Epoxycaulerpenynes: Reactivity, and Diastereoselective and Highly Regioselective Synthesis by Dimethyldioxirane Oxidation of Caulerpenyne

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Caulerpenyne (**1**), the abundant sesquiterpene of the green seaweed *Caulerpa taxifolia*, has been epoxidized with dimethyldioxirane. The reaction proceeds with significant regioselectivity and moderate diastereoselectivity, the addition of oxygen occurring preferentially at the C(6)=C(7) double bond thereby giving (6*S*,7*S*)- and (6*R*,7*R*)-epoxycaulerpenynes **10** and **12** in an approximately 2:1 molar ratio besides a small amount of 10,11-epoxycaulerpenyne as an equimolecular diastereomeric mixture **8**. The epoxides underwent rearrangement under acidic conditions; the 6,7-epoxides were easily converted into allylic alcohols, whereas the 10,11 isomers required more drastic acidic conditions and gave complex mixtures containing two diastereoisomeric 1,4-dioxanes and an enynone. The high reactivity of 6,7-epoxycaulerpenynes suggests their involvement in the biogenetic pathways of the alga.

Introduction

The tropical green alga *Caulerpa taxifolia* (Vahl) C. Agardh (Chlorophyta) was first observed in the Mediterranean Sea in 1979. Its introduction in the salt water off the coast of Monaco (Cote d'Azur)[1] was probably accidental. It quickly spread in the temperate waters of the Mediterranean; by the end of 1994 the seaweed-covered region was estimated to be more than 1500 ha. Biological studies have proved that the alga, by competing with the endemic ecosystems, has an effect on the local biodiversity. Moreover, its secondary metabolites have been shown to exhibit bioactivity towards bacteria, microphytes, macroalgae, ciliates, invertebrates, and vertebrates.[2] Thus, ecological and toxicological risks have been envisaged.

We have recently studied the apolar extracts of *C. taxifolia* and have characterized the abundant sesquiterpene caulerpenyne (**1**), previously found in the Mediterranean *C. prolifera*,[3] as well as some minor products.[4] The latter are probably derived from **1** through hydrolysis of the 1,4-diacetoxybutadiene moiety (**2**−**4**), by degradation (**5**, **6**), or by oxidation of the C(6)=C(7) or C(10)=C(11) double bonds (**7**−**9**) (Figure 1). The allylic alcohol caulerpenynol **9**[4b,5] is presumably derived, enzymatically or otherwise, from rearrangement of (6*S*,7*S*)-epoxycaulerpenyne (**10**, which is not found in the algal extract) (Figure 1).
Biologists have carried out numerous bioassays using **1**,[2] the abundant sesquiterpene of *C. taxifolia* (1.53% of the freeze-dried seaweed).[4a] However, a full investigation of the minor natural products has not been accomplished because of the small amounts isolated. To the best of our knowledge, bioassays have been widely investigated for the crude extracts of *C. taxifolia* and for **1**, much less extensively for **8** and **9**, and rarely for the other minor metabolites. Among these products, the diastereomeric mixture of 10,11-epoxycaulerpenyne[4a] and caulerpenynol have shown higher toxicity towards ciliates than **1**. Thus, it is of interest to evaluate the bioactivities of all the constituent epoxides and allylic alcohols. Therefore, we have explored means of obtaining these compounds in adequate quantities, starting from caulerpenyne.

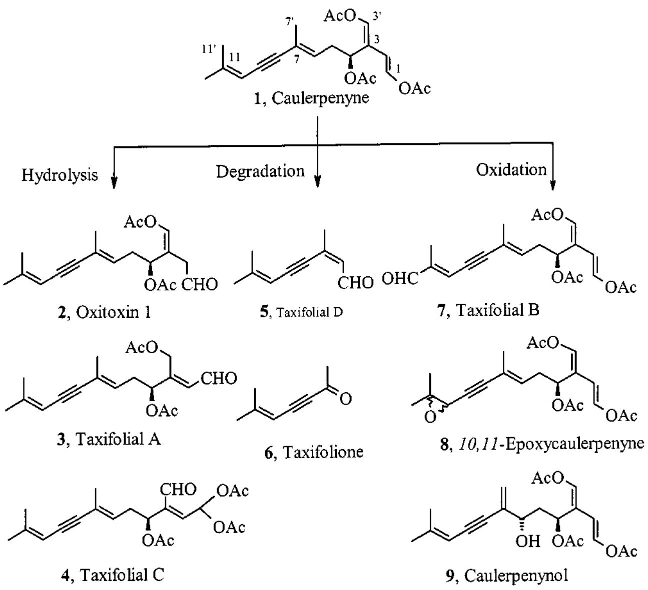

Figure 1. Structures of all the metabolites isolated from apolar extracts of the seaweed *C. taxifolia* as probable by-products of the abundant sesquiterpene **1**

We report herein on caulerpenyne oxidation with dimethyldioxirane (DMDO), as well as on Lewis acid mediated epoxide opening to give allylic alcohols and diols. Recently, we demonstrated that **1** undergoes chlorophyll-sensitized photodegradation,[6] and shows reactivity towards amines.[7]

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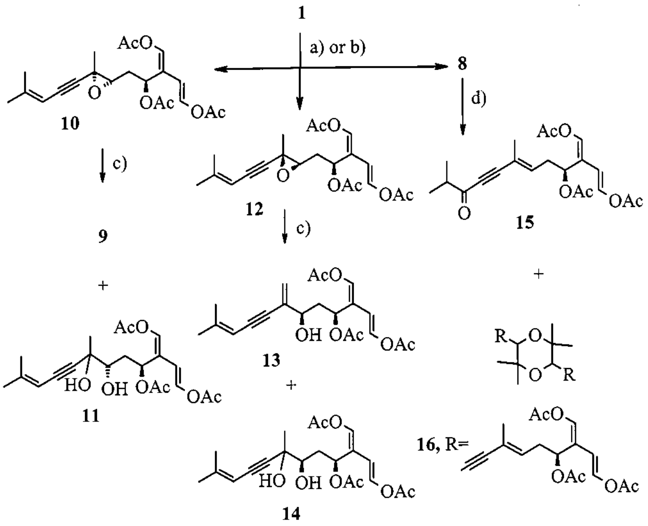
Results and Discussion

Epoxidation of Caulerpenyne with DMDO

Caulerpenyne was isolated from the ethanolic extracts of Mediterranean *C. prolifera*[3] and then treated with acetone solutions of DMDO[8] in four different solvents, affording the epoxides **8**, **10** and **12** (Scheme 1). This methodology represents a significant improvement on the previously reported epoxidation of **1** with 3-chloroperbenzoic acid (*m*CPBA)[4b] (Table 1). In fact, this latter reaction displayed (a) similar reactivities of the C(6)=C(7) and C(10)=C(11) double bonds, (b) no diastereoselectivity, (c) low yields, and (d) instability of **10** and **12** (they were found to be susceptible to acid-catalysed addition of H_2O even after HPLC purification). On the contrary, the reaction with DMDO showed a high degree of diastereoselectivity with preferential attack at the C(6)=C(7) double bond. Moreover, the epoxides have been found to be stable after purification by HPLC and may be stored in ethyl acetate at −20°C for several months.



Scheme 1. Epoxidation of caulerpenyne **1** and acidic rearrangement of epoxides **8**, **10**, and **12**: (a) *m*CPBA, CH_2Cl_2, 0°C;[4b] (b) DMDO in acetone, 20°C; (c) $CuSO_4$, $CHCl_3$, room temp.; (d) $MgBr_2·O(C_2H_5)_2$, C_6H_6, 65°C

In preliminary studies, we determined the optimal amount of dioxirane for the maximum production of epoxides. The concentrations of the desired products were assessed by HPLC analyses of the reaction mixtures obtained with progressive additions of DMDO to an acetone solution of **1**. The data, presented in Figure 2, suggest that the highest yields of **10** and **12** can be achieved with a DMDO/**1** molar ratio of 0.75. At a higher ratio, the yields decrease, probably due to polyepoxidations or competitive reactions at the 1,4-diacetoxybutadiene group.

Subsequently, we established the yields in four different solvent systems: CH_3OH/acetone (9:1), $CHCl_3$/acetone (9:1), acetone, and hexane/acetone (9:1). The reactions were stopped once the concentrations of the products, as assessed by HPLC, reached steady values. Our data (Table 1), in agreement with a previous paper,[9] suggest a relative rate proportional to the solvent polarity; the latter also modifies the regio- and diastereoselectivity (Table 1, entries 3−6). In fact, on changing the solvent system from CH_3OH/acetone (9:1) to $CHCl_3$/acetone (9:1), to acetone, and finally to hexane/acetone (9:1), the (**10** + **12**)/**8** isomeric ratio increased from about 14 to 17, to 39, and to 136, respectively. Concomitantly, the **10**/**12** diastereomeric ratio increased from about 1.7 to 1.9, to 2.0, and to 2.8, respectively. Average values and standard errors, as quoted in Table 1, were derived from a set of five experimental results.

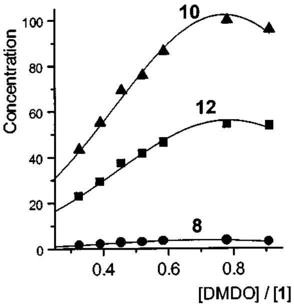


Figure 2. Relative concentrations of **8**, **10**, and **12** vs. DMDO/**1** molar ratio in the epoxidation of **1** with dimethyldioxirane; fitted graphs suggest [DMDO]/[**1**] = 0.75 for the highest yield of epoxycaulerpenynes

It seems unlikely that steric effects are responsible for the regioselectivity achieved in the DMDO epoxidation of **1**; indeed, the C(6)=C(7) and C(10)=C(11) double bonds in this molecule do not differ significantly in terms of steric shielding or electron density. It is possible that the regioselectivity stems from specific dipolar interactions between the incoming DMDO and the C(4) acetoxy group of **1**. This working hypothesis requires further verification. On the other hand, the observed diastereoselectivity might be accounted for on the basis of the well-known sensitivity of dioxiranes to steric effects;[8a] in fact, molecular mechanics (MM) calculations[10] on **1**, relating to the rotations of the dihedral angles C(3)−C(4)−C(5)−C(6) and C(4)−C(5)−C(6)−C(7), suggest the involvement of two low-energy conformers (**1**-down and **1**-up, Figure 3). They differ in energy by 0.35 kcal mol^{-1}, corresponding to a **1**-down/**1**-up population ratio of 2:1 (see Experimental Section). Apparently, preferential attack of dimethyldioxirane at the less-encumbered plane of the C(6)=C(7) double bond leads to the formation of about twice as much **10** as **12** by reaction with the major (**1**-down) and minor (**1**-up) conformers, respectively.

Furthermore, these experiments have shown that a lower solvent polarity reduces the total yield of epoxides (Table 1). On the other hand, their yield also decreases using the protic, nucleophilic CH_3OH as solvent (Table 1, entry 3).

Acidic Rearrangement of Epoxycaulerpenynes

Finally, we studied the acid-catalysed reactivity of epoxycaulerpenynes in $CHCl_3$ solution at room temperature. Traces of a weak Lewis acid (Cu^{2+}) were found to induce the complete conversions of **10** (in 20 h) and **12** (in 4 h) into

Table 1. Experimental results pertaining to the synthesis of **8**, **10**, and **12** by epoxidation of **1**

Entry[a]	Reagents and conditions	**8** + **10** + **12**[b]	**1**[c]	(**10** + **12**)/**8**[d]	**10**/**12**[d]
1	*m*CPBA (1.87 equiv.), $NaHCO_3$, CH_2Cl_2, 0°C, 1 h[4b]	28	0	0.5	0.8
2	*m*CPBA (1.8 equiv.), Na_2HPO_4, CH_2Cl_2, 0°C, 1 h[4b]	65	0	1.7	1.0
3	DMDO (0.75 equiv.), CH_3OH/acetone, 9:1, 20°C, 10 min	64 ± 2	6 ± 1	13.8 ± 0.6	1.73 ± 0.05
4	DMDO (0.75 equiv.), $CHCl_3$/acetone, 9:1, 20°C, 11 min	88 ± 3	8 ± 1	17.1 ± 0.7	1.87 ± 0.06
5	DMDO (0.75 equiv.), acetone, 20°C, 18 min	82 ± 3	13 ± 1	39.2 ± 0.8	2.05 ± 0.06
6	DMDO (0.75 equiv.), hexane/acetone, 9:1, 20°C, 25 min	77 ± 2	9 ± 1	136 ± 2	2.85 ± 0.08

[a] Arithmetic mean values and standard errors in entries 3−6 are derived from five experimental results. − [b] Total yield of HPLC-purified epoxides, in percent, based on reacted **1**. − [c] Unreacted **1**, in percent. − [d] Molar ratio.

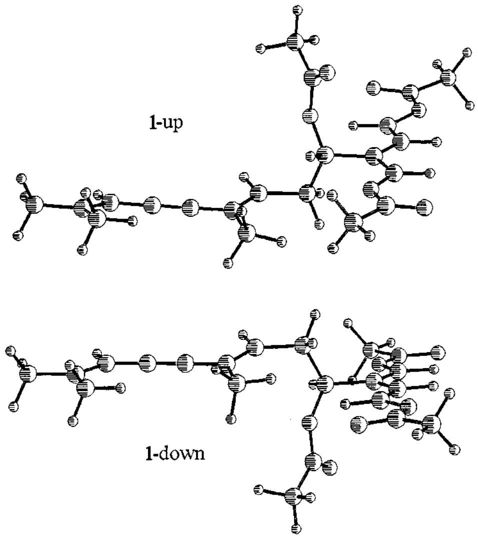
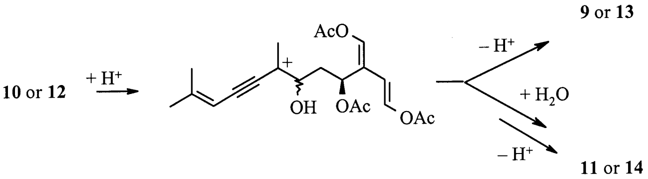


Figure 3. Lowest-energy conformers of caulerpenyne **1** as calculated by PC MODEL computer program;[9] conformer **1**-down is found to be more stable than **1**-up (ΔH = 0.35 kcal mol^{-1})



Scheme 2. Probable ionic mechanism for transformation of epoxides **10** or **12** to allylic alcohols **9** or **13** and diols **11** or **14**

the allylic alcohols **9** and **13**, respectively. When wet solvents were used, the reaction also produced some polar compounds. The reaction was repeated three times and the mixtures derived from **10** were purified; HPLC separation gave **9** and the two diastereomers of **11** in a 1.15 ± 0.05 molar ratio. Analogously, **13** and a pair of pure diols **14** in a 1.25 ± 0.05 molar ratio were obtained starting from **12**. It is likely that the epoxide rearrangement takes place through the C(7) cations, which are stabilized by conjugated enynic electrons. These carbocations can undergo conversion into allylic alcohols or, alternatively, can add H_2O to give the diols (Scheme 2).

Our results suggest that (i) rearrangement of **10** to naturally occurring **9**[4b] does not necessarily require enzymatic catalysis, (ii) the (6*S*,7*S*)-epoxide must be a natural by-product, and (iii) the allylic alcohol **9** must derive from **10** during the workup.

The absolute configuration of **9**, previously established[4b] by the Mosher method,[11] was used as a starting point for the assignment of the stereostructures of the allylic alcohol **13**, the epoxides **10** and **12,** and the diols **11** and **14** (Scheme 1). In fact, **13** is an epimer of **9** at C(6), the 6,7-epoxides are found to be chemically related to the allylic alcohols (**9** and **13** are chemically derived from **10** and **12**, respectively), and the absolute configuration at C(6) of the diols **11** and **14** may be assigned on the basis of the hypothesis outlined in Scheme 2. However, the (*R*) or (*S*) chirality at the tertiary alcohol moiety remains unassigned for the two diastereomers of **11** and **14**.

Following the above acidic treatment, the isomers **8** remained unchanged and hence their transformation required more drastic conditions. Reaction of the 10,11-epoxides was accomplished by treating them with a solution of $MgBr_2-Et_2O$ in benzene for 12 h at 65°C. This stronger Lewis acid[12] led to the formation of a complex mixture, in which we identified the enynone **15** (4%) and two inseparable diastereomeric 1,4-dioxanes (**16**) in an approximately 1:1 molar ratio (58%).

Presumably, **8** reacts via two alternative pathways, with bromohydrins and stable carbocations probably being involved in the rearrangement to ketone **15**[13] and to dioxanes **16**, respectively. In the latter path, the ionic intermediates must reach a sufficiently high steady-state concentration such that dimerization becomes feasible.[14]

Conclusion

In summary, we have shown that (i) dimethyldioxirane converts caulerpenyne into its 10,11- and 6,7-epoxides in a rapid, high-yielding, and highly regioselective process; (ii) the epoxycaulerpenynes show different reactivities in acidic solutions (stability: **8** > **10** > **12**); (iii) all the epoxides, alcohols, and diols depicted in Scheme 1 can easily be obtained in sufficient quantities for their complete bioassay evaluations; (iv) DMDO oxidation furnishes 6,7- and 10,11-epoxycaulerpenynes in a stable form, in contrast to a previously reported procedure using *m*CPBA.[4b]

Of the oxidation products of **1**, the epoxides **8** and the allylic alcohol **9** have been isolated from the apolar extract of *C. taxifolia*. The findings reported herein suggest that **10** and **11**, though elusive, must be present in the algal metabolic pool, which should also contain **12−14**. These results have stimulated us to carry out an exhaustive examination of the metabolites of *C. taxifolia*, the polar extracts of which are currently under investigation

Experimental Section

General Remarks: All solvent evaporations were carried out under reduced pressure. When anhydrous conditions were required, reactions were performed in oven-dried glassware using solvents (CH_2Cl_2 or $CHCl_3$) freshly distilled from CaH_2. − TLC: Merck silica gel 60 PF_{254} plates. − Flash chromatography: Merck LiChroprep Si60 stationary phase, 25−40 µm. − HPLC: Merck LiChrosorb Si60, 7 µm, 25 × 0.4 or 25 × 1 cm columns, t_R = retention time, UV detection at 254 nm. − UV: Perkin−Elmer Lambda-3 spectrophotometer; λ_{max} in nm, ε in mol^{-1} L cm^{-1}. − Polarimetry: Jasco DP-181 polarimeter. − NMR: Varian XL-300 instrument at 299.94 MHz and 75.43 MHz for ^1H and ^{13}C, respectively; spectra were recorded in C_6D_6 solution, C_6HD_5 ($\delta = 7.15$)/C_6D_6 ($\delta = 128.00$) as internal standard; δ in ppm, coupling constants (J) in Hz. − MS (EI): Kratos MS80 with home-built acquisition system.

Calculations on Caulerpenyne (1): Molecular mechanics calculations were performed using the computer program PC MODEL 1.0 for Windows (Serena Software), setting the dielectric constant equal to 1.5. The 1,4-acetoxybutadiene moiety was marked as a planar π system and low-energy conformers were searched by rotations of the dihedral angles C(3)−C(4)−C(5)−C(6) and C(4)−C(5)−C(6)−C(7). For the two lowest local minima detected, MMX force field calculations were performed, leading to the conformers **1**-down (15.46 kcal mol^{-1}) and **1**-up (15.81 kcal mol^{-1}). From $\Delta H = 0.35$ kcal mol^{-1}, relative populations of the conformers were calculated from the Boltzmann distribution (**1**-down/**1**-up = 2:1).

Isolation of Caulerpenyne (1): The seaweed *C. prolifera* was harvested in July 1994 in the area of Vulcano Island, Sicily, at a depth of 3−4 m and was immediately soaked in 95% ethanol. After cold storage of these samples for three years, the solvent was decanted off and the alga was further extracted with fresh ethanol. The combined organic phases were subjected to flash chromatography and HPLC as described previously[4a] furnishing caulerpenyne.

Preparation of Dimethyldioxirane (DMDO) in Acetone: A solution of dimethyldioxirane in acetone was prepared as described previously,[8c] starting from potassium monoperoxysulfate, and was stored at −20°C. The concentration of DMDO was estimated as ca. 0.07 M.

Reaction of 1 with Increasing Quantities of Dimethyldioxirane: A series of reactions were performed in which the amount of DMDO in acetone added to solutions of **1** (0.0098 mmol each) in acetone (0.6 mL) was increased up to 0.01 mmol. Each mixture was stirred in the dark for 10 min at 20°C, then the solvent was evaporated and the residue was flash-chromatographed on silica gel (1 g) eluting with *n*-hexane/ethyl acetate (1:1; 12 mL). The products were analysed by HPLC [mobile phase *n*-hexane/ethyl acetate (85:15); flow rate 1.2 mL/min]. From the chromatographic results, we calculated the concentrations of **8**, **10**, and **12**, which are related to the DMDO/**1** molar ratio in the graph shown in Figure 2.

Epoxidation of 1 with DMDO in Solvents of Varying Polarity: Four reactions were set up in which DMDO (0.007 mmol) in acetone (0.1 mL) was added to solutions of **1** (3.48 mg, 0.0093 mmol) in 0.9 mL of hexane, acetone, $CHCl_3$, and CH_3OH. Each mixture was stirred in the dark and aliquots were analysed by HPLC [mobile phase *n*-hexane/ethyl acetate (65:35); flow rate 1.2 mL/min] at intervals of 3 min. From the chromatographic data, the optimum reaction times giving the highest yields of epoxides were found to be 25 min in hexane, 18 min in acetone, 11 min in $CHCl_3$, and 10 min in CH_3OH. The four reactions were then repeated under the same conditions using 0.07 mmol of DMDO and 34.8 mg of **1**, and were worked-up after the aforementioned reaction times. Preparative HPLC [mobile phase *n*-hexane/ethyl acetate (85:15); flow rate 6 mL/min] gave **8** (t_R = 10 min), **10** (t_R = 11.2 min), and **12** (t_R = 12.5 min). Again, each reaction was performed five times, and quantitative HPLC analyses were performed to obtain average molar ratios, yields, and standard errors, as collected in Table 1.

(4*S*,6*S*,7*S*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-epoxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (10) (data not previously reported because of its instability): $[\alpha]_D^{20} = -42.0$ (c = 0.09 in EtOH). − UV (EtOH): λ_{max} (lg ε) = 242 nm (4.35). − MS (EI); *m/z* (%): 390 [$M^{+\cdot}$] (2.3), 348 [$M^{+\cdot} - CH_2CO$] (0.5), 330 [$M^{+\cdot}$ − AcOH] (2.5), 288 (4.3), 270 [$M^{+\cdot}$ − 2 AcOH] (2.1), 246 (4.2), 228 (5.9), 149 (67), 43 (100).

(4*S*,6*R*,7*R*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-epoxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (12) (data not previously reported because of its instability): $[\alpha]_D^{20} = -25.0$ (c = 0.08 in EtOH). − UV (EtOH): λ_{max} (lg ε) = 241 nm (4.36). − MS (EI); *m/z* (%): 390 [$M^{+\cdot}$] (0.1), 330 [$M^{+\cdot}$ − AcOH] (0.9), 288 (5.0), 270 [$M^{+\cdot}$ − 2 AcOH] (2.1), 246 (4.2), 228 (5.9), 149 (67), 43 (100).

Acid-Catalysed Rearrangement of (6*S*,7*S*)-Epoxycaulerpenyne (10): (6*S*,7*S*)-Epoxycaulerpenyne was found to be stable in ethyl acetate solution at −20°C, but it readily rearranged upon dissolution in $CHCl_3$ containing a small quantity of $CuSO_4$. In a typical experiment, **10** (30 mg, 0.07 mmol) in $CHCl_3/H_2O$ (97:3; 1 mL) containing $CuSO_4$ (2.1 mg) was stirred in the dark at room temperature for 20 h. The solvent was then evaporated, the residue was flash-chromatographed on silica gel [mobile phase *n*-hexane/ethyl acetate (1:1)], and further purified by HPLC (mobile phase hexane/ethyl acetate gradient), giving **9** (18.5 mg, 62%) and a polar mixture of two compounds. These were further chromatographed [HPLC, mobile phase *n*-hexane/ethanol (93:7), flow rate 5.0 mL/min] to give pure diastereomers **11** (major, 3.7 mg, 11.8%; minor, 3.2 mg, 10.2%). Using freshly dried solvent (CH_2Cl_2 or $CHCl_3$), the diols **11** were only obtained in trace amounts, while the yield of **9** was increased (73%).

(4*S*,6*S*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-dihydroxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (11-major): $[\alpha]_D^{20} = -16.5$ (c = 0.65 in MeOH). − UV (MeOH): λ_{max} (lg ε) = 235 nm (4.13). − ^1H NMR (C_6D_6): δ = 7.95 (dd, J = 12.6, 0.6, 1-H), 5.80 (dd, J = 12.6, 0.6, 2-H), 6.59 (dd, J = 10.8, 3.0, 4-H), 2.67 and 1.85 (ddd, J = 14.4, 10.8, 1.8 and ddd, J = 14.4, 10.8, 3.0, respectively, 2 H, 5-H), 3.91 (dd, J = 10.8, 1.8, 6-H), 5.29 (qq, J = 1.2, 1.2, 10-H), 1.46 (br. s, 3 H, 12-H), 7.34 [br. s, 3-(=C*H*OAc)], 1.43 (s, 3 H, 7-CH_3), 1.82 (br. s, 3 H, 11-CH_3), 1.55 [s, 1-OAc or 3-(=CHO*Ac*)], 1.73 (s, 4-OAc), 1.60 [s, 3-(=CHO*Ac*) or 1-OAc]. − ^{13}C NMR (C_6D_6): δ = 137.24 (d, C-1), 110.07 (d, C-2), 120.22 (s, C-3), 67.41 (d, C-4), 36.26 (t, C-5), 74.19 (d, C-6), 71.28 (s, C-7), 93.67 (s, C-8), 83.45 (s, C-9), 105.23 (d, C-10), 149.00 (s, C-11), 24.46 (q, C-12), 134.45 [d, 3-(=**C**HOAc)], 24.01 (q, 7-**C**H_3), 20.96 (q, 11-**C**H_3), 19.94 and 167.25 [q and s, respectively, 1-OAc or 3-(=CHO*Ac*)], 20.44 and 170.02 (q and s, respectively, 4-OAc), 19.87 and 166.81 [q and s, respectively, 3-(=CHO*Ac*) or 1-OAc]. − MS (EI); *m*/*z* (%): 348 [$M^{+\cdot}$ − AcOH] (0.3), 306 (1.0), 123 (62), 43 (100).

(4*S*,6*S*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-dihydroxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (11-minor): $[\alpha]_D^{20}$ = −21.8 (*c* = 0.5 in MeOH). − UV (MeOH): λ_{max} (lg ε) = 235 nm (4.24). − ^{1}H NMR (C_6D_6): δ = 7.92 (dd, J = 12.6, 0.6, 1-H), 5.80 (dd, J = 12.6, 0.6, 2-H), 6.57 (dd, J = 10.9, 3.0, 4-H), 2.61 and 2.04 (ddd, J = 14.4, 10.9, 2.4 and ddd, J = 14.4, 11.1, 3.0, respectively, 2 H, 5-H), 3.76 (dd, J = 11.1, 2.4, 6-H), 5.24 (qq, J = 1.2, 1.2, 10-H), 1.43 (br. s, 3 H, 12-H), 7.32 [br. s, 3-(=CH−)], 1.51 (s, 3 H, 7-CH_3), 1.78 (br. s, 3 H, 11-CH_3), 1.55 [s, 1-OAc or 3-(=CHO*Ac*)], 1.69 (s, 4-OAc), 1.60 [s, 3-(=CH−O*Ac* or 1-OAc]. − ^{13}C NMR (C_6D_6): δ = 137.23 (d, C-1), 110.01 (d, C-2), 120.12 (s, C-3), 67.45 (d, C-4), 36.98 (t, C-5), 74.63 (d, C-6), 71.45 (s, C-7), 93.13 (s, C-8), 83.58 (s, C-9), 105.32 (d, C-10), 148.84 (s, C-11), 24.42 (q, C-12), 134.33 [d, 3-(=**C**HOAc)], 26.56 (q, 7-**C**H_3), 20.93 (q, 11-**C**H_3), 19.93 and 166.27 [q and s, respectively, 1-OAc or 3-(=CH−O*Ac*)], 20.42 and 170.17 (q and s, respectively, 4-OAc), 19.86 and 166.76 [q and s, respectively, 3-(=CH−O*Ac* or 1-OAc)]. − MS (EI); *m*/*z* (%): 348 [$M^{+\cdot}$ − AcOH] (0.3), 306 (0.8), 123 (48), 43 (100).

Acid-Catalysed Rearrangement of (6*R*,7*R*)-Epoxycaulerpenyne (12): (6*R*,7*R*)-Epoxycaulerpenyne (26 mg, 0.067 mmol) was allowed to rearrange in the presence of Cu^{2+} for 4 h. Workup of the reaction mixture as in the case of **10** (see above) gave **13** (14.9 mg, 57% in wet $CHCl_3$ or 17.3 mg, 66% in dry $CHCl_3$, respectively), along with **14** (major, 2.5 mg, 9.1%; minor, 2.0 mg, 7.3%) under wet conditions.

(4*S*,6*R*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-dihydroxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (14-major): $[\alpha]_D^{20}$ = −18.4 (*c* = 0.5 in MeOH). − UV (MeOH): λ_{max} (lg ε) = 236 nm (4.27). − ^{1}H NMR (C_6D_6): δ = 7.91 (dd, J = 12.5, 0.7, 1-H), 5.79 (dd, J = 12.5, 0.9, 2-H), 6.58 (dd, J = 9.9, 5.4, 4-H), 2.46 and 2.31 (ddd, J = 13.8, 9.9, 2.1 and ddd, J = 13.8, 10.5, 5.4, respectively, 2 H, 5-H), 3.51 (br. d, J = 10.5, 1.8, 6-H), 5.26 (qq, J = 1.2, 1.2, 10-H), 1.44 (br. s, 3 H, 12-H), 7.34 [br. s, 3-(=CH−)], 1.46 (s, 3 H, 7-CH_3), 1.78 (br. s, 3 H, 11-CH_3), 1.56 (s, 1-OAc), 1.669 [s, 4-OAc or 3-(=CHO*Ac*)], 1.666 [s, 3-(=CHO*Ac*) or 4-OAc]. − ^{13}C NMR (C_6D_6): δ = 137.60 (d, C-1), 109.69 (d, C-2), 118.93 (s, C-3), 68.27 (d, C-4), 36.05 (t, C-5), 75.75 (d, C-6), 71.60 (s, C-7), 93.04 (s, C-8), 83.62 (s, C-9), 105.24 (d, C-10), 148.89 (s, C-11), 24.44 (q, C-12), 135.92 [d, 3-(=CH−)], 26.38 (q, 7-CH_3), 20.97 (q, 11-CH_3), 19.93 and 167.27 [q and s, respectively, 1-OAc or 3-(=CH−O*Ac*)], 20.57 and 169.46 (q and s, respectively, 4-OAc), 19.90 and 166.99 [q and s, respectively, 3-(=CH−O*Ac*) or 1-OAc]. − MS (EI); *m*/*z* (%): 348 [$M^{+\cdot}$ − AcOH] (1.3), 306 (1.8), 288 (2.1), 246 (5.4), 228 (7.8), 123 (71), 43 (100).

(4*S*,6*R*,1*E*)-3-[(*Z*)-Acetoxymethylene]-6,7-dihydroxy-7,11-dimethyldodeca-1,10-dien-8-yne-1,4-diyl Diacetate (14-minor): $[\alpha]_D^{20}$ = −27.0 (*c* = 0.4 in MeOH). − UV (MeOH): λ_{max} (lg ε) = 236 nm (4.29). − ^{1}H NMR (C_6D_6): δ = 7.95 (dd, J = 12.6, 1-H), 5.82 (dd, J = 12.6, 0.9, 2-H), 6.58 (dd, J = 9.9, 5.4, 4-H), 2.49 and 2.14 (ddd, J = 13.5, 9.9, 2.1 and ddd, J = 13.5, 10.5, 5.4, respectively, 2 H, 5-H), 3.66 (br. d, J = 10.5, 2.1, 6-H), 5.23 (qq, J = 1.2, 1.2, 10-H), 1.45 (br. s, 3 H, 12-CH_3), 7.36 [br. s, 3-(=CH−)], 1.42 (s, 3 H, 7-CH_3), 1.75 (br. s, 3 H, 11-CH_3), 1.56 (s, 1-OAc), 1.69 [s, 4-OAc or 3-(=CHO*Ac*)], 1.66 [s, 3-(=CHO*Ac*) or 4-OAc]. − ^{13}C NMR (C_6D_6): δ = 137.55 (d, C-1), 109.69 (d, C-2), 119.15 (s, C-3), 68.27 (d, C-4), 35.28 (t, C-5), 75.16 (d, C-6), 71.33 (s, C-7), 93.52 (s, C-8), 83.41 (s, C-9), 105.14 (d, C-10), 148.85 (s, C-11), 24.45 (q, C-12), 136.76 [d, 3-(=CH−)], 23.94 (q, 7-CH_3), 20.90 (q, 11-CH_3), 19.92 and 167.17 [q and s, respectively, 1-OAc or 3-(=CH−O*Ac*)], 20.57 and 169.27 (q and s, respectively, 4-OAc), 19.92 and 167.03 [q and s, respectively, 3-(=CH−O*Ac*) or 1-OAc]. − MS (EI); *m*/*z* (%): 348 [$M^{+\cdot}$ − AcOH] (1.1), 306 (1.3), 288 (1.4), 246 (4.4), 228 (8.3), 123 (60), 43 (100).

Acid-Catalysed Rearrangement of 10,11-Epoxycaulerpenyne (8): Epoxides **8** were found to be stable under the acidic conditions used for the rearrangements of **10** and **12**. Thus, their rearrangement was performed in the presence of magnesium bromide−diethyl ether [$MgBr_2{\cdot}O(C_2H_5)_2$]. In a typical experiment, **8** (20 mg, 0.05 mmol) in C_6H_6 (0.5 mL) containing $MgBr_2{\cdot}O(C_2H_5)_2$ (1.5 mg) was stirred in the dark at 65 °C for 12 h. The solvent was then evaporated, the residue was flash-chromatographed on silica gel [mobile phase *n*-hexane/ethyl acetate (1:1)], and further purified by HPLC [mobile phase *n*-hexane/ethanol (95:5)], to give **15** (0.8 mg, 4.1%) and an inseparable mixture of dimers **16** (11.5 mg, 57.5%) in a 52:48 molar ratio, as determined by ^{1}H NMR.

(4*S*,1*E*,6*E*)-3-[(*Z*)-Acetoxymethylene]-7,11-dimethyldodeca-10-oxo-1,6,10-trien-8-yne-1,4-diyl Diacetate (15): UV (MeOH): λ_{max}(lg ε) = 239 nm (4.15). − ^{1}H NMR (C_6D_6): δ = 7.88 (d, J = 12.8, 1-H), 5.70 (dd, J = 12.8, 0.9, 2-H), 6.09 (dd, J = 7.4, 7.2, 4-H), 2.51 and 2.34 (m, 2 H, 5-H), 6.01 (ddq, J = 7.4, 7.4, 1.3, 6-H), 2.39 (m, 11-H), 1.03 (d, J = 7.3, 3 H, 11-CH_3 and 3 H, 12-H), 1.60 (br. s, 7-CH_3), 1.65, 1.57 and 1.55 [3 s, 1-OAc, 3-(=CH−O*Ac*) and 4-OAc]. − MS (EI); *m*/*z* (%): 390 [$M^{+\cdot}$] (3.0), 347 (4), 43 (100).

Mixture of the Two Dimers 16: ^{1}H NMR (C_6D_6): δ = 7.90 (d, J = 12.5, 1-H), 5.69 (dd, J = 12.5, 0.9, 2-H), 6.10 (dd, J = 7.5, 7.5, 4-H), 2.52 and 2.39 (m, 2 H, 5-H), 5.83 (tq, J = 7.5, 1.8, 6-H), 4.478 and 4.471 (2 s, 10-H), 1.322, 1.316 and 1.294 (superimposed s, 3 H, 12-H and 3 H, 11-CH_3), 7.245 and 7.232 [2 s, 3-(=CH−)], 1.62 (s, 3 H, 7-CH_3), 1.57 [(s, 1-OAc or 3-(=CHO*Ac*)], 1.65 (s, 4-OAc), 1.58 and 1.59 [s, 3-(=CH−O*Ac*) or 1-OAc]. − ^{13}C NMR (C_6D_6): δ = 137.42 (d, C-1), 109.58 and 109.54 (d, C-2), 118.95 and 118.90 (s, C-3), 68.64 and 68.62 (d, C-4), 32.26 (t, C-5), 133.33 (d, C-6), 120.56 and 120.54 (s, C-7), 91.19 and 91.15 (s, C-8), 84.18 and 84.15 (s, C-9), 52.04 and 51.87 (d, C-10), 72.75 and 72.69 (s, C-11), 26.09, 25.95, 25.90 and 25.88 (q, C-12 and 11-CH_3), 135.12 [d, 3-(=**C**H−OAc)], 17.11 (q, 7-CH_3), 19.91 and 167.31 (q and s, respectively, 1-OAc), 20.34 and 169.14 (q and s, respectively, 4-OAc), 19.83 and 166.63/166.56 [q and s, respectively, 3-(=CH−O*Ac*)]. − MS (EI); *m*/*z* (%): 628.3 [$M^{+\cdot}$ − 2 AcOH] (1.1), 43 (100).

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