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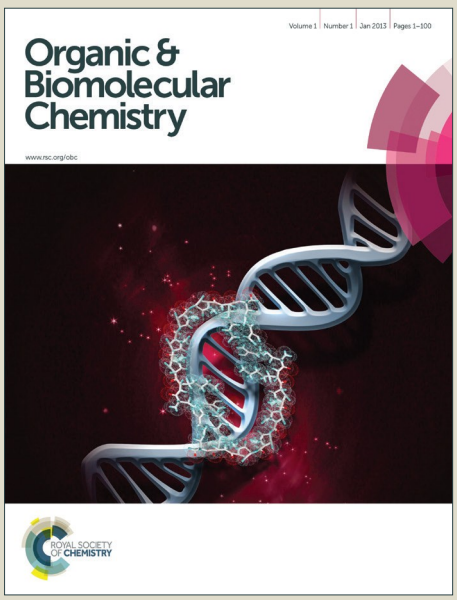

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Preparation of oxocene terpenes. First enantiospecific synthesis of cytotoxic arenaran A

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First syntheses of cytotoxic marine arenarans A and B starting from commercial (-)-sclareol, are reported. The oxocene ring of the target compound is formed *via* a ring-closing metathesis, a process that depends on certain structural requirements. The *trans*-fused structure of the natural product is confirmed by comparison with the *cis*-fused isomer, also synthesized. This synthetic strategy is also aplicable to the synthesis of other oxocene terpenes.

Introduction

Although terpenes containing eight-membered ether rings are infrequent in nature, their biological activities are of interest. Arenaran A (**1**) and B (**2**), two sesquiterpene ethers isolated from the marine sponge *Dysidea arenaria,* belong to this type of compound. Compound **1** is *in vitro*-active against several types of cancer cells, with reported IC50 values (μg/mL) of 9.51 (A-549, human lung carcinoma), 9.11 (HT-29, human colon adenocarcinoma), 5.28 (HCT-29, human colon adenocarcinoma) and 3.17 (P-388 murine leukemia). Another example of oxocane terpene is the labdane type brominated diterpene **3,** isolated from the red alga *Laurencia obtuse.*[2]

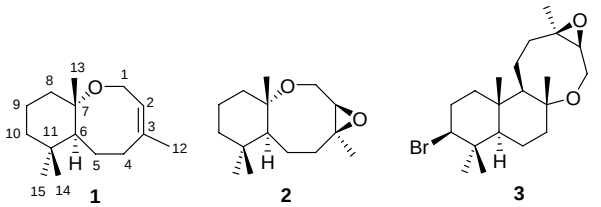
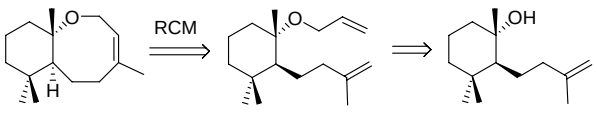


Figure 1. Natural oxocane terpenes.

Despite the rare structure of this type of compound, which is biogenetically related to aplysistatins and other bioactive metabolites, and the relevant biological activity observed in some cases, no syntheses of these oxocane terpenes have yet been reported. The structure of arenaran A (**1**) has been established in 2D NMR experiments, utilizing mainly H-C COSY correlations (J = 140 and J = 9 Hz); however, this result is insufficient to characterise the *trans*-fused union assigned. Moreover, the absolute configuration of natural terpene **1** remains unknown.

Results and discussion

These considerations, together with the possibility of preparing large quantities of arenaran A (**1**) in order to conduct an in-depth study of its biological activity, encouraged us to develop a synthetic route towards compound **1** and related terpenes. In this respect, the only relevant antecedent is a study aimed at the synthesis of arenaran A reported by Reggelin et al.[3] These authors essayed the construction of the bicyclic oxocene structure of **1** based on the intramolecular attack of an allyl alcohol on an alkenyl sulfoximine. The failure of their attempt highlights the difficulty of forming an eight-membered ring. In view of this outcome, we planned to create the oxocene ring via a ring-closing metathesis (RCM) process, as shown in Scheme 1.



Scheme 1. Retrosynthesis of arenaran A (**1**) *via* ring-closing metathesis.

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Electronic Supplementary Information (ESI) available: Copy of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x

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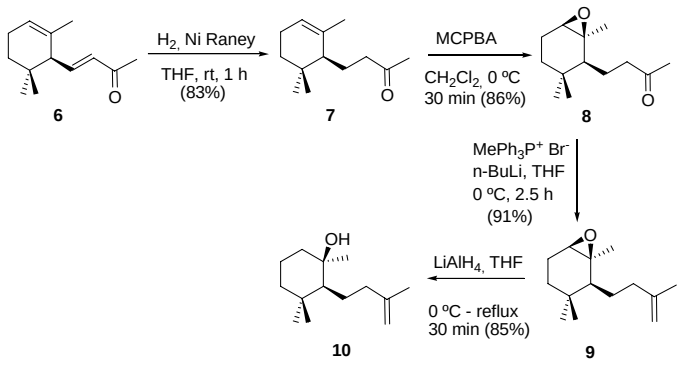
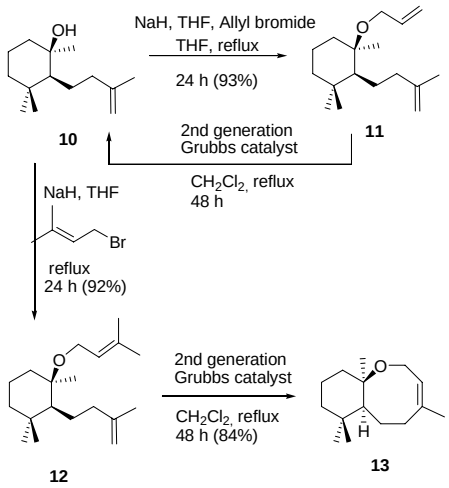
In order to determine the reaction conditions, we first investigated the use of α-ionone (**6**) as a starting material. Considering the chemical behaviour of compound **6** previously reported,[4] the utilization of this terpene as the synthetic precursor should provide alcohol **10**, the epimer of compound **5**, and consequently the complete sequence should lead to the corresponding *cis*-fused epi-arenanan A (**13**). Scheme 2 shows the synthesis of alcohol **10** from α-ionone (**6**). Epoxydation of dihydro-α-ionone (**7**) gave the expected epoxyketone **8**, which after methylenation and treatment with $LiAlH_4$ provided alcohol **10**.



Scheme 2. Synthesis of alcohol **10** from α-ionone (**6**).

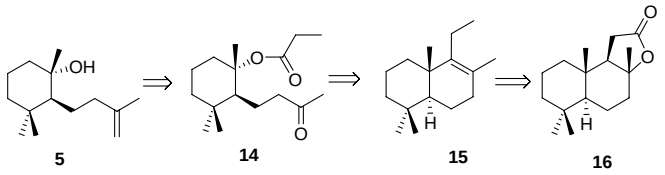
This alcohol was then transformed into epi-arenaran A (**13**), following the above retrosynthetic plan (Scheme 3). The reaction of alcohol **10** with allyl bromide under basic conditions leads to ether **11**, which unexpectedly failed to give the desired RCM after treatment with second-generation Grubbs catalyst, instead generating alcohol **10**. Under these reaction conditions, ether **12**, derived from dimethylallyl bromide, underwent the desired ring-closing metathesis, affording compound **13**, the *cis*-fused stereoisomer of arenaran A.



Scheme 3. Synthesis of epi-arenaran A (**13**) from alcohol **10**.

At this point, it is very important to note that the preparation of alcohol **5** in enantiopure form, the precursor of arenaran A (**1**), from α-ionone (**6**) can be achieved *via* the corresponding diatereoisomer of epoxyketone **8**, with the epoxy group on the α side; however, the preparation of this epoxyketone from α-ionone (**6**), reported by Serra, involves a very long synthetic sequence (10 steps), including a low yield lipase-mediated acetylation reaction.[4]

Taking into account these difficulties, we investigated the preparation of enantiopure alcohol **5**. A first synthetic proposal for obtaining this alcohol from commercial (+)-sclareolide (**16**) is depicted in scheme 4. Alcohol **5** is obtained from ketoester **14**, resulting from the Baeyer-Villiger oxidation of diketone derived from alkene **15**, which is easily prepared from lactone **16**.



Scheme 4. Retrosynthesis of alcohol **5** from (+)-sclareolide (**16**)

Scheme 5 shows the synthetic sequence for the intended synthesis of ketoester **14** from lactone **16**. Reduction of iodide **17** with Raney Ni, following a procedure developed in our laboratory, gave alkene **15**, which was then converted into diketone **18**. However, all attempts at obtaining the desired ketoester **14**, *via* a Baeyer-Villiger oxidation of diketone utilizing a variety of reaction conditions were unsuccessful, producing instead the ketoester **19**. These results highlight the difficulty of achieving oxidation of the ketone group linked to the quaternary carbon, probably due to steric hindrance. This outcome contrasts with that of the related, but more rigid 1-decalones;[5] however, the possibility of utilizing these ketones as a starting material for preparing alcohol **5** must be discarded due to the further difficulties arising from the tendency of the subsequent reduction products to dehydrate, affording bicyclic enol ethers.

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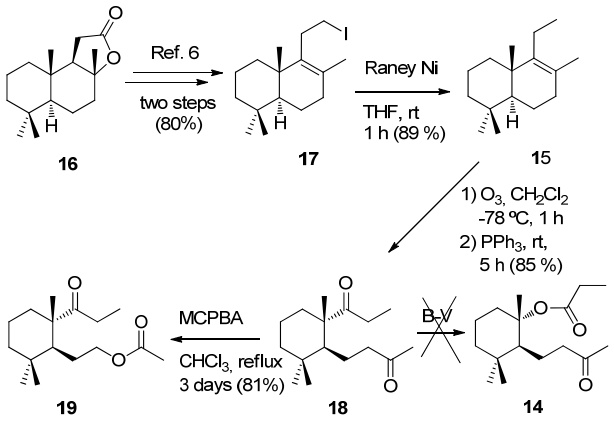
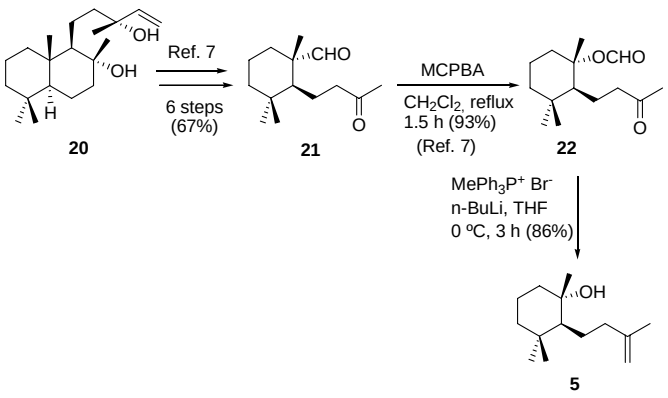


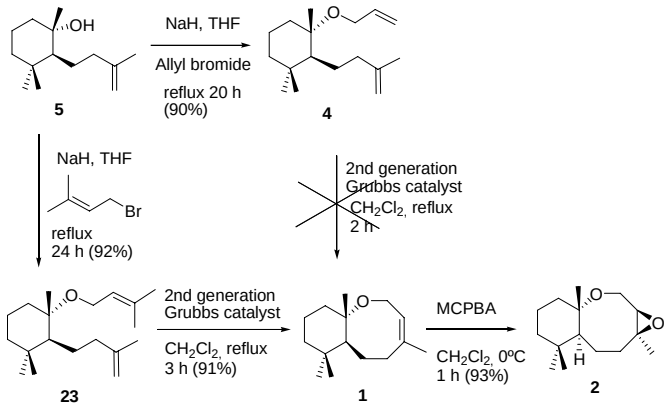
Scheme 5. Attempts at preparing ketoester **14** from (+)-sclareolide (**16**)

The above difficulties were circumvented by utilizing commercial (-)-sclareol (**20**) as a starting material. Thus, alcohol **5** was prepared from this diterpene, *via* ketoester **22**, resulting from the Baeyer-Villiger oxidation of ketoaldehyde **21**, utilizing a procedure developed in our laboratory[7] (see Scheme 6). At this point, it is interesting to note the different behaviour of the aldehyde group attached to the quaternary carbon, present in the compound **21,** from that of the ketone group joined to the same carbon atom, which has compound **18**; the first of these undergoes Baeyer-Villiger oxidation in good yield, under the usual reaction conditions, and so methylenation of ketoester **22** leads in good yield to the desired alcohol **5**.



Scheme 6. Synthesis of alcohol **5** from (-)-sclareol (**20**)

Alcohol **5** was then transformed into arenaran A (**1**) following a similar procedure to that utilized for the *cis*-fused isomer **13.** First, the O-allyl ether **4** was prepared, but this dialkene also failed to give the metathesis process. However, the *O*-dimethylallyl ether **23** underwent the desired reaction, affording arenaran A (**1**). At this point it is important to note that ether **23** undergoes the RCM much faster than its epimer **12**. The further epoxidation of compound **1** gave arenaran B (**2**) (Scheme 7).



Scheme 7. Synthesis of arenaran A (**1**) and B (**2**) from alcohol **5**.

As mentioned above, the structural elucidation performed by Crews et al. for the natural arenaran A, based on 2D NMR experiments, does not allow us to establish unequivocally the *trans*-fused union proposed by these authors.[1] However, after preparing both stereoisomers, we will be able to confirm this proposal. Tables 1 and 2 show the ^{13}C and ^{1}H NMR chemical shifts for epi-arenaran A (**13**) (with the *cis*-fused union), for the synthetic arenaran A (**1**), reported here, and for the natural arenaran A. NMR data for the synthetic and natural arenarans B (**2**) are shown in table 3.

Table 1. ^{13}C NMR chemical shifts for epi-arenaran A (**13**) and for the synthetic and natural arenarans A (**1**).

epi-Arenaran A (**13**)[a]	Synthetic Arenaran A (**1**)[a]	Synthetic Arenaran A (**1**)[b]	Natural Arenaran A (**1**)[b] (ref. 1)
140.6 (C)	132.9 (C)	133.1 (C)	132.8 (C)
123.6 (CH)	123.3 (CH_2)	124.7 (CH)	124.5 (CH)
77.4 (C)	80.2 (C)	79.5 (C)	79.3 (C)
56.4 (CH_2)	61.1 (CH)	61.8 (CH_2)	61.5 (CH_2)
55.5 (CH)	45.4 (CH_2)	46.1 (CH)	45.9 (CH)
42.8 (CH_2)	41.9 (CH)	42.6 (CH_2)	42.4 (CH_2)
41.9 (CH_2)	35.2 (CH_3)	35.7 (CH_2)	35.5 (CH_2)
35.5 (CH_2)	34.0 (C)	34.5 (C)	34.3 (C)
34.1 (C)	32.3(CH_2)	33.4 (CH_3)	33.1 (CH_3)
31.4 (CH_3)	28.9 (CH_3)	29.7 (CH_2)	29.5 (CH_2)
25.2 (CH_2)	25.0(CH_2)	26.4 (CH_3)	26.1 (CH_3)
24.6 (CH_3)	24.1 (CH_3)	24.9 (CH_2)	24.7 (CH_2)
21.1 (CH_3)	21.9 (CH_2)	23.2 (CH_3)	23.0 (CH_3)
18.0 (CH_2)	21.0 (CH_2)	22.1 (CH_3)	21.9 (CH_3)
15.1 (CH_3)	19.7 (CH_3)	20.5 (CH_2)	20.1 (CH_2)

[a]CD_3OD, [b]C_6D_6

Table 2. ^{1}H NMR chemical shifts for epi-arenaran A (**13**) and for the synthetic and natural arenarans A (**1**).

epi-Arenaran A (**13**)[a]	Synthetic Arenaran A (**1**)[a]	Synthetic Arenaran A (**1**)[b]	Natural Arenaran A (**1**)[b] (ref. 1)
5.43 (t, J=6.9)	5.15 (br s)	5.07 (br s)	5.06 (br s)
3.96 (dd, J=7.0,13.8)	4.22 (dd, J=2.1,18.4)	4.11 (br s)	4.06 (br s)
3.76 (dd, J=6.9,13.8)	4.03 (d, J=18.4)	3.68 (ddd, J=19.5, 11.3)	3.67 (ddd, J=19.9,11.5. 1.3)
2.40-2.03 (m)	3.37 (m)	1.68 (m)	1.68 (m)
1.96 (ddd, J=3.1,13.1)	1.76 (ddd, J=4.5,12.7)	1.68 (s)	1.67 (s)
1.87 (m)	1.69 (s)	1.63 (m)	1.63 (m)
1.76 (ddd, J=3.3,13.4)	1.65 (m)		
1.71 (s)	1.61-1.58 (m)	1.62 (m)	1.62 (m)
1.45-1.40 (m)	1.55 (m)	1.52 (m)	1.51 (m)
1.34 (d, J=3.0)	1.51 (m)	1.35 (m)	1.34 (m)
1.20 (m)	1.46 (dt, J=3.0,13.5)	1.31 (m)	1.31 (m)
1.13 (s)	1.35-1.32 (m)	1.29 (s)	1.26 (s)
1.08 (dd, J=4.0,13.4)	1.25 (s)	1.25 (m)	1.25 (m)
1.03 (s)	1.16 (ddd, J=4.1,13.3)	0.86 (s)	0.85 (s)
0.89 (s)	0.91 (s)	0.78 (s)	0.79 (s)

[a]CD_3OD, [b]C_6D_6

Table 3. ^{1}H and ^{13}C NMR data in $CDCl_3$ for the synthetic and natural arenarans B (**2**).

Synthetic Arenaran B (**2**)	Natural Arenaran B (**2**) (ref. 1)	Synthetic Arenaran B (**2**)	Natural Arenaran B (**2**) (ref. 1)
4.02 (dd, J=17.6, 1.7)	4.02 (dd, J=15.6, 2.1)	80.0 (C)	80.0 (C)
3.90 (d, J=17.6)	3.89 (d, J=15.6)	64.1 (CH)	64.1 (CH)
2.79 (s)	2.79 (d, J=2.1)	60.8 (C)	60.8 (C)
2.42 (dt, J=13.4, 4.9)	2.41 (dt, J=13.5, 5.1)	58.1 (CH_2)	58.2 (CH_2)
1.86 (dt, J=13.2, 3.9)	1.86 (dt, J=13.5, 3.6)	44.7 (CH)	45.0 (CH)
1.67 (m)	1.67 (m)	42.2 (CH_2)	42.4 (CH_2)
1.58 (m)	1.58 (m)	35.9 ((CH_2)	36.0 ((CH_2)
1.50 (m)	1.50 (m)	34.7 (C)	35.5 (C)
1.45 (m)	1.45 (m)	33.2 (CH_3)	33.3 (CH_3)
1.40 (m), 1.21 (m)	1.40 (m), 1.21 (m)	31.8 (CH_2)	32.7 (CH_2)
1.35 (m)	1.35 (m)	22.9 (CH_3)	23.0 (CH_3)
1.29 (s)	1.21 (s)	22.5 (CH_3)	22.6 (CH_3)
1.16 (s)	1.16 (s)	22.0 (CH_2)	22.1 (CH_2)
0.98 (s)	0.97 (s)	21.5 (CH_3)	21.9 (CH_3)
0.85 (s)	0.84 (s)	19.9 (CH_2)	20.0 (CH_2)

As can be seen in tables 1 and 2, there is an excellent correlation of spectral data between the synthetic and the natural arenaran A (**1**), while those of the *cis*-fused steroisomer (epi-arenaran A, **13**) are very discordant. This finding corroborates the *trans*-fused stereochemistry proposed for natural arenaran A by Crews et al. On the other hand, the *Z* configuration of the carbon-carbon double bond of arenaran A has been confirmed on the basis of the observed NOE effect between Me-12 (δ 1.68) and H-2 (δ 5.07) (see Electronic Supplementary Information). The NMR data of the synthetic and natural arenarans B (**2**), which are placed in order of decreasing δ in table 3, showed some discrepancies. In order to dispel doubts, a thorough study on the structure of synthetic arenaran B (**2**) has been conducted. This includes 1D and 2D NMR spectra at 500 MHz (TOCSY, COSY, HSQC, HMBC and NOESY experiments). This allowed us to corroborate unequivocally the proposed structure for this compound, and to assign correctly the ^{1}H and ^{13}C NMR signals (Table 4). The β disposition of the epoxide group has been confirmed on the basis of the observed NOE effect between H-2 (δ 2.79) and H-6 (δ 1.50). All these experiments are included in the Electronic Supplementary Information. With respect to the absolute stereochemistry of natural arenaran A, it should be noted that the optical rotation for the natural

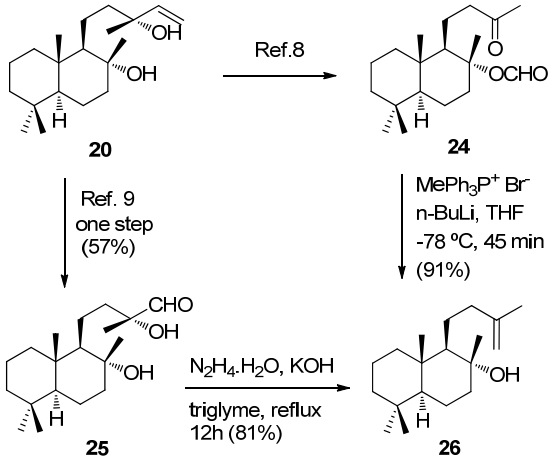
Table 4. ^{1}H and ^{13}C NMR assignments for synthetic arenaran B (**2**).

Carbon or Proton	^{1}H	^{13}C
1	4.03 (dd, J=15.9, 2.3) 3.90 (d, J=15.9)	58.2 (CH_2)
2	2.79 (d, J=2.3)	64.2 (CH)
3		60.9 (C)
4	2.43 (ddd, J=13.4, 4.3, 4.3) 1.88 (ddd, J=13.4, 13.4, 4.3)	32.0 (CH_2)
5	1.68 (tt, J=13.4, 4.3) 1.61 (tdd, J=13.4, 4.3, 4.3)	22.2 (CH_2)
6	1.50 (dd, J=13.4, 4.3)	44.9 (CH)
7		80.2 (C)
8	1.72 (ddd, J=13.5, 3.8, 3.8) 1.33 (ddd, J=13.5, 13.5, 3.8)	36.1 (CH_2)
9	1.55 (dp, J=13.5, 3.8) 1.45 (ddd, J=13.5, 3.8, 3.8)	20.0 (CH_2)
10	1.39 (ddd, J=13.5, 3.8, 3.8) 1.19 (ddd, J=13.5, 13.5, 3.8)	42.4 (CH_2)
11		34.8 (C)
12	1.30 (s)	23.1 (CH_3)
13	1.16 (s)	22.7 (CH_3)
14	0.85 (s)	21.7 (CH_3)
15	0.98 (s)	33.4 (CH_3)

compound ($[\alpha]_D^{25}$: +154.0; c 0.01, $CHCl_3$) is very discordant from that measured in our laboratory for synthetic arenaran A ($[\alpha]_D^{25}$: -32.1; c 0.01, $CHCl_3$); however, the optical rotation of synthetic arenaran B (**2**) ($[\alpha]_D^{25}$: -24.9; c 0.2, $CHCl_3$) is very

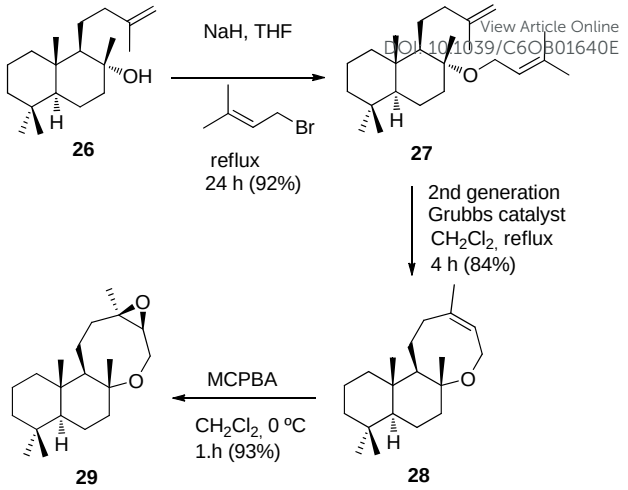
similar to that described for the natural epoxyde ($[\alpha]_D^{25}$: -24.4; c 0.23, $CHCl_3$). This finding leads us to believe that the $[\alpha]_D^{25}$ value previously reported for natural arenaran A (**1**) might be mistaken, and that the absolute stereochemistry proposed by Crews et al for this compound is correct, because of its correlation with (-)-sclareol (**20**).

Utilizing a similar strategy, commercial (-)-sclareol (**20**) was transformed into the oxocene epoxide **29,** *via* alcohol **26** (Scheme 9). This was synthesized in two alternative ways. First, methylenation of ketoester **24**, whose efficient preparation in one step from (-)-sclareol (**20**) has been developed by our group,[8] gave in high yield alcohol **26**. Alternatively, aldehyde **25**, previously synthesised in our laboratory,[9] was converted into this alcohol under the Wolff-Kishner conditions; to the best of our knowledge, this transformation of a α-hydroxyaldehyde into an alkene has not yet been described (Scheme 8).



Scheme 8. Synthesis of alcohol **26** from (-)-sclareol (**20**)

Next, alcohol **26** was transformed into the oxocene epoxide **29**, the 3-debromoderivative of marine metabolite **3**. Treatment of dimethylallyl ether **27** with second-generation Grubbs catalyst afforded in good yield oxocene **28**, which underwent stereoselective epoxydation, after reaction with MCPBA at 0 °C, to give epoxide **29**, the 3-debromoderivative of natural terpene **3**. The ^{13}C NMR chemical shifts of carbons of bicyclic ether moiety of epoxyde **29** are similar to that reported for natural terpene **3**.



Scheme 9. Synthesis of oxocene epoxide **29** from alcohol **26.**

Experimental

Materials and methods

Unless stated otherwise, reactions were performed in oven-dried glassware under an argon atmosphere using dry solvents. Solvents were dried as follows: THF over Na–benzophenone, and DCM and MeOH over CaH_2. Thin-layer chromatography (TLC) was performed using F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution 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-EtOAc mixtures of increasing polarity.^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. $CDCl_3$ was treated with K_2CO_3. Chemical shifts (δ H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak and tetramethylsilane. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, and m denoting singlet, broad singlet, doublet, broad 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, using FAB with thioglicerol or glycerol matrix doped in NaI 1%.

Synthetic procedures

4-(2,6,6-trimethylcyclohex-2-enyl)butan-2-one (7). Ni Raney (50% in water, 6 mL) was added to a solution of α-ionone (**6**)(10.0 g, 52 mmol) in THF (120 mL), and the mixture was stirred under an ordinary hydrogen pressure (balloon) at room temperature for 1 h. Then, the reaction mixture was filtered through a silicagel-Na_2SO_4 pad (100 g), eluting with acetone (100 mL). After evaporation of the solvent under vacuum, ketone **7** (8.39 g, 83%) was obtained, as a colourless oil. Compound **7** showed identical spectroscopic properties to those reported in the literature.[10,11]

4-((1S,2S,6R)-1,3,3-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-yl)butan-2-one (8). *m*-Chloroperbenzoic acid (70%, 4.92 g, 20.00 mmol) was added to a solution of dihydro-α-ionone (**7**)(3.52 g, 18.11 mmol) in dichloromethane (70 mL), cooled at 0 °C, and the reaction mixture was stirred for 30 min. Then, a 10% Na_2SO_3 solution (10 mL) was added, and the mixture was extracted with EtOAc (3 x 20 mL). The organic phase was successively washed with sat. $NaHCO_3$ (3 x 30 mL) and brine (2 x 30 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, compound **8** (3.27 g, 86%) was obtained as a colourless syrup. Compound **8** exhibited identical properties to those reported in the literature.[4]

(1S,6R)-1,3,3-Trimethyl-2-(3-methylbut-3-en-1-yl)-7-oxabicyclo[4.1.0]heptane (9). 2M n-BuLi in cyclohexane (7.8 mL, 15.7 mmol) was added to a solution of methyltriphenylphosphonium bromide (5.59 g, 15.7 mmol) in anhydrous THF (75 mL), and the mixture was stirred at 0 ºC under an argon atmosphere for 15 min. Then, a solution of ketone **8** (3 g, 14.26 mmol) in anhydrous THF (2 mL) was added, and the resulting mixture was kept stirring for 2.5 h. Then, the reaction was carefully quenched with water (10 mL), and the solvent was evaporated. Then, ether (100 mL) was added and the organic phase was washed with water (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na2SO4 and evaporated to afford a crude product that was purified by column chromatography on silica gel (10% EtOAc/hexane) to yield epoxide **9** (2.67 g, 91%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (s, 3H), 0.88 (s, 3H), 1.28 (m, 1H), 1.33 (s, 3H), 1.46-1.58 (m, 2H), 1.37 (m, 1H), 1.75 (s, 3H), 1.83 (m, 1H), 1.92 (dd, J = 15.5, 6.1 Hz, 1H), 2.05 (m, 1H), 2.29 (m, 1H), 2.93 (s, 1H), 4.71 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3 (CH_2), 22.8 (CH_3), 25.8 (CH_2), 27.1 (CH_3), 27.1 (CH_2), 27.5 (CH_3), 27.9 (CH), 31.6 (C), 37.7 (CH_2), 46.9 (CH_3), 59.8 (C), 60.3 (CH), 109.7 (CH_2), 146.8 (C). IR (film): 756, 884, 1095, 1182, 1216, 1366, 1376, 1449, 1649, 3073 cm^{-1}.HRMS (FAB) m/z calcd for $C_{14}H_{24}ONa$ (M + Na^+) 231.1725, found 231.1733.

(1R,2S)-1,3,3-Trimethyl-2-(3-methylbut-3-en-1-yl) cyclohexan-1-ol (10). $LiAlH_4$ (130 mg, 3.43 mmol) was added to a solution of epoxide **9** (2.5 g, 12.00 mmol) in anhydrous THF (50 mL) at 0 °C. The mixture was stirred at reflux under an argon atmosphere for 30 min, at which time TLC showed no **9** remaining. Then, the mixture was poured into ice and the solvent was evaporated. Ether (100 mL) was added and the phases were shaken. The organic phase was washed with water (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4, and evaporated to give alcohol **10** (2.15 g, 85%) as a yellow oil. ^{1}H RMN ($CDCl_3$, 400 MHz): δ 0.87 (s, 3H), 0.97 (s, 3H), 1.17 (s, 3H), 1.25 (br s, 2H), 1.33-1.47 (m, 4H), 1.53-1.65 (m, 2H), 1.75 (m, 1H), 1.75 (s, 3H), 2.05 (m, 2H), 4.69 (s, 2H). ^{13}C RMN ($CDCl_3$, 101 MHz): δ 18.3 (CH_2), 21.4 (CH_3), 22.5 (CH_3), 24.3 (CH_2), 30.8 (CH_3), 32.0 (CH_3), 34.7 (C), 41.1 (CH_2), 41.7 (CH_2), 41.8 (CH_2), 54.0 (CH), 73.0 (C) 109.5 (CH_2), 146.5 (C). IR (film): 757, 884, 909, 930, 1024, 1042, 1099, 1178, 1214, 1378, 1386, 1454, 1648, 3072, 3400-3600 cm^{-1}. HRMS (FAB) m/z calcd for $C_{14}H_{26}ONa$ (M + Na^+) 233.1881, found 233.1876.

(1R, 2S)-1-(Allyloxy)-1,3,3-trimethyl-2-(3-methylbut-3-en-1-yl)cyclohexane (11). NaH (208 mg, 5.20 mmol, 60% dispersion in mineral oil) was added to a solution of alcohol **10** (470 mg, 2.238 mmol) in anhydrous THF (20 mL) at 0 °C under an argon atmosphere, and allyl bromide (0.4 mL, 4.62 mmol) was added, and the reaction mixture was kept stirring at reflux for 24 h, at which time TLC showed no **10** remaining. The mixture was poured into ice and the solvent was evaporated under vacuum. Then ether (50 mL) was added and the organic phase was washed with water (3 x 15 mL) and brine (2 x 15 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (5% EtOAc/hexane), afforded ether **11** (520 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (s, 3H), 0.99 (s, 3H), 1.07 (dd, *J* = 14.1, 3.8 Hz, 1H), 1.12 (s, 3H), 1.16 (dd, *J* = 13.4, 3.6 Hz, 1H), 1.27-1.34 (m, 2H), 1.36-1.45 (m, 2H), 1.53-1.64 (m, 2H), 1.75 (s, 3H), 1.93-2.12 (m, 3H), 3.82 (d, *J* = 4.8 Hz, 2H), 4.68 (d, *J* = 5.0 Hz, 2H), 5.9 (m, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.4 (CH_2), 22.5 (CH_3), 24.1 (CH_2), 24.5 (CH_3), 32.2 (CH_3), 34.9 (C), 34.93 (CH), 41.8 (CH_2), 42.2 (CH_2), 56.0 (CH), 61.6 (CH_2), 22.1 (CH_3), 76.7 (C), 109.3 (CH_2), 114.1 (CH_2), 136.6 (CH), 146.9 (C). IR (film): 917, 1065, 1075, 1154, 1171, 1264, 1372, 1454, 1647 cm^{-1}. HRMS (FAB) m/z calcd for $C_{17}H_{30}ONa$ (M + Na^+) 273.2194, found 273.2201.

Treatment of ether 11 with 2nd Generation Grubbs catalyst. Obtention of alcohol 10. 2nd Generation Grubbs catalyst (20 mg). was added to a solution of ether **11** (170 mg, 0.68 mmol) in anhydrous CH_2Cl_2 (30 mL), and the mixture was kept stirring at reflux under an argon atmosphere for 48 h. Then, solvent was evaporated and the crude product was purified by column chromatography (20% EtOAc/hexane) to yield alcohol **10** (124 mg, 87%).

(2S, 3R)-1,1,3-Trimethyl-3-((3-methylbut-2-en-1-yl)oxy)-2-(3-methylbut-3-en-1-yl)cyclohexane (12). NaH (208 mg, 5.2 mmol, 60% dispersion in mineral oil) was added to a solution of alcohol **10** (0.5 g, 2.38 mmol) in anhydrous THF (20 mL) at 0 °C under an argon atmosphere, and 3,3-dimethylallyl bromide (0.4 mL, 3.46 mmol) was added, and the reaction mixture was kept stirring at reflux for 24 h, at which time TLC showed no **10** remaining. The mixture was poured into ice and the solvent was evaporated under vacuum. The aqueous phase was extracted with ether (2 x 30 mL) and the organic phase was

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washed with water (3 x 15 mL) and brine (2 x 15 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (5% EtOAc/hexane), afforded ether **12** (0.61 g, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (s, 3H), 0.97 (s, 3H), 1.05 (dd, *J* = 13.9, 3.8 Hz, 1H), 1.12 (s, 3H), 1.15 (dd, *J* = 13.3, 3.6 Hz, 1H), 1.27-1.33 (m, 2H), 1.34-1.42 (m, 2H), 1.63 (s, 3H), 1.69 (s, 1H), 1.71 (s, 3H), 1.75 (s, 3H), 1.96-2.01 (m, 2H), 2.04 (m, 2H), 3.79 (d, *J* = 6.2 Hz, 2H), 4.68 (d, *J* = 10.0 Hz, 2H), 5.28 (tt, *J* = 6.3, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.0 (CH_3) 18.5 (CH_2), 22.0 (CH_3), 22.5 (CH_3), 24.2 (CH_2), 24.6 (CH_3), 25.7 (CH_3), 32.2 (CH_3), 34.9 (C), 35.0 (CH_2), 41.9 (CH_2), 42.4 (CH_2), 56.0 (CH), 57.7 (CH_2), 76.5 (C), 109.3 (CH_2), 123.3 (CH), 133.3 (C), 147.0 (C). IR (film): 909, 1029, 1106, 1374, 1450, 1648 cm^{-1}. HRMS (FAB) m/z calcd for $C_{19}H_{34}ONa$ (M + Na^+) 301.2507, found 301.2498.

(6aS,10aR,Z)-4,7,7,10a-Tetramethyl-5,6,6a,7,8,9,10,10a-octahydro-2H-benzo[b]oxocine (epi-arenaran A) (13). 2nd Generation Grubbs catalyst (20 mg) was added to a solution of ether **12** (200 mg, 0.72 mmol) in anhydrous CH_2Cl_2 (40 mL), and the reaction mixture was kept stirring at reflux under an argon atmosphere for 48 h. Then, the solvent was evaporated and the crude product was purified by column chromatography (3% EtOAc/hexane) to yield ether **13** (0.13 g, 84%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.89 (s, 3H), 1.03 (s, 3H), 1.08 (dd, *J* = 13.4, 4.0 Hz, 1H), 1.13 (s, 3H), 1.20 (m, 1H), 1.34 (d, *J* = 3.0 Hz, 2H), 1.40-1.45 (m, 2H), 1.71 (s, 3H), 1.76 (dd, *J* = 13.4, 3.3 Hz, 1H), 1.87 (m, 1H), 1.96 (dd, *J* = 13.1, 3.1 Hz, 1H), 2.03-2.40 (m, 2H), 3.76 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.96 (dd, *J* = 13.8, 7.0 Hz, 1H), 5.43 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 15.1 (CH_3), 18.0 (CH_2), 21.1 (CH_3), 24.6 (CH_3), 25.2 (CH_2), 31.4 (CH_3), 34.1 (C), 35.5 (CH_2), 41.9 (CH_2), 42.8 (CH_2), 55.5 (CH), 56.4 (CH_2), 77.4 (C), 123.6 (CH), 140.6 (C). IR (film): 1052, 1071, 1095, 1153, 1176, 1212, 1364, 1386, 1454, 1475, 1671 cm^{-1}. HRMS (FAB) m/z calcd for $C_{15}H_{26}ONa$ (M + Na^+) 245.1881, found 245.1876.

(4aS,8aS)-8-ethyl-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (15). 5 mL of an aqueous suspension of Raney nickel (Aldrich, cat. 221678) was added to a stirred solution of **17** (2.5 g, 7.22 mmol) in THF (30 mL) and the mixture was further stirred at room temperature for 1h, under an ordinary hydrogen pressure (balloon). Then the mixture was diluted with diethyl ether (50 mL) and filtered on silca gel –Na_2SO_4 mixture (10: 16 g) column, washed with diethyl ether (10 mL) to yield **15** as colorless oil (1.42 g, 89%). $[\alpha]_D^{20}$ +67.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (s, 3H), 0.87 (s, 3H), 0.92 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 1.56 (s, 3H), 0.99 – 1.70 (m, 8H), 1.75 – 2.08 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.1 (CH_3), 19.07 (CH_3), 19.09 (CH_3), 19.3 (CH_2), 20.0 (CH_2), 20.5 (CH_3), 21.7 (CH_2), 33.3 (CH_2), 33.61 (C), 33.63 (CH_3), 36.9 (CH_2), 39.1 (C), 41.8 (CH_2), 51.9 (CH), 125.0 (C), 142.3 (C). IR (film): 1374, 1457, 1644 cm^{-1}. HRMS (FAB) m/z calcd for $C_{16}H_{28}Na$ (M + Na^+) 243.2089, found 243.2093.

4-((1S,6S)-2,2,6-trimethyl-6-propionylcyclohexyl)butan-2-one (18). O_3/O_2 was bubbled through a solution of compound **15** (2.0 g, 9.09 mmol) in CH_2Cl_2 (60 mL) cooled at -78 °C for 1 h, after which time TLC showed no remaining starting material. Then, argon was bubbled through the solution for 5 min, and triphenylphosphine (2.6 g, 9.9 mmol) was added, and the mixture was further stirred at room temperature for 5 h. After evaporation of the solvent under vacuum, the resulting crude product was purified by column chromatography on silica gel (25% EtOAc/ hexane) giving diketone **18** (1.95 g, 85 %), as a colourless syrup. $[\alpha]_D^{20}$ -16.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (s, 3H), 0.88 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 1.18 (m, 1H), 1.28 – 1.75 (m, 8H), 2.05 (s, 3H), 2.25 – 2.68 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.5 (CH_3), 17.2 (CH_3), 18.2 (CH_2), 22.1 (CH_2), 22.5 (CH_3), 29.8 (CH_3), 30.6 (CH_2), 33.4 (CH_3), 34.3 (C), 37.1 (CH_2), 41.2 (CH_2), 45.5 (CH_2), 47.7 (CH), 52.8 (C), 209.0 (C), 217.6 (C). IR (film): 772, 957, 1161, 1355, 1460, 1697, 1715 cm^{-1}. HRMS (FAB) m/z calcd for $C_{16}H_{28}O_2Na$ (M + Na^+) 275.1987, found 275.1979.

2-((1S,6S)-2,2,6-trimethyl-6-propionylcyclohexyl)ethyl acetate (19). *m*-Chloroperbenzoic acid (70%, 493 mg, 2.158 mmol) was added to a solution of compound **18** (272 mg; 1.079 mmol) in chloroform (10 mL), and the reaction mixture was stirred at reflux for 3 days, at which TLC showed no remaining starting material. Then, a 10% Na_2SO_3 solution (1 mL) was added, and the mixture was stirred for an additional 15 min. Then the reaction was extracted with EtOAc (3 x 10 mL) and the organic phase was successively washed with sat. $NaHCO_3$ (5 x 10 mL) and brine (2 x 10 mL), and dried over anhydrous Na_2SO_4 and evaporated to give a crude residue, which, after column chromatography on silica gel (10% EtOAc/hexane), afforded **19** (234 mg, 81%) as a colourless syrup. $[\alpha]_D^{20}$ -13.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (s, 3H), 0.90 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 1.18 – 1.74 (m, 9H), 1.99 (s, 3H), 2.40 – 2.56 (m, 2H), 3.79 – 3.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.5 (CH_3), 17.5 (CH_3), 18.2 (CH_2), 21.0 (CH_3), 22.7 (CH_2), 27.2 (CH_2), 30.5 (CH_2), 33.1 (CH_3), 34.0 (C), 36.3 (CH_2), 40.8 (CH_2), 44.7 (CH), 52.5 (C), 65.1 (CH_2), 170.9 (C), 216.9 (C). IR (film): 957, 1096, 1355, 1459, 1697, 1714, 3072 cm^{-1}. HRMS (FAB) m/z calcd for $C_{16}H_{28}O_3Na$ (M + Na^+) 291.1936, found 291.1944.

(1S,2S)-1,3,3-Trimethyl-2-(3-oxobutyl) cyclohexyl formate (22). *m*-Chloroperbenzoic acid (70%, 1.37 g, 5.58 mmol) and $NaHCO_3$ (0.56 g, 6.69 mmol) was added to a solution of ketoaldehyde **21** (0.5 g, 2.23 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred under reflux for 1.5 h. Then, 10% aq Na_2SO_3 (5 mL) was added and the mixture was further stirred at room temperature for 15 min. Then, EtOAc (20 mL) was added and the organic phase was washed with water (3 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and evaporated to give formate **22** (0.49 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (s, 3H), 0.98 (s, 3H), 1.14-1.28 (m, 1H), 1.30-1.40 (m, 1H), 1.43-1.50 (m, 1H), 1.50-1.60 (m, 3H), 1.55 (s, 3H), 1.60-1.75 (m, 3H), 2.16 (s, 3H), 2.48 (dt, *J* = 12.0, 3.0 Hz, 1H), 2.51-2.59 (m, 1H), 2.65-2.73 (m, 1H), 8.05 (s, 1H). ^{13}C NMR

($CDCl_3$, 100 MHz): δ 19.8 (CH_2), 20.2 (CH_2), 20.9 (CH_3), 21.7 (CH_3), 30.0 (CH_3), 32.7 (CH_3), 35.8 (C), 38.6 (CH_2), 40.6 (CH_2), 45.9 (CH_2), 53.2 (CH), 88.9 (C), 209.3 (C), 160.5 (CH). HRMS (FAB) m/z calcd for $C_{14}H_{24}O_3Na$ (M + Na^+) 263.1623, found 263.1619.

(1S,2S)-1,3,3-Trimethyl-2-(3-methylbut-3-en-1-yl) cyclohexan-1-ol (5). 2M *n*-BuLi in cyclohexane (1.25 mL, 2.5 mmol) was added to a solution of methyltriphenylphosphonium bromide (0.91 g, 2.5 mmol, 98%) in anhydrous THF (25 mL), and the mixture was stirred at 0 °C under an argon atmosphere for 15 min. Then, a solution of ketoester **22** (0.3 g, 1.25 mmol) in anhydrous THF (0.3 mL) was added, and the resulting mixture was kept stirring for 3 h. Then, the reaction was carefully quenched with water (0.5 mL). The solvent was evaporated and ether was added (25 mL), and the organic phase was washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated to afford a crude product that was purified by column chromatography on silica gel (20% EtOAc/hexane) to yield alcohol **5** (0.23 g, 86%) as a yellow oil. $[\alpha]_D^{20}$ +6.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (s, 3H), 0.95 (s, 3H), 1.11 (t, *J* = 4.5 Hz, 1H), 1.17 (s, 3H), 1.21 (dd, *J* = 13.0, 4.0 Hz, 1H), 1.25 (s, 1H), 1.37 (m, 1H), 1.31 (dd, *J* = 12.3, 4.1 Hz, 1H), 1.40-1.50 (m, 2H), 1.52-1.64 (m, 2H), 1.75 (s, H), 2.11 (m, 1H), 2.20 (m, 1H), 4.70 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5 (CH_2), 21.4 (CH_3), 22.6 (CH_3), 23.2 (CH_3), 24.4 (CH_2), 32.8 (CH_3), 35.6 (C), 40.9 (CH_2), 41.5 (CH_2), 43.6 (CH_2), 56.8 (CH), 74.1 (C), 109.7 (CH_2), 147.1 (C). IR (film): 883, 911, 1063, 1100, 1161, 1373, 1388, 1459, 1648, 1714, 3072, 3300-3600 cm^{-1}.HRMS (FAB) m/z calcd for $C_{14}H_{26}ONa$ (M + Na^+) 233.1881, found 233.1890.

(1S, 2S)-1-(Allyloxy)-1,3,3-trimethyl-2-(3-methylbut-3-en-1-yl)cyclohexane (4). NaH (250 mg, 6.24 mmol, 60% dispersion in mineral oil) was added to a solution of alcohol **5** (564 mg, 2.70 mmol) in anhydrous THF (20 mL) at 0 °C under an argon atmosphere, and allyl bromide (0.5 mL, 5.54 mmol) was added, and the reaction mixture was kept stirring at reflux for 20 h, at which time TLC showed no **5** remaining. The mixture was poured into ice and the solvent was evaporated under vacuum. Then ether (50 mL) was added and the organic phase was washed with water (3 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (5% EtOAc/hexane), afforded ether **4** (618 mg, 90%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.25 (dd, *J*=1.7, 17.2 Hz, 1H), 5.05 (dd, *J*=1.7, 10.4 Hz, 1H), 4.65 (s, 2H), 3.92-3.83 (m, 2H), 2.22 (m, 1H), 2.01 (m, 1H), 1.72 (s, 3H), 1.65-1.52 (m, 2H), 1.41-1.28 (m, 5H), 1.24 (s, 1H), 1.19 (m, 1H), 1.14 (s, 3H), 0.95 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C), 136.5 (CH), 114.6 (CH_2), 108.9 (CH_2), 78.5 (C), 60.9 (CH_2), 53.5 (CH), 41.2 (CH_2), 40.7 (CH_2), 37.7 (CH_2), 35.4 (C), 32.9 (CH_3), 25.2 (CH_2), 22.6 (CH_3), 22.1 (CH_3), 19.9 (CH_2), 19.8 (CH_3). IR (film): 1074, 1155, 1264, 1374, 1455, 1648 cm^{-1}. HRMS (FAB) m/z calcd for $C_{17}H_{30}ONa$ (M + Na^+) 273.2194, found 273.2185.

Treatment of ether 4 with 2nd Generation Grubbs catalyst. 2nd Generation Grubbs catalyst (22 mg). was added to a solution of ether **4** (187 mg, 0.75mmol) in anhydrous CH_2Cl_2 (30 mL), and the mixture was kept stirring at reflux under an argon atmosphere for 2 h. Then, solvent was evaporated affording a crude product, which consists of a complex mixture and starting material.

(2S,3S)-1,1,3-Trimethyl-3-((3-methylbut-2-en-1-yl)oxy)-2-(3-methylbut-3-en-1-yl)cyclohexane (23). NaH (34 mg, 0.86 mmol, 60% dispersion in mineral oil) was added to a solution of alcohol **5** (147 mg, 0.7 mmol) in anhydrous THF (12.5 mL) at 0 °C under an argon atmosphere, and 3,3-dimethylallyl bromide (0.24 mL, 20.77 mmol) was added, and the reaction mixture was kept stirring at reflux for 24 h, at which time TLC showed no **5** remaining. The mixture was poured into ice and the solvent was evaporated under vacuum. Then ether (25 mL) was added and the organic phase was washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (3% EtOAc/hexane), afforded ether **23** (179 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ +21.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (s, 3H), 0.97 (s, 3H), 1.17 (s, 3H),), 1.26 (s, 1H), 1.31-1.33 (m, 2H), 1.36 (m, 1H), 1.43-1.46 (m, 2H), 1.56-1.59 (m, 3H), 1.64 (s, 3H), 1.71 (s, 3H), 1.73 (s, 3H), 2.03 (m, 1H), 2.24 (m, 1H), 3.82-3.90 (m, 2H), 4.67 (s, 2H), 5.27 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.02 (CH_3), 20.0 (CH_2), 20.3 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 25.2 (CH_2), 25.8 (CH_3), 32.9 (CH_3), 35.4 (C), 37.3 (CH_2), 40.5 (CH_2), 41.2 (CH_2), 53.0 (CH), 56.8 (CH_2), 78.2 (C), 108.9 (CH_2), 122.8 (CH), 134.4 (C), 147.6 (C). IR (film): 754, 960, 1074, 1124, 1276, 1721 cm^{-1}. HRMS (FAB) m/z calcd for $C_{19}H_{34}ONa$ (M + Na^+) 301.2507, found 301.2509.

Arenaran A (1). 2nd Generation Grubbs catalyst (10 mg) was added to a solution of ether **23** (62 mg, 0.223 mmol) in anhydrous CH_2Cl_2 (30 mL), and the mixture was kept stirring at reflux under an argon atmosphere for 3 h. Then, solvent was evaporated and the crude product was purified by column chromatography (3% AcOEt/hexane) to yield **1** (45 mg, 91%). $[\alpha]_D^{20}$ -32.1 (*c* 0.01, $CHCl_3$). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.91 (s, 3H), 1.16 (ddd, *J* = 13.3, 4.1 Hz, 1H), 1.25 (s, 3H), 1.35-1.32 (m, 2H), 1.46 (dt, *J* = 13.5, 3.0 Hz, 1H), 1.51 (m, 2H), 1.55 (m, 2H), 1.61-1.58 (m, 2 H), 1.65 (m, 2H), 1.69 (s, 3H), 1.76 (ddd, *J* = 12.7, 4.5 Hz), 3.37 (m, 2H), 4.03 (d, *J* = 18.4 Hz), 4.22 (dd, *J* = 18.4, 2.1 Hz), 5.15 (br s). ^{13}C NMR (CD_3OD, 100 MHz): δ 19.7 (CH_3), 21.0 (CH_2), 21.9 (CH_2), 24.1 (CH_3), 25.0 (CH_2), 28.9 (CH_3), 32.3 (CH_2), 34.0 (C), 35.2 (CH_3), 41.9 (CH), 45.4 (CH_2), 61.1 (CH), 80.2 (C), 123.3 (CH_2), 132.9 (C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (s, 3H), 0.91 (s, 3H), 1.16 (dd, *J* = 13.3, 4.1 Hz, 1H), 1.25 (s, 3H), 1.32-1.35 (m, 2H), 1.46 (dt, *J* = 13.5, 3.0 Hz, 1H), 1.51 (m, 1H), 1.55 (m, 1H), 1.58-1.61 (m, 2H), 1.65 (m, 1H), 1.69 (s, 3H), 1.76 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.37 (m, 1H), 4.03 (d, *J* = 18.4 Hz, 1H), 4.22 (dd, *J* = 18.4, 2.1 Hz, 1H), 5.15 (br s, 1H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.1 (CH_2), 22.0 (CH_3), 22.9 (CH_3), 24.5 (CH_2), 26.3 (CH_3), 29.4 (CH_2), 33.3 (CH_3), 34.5 (C), 35.5 (CH_2),

42.3 (CH_2), 45.7 (CH), 61.5 (CH_2), 79.8 (C), 123.7 (CH), 133.3 (C). HRMS (FAB) m/z calcd for $C_{15}H_{26}ONa$ (M + Na^+) 245.1881, found 245.1893.

Arenaran B (2). *m*-Chloroperbenzoic acid (70%, 50.0 mg, 0.20 mmol) was added to a solution of compound **1** (28 mg, 0.126 mmol) in CH_2Cl_2 (12.5 mL) at 0 °C, and the mixture was stirred for 1 h. Then a 10% Na_2SO_3 solution (5 mL) was added and the mixture was further stirred for 15 min. Then, EtOAc (10 mL) was added, and the organic phase was washed with sat $NaHCO_3$ (3 x 10 mL) and brine (2 x 10 mL), and dried over anh Na_2SO_4. Evaporation of the solvent under vacuum gave finally epoxide **2** (28 mg, 93%) as a low m.p. solid. $[\alpha]_D^{25}$: -24.9 (*c* 0.2, $CHCl_3$) (lit.[1]: -24.4 (*c* 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (s, 3H), 0.98 (s, 3H), 1.16 (s, 3H), 1.29 (s, 3H), 1.21 (m, 1H), 1.40 (m, 1H), 1.45 (m, 1H), 1.50 (m, 1H), 1.58 (m, 1H), 1.67 (m, 1H), 1.86 (dt, *J* = 13.2, 3.9 Hz, 1H), 2.42 (dt, *J* = 13.4, 4.9 Hz, 1H), 2.79 (s 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.02 (dd, *J* = 17.6, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9 (CH_2), 21.5 (CH_3), 22.0 (CH_2), 22.5 (CH_3), 22.9 (CH_3), 31.8 (CH_2), 33.2 (CH_3), 34.7 (C), 35.9 ((CH_2), 42.2 (CH_2), 44.7 (CH), 58.1 (CH_2), 60.8 (C), 64.1 (CH), 80.0 (C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (s, 3H), 0.98 (s, 3H), 1.16 (s, 3H), 1.19 (ddd, J = 13.5, 13.5, 3.8 Hz, 1H), 1.30 (s, 3H), 1.33 (ddd, J = 13.5, 13.5, 3.8 Hz, 1H), 1.39 (ddd, J = 13.5, 3.8, 3.8 Hz, 1H), 1.45 (ddd, J = 13.5, 3.8, 3.8 Hz, 1H), 1.50 (dd, J = 13.4, 4.3 Hz, 1H), 1.55 (dp, J = 13.5, 3.8 Hz, 1H), 1.61 (tdd, J = 13.4, 4.3, 4.3 Hz, 1H), 1.68 (tt, J = 13.4, 4.3 Hz, 1H), 1.72 (ddd, J = 13.5, 3.8, 3.8 Hz, 1H), 1.88 (ddd, J = 13.4, 13.4, 4.3 Hz, 1H), 2.43 (ddd, J = 13.4, 4.3, 4.3 Hz, 1H), 2.79 (d, J = 2.3 Hz, 1H), 3.90 (d, J = 15.9 Hz, 1H), 4.03 (dd, J = 15.9, 2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.0 (CH_2), 21.7 (CH_3), 22.2 (CH_2), 22.7 (CH_3), 23.1 (CH_3), 32.0 (CH_2), 33.4 (CH_3), 34.8 (C), 36.1 (CH_2), 42.4 (CH_2), 44.9 (CH), 58.2 (CH_2), 60.9 (C), 64.2 (CH), 80.2 (C).

(1R,2R,4aS,8aS)-2,5,5,8a-Tetramethyl-1-(3-methylbut-3-en-1-yl)decahydronaphthalen-2-ol (26). 2 M *n*-BuLi in cyclohexane (1.7 mL, 3.3 mmol) was added to a solution of methyltriphenylphosphonium bromide (15.75 g, 60 mmol, 98%) in anhydrous THF (75 mL), and the mixture was stirred at -78ºC under an argon atmosphere for 15 min. Then, a solution of ketoester **24**(3.8 g, 12 mmol) in anhydrous THF (2 mL) was added, and the resulting mixture was kept stirring for 45 min. Then, the reaction was carefully quenched with water (5 mL), and the solvent was evaporated. Then, ether (100 mL) was added, and the organic phase was washed with water (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and evaporated to afford a crude product that was purified by column chromatography on silica gel (20% EtOAc/hexane) to yield alcohol **26** (3.4 g, 91%). $[\alpha]_D^{20}$ +8.5 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.79 (s, 3H), 0.80 (s, 3H), 0.86 (s, 3H), 0.92 (dd, *J* = 12.1, 2.3 Hz, 1H), 0.97 (dd, *J* = 12.7, 3.8 Hz, 1H), 1.05 (t, *J* = 4.0 Hz, 1H), 1.14 (s, 3H), 1.25 (br s, 1H), 1.28 (s, 1H), 1.35-1.40 (m, 2H), 1.41 (s, 1H), 1.43 (m, 1H), 1.53-1.61 (m, 2H), 1.62-1.67 (m, 3H), 1.73 (s, 3H), 1.86 (dt, *J* = 12.2, 3.1 Hz, 1H), 2.04-2.14 (m, 2H), 4.69 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.5 (CH_3), 18.5 (CH_2), 20.6 (CH_2), 21.5 (CH_3), 22.6 (CH_3), 23.6 (CH_2), 23.9 (CH_3), 33.3 (C), 33.4 (CH_3), 39.2 (C), 39.7 (CH_2), 41.3 (CH_2), 42.0 (CH_2), 44.6 (CH_2), 56.2 (CH), 61.5 (CH), 74.1 (C), 109.6 (CH_2), 147.1 (C). IR (film): 882, 968, 1083, 1103, 1386, 1455, 1648, 1727, 3300-3500 cm^{-1}. HRMS (FAB) m/z calcd for $C_{19}H_{34}ONa$ (M + Na^+) 301.2507, found 301.2499.

Treatment of aldehyde 25 with N_2H_4-KOH. Obtention of alcohol 26. Hydrazine (2 mL, 41.2 mmol) was added to a solution of aldehyde **25** (2.0 g, 6.5 mmol) in triethyleneglycol dimethyl ether (20 mL) and the mixture was stirred under reflux for 1 h, then KOH (2.31 g, 41.25 mol) was added and the mixture was stirred at reflux for an additional 11h. Then, the mixture was kept at room temperature and H_2O (10 mL) was added. EtOAc (50 mL) was added and the organic phase was washed with H_2O (10 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na_2SO_4 and evaporated to give a crude product which after column chromatography on silica gel (10% EtOAc/hexane), afforded alcohol **26** (1.6 g, 81%) as a colourless oil.

(4aS,5R,6R,8aS)-1,1,4a,6-Tetramethyl-6-((3-methylbut-2-en-1-yl)oxy)-5-(3-methylbut-3-en-1-yl)decahydronaphthalene (27). NaH (100 mg, 2.5 mmol, 60% dispersion in mineral oil) was added to a solution of alcohol **26** (180 mg, 0.647 mmol) in anhydrous THF (100 mL) at 0 °C under an argon atmosphere, and 3,3-dimethylallyl bromide (0.2 mL, 1.73 mmol) was added, and the reaction mixture was kept stirring at reflux for 24 h, at which time TLC showed no **26** remaining. The mixture was poured into ice and the solvent was evaporated under vacuum. Then, ether (100 mL) was added and the organic phase was washed with water (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (5% EtOAc/hexane), afforded ether **27** (206 mg, 92%). $[\alpha]_D^{20}$ -7.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.79 (s, 3H), 0.83 (s, 3H), 0.85 (s, 3H), 0.90 (dd, *J* = 12.3, 2.2 Hz, 1H), 0.97 (dd, *J* = 12.9, 3.6 Hz, 1H), 1.14 (s, 3H), 1.25 (s, 2H), 1.35-1.44 (m, 2H), 1.54-1.61 (m, 4H), 1.63 (s, 3H), 1.65-1.68 (m, 3H), 1.71 (s, 3H), 1.72 (s, 3H), 1.84 (dt, *J* = 12.2, 3.3 Hz, 1H), 2.01 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.17 (dd, *J* = 13.3' 4.6 Hz, 1H), 3.81-3.90 (m, 2H), 4.65 (br s, 2H), 5.25 (tt, *J* = 6.4, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.9 (CH_3), 18.1 (CH_3), 18.5 (CH_2), 20.1 (CH_2), 20.8 (CH_3), 21.5 (CH_3), 22.6 (CH_3), 24.3 (CH_2), 25.8 (CH_3), 33.2 (C), 33.4 (CH_3), 38.5 (CH_3), 39.2 (C), 40.1 (CH_2), 41.0(CH_2), 42.1 (CH_2), 56.1 (CH), 56.8 (CH_2), 58.1 (CH), 78.3 (C), 108.9 (CH_2), 122.9 (CH), 134.3 (C), 147.6 (C). IR (film): 973, 1035, 1058, 1079, 1131, 1386, 1446, 1647 cm^{-1}. HRMS (FAB) m/z calcd for $C_{24}H_{42}ONa$ (M + Na^+) 369.3133, found 369.3141.

(6aR,8aS,12aS,12bR,Z)-4,6a,9,9,12a-Pentamethyl-2,3,6a,7,8,8a,9,10,11,12,12a,12b-dodecahydro-1H-naphtho[2,1-b]oxocine (28). 2nd Generation Grubbs catalyst (30 mg) was added to a solution of ether **27** (310 mg, 0.895 mmol) in anhydrous CH_2Cl_2 (40 mL). The mixture was kept stirring at reflux under an argon atmosphere for 4 h. Then, the solvent was evaporated and the crude product was purified by column chromatography (3% AcOEt/hexane) to yield **28** (218 mg, 84%). $[\alpha]_D^{20}$ +40.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR (CD_3OD, 400

MHz): δ 0.80 (s, 3H), 0.82 (dd, *J* = 12.2, 2.5 Hz, 1H), 0.87 (s, 3H), 0.88 (s, 3H), 1.13 (dd, *J* = 13.3, 3.8 Hz, 1H), 1.24 (s, 3H), 1.30 (dd, *J* = 12.6, 3.5 Hz, 1H), 1.34-1.43 (m, 3H), 1.50 (dd, *J* = 12.0, 3.8 Hz, 1H), 1.54-1.58 (m, 2H), 1.60-1.66 (m, 3H), 1.68 (br d, *J* = 1.5 Hz, 3H), 1.70-1.73 (m, 2H), 1.82 (dd, *J* = 13.1, 4.5 Hz, 1H), 3.37 (dd, *J* = 12.7, 4.4 Hz, 1H), 4.03 (d, *J* = 18.4 Hz, 1H), 4.23 (dd, *J* = 18.4, 2.0 Hz, 1H), 5.15 (s, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 15.8 (CH_3), 18.8 (CH_2), 20.1 (CH_2), 21.8 (CH_3), 23.4 (CH_2), 23.9 (CH_3), 26.2 (CH_3), 29.2 (CH_2), 33.3 (C), 33.6 (CH_3), 36.3 (CH_2), 38.0 (C), 40.6 (CH), 41.8 (CH), 50.3 (CH), 55.9 (CH), 61.7 (CH_2), 79.9 (C), 123.5 (CH), 133.7 (C). IR (film): 1052, 1111, 1127, 1218, 1384, 1450 cm^{-1}. HRMS (FAB) m/z calcd for $C_{20}H_{34}ONa$ (M + Na^+) 313.2507, found 313.2516.

4aS,6aR,8aS,9aR,11bS)-4,4,6a,9a,11b-Pentamethyltetradecahydro-1H-naphtho[2,1-b]oxiren[2,3-f]oxocane (29). *m*-Chloroperbenzoic acid (70%, 147 mg, 0.6 mmol) was added to a solution of compound **28** (125 mg, 0.431 mmol) in dichloromethane (10 mL), cooled at 0 °C, and the reaction mixture was stirred for 1 h, at which TLC showed no remaining starting material. Then, a 10% Na_2SO_3 solution (10 mL) was added, and the mixture was stirred for an additional 15 min. Then the reaction was extracted with EtOAc (3 x 20 mL). The organic phase was successively washed with sat. $NaHCO_3$ (3 x 30 mL) and brine (2 x 30 mL), and dried over anh Na_2SO_4 and evaporated to give a crude residue, which, after column chromatography on silica gel (5% EtOAc/hexane), afforded epoxyde **29** (2.3 g, 93%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.81 (s, 3H), 0.86 (s, 3H), 0.90 (s, 3H), 1.16 (s, 3H), 1.29 (s, 3H), 1.90 – 1.21 (m, 15H), 2.44 (dd, *J* = 13.3, 5.5 Hz, 1H), 2.80 (d, *J* = 2.0 Hz, 1H), 3.89 (d, *J* = 15.8 Hz, 1H), 4.03 (dd, *J* = 15.8, 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) : δ 15.33 (CH_3), 18.96 (CH_2), 20.02 (CH_2), 20.82 (CH_2), 21.95 (CH_3), 23.09 (CH_3), 23.68 (CH_3), 31.72 (CH_2), 33.47 (C), 33.77 (CH_3), 36.93 (CH_2), 38.35 (C), 40.88 (CH_2), 41.84 (CH_2), 49.51 (CH), 56.17 (CH), 58.31 (CH_2), 61.10 (C), 64.22 (CH), 80.33 (C). HRMS (FAB) m/z calcd for $C_{20}H_{34}O_2Na$ (M + Na^+) 329.2457, found 329.2461.

Conclusions

In summary, the first synthesis of arenaran A (**1**) and B (**2**), utilizing a ring-closing metathesis (RCM) process, starting from commercial (-)-sclareol (**20**) is reported. For the RCM process to be successfully applied, some structural requirements must be met. The *trans*-fused structure of the natural products is corroborated by comparison of their spectroscopic data with those of the *cis*-fused isomer (epi-arenaran A, **13**), which was also synthesized. This strategy can also be utilized for preparing other natural oxocene terpenes. Thus, the epoxide **29**, the 3-debromoderivative of the natural terpene **3**, has been synthesized from the diterpene **20**.

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