Polyoxygenated Eudesmanes and *trans*-Chrysanthemanes from the Aerial Parts of *Santolina insularis*

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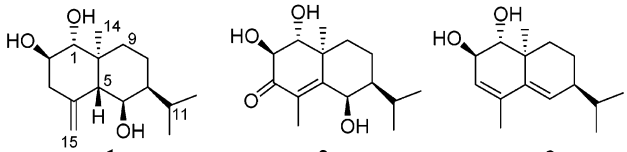
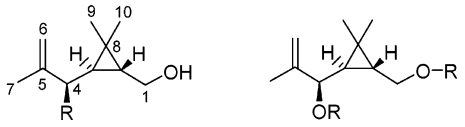
The eudesmane sesquiterpenoids **1**−**3** and the *trans*-chrysanthemyl monoterpenoid **4** have been isolated from the aerial parts of *Santolina insularis*, a bush endemic to Sardinia. The absolute stereostructures of these novel compounds and of two known but incompletely characterized chrysanthemanes (**5**, **6**) were established by spectroscopic techniques and by application of the modified Mosher method. The presence of the *p*-menthane aldehyde eucamalol (**7**) gives credit to the widespread use of *S. insularis* to fend off mosquitoes.

The genus *Santolina* (Compositae, tribe Anthemiadeae) is a taxonomically complex assembly of species whose classification has been subjected to numerous revisions.[1] Plants from this genus have been intensely investigated from a chemical and a pharmacological standpoint on account of their rich ethnopharmacology, which includes both medicinal (antispamodic, antiseptic, antiinflammatory, antihelmintic) and insecticidal uses.[2,3] As part of a program aimed at the isolation of bioactive secondary metabolites from endemic Mediterranean species, we have investigated *S. insularis* (Genn. ex Fiori) Arrigoni, a bush endemic to Central and Southern Sardinia (Italy), where its aerial parts are traditionally used as a vermifuge and to repel insects.[4] Recently, the essential oil of *S. insularis* has been shown to possess powerful antiherpetic activity,[5] but nothing is known on its antiviral constituent(s).

Phytochemical analysis of an acetone extract from the defatted aerial parts of *S. insularis* yielded three novel eudesmane sesquiterpenoids (**1**−**3**) and four monoterpenoids (**4**−**7**), one of which (**4**), possessing a chrysanthemyl skeleton, is new.

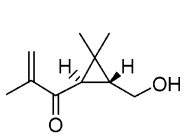


1 **2** **3**



4 R = OH
5 R = OOH

4a R = *S*-MTPA
4b R = *R*-MTPA



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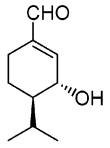

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Results and Discussion

Aerial parts of *S. insularis*, collected on the island of Sardinia during blossom in 2001, were first sun-dried and then pulverized. The powder obtained was exhaustively extracted first with *n*-hexane and then with acetone. The acetone extract (12 g) was subjected to medium-pressure liquid chromatography (MPLC) over a column packed with silica gel and afforded two terpenoid-rich fractions, which were further purified by HPLC, eventually affording the sesquiterpene polyols **1**−**3** and the monoterpenoids **4**−**7**.

HRMS data indicated a molecular formula $C_{15}H_{26}O_3$ for **1**, implying three unsaturation degrees. The assignments of the ^{1}H and ^{13}C NMR signals (C_6D_6, Table 1) in terms of structure **1** were assisted by 2D NMR measurements (COSY, HMQC, and HMBC). Thus, inspection of the ^{1}H−^{1}H COSY spectrum sorted the multiplet resonances of the ^{1}H NMR spectrum into two spin systems, next associated by the HMQC spectrum to their corresponding carbon atoms. The first fragment, connecting H-1 to H_2-3, features two oxymethines at C-1 (δ_C 84.0; δ_H 3.20) and C-2 (δ_C 72.2; δ_H 3.60), respectively. In turn, H_2-3 showed long-range coupling to the sp^2 CH_2-15 group (δ_C 109.7, HMQC coupled to δ_H 4.92 and 5.12, both broad singlets). The second fragment, connecting H-5 to H_2-9, was decorated by an isopropyl branching at C-7 and featured a third oxymethine at C-6 (δ_C 70.0; δ_H 4.15). An uncoupled methyl group (δ_C 13.0; δ_H 0.78, s) completed the series of the protonated carbons, leaving only two unprotonated carbon atoms (δ_C 144.0 and 40.2) to assign. Analysis of the HMBC $^{2,3}J_{C-H}$ correlations connected the two proton spin systems. Thus, the detection of cross-peaks between H_2-15 and C-4, C-3, and C-5 located the *exo*-methylene at C-4 and furnished the first link between the two spin systems, the second one being identified in the aliphatic nonprotonated carbon (C-10) by inspection of the cross-peaks of the methyl singlet H_3-14 (correlation with C-10, C-1, C-5, and C-9). Thus, **1** was a 1,2,6-trihydroxyeudesm-4(15)-ene derivative.

The relative configuration of **1** was assigned analyzing scalar ($^3J_{HH}$) and dipolar (ROESY correlations) couplings of the protons attached to the ring (Figure 1). In particular, the value of $J_{H-1/H-2}$ (8.9 Hz) is typical of *trans*-diaxial

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Table 1. ^{13}C (125 MHz) and ^{1}H (500 MHz) NMR Data of Eudesmane Derivatives **1**−**3** in C_6D_6

	1		**2**		**3**	
pos	δ_C (mult.)	δ_H (mult., *J* in Hz)	δ_C (mult.)	δ_H (mult., *J* in Hz)	δ_C (mult.)	δ_H (mult., *J* in Hz)
1	84.0 (CH)	3.20 (d, 8.9)	77.4 (CH)	3.27 (d, 11.2)	81.2 (CH)	3.08 (d, 8.1)
2	72.2 (CH)	3.60 (m)	73.1 (CH)	4.05 (d, 11.2)	70.9 (CH)	4.07 (bd, 8.1)
3a	44.0 (CH_2)	2.62 (dd, 12.8, 5.9)	197.1 (C)		125.5 (CH)	5.39 (bs)
3b		2.10 (dd, 12.8, 3.2)				
4	144.0 (C)		128.2 (C)		132.8 (C)	
5	50.7 (CH)	2.15 (d, 10.8)	160.3 (C)		141.4 (C)	
6	70.0 (CH)	4.15 (dd, 10.8, 4.5)	64.4 (CH)	4.50 (d, 2.2)	126.9 (CH)	5.69 (d, 4.4)
7	44.7 (CH)	1.70[a]	38.3 (CH)	1.08 (dq, 9.2, 2.2)	39.7 (CH)	1.83 (m)
8a	22.9 (CH_2)	1.60 (m)	19.9 (CH_2)	1.63[a]	20.0 (CH_2)	1.66 (m)
8b		1.71[a]		1.28 (m)		1.77 (m)
9a	32.3 (CH_2)	1.50 (m)	26.1 (CH_2)	2.05 (dd, 13.6, 8.5)	31.0 (CH_2)	1.57 (dd, 13.2, 7.8)
9b		1.30 (m)		1.42 (dd, 13.6, 9.2)		1.30 (dd, 13.2, 4.4)
10	40.2 (C)		37.3 (C)		37.7 (C)	
11	30.1 (CH)	2.01 (m)	29.2 (CH)	1.61[a]	32.9 (CH)	1.50 (m)
12	25.3 (CH_3)	0.95 (d, 7.3)	18.1 (CH_3)	0.80 (d, 7.3)	20.1 (CH_3)	0.85 (d, 7.3)
13	25.5 (CH_3)	1.05 (d, 7.3)	18.1 (CH_3)	0.88 (d, 7.3)	20.2 (CH_3)	0.89 (d, 7.3)
14	13.0 (CH_3)	0.78 (s)	14.8 (CH_3)	1.03 (s)	16.6 (CH_3)	1.03 (s)
15a	109.7 (CH_2)	4.92 (bs)	9.0 (CH_3)	1.74 (s)	19.1 (CH_3)	1.70 (s)
15b		5.12 (bs)				

[a] Overlapped with other signals.

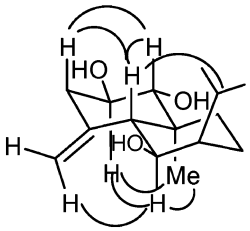
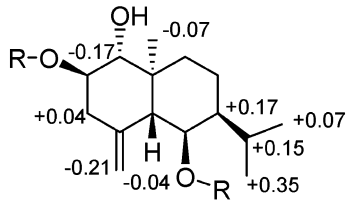


Figure 1. Spatial couplings of compound **1** evidenced through the ROESY spectrum.



1a R = *S*-MTPA
1b R = *R*-MTPA

Figure 2. Application of the modified Mosher's method to determine the absolute configuration at C-2 and C-6 of **1**. $\Delta\delta$ ($S - R$) values are given in ppm.

oxymethine protons. A diaxial relationship was also evident between H-5 and H-6 ($J_{H-5/H-6}$ = 10.8 Hz), while the coupling constant $J_{H-6/H-7}$ (4.5 Hz) was diagnostic of an axial−equatorial relationship, suggesting the axial orientation of the isopropyl group. The ROESY cross-peaks H-1/H-5, CH_3-14/H-6, CH_3-14/H-2, and H-11/H-5 (Figure 1) further confirmed that the *trans*-decalin system of **1** adopts a conformation that places the isopropyl on ring B and the angular methyl in an axial orientation.

Owing to the presence of a rigid bicyclic system, **1** is easily amenable to Mosher methodology to assess the absolute configuration of secondary alcohols.[6] To this aim, two aliquots of **1** were treated with (−)- and (+)-MTPA chloride in dry pyridine at room temperature, providing the *S* (**1a**) and *R* (**1b**) MTPA 2,6-diesters, respectively (Figure 2). Most likely, the neopentyl C-1 hydroxyl group was too hindered to react with the bulky MTPA chloride, under these conditions. The obtained distribution of $\Delta\delta$ ($S - R$) values (Figure 2) for the protons neighboring C-2 and C-6 indicates a 2*R*,6*R* configuration. It is worth noting that the ring junction of **1** differs from that generally found in eudesmanes from plants of the Compositae family. Indeed, **1** belongs to the "umbelliferous" configurational type of eudesmanes,[7] a finding not unprecedented in plants from the genus *Santolina*.[8]

The ^{1}H and ^{13}C NMR spectra (Table 1) of **2** ($C_{15}H_{24}O_4$, HRMS) were similar to those of **1**. Indeed, three oxymethines were still present, while a ketone carbonyl (δ_C 197.1) accounted for the fourth oxygen atom and the higher unsaturation degree required by the molecular formula. Analysis of the COSY spectrum of **2** revealed two distinct spin systems: one encompassing the oxymethines H-1 and H-2, and the other spanning the methines at C-6 (oxygenated) and C-9, with an isopropyl substitution at C-7. The HSQC spectrum was instrumental in associating the proton resonances with those of the protonated carbon atoms, leading to a straightforward rationalization of the HMBC spectrum. Thus, HMBC correlations of the methyl singlet at δ 1.74 (H_3-15) with the carbonyl carbon (C-3) and with the sp^2 carbons C-4 (δ_C 128.2) and C-5 (δ_C 160.3) indicated the presence of an α-methyl enone. The upfield resonance of the allylic methyl C-15 (δ_C 9.0) fits well its location on an α-enone carbon. Linkage of the glycol spin system to the ketone carbonyl was indicated by HMBC cross-peaks of H-2 (δ_H 4.05) with both C-3 and C-4, while HMBC cross-peaks of H-6 (δ_H 4.50) with both C-4 and C-5 joined the second fragment to the other terminus of the conjugated system. Finally, HMBC correlations of H_3-14 (δ_H 1.03) with C-1, C-10, C-5, and C-9 completed the definition of the planar structure of compound **2**.

The relative configuration of **2** was inferred from the measured values of vicinal couplings and the pattern of ROESY cross-peaks. In particular, $J_{H-1/H-2}$ (11.2 Hz), though diagnostic of a diaxial orientation, was significantly different from the value measured in **1**, presumably because of the adjacent carbonyl rather than torsional differences. An axial orientation was also assigned to CH_3-14 and H-6 on the basis of ROESY cross-peaks H-2/H_3-14 and H_3-14/H-6. Finally, the small value of $J_{H-6/H-7}$ (2.2 Hz) revealed the equatorial nature of H-7.

Compared to **1**, the molecular formula of **3** ($C_{15}H_{24}O_2$, HRMS) showed the loss of a water molecule. Combined inspection of ^{1}H, ^{13}C, COSY, and HSQC NMR spectra of **3** indicated the presence of two trisubstituted double bonds (δ_C 125.5, δ_H 5.39; δ_C 132.8, unprotonated; δ_C 141.4,

Table 2. ^{13}C (125 MHz) and ^{1}H (500 MHz) NMR Data of **4** and **6** in $CDCl_3$

	4		**6**	
pos	δ_C (mult.)	δ_H (mult., *J* in Hz)	δ_C (mult.)	δ_H (mult., *J* in Hz)
1a	63.1 (CH_2)	3.52 (dd, 12.0, 11.0)	62.1 (CH_2)	3.65 (dd, 12.0, 8.5)
1b		3.69 (dd, 12.0, 5.5)		3.78 (dd, 12.0, 10.5)
2	32.2 (CH)	0.80 (ddd, 11.0, 5.5, 5.0)	35.1 (CH)	1.92 (ddd, 10.5, 8.5, 5.0)
3	34.8 (CH)	0.70 (dd, 10.0, 5.0)	34.0 (CH)	2.10 (d, 5.0)
4	76.8 (CH)	3.68 (d, 10.0)	198.4 (C)	
5	147.5 (C)		147.1 (C)	
6a	111.2 (CH_2)	4.98 (bs)	123.2 (CH_2)	5.92 (bs)
6b		4.80 (bs)		5.75 (bs)
7	18.1 (CH_3)	1.70 (s)	18.1 (CH_3)	1.90 (s)
8	20.8 (C)		25.6 (C)	
9	21.9 (CH_3)	1.22 (s)	20.3 (CH_3)	1.32 (s)
10	21.8 (CH_3)	1.12 (s)	21.0 (CH_3)	1.05 (s)

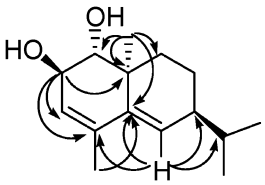


Figure 3. Key $^{2,3}J$ H→C correlations exhibited by the HMBC spectrum of compound **3**.

unprotonated; δ_C 126.9, δ_H 5.69), the former attached to a fragment composed by two vicinal oxymethines (δ_C 81.2, δ_H 3.08; δ_C 70.9, δ_H 4.07) and the latter linked to a fragment identical to the C-7/C-9 moiety of both **1** and **2**. The presence of an *s-trans* conjugated diene system was responsible for the intense absorption at λ_{max} 236 nm (log ϵ = 4.4) in the UV (CH_3CN) spectrum of **3**. The observations were further complemented by a set of diagnostic HMBC correlations (Figure 3), eventually leading to the 1,2-dihydroxyeudesma-3,5-diene structure of **3**. The value of $J_{H-1/H-2}$ = 8.2 Hz, indicating the *trans* (diaxial) orientation of H-1 and H-2, and the detection of the ROESY cross-peaks H-2/CH_3-14 and H-9ax/H-1 and H-9ax/H-11 settled the relative configuration of the four stereogenic centers and showed that the three eudesmanes **1**−**3** are homogeneous in terms of relative configuration. The absolute configuration of compounds **2** and **3** was assumed to be identical to that of **1** on account of the similarity of their relative configurations.

Three monoterpenoids based on the chrysanthemyl skeleton (**4**−**6**) and differing in the functionality at C-4 were also characterized. HRMS analysis established the molecular formula $C_{10}H_{18}O_2$ for **4**. The following elements could be recognized in the ^{1}H NMR spectrum of **4** ($CDCl_3$, Table 2, COSY analysis): (i) a system (C-1 to C-4) made up by an oxymethine and an oxymethylene separated by two high-field aliphatic methines); (ii) two singlets in the sp^2 region (δ 4.98 and 4.80) allylically coupled to H-4; (iii) a broad methyl singlet at δ 1.70 allylically coupled with the two sp^2 signals; (iv) two methyl singlets at δ 1.12 and 1.22. After associating all these signals with those of the directly bonded carbon atoms through the HMQC experiment, HMBC correlations were used to define the planar structure of compound **4**. The detection of cross-peaks of the methyl protons at δ 1.12 and 1.22 with the unprotonated carbon at δ 20.8 and both C-2 and C-3 established the presence of a *gem*-dimethyl-substituted cyclopropane moiety. Further key HMBC correlations were those of H-4 with C-5, C-6, and C-7, unambiguously identifying **4** as a novel chrysanthemol derivative bearing an hydroxyl group at C-4. The *trans* geometry of the three-membered ring was established on the basis of ROESY couplings (H-2/H-4 and H_2-1/H-3) and was in accordance with the measured value of $J_{H-2/H-3}$ (5.0 Hz).[9,10] The absolute configuration of the hydroxymethine carbon was assessed by application of modified Mosher methodology for secondary alcohols.[6] Thus, treatment of two aliquots of **4** with (−)- and (+)-MTPA chloride in dry pyridine provided the diesters **4a** and **4b**, respectively. The pattern of $\Delta\delta$ ($S - R$) values (see Experimental Section) assigned an *R* configuration at C-4. It was not possible to relate the configuration of C-4 to that of the ring carbons C-2 and C-3, but the 2*R*,3*R* configuration of all chrysanthemyl derivatives known to date seems likely.[9]

The molecular formula of **5** ($C_{10}H_{18}O_3$, HRMS) showed one additional oxygen atom compared to **4**. The ^{1}H NMR spectra of **4** and **5** featured the same spin systems, suggesting that **5** was the hydroperoxyl analogue of **4**, a constituent of the African plant *Eriocephalus kingesii* (Compositae), uncompletely characterized in configurational terms.[11] Comparison with the published spectroscopic data[11] showed the identity of the two compounds. The configuration of **5** was assessed by reduction with triphenylphosphine to a compound identical ($[\alpha]_D$ and NMR data) to **4**.

Compared to **4**, the molecular formula of the chrysanthemyl derivative **6** ($C_{10}H_{16}O_2$, HRMS) showed a further unsaturation degree. Indeed, inspection of the ^{1}H and ^{13}C NMR spectra of **6** ($CDCl_3$, Table 2) revealed the replacement of the secondary hydroxyl with a ketone carbonyl (δ_C 198.4). Accordingly, the ^{1}H NMR resonances of the cyclopropane methines H-2 and H-3 suffered a significant downfield shift ($\Delta\delta_H$ = 1.12 and 1.40, respectively), paralleled by that observed for the sp^2 H_2-6 protons ($\Delta\delta_H$ 0.94 and 0.95, respectively), as a result of the conjugation of the double bond with the ketone group. Assignment of all the ^{13}C and ^{1}H resonances by 2D techniques (COSY, HMQC, HMBC) led to structure **6**. Especially diagnostic were the $^{2,3}J_{CH}$ correlations of H-3 with C-4, C-5, C-2, C-8, and C-9 and of H-2 with C-1, C-3, C-8, and C-4, while the NOE enhancement of H_2-1 upon irradiation of H-3 and the $J_{H-2/H-3}$ value (5.0 Hz) pointed to a chrysanthemyl derivative of the *trans*-type. Compound **6** was reported as a constituent of *Artemisia tridentata cana*,[10] but could be isolated only as a *tert*-butyldimethylsilyl derivative.

The *p*-menthane monoterpenoid eucamalol (**7**) was also obtained in good yields from the extract containing **1**−**6**. Eucamalol is the mosquito-repellent principle of *Eucalyptus camaldulensis* and has been reported to outperform *N*,*N*-diethyl-*m*-toluamide in terms of potency.[12,13] The presence of eucamalol in *S. insularis* gives credit to the widespread use of this plant to fend off mosquitoes[4] and further exemplifies the potential of plants to provide biodegradable alternatives to synthetic agents of growing concern because of their environmental persistency.[14]

Experimental Section

General Experimental Procedures. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer 192 polarimeter equipped with a sodium lamp (λ_{max} = 589 nm) and a 10 cm microcell. IR (KBr) spectra were recorded on a Bruker model IFS-48 spectrophotometer. Ultraviolet spectra were obtained in CH_3CN using a Beckman DU70 spectrophotometer. Low-resolution FAB (CsI ions, glycerol matrix) and low- and high-resolution EI mass spectra (70 eV, direct inlet) were performed on a VG Prospec (FISONS) mass spectrometer. ES mass spectra were recorded on a LCQ Finnigan MAT mass spectrometer. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were measured on a Bruker AMX-500 spectrometer; chemical shifts are referenced to the residual solvent signal ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$; C_6D_6: $\delta_H = 7.18$, $\delta_C = 128.0$). The multiplicities of ^{13}C NMR resonances were determined by DEPT experiments. One-bond heteronuclear $^1H-^{13}C$ connectivities were determined with the HMQC or HSQC experiments. Two- and three-bond $^1H-^{13}C$ connectivities were determined by HMBC experiments optimized for a $^{2,3}J$ of 8 Hz. Nuclear Overhauser effect (NOE) measurements were performed by 2D ROESY experiments. Medium-pressure liquid chromatography (MPLC) was performed using a Büchi 861 apparatus with Merck SI60 (230−400 mesh) stationary phase. High-performance liquid chromatography (HPLC) separations in isocratic mode were achieved on a Beckmann apparatus equipped with refractive index detector and with Phenomenex LUNA SI60 (250 × 10 mm and 250 × 4 mm) columns.

Plant Material. Specimens of *Santolina insularis* (Genn. ex Fiori) Arrigoni were collected near Arzana (Nu), Sardinia (Italy), in June 2001. The plant was identified by M.B., and a voucher specimen (ref. no. 0707000) is held at Dipartimento di Scienze Botaniche, Cagliari (Italy).

Extraction and Isolation. Dried aerial parts of *S. insularis* (stems and leaves, 250 g) were pulverized, defatted with *n*-hexane (4 × 2 L), and then extracted with acetone (4 × 2 L) at room temperature, affording 12 g of a dark gum. This was fractionated by MPLC column chromatography (silica gel) using a solvent gradient system from *n*-hexane/EtOAc, 9:1, to EtOAc/MeOH, 9:1, and affording 10 main fractions (A−J). Fraction F (130 mg) obtained by elution with *n*-hexane/EtOAc, 4:6, was further purified by HPLC on a SI60 250 × 10 column (*n*-hexane/EtOAc, 1:1, as eluant) and then by analytical HPLC (SI60 250 × 4 column, *n*-hexane/EtOAc, 55:45, as eluant) to yield **1** (12.0 mg, 0.005% of dried aerial parts), **2** (2.0 mg, 0.0008%), **3** (1.5 mg, 0.0006%), and **4** (7.5 mg, 0.003%). Fraction D (82 mg) obtained by elution with *n*-hexane/EtOAc, 6:4, was first purified by HPLC on a SI60 250 × 10 column (*n*-hexane/EtOAc, 7:3) and then by HPLC on a SI60 250 × 4 column (*n*-hexane/EtOAc, 7:3) to afford **5** (21.3 mg, 0.009%), **6** (7.2 mg, 0.003%), and **7** (38.5 mg, 0.015%).

(1*R*,2*R*,5*R*,6*R*,7*S*,10*S*)-Eudesma-4(15)-en-1,2,6-triol (1): colorless amorphous solid; $[\alpha]_D^{25}$ −15.5° (*c* 0.07, $CHCl_3$); IR (KBr) ν_{max} 3520 cm^{-1}; ^1H (C_6D_6, 500 MHz) and ^{13}C (C_6D_6, 125 MHz) NMR spectra, Table 1; ESIMS (positive ions) *m/z* 277 $[M + Na]^+$, 531 $[2M + Na]^+$; EIMS (70 eV) *m/z* 254 $[M]^+$ (5), 239 (20), 236 (100), 221 (45); HREIMS *m/z* 254.1901 (calcd for $C_{15}H_{26}O_3$, 254.1882).

Preparation of MTPA Ester Derivatives of Compound 1. Compound **1** (2.2 mg) was dissolved in 0.8 mL of dry pyridine, treated with an excess of (−)-MTPA chloride (20 μL), and then maintained at room temperature with stirring overnight. After removal of the solvent, the reaction mixture was purified by HPLC on a SI60 column (eluent *n*-hexane/EtOAc, 8:2), affording (*S*)-MTPA ester **1a** in a pure state (2.0 mg). Using (+)-MTPA chloride, the same procedure afforded (*R*)-MTPA ester **1b** in the same yield.

(*S*)-MTPA 2,6-diester (1a): amorphous solid; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 and 7.45 (MTPA phenyl protons); 5.42 (H-6, dd, *J* = 10.8, 4.8 Hz); 4.98 (H-2, ddd, *J* = 9.1, 5.9, 3.2 Hz); 4.83 (H-15a, bs); 4.41 (H-15b, bs); 3.53 (MTPA OCH_3, s); 3.38 (H-1, d, *J* = 9.1 Hz); 2.62 (H-3a, dd, *J* = 12.8, 5.9 Hz); 2.36 (H-5, d, *J* = 10.8 Hz); 2.07 (H-3b, dd, *J* = 12.8, 3.2 Hz); 1.84 (H-11, overlapped); 1.82 (H-7, overlapped); 1.71 (H-8a, m); 1.62 (H-8b, m); 1.56 (H-9a, m); 1.31 (H-9b, m); 0.84 (H_3-14, s); 0.83 (H_3-12, d, *J* = 7.3 Hz); 0.80 (H_3-13, d, *J* = 7.3 Hz); FABMS (glycerol matrix, positive ions) *m/z* 687 $[M + H]^+$.

(*R*)-MTPA 2,6-diester (1b): amorphous solid; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 and 7.55 (MTPA phenyl protons); 5.52 (H-6, dd, *J* = 10.8, 4.8 Hz); 5.05 (H-2, overlapped); 5.04 (H-15a, bs); 4.62 (H-15b, bs); 3.55 (H-1, d, *J* = 9.1 Hz); 3.49 (MTPA OCH_3, s); 2.61 (H-3a, dd, *J* = 12.8, 5.9 Hz); 2.40 (H-5, d, *J* = 10.8 Hz); 2.03 (H-3b, dd, *J* = 12.8, 3.2 Hz); 1.70 (H-8a, overlapped); 1.69 (H-11, overlapped); 1.65 (H-7, overlapped); 1.65 (H-8b, overlapped); 1.58 (H-9a, m); 1.38 (H-9b, m); 0.90 (H_3-14, s); 0.73 (H_3-12, d, *J* = 7.3 Hz); 0.48 (H_3-13, d, *J* = 7.3 Hz); FABMS (glycerol matrix, positive ions) *m/z* 687 $[M + H]^+$.

(1*R*,2*S*,6*R*,7*S*,10*S*)-1,2,6-Trihydroxyeudesma-4-en-3-one (2): colorless amorphous solid; $[\alpha]_D^{25}$ −16.1° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 3520, 3370, 1670, 1653 cm^{-1}; ^1H (500 MHz, C_6D_6) and ^{13}C (125 MHz, C_6D_6) NMR spectra, Table 1; ESIMS (positive ions) *m/z* 291 $[M + Na]^+$; EIMS (70 eV) *m/z* 268 $[M]^+$ (35), 253 (12), 225 (88), 207 (32), 91 (100); HREIMS *m/z* 268.1649 (calcd for $C_{15}H_{24}O_4$, 268.1675).

(1*R*,2*R*,7*S*,10*S*)-Eudesma-3,5-dien-1,2-diol (3): colorless amorphous solid; $[\alpha]_D^{25}$ −11.0° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 3530, 3380 cm^{-1}; UV (CH_3CN) λ_{max} 236 nm (log ϵ = 4.4); ^1H (500 MHz, C_6D_6) and ^{13}C (125 MHz, C_6D_6) NMR spectra, Table 1; ESIMS (positive ions) *m/z* 259 $[M + Na]^+$; EIMS (70 eV) *m/z* 236 $[M]^+$ (45), 221 (22), 218 (67), 193 (82), 89 (100); HREIMS *m/z* 236.1789 (calcd for $C_{15}H_{24}O_2$, 236.1776).

(2*R*,3*R*,4*R*)-5-Chrysanthemen-1,4-diol (4): colorless amorphous solid; $[\alpha]_D^{25}$ −2.0° (*c* 0.05, $CHCl_3$); IR (KBr) ν_{max} 3540 cm^{-1}; ^1H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR spectra, Table 2; EIMS (70 eV) *m/z* 170 $[M]^+$ (55), 152 (100), 139 (77); HREIMS *m/z* 170.1327 (calcd for $C_{10}H_{18}O_2$, *m/z* 170.1307).

Preparation of MTPA Ester Derivatives of Compound 4. Compound **4** (1 mg) was dissolved in 0.5 mL of dry pyridine, treated with (−)-MTPA chloride (15 μL), and then maintained overnight at room temperature under stirring. After removal of the solvent, the reaction mixture was purified by HPLC on a SI60 column (eluent *n*-hexane/EtOAc, 9:1), affording (*S*)-MTPA 1,4-diester **4a** in a pure state (1.2 mg). Using (+)-MTPA chloride, the same procedure afforded (*R*)-MTPA 1,4-diester **4b** in the same yield.

(*S*)-MTPA 1,4-diester (4a): amorphous solid; ^1H NMR ($CDCl_3$) δ 7.35 and 7.45 (MTPA phenyl protons); 5.01 (H-4, d, *J* = 10.0 Hz); 4.88 (H-6a, bs); 4.80 (H-6b, bs); 4.42 (H-1a, dd, *J* = 12.0, 5.5 Hz); 4.11 (H-1b, dd, *J* = 12.0, 11.0 Hz); 3.59 (MTPA OCH_3, s); 1.55 (H_3-7, s); 1.04 (H_3-9, s); 1.03 (H-3, overlapped); 1.02 (H_3-10, s); 0.95 (H-2, ddd, *J* = 11.0, 5.5, 5.0); FABMS (glycerol matrix, positive ions) *m/z* 603 $[M + H]^+$.

(*R*)-MTPA 1,4-diester (4b): amorphous solid; ^1H NMR ($CDCl_3$) δ 7.32 and 7.55 (MTPA phenyl protons); 4.93 (H-4, d, *J* = 10.0 Hz); 4.88 (H-6a, bs); 4.80 (H-6b, bs); 4.32 (H-1a, dd, *J* = 12.0, 5.5 Hz); 4.04 (H-1b, dd, *J* = 12.0, 11.0 Hz); 3.64 (MTPA OCH_3, s); 1.62 (H_3-7, s); 0.96 (H_3-9, s); 0.88 (H_3-10, s); 0.83 (H-3, overlapped); 0.80 (H-2, overlapped); FABMS (glycerol matrix, positive ions) *m/z* 603 $[M + H]^+$.

Application of the Mosher's Method to 4. $\Delta\delta$ ($S - R$): −0.07 ppm (H_3-7); 0 ppm (H_2-6); +0.20 ppm (H-3); +0.14 ppm (H_3-9); +0.08 ppm (H_3-10). These differences imply the *R* configuration at C-4.

Conversion of the Hydroperoxide 5 to the Alcohol 4. Compound **5** (2.0 mg) and triphenylphosphine (4.2 mg) were dissolved in ether (1 mL) and stirred at room temperature for 3 h. Then the solvent was removed under reduced pressure, and the obtained residue was purified by silica gel HPLC (SI60 250 × 4 column, *n*-hexane/EtOAc, 55:45, as eluant) to give pure compound **4** (1.5 mg).

(2*R*,3*R*)-1-Hydroxy-5-chrysanthemen-4-one (6): colorless amorphous solid; $[\alpha]_D^{25}$ −10.0° (*c* 0.02, $CHCl_3$); IR (KBr) ν_{max} 3540, 3090, 1665, 1630, 1450 cm^{-1}; ^1H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR spectra, Table 2; ESIMS (positive ions) *m/z* 191 $[M + Na]^+$; EIMS (70 eV) *m/z* 168 $[M]^+$ (15), 153 (55), 150 (100), 137 (77), 127 (62); HREIMS *m/z* 168.1159 (calcd for $C_{10}H_{16}O_2$, *m/z* 168.1150).

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