 Duren (0.015-0.04 mm). Reactions were carried out in an argon atmosphere when necessary. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. THF was distilled from sodium benzophenone ketyl. Organic extracts were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure on a Büchi rotary evaporator.

*Conversion of the intermediate **2a** into the cyclopropane **6***

To a solution of **2a** (477 mg, 1.23 mmol) in dry toluene (18 mL) at room temperature was added a solution of Et_2Zn in hexane (7.5 mL, 7.38 mmol). CH_2I_2 (1.17 mL, 14.70 mmol) was then added dropwise under inert atmosphere. After being stirred for 1 h 40 min at room temperature, saturated aqueous NH_4Cl (6 mL) was added and the mixture was extracted with ether. The extracts were washed, dried, filtered and concentrated. The residue was purified by MPLC (hexane-ethyl acetate 97.5:2.5) to afford the cyclopropane **6** (453 mg, 92%) as a white solid: mp 138-139 °C (from MeOH); $[\alpha]^{25}_D$ +62 (*c* 6.0, $CHCl_3$); ν_{max}/cm^{-1} 3080, 3050, 1660, 1425, 1360, 1260, 1200, 1165, 1010, 910, 840 and 770; δ_H (400 MHz; $CDCl_3$) 6.61 (1 H, br s, H-12), 1.70 (3 H, br s, H-16), 1.63 (1 H, dd, *J* 12.5 and 7.5, H-9), 1.03 and 1.02 (3 H each, each s, H-19 and H-17), 0.91 (3 H, s, H-20), 0.83 (9 H, s, Me_3CSi), 0.53 (1 H, ddd, *J* 14.0, 14.0 and 6.5, H-1α), 0.49 (1 H, d, *J* 4.5, H-18β), 0.21 (1 H, d, *J* 4.5, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si); δ_C (75 MHz; $CDCl_3$) 205.81 (C14), 143.38 (C12), 132.92 (C13), 58.23 (C3), 53.73 (C5), 49.90 (C9), 44.59 (C8), 35.68 (C10), 35.05 (C1), 33.83 (C7), 28.84 (C2, C18), 25.73 (Me_3CSi), 23.89 (C11), 21.93 (C4), 21.71 (C6), 18.06 (C17), 17.87 (Me_3CSi), 16.31 (C16), 15.45 (C19), 13.08 (C20), -3.85 and -3.09 (Me_2Si) ; *m/z* (EI) 403 (M^+ + 1, 10%), 402 (M^+, 40), 346 (25), 345 (90), 317 (5),

$C_{25}H_{42}O_2Si$ (M^+) 402.2954, found 402.2954.

*Preparation of enol ether **8** from cyclopropane **6***

To a suspension of methoxymethyldiphenylphosphine oxide (124 mg, 0.51 mmol) in THF (0.34 mL) at 0°C under an argon atmosphere a 0.6 M solution of LDA in THF (0.67 mL, 0.40 mmol) was added dropwise and stirred until full dissolution (red solution). This solution was cooled to –78 °C, and then a solution of **6** (68 mg, 0.17 mmol) in THF (0.9 mL) was added to it dropwise. The mixture was allowed to warm to room temperature and after being stirred for 1 h at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1 mL), then poured into water and extracted with ether. The diethyl ether solution was washed, dried, filtered and concentrated. The residue was chromatographed (hexane-diethyl ether 9:1) to give the enol ether **8** (66 mg, 90%) as a white solid: mp 124-125 °C (from methanol); $[\alpha]^{25}_D$ +130.3 (*c* 3.7, $CHCl_3$); ν_{max}/cm^{-1} 3050, 2960, 2930, 2860, 1645, 1620, 1455, 1250, 1190, 1120, 830, 770 and 670; δ_H (400 MHz; $CDCl_3$) 5.76 (1 H, s, H-15), 5.31 (1 H, br s, H-12), 3.51 (3 H, s, MeO), 1.94 (3 H, br s, H-16), 1.03 (3 H, s, H-19), 0.99 (3 H, s, H-17), 0.84 (9 H, s, Me_3CSi), 0.82 (3 H, s, H-20), 0.47 (1 H, d, *J* 6.0, H-18β), 0.21 (1 H, d, *J* 6.0, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si); δ_C (75 MHz; $CDCl_3$) 141.77 (C15), 130.30 and 128.16 (C13, C14), 124.36 (C12), 59.73 (MeO), 58.47 (C3), 54.38 (C5), 49.43 (C9), 38.52 (C7), 35.91 and 35.44 (C8, C10), 35.50 (C1), 29.04 (C2), 28.82 (C18), 25.85 (*Me*$_3$CSi), 24.08 (C11), 23.74 (C16), 22.60 (C6), 22.10 (C4), 22.01 (C17), 17.87 (Me_3*C*Si), 15.57 (C19), 12.65 (C20), -3.02 and -3.81 (Me_2Si); *m/z* (EI) 431 (M^++1, 35%), 430 (M^+, 100), 416 (30), 415 (69), 374 (15), 373 (41), 283 (14), 225 (25), 211 (19), 189 (17), 175 (15), 163 (11), 149 (17), 75 (24) and 73 (56). HRMS calcd. for $C_{27}H_{46}O_2Si$ (M^+) 430.3267, found 430.3267.

*Conversion of the enol ether **8** into the aldehyde **9***

To a mixture of the enol ether **8** (65 mg, 0.15 mmol) and NaI (23 mg, 0.15 mmol) in CH_3CN (0.9 mL) and CH_2Cl_2 (1.35 mL) at 20 °C was added trimethylsilyl chloride (19 μL, 0.15 mmol); the reaction mixture became a dark orange solution. After stirring for only 3 min the reaction mixture was poured into water and extracted with diethyl ether. The residue obtained after usual work-up was purified by column chromatography (hexane-diethyl ether 7:3) to give the aldehyde **9** (57 mg, 90%) as a white solid: mp 156-157 °C (from pentane); $[\alpha]^{25}_D$ +16.1 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3060, 2970, 2940, 2870, 2780, 1670, 1460, 1415, 1260, 840 and 780; δ_H (300 MHz; $CDCl_3$) 10.00 (1 H, s, H-15), 2.63 (1 H, ddd, *J* 13.0, 3.5 and 3.5), 1.98 (3 H, s, H-16), 1.19 (3 H, s, H-17), 1.00 (3 H, s, H-19), 0.83 (9 H, s, Me_3CSi), 0.80 (3 H, s, H-20), 0.48 (1 H, d, *J* 4.5, H-18β), 0.20 (1 H, d, *J* 4.5, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si); δ_C (75 MHz; $CDCl_3$) 192.54 (C15), 153.41 (C14), 143.72 (C13), 58.29 (C3), 54.33 (C5), 52.25 (C9), 37.42 (C8), 36.85 and 36.65 (C7, C12), 35.88 (C1), 35.60 (C10), 29.28 (C2), 29.17 (C18), 25.79 (*Me*$_3$CSi), 22.38 (C6), 22.14 (C4), 21.12 (C17), 19.09 (C16), 17.92 (Me_3*C*Si), 17.79 (C11), 15.37 (C19), 12.15 (C20), -3.04 and -3.78 (Me_2Si); *m/z* (EI) 417 (M^+ + 1, 8%), 416 (M^+, 23), 360

(23), 359 (77), 213 (12), 212 (23), 211 (100), 75 (23) and 73 (44). HRMS calcd. for $C_{26}H_{44}O_2Si$ (M^+) 416.3110, found 416.3110.

*Isomerisation of **9** to the unconjugated aldehyde **10***

To a cooled (-78 °C) solution of aldehyde **9** (44 mg, 0.11 mmol) in THF (1.25 mL) a solution of 0.6 M LDA in THF (0.26 mL, 0.16 mmol) was added dropwise during 5 min; the mixture became a yellow solution. After 15 min HMPA (92 μL) was added and the mixture was stirred for 20 min more. A mixture of cold water-THF 1:3 (2 mL) was then added and the reaction mixture was poured into cold water (5 °C) and extracted with diethyl ether. The combined extracts were washed, dried, filtered and concentrated. The residue was purified by column chromatography (hexane-diethyl ether 9:1) to afford the aldehyde **10** (22 mg, 50%) as a white solid and 11 mg (25%) of starting material, mp 97-98 °C (from methanol); $[\alpha]^{25}_D$ +69.7 (*c* 2.2, $CHCl_3$); ν_{max}/cm^{-1} 3060, 2930, 2860, 1720, 1640, 1460, 1430, 1380, 1250, 1190, 900, 830, 770 and 670; δ_H (300 MHz; $CDCl_3$) 9.86 (1 H, d, *J* 4.8, H-15), 4.86 (1 H, br s, H-16a), 4.45 (1 H, br s, H-16b), 1.17 (3 H, s, H-17), 1.00 (3 H, s, H-19), 0.83 (9 H, s, Me_3CSi), 0.81 (3 H, s, H-20), 0.48 (1 H, d, *J* 5.0, H-18β), 0.21 (1 H, d, *J* 5.0, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si); δ_C (75 MHz; $CDCl_3$) 205.65 (C15), 144.80 (C13), 109.21 (C16), 67.99 (C14), 58.19 (C3), 54.79 and 54.41 (C5, C9), 40.21 and 36.57 (C7, C12), 38.84 (C8), 35.93 (C1), 35.84 (C10), 29.18 (C2), 29.04 (C18), 25.77 (Me_3CSi), 22.42 and 22.21 (C6, C11), 22.09 (C4), 17.90 (Me_3CSi), 17.04 (C17), 15.40 (C19), 12.49 (C20), -3.06 and -3.81 (Me_2Si); *m/z* (EI) 417 (M^+ + 1, 5%), 416 (M^+, 19), 360 (17), 359 (57), 213 (11), 212 (23), 211 (100), 155 (10), 75 (29) and 73 (55). HRMS calcd. for $C_{26}H_{44}O_2Si$ (M^+) 416.3110, found 416.3119.

*Conversion of the aldehyde **10** into the epoxides mixture **11***

To a solution of aldehyde **10** (120 mg, 0.29 mmol) in CH_2Cl_2 (10.2 mL) was added a 0.5 M buffer solution of $Na_2HPO_4/KHPO_4$ (10.2 mL, pH= 8). The mixture was then cooled to 5 °C and MCPBA (41 mg, 0.20 mmol) was added. After being stirred for 16 h MCPBA (39 mg, 0.17 mmol) was added again. The reaction mixture was stirred for 2 days at the same temperature (5°C), and then diluted with diethyl ether. The diethyl ether solution was washed first with 0.5 M $Na_2S_2O_4$, then with saturated aqueous Na_2CO_3 and finally with brine. After drying and removal of the solvent, the residue was chromatographed over silica gel using hexane-ethyl acetate (95:5) as eluent to give 19 mg (16%) of starting material and a mixture of four epoxides **11** (94 mg, 76%) in an approximate 55:23:16:6 ratio (determined by integration of ^1H NMR signals). ^1H NMR data of major product (from the mixture) are given: δ_H (400 MHz; $CDCl_3$) 9.55 (1 H, d, *J* 4.0, H-15), 3.11 (1 H, dd, *J* 4.1 and 1.9, H-16a), 2.68 (1 H, dd, *J* 4.1 and 1.0, H-16b), 2.41 (1 H, d, *J* 4.0, H-14), 1.23 (3 H, s, H-17), 0.99 (3 H, s, H-19), 0.83 (9 H, s, Me_3CSi), 0.81 (3 H, s, H-20), 0.21 (1 H, m, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si).

Preparation of spongia-13(16),14-dien-3-one **12**

To a solution of epoxides **11** (22 mg, 0.051 mmol) in CH_2Cl_2 (0.18 mL) and DMSO (0.27 mL) was added a solution of anhydrous PTSA in DMSO (0.27 mL, 330 mg PTSA/mL). The reaction mixture was warmed to 50°C and after being stirred for 8 h the reaction mixture was diluted with diethyl ether and worked up as usual to give the furanoketone **12** (8.1 mg, 53%) as a white solid: mp 116-117 °C (from hexane) (lit.,[6b] 120-121 °C); $[\alpha]^{20}_D$ +11.8 (*c* 3.5, $CHCl_3$); ν_{max}/cm^{-1} 2950, 2910, 2840, 1690, 1450, 1380, 1030 and 790; δ_H (400 MHz; $CDCl_3$) 7.08 (1 H, d, *J* 1.7, H-15), 7.04 (1 H, ddd, *J* 3.0, 1.7 and 1.7, H-16), 2.78 (1 H, dd, *J* 15.9 and 6.1, H-12β), 2.58-2.40 (3 H, m), 2.12 (1 H, m), 2.02 (1 H, ddd, *J* 12.9, 7.5 and 4.8), 1.22 (3 H, s, H-17), 1.08 (3 H, s, Me), 1.06 (3 H, s, Me) and 0.98 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 217.77 (C3), 136.92 (C16), 136.86 (C14), 135.15 (C15), 119.56 (C13), 55.35 and 54.84 (C5, C9), 47.38 (C4), 40.17 (C7), 39.15 (C1), 36.90 (C10), 34.06 (C8), 33.91 (C2), 26.78 (C17), 25.71 (C18), 20.91 (C19), 20.69 (C12), 19.78 and 18.73 (C6, C11), 16.19 (C20); *m/z* (EI) 301 (M^++1, 18%), 300 (M^+, 80), 286 (21), 285 (100), 267 (15), 147 (18) and 133 (10). HRMS calcd. for $C_{20}H_{28}O_2$ (M^+) 300.2089, found 300.2085.

Spongia-13(16),14-diene **1**

A solution of the ketone **12** (10 mg, 0.034 mmol), KOH 85% (60 mg, 0.91 mmol), 0.38 mL of di(ethylene glycol) and 0.03 mL of hydrazine monohydrate was stirred at 120 °C for 2 hours. The temperature was then brought to 220 °C while a slow stream of argon was maintained; this process took 30 minutes. The mixture was then stirred at this temperature for 15 additional minutes. The reaction mixture was cooled, poured over saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was washed, dried, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel using hexane-diethyl ether (9:1) as eluent to afford spongian **1** (7.1 mg, 75%) as a colorless solid, mp 112-113 °C (from methanol) (lit.,[7] 115-116 °C) $[\alpha]^{26}_D$ –21.1 (*c* 0.5, $CHCl_3$) (lit.,[7] –32.7, *c* 0.26); ν_{max}/cm^{-1} 1460, 1390, 1380, 1370, 1040, 895 and 770; δ_H (300 MHz; $CDCl_3$) 7.06 (1 H, d, *J* 1.6, H-15), 7.02 (1 H, ddd, *J* 1.6, 1.6 and 1.2, H-16), 2.74 (1 H, dddd, *J* 16.2, 6.2, 1.7 and 1.2, H-12β), 2.42 (1 H, dddd, *J* 16.2, 12.0, 7.1 and 1.6, H-12α), 2.07 (1 H, m, H-7β), 1.20 (3 H, d, *J* 0.7, H-17), 0.88 (3 H, s, H-20), 0.85 (3 H, s, H-18), 0.82 (3 H, s, H-19); δ_C (75 MHz; $CDCl_3$) 137.77 (C14), 136.67 (C16), 134.97 (C15), 119.87 (C13), 56.76 (C5), 56.29 (C9), 42.13 (C3), 41.16 (C7), 39.97 (C1), 37.63 (C10), 34.35 (C8), 33.37 (C4, C18), 26.28 (C17), 21.43 (C19), 20.71 (C12), 18.80 (C11), 18.54 (C2), 18.05 (C6), 16.33 (C20); *m/z* (EI) 287 (M^++1, 13%), 286 (M^+, 63), 272 (20) and 271 (100). HRMS calcd. for $C_{20}H_{30}O$ (M^+) 286.2297, found 286.2295.

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