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Conformational Analysis of the 10- and 13-Hydroxy Derivatives of Cembrene

Alexey V. Vorobjev,* Makhmut M. Shakirov, and Victor A. Raldugin

Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences,
Academician Lavrentjev Avenue 9, Novosibirsk 630090, Russia

Clayton H. Heathcock

Department of Chemistry, University of California at Berkeley, Berkeley, California 94720

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Conformational analysis of 10- and 13-hydroxycembrenes **4**, **5**, **7**, and **8** has been carried out using NMR methods and molecular mechanics calculations. The results indicate that the conformational states of all investigated compounds in solution are characterized by the same orientation of double bonds with respect to the average plane of the macrocycle. Alcohols **4** and **8** are conformationally homogeneous, and their solution conformations correspond to the known solution (and crystal) conformation of cembrene (**1**). In the case of alcohols **5** and **7**, there is additional conformational flexibility in the C(8)–C(11) molecular fragment. The influence of simple substituent (hydroxy group) effects and an intramolecular OH* π-hydrogen bond on conformational states of the cembranoids are discussed.

The cembrane diterpenoids are a large and varied group of natural products that have been detected in terrestrial (plants, insects) and marine organisms.[1] A clear understanding of the conformational properties of cembranoids is desirable for two reasons. First, such an understanding might reveal relationships between structure and the remarkable biological activity of some cembranoids.[1,2] Second, it would prove useful in designing effective methods for the total synthesis of cembranoids.[3]

Stereostructures of cembranoids are generally elucidated by X-ray diffraction. Although quite powerful as a method for determining the gross structure of a molecule, this technique fails to give any data about the preferred conformations in solution or about the energy differences between various conformations that might coexist. To study these elements of structure, NMR spectroscopy is commonly used. This method is quite effective when a single conformation exists in solution; furthermore, evaluation of NMR data such as NOE and *J* coupling permits one to determine whether or not the crystal structure is retained in solution.[4] However, if the compound of interest is conformationally flexible or no solid state structure is known, NMR structural analysis is often less conclusive. In such cases, only the preferred conformations of the whole molecule[5] or of certain molecular fragments[6] can be derived. Two methods are used to evaluate conformational flexibility: (1) recording NMR spectra over a range of temperatures[4b,7] and (2) measurement of carbon-13 spin–lattice relaxation times.[8] During the last decade, it has become possible to carry out conformational analysis by using a combination of NMR spectroscopy and conformational searching.[9] However, only a few cembranoids have been subjected to such enhanced solution conformational analysis,[7c,10] probably because of the relative complexity of the NMR spectra of cembranoids and the difficulty of extracting the conformationally relevant parameters.

Previously, we have reported the use of NMR analysis and molecular mechanics calculations to determine the solution conformation ($CDCl_3$) of cembrene (**1**).[11] This study revealed that the crystal structure of **1** is retained in solution. Concurrently, P. Bigler and co-workers reported that the solution ($CDCl_3$) conformation of cembrenol (**2**) is virtually identical to the X-ray structure of **1**; another low-energy conformer, approximately 1.3 kcal/mol higher in energy, was indicated by computational methods.[7c] These results greatly contrast the conformational behavior of sacrophytol A (**3**), a natural antitumor promoter that is a close structural analog of **1**, which was found by Kobayashi and co-workers to take at least three and possibly four different conformations in solution (CD_2Cl_2).[10c]

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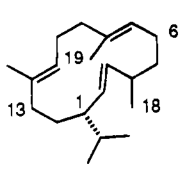

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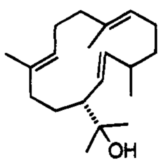

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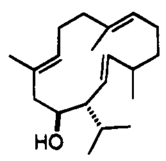

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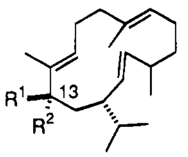

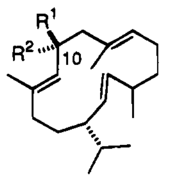

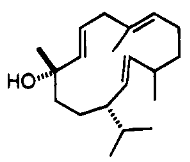

4: R^1 = OH, R^2 = H
5: R^1 = H, R^2 = OH
6: R^1 = H, R^2 = OAc

7: R^1 = OH, R^2 = H
8: R^1 = H, R^2 = OH
9: R^1 + R^2 = O

10

This observation prompted us to investigate the conformational properties of 10- and 13-hydroxycembrenes (compounds **4**, **5**, **7**, and **8**) to elucidate the influence of the hydroxy group on conformational state and consequently on the flexibility of cembrene-related compounds.

Results and Discussion

Syntheses. Cembrene alcohols **4** and **5** were prepared from **1** by oxidation with selenium dioxide in the presence of *tert*-butyl hydroperoxide, according to our previous report.[12] Alcohol **5** was treated with an excess of acetic anhydride to give acetate **6**.

Compounds **7** and **8** were synthesized from tertiary alcohol **10**, a known product of photoxidation of **1**.[13] Oxidation of alcohol **10** by pyridinium chlorochromate gave as the sole product ketone **9**, which was reduced with lithium aluminum hydride to obtain an approximate 4:1 mixture of alcohols **7** and **8**. Cembranoids **8** and **9** have been detected in soft corals, and the stereostructure of **8** has been determined by the X-ray analysis of the *p*-bromobenzoate derivative.[14]

NMR Study. The first goal of the conformational analysis was to compare the experimental values of vicinal proton coupling constants (^3J) determined for alcohols **4**, **5**, **7**, and **8** with those for **1**, whose conformation in solution is known. As shown in Table 1, the ^3J values observed for alcohols **4** and **8** are practically identical to those of **1**. Thus, we can reasonably conclude that the solution conformations of **4** and **8** are the same as the solution conformation of **1**. On the other hand, Table 1 shows that there are some significant differences between the ^3J values of alcohols **5** and **7**, relative to those of **1**, **4**, or **8**. Hence, alcohols **5** and **7** presumably have a solution conformation that is different from that of **1**, or exist as mixtures of interconverting conformers.

Important preliminary conclusions can be deduced from the data in Table 1. Replacement of the pseudoequatorial hydrogen atoms at C(10) or C(13) in the cembrene molecule, which has a conformation corresponding to its X-ray structure (conformer **A**$_1$ in Figure 1), by hydroxy groups (e.g., compounds **4** and **8**) does not change the solution conformation, whereas placing a hydroxy group in a pseudoaxial position (compounds **5** and **7**) destabilizes this conformation. When the size of the pseudoaxial substituent is larger than OH, there are further discrepancies in ^3J, as shown by comparing the data for acetate **6** with those for alcohol **5** and hydrocarbon **1**.

Once the solution conformations of compounds **4** and **8** had been elucidated, a detailed analysis of compounds **5** and **7** was undertaken. The ^{1}H NMR spectrum of alcohol **5** was characteristic. It showed the signal of H(13) as a broadened envelope ($W_{1/2}$ = 10 Hz, solution in CDCl$_3$). The shape of the signal was unchanged when D$_2$O or gaseous HCl was added to the NMR tube or by irradiation of H(20) or H(11). Thus, the broadening is not caused by intermolecular exchange of the hydroxy proton or by long-range coupling interactions and can be attributed to conformational interconversion that is slow on the NMR time scale. A similar process has previously been observed in the room temperature NMR spectrum of another cembranoid.[15]

At lower temperatures, the spectrum of alcohol **5** was broadened and resonances of H(3) and H(13) decoalesced asymmetrically. At −85 °C, they appeared as two signals, each in a ratio of 10:1. Further temperature decreases caused increasing population of the minor conformer; the integrated signals of the two conformers became equal at −110 °C. This tendency was continued down to −135 °C. The energy barrier for interconversion of the two conformers was calculated by the coalescence method to be 8.8 kcal/mol for conversion of minor to major conformer and 9.7 kcal/mol for the reverse transformation. These values agree with published data for analogous compounds (e.g., 11-membered-ring trienes of the humulene type).[16]

The observed temperature-dependent conformational redistribution results from a difference in entropy of the two conformations. This would indicate a contribution from some intramolecular interaction whose influence becomes more important in one of the conformers at lower temperatures. We propose that this interaction is an intramolecular hydrogen bond between the hydroxy proton and one of the remote double bonds. This hypothesis is supported by the following facts. First, the IR spectrum of compound **5** shows two bands in the OH region, one at 3610 cm^{-1} corresponding to "free" OH[17] and another at 3550 cm^{-1} resulting from a species in which the OH group is hydrogen bonded to a remote double bond. If it assumed that the intensity ratio (1:4) of these OH bands is at least a fair indication of relative composition,[18] it may be concluded that the major C−O rotamer is the one with the intramolecular hydrogen bond. This is consistent with the value of $^3J_{\mathrm{H,OH}}$ = 10 Hz corresponding[19] to predominant population of the anti rotamer, which is geometrically most able to hydrogen bond to the $\Delta^{2,3}$-double bond. To estimate the influence of such a hydrogen bond on the conformational state, its energy has been estimated by substituting $\Delta\nu$ (the difference between the frequencies of "free" and bonded hydroxy in the infrared spectrum) in the relationship ΔH =

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Table 1. $^3J_{\mathrm{H_i,H_j}}$ **in** ^{1}**H NMR Spectra of Compounds 1, and 4–8 (Hz)**

	experimental[a]						calculated[d]	
i–j	1[b]	4[b]	5[b]	6	7	8	conformer A_1[e]	conformer A_3[e]
1-2	9.5	9.0	9.0	8.5	8.5	9.0	10.9	10.2
1-14α	12.0	12.0	12.0	10.5	10.7	12.0	12.3	12.3
1-14β	2.5	2.5	2.0	2.5	5.0	2.7	2.0	3.2
5-6α	9.0	8.8	8.5	8.0	7.0	9.0	6.4	6.5
5–6β	6.1	6.0	6.0	7.0	8.2	6.0	6.0	3.2
7–6α	3.1	3.0	3.5	5.5	5.5	3.1	3.0	3.1
7–6β	10.9	11.0	9.5	6.5	7.0	11.0	11.3	11.4
10α–9α	*c*	*c*	*c*	*c*	4.5		2.4	3.6
10α–9β	*c*	*c*	*c*	*c*	8.9		2.3	11.4
10β–9α	*c*	*c*	*c*	*c*		11.0	11.1	2.3
10β–9β	*c*	*c*	*c*	*c*		4.8	4.5	2.1
11–10α	1.5	2.5	4.5	4.0	8.2		3.0 (4.3 for 7)	5.7 (6.4 for 7)
11–10β	7.5	8.0	6.5	7.0		8.0	7.7 (8.2 for 8)	8.0 (8.0 for 8)
13α–14α	3.7	4.5			6.1	3.6	3.6 (4.3 for 4)	4.3 (4.9 for 4)
13α–14β	13.5	11.5			9.0	13.5	14.3 (11.1 for 4)	14.0 (10.8 for 4)
13β–14α	3.7		3.5	4.0	6.1	3.6	3.3 (1.3 for 5)	2.7 (1.1 for 5)
13β–14β	4.5		4.0	6.0	6.1	4.4	3.7 (3.1 for 5)	4.3 (3.5 for 5)

[a] Estimated error ±0.2 Hz. [b] Data for compounds **1**,[11] **4**,[12] and **5**[12] are taken from previous papers. [c] The ^3J values of H(9)–H(10) in the spectra of compounds **1**, **4**, **5**, and **6** cannot be determined because these protons are in strongly coupled spin systems. [d] See Computational Methods section in the Experimental Section. [e] The values given are those calculated for conformers $\mathbf{A}_1$ and $\mathbf{A}_3$ of compound **1** because the calculated values for compounds **4–8** were generally found to be very similar to those for analogous conformations of **1**. Exceptions are given in parentheses for several cases were the calculated values of ^3J differed from those of **1** by more than 0.3 Hz.

$-0.00264\Delta\nu - 0.0572$.[19] This calculation gives ΔH of about −1.5 kcal/mol, showing that such a hydrogen bond could cause a substantial conformational change.[20,21]

Second, the ^{1}H NMR spectrum of acetate **6** also showed signals due to two conformers at low temperature. At −100 °C resonances of H-3 and H-13 decoalesce asymmetrically, giving two unequal signals each. However, in this case the ratio of the two conformations was constant (4:1, within the limits of detection) in the range −110 to −130 °C.

There is good agreement between the observed ^3J differences and the variable-temperature behavior of compounds **1**, **5**, and **6**. The variable-temperature spectra of alcohol **5** showed a small amount of a minor conformer (ratio 10:1 at −85 °C) and small differences in ^3J, relative to cembrene (**1**). On the other hand, acetate **6** has more of the minor conformer (ratio 4:1 at −110 °C) and correspondingly larger differences in ^3J, relative to cembrene.

Molecular Mechanics Calculations. We selected compound **5** for molecular mechanics calculations because there is experimental evidence that it exists as a pair of interconverting conformers. From previous conformational analysis of cembranoids, it is known that substituents attached to endocyclic trans double bonds should be approximately perpendicular to the average plane of the ring to minimize transannular repulsion.[10c] If we assume that this holds for alcohol **5**, four minimum strain conformers, **A** (α,α), **B** (β,α), **C** (α,β), and **D** (β,β), are expected.[22] To find these conformers, a dihedral angle driver routine was employed, starting from conformation $\mathbf{A}_1$, which corresponds to the X-ray structure of **1**. Rotations of the C(5)–C(6)–C(7)–C(8) and C(14)–C(13)–C(12)–C(11) torsion angles in consecutive order were carried out with increments of 10° in two directions, corresponding to rotation of vinyl hydrogen or vinyl methyl through the inside of the macrocycle. Energy minimization of the structures derived in this way revealed eight energy minima and some barriers between them. When the constraints were removed and the calculations repeated, these minima are preserved. Conformers corresponding to the calculated minima are depicted in Figure 1 (about conformer $\mathbf{A}_3$, see below).

The eight minimum-energy conformations can be grouped into two families, $\mathbf{A}_1$, $\mathbf{B}_1$, $\mathbf{C}_1$, $\mathbf{D}_1$ and $\mathbf{A}_2$, $\mathbf{B}_2$, $\mathbf{C}_2$, $\mathbf{D}_2$. Distinctions between the two families are most apparent in two dihedral angles, C(2)–C(1)–C(14)–C(13) and C(1)–C(14)–(13)–C(12), showing that the families differ mainly in the conformation of the C(1)–C(14)–C(13) fragment (Table 2). The starting conformation $\mathbf{A}_1$ has the lowest strain energy, and the rest are calculated by application of the Boltzman equation to be insignificantly populated.

The molecular mechanics calculations imply that inversion of orientation of the double bonds has a relatively low barrier but causes substantial increase of steric energy. Hence, the possibility exists that the conformational interconversions observed in the ^{1}H NMR spectra of compounds **5** and **6** are not caused by rotation of double bonds but are due to an additional rotational freedom in X–C(sp^3)–C(sp^3) fragments. This point of view is in agreement with our preliminary conclusions derived from ^3J analysis (vide infra). That is, the conformational equilibria are observed only for those alcohols (**5** and **7**) that would have hydroxy groups in the more strained pseudoaxial position, if the macrocycle adopts the same conformation as **1**.

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(20) There have been several reports of intramolecular hydrogen bonding of a hydroxy proton to allylic double bonds. (a) Methallyl alcohol: Caminati, W.; Fantoni, A. C.; Velino, B.; Siam, K.; Schaefer, L.; Ewbank, J. D.; Van Alsenoy, C. J. *J. Mol. Spectrosc.* **1987**, *124*, 72. (b) 1,4-Pentadien-3-ol: Marstokk, K. M.; Moellendal, H. *Acta Chem. Scand.* **1990**, *44*, 18. (c) 3-Furanmethanol: Marstokk, K. M.; Moellendal, H. *Acta Chem. Scand.* **1993**, *47*, 849.

(21) It is important to note that the IR experiments discussed in this paragraph let us draw direct conclusions about the existence of an intramolecular hydrogen bond in the major conformer only, since it greatly predominates at room temperature. We know nothing from the IR experiments about possible hydrogen bonding in the minor conformer. However, because the population of this conformer increases markedly as the temperature is lowered, we assume it has smaller entropy due to an intramolecular hydrogen bond that is even stronger than the one observed in the major conformer.

(22) The α,β-designations describe the orientation of C(8)–methyl and C(12)–methyl groups, respectively, with regard to the average plane of macrocycle.

(23) The g+/g−/a nomenclature describes the general dihedral angular relationships of any carbon–carbon chain backbone. The assignment requires that a priority be established by Kahn–Ingold–Prelog sequence rule for the R group.

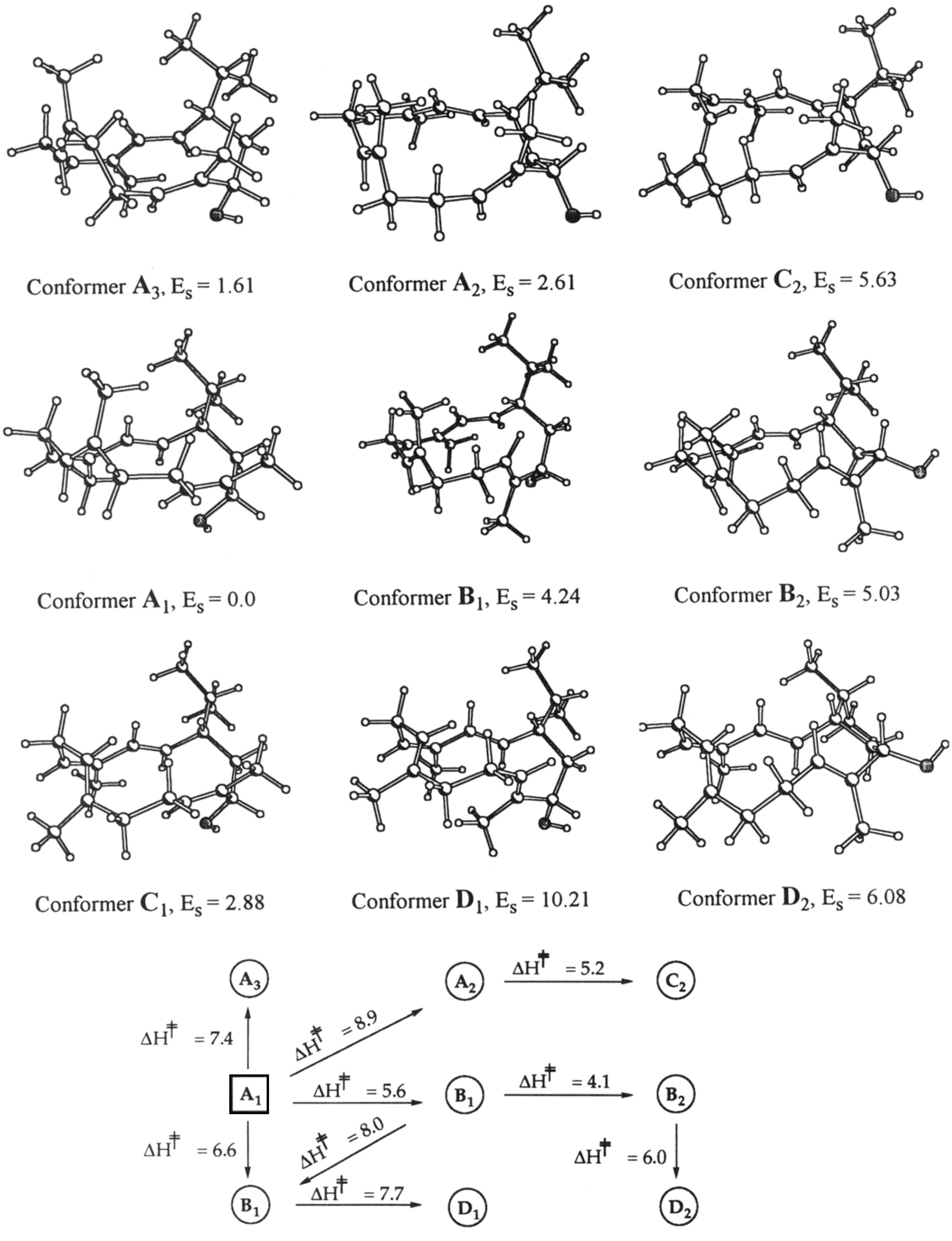


Figure 1. Representation of MM2 calculated low-energy conformers, their relative steric energies (*E*s, kcal/mol), and some energy barriers ($\Delta H^{\ddagger}$ kcal/mol) between minima for compound **5**.

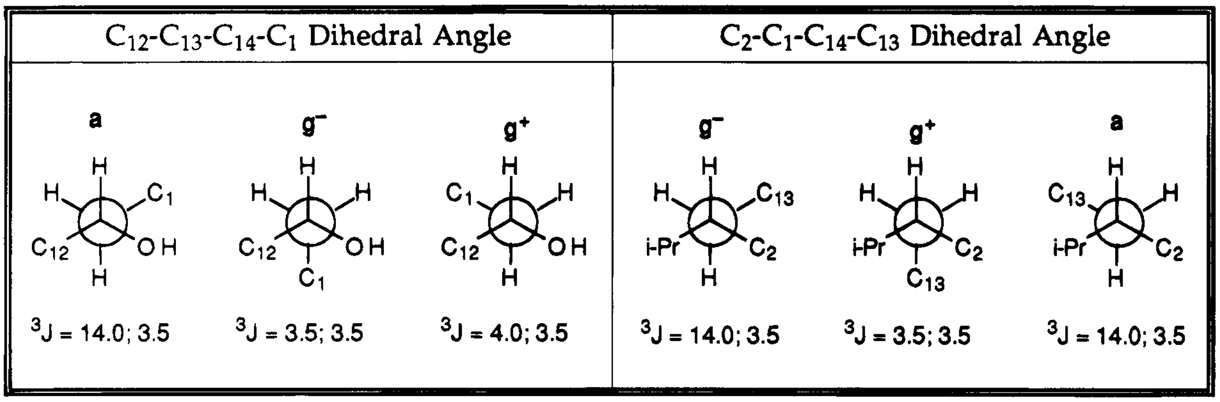
Three staggered conformations (g^+, g^-, a)[23] are theoretically possible for each of the ethane fragments C(8)–C(9)–C(10)–C(11), C(12)–C(13)–C(14)–C(15) and C(13)–C(14)–C(1)–C(2). However, some of these conformations are impossible because of ring size and others may be ruled out on the basis of observed ^3J values. First, only two conformers, g^+ and g^-, are possible for the C(8)–C(9)–C(10)–C(11) torsion angle; the a conformation is not possible even with Dreiding models. Second, the experimental ^3J values of 3.5 and 4.0 Hz for H(13)–H(14) indicate that the C(12)–C(13)–C(14)–C(1) subunit is locked in the g^- conformation (Table 3). Finally, the very different ^3J values of 12.0 and 2.0 Hz for H(1)–H(14) suggest that the C(13)–C(14)–C(1)–C(2) unit has either the g^- or the a conformation.

Assuming all of the constraints that have been discussed, there are four remaining conformations, $\mathbf{A}_1$ (g^-, g^-, g^-), $\mathbf{A}_3$ (g^+, g^-, g^-), $\mathbf{A}_4$ (g^-, g^-, a), and $\mathbf{A}_5$ (g+, g^-, a).[24]

Table 2. Summary Data for Conformers of 5 and Steric Energies and Endocyclic Torsion Angles from Molecular Mechanics Calculations

	conformers								
	A_1	A_2	A_3	B_1	B_2	C_1	C_2	D_1	D_2
E_{rel}, kcal/mol	0.0	2.61	1.61	4.24	5.03	2.88	5.63	10.21	6.08
E_{abs}, kcal/mol	18.96	21.57	20.57	23.20	23.99	21.84	24.59	29.17	25.04
	torsion angles, deg								
C_1-C_4	−176	−169	−173	−173	−175	−176	−168	−168	169
C_2-C_5	173	158	167	168	160	172	155	152	160
C_3-C_6	0	−1	−1	−1	−3	−2	−2	−2	−12
C_4-C_7	−71	−65	−57	−65	−57	−60	−58	−59	−51
C_5-C_8	131	133	133	131	147	−60	−70	−65	−50
C_6-C_9	−177	174	−171	178	178	174	−178	177	170
C_7-C_{10}	118	139	14	128	135	−32	−10	−8	−1
C_8-C_{11}	−61	−68	64	−53	−64	−60	−73	−69	−68
C_9-C_{12}	−158	134	88	−58	−87	−175	162	−3	−79
$C_{10}-C_{13}$	−179	179	177	−178	−177	176	173	−173	−167
$C_{11}-C_{14}$	120	60	106	−20	−90	114	53	−60	−100
$C_{12}-C_1$	−54	59	−51	−55	87	−49	63	−35	75
$C_{13}-C_2$	−64	−152	−59	−44	−139	−57	−137	−39	−94
$C_{14}-C_3$	127	117	136	122	119	131	119	136	137

Table 3. Summary of Projections and Calculated ^3J for Staggered Conformations



As a result of geometry optimization of these conformers, it appears that conformers A_4 and A_5 convert to the A_1 and A_3, respectively. Consequently, only the A_1 and A_3 (Figure 1) conformers are stable enough to contribute to the conformational equilibrium observed by proton NMR spectroscopy at low temperature.

In order to test the reality of values obtained for strain energies, we have expanded the calculations to all the compounds investigated. The differences between the relative energies for the A_1 and A_3 conformers were very similar for **1** and alcohols **4** and **5** (1.44, 1.56, and 1.61 kcal/mol, respectively). The relative strain energy was remarkably larger (3.14 kcal/mol) for alcohol **8** and smaller (0.97 kcal/mol) for alcohol **7**.

These results are consistent with the idea that compounds **1**, **4**, and **8** exist in solution as one conformer A_1, whereas alcohol **7** exists as a time-averaged equilibrium between conformations A_1 and A_3. The only compound for which there is a discrepancy between the experimental data and the calculated conformations is alcohol **5**. Alcohol **5** is similar to **1** and alcohol **4** with respect to the difference between relative energies for the A_1 and A_3 conformations. However, there are discrepancies in its ^3J values, compared to those observed in **1** and **4**.

It is obvious that a more detailed conformational analysis using methods for conformational searching[9] would lead to a more complete finding of minima on the conformational hyperface. We therefore carried out such a systematic search using the Macromodel program.[25]

Some 1500 randomly-generated structures were evaluated for **1**, yielding nine unique conformations[26] in the 0−3 kcal/mol energy region. When the rotamers around the bond to the isopropyl group were rejected, only four low-energy conformers (17.21, 18.67, 19.81, and 19.89 kcal/mol) remained. The three lowest conformers correspond to A_1, A_3, and C_1, respectively. The fourth belongs to the B-series, but differs from B_1 and B_2. However, this conformer, not discovered in the dihedral driver approach, is not expected to have a significant effect on the conformational equilibrium because of its relatively high energy.

In the same way, evaluation of 2000 initial structures of alcohol **5** gave 24 unique conformations, which reduced to seven low-energy conformers (19.17, 20.84, 21.17, 21.35, 21.62, 21.89, and 21.95 kcal/mol) after rejecting isopropyl rotamers.[26] Four from the low-energy conformers (first, second, third, and seventh) correspond to A_1, A_3, B_x, and C_1 conformations, respectively. Conformer B_x is identical with the fourth lowest conformation found for **1**. All these four conformers have the same orientation of the conjugated diene system, which is obvious in the crystal structure of **1** and all previously discussed

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[24] The g+/g−/a nomenclature was used to describe the torsion angles about C(8)−C(11), C(12)−C(1), and C(13)−C(2) fragments, respectively.

[25] Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

[26] E-mail request for atom coordinates of the all conformers should be addressed to root@orchem.nsk.su. Please put in Subject: "For A. Vorobjev".

Table 4. ^{1}H and ^{13}C NMR Spectral Data of Acetate 6, Alcohols 7 and 8, and Ketone 9

	6^a		**7**^{c}		**8**^{c}		**9**^{d}	
atom	δ ^{13}C mult^e	δ ^{1}H mult (J)^b	δ ^{13}C mult^e	δ ^{1}H mult (J)^b	δ ^{13}C mult^e	δ ^{1}H mult (J)^b	δ ^{13}C mult^e	δ ^{1}H mult (J)^b
1	45.48 d	no values	48.58 d	1.81 ddddd (10.7; 8.5; 5.0; 1.8; 1.0)	48.44 d	1.51 m	48.37 d	no values
2	130.89 d	5.45 dd (16.0, 8.5)	127.72 d	5.39 dd (16.0; 8.5)	130.59 d	5.15 dd (15.4; 9.5)	130.83 d	5.16 dd (16.0; 9.0)
3	128.22 d	6.00 d (16.0)	128.21 d	6.09 dd (16.0; 1.0)	130.31 d	5.98 d (15.4)	130.57† d	6.10 d (16.0)
4	134.62 s	–	134.60 s	–	135.17 s	–	135.38 s	–
5	127.59† d	5.53 br t (8.0; 7.0)	125.88 d	5.53 ddq (8.2; 7.0; 1.2)	125.23 d	5.51 ddq (9.0; 6.0; 1.3)	125.55‡ d	5.56 br t (8.0)
6	25.93 t	α 2.64 m (15.0; 8.0; 5.5); β 2.75 m (15.0; 6.5; 7.0)	26.04 t	α 2.65 dddqq (16.0; 7.0; 5.5; 1.2; 1.2); β 2.77 ddd (16.0; 8.2; 7.0)	25.92 t	α 2.37 dddd (15.2; 9.0; 3.1; 3.1); β 2.54 dddq (15.2; 11.0; 6.0; 1.3)	26.37 t	α 3.12 m; β 2.44 m
7	126.21† d	5.00 br t (6.5; 5.5)	128.13 d	5.05 ddq (7.0; 5.5; 1.2)	128.33 d	5.11 m	131.39‡ d	5.31 br d (10.0)
8	131.74‡ s	–	129.59 s	–	128.01 s	–	127.03 s	–
9	33.42 t	no values	46.61 t	α 2.40 ddq (13.0; 4.5; 1.2); β 2.08 dd (13.0; 8.2)	48.41 t	β 2.54 dddq (12.0; 4.8; 3.1; 1.3)	57.27 t	α 3.03 d (12.5); β 2.77 brd (12.5)
10	24.03 t	no values	67.27 d	4.45 ddd (8.2; 8.2; 4.5)	64.81 d	4.52 ddd (11.0; 8.0; 4.8)	209.72 s	–
11	125.96† d	5.21 br t (7.0; 4.0)	131.34 d	5.24 dq (8.2; 1.4)	128.97 d	5.13 m	123.11† d	6.16 s
12	131.77‡ s	–	140.02 s	–	139.61 s	–	157.17 s	–
13	79.12 d	5.11 br t (6.0; 4.0)	39.25 t	α 2.14 ddd (13.5; 9.0; 6.1); β 1.92 ddd (13.5; 6.1; 6.1)	36.37 t	α 1.98 ddd (13.5; 13.5; 3.6); β 2.07 m	38.31 t	no values
14	38.00 t	α 1.63 ddd (14.5; 10.5; 4.0); β 1.75 ddd (14.5; 6.0; 2.5)	27.88 t	β 1.32 dddd (14.0; 10.7; 9.0; 6.1)	26.94 t	α 1.23 dddd (13.5; 12.0; 3.6; 3.6); β 1.71 dddd (13.5; 13.5; 4.4; 2.7)	27.24 t	no values
15	38.00 d	no values	33.35 d	1.56 septd (6.5; 5.0)	32.71 d	1.48 m	36.63 d	no values
16	19.03§ q	0.81 d (6.5)	19.19† q	0.80 d (6.5)	19.78† q	0.80 d (6.5)	19.60§ q	0.80 d (6.8)
17	20.04§ q	0.83 d (6.5)	20.15† q	0.83 d (6.5)	20.61† q	0.84 d (6.5)	20.67§ q	0.83 d (6.8)
18	19.39§ q	1.78 s	19.96 q	1.77 dd (1.2; 1.2)	19.71 q	1.77 dd (1.3; 1.3)	19.89 q	1.80 dd (1.3; 1.3)
19	15.36 q	1.54 s	15.22 q	1.66 ddd (1.2; 1.2; 1.2)	15.22 q	1.60 d (1.3)	15.58 q	1.62 s
20	11.99 q	1.54 s	17.88 q	1.64 d (1.4)	14.05 q	1.68 br s	16.83 q	2.08 d (1.0)

[a] Assignments were made by comparison with **5** and by off−resonance spin decoupling for ^{13}C multiplets or by homonuclear spin decoupling experiments for ^{1}H signals. Signals for CH_3COO: 170.80 s, 21.27 q (^{13}C); 1.97 s (^{1}H). [b] ±0.2 Hz, sign of the coupling constants not determined. [c] Assignments were aided by ^{1}H−^{1}H COSY, ^{1}H−^{13}C COSY, and homonuclear spin decoupling experiments for ^{1}H signals. [d] Assignments were made by off−resonance spin decoupling for ^{13}C multiplets or by homonuclear spin decoupling experiments for ^{1}H signals. [e] Values with identical superscipts (†, ‡, §) within a column may be interchanged.

conformers. The other three conformers (fourth, fifth, and sixth) have the inverted orientation of the conjugated diene system; the dihedral angle between H_1 and H_2 is about 0° and methyl group at C_4 is β-oriented.

Thus, there appear to be no low-energy alterations to $\mathbf{A}_1$ and $\mathbf{A}_3$ conformers for either **1** or **5**, since a systematic conformational search found no other conformers within the lowest 2.0 kcal/mol, which includes about 97% of all conformational space.

Comparison of the ring shapes of the low-energy conformers derived by molecular mechanics calculations with structures of similar hydroxycembrenes would be of interest. However, for neither the low-energy conformers of cembrenol (**2**) obtained by computational methods[7c] or the X-ray structure of the *p*-bromobenzoate derivative of 10α-hydroxycembrene (**8**)[14] were atomic coordinates or endocyclic angle data published.

Conclusions. The macrocyclic cembrane diterpenoids are usually considered to be conformationally flexible compounds that can theoretically adopt a large number of conformations. However, only a few (or even one) conformers are stable enough to contribute to the conformational equilibrium. The results of the conformational analysis of 10- and 13-hydroxycembrenes allow one to make the following generalizations. There are two main types of conformational effects in cembrane macrocycles, inversion of the orientations of the double bonds and torsional changes in ethane fragments. Since energy barriers for these processes appear to be relatively low, the influence of simple substituents (namely, the hydroxy group) on the conformational state becomes important and can lead to conformational distortions in the immediate environment of the functional group, as well as in remote fragments.

Experimental Section

General. NMR spectra were recorded with a Bruker AM-400 spectrometer (400.13 MHz for ^{1}H and 100.614 MHz for ^{13}C) for solutions in $CDCl_3$ or CF_2Cl_2 (variable temperature experiments) at concentrations of about 10^{-2} M. The ^{1}H and ^{13}C chemical shifts were assigned by ^{1}H−^{1}H COSY and ^{1}H−^{13}C COSY homonuclear spin decoupling experiments and were referenced to solvent signals taken as standard: $CDCl_3$, δ 7.24 ppm for ^{1}H and δ 76.90 ppm for ^{13}C. Infrared (IR) spectra were obtained with a UR-20 spectrometer and were recorded as CCl_4 solutions with concentrations of 1% and 0.05% (to exclude the possibility of intermolecular hydrogen bonding). Optical rotations were measured with a Zeiss polarimeter. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. Combustion analyses were performed with a Carlo Erba 1106 Autoanalyzer. Column chromatography was performed on LACHEMA silica gel (Silicagel L, 100−160 μm). Fractions were eluted with a hexane−diethyl ether gradient system and analyzed by TLC (Silufol plates, Kavalier) with visualization by spraying with H_2SO_4.

Computational Methods. Computer modeling was carried out with the Macromodel program (version 3.5a) using a Silicon Graphics Personal IRIS workstation or a DecStation 3000/400 running OSF 1.2. Structures were energy minimized with the following parameters: force field, MM2* with a distance-dependent dielectric mode, minimization algorithm, the Block Diagonal Newton Raphson in Cartesian coordinate space; convergent criteria, until the rms energy gradient was less than 0.05 kJ/Å·mol.

Dihedral driving procedures were performed using the MMP2 program[27] on an IBM PC/AT. Structures were energy minimized in dipole−dipole interaction mode. Initial calculations started with atomic coordinates antipodal to those reported for the X-ray structure of cembrene (**1**).[28] The value

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(27) MMP2 program, QCPE#395.

(28) Drew, M. G. B.; Templeton, D. H.; Zalkin, A. *Acta Crystallogr.* **1969**, *B25*, 261−267.

of the H−C−O−H dihedral angle was taken about −60° before energy minimiztion of all conformations.

Vincinal proton coupling constants (^3J) were calculated with the appropriate coupling equation for H-C(sp^3)−C(sp^3)−H[29] or H−C(sp^2)−C(sp^3)−H[30] systems.

Cembrene (1)[31] was isolated from the resin of *Pinus sibirica* Du Tour and compounds **4**,[12] **5**,[12] and **10**[13] were derived from **1** as previously described.

(1*S*,2*E*,4*Z*,7*E*,11*E*,13*S*)-13-Acetoxycembra-2,4,7,11-tetraene (6). A solution of **5** (0.1 g, 0.35 mmol) in pyridine (5 mL) was treated with acetic anhydride (1 mL) at room temperature for 12 h. The mixture was diluted with ether (50 mL), and the solution obtained was washed in sequence with 10% HCl solution (100 mL), saturated NaCl (100 mL), saturated $NaHCO_3$ (100 mL), and NaCl solutions. The ether solution was then dried (Na_2SO_4), evaporated under reduced pressure, and chromatographed on silica gel (2 g). Elution with 3% ether in hexane gave 0.1 g of acetate **6** as a colorless oil with $[\alpha]20_D$ −6.7 (*c* 4.5 g/100 mL, $CHCl_3$). For ^1H and ^{13}C NMR spectra, see Table 4.

(1*S*,2*E*,4*Z*,7*E*,11*E*)-Cembra-2,4,7,11-tetraen-10-one (9). A solution of alcohol **10** (0.68 g, 2.36 mmol) in 5 mL of CH_2Cl_2 was added to a stirring suspension of pyridinium chlorochromate (1.0 g, 4.7 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 1.5 h, passed through a column of silica gel (8 g, eluted with 80 mL of Cll_2Cl_2), and evaporated to dryness. Chromatography of the resulting crude oil over silica gel (18 g) gave 0.33 g (48%) of the desired ketone **9** (elution with 2% ether in hexane) and 0.31 g of the starting material (elution with 10% ether in hexane). The product was obtained as a colorless oil with $[\alpha]20_D$ +375 (*c* 2.4 g/100 mL; $CHCl_3$) (lit.[14] $[\alpha]_D$ +313.9 (*c* 2.0 g/100 mL; $CHCl_3$) and +345.0 (*c* 0.75 g/100 mL; $CHCl_3$)). IR(CCl_4): 1620 and 1685 cm^{-1} (C=C−C−O). The ^1H and ^{13}C NMR data are given in Table 4. The ^1H NMR spectra are in agreement with those previously reported.[14] Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.63; H, 10.32.

Alcohols 7 and 8. To a solution of ketone **9** (0.08 g, 0.28 mmol) in absolute ether (20 mL) was added a solution of $LiAlH_4$ (0.1 g, 2.6 mmol). The resulting mixture was stirred at room temperature for 10 min, diluted with ether (50 mL), and washed in sequence with 10% HCl solution (50 mL), saturated $NaHCO_3$ (50 mL), and saturated NaCl (50 mL) solutions. The ether solution was dried (Na_2SO_4) and evaporated under reduced pressure, and the residue was chromatographed on silica gel (2 g). Elution with 10% ether in hexane gave 0.065 g of alcohol **7** and 0.015 g of alcohol **8**.

(1*S*,2*E*,4*Z*,7*E*,10*S*,11*E*)-Cembra-2,4,7,11-tetraen-10-ol (7). White powder with mp 71−72 °C (hexane), $[\alpha]20_D$ +15 (*c* 1.3 g/100 mL; $CHCl_3$). IR (CCl_4): 3620 cm^{-1} (OH). For ^1H and ^{13}C NMR spectra see Table 4. Anal. Calcd for $C_{20}H_{32}O$: C, 83.33; H, 11.11. Found: C, 83.12; H, 11,79.

(1*S*,2*E*,4*Z*,7*E*,10*R*,11*E*)-Cembra-2,4,7,11-tetraen-10-ol (8). White powder with mp 143-144 °C (hexane) (lit. 126-127 °C;[14] 143-145 °C[4b]), $[\alpha]20_D$ +139 (*c* 0.69 g/100 mL; $CHCl_3$) (lit.[14] +155 (*c* 0.94 g/100 mL; $CHCl_3$)). IR(CCl_4): 3620 cm^{-1} (OH). For ^1H and ^{13}C NMR spectra, see Table 4.

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