Naturally Occurring Cembranes from an Australian *Sarcophyton* Species

Ngoc Bich Pham, Mark S. Butler, and Ronald J. Quinn*

AstraZeneca R&D Griffith University, Brisbane, Australia 4111

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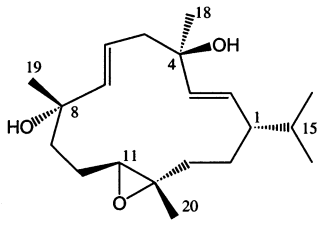
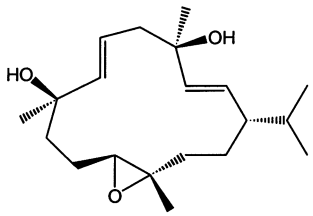
Naturally occurring cembranes **1**−**4** have been isolated from a *Sarcophyton* sp. These compounds have not previously been found to occur in nature but had been obtained as intermediates in a synthetic modification from tobacco. The absolute stereochemistries of **3** and **4** were determined. Compounds **1** and **2** inhibited the binding of [^{3}H]8-cyclopentyl-1,3-dipropylxanthine to rat-brain adenosine A_1 receptors.

Cembranes, 14-membered ring diterpenes, have been reported to have antitumor,[1,2] antimicrobial,[3] and neuroprotective[4] activities. Furthermore, they reportedly inhibit pancreatic carcinogenesis without displaying any toxic effects,[5] but are toxic to fish[6] and are believed to play a role in the protection of soft corals from predators.[7] The first cembrane-type compound was isolated in 1951 from the oleoresin of *Pinus albicaulis*.[8] Other compounds were later found to occur in exudate of many other pine trees, tobacco leaves or flowers, and marine organisms. Extracts of a soft coral (*Sarcophyton* sp.) inhibited the binding of [^{3}H]8-cyclopentyl-1,3-dipropylxanthine ([^{3}H]DPCPX), an A_1 selective antagonist ligand to rat-brain adenosine A_1 receptors. Here we report the isolation and structure elucidation of **1**−**4** by using 1D and 2D NMR techniques, as well as a study of their activity in this assay. These compounds had previously been reported as products of degradation reactions from diterpenoids of tobacco, which have been studied thoroughly. Since these diterpenoids are prone to biodegradation, they account for the presence of the large number of odoriferous nor-diterpenoids encountered in tobacco. One of the isolated compounds (**1**) was characterized,[9,10] and one (**2**) had only partial ^{1}H NMR data reported,[11] while the other two (**3**, **4**) neither had NMR data nor were they purified.[11]

It is generally assumed that the cembrane skeleton originates from a cyclization of geranylgeranyl pyrophosphate. Cyclization via the antipode I pathway leads to the β series, while the antipode II pathway leads to the α series. It has been noted that all cembrane diterpenes of known absolute configuration at C1 reported from the order Alcyonacea belong to the α series, while all cembrane derivatives isolated from the order Gorgonacea belong to the β series.[12]



(**1**)



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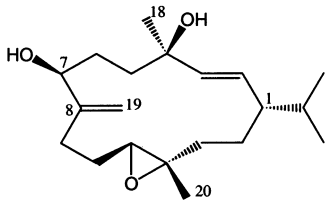
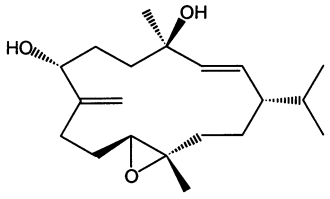


(**3**)



(**4**)

Results and Discussion

Compound **1** was obtained as a white solid with $[\alpha]_D$ −8.2° (*c* 0.29, $CHCl_3$). HRESIMS established the molecular formula as $C_{20}H_{34}O_3$, and its IR spectrum (ν_{max} 3400 cm^{-1}) suggested the presence of hydroxyl groups. The ^{1}H NMR spectrum of **1** showed resonances for an isopropyl group and two *E* double bonds (J = 15.6 Hz). Analysis of 1D and 2D NMR data (Table 1) showed that **1** was a cembrane derivative, which contained $\Delta^{2,3}$, $\Delta^{6,7}$, 4,8-hydroxyl, and 11,12-epoxy groups. Cembrane **1** was previously synthesized from a natural product, (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol, isolated from a wax extract of green leaves of Greek tobacco.[10] The stereochemistry of the synthesized **1** was established by X-ray analysis. The HMQC and HMBC data obtained for **1** established that the resonances for C4 and C8, for C9 and C13, and for C18 and C19 were 72.1 and 73.2 ppm, 38.3 and 36.0 ppm, and 26.5 and 27.8 ppm, reversed from the original assignments reported. Thus, the naturally occurring compound **1** was assigned as (1*S*,2*E*,4*R*,6*E*,8*S*,11*S*,12*S*)-11,12-epoxy-2,6-cembrane-4,8-diol.

Compound **2** was obtained as a white solid with $[\alpha]_D$ −6.5° (*c* 0.26, $CHCl_3$). HRESIMS established the molecular

* To whom correspondence should be addressed. Tel: 617 3875 6000. Fax: 617 3875 6001. E-mail: R.Quinn@az.gu.edu.au.

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Table 1. ^{1}H and ^{13}C NMR and HMBC Data of **1** and **2**

	1			**2**	
position	^{1}H[a] δ (mult., J in Hz)	^{13}C[b] δ	HMBC[a] (C. no)	^{1}H[a] δ (mult., J in Hz)	^{13}C[b] δ
1	1.65 (m)	46.7		1.70 (m)	47.3
2	5.30 (dd, 15.6, 8.8)	131.0	1, 3, 4, 14	5.21 (dd, 15.6, 9.2)	130.1
3	5.52 (d, 15.6)	138.1	1, 2, 4, 18	5.64 (d, 15.6)	138.0
4		72.1			72.3
5	2.47 (ddd, 14.0, 6.8, 1.2)	47.1	4, 6, 7, 18	2.14 (dd, 14.4, 10.4)	46.8
	2.29 (ddd, 14.0, 7.2, 1,2)		4, 6, 7, 18	2.55 (td, 14.4, 2.4)	
6	5.76 (ddd, 15.6, 7.2, 6.8)	124.2	4, 5, 7, 8	5.94 (ddd, 15.6, 10.8, 2.8)	122.0
7	5.61 (td, 15.6, 1.2)	138.5	5, 6, 8, 19	5.57 (dd, 15.6, 2.0)	139.2
8		73.2			73.3
9	1.80 (m)	38.3	7, 8, 10, 11, 19	1.79 (t, 4.0)	37.9
10	1.65 (m)	23.7		1.90 (dd, 8.0, 2.0)	22.2
	1.30 (m)			1.25 (m)	
11	2.97 (dd, 13.2, 2.4)	64.1	9, 10	2.98 (dd, 11.0, 2.0)	65.6
12		61.2			61.2
13	1.93 (td, 13.6, 4.0)	36.0	1, 11, 12	1.95 (dt, 13.2, 4.0)	36.1
	1.05 (m)		1, 11, 12	1.02 (m)	
14	1.55 (m)	27.4		1.57 (m)	27.8
15	1.52 (m)	33.3	2, 16, 17	1.52 (m)	33.2
16	0.86 (d, 6.8)	20.1	1, 15, 17	0.86 (d, 6.8)	20.3
17	0.82 (d, 6.8)	19.4	1, 15, 16	0.82 (d, 6.8)	19.4
18	1.43 (s)	26.5	3, 4, 5	1.39 (s)	27.3
19	1.35 (s)	27.8	7, 8, 9	1.30 (s)	30.9
20	1.18 (s)	15.6	11, 12, 13, 14	1.18 (s)	15.4

[a] Spectra recorded in $CDCl_3$, 400 MHz at 25 °C. [b] Spectra recorded in $CDCl_3$, 100 MHz at 25 °C.

formula $C_{20}H_{34}O_3$. Literature review showed that compound **2** had been previously reported as one of the products of the photooxidation of 11*S*,12*S*-epoxyisocembrol.[11] The compound had been suggested to have an 8*R*-configuration by comparing its ^{1}H NMR data with those of the 8*S*-epimer (**1**). Since only partial ^{1}H NMR data were reported,[11] a detailed comparison of the ^{13}C NMR spectra for **1** and **2** revealed that the assignment is correct. The change at C8 from *S* in **1** to *R* in **2** was indicated by the ^{13}C NMR chemical shift of the Me-19 groups (27.8 ppm in **1** and 30.9 ppm in **2**). Moreover, larger upfield β- and downfield γ-shifts were observed for C7 (139.2 ppm in **2** vs 138.5 ppm in **1**) and C6 (122.0 ppm in **2** vs 124.2 ppm in **1**), respectively. This was consistent with the relative change in orientation of the hydroxyl group connecting to C8. Therefore, compound **2** is (1*S*,2*E*,4*R*,6*E*,8*R*,11*S*,12*S*)-11,12-epoxy-2,6-cembrane-4,8-diol.

Compound **3** was isolated as an amorphous white substance, $[\alpha]_D$ +20.7° (*c* 0.14, $CHCl_3$), and had the molecular formula $C_{20}H_{34}O_3$, as deduced by HRESIMS and ^{13}C NMR data; the formula indicates four degrees of unsaturation. The ^{1}H NMR spectrum confirmed the presence of two methyl groups at δ 1.35 (s) and 1.22 (s), an oxymethine proton at δ 4.15 (dd, J = 8.2, 5.2 Hz), an isopropyl group [δ 0.82, 0.89 (each 3H, d, J = 7.2 Hz), 1.50 (m)], and two olefinic protons (δ 5.65 and 5.32). The ^{13}C NMR spectrum, exhibiting 20 signals, indicated the presence of an *exo* methylene group (113.0 and 148.6 ppm), two hydroxyl-bearing carbon atoms (72.8 and 77.8 ppm), and two other oxygenated carbons (61.7, 63.2 ppm) and confirmed the presence of a second double bond (132.4 and 137.6 ppm) as deduced by ^{1}H NMR spectrum. Thus, to satisfy four degrees of unsaturation, compound **3** had to be bicyclic. Interpretation of the 2D NMR (HMQC, g-COSY, and HMBC) showed that **3** contained a cembrane ring with two methyl groups and an *exo* methylene group as substituents, which accounted for all 20 carbon and 32 hydrogen atoms. The two hydroxyl groups were positioned at C4 and C7 due to their ^{13}C chemical shifts at 72.8 and 77.8 ppm. The remaining two oxygen atoms were connected to C11 and C12. Since all hydrogens were assigned and one ring system was required, an epoxy group must be present. Comparison of ^{13}C NMR chemical shifts for C11 and C12 with those in other epoxy-containing compounds verified this assignment and confirmed the gross structure of **3** as 11,12-epoxy-2,8(19)-cembradiene-4,7-diol. The compound was previously reported as a product synthesized from a tobacco constituent,[11] but its physical and spectral data were not included in that report.

Compound **4** was isolated as an amorphous white substance, $[\alpha]_D$ +14.2° (*c* 0.14, $CHCl_3$) and had the molecular formula $C_{20}H_{34}O_3$ with four degrees of unsaturation, as deduced by HRESIMS and ^{13}C NMR data. Comparison of ^{1}H and ^{13}C NMR data of cembrane **4** with that for cembrane **3** suggested that they had the same gross structure, which was confirmed by HMQC and HMBC data (Table 2). The only differences were the chemical shifts of proton and carbon atoms around chiral center C7, which suggested that **3** and **4** are epimeric at C7.

Comparison of the ^{13}C NMR spectra of **3** and its isomer **4** revealed differences in chemical shifts of carbon atoms C7, C8, and C19. Downfield shifts of C7 (+3.3 ppm) and C19 (+2.8 ppm) and an upfield shift of C8 (−2.0 ppm) were observed in **3** compared to **4**. The same observation was made for isomers of a known cembranoid, isolated from an extract of Greek tobacco, bearing the same moiety.[13,14] On the basis of these spectral data, the stereochemistry of C7 was predicted as 7*S* for **3** and 7*R* for **4**. The β- and γ-shifts can be explained by n−π interaction. Examination of a series of cyclic allylic alcohols and ethers showed that when the oxygen atoms were fixed at an anti-clinal position with respect to the double bond (torsional angle 120°), the through-space interaction between the π-type n-orbital of the oxygen atom and the vacant pπ*-orbital resulted in a decrease of the electron density of the oxygen atoms.[15] The enhanced effective electronegativity of this oxygen attenuated the hyperconjugative through-bond interaction between the C−O σ-orbital and the pπ-orbital. Therefore, the electron delocalization of the π-orbital resulted in the upfield β-shift and downfield γ-shifts. Such a trend was not observed if the oxygen atom was placed at the syn-periplanar position with respect to the double bond (torsional angle 0°). On the basis of the observed β- and γ-shifts for C8 and C19, the OH group of **3** and **4** should have anti-

Table 2. ^{1}H and ^{13}C NMR Data of **3** and **4**

	3			**4**	
position	^{1}H[a] δ (mult., J in Hz)	^{13}C[b] δ	HMBC[a] (C. no)	^{1}H[a] δ (mult., J in Hz)	^{13}C[b] δ
1	1.74 (m)	47.8		1.73 (m)	48.1
2	5.32 (dd, 15.6, 8.7)	132.4	1, 4, 15	5.33 (dd, 16.0, 8.8)	132.7
3	5.65 (d, 15.6)	137.6	1, 18	5.58 (d, 16.0)	137.6
4		72.8			73.1
5	1.37 (m)	40.6	6, 7	1.68 (m)	38.4
	1.72 (m)		3, 4, 6, 18		
6	1.58 (m)	30.6	4, 5, 7, 8	1.72 (m)	30.6
	1.76 (m)		5, 7, 8		
7	4.15 (dd, 8.2, 5.2)	77.8	6, 9, 19	4.10 (dd, 4.0, 3.6)	74.5
8		148.6			150.6
9	2.23 (m)	25.5	7, 8, 10, 11, 19	2.36 (dd, 7.2, 8.0)	28.9
				1.84 (m)	
10	2.22 (m)	25.4	8, 9, 11	1.98 (m)	26.0
				1.62 (m)	
11	2.54 (dd, 12.6, 4.8)	63.2	9, 10	2.57 (dd, 12.8, 4.8)	62.6
12		61.7			61.5
13	1.90 (m)	33.5	1, 11, 12, 14	1.89 (m)	33.2
	1.15 (m)		11, 12, 14, 20	1.15 (m)	
14	1.67 (m)	30.0	1, 2, 12, 13	1.56 (m)	29.7
15	1.50 (m)	30.8	1, 2, 16, 17	1.52 (m)	30.8
16	0.82 (d, 7.2)	21.0	1, 15, 17	0.82 (d, 6.8)	21.1
17	0.89 (d, 7.2)	20.5	1, 15, 16	0.88 (d, 6.8)	20.5
18	1.35 (s)	28.3	3, 4, 5	1.34 (s)	27.2
19	5.02 (s)	113.0	7, 8, 9	5.08 (s)	110.2
	5.04 (s)		7, 8, 9	5.26 (s)	
20	1.22 (s)	16.6	11, 12, 13	1.21 (s)	17.0

[a] Spectra recorded in $CDCl_3$, 400 MHz at 25 °C. [b] Spectra recorded in $CDCl_3$, 100 MHz at 25 °C.

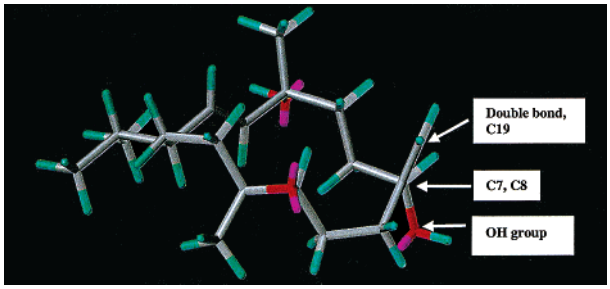

Figure 1. Conformation of cembrane **3** at its minimum energy.

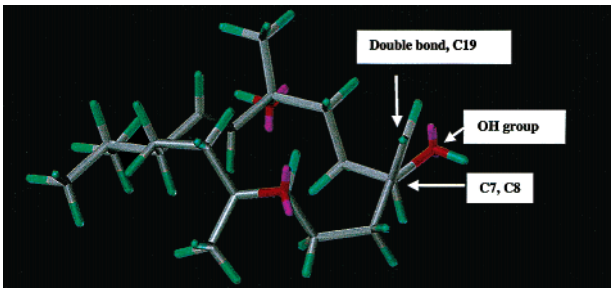

Figure 2. Conformation of cembrane **4** at its minimum energy

clinal (or close to anti-clinal) and syn-periplanar (or close to syn-periplanar) conformation positions, respectively, with respect to the double bond. MacroModel[16] was used to find the minimum energy conformation of the two epimers (7*R* and 7*S*), showing that for the 7*S*-epimer the torsional angle was 142.7°, and for the 7*R*-epimer, it was 32.1° (Figures 1 and 2). These results are consistent with the prediction by comparison of the spectral data.

The above stereochemistry assignment was then verified by the Mosher ester procedure. Treatment of two separate portions of **3** with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in dry pyridine provided mono-ester derivatives *S*-Mosher ester and *R*-Mosher ester of **3**, respectively. Diagnostic ^{1}H NMR chemical shift differences between the diastereomeric MTPA esters ($\Delta(\delta_S - \delta_R)$; H19 (+14.0 Hz), H20 (+12.0 Hz), H18 (−8.0 Hz), H3 (−16.4 Hz), H2 (−5.2 Hz)) were consistent with a 7*S*-configuration for **3**. Thus, **4** was deduced to have 7*R*-configuration.

As discussed in the Introduction, cembranes isolated from the order Alcyonacea will have an α conformation with the isopropyl group pointing down at position C1, and as compounds **2** and **1** have been proved to have an α conformation (1*S*) by synthesis, it was surmised that compounds **3** and **4** also have the 1*S*-configuration. The geometry of the double bond $\Delta^{2,3}$ of **3** and **4** was assigned as *trans* from the large coupling constants between H2 and H3 (J = 15.6 Hz). The ^{13}C NMR shift values of C2 and C18 of **3** (132.4 and 28.3 ppm) and **4** (132.7 and 27.2 ppm) were compared with those of **2** and **1** and compounds with similar structures. They are only consistent with a 4*R*-configuration.[9,10,17,18] The carbon chemical shifts of C11 and C12 (63.2 and 61.7 ppm) and C20 (16.6 ppm) established the C11(*S*), C12(*S*) configuration around the epoxide.[19−21]

Thus, the naturally occurring compound **3** is (1*S*,2*E*,4*R*,7*S*)-11,12-epoxy-2,8(19)-cembradiene-4,7-diol, and compound **4** is (1*S*,2*E*,4*R*,7*R*)-11,12-epoxy-2,8(19)-cembradiene-4,7-diol.

Cembranes **1** and **2** inhibited [^{3}H]DPCPX binding to rat-brain adenosine A_1 receptors with an IC_{50} of 300 μM. Cembranes **3** and **4** did not show any binding activity up to the concentration of 300 mM. The affinity of cembranes to A_1 receptors is dependent on the conformation of the ring system, as an exocyclic double bond in **3** and **4** results in a significant loss of affinity of the receptor.

Experimental Section

General Experimental Procedures. Solvents used were Omnisolv MeOH and milli-Q filtered water. The flash column (150 mm × 40 mm i.d.) was packed with Diol-NP (30−40 μm). A YMC normal-phase Diol (5 μm, 4.6 mm i.d. × 150 mm) column was used for semipreparative chromatography using a Waters 600 pump equipped with a 996 PDA. NMR spectra

were recorded on a Varian Inova 400 MHz spectrometer with ^{1}H and ^{13}C chemical shifts referenced to the solvent peak δ 7.24 and 77.0 ppm ($CDCl_3$). LRESMS were recorded on a single quadrupole VG platform II mass spectrometer with MassLynx Version 1 used for data acquisition, and HRESIMS were measured on a Bruker BioAPEX 47e mass spectrometer.

Soft Coral Material. A specimen of *Sarcophyton* sp. was collected at the depth of 3 m, North Point of Big Woody Island, Hervey Bay, Queensland, Australia. It was identified as *Sarcophyton* sp. (phylum Cnidaria, class Anthozoa, order Alcyonacea, family Alcyoniidae). A voucher specimen QMG306318 has been deposited at the Queensland Museum, South Brisbane, Queensland, Australia. It was a mushroom-shaped colony: capitulum smooth with open folds at periphery of disk, outward turned margin hanging downward over the stalk; large distinct autozooids 1.0−1.9 mm apart and up to 3 mm long; its polyps are dimorphic, autozooids up to 3 mm long; fleshy stalk of sclerites embedded in coenchyme transected by vascular canals.

Extraction and Isolation. The freeze-dried sample (5 g) was exhaustively extracted with CH_2Cl_2. The extract was subjected to normal-phase Diol flash chromatography and eluted with hexane, hexane−EtOAc (1:1), EtOAc, and methanol. The hexane−EtOAc (1:1) fraction was subjected to semipreparative Diol HPLC and eluted at 3 mL/min isocratically with hexane−2-propanol (90:10) to give three fractions containing cembrane compounds. Fraction A eluted at 8−10 min, fraction B at 12−13 min, and fraction C at 13−15 min. These fractions were subjected again to semipreparative Diol HPLC and eluted at 3 mL/min isocratically with hexane−2-propanol (95:5) to give **2** (4.1 mg, 18−20 min), **1** (3.6 mg, 31−32 min), **3** (2 mg, 35−37 min), and **4** (2 mg, 39−41 min).

Receptor Binding Assays. Binding of **1**−**4** to rat-brain A_1 receptors was performed as described previously.[22] Data were analyzed using a nonlinear, least-squares regression program (Prism 2.0) to determine IC_{50} values.

Molecular Modeling. Molecular modeling studies were performed using MacroModel, version 6.0, on a Silicon Graphics workstation.

(1*S*,2*E*,4*R*,6*E*,8*S*,11*S*,12*S*)-11,12-Epoxy-2,6-cembrane-4,8-diol (1): white powder, $[\alpha]^{25}_D$ −8.20° (*c* 0.28 in $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 208 (1 400); IR (film) 3399, 2959, 1724, 1650, 1457, 1371, 1143, 983 cm^{-1}; (+)-HRESIMS *m*/*z* 345.2401 (calcd for $C_{20}H_{34}O_3Na$, 345.2400); NMR data, see Table 1.

(1*S*,2*E*,4*R*,6*E*,8*R*,11*S*,12*S*)-11,12-Epoxy-2,6-cembrane-4,8-diol (2): white powder, $[\alpha]^{25}_D$ −6.50° (*c* 0.26 in $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 208 (1 600); IR (film) 3399, 2957, 1734, 1650, 1456, 1378, 1143, 980 cm^{-1}; (+)-HRESIMS *m*/*z* 345.2396 (calcd for $C_{20}H_{34}O_3Na$, 345.2400); NMR data, see Table 1.

(1*S*,2*E*,4*R*,7*S*)-11,12-Epoxy-2,8(19)-cembradiene-4,7-diol (3): white powder, $[\alpha]^{25}_D$ +20.70° (*c* 0.14 in $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 203 (1 800); IR (film) 3406, 2957, 1730, 1648, 1457, 1383, 1069, 978 cm^{-1}; (+)-HRESIMS *m*/*z* 345.2401 (calcd for $C_{20}H_{34}O_3Na$, 345.2400); NMR data, see Table 2.

(1*S*,2*E*,4*R*,7*R*)-11,12-Epoxy-2,8(19)-cembradiene-4,7-diol (4): white powder, $[\alpha]^{25}_D$ +14.20° (*c* 0.14 in $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 203 (2 100); IR (film) 3399, 2959, 1724, 1457, 1379, 1053 cm^{-1}; (+)-HRESIMS *m*/*z* 345.2391 (calcd for $C_{20}H_{34}O_3Na$, 345.2400); NMR data, see Table 2.

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