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Synthesis of Cyclosiphonodictyol A and its bis(Sulfato)

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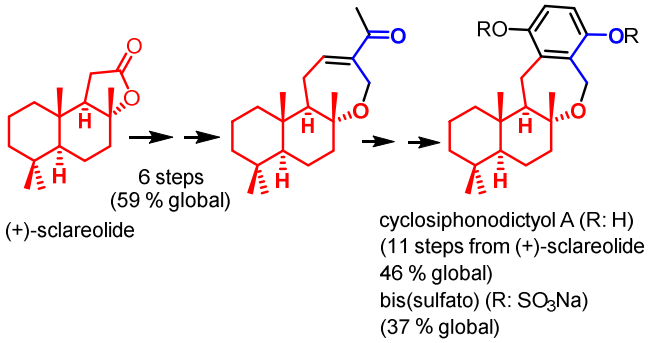


ABSTRACT

The first synthesis of the marine benzoxepane hydroquinone cyclosiphonodictyol A and its bis(sulfato) from commercial (+)-sclareolide is reported. The key steps of the synthetic sequence (11 steps, 46% global) are the nucleophilic attack of a hindered tertiary alkoxide, a ring-closing metathesis reaction and the Diels-Alder cycloaddition of a dienol acetate.

INTRODUCTION

Marine organisms are an important source of natural products which have aroused great interest because of their structural variety and the wide range of biological activities that many of them exhibit. One such organism is the tropical marine sponge *Aka coralliphagum* (or *Siphonodictyon coralliphagum*), due to the considerable number of bioactive metabolites, usually with a sesquiterpene hydroquinone structure,[1] that have been isolated from it, such as liphagal[2] and corallidictyals A-D.[3]

Another important group of metabolites that have been isolated from this sponge are the siphonodictyals, which have an aryl and an acyclic or bicyclic-sesquiterpene moiety and contain aldehyde, carboxylic acid, imine or sulfate ester groups, among others. Siphonodictyal A (**1**) and B (**2**) were the first compounds of this family to be isolated, by Faulkner et al. in 1981.[4] The same authors reported the isolation of siphonodictyal C (**3**) and E (**7**) a few years later.[5] Subsequently, Köck et al. isolated siphonodictyals B1-B3 (**4-6**),[6] and this was followed very recently by siphonodictyals E1-E3 (**8-10**).[7] Two structurally related metabolites are the benzoxepane derivatives bis-(sulfato)cyclosiphonodictyol A (**12**), reported in 1995 by Wright et al.,[8] and the related hydroquinone cyclosiphonodictyol A (**11**), recently described (Figure 1).[7]

Some of the above metabolites exhibit significant biological activity. Compounds **1**,[4] **2**[4] and **3** inhibit the growth of *Staphylococcus aureus* and *Bacillus subtilis,* and the latter also inhibits the marine bacterium *Vibrio anguillarum*[5] and the CDK4/cyclin D1 complexation.[9] Siphonodictyal B1 (**4**) increases intracellular calcium to levels comparable to those of the Ca^{2+}-ATPase (SRCA) inhibitor thapsigargin,[6b] and siphonodictyal B3 (**6**) has a radical-scavenging activity that is comparable with that of the known lipophylic antioxidant BHT.[10]

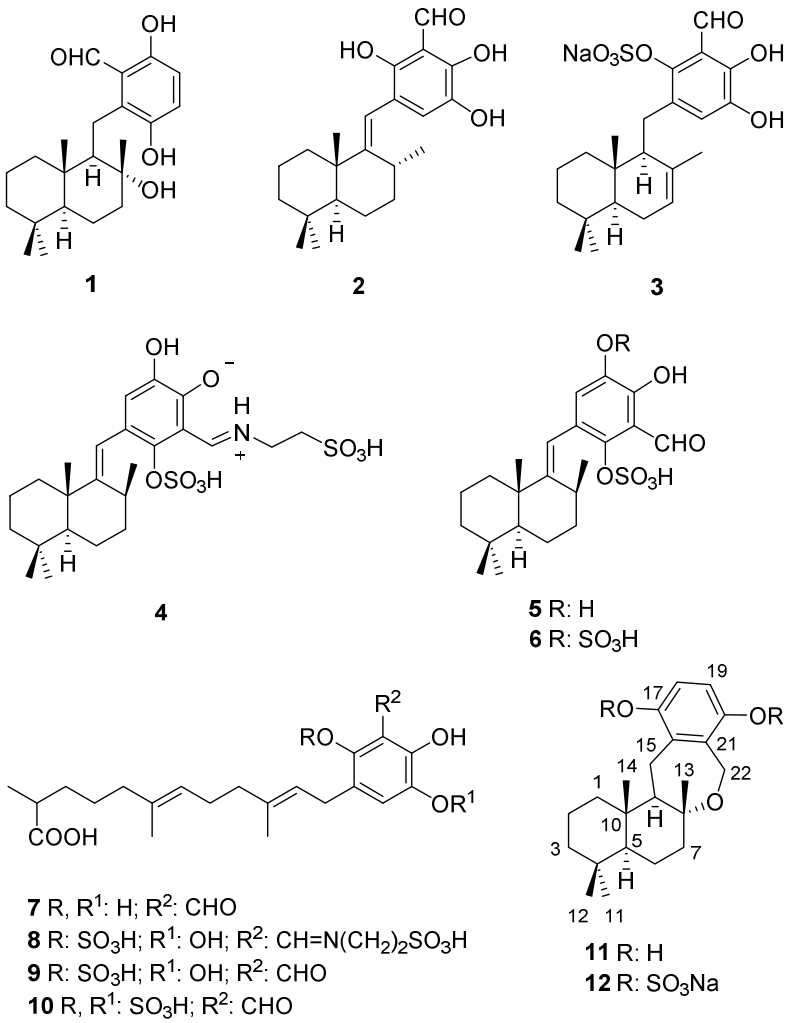


Figure 1. Some representative siphonodictyals and related metabolites.

The development of synthetic processes for the above compounds is of interest, not only because of the significant biological activity exhibited in some cases, but also because it allows their structures to be established unequivocally. In this respect, siphonodictyal B (**2**) was first isolated by Faulkner in 1981.[4] The structure originally proposed for this compound was subsequently revised by Faulkner and Clardy in 1986,[5] and later revised again (in terms of its configuration at C-8) to its correct structure **2**, on the basis of George's total synthesis.[11]

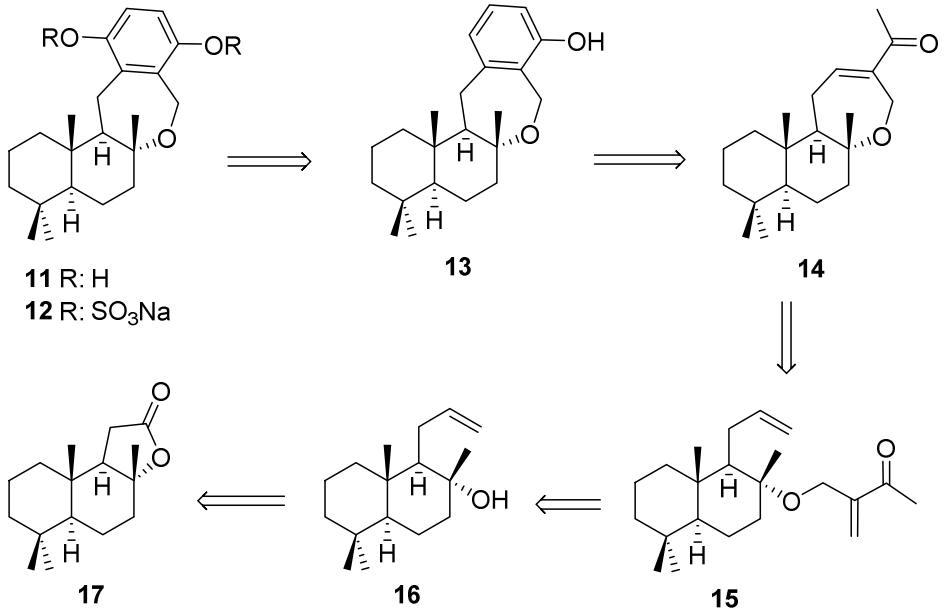
Similarly, the structure of siphonodictyal C (**3**), described by Faulkner et al. as a desulfated compound,[5] was later revised as the correct structure **3**.[9] In this context, too, the structures originally proposed for siphonodictyals B1-B3 (**4-6**) should probably be corrected to the corresponding 8-epimers, in view of their spectroscopic similarities to compound **2**.

The synthesis of siphonodictyals has been reported only recently, and for a limited number of these compounds. For example, the preparation of a protected (±)-siphonodictyal C (**3**), by the condensation of an aryllithium with (±)-drimenal, has been described; in this case, the aldehyde group of target compounds was introduced in the final steps of the process.[12] A similar strategy has been utilized for the synthesis of (-)-siphonodictyal B (**2**), starting from a drimanal synthesised from commercially available (+)-sclareolide.[11,13] Very recently, a divergent synthesis of compound **2** was reported, in which the meroterpene skeleton was obtained through a palladium-catalysed direct cross-coupling reaction of a drimanal hydrazone, synthesised from (+)-sclareolide, and an iodobenzaldehyde, and the subsequent iodine-promoted sunlight-induced olefin Z/E isomerisation reaction.[3c]

RESULTS AND DISCUSSION

The present study focuses on cyclosiphonodictyol A (**11**) and its bis-(sulfato) **12**, which have not previously been synthesised. These compounds contain an oxepanyl moiety frequently found in nature, mainly in marine metabolites, such as cytotoxic aplysistatins and anti-inflammatory palisadins.[14] The retrosynthesis of natural benzoxepanes **11-12** is outlined in Scheme 1.

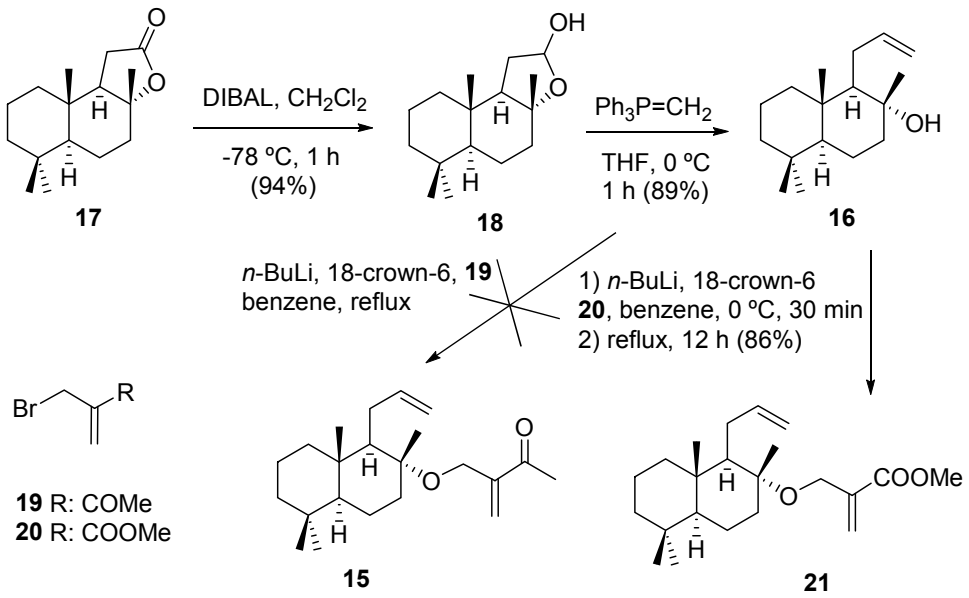
Scheme 1. Retrosynthesis of benzoxepanes **11-12** from commercial (+)-sclareolide (**17**).



The aromatic ring of phenol **13** is elaborated through the Diels-Alder cycloaddition of dienol ester derived from methylketone **14**, whose oxepane ring is formed via the ring-closing metathesis of oxy-ketone **15**, derived from alcohol **16**, which is easily prepared from lactone **17**.

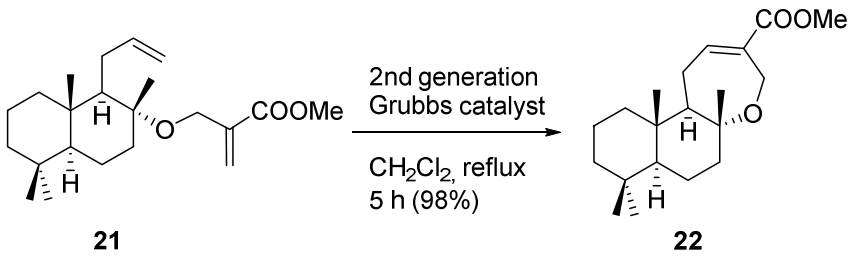
To do this, the synthesis of ketone **15** was first attempted (Scheme 2). However, the treatment of hydroxy alkene **16**, resulting from the methylenation of lactol **18**,[15] with bromoketone **19** in benzene, in the presence of *n*-BuLi and 18-crown-6 ether, did not provide the desired oxy-ketone **15.** At room temperature the reaction did not take place; when the temperature was increased, decomposition of the bromo derivative **19** was observed. In view of the low reactivity of tertiary alcohol **16** and the lability of bromo ketone **19**, the use of bromo ester **20**, as an alkylating agent, was then considered. This approach, under the above reaction conditions after refluxing for 12 h, produced the desired oxy-ester **21** in good yield.

Scheme 2. Synthesis of oxy ester **21** from commercial (+)-sclareolide (**17**).



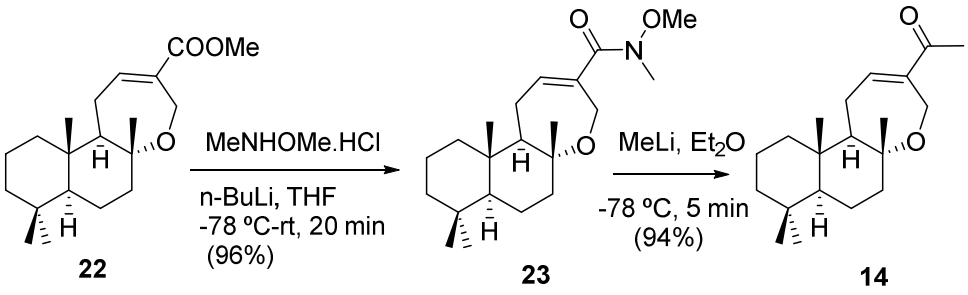
The construction of the oxepane ring was then investigated (Scheme 3). When the oxy ester **21** was treated with second-generation Grubbs catalyst,[16] the desired oxepane ester **22** was obtained in almost quantitative yield.

Scheme 3. Construction of the oxepane ring. Synthesis of ester **22**.



Next, the oxepane enone **14**, a precursor of the target compounds, was synthesised from ester **22**, via the corresponding Weinreb amide **23** (Scheme 4). After treating amide **23** with MeLi at -78 ºC, ketone **14** resulted in a high yield.

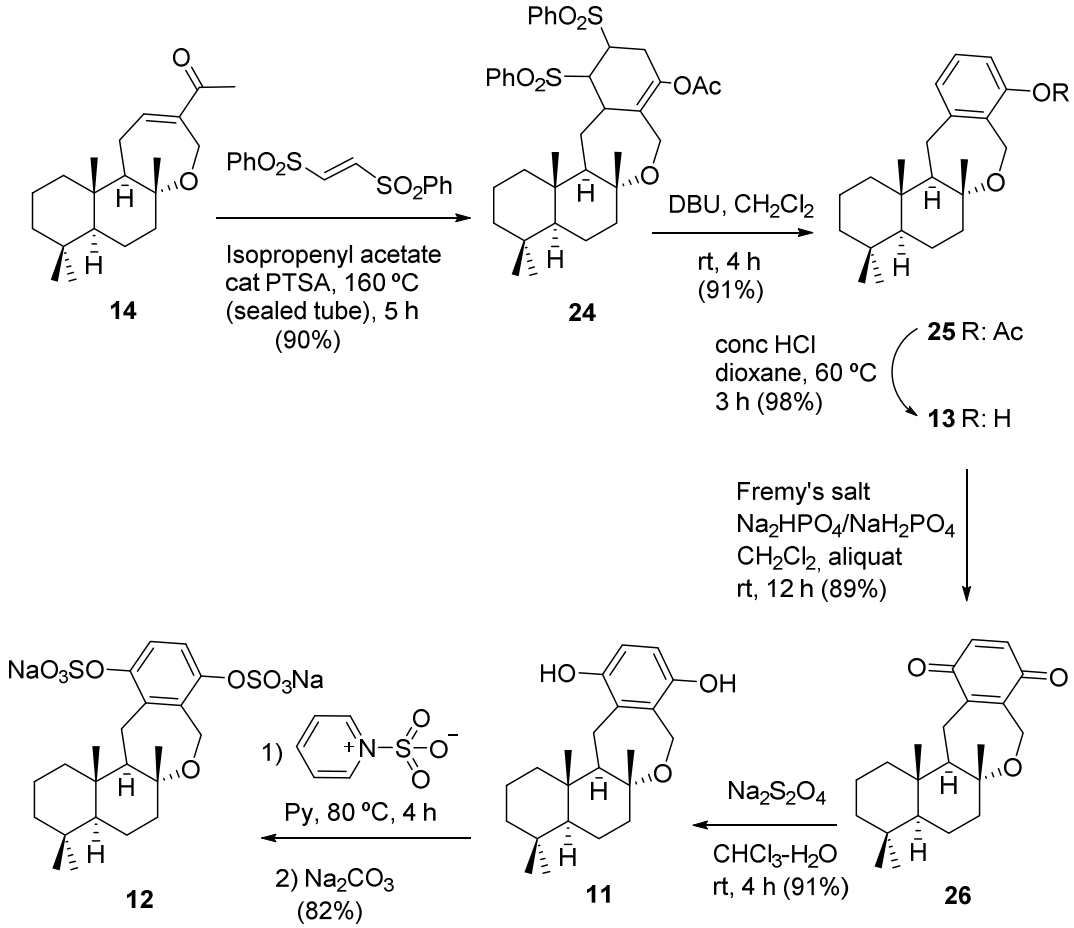
Scheme 4. Synthesis of enone **14** from ester **22**.



Finally, the construction of the aromatic ring was undertaken (Scheme 5). To do so, enone **14** was treated with *trans*-1,2-bis(phenylsulfonyl)ethylene and isopropenyl acetate in the presence of catalytic p-toluenesulphonic acid in a sealed tube for 5 h, which produced a mixture of cycloadducts **24** in 90% yield.[17] When these were treated with DBU in dichloromethane at room temperature for 4 h, acetate **25** was resulted.[18] This was converted into phenol **13** by heating a solution in dioxane in the presence of concentrated hydrochloric acid. The further treatment of compound **13** with Fremy's salt gave 1,4-benzoquinone **26**,[19] which after reduction with sodium hydrosulphite gave cyclosiphonodictyol A (**11**) in almost quantitative yield. This hydroquinone is air sensitive, being slowly transformed into quinone. The NMR data obtained for the DMSO-d_6 solution of synthetic **11** were similar to that previously reported for the natural compound.[7] In fact, the ^{13}C NMR data are identical. Compound **11** was finally converted into its bis(sulfato) **12**, after successive treatment with pyridine-sulphur trioxide and Na_2CO_3. The spectroscopic data of

synthetic compound **12** were consistent with those reported for the natural product;[8] however a complete comparison was not feasible because of the low solubility of the synthetic bis(sulfato) in CD_3OD.

Scheme 5. Synthesis of cyclosiphonodictyol A (**11**) and its bis(sulfato)(**12**).



CONCLUSIONS

In summary, the first synthesis of the marine metabolite cyclosiphonodictyol A (**11**) and its bis-(sulfato) **12** from the commercially available lactone (+)-sclareolide (**17**) is reported. The nucleophilic attack of a hindered tertiary alkoxide, a ring-closing metathesis reaction and the Diels-Alder cycloaddition of a dienol acetate are the key steps of the synthetic sequence (11 steps, 46% global). This procedure can be utilized to achieve the synthesis of other siphonodictyals, such as compound **1**, that are not readily accessible.

EXPERIMENTAL SECTION

General Procedures

Unless stated otherwise, reactions were performed in oven-dried glassware under an argon atmosphere using dry solvents. Organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. An oil bath was used as the heating source for the reactions that require heating. Thin-layer chromatography (TLC) was performed using F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution in ethanol staining. Flash chromatography was performed on silica gel (230-400 mesh). Chromatography separations were carried out by conventional column on silica gel 60 (230-400 Mesh), using hexanes-AcOEt (AcOEt-hexane) or diethyl ether-hexanes (ether-hexane) mixtures of increasing polarity. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 400 MHz, and at 125 and 100 MHz, respectively. Chemical shifts (δ H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak and tetramethylsilane. Data for

^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, t, q and m denoting singlet, broad singlet, doublet, triplet, quartet and multiplet, respectively. *J* = coupling constant in Hertz (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0) and the signals were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. Infrared spectra (IR) were recorded as thin films or as solids on a FTIR spectrophotometer with samples between sodium chloride plates or as potassium bromide pellets and are reported in frequency of absorption (cm^{-1}). Only selected absorbances (ν_{max}) are reported. ($[\alpha]_D$) measurements were carried out in a polarimeter; utilizing a 1dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in mg/mL. HRMS were recorded on a spectrometer, utilizing a Q-TOF analyzer, and ESI^+ ionization.

Experimental Procedures

(1R,2R,4aS,8aS)-1-allyl-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (16).

n-BuLi (2.5 M in *n*-hexane, 3.2 mL, 7.92 mmol) was added to a solution of $MePPh_3Br$ (2.89 g, 7.92 mmol) in dry THF (15 mL) at 0 ºC under Ar atmosphere and the mixture was stirred at this temperature for 30 min. Then, a solution of **18** (1 g, 3.96 mmol) in dry THF (10 mL) was added via cannula and the reaction was stirred for 1 h. At this time, TLC showed no starting material, and H_2O (10 mL) was added. The solvent was removed in vaccum and Et_2O (50 mL) was added. The organic layer was washed with H_2O (2 x 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrate under vacuum. The crude was purified by flash chromatography (10%

ether/hexane) to yield 882 mg of **16** (89%) as colourless syrup. $[\alpha]_D^{25}$= -3.6 (c 5.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.96 (dddd, J = 16.6, 10.0, 7.9, 6.3 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.92 (dd, *J* = 10.1, 1.7 Hz, 1H), 2.29 – 2.15 (m, 2H), 1.84 (ddd, *J* = 12.5, 12.5, 3.2 Hz, 1H), 1.74 – 1.51 (m, 4H), 1.48 – 1.37 (m, 2H), 1.36 – 1.21 (m, 2H), 1.19 (s, 3H), 1.12 (dd, *J* = 13.5, 4.2 Hz, 1H), 0.94 (dd, *J* = 12.2, 2.5 Hz, 2H), 0.87 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H).^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ: 142.5 (CH), 114.3 (CH_2), 74.5 (C), 61.4 (CH), 56.2 (CH), 44.1 (CH_2), 42.0 (CH_2), 40.2 (CH_2), 39.0 (C), 33.6 (CH_3), 33.4 (C), 30.0 (CH_2), 24.5 (CH_3), 21.7 (CH_3), 20.4 (CH_2), 18.7 (CH_2), 15.5 (CH_3). IR (film): 3409, 2923, 2867, 1636, 1462, 1387, 1083, 1000, 939, 906 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{30}ONa$ 273.2194, found 273.2187.

Methyl 2-((((1R,2R,4aS,8aS)-1-allyl-2,5,5,8a-tetramethyldecahydronaphthalen-2-yl)oxy)methyl)acrylate (21).

A solution of *n*-BuLi (2.5 M in *n*-hexane, 1.9 mL, 4.8 mmol) and ether/18-Crown-6 (1.3 g, 4.8 mmol) was added at 0º C to a solution of **16** (755 mg, 3.02 mmol) in dry benzene (15 mL). After 30 min stirring at 0 ºC, **20** (1.5 mL, 12 mmol) was added and the mixture was warmed to reflux. After 12 h, TLC showed no starting material. Then, ice was added slowly to quench the reaction and solvent was removed in vacuum. Ether (50 mL) was added to the crude product and the organic phase was washed with H_2O (2 x 20 mL) and brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrate under vacuum to give a product which was directly purified by flash chromatography (5% ether/hexane) to yield 904 mg of **21** (86%) as colourless syrup. $[\alpha]_D^{25}$= -5.9 (c 13.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.23 (d, *J* = 2.0 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.85 (m, 1H), 4.91 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.82 (d, *J* = 10.0 Hz, 1H), 4.12 (ddd, *J* = 14.7, 14.7, 2.1 Hz, 1H), 4.04 (ddd, *J* = 14.7, 14.7 2.0 Hz, 1H), 3.75 (s,

3H), 2.31 (m, 1H), 2.02 (m, 1H), 1.86 (dt, *J* = 12.2, 3.3 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.61 – 1.48 (m, 2H), 1.48 – 1.32 (m, 2H), 1.32 – 1.19 (m, 2H), 1.15 (s, 3H), 0.97 – 0.87 (m, 3H), 0.86 (s, 6H), 0.79 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 166.8 (C), 142.5 (CH), 138.7 (C), 124.7 (CH_2), 113.2 (CH_2), 78.8 (C), 58.6 (CH), 58.4 (CH_2), 56.1 (CH), 51.8 (CH_3), 42.1 (CH_2), 40.5 (CH_2), 39.5 (C), 38.4 (CH_2), 33.6 (CH_3), 33.3 (C), 29.9 (CH_2), 21.6 (CH_3), 20.4 (CH_3), 20.1 (CH_2), 18.5 (CH_2), 15.9 (CH_3). IR (film): 2926, 1721, 1437, 1387, 1217, 1200, 1156, 1085, 772 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{37}O_3$ 349.2743, found 349.2748.

Methyl (5aR,7aS,11aS,11bR)-5a,8,8,11a-tetramethyl-1,4,5a,6,7,7a,8,9,10,11,11a,11b-dodecahydronaphtho[2,1-b]oxepine-3-carboxylate (22).

To a solution of **21** (0.5 g, 1.43 mmol) in dry CH_2Cl_2 (20 mL) was added the second-generation Grubbs catalyst (61 mg, 0.07 mmol) at room temperature under argon atmosphere. The mixture was refluxed for 5 h and concentrated. The residue was purified by flash chromatography on silica gel column (10% ether / hexane) to yield the product **22** (448 mg, 98 %) as colorless oil. $[\alpha]_D^{25}$= +47.8 (c 4.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (m, 1H), 4.44 – 4.40 (m, 2H), 3.69 (s, 3H), 2.37 – 2.25 (m, 2H) , 1.73 (tt, *J* = 9.3, 2.8 Hz, 3H), 1.68 – 1.54 (m, 4H), 1.49 – 1.28 (m, 3H), 1.24 (s, 3H), 1.13 (td, *J* = 13.4, 4.2 Hz, 1H), 0.90 (d, *J* = 2.5 Hz, 1H), 0.87 (s, 3H), 0.79 (s, 3H), 0.79 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 167.1 (C), 144.9 (CH), 133.7 (C), 79.0 (C), 58.7 (CH_2), 56.2 (CH), 55.7 (CH), 51.7 (CH_3), 42.0 (CH_2), 39.9 (CH_2), 38.5 (C), 38.0 (CH_2), 33.5 (C), 33.5 (CH_3), 24.3 (CH_2), 22.5 (CH_3), 21.4 (CH_3), 20.7 (CH_2), 18.7 (CH_2), 16.1 (CH_3). IR (film): 2924, 1711, 1435, 1383, 1244, 1060, 774 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{33}O_3$ 321.2430, found 321.2427.

(5aR,7aS,11aS,11bR)-N-methoxy-N,5a,8,8,11a-pentamethyl-1,4,5a,6,7,7a,8,9,10,11,11a,11b-dodecahydronaphtho[2,1-b]oxepine-3-carboxamide (23).

To a stirred solution of *N,O*-dimethyl-hydroxylamine HCl (0.84 g, 8.6 mmol) in dry THF (8 mL) at -78 ºC was added a solution of *n*-BuLi (2.5 M in hexane, 6.7 mL, 16.8 mmol) under Ar atmosphere. The reaction mixture was warmed to rt and stirred for 20 min. The solution of lithium *N,O*-dimethyl hydroxylamine was recooled to -78 ºC, and a solution of **22** (0.45 g, 1.41 mmol) in dry THF (5 mL) at -78º C was added dropwise via cannula. After 20 min, TLC showed no starting material. The reaction was quenched at -78º C with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum. The residue was purified by flash column chromatography on silica gel column (25% EtOAc / hexane) to afford 472 mg of Weinreb amide **23** (96%) as colorless syrup. $[\alpha]_D^{25}$= +35.4 (c 15.7, $CHCl_3$). ^{1}H NMR (400 MHz, , $CDCl_3$) δ: 6.37 (dd, *J* = 7.5, 3.0, 1H), 4.48 (d, J = 16.4 Hz, 1H) , 4.10 (dd, *J* = 16.4, 2.0 Hz, 1H), 3.64 (s, 3H), 3.20 (s, 3H), 2.36 – 2.18 (m, 2H), 1.79 – 1.69 (m, 4H), 1.69 – 1.54 (m, 4H), 1.48 – 1.28 (m, 2H), 1.25 (s, 3H), 1.14 (ddd, *J* = 13.4, 13.4, 4.3 Hz, 1H), 0.91 (d, *J* = 2.5 Hz, 1H), 0.88 (s, 3H), 0.79 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 170.6 (C), 137.6 (C), 137.6 (CH), 79.2 (C), 61.0 (CH_3), 60.1 (CH_2), 56.2 (CH), 55.8 (CH), 42.1 (CH_2), 40.0 (CH_2), 38.6 (C), 38.5 (CH_2), 33.7 (CH_3), 33.5 (C), 33.5 (CH_3), 24.3 (CH_2), 22.6 (CH_3), 21.4 (CH_3), 20.7 (CH_2), 18.8 (CH_2), 16.1 (CH_3). IR (film): 2924, 1658, 1628, 1458, 1381, 1203, 1088, 1048, 772 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{35}NO_3$ 350.2695, found 350.2696.

1-((5aR,7aS,11aS,11bR)-5a,8,8,11a-tetramethyl-1,4,5a,6,7,7a,8,9,10,11,11a,11b-dodecahydronaphtho[2,1-b]oxepin-3-yl)ethan-1-one (14).

A solution of MeLi (1.6 M in diethyl ether, 0.53 mL, 0.85 mmol) was added dropwise to a solution of **23** (270 mg, 0.77 mmol) in dry Et_2O (6 mL) at -78 ºC under Ar atmosphere and stirred for 5 min. At this time, TLC showed full consumption of starting material. The reaction was quenched with water at -78 ºC. Ether (30 mL) was added and the organic phase was washed with H_2O (2 x 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum for purified the crude in flash column chromatography (5% AcOEt / hexane) affording 220 mg of **14** (94%) as colorless syrup. $[\alpha]_D^{25}$= +77.7 (c 12.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (dd, *J* = 8.0, 2.2 Hz, 1H), 4.51 (dd, *J* = 16.8, 2.1 Hz, 1H), 4.40 (d, *J* = 16.9 Hz, 1H), 2.56 – 2.30 (m, 2H), 2.29 (s, 3H), 1.82 – 1.71 (m, 3H), 1.70 – 1.61 (m, 4H), 1.53 – 1.33 (m, 3H), 1.27 (s, 3H), 1.17 (ddd, *J* = 13.5, 13.5, 4.3 Hz, 1H), 0.93 (m, 1H), 0.90 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 198.7 (C), 145.7 (CH), 143.4 (C), 78.9 (C), 57.9 (CH_2), 56.2 (CH), 55.5 (CH), 42.0 (CH_2), 39.9 (CH_2), 38.6 (C), 37.7 (CH_2), 33.5 (C), 33.5 (CH_3), 25.8 (CH_3), 24.5 (CH_2), 22.7 (CH_3), 21.3 (CH_3), 20.7 (CH_2), 18.7 (CH_2), 16.2 (CH_3). IR (film): 2923, 1662, 1384, 1243, 1219, 1104, 722 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{33}O_2$ 305.2481, found 305.2477.

(4aS,6aR,13aR,13bS)-4,4,6a,13b-tetramethyl-11,12-bis(phenylsulfonyl)-1,2,3,4,4a,5,6,6a,8,10,11,12,12a,13,13a,13b-hexadecahydrobenzo[e]naphtho[2,1-b]oxepin-9-yl acetate (24).

trans-1,2-Bis(phenylsulfonyl)ethylene (250 mg, 0.79 mmol) and *p*-toluenesulfonic acid (14 mg, 0.07 mmol) were added to a solution of **14** (173 mg, 0.57 mmol) in isopropenyl acetate (4 mL),

and the mixture was heated at 160 ºC for 5 h in a sealed tube. At this time, TLC showed no remaining starting material. The reaction was allowed to rt and the crude was purified by flash chromatography on silica gel (30% AcOEt / hexane), affording 336 mg of an irresolvable mixture of adducts **24** (90%), as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (dd, *J* = 3.6, 1.1 Hz, 2H), 7.96 (dd, *J* = 3.6, 1.5 Hz, 2H), 7.72 (m, 1H), 7.68 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 4.33 – 4.23 (m, 3H), 4.05 (d, *J* = 16.9 Hz, 1H), 4.00 (br s, 1H), 3.51 (m, 1H), 2.63 (m, 1H), 2.53 (m, 1H), 2.15 (m, 1H), 2.11 (s, 3H), 2.07 (m, 1H), 1.70 – 1.55 (m, 3H), 1.51 – 1.40 (m, 3H), 1.32 – 1.12 (m, 4H), 1.02 (ddd, *J* = 13.2, 13.2, 4.4 Hz, 1H), 0.93 (s, 3H), 0.83 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 167.9 (C), 138.0 (C), 137.2 (C), 135.7 (C), 134.4 (CH), 134.3 (CH), 129.7 (2 CH), 129.6 (2 CH), 129.3 (2 CH), 129.1 (2 CH), 124.3 (C), 79.0 (C), 60.7 (CH), 58.6 (CH_2), 55.9 (CH), 55.9 (CH), 51.2 (CH), 41.7 (CH_2), 39.8 (CH_2), 38.5 (C), 38.5 (CH_2), 33.5 (CH), 33.4 (C), 30.1 (CH_3), 29.1 (CH_2), 23.5 (CH_3), 23.3 (CH_2), 21.6 (CH_3), 20.9 (CH_3), 20.3 (CH_2), 18.8 (CH_2), 15.9 (CH_3). IR (film): 1308, 1217, 1198, 1145, 1082, 752, 689, 564 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{36}H_{47}O_7S_2$ 655.2763, found 655.2773.

(4aS,6aR,13aR,13bS)-4,4,6a,13b-tetramethyl-1,2,3,4,4a,5,6,6a,8,13,13a,13b-dodecahydrobenzo[e]naphtho[2,1-b]oxepin-9-yl acetate (25).

To a solution of **24** (350 mg, 0.53 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise at room temperature DBU (0.16 mL, 1.07 mmol) and the reaction mixture was stirred for 4 h. At this time, TLC showed full consumption of starting material. The solvent was evaporated and ether (20 mL) was added. The organic layer was washed with H_2O (2 x 8 mL) and brine (8 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash

chromatography on silica gel (7% AcOEt / hexane), affording 179 mg (91%) of **25** as a white solid. $[\alpha]_D^{25}$= -57.8 (c 9.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 15.0 Hz, 1H), 2.98 (dd, *J* = 15.1, 9.7 Hz, 1H), 2.69 (d, *J* = 15.2 Hz, 1H), 2.28 (s, 3H), 1.91 (m, 1H), 1.79 – 1.45 (m, 5H), 1.42 (s, 3H), 1.40 – 1.23 (m, 3H), 1.11 (ddd, *J* = 13.5, 13.5, 4.3 Hz, 1H), 0.99 – 0.88 (m, 2H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 169.8 (C), 148.0 (C), 145.2 (C), 132.1 (C), 127.9 (CH), 126.5 (CH), 119.6 (CH), 79.8 (C), 58.7 (CH), 57.8 (CH_2), 55.9 (CH), 42.0 (CH_2), 40.8 (CH_2), 39.3 (CH_2), 38.8 (C), 33.5 (C), 33.5 (CH_3), 30.5 (CH_2), 21.5 (2 x CH_3), 21.0 (CH_3), 20.4 (CH_2), 18.7 (CH_2), 15.8 (CH_3). IR (film): 2924, 1763, 1463, 1367, 1204, 1039, 771 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{35}O_3$ 371.2586, found 371.2584.

(4aS,6aR,13aR,13bS)-4,4,6a,13b-tetramethyl-1,2,3,4,4a,5,6,6a,8,13,13a,13b-dodecahydrobenzo[e]naphtho[2,1-b]oxepin-9-ol (13).

Conc. hydrochloric acid (0.5 mL) was added to a stirred solution of **25** (125 mg, 0.34 mmol) in dioxane (4 mL) and the reaction mixture was warmed at 60 ºC. After 3 h TLC showed no starting material remaining. Ether (30 mL) was added and the organic layer was washed with H_2O (4 x 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum. The crude product was purified by flash chromatography (10% AcOEt / hexane) to yield 109 mg of **13** (98%) as a white solid. $[\alpha]_D^{25}$= -33.4 (c 6.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.95 (t, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 2.95 (dd, *J* = 15.1, 9.6 Hz, 1H), 2.62 (d, *J* = 15.1 Hz, 1H), 1.92 (dd, *J* = 12.8, 3.6 Hz, 1H), 1.82 – 1.47 (m, 4H), 1.44 (s, 3H), 1.41 – 1.24 (m, 4H), 1.11

(ddd, *J* = 13.5, 13.5, 4.4 Hz, 1H), 0.96 – 0.87 (m, 2H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 152.8 (C), 145.5 (C), 127.9 (CH), 126.7 (C), 121.2 (CH), 113.4 (CH), 79.8 (C), 59.1 (CH), 57.1 (CH_2), 56.0 (CH), 42.1 (CH_2), 40.8 (CH_2), 39.4 (CH_2), 38.8 (C), 33.6 (C), 33.5 (CH_3), 30.4 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 20.4 (CH_2), 18.8 (CH_2), 15.8 (CH_3). IR (film): br 3273, 2924, 1738, 1466, 1366, 1217, 1031, 771 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{33}O_2$ 329.2481, found 329.2480.

(4aS,6aR,13aR,13bS)-4,4,6a,13b-tetramethyl-1,2,3,4,4a,5,6,6a,8,13,13a,13b-dodecahydrobenzo[e]naphtho[2,1-b]oxepine-9,12-dione (26).

Potassium nitrosodisulfonate (350 mg, 1,3 mmol) was added to a stirred solution of **13** (70 mg, 0.21 mmol) in CH_2Cl_2 (20 mL), Na_2HPO_4/NaH_2PO_4 buffer (5 mL) and Aliquat336. After overnight, TLC showed no starting material. Then, the solvent was evaporated and ether (30 mL) was added. The organic layer was washed with H_2O (2 x 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography on silica gel (5% AcOEt / hexane) to give **26** (64 mg, 89%) as a yellow oil. $[\alpha]_D^{25}$= +341.5 (c 9.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.71 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 10.0 Hz, 1H), 4.66 (dd, *J* = 18.0, 2.3 Hz, 1H), 4.56 (dd, *J* = 18.1, 4.2 Hz, 1H), 2.98 (d, *J* = 18.4 Hz, 1H), 2.33 (m, 1H), 1.89 – 1.73 (m, 3H), 1.69 – 1.55 (m, 5H), 1.50 – 1.31 (m, 2H), 1.29 (s, 3H), 1.25 (m, 1H), 1.11 (td, *J* = 13.5, 4.2 Hz, 1H), 0.87 (s, 6H), 0.80 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 187.4 (C)x2, 146.6 (C), 143.6 (C), 136.4 (CH), 136.1 (CH), 79.5 (C), 56.7 (CH_2), 56.4 (CH), 55.5 (CH), 42.1 (CH_2), 39.8 (CH_2), 39.0 (C), 37.3 (CH_2), 33.6 (C), 33.5 (CH_3), 22.6 (CH_3), 21.3 (CH_3), 21.1 (CH_2), 20.6 (CH_2), 18.6 (CH_2), 16.1 (CH_3). IR (film): 2925, 1650,

1454, 1386, 1298, 1217, 814, 771 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{31}O_3$ 343.2273, found 343.2269.

(4aS,6aR,13aR,13bS)-4,4,6a,13b-tetramethyl-1,2,3,4,4a,5,6,6a,8,13,13a,13b-dodecahydrobenzo[e]naphtho[2,1-b]oxepine-9,12-diol (cyclosiphonodictyol A, 11).[7]

$Na_2S_2O_4$ (224 mg, 1.1 mmol) was added to a suspension of quinone **26** (75 mg, 0.22 mmol) in 8 mL of H_2O-$CHCl_3$ (1:1) and the mixture was stirred for 4 h, at which time TLC showed no starting material. $CHCl_3$ was removed under vacuum and ether (15 mL) was added. The organic layer was washed with H_2O (2 x 5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and removed in vacuum to afford 69 mg of **11** (91%). The product could not purify because is extremely air sensitive and back to quinone. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.51 (d, *J* = 8.5 Hz, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 4.84 (d, *J* = 15.2 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 3.10 (d, *J* = 15.6 Hz, 1H), 2.54 (dd, *J* = 15.6, 9.6 Hz, 1H), 1.98 (ddd, *J* = 12.7, 12.7 3.7 Hz, 1H), 1.77 – 1.51 (m, 6H), 1.39 – 1.28 (m, 3H), 1.21 (m, 1H), 1.11 (ddd, *J* = 13.5, 13.5, 4.3 Hz, 1H), 0.96 – 0.88 (m, 3H), 0.86 (s, 3H), 0.85 (s, 3H), 0.81 (s, 3H). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.49 (s, 1H), 8.42 (s, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 4.65 (d, *J* = 14.9 Hz, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 3.07 (d, *J* = 15.4 Hz, 1H), 2.34 (dd, *J* = 15.5, 9.5 Hz, 1H), 1.92 (d, *J* = 12.9 Hz, 1H), 1.66 – 1.58 (m, 3H), 1.49 – 1.36 (m, 3H), 1.35 (m, 1H), 1.33 (s, 3H), 1.20 (m, 1H), 1.09 (dt, *J* = 13.5, 4.2 Hz, 1H), 0.88 (m, 1H), 0.84 (s, 3H), 0.80 (s, 3H), 0.79 (s, 3H), 0.76 (m, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ: 146.7 (C), 146.5 (C), 130.9 (C), 128.7 (C), 114.7 (CH), 113.6 (CH), 80.0 (C), 57.5 (CH_2), 56.1 (CH), 55.5 (CH), 42.2 (CH_2), 39.7 (CH_2), 38.9 (C), 33.6 (C), 33.5 (CH_3), 29.9 (CH_2), 21.9 (CH_3), 21.6 (CH_2), 21.5 (CH_3), 20.5 (CH_2), 18.8 (CH_2), 15.8 (CH_3). IR (film): br 3334, 2923, 1738, 1365, 1259, 1217, 1024, 772 cm^{-1}. ^{13}C {^{1}H} NMR (125

MHz, DMSO-d_6) δ: 146.5 (C), 146.4 (C), 129.9 (C), 127.7 (C), 113.7 (CH), 112.3 (CH), 78.5 (C), 58.1 (CH), 56.7 (CH_2), 55.4 (CH), 41.6 (CH_2), 40.1 (CH_2), 39.4 (CH_2), 38.2 (C), 33.1 (CH_3), 33.1 (C), 21.6 (CH_3), 21.2 (CH_3), 20.8 (CH_2), 19.8 (CH_2), 18.2 (CH_2), 15.3 (CH_3). HRMS (ESI/TOF) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{32}O_3Na$ 367.2249, found 367.2246.

The NMR spectra in DMSO-d_6 are similar to that previously described for the natural product. In fact, the 13C NMR data are identical.

***Bis*(sulfato)-cyclosiphonodictyol A (12).**[8]

To a solution of **11** (30 mg, 0.087 mmol) in dry pyridine (1 mL) was added SO_3•Py (143 mg, 0.9 mmol) and the reaction mixture was heated to 80º C for 4 h. At this time, TLC showed no starting material. The reaction was cooled to 0 ºC and quenched with a saturated solution of Na_2CO_3 (1 mL) dropwise. The solvent was concentrated in vacuum and dried with Ar. The solid residue was purified by column chromatography on silica gel (30% MeOH / $CHCl_3$) to afford 39 mg of disulfate **12** (82%) as a white solid. $[\alpha]_D^{25}$= +12.3 (c 10.0, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.08 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 4.72 (d, *J* = 15.3 Hz, 1H), 4.56 (d, *J* = 15.3 Hz, 1H), 3.24 (d, *J* = 15.9 Hz, 1H), 2.39 (dd, *J* = 15.9, 9.6 Hz, 1H), 1.99 (m, 1H), 1.69 – 1.53 (m, 4H), 1.47 – 1.32 (m, 2H), 1.31 (s, 3H), 1.24 (m, 1H), 1.14 – 1.03 (m, 2H), 0.95 (m, 1H) 0.83 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H), 0.74 (m, 1H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ: 146.6 (C), 145.9 (C), 135.5 (C), 133.9 (C), 120.1 (CH), 119.2 (CH), 78.4 (C), 57.6 (CH_2), 55.5 (CH), 48.6 (CH), 41.7 (CH_2), 39.9 (CH_2), 38.9 (CH_2), 38.3 (C), 33.2 (CH_3), 33.1 (C), 22.0 (CH_2), 21.7 (CH_3), 21.3 (CH_3), 19.9 (CH_2), 18.3 (CH_2), 15.4 (CH_3). IR (film): br 3431, 2924, 1462, 1219, 1059, 1032, 1000, 831, 782, 583 cm^{-1}. HRMS (ESI/TOF) *m/z*: $[M-2Na+H]^-$ calcd for $C_{22}H_{31}O_9S_2$ 503.1409, found 503.1404.

The NMR data for the DMSO-d_6 solutions of synthetic compound are close to that reported for the CD_3OD solutions of the natural product. A complete comparison was not feasible due to the low solubility of the synthetic bis(sulfato) in CD_3OD.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all described compounds.

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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