188. Adriadysiolide, the First Monoterpenoid Isolated from a Marine Sponge

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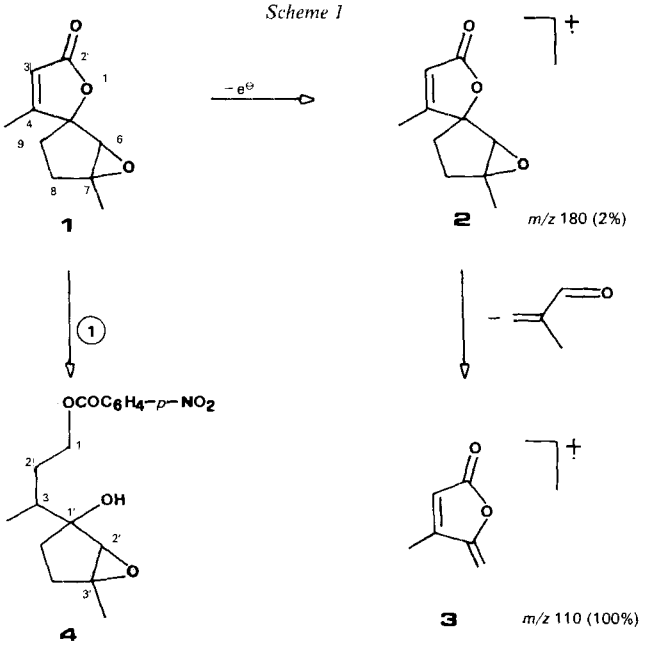
Spectra and chemical transformations allow to establish the gross structure 6,7-epoxy-4,7-dimethyl-1-oxa-spiro[4.4]non-3-en-2-one for adriadysiolide (**1**), the first monoterpenoid isolated from a marine sponge, a *Dysidea* sp. of the Adriatic Sea. Its configuration *5R*,6S*,7S** as given in **1a** is derived from diastereoselective total syntheses of both **1a** and its diastereoisomer **1b** *via* stereochemically predictable peracid epoxidations of olefinic precursors. Thus, OH assistance in allylic alcohol **8** leads to oxirane **13** which is subjected to methyl cuprate conjugate addition to give epiadriadysiolide (**1b**), whilst electronic deactivation by a neighboring heterocyclic O-atom in intermediate **5**, derived from **8** mainly leads to adriadysiolide (**1a**). Comparative ^{1}H-NMR shift-reagent effects with **1a** and **1b**, evaluated with the aid of molecular-mechanics calculations, support these conclusions.

Various polyhalogenated monoterpenoids have been isolated either from marine plants of the division Rhodophyta, order Gigartinales, families Plocamiaceae and Rhyzophyllidaceae [1a], or, as dietary products, from marine mollusks of the order Opisthobranchia [2].

In contrast, only a few non-halogenated marine monoterpenoids are known and none has been isolated from sponges, though many of them are rich of terpenoids. As regards linear monoterpenoids, geraniol, nerol, and their simple oxidized or reduced derivatives have been found in the bryozoan *Flustra foliacea* [3]. Geranylquinones have been isolated from either a *Cystophora* sp. (Phaeophytaphyta, Sargassaceae) [4] or from two different species of *Aplidium* (Chordata, Ascidiacea) [5], one of which also contains the first described natural nerylquinones [5b]. Finally, rare examples of cyclic, non-halogenated monoterpenoids have been isolated from *Ochtodes crockeri* (Rhyzophyllidaceae) [1b].

We report here on the first monoterpenoid, adriadysiolide, isolated from a marine sponge, a *Dysidea* sp. (Dictyoceratida, Dysideidae) collected in the North-Adriatic Sea. The gross structure **1** *(Scheme 1)* for adriadysiolide can be deduced from spectra. Thus, accurate MS measurements establish the composition $C_{10}H_{12}O_3$ for the molecular ion. UV absorption at 215 nm and IR absorptions at 1745, 1635, and 980 cm^{-1} suggest a γ-butenolide, with a CH_3 group in β-position as suggested by the ^{1}H-NMR-spectrum (*d* at 2.14 and *q* at 5.80 ppm). There must be two additional rings, and the absence of exchangeable protons and the presence of both a *d* at 64.9 and a br. *s* at 64.4 ppm in the ^{13}C-NMR spectrum are compatible with a trisubstituted epoxide. Therefore, there must also be a five-membered saturated carbocycle, spirocyclized at C(γ) of the butenolide (C(γ) at 94.0 (*s*)). Accordingly, both heteronuclear ^{13}C-NMR and homonuclear ^{1}H-NMR decouplings indicate the 6,7-position for the epoxide group in **1**. These conclusions are further supported by the MS fragmentation, in particular of the molecular ion **2** at both the C(5)–C(6) and the C(8)–C(9) bond to give **3** *(Scheme 1)*.

Scheme 1



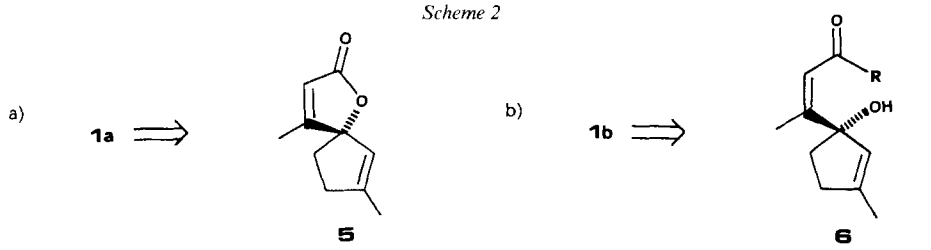
① a) $LiAlH_4$, THF, 0°, 2 h; b) *p*-$NO_2C_6H_4COCl$, pyridine, r.t., 2 h; 14% overall

Reaction of **1** with $LiAlH_4$ at low temperature led mainly to reduction of the butenolide group. The expected diol was isolated as the *p*-nitrobenzoate **4** *(Scheme 1)*, albeit in low yield (14%) and further supports the gross structure **1** for adriadysiolide. However, NOE and shift-reagent ^{1}H-NMR studies of either **1** or **4** did not allow us to decide in favour of either structure **1a** or **1b** for adriadysiolide[1]) owing to similar internuclear distances between corresponding protons in the two epimers.

As we were unable to obtain adriadysiolide in a crystalline form suitable for diffraction analysis and as the search for the same sponge proved difficult, we turned our attention to the synthesis of **1**. We planned to exploit either the activation by an allylic OH group [6] *(Scheme 2b)* or the deactivation by the heterocyclic O-atom of a lactone group [7] *(Scheme 2a)* in peracid epoxidations of suitable olefinic precursors. Only effects

[1]) No absolute-configuration significance is to be attached to any of the structural formulae in this work.

Scheme 2



of the former type are firmly established [6], whilst effects of the latter type find exemplification in only a few, though notable cases [7]. With **5** in particular, there is the additional factor that the side of the molecule which is free from electronic O-repulsion experiences steric crowding by the butenolide CH_3 group. Therefore, we decided to complement the synthetic work with NMR studies of both diastereoisomers **1a** and **1b**.

The plan of *Scheme 2a* was realized with high diastereoselectivity as shown in *Scheme 3*. Thus, 3-methyl-2-cyclopenten-1-one (**7**) was treated with ethyl 3-lithiopropiolate under carefully controlled conditions of concentration and temperature[2]) and then at room temperature successively with HCl and a buffer solution of pH 7 to give the sensitive[3]) hydroxy ester **8** in 63% isolated yield. Conjugate addition of methyl cuprate [10] to **8** followed by acidic treatment led directly to the desired butenolide **5** in 78% isolated yield. Treatment of **5** with *m*-chloroperbenzoic acid/$NaHCO_3$ gave very slowly a 9:1 mixture of a less polar (**1a**) and a more polar isomer **1b**, respectively (82% overall yield). The less polar **1a** proved identical to natural adriadysiolide.

The plan of *Scheme 2b* was realized as shown in *Scheme 4*. *m*-Chloroperbenzoic-acid treatment of the intermediate allylic alcohol **8** (see *Scheme 3*) gave quickly oxirane **13** in 90% isolated yield. Choosing the lowest practicable temperature in order to minimize attack at the epoxide centres, conjugate addition of methyl cuprate to **13** accompanied by cyclization occurred in a modest yield (20%) to give the unnatural epimer **1b** of adriadysiolide.

With both epimers **1a** and **1b** at hand, it is now possible to confirm their structures by NMR spectrometry. Thus, though coordination of [Eu(fod)$_3$] at the lactone C=O group was expected [11], the fact that H–C(6) undergoes a much larger shift than Me–C(4) *(Table)*, in spite of the fact that both groups are at about the same distances from the C=O group, indicates coordination of [Eu(fod)$_3$] also at the oxirane O-atom. Moreover, both H–C(3) and Me–C(4), which are at the same distance from the C=O group in both isomers, undergo dramatically larger shifts in the natural than in the unnatural isomer.

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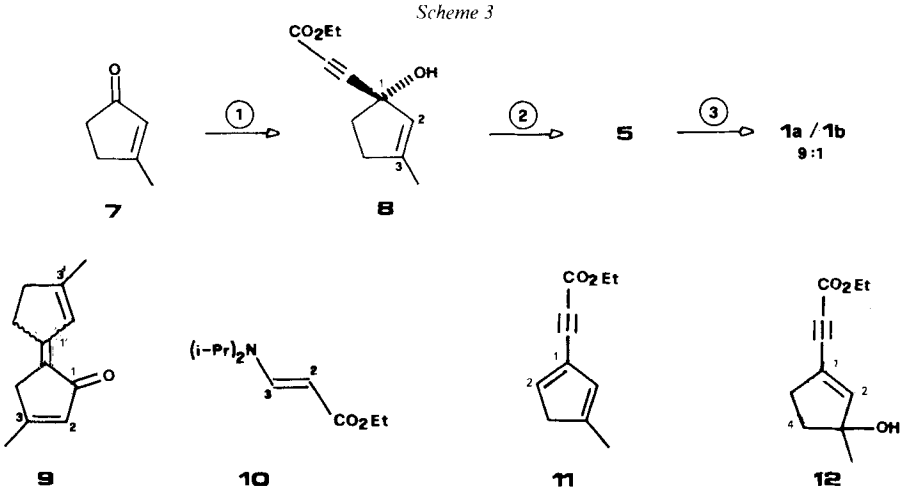
[2]) When higher concentrations of the reagents were used (1.01 mmol of **7**, 1.49 mmol of ethyl propiolate, and 1.49 mmol of lithium diisopropylamide (LDA) in 2 ml of THF), self condensation of **7** occurred with the result that (*E*)-**9** (9.7 mg, 7%) and (*Z*)-**9** (4.2 mg, 3%) were also formed besides **8** (65 mg, 42%). Moreover, when the reaction mixture was quenched with a buffer solution of pH 7 at low temperature under otherwise identical conditions to those of the optimized procedure above, product **10** of conjugate attack of LDA to ethyl propiolate was obtained, too [8]. The need for a careful choice of the conditions for ① in *Scheme 3* was not surprising. In fact, whilst there are many reports of successful conjugate additions of ethyl 3-lithiopropiolate to both cyclic ketones and linear enones [9], that of *Scheme 3* is a rare if not unique case with cyclic, enolizable enones.

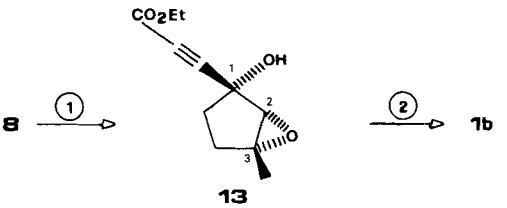
[3]) Compound **8**, on standing in the NMR tube in $CDCl_3$ solution at 22°, was transformed into **12** *via* an NMR-detectable intermediate (either **11** or a double-bond isomer).

Scheme 3



① a) LiC≡CCO$_2$Et (0.37M, THF), – 60°; b) aq. 6M HCl, r.t.; c) buffer soln. (pH 7)
② MeLi, CuBr·SMe$_2$, Et$_2$O, – 30°; 78%
③ *m*-ClC$_6$H$_4$CO$_3$H/NaHCO$_3$, CH$_2$Cl$_2$, r.t.; 82%

Scheme 4



① *m*-ClC$_6$H$_4$CO$_3$H/NaHCO$_3$, CH$_2$Cl$_2$, r.t., 2 h; 90%
② Me$_2$CuLi, Et$_2$O, – 30°, 2 h; 20%

Table. *Slopes* $\Delta\delta_H \cdot 10^2$ vs. *either [Eu(fod)$_3$]/***1a** *or [Eu(fod)$_3$]/***1b** *Increasing Concentration Ratio in* $CDCl_3$

	H–C(3)	H–C(6)	Me–C(4)	Me–C(7)
Natural isomer **1a**	0.990	0.625	0.319	0.225
Unnatural isomer **1b**	0.560	0.446	0.196	0.177

Thus, the natural isomer must have the *'anti'* structure **1a** where both H–C(3) and Me–C(4) are closer to the oxirane O-atom than in the *'syn'* structure **1b**. Finally, the larger shifts for both H–C(6) and Me–C(7) in the natural isomer **1a** must reflect their closer vicinity to the butenolide C=O group[4]).

[4]) In contrast, NOE studies proved of little help although, faced with the problem of dealing with very small differences in internuclear distances for corresponding nuclei, we have carried out molecular-mechanics calculations which are believed to better approach the molecular shape than molecular models [12]. Such calculations suggest that the largest difference between **1a** and **1b** occurs in the inter-proton distance *Me*–C(4) · · · *H*–C(6). However, even at high field, irradiation at Me–C(4) also affected the two methylene groups so that inconclusive data were obtained. On the other hand, owing to the anticipated facile internal relaxation of CH_3 groups, irradiation at H–C(6) failed to result in any substantial NOE effect at Me–C(4).

Adriadysiolide (**1a**) is a regular monoterpenoid of novel skeleton which can be formally imagined to derive biogenetically from 4-oxogeranic acid *via* C(8)–C(4) cyclization followed by lactonization. Alternatively, as there is no previous example of monoterpenoids from sponges, the hypothesis may be considered of a biodegradative route to adriadysiolide from higher terpenoids. However, no suitable such precursor has ever been isolated from sponges of the family Dysideidae whose terpenoids can most economically be imagined to result from either 1,6- or 2,7-cyclization of linear terpenoids to give intermediate monocyclofarnesol [13] or 3-alkyl-*p*-menthene [14] skeletons, respectively.

We thank Mr. *A. Slomp* and Mr. *A Sterni* for recording the mass spectra, Dr. *R. Pronzato*, Università di Genova, for the taxonomic study, and the *Provincia Autonoma di Trento, Assessorato Agricoltura*, the *CNR* and *MPI* (Progetti di Interesse Nazionale), Roma, for financial support.

Experimental Part

1. *General.* All glassware for syntheses was assembled and then flame-dried under vacuum. The reactants were transferred by means of a hypodermic syringe under dry N_2. THF and Et_2O were distilled from $LiAlH_4$, whilst CH_2Cl_2 was distilled from CaH_2 and then stored on 4-Å molecular sieves. Commercial organolithium reagents *(Fluka)* were standardized by acid-base titration [18]. Ethyl propiolate *(Aldrich)* was used directly, whilst 3-methylcyclopent-2-en-1-one *(Fluka)* was distilled (74°/15 Torr) before use. *m*-Chloroperbenzoic acid *(Fluka)* was standardized by iodometric titration [19]. Yields are given with respect to reacted substrates. Flash chromatography: *Merck-Kieselgel 60*, 20–50 mμ. TLC: *Merck-Si$_{F254}$* plates. Silica-gel HPLC and reverse-phase HPLC: 25 × 1-cm columns filled with *Merck-LiChrosorb Si-60* (7 mμ) or *Merck-LiChroprep RP-18* (7 mμ), resp.; UV monitoring at 230 nm, solvent flux 5 ml·min^{-1}. M.p.: *Kofler* hot-stage microscope. Polarimetric data: *Jasco-DIP-181* polarimeter. UV spectra (λ_{max} in nm, ε in mol^{-1}·l·cm^{-1}): *Perkin-Elmer-Lambda-3* spectrophotometer. IR spectra ($\tilde{\nu}_{max}$ in cm^{-1}): *Perkin-Elmer-337* spectrometer. NMR spectra (δ in ppm, from TMS): unless otherwise stated, *Varian-XL-300* spectrometer (^{1}H at 300 MHz, ^{13}C at 75.4 MHz), *J* in Hz, multiplicities from APT [15]; ^{1}H-NMR at 80 MHz on *Varian-CFT20* speetrometer modified for proton; shift reagent [Eu(fod)$_3$] from *C. Erba.* MS (EI; *m/z* (%)): high-resolution MS and linked scans [16] on *VG-ZAB2F* spectrometer; low resolution MS on home-built spectrometer based on the *ELFS-4-162-8-Extranuclear* quadrupole [17].

2. *Collection, Identification, and Isolation Procedures.* The sponge, collected by scuba diving in August 1984 three miles offshore Jesolo Lido, Northern coast of Venezia, at a depth of 20 m, was immediately stored in EtOH. The sponge, looking like morphologically identical to *Dysidea avara*, while not containing its typical products avarol and avarone [20], was preliminarily classified as a *Dysidea* sp.[5]). The sponge was extracted with EtOH and the extract evaporated to leave an aqueous residue which was extracted with EtOAc. The residue from evaporation of the EtOAc extract (0.7 g) was subjected to flash chromatography (gradient elution with hexane/EtOAc). Adriadysiolide (**1a**), which was eluted after the sterols, was further subjected to reverse-phase HPLC chromatography with H_2O/CH_3CN 7:3 (t_R 10 min) and then to silica-gel HPLC chromatography with hexane/EtOAc 7:3 (t_R 12 min; 0.015 g, 0.02% of dry-sponge weight).

3. *Natural Adriadysiolide (= (+)-(5R*,6S*,7S*)-6,7-Epoxy-4,7-dimethyl-1-oxaspiro[4.4]non-3-en-2-one* (**1a**). Microcrystalline, colourless powder. M.p. (hexane) 76–77°. $[\alpha]_{435}^{20} = +2.1°$, $[\alpha]_{546}^{20} = +1.4°$, and $[\alpha]_{589}^{20} = 0°$ (*c* = 0.625, MeOH). UV (MeOH): 215 (10000). IR (KBr): 1745*vs*, 1635*m*, 960*s*. ^{1}H-NMR ($CDCl_3$; double irradiations within square brackets, indicating the δ of irradiation and the resulting change after the arrow): 5.80 (*q*, *J* = 1.6, H–C(3) [2.14 → *s*]); 3.08 (br. *s*, H–C(6) [1.63 and 1.51 → sharpening]); 2.14 (*d*, *J* = 1.6, Me–C(4) [5.80 → *s*]); 2.10 – 1.88 (*m*, 2H–C(9), H_α–C(8) [3.08 → simplification]); 1.63 (*dddd*, J_{gem} = 14.1, *J* = 5.4, 3.0, 1.0, H_β–C(8) [3.08 → *ddd*, with loss of *J* = 1.0]); 1.51 (*s*, Me–C(7) [3.08 → sharpening]). ^{13}C-NMR ($CDCl_3$; fully coupled spectrum; within square brackets, low-power heteronuclear selective decouplings): 171.6 (br. *d*, *J*(2,*H*–C(3)) = 9.0, C(2) [2.14 or 5.80 → *d*, *J*(2,*H*–C(3)) = 9.0, or br. *s*, resp.]); 169.3 (*m*, C(4) [2.14 or 5.80 → *d*, *J*(4,*H*–C(3)) = 4.0, or br. *q*, *J*(4,*Me*–C(4)) = 2.0, resp.]); 117.0 (*dq*, *J*(C,H) = 176.0, *J*(3,*Me*–C(4)) = 5.0, C(3)

[5]) The taxonomic identification was carried out by Dr. *R. Pronzato*, Università di Genova.

[2.14 or 5.80 → *d*, *J*(C,H) = 176.0, or *q*, *J*(3,*Me*–C(4)) = 5.0, resp.]); 94.0 (br. *s*, C(5) [2.14 or 3.08 → sharpening]); 64.9 (br. *d*, *J*(C,H) = 170.0, C(6) [1.51 or 3.08 → *d* or br. *s*, resp.]); 64.4 (br. *s*, C(7) [1.51 → *s*]); 31.0 (br. *t*, *J*(C,H) = 130.0, C(8) or C(9)); 30.5 (*t*, *J*(C,H) = 126.0, C(9) or C(8)); 17.0 (*q*, *J*(C,H) = 124.0, *Me*–C(7) [1.51 → *s*]); 13.6 (br. *q*, *J*(C,H) = 124.0, *Me*–C(4) [2.14 → *s*]). MS: 180 (2, $M^{+\cdot}$), 162 (4, $M^{+\cdot} - H_2O$), 151 (31, $M^{+} - CHO$), 137 (27, $M^{+} - 43$), 134 (23, 162 – 28), 111 (37, $M^{+} - 69$), 110 (100, $M^{+\cdot} - C_4H_6O$), 82 (80, 110 – 28), 69 (33), 68 (89), and 43 (53); B/E [16] on M^{+}, 162 and 151 signals. HR-MS: 180.0793 ± 0.006 ($M^{+\cdot}$; calc. 180.0787).

4. *Reaction of* **1a** *with* $LiAlH_4$. To a soln. of **1a** in 3 ml of THF at 0°, $LiAlH_4$ (1.2 mol-equiv.) was added and stirred for 2 h. Then, H_2O was added, the mixture filtered, and the filtrate extracted with Et_2O. After Et_2O evaporation, the residue (TLC; 3 major spots) was reacted with *p*-nitrobenzoyl chloride (1.2 mol-equiv.) in 1 ml of dry pyridine and the mixture stirred for 2 h at r.t. H_2O was added, the mixture extracted with Et_2O, and the org. layer washed with sat. aq. $CuSO_4$ soln. Evaporation gave 3 mg of a mixture which was subjected to reverse-phase HPLC (gradient elution with CH_3CN/H_2O) to give **4** (0.002 g, 14%). No attempts were made to isolate the other products.

3-(2',3'-Epoxy-1'-hydroxy-3'-methylcyclopentyl)butyl p-*Nitrobenzoate* (**4**): ^{1}H-NMR (C_6D_6): 7.72, 7.67 (A_2B_2, J_{AB} = 9.0, 4 arom. H); **4**.29, 4.24 (*AB* of *ABXX'* J_{AB} = 11.4, $J_{AX} = J_{BX} = J_{AX'} = J_{BX'}$ = 4.3, 2 H–C(1)); 2.80 (*s*, H–C(2')); 1.68 (*m* and *X* of *ABXX'*, H–C(3) and 1 H of 2 H–C(2), resp.); 1.50–1.25 (*m* and *X'* of *ABXX'* 2 H–C(4'), 2 H–C(5') and 1 H of 2 H–C(2), resp.); 1.17 (*s*, Me–C(3')); 0.93 (*d*, *J* = 6.2, Me–C(3)); irradiation at 1.68 → 0.93 (*s*), 4.24 (*AB* of *ABX'*, *J* = 11.4, 4.3). MS: 305 (1, $M^{+} - 30$), 290 (2, 305 – Me), 185 (0.5), 167 (5), 150 (56), 137 (23), 120 (100), 109 (5), 98 (21), 85 (11), 71 (12).

5. *Reaction of 3-Methylcyclopent-2-en-1-one* (**7**) *with Ethyl Propiolate*. To a soln. of dry diisopropylamine (0.63 ml, 4.47 mmol) in 12 ml of THF at – 10° were added 2.73 mmol of 1.63M BuLi in hexane. The mixture was stirred for 15 min at – 10° then cooled to – 78°, and ethyl propiolate (0.45 ml, 4.47 mmol) was added slowly. After stirring for 1 h at – 78°, **7** (0.30 ml, 3.03 mmol) was added and stirred for 1 h at – 60°. The mixture was warmed up to r.t. within 1.5 h, made nearly neutral with 6M aq. HCl, then neutral with a buffer solution (pH 7), and finally extracted with Et_2O. The org. layer was washed in turn with 5% aq. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated. The residue was subjected to flash chromatography (hexane/EtOAc 7:3) followed by silica-gel HPLC with the same eluent to give **8** (0.370 g, 63%).

Ethyl 1-Hydroxy-3-methylcyclopent-2-ene-1-propiolate (**8**): Pale yellow oil. IR (neat): 3395*s*, 2225*m*, 1710*vs*. ^{1}H-NMR ($CDCl_3$): 5.43 (*q*, *J* = 1.6, H–C(2)); 4.21 (*q*, *J* = 7.5, CH_3CH_2O); 2.50 (*ddd*, *J* = 13.8, 7.4, 4.9, H_β–C(5)); 2.45 (*m*, H_β–C(4)); 2.32 (*m*, H_α–C(4)); 2.30 (br. *s*, OH); 2.19 (*ddd*, *J* = 13.8, 8.4, 5.1, H_α–C(5)); 1.77 (*d*, *J* = 1.6, Me–C(3)); 1.23 (*t*, *J* = 7.5, CH_3CH_2O). ^{1}H-NMR (C_6D_6): 5.22 (*m*, H–C(2)); 3.88 (*q*, *J* = 7.1, CH_3CH_2O); 1.35 (br. *s*, Me–C(3)); 0.85 (*t*, *J* = 7.1, CH_3CH_2O); 2.50–1.50 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 153.72 (*s*, *C*OO); 148.05 (*s*, C(3)); 127.34 (*d*, C(2)); 89.32 (*s*, C(α)); 77.78 (*s*, C(β)); 75.74 (*s*, C(1)); 62.09 (*t*, CH_3CH_2O); 41.17 (*t*, C(5)); 35.21 (*t*, C(4)); 16.64 (*q*, CH_3–C(3)), 14.0 (*q*, CH_3CH_2O). MS: 176 (30, $M^{+} - H_2O$), 148 (27), 104 (100).

Ethyl 4-Methylcyclopenta-1,4-diene-1-propiolate (**11**): Oil. ^{1}H-NMR ($CDCl_3$): after 30 min at 22°, mixture of products of type **11** with transposition of the double bonds within the five-membered ring. MS: 148 (57, $M^{+} - 28$), 120 (69), 96 (100), 80 (7), 65 (1).

Ethyl 3-Hydroxy-3-methylcyclopent-1-ene-1-propiolate (**12**): Oil. IR (neat): 3410*vs*, 2205*s*, 1710*vs*, 1615*w*. ^{1}H-NMR ($CDCl_3$): 6.24 (*dd*, *J* = 1.5, 2.0, H–C(2)); 4.23 (*q*, *J* = 7.5, CH_3CH_2O); 2.63 (*dddd*, J_{gem} = 14.7, *J* = 8.3, 4.9, 1.5) and 2.50 (*dddd*, J_{gem} = 14.7, *J* = 8.3, 6.4, 2.0, CH_2(5)); 2.04 (*ddd*, J_{gem} = 13.8, *J* = 8.3, 4.9) and 1.98 (*ddd*, J_{gem} = 13.8, *J* = 8.3, 6.4, CH_2(4)); 1.85 (br. *s*, OH); 1.38 (*s*, CH_3–C(3)); 1.30 (*t*, *J* = 7.5, CH_3CH_2O). ^{13}C-NMR ($CDCl_3$): 153.81 (*s*, COO); 148.93 (*d*, C(2)); 123.17 (*s*, C(1)); 83.28, 82.93, 82.49 (3*s*, C(α), C(β), C(3)); 62.13 (*t*, CH_3CH_2O); 39.56 (*t*, C(4)); 34.17 (*t*, C(5)); 26.86 (*q*, Me–C(3)); 13.99 (*q*, CH_3CH_2O). MS: 194 (2, $M^{+\cdot}$), 179 (25, $M^{+} - CH_3$), 176 (30, $M^{+\cdot} - H_2O$), 131 (64), 103 (31), 104 (100), 78 (16), 77 (43).

3-Methyl-5-(3-methylcyclopent-2-enylidene)cyclopent-2-en-1-one (**9**): *(Z)-Isomer:* colourless microcystalline powder. M.p. 92–93°. ^{1}H-NMR ($CDCl_3$): 7.36 (*m*, H–C(2')); 6.03 (*m*, H–C(2)); 3.0 (br. *s*, CH_2(4)); 2.59 (*m*, CH_2(5')); 2.46 (*m*, CH_2(4')); 2.11 (*d*, *J* = 1.8, Me–C(3)); 1.98 (*d*, *J* = 1.8, Me–C(3')); double irradiation at 1.98 → 7.36 (*t*, *J* = 1.8), 2.46 (simplified *m*); irradiation at 2.11 → 6.03 (*t*, *J* = 1.8); irradiation at 2.46 → 2.59 (*s*), 7.36 (simplified *m*); irradiation at 2.59 → 3.0 (sharpened *m*); irradiation at 3.0 → 2.59 (simplified *m*); irradiation at 6.03 → 2.11 (simplified *d*); irradiation at 7.36 → 1.98 (simplified *d*), 2.46 (simplified *m*). ^{13}C-NMR ($CDCl_3$): 198.0 (*s*, C(1)); 165.70 (*s*); 155.54 (*s*); 133.36 (*d*, C(2')); 127.4 (*d*, C(2)); 122.15 (*s*); 38.40 (*t*, C(4)); 35.25 (*t*); 30.78 (*t*); 18.78 (*q*, *Me*–C(3)); 18.04 (*q*, *Me*–C(3')); the other expected *s* could not be detected.

(E)-Isomer: Colourless microcrystalline powder. M.p. 91–92°. ^{1}H-NMR ($CDCl_3$): 6.06 (*m*, H–C(2)); 6.00 (*m*, H–C(2')); 3.11 (*m*, CH_2(5')); 3.09 (*m*, CH_2(4)); 2.54 (*m*, CH_2(4')); 2.11 (*d*, *J* = 1.8, Me–C(3)); 2.00 (*d*, *J* = 1.7,

Me–C(3')); double irradiation at 2.00 → 6.00 (*t*, *J* = 1.7), 2.54 (*dt*, *J* = 6.8, 1.7); irradiation at 2.11 → 6.06 (*t*, *J* = 1.8); irradiation at 2.54 → 6.00 (simplified *m*); irradiation at 3.11 → 2.54 (*s*); irradiation at 6.00 → 2.00 (simplified *d*); irradiation at 6.06 → 2.11 (simplified *d*), 2.46 (simplified *m*). ^{13}C-NMR ($CDCl_3$): 198.06 (*s*, C(1)); 167.15 (*s*, C(3)); 162.0 (*s*, C(1')); 155.86 (*s*, C(3')); 133.78 (*d*, C(2')); 128.14 (*d*, C(2)); 121.55 (*s*, C(5)); 38.07 (*t*, C(4)); 37.46 (*t*, C(4')); 30.06 (*t*, C(5')); 18.72 (*q*, *Me*–C(3)); 18.10 (*q*, *Me*–C(3')). MS: 174 (100, M^+), 159 (45, $M^+ - CH_3$), 131 (79), 91 (20), 80 (7).

*Ethyl 3-(*N,N-*Diisopropylamino)prop-2-enoate* (**10**): IR (neat): 1690*s*, 1610*vs*, 1190*s*, 1135*s*, 950*m*. ^{1}H-NMR (C_6D_6, 80 MHz): 7.79 (*d*, *J* = 13.2, H–C(3)); 4.95 (*d*, *J* = 13.2, H–C(2)); 3.84 (*q*, *J* = 7.1, CH_3CH_2O); 3.1 (*sept.*, *J* = 6.8, 2 $(CH_3)_2CH$); 1.17 (*t*, *J* = 7.1, CH_3CH_2O); 0.71 (*d*, *J* = 6.8, 2 $(CH_3)_2CH$). MS: 199 (50, M^+), 184 (75, M^+ – Me), 156 (72, M^+ – 43), 154 (100, M^+ – OEt), 43 (54).

6. *4,7-Dimethyl-1-oxaspiro[4.4]nona-3,6-dien-2-one* (**5**). To a soln. of CuBr · SMe_2 (0.256 g, 1.25 mmol) in 5 ml of dry Et_2O at – 10° under Ar were added 1.55 ml (2.45 mmol) of 1.6M MeLi in Et_2O. The mixture was stirred at – 10° for 10 min, then more MeLi was added until a colourless soln. was obtained. At – 30°, **8** (0.200 g, 1.03 mmol) in Et_2O was added with stirring within 1.5 h. The mixture was warmed up to 0° and 1M cold, aq. HCl added with stirring within 30 min. The mixture was extracted with Et_2O, the org. phase washed with sat. aq. $NaHCO_3$ soln., sat. NaCl soln., H_2O, dried (Na_2SO_4), and evaporated, and the residue was subjected to flash chromatography with hexane/EtOAc 7:3 to give **5** which was further purified by silica-gel HPLC with hexane/EtOAc 73:27, t_R 10 min (0.130 g, 78%). IR (neat): 1750*vs*, 1650*m*, 1455*m*, 945*s*. ^{1}H-NMR ($CDCl_3$): 5.675 (*q*, *J* = 1.5, H–C(3)); 5.036 (*m*, H–C(6)); 2.65–2.15 (*m*, 2 H–C(8), 2 H–C(9)); 1.913 (*d*, *J* = 1.5, Me–C(4)); 1.817 (br. *d*, *J* = 1.2, Me–C(7)). ^{13}C-NMR ($CDCl_3$): 172.30 (*s*, C(2)); 170.06 (*s*, C(4)); 151.07 (*s*, C(7)); 122.95 (*d*, C(6)); 115.68 (*d*, C(3)); 101.28 (*s*, C(5)); 36.07 (*t*, C(9)); 33.24 (*t*, C(8)); 16.74 (*q*, *Me*–C(7)); 12.93 (*q*, *Me*–C(4)). MS: 164 (60, M^+), 149 (85, M^+ – Me), 120 (41), 105 (100).

7. *Epoxidation of* **5**. To a soln. of **5** (0.106 g, 0.65 mmol) in 5 ml of dry CH_2Cl_2 at 0° were added first 1 mol-equiv. each of 75% *m*-$ClC_6H_4CO_3H$ and $NaHCO_3$ and after 24 h, further peracid and base up to a total of 0.177 g (1.04 mmol) of *m*-$ClC_6H_4CO_3H$ and 0.113 g (1.3 mmol) of $NaHCO_3$. The mixture was warmed up to r.t. and stirred for 48 h, the precipitated white solid filtered and discarded, and the filtrate evaporated at reduced pressure. The residue was dissolved in Et_2O, the org. phase washed with 10% aq. $NaHSO_3$ soln., sat. aq. $NaHCO_3$ soln., and H_2O, dried ($NaSO_4$), and evaporated, and the residue (0.098 g; ^{1}H-NMR: **1a**/**1b** 9:1 subjected to silica-gel HPLC with hexane/i-PrOH 85:15, giving **1a** (0.085 g, 73%) and **1b** (0.010 g, 8.6%). TLC (hexane/i-PrOH 9:1) R_f 0.50 and 0.1, resp. **1a**: data identical to those of natural adriadysiolide.

*(5*R**,6*R**,7*R**)-6,7-Epoxy-4,7-dimethyl-1-oxaspiro[4.4]non-3-en-2-one* (**1b**): Colourless microcrystalline powder. M.p. (hexane) 87–88°. ^{1}H-NMR ($CDCl_3$): 5.82 (*q*, *J* = 1.6, H–C(3)); 3.12 (*s*, H–C(6)); 2.06 (*d*, *J* = 1.6, Me–C(4)); 2.25–1.25 (*m*, 4 H); 1.53 (*s*, Me–C(7)). ^{13}C-NMR: 171.83 (*s*, C(2)); 167.47 (*s*, C(4)); 117.00 (*d*, C(3)); 94.41 (*s*, C(5)); 64.81 (*d*, C(6)); 63.43 (*s*, C(7)); 30.79 (*t*, C(8) or C(9)); 28.89 (*t*, C(9) or C(8)); 15.57 (*q*, *Me*–C(7)); 13.46 (*q*, *Me*–C(4)). MS: 180 (2, M^+), 162 (3, $M^+ - H_2O$), 151 (30, 162 – 28), 111 (51, M^+ – 69), 110 (100, $M^+ - C_4H_6O$), 82 (55, 110 – 28), 69 (35), 68 (45).

8. *Epoxidation of* **8**. To a soln. of 75% *m*-$ClC_6H_4CO_3H$ (0.114 g, 0.676 mmol) and $NaHCO_3$ (0.073 g, 0.85 mmol) in 10 ml of CH_2Cl_2 at 0° **8** (0.076 g, 0.39 mmol) in CH_2Cl_2 was added with stirring within 2 h whereby **8** completely disappeared (TLC). The mixture was filtered, the filtrate evaporated, its residue dissolved in Et_2O, and the org. phase washed with 10% aq. $NaHSO_3$ soln., sat. aq. $NaHCO_3$ soln., H_2O, dried (Na_2SO_4), and evaporated. Flash chromatography with hexane/AcOEt 7:3 gave *ethyl 2,3-epoxy-1-hydroxy-3-methylcyclopentane-1-propiolate* (**13**; 0.074 g, 90%) as a pale-yellow oil. IR (neat): 3420*vs*, 2220*s*, 1720*vs*. ^{1}H-NMR (C_6D_6): 3.85 (*q*, *J* = 7.5, CH_3CH_2O); 3.19 (*s*, H–C(2)); 1.9–1.2 (*m*, 2 H–C(4), 2 H–C(5), OH); 1.01 (*s*, Me–C(3)); 0.82 (*t*, *J* = 7.5, CH_3CH_2O). ^{13}C-NMR (C_6D_6): 153.36 (*s*, COO); 86.98 (*s*, C(α)); 77.86 (*s*, C(β)); 74.08 (*s*, C(1)); 66.75 (*d*, C(2)); 63.44 (*s*, C(3)); 62.03 (*t*, CH_3CH_2O); 35.57 (*t*, C(5)); 30.10 (*t*, C(4)); 17.27 (*q*, *Me*–C(3)); 13.76 (*q*, CH_3CH_2O). MS: 195 (1, $M^+ - CH_3$), 165 (60, $M^+ - OCH_2CH_3$), 136 (100), 108 (55), 97 (36), 84 (80), 69 (47), 57 (51) 55 (57).

9. *Epiadriadysiolide* (**1b**). To CuBr · SMe_2 (0.0323 g, 0.157 mmol) in 1 ml of dry Et_2O at 0° under Ar, 1.5M MeLi in hexane was added until a colourless soln. was obtained. The soln. was stirred for 10 min at – 10°. At – 30°, **13** (0.030 g, 0.143 mmol) in Et_2O was added, and the mixture was stirred at – 30° for 2 h, then warmed up to – 20°, quenched with NH_4Cl soln., and extracted with Et_2O. The org. layer was washed with aq. $NaHCO_3$ soln. and H_2O, dried ($NaSO_4$), and evaporated and the residue (0.028 g) subjected to prep. TLC with hexane/AcOEt 7:3 giving **1b** (0.0052 g, 20%). Minor products were not investigated.

10. *Shift-Reagent Studies with* **1a** *and* **1b**. To adriadysiolide (**1a**; 2.39 mg, 0.01327 mmol) in 0.5 ml of $CDCl_3$ was added an equimolar amount of [Eu(fod)$_3$] in 20-µl portions of a 0.047M soln. in $CDCl_3$. The same procedure was applied to **1b** (0.95 mg, 0.00527 mmol).

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