Extensive 1D, 2D NMR Spectra of Some [7.0]Metacyclophanes and X-ray Analysis of (±)-Myricanol

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From the hexane extract of the bark of *Myrica cerifera*, the pentacyclic triterpenes taraxerol and myricadiol were isolated. The EtOH extract afforded the [7.0]metacyclophanes, (±)-myricanol (**4**), and myricanone (**7**). Accurate ^{1}H- and ^{13}C-NMR spectral assignments have been made for (±)-myricanol (**4**), 5,11,17-tri-*O*-acetyl-(±)-myricanol (**5**), 11-*O*-methyl-(±)-myricanol (**6**), and myricanone (**7**) by a study of the [1]H−^{1}H-COSY, [1]H−^{13}C-COSY (HETCOR), selective INEPT, and 1D NOE experiments. The structure of (±)-myricanol was established by a single crystal X-ray analysis. Molecular mechanics MM-3(94) calculations have been made for (*R,Sa*)- and (*S,Sa*)-myricanol, and the bond lengths, bond angles, and the torsion angles have been calculated for the energy-minimized conformation.

A decoction of the leaves of *Myrica cerifera* L. (bayberry, wax myrtle) (family Myricaceae) is used in folk medicine as an anesthetic,[1] and the bark is recommended for the treatment of ulcers and in gallbladder dysfunction.[2,3] Endothelin (ET), a peptide family consisting of three peptides recently discovered by Yanagisawa *et al.*,[4,5] has been found to be one of the most potent vasoconstrictors known, suggesting that the receptor for ET in most tissues contributes to many regulatory functions of the body. A novel nonpeptide ET antagonist, myricerone caffeoylester (**1**), has been isolated from the branches of *Myrica cerifera*.[6] In an investigation to follow the biological activity of various extracts of the bark of *M. cerifera,* we purified the hexane, CHCl₃, and 95% EtOH extracts by chromatographic separation. The hexane extract gave taraxerol (**2**) and myricadiol (**3**). Purification of the EtOH extract led to the isolation of two [7.0]metacyclophanes: (±)-myricanol (**4**) and myricanone (**7**). This paper describes the characterization of these compounds by extensive ^{1}H- and ^{13}C-NMR spectral assignments and by an X-ray diffraction study of (±)-myricanol. Molecular mechanics calculations have been obtained for (*R*)-myricanol and (*S*)-myricanol using MM-3(94).

Results and Discussion

Ground bark of *M. cerifera* was extracted in a Soxhlet apparatus with hexane, CHCl₃, and 95% EtOH. The hexane extract after chromatographic separation on SiO₂ gave taraxerol (**2**)[7,8] and myricadiol (**3**),[8,9] identified by mp, IR, and ^{13}C-NMR spectral comparison with authentic samples. Isolation of these triterpenoids has been reported from the roots of this plant.[10]

Chromatographic separation of the EtOH extract on SiO₂ gave an optically inactive compound, mp 205−206 °C. The ORD and CD spectrum also did not exhibit any Cotton effect. The molecular formula, C₂₁H₂₆O₅ (MW 358), was derived for the compound by HRMS (*m/z* 358.1780) and also confirmed by ^{13}C-NMR spectral and DEPT data. The ^{1}H-NMR spectrum shows signals for two methoxyls (δ 3.88, 3.99), four aromatic protons (δ 6.91, *s*, H-19), ABX pattern: 7.18 (d, *J* = 2 Hz, H-18), 6.90 (d, *J* = 8 Hz, H-16), and 7.09 (dd, *J* = 2, 8 Hz, H-15) and two phenolic OH groups (δ 5.88, 7.66). These data suggested a meta-substituted biphenyl ring. One of the rings carries three oxygen substituents and a single hydrogen, and the second aromatic ring carries only one oxygen substituent. The biphenyl ring should be attached to a seven-carbon methylene chain forming a large-membered ring system. The side chain contains the fifth OH group δ 4.10 (t, *J* = 9.7 Hz), suggesting that this carbon atom is flanked by two methylenes. A literature search indicated that this compound is similar to the [7.0]metacyclophane, myricanol (**4A**), isolated from *Myrica nagi,* as an optically active compound, mp 105−125 °C, [α]ᴅ −65.6°, with an 11*R*-configuration, determined by the X-ray structure determination of 16-bromomyricanol.[11−13] Myricanol has also been isolated from *Myrica rubra* Sieb *et* Zucc., mp 95−105 °C, [α]ᴅ −62.9°,[14] [α]ᴅ −27.6,°[15] from *M. gale* L.,[16] and from *Myria esculenta* [α]ᴅ −64°.[17] The metacyclophane isolated by us appeared different in its mp, rotation, and ^{1}H-NMR chemical shift for the carbinyl proton [δ 4.50 m C₅D₅N, 4.90 m C₆H₆,[13] 3.90 m CD₃COCD₃[17]] for 11*R*-myricanol in **4A**. Sun *et al.* have not made definite assignments for the six methylene protons of **4A**, but have given the range δ 1.45−2.95 (6 × −CH₂−).[17]

Table 1. ^{13}C- NMR Chemical Shifts and Assignments for (±)-Myricanol (**4**), (*R*)-Myricanol (**4A**),[17] 5,11,17-Tri-*O*-acetyl (±)-myricanol (**5**), 11-Methoxy (±)-myricanol (**6**), and Myricanone (**7**), (**7A**)[17] in CDCl$_3$[a]

c no.	4	4A	5	6	7	7A
1	124.8 s	129.7	131.4 s	124.7 s	125.5 s	128.8
2	123.5 s	123.1	127.6 s	123.5 s	123.3 s	123.2
3	146.0 s	148.8	145.0[b] s	145.9 s	146.1 s	147.8
4	138.7 s	138.8	143.0 s	138.7 s	138.8 s	138.7
5	147.8 s	146.5	145.9[b] s	147.8 s	147.9 s	146.0
6	122.7s	124.8	127.6 s	122.6 s	123.1 s	125.4
7	25.5 t	34.3	24.8 t	25.5 t	26.9 t	26.8
8	25.8 t	22.8	25.8 t	25.4 t	24.6 t	21.8
9	23.0 t	25.3	22.9 t	22.8 t	21.9 t	24.4
10	39.5 t	25.3	35.9 t	33.9 t	46.2 t	42.5
11	68.7 d	68.3	72.1 d	78.5 d	213.5 t	213.0
12	34.8 t	26.7	32.0 t	33.3 t	42.6 t	46.0
13	27.0 t	39.3	27.7 t	27.1 t	29.0 t	28.3
14	130.7 s	130.9	128.0 s	131.3 s	132.4 s	128.8
15	130.0 d	132.9	129.8 d	130.0 d	129.0 d	132.2
16	116.9 d	116.9	123.3 d	116.9 d	117.0 s	116.8
17	151.5 s	150.8	149.1[b] s	151.4 s	151.8 s	151.6
18	133.2 d	123.1	134.6 d	133.1 d	132.5 d	123.3
19	129.5 d	129.3	129.6 d	129.6 d	129.0 d	128.8
20	61.5 q	61.3	61.0 q	61.5 q	61.5 q	61.3[b]
21	61.4 q	61.3	60.8 q	61.5 q	61.5 q	61.4[b]
22			56.6 q			
CO			170.9 s			
CO			170.2 s			
CO			168.9 s			
CH$_3$			20.5 q			
CH$_3$			21.4 q			
CH$_3$			20.4 q			

[a] The multiplicities were based on DEPT experiment. [b] These values may be interchanged in the vertical column.

However, they have assigned chemical shifts for all the carbons of the molecule, and the ^{13}C-NMR values were closely similar to the compound isolated by us (Table 1). We surmised that the assignments may be arbitrary because no details of NMR experiments were given; therefore, we undertook to establish the ^{1}H and ^{13}C assignments and the position of the substituents in the isolated [7.0]metacyclophane by detailed spectral studies.

1 Myricerone caffeoyl ester

2 Taraxerol R = H
3 Myricadiol R = OH

4 (±)- Myricanol R^1= R^2=H; *(4A 11R-Myricanol)*
5 5,11,17-Tri-*O*-acetyl (±)-myricanol R^1= R^2= Ac
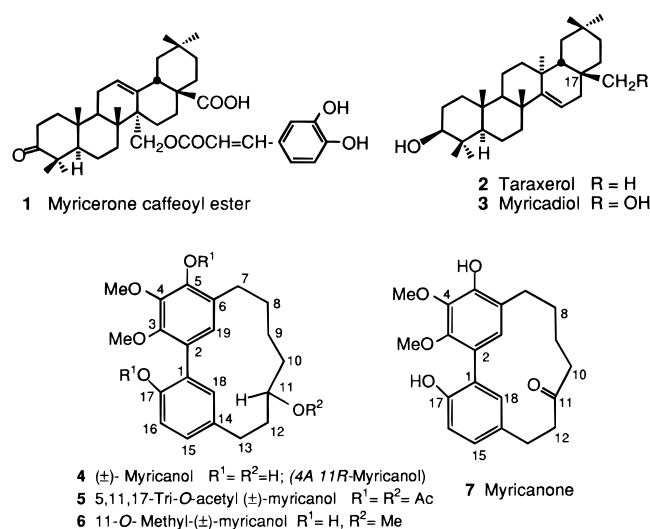**6** 11-*O*- Methyl-(±)-myricanol R^1= H, R^2= Me

7 Myricanone

Table 1 lists the ^{13}C-NMR signals for the compound; the multiplicities were assigned with a DEPT experiment. The carbon multiplicities and the one-bond ^{1}H–^{13}C-coupled partners were confirmed using a HETCOR spectrum. Table 2 gives the ^{1}H-NMR assignments for the isolated cyclophane. The side chain containing six methylenes and one methine attached to a hydroxyl

group showed a scalar-coupled spin system. Thus, a one-bond correlation could be delineated: [H-7a−H-7b−H-8−H-9a−H-9b−H-10−H-11−H-12a−H-12b−H13]. There are two benzylic methylenes, one of which appears at δ 2.90 (m) and the other at δ 2.55 (m), 2.79 (dt J = 18.2, 2.5 Hz). The signal at δ 2.90 was assigned to H-13, because this exhibited a long-range coupling with H-18, and the protons at δ 2.55, 2.79 were assigned to H-7a and H-7b, because they correlated with H-19 in the COSY spectrum (Table 3). This assignment was also confirmed in the 1D-difference NOE experiment. Location of the secondary OH at C-11 δ 4.10 (H-11) was inferred from the COSY spectrum, which showed correlation with H-10b, H-12a, and H-12b and long-range couplings with H-9b and H-13. 1D-Difference NOE experiments gave proton connectivities of other methylenes. The HETCOR spectrum facilitated the assignment of the carbons correlating with the methylene protons and also carbons C-15, C-16, C-18, and C-19 connected with the aromatic protons. Location of the two methoxyl and the two hydroxyl groups was established from selective INEPT experiments, (Table 4). Assignment of the remaining quaternary carbons, C-1, C-2, C-6, and C-14, was completed by additional selective INEPT experiments summarized in Table 4. These data indicated that this cyclophane has structure **4** and should be (±)-myricanol. Table 1 lists the ^{13}C- assignments made by Sun *et al.* for 11*R*-myricanol (**4A**).[17] The present study shows that the assignments for **4A** made earlier for the carbons C-1, C-3, C-5, C-6, C-7, C-8, C-9, C-10, C-12, C-13, C-15, and C-18 need to be revised.

Acetylation of (±)-myricanol gave 5,11,17-tri-*O*-acetyl (±)-myricanol, mp 138−141 °C (**5**); lit. triacetyl-*R*-myricanol (**5A**) mp 70−80 °C.[13] The ^{13}C- and the ^{1}H-NMR assignments for **5** are shown in Tables 1 and 2, and the ^{1}H−^{1}H correlations (COSY) are given in Table 3. The ^{13}C- and the ^{1}H-NMR spectra of **5** at 25° gave broad peaks as a result of the loss of hydrogen bonding indicative of the mobility of the ring system. However, the low temperature ^{1}H- and ^{13}C-NMR spectra at −30° gave rise to sharp peaks. The NOEs of **5** were very useful in arriving at the structure, and some of the significant NOEs are shown in Figure 1, indicating the percent enhancements. In earlier studies, methylation of **4A** with CH$_2$N$_2$ gave 5-*O*-methyl myricanol, and methylation with K$_2$CO$_3$−Me$_2$SO$_4$ in Me$_2$CO gave 5,17-di-*O*-methylmyricanol. 5,11,17-Tri-*O*-methylmyricanol has been obtained by methylation of **4A** with NaOH in MeOH.[11−13] *O*-Methylation of alcohols with trimethyl-silyldiazomethane (TMSCHN$_2$) in the presence of 42% aqueous fluoboric acid has recently been reported.[18] Methylation of (±)-myricanol under these conditions afforded 11-*O*-methyl (±)-myricanol (**6**). The ^{13}C- and the ^{1}H-NMR spectral assignments for **6** are given in Tables 1 and 2, respectively. The 1D NOE spectrum indicated an NOE between H-11 (δ 3.53) and 11-OCH$_3$ (δ 3.28) and between H-18 (δ 7.20) and H-19 (δ 6.92), showing the influence of the carbinyl proton on the aromatic protons of the biphenyl ring. Assignment of the quaternary carbons C-3, C-4, C-5, C-6, and C-19 was based on selective INEPT experiments. Saturation of the benzylic methylene protons at δ 2.58 and 2.80 assigned to H-7a and H-7b, resulted in enhancement of the carbon signals at δ 122.6 (two bonds), 147.8, and 129.6 (both three bonds separated), assigned to C-6, C-5, and C-19, respectively. These data and the other results

Table 2. ^1H NMR Chemical Shifts and Assignments for ($\pm$) Myricanol (**4**), 5,11,17-Tri-*O*-acetyl($\pm$)-myricanol (**5**), 5-Methoxy($\pm$)-myricanol (**6**), and Myricanone (**7**) in $CDCl_3$

^1H	**4** δ (J = Hz)	**5** δ (J = Hz)	**6** δ (J = Hz)	**7** δ (J = Hz)
H-7a	2.55, m	2.20	2.58	2.72, m
H-7b	2.79, dt (18.2, 2.5)	2.68	2.80	
H-8	1.92, m	2.22	1.95	1.95, m
H-9a	1.55, m	1.45	1.60	1.85, m
H-9b	1.70, m	1.80	1.70	
H-10a	1.52, m	1.60	1.60	2.75, m
H-10b	1.90, m	1.80	1.80	
H-11	4.10, t (9.7)	5.01, t (14.2)	3.53, t (7.6)	
OH-11	1.55, m			
H-12a	1.68, m	2.00	1.71	2.78, m
H-12b	2.31, m	2.20	2.16	
H-13a	2.90, m	2.72	2.89	3.02, m
H-13b		2.92		
H-15	7.09, dd (2.0, 8.0)	7.15 dd (2.0, 8.0)	7.11 dd (2.0, 8.0)	7.06, dd (2.0, 8.0)
H-16	6.90, d (8.0)	7.20, d (8.0)	6.91, d (8.0)	6.88, d (8.0)
H-18	7.18, d (2.0)	7.21, d (2.0)	7.20, d (2.0)	6.75, d (2.0)
H-19	6.91, s	6.89, s	6.92, s	6.61, s
H-20	3.88, s	3.65, s	3.89, s	3.81, s
H-21	3.99, s	3.90, s	4.01, s	3.98, s
OH-5	5.88, br s		5.90, s	5.83, s
OH-17	7.66		7.69, s	7.63, s
OAc-11		1.99, s		
OAc-17		2.28, s		
OAc-5		2.35, s		
OMe-11			3.28, s	

Table 3. ^1H-^1H COSY Correlations of ($\pm$)-Myricanol (**4**), 5,11,17-Tri-*O*-acetyl($\pm$) myricanol (**5**), 11-*O*-Methylmyricanol (**6**), and Myricanone (**7**) in $CDCl_3$

	obs. correlations			
proton	**4**	**5**	**6**	**7**
H-7a	H-7b, H-8, H-9b*,^{a} H-19*	H-7b, H-19*	H-7b, H-8, H-9*, H-19*	H-8, H-19*
H-7b	H-7a, H-8, H-19*	H-7a, H-8, H-19*	H-7a, H-8, H-19	
H-8	H-7a, H-7b, H-9a, H-9b, H-19*	H-7b, H-9a, H-9b	H-7a, H-7b, H-9a, H-9b	H-7
H-9a	H-8, H-9b	H-8, H-9b	H-7a, H-8, H-9b	H-10
H-9b	H-7a*, H-9a, H-10b	H-8, H-9a	H-8, H-9a	
H-10a		H-10b, H-11	H-11	H-9
H-10b	H-9b, H-11*	H-10a, H-11	H-11, H-18 (weak)*	
H-11	H-9b, H-10b, H-12a, H-12b, H-13*	H-10a, H-10b	H-10a, H-10b	
		H-12a, H-12b		
H-12a	H-11, H-12b, H-13	H-11, H-12b, H-13	H-12b, H-13	H-13
H-12b	H-11, H-12a, H-13, H-18*	H-11, H-12a, H-13b	H-12a, H-13	
H-13a	H-11*, H-12a, H-12b, H-15*, H-18*	H-13b	H-12a, H-12b, H-15, H-18	H-12, H-15, H-16
H-13b	H-12a, H-12b	H-12a, H-12b, H-13a, H-15		
H-15	H-13a*, H-16, H-18*	H-13b	H-13, H-16, H-18, OMe-11	H-13, H-16, H-18
H-16	H-15, H-18*		H-15	H-13, H-15
H-18	H-12b*, H-13*, H-15*, H-16*	OMe-21, OAc-5, OAc-17	H-10b (weak)*, H-15 OMe-11	H-15
H-19	H-7a*, H-7b*, H-8*, OMe-20*, OMe-21*	H-7a, H-7b	H-7a, H-7b, OMe-20, OMe-21	H-7
OMe-20	H-19*		H-19	OH-5
OMe-21	H-19*	H-18	H-19	OH-5
OAc-5		H-18		
OAc-17		H-7, H-19		
OH-5				
OMe-11			H-15, H-18	

^{a} * Indicates long-range coupling.

of the selective INEPT experiments are shown in Figure 2.

Another cyclophane, $C_{21}H_{24}O_5$, mp 191–192 °C, isolated during the chromatographic separation, was identified as ($\pm$)-myricanone (**7**)[11–13] by comparison with an authentic sample. The ^{13}C- and ^1H-NMR chemical shift assignments have been listed in Tables 1 and 2, respectively. In earlier literature,[11–13] only the aromatic protons H-15, H-16, H-18, and H-19 have been assigned. The side chain methylene protons have been combined by Sun *et al.* at δ 1.65–1.95 (2 $\times$ $-CH_2-$) and δ 2.60–3.00 (4 $\times$ $-CH_2-$).[17] However, they have made definite assignments for the carbon atoms of myricanone (**7**), and these have been given in Table 1. In the present investigation, COSY (Table 3), HETCOR, and selective
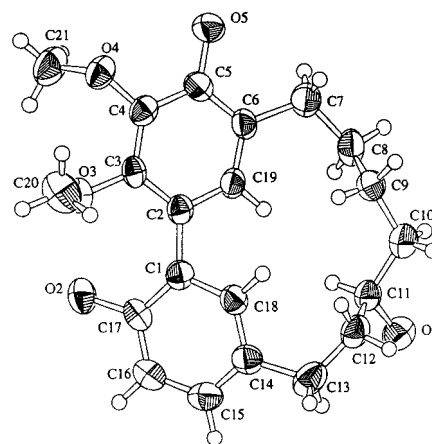
INEPT (Table 4) experiments on **7**, enabled definitive assignments for the protons and the carbon atoms. The proton assignments have been given in Table 2. The ^{13}C values for C-1, C-3, C-5, C-6, C-8, C-9, C-10, C-12, C-14, C-15, and C-18 differ widely from those reported (Table 1). On the basis of the present study, the published values for chemical shifts need to be revised. Takeda *et al.*[15] have assigned the ^{13}C- signal of myricanone at δ 132.4 to C-15; this signal should be assigned to C-18 as it correlates with δ 6.75 (d, J = 2 Hz) in the HETCOR spectrum, and the resonance at δ 129.0 (d), which correlates with δ 7.06 (dd, J = 2.0, 8.0 Hz), should be assigned to C-15.

Because we were unable to obtain an authentic sample of ($\pm$)-myricanol and our structure was derived

Table 4. Long-Range (Two and Three Bond) Heteronuclear ¹H–¹³C Scalar Couplings[a] of (±)-Myricanol (**4**) and Myricanone (**7**)

¹H saturated assigned to δ		enhanced carbon signal δ[b]		
		strong	medium	weak
(±)-myricanol (4)				
OMe-20	3.88	C-3 (146.0)		
OMe-21	3.99	C-4 (138.7)	C-21 (61.4)	
H-11	4.10		C-13 (27.0)	
OH-5	5.88	C-6 (122.7)	C-4 (138.7)	
H-16	6.90	C-1 (124.8), C-14 (130.7)		C-17 (151.5)
H-19	6.91	C-1 (124.8), C-3 (146.0)	C-5 (147.8)	
H-15	7.09	C-17 (151.5)	C-18 (133.2)	
H-18	7.18	C-17 (151.5)	C-2 (123.5)	C-15 (130.0)
OH-17	7.66	C-17 (151.5), C-16 (116.9)		
myricanone (7)				
OMe-20	3.81	C-3 (146.1)	C-21 (61.5)	
OMe-21	3.98	C-4 (138.8)	C-21 (61.5)	
OH-5	5.83	C-5 (147.9), C-6 (123.1)	C-4 (138.8)	
H-19	6.61	C-5 (147.9), C-3 (146.1) C-1 (125.5)	C-7 (26.9)	C-4 (138.8)
H-18	6.75	C-17 (151.8), C-15 (129.0) C-2 (123.3)		C-13 (29.0)
C-16	6.88	C-14 (132.4), C-1 (125.5)	C-17 (151.8)	C-15 (129.0)
OH-17	7.63	C-17 (151.8), C-16 (117.0)		C-1 (125.5)

[a] From selective INEPT experiments. [b] Strong 100%, medium 40–60%, weak < 40%.
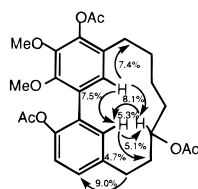
Figure 1. Some significant 1D NOEs observed for 5,11,17-triacetyl (±)-myricanol (**5**).
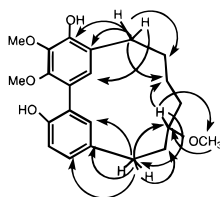
Figure 2. Selective INEPT data for 11-*O*-methyl(±)-myricanol (**6**), showing ¹H → ¹³C.

entirely on the basis of NMR studies, we decided to carry out an X-ray crystal analysis to establish the structure of the isolated cyclophane.

Crystals of (±)-myricanol were obtained by recrystallization from EtOAc. X-ray studies were performed using an Enraf-Nonius CAD-4 diffractometer.[19] The structure was solved by direct methods and refined by full-matrix least-squares to final R = 0.069 (R$_w$ = 0.096) using 3405 independent observations with I > 3 σ(I). The crystal structure contained two independent molecules of (±)-myricanol (mol. 1) and (mol. 2) in the asymmetric unit of the triclinic space group $P\bar{1}$. An ORTEP drawing of one of the independent molecules is shown in Figure 3; the asymmetric center at C-11 has the *R* configuration.

The primary difference between the two molecules is the orientation of the methoxyl group at C-4; the dihedral angle C3−C4−O4−C21 in the molecule 1 is 70.5° and the same angle in the alternate molecule is −90.8°. The crystal structure of 16-bromo-*R*-myricanol[11,13] closely resembles the molecule shown in Figure 3, including the orientation of the methoxyl at C-4. The distortions of the phenyl rings described for the 16-bromo derivative are also observed in the unsubstituted structures. The sum of the angles around

Figure 3. ORTEP drawing of (±)-myricanol (**4**).

C-1 and C-2 is nearly 360°, so there is essentially no out-of-plane distortion at these atoms. The C1−C2−C3 and C2−C1−C17 angles have expanded to approximately 128°, whereas the other two angles around C-1 and C-2 have contracted to an average of 116°. The most significant short intramolecular contacts (< 2.40 Å, van der Waal's diameter for hydrogen) between the hydrogens of the phenyl rings are at C-18 and C-19, and the hydrogens on the bridging carbon atoms were: H(C-18)···H(C-12) 2.00 Å; H(C-19)···H(C-8) 2.04 Å; and H(C-19)···H(C-9) 2.25 Å. In addition, the hydrogens on C-18 and C-19 are separated by only 2.16 Å. A hydrogen-bonding network occurs among all three −OH groups in (±)-myricanol, of molecule 1 (unprimed) and two −OH groups in molecule 2 (primed). Intermolecular contacts are: O1···O5′ 2.771(6) Å, O2···O1′ 2.783(6) Å and O5···O1′ 2.731(6) Å. The myricanol structure contains one asymmetric center and is also axially disymetric due to the twisted biphenyl. The structure could exist as two pairs of enantiomers: *(R,Ra), (S,Sa)* and *(R,Sa), (S,Ra)* where the "a" prefix indicates the chirality of the axially disymmetric biphenyl.[20] If the barrier to rotation is small and interconversion of the axially disymmetric moiety is fast at room temperature, then interconversion between diastereoisomers is possible; that is *(R,Ra) = (R,Sa)* or *(S,Sa) = (S,Ra)*. The X-ray structure contains only the enantiomeric pair
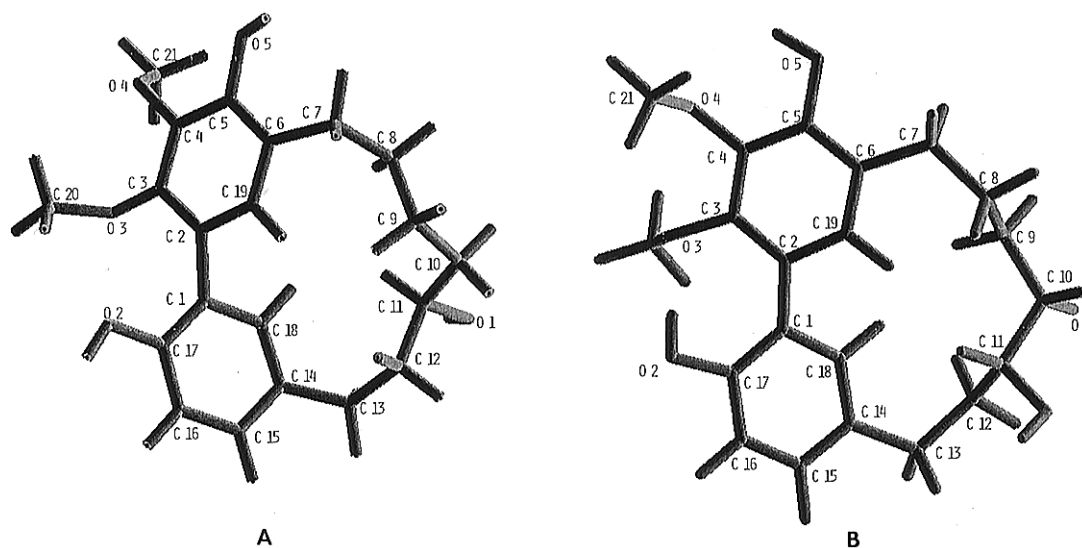
Figure 4. Perspective drawings of (**A**) (*S,Sa*)-myricanol and (**B**) (*R,Sa*)-myricanol, from molecular mechanics calculations.

(R,Sa) and *(S,Ra).* The bond lengths and bond angles and their estimated standard deviations have been provided.[19]

The molecular mechanically derived results were obtained using the MM-3(4)[21] force field implemented on a Silicon Graphics INDIGO2 EXTREME. Using the MM-3(94) methodology, a stochastic search was performed, and 500 conformations of (*R,Sa*)-myricanol and (*S,Sa*)-myricanol were examined to determine the global energy conformer of each compound. A full-matrix calculation was performed on the global energy conformer of both (*R,Sa*)- and (*S,Sa*)-myricanol to ensure that a global minimum structure had, indeed, been found. Bond lengths, bond angles, and torsion angles were examined and compared with the X-ray crystal data. All bond lengths agree considerably well when compared with (±)-myricanol (**4**). The distance between H-11 and H-18 for (*R,Sa*)- and (*S,Sa*)-myricanol is 1.942 Å and 2.283 Å, respectively; the distance between H-11 and H-19 for (*R,Sa*)- and (*S,Sa*)-myricanol is 3.423 Å and 1.893 Å, respectively; and the distance between H-18 and H-19 for (*R,Sa*)- and (*S,Sa*)-myricanol is 2.837 Å and 2.862 Å, respectively.

The most significant difference between the X-ray structure and the molecular mechanics structure is the amount of twist of the biphenyl ring system around the C1−C2 bond. The C18−C1−C2−C3 dihedral angle in the X-ray result is ∼135°, whereas the calculated result is ∼109°; that is, the rings are more nearly perpendicular in the molecular mechanics structure. Not surprisingly, there are additional dihedral angle differences involving the methoxy groups.

An energy minimization using MM-3(94) was performed on the *(R,Sa)* and *(S,Sa)* diastereomeric pair; the results indicated that the *(R,Sa)* diastereomer was more stable than the *(S,Sa)* diasteromer by 2.72 kcal/mole. A full-matrix minimization was performed only on the lowest energy structures as calculated, using the stochastic searching algorithm implemented in MM-3(94). The torsion angles of the two molecules of (±)-myricanol (mol. 1 and mol. 2) observed in the X-ray structure and the values calculated by MM-3(94) for (*R,Sa*)- and (*S,Sa*)-myricanol (Figure 4) have been provided.[19]

Experimental Section

General Experimental Procedures. Mps were determined on a Thomas-Kofler hot stage equipped with a microscope and polarizer. IR spectra were recorded with a Perkin-Elmer model 1421 spectrophotometer, and specific rotations were measured on a Perkin-Elmer model 141 polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL 300 (300 MHz for ^{1}H, and 75.5 MHz for ^{13}C) and Varian 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometers. Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad signals, respectively. Chromatographic separations were carried out by vacuum−liquid chromatography (VLC)[22] on SiO_2, Merck 60H Art. 7736. Purifications on a Chromatotron[23] were carried out on rotors coated with 1 mm thick layer of SiO_2 (EM 7749).

Plant Material. The bark of *M. cerifera* was identified, collected, and supplied by Starwest Botanicals Inc., Rancho Cardova, CA 95742, and Frontier Cooperative Herbs, P.O. Box 299, Norway, IA 52318. An authenticated voucher specimen of this plant is deposited in the offices of these companies.

Extraction of Bark. The dried and powdered bark of *M. cerifera* (240 g) was extracted in a Soxhlet apparatus with hexane and the solvent evaporated under vacuum to afford residue **A** (2.1 g). The plant was successively extracted with $CHCl_3$ and 95% EtOH and the solvent evaporated to give $CHCl_3$ (**B** 4.9 g) and EtOH (**C** 14.0 g) extracts.

Isolation of Taraxerol and Myricadiol. The extract **A** (2 g) was warmed with $CHCl_3$ (15 mL) and a few drops of MeOH. On cooling, the precipitated solid (250 mg) was separated by filtration and recrystallized to give myricadiol (**3**, 150 mg), mp 270−271 °C; lit.[9] mp 273−274 °C; ms *m/z* 342; identical in its IR, and ^{13}C-NMR spectral[8] comparison with an authentic sample. The mother liquor was chromatographed (VLC) on SiO_2, the gradient eluted with hexane, $CHCl_3$, and MeOH, and 50-mL fractions were collected. The fraction that eluted with $CHCl_3$−1% MeOH (200 mL) was evaporated and purified on a SiO_2 rotor by elution with hexane containing increasing percentages of $CHCl_3$. The fractions (150 mL) that eluted with $CHCl_3$ were combined

(200 mg) and crystallized to afford taraxerol (**2**, 100 mg), mp 277–280 °C, identical in its TLC, IR, and ^{13}C-NMR spectral[7,8] comparison with an authentic sample.

Isolation of (±)-Myricanol (4) and Myricanone (7). A solution of the EtOH extract **C** (5.2 g) in EtOH (10 mL) was added to SiO$_2$ (no. 7736, 5 g) and the mixture dried on a rotavap. The adsorbed mixture was applied to a VLC column and eluted with increasing percentages of hexane, C$_6$H$_6$, EtOAc, and MeOH. Fractions that eluted with hexane, C$_6$H$_6$ (100%), and EtOAc (100%) gave myricanone (**7**, 30 mg), mp 191–192 °C; lit., mp 194–196 °C,[13] 191–193 °C,[14] 188–191 °C;[15] IR (Nujol) ν max 3380, 2910, 2825, 1700, 1605, 1500, 1490, 1400, 1350, 1260, 1220, 1100, 1065, 1040 cm^{-1}; MS, m/z (M$^+$) 356 (100), 313 (22), 285 (30), 271 (23), 257 (18), identical in its TLC, MMP, and IR spectral comparison with an authentic sample. The fraction that eluted with EtOAc–2% MeOH gave (±)-myricanol (**4**, 120 mg). Two crystallizations from EtOAc afforded colorless cubes, mp 205–206 °C, [α]$_D$ 0° (CHCl$_3$); lit. **4A**, mp 105–125 °C, [α]$_D$ –65.6°,[13] 95–105 °C, [α]$_D$ –62.9°,[14] [α]$_D$ –27.6°[15]; IR (Nujol) ν max 3575, 3480, 2920, 1610, 1490, 1400, 1350, 1280, 1230, 1108, 1060, 1050, 960 cm^{-1}. HRMS, 358.1780; calcd for C$_{21}$H$_{26}$O$_5$, 358.1780; EIMS, m/z (M$^+$) 358 (100), 340, 273 (15), 271 (15); λ max (EtOH) 261, 298 nm (log ϵ 4.10, 3.94).

5,11,17-Tri-*O*-Acetyl-(±)-myricanol (5). A solution of **4** (55 mg) in C$_5$H$_5$N (1 mL) and Ac$_2$O (2 mL) was kept at room temperature for 3 days. It was poured over crushed ice and the precipitate collected by filtration. The residue (55 mg) in CHCl$_3$ (2 mL) was purified on a SiO$_2$ rotor and eluted with hexane and increasing percentages of CHCl$_3$. The fraction eluted with hexane–CHCl$_3$ (1:1) gave (**5**, 40 mg), mp 154–156 °C (5,11,17-tri-*O*-acetyl(*R*)-myricanol (**5A**), lit.[13] mp 70–80 °C, lit.[14] 71–78 °C.

11-*O*-Methyl-(±)-myricanol (6). To a solution of **4** (25 mg) in CHCl$_3$ (3 mL) and 42% aqueous fluoboric acid (HBF$_4$, 4 drops) cooled to 0 °C and magnetically stirred, was added dropwise, TMSCHN$_2$ (3 drops), kept at room temperature for 2 h; the mixture was poured on crushed ice, and extracted with CHCl$_3$ (25 mL × 3); the CHCl$_3$ layer was dried (Na$_2$SO$_4$) and the solvent removed. The gummy solid (28 mg), on addition of a few drops of MeOH, gave colorless needles. The compound was purified on a SiO$_2$ rotor and eluted with hexane and increasing percentages of CHCl$_3$. Fractions eluted with hexane–CHCl$_3$ (70:30, 200 mL) afforded (**6**, 10 mg), mp 98–105 °C.

References and Notes

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(19) Tables have been provided for a) crystal data of (±) myricanol **4**, (b) bond lengths for mol. 1 and mol. 2 (X-ray) of (±)-myricanol **4** and (*R,Sa*)-myricanol and (*S,Sa*)-myricanol by MM-3(94), (c) bond angles for mol. 1 and mol. 2 (X-ray) of **4** and (*R,Sa*)-myricanol and (*S,Sa*)-myricanol by MM-3(94), and (d) torsion angles (deg) with esd's in parentheses for mol. 1 and mol. 2 of (±)myricanol **4** (X-ray) and (*R,Sa*)-myricanol and (*S,Sa*)-myricanol by molecular mechanics calculations, as supporting information. Hydrogen coordinates, thermal parameters, bond distances, and angles, and observed calculated structure factors have been deposited with the Cambridge Crystallographic Data Centre and can be obtained upon request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.
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