as slightly yellow crystals, mp 343-345 °C.

X-ray Crystallography. Crystals were colorless prisms and preliminary X-ray investigation indicated a monoclinic unit cell. The crystal used for data collection was approximately 0.3 × 0.15 × 0.1 mm.[3] With 15 reflections, measured at $\pm\theta$ angles between 20° and 30°, least-squares refinement produced a cell with dimensions a = 11.982 (1) Å, b = 16.383 (1) Å, c = 12.509 (1) Å, β = 116.71 (1)° (assumed wavelength for Cu Kα: 1.5418 Å). The space group was uniquely determined as $P2_1/a$. Assuming four molecules of colchicine, the calculated crystal density of 1.209 g cm^{-3} was reasonable. The phase problem was solved with MITHRIL.[40] The distribution of intensities was centric, and all heavy atoms of the molecule were visible in the E-map. The structure was refined by standard methods using the programs of XRAY72[41] (isotropic followed by anisotropic refinement of heavy atoms, finding H atoms in a difference map, and finally refinement of all atoms with isotropic H thermal parameters). The anisotropic temperature factor used had the form exp$-(2\pi^2(\sum_i\sum_j(U_{ij}h_ih_ja^*_ia^*_j)))$.

In the course of refinement, two large peaks at a separation of 2.8 Å were found and assigned as O atoms of water molecules. The appropriate H atoms were found after refinement. With 4436 observations (2750 with $I > \sigma(I)$) and a maximum $\sin\theta/\lambda$ of 0.6233 Å^{-1}, the final conventional R factor was 4.7%. The final molecular dimensions are given in Table 3 (supplementary material), and it can be seen that they are as might be expected from the formula. The crystal density calculated on a basis of the final deduced crystal contents is 1.318 g cm^{-3}.

Acknowledgment. We thank Drs. J. Schreiber and A. Eschenmoser from the Laboratorium für Organische Chemie, ETH Zürich, for a generous gift of colchicine.

Supplementary Material Available: Tables of final atomic coordinates for the heavier atoms and of bond distances and angles (2 pages). Ordering information is given on any current masthead page.

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Conformations of Germacra-1(10),4-dien-6,12-olides and -8,12-olides. A Comparison of X-ray Diffraction, NMR, and Molecular Mechanics Derived Conformations

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Conformations of the ten-membered ring *trans,trans*-germacradiene lactones have been investigated. X-ray diffraction, NMR, and molecular mechanics all indicate that the 6,12-olides exist in solution and in the solid state as the 1UU conformer with crossed double bonds and an up-up arrangement of the two ring methyl groups. In costunolide this conformer is more stable by 3.55 kcal/mol. Molecular mechanics predicts the barrier between 1UU and the next lowest conformer to be 22.1 kcal/mol. In the 8,12-olides the 2DD (both methyl groups down) and 2UD are almost isoenergetic with a calculated barrier of 18.4 kcal/mol. In this series the ring substituents determine which conformer is of lowest energy. Line broadening or multiple NMR signals are common. The crystal structure of 3-acetoxy-6-hydroxygermacra-1(10),4-dien-8,12-olide is reported.

A wide variety of germacra-1(10),4-dien-6,12-olides, -8,12-olides, and their derivatives have been isolated from plant sources.[1] These ten-membered ring sesquiterpenes have been investigated by NMR, X-ray diffraction, and other spectroscopic techniques. X-ray diffraction studies provide a detailed analysis of the ten-membered ring conformation in the solid state; however, a number of the germacranolides show broadened NMR signals or even multiple NMR signals indicative of conformational equilibria in solution. A few of the conformational mixtures have been investigated by low temperature and NOE methods and the structures of the solution conformers assigned. The conformations of ten-membered rings have been the subject of a number of earlier investigations,[2] and the stable conformations are those which tend to follow the diamond lattice. In germacratrienes, such as agerol, the double bonds are in a crossed orientation with the methyl groups syn with respect to the ring.[2a,d] The influence of lactone rings and ring substituents has not been systematically investigated. Molecular mechanics (MM) calculations have been applied successfully to the study of many hydrocarbons including ten-membered rings,[2a,c-h] and reliable predictions of conformations, heats of formation, steric energies, and in some cases estimates of energy barriers between conformers have resulted. Enough data are now available on germacradienolide-type terpenes to permit a comparison of the low energy conformers identified by X-ray diffraction, NMR, and molecular mechanics studies and to estimate the relative magnitudes of conformational barriers.

Discussion

The *trans,trans*-germacradienolides are usually discussed in terms of the four conformations which are labeled in Figure 1 as 1UU, 1UD, 1DU, 1DD and 2UU, 2UD, 2DU, 2DD. The 1 and 2 refer to the 6,12-and 8,12-olides, respectively, while U (up) and D (down) refer to the orientation of the C(10) and C(4) methyl groups on the ten-membered ring.[3] The lowest energy conformers corre-

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[1] Fischer, N. H.; Oliver, E. J.; Fischer, H. D. In *Progress in the Chemistry of Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: Wienheim, 1979; Vol. 38, p 48.

[2] (a) White, D. N. J.; Bovill, M. S. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1610. (b) Takeda, K. *Tetrahedron* **1974**, *30*, 1525. (c) Dunitz, J. O.; Iberg, J. A. *Perspect. Struct. Chem.* **1968**, *2*, 21. (d) Messerotti, W.; Pagnoni, V. M.; Trave, R.; Zandsi, R.; Andreeti, G. D.; Bocelli, G.; Sgarabotto, P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 217. (e) White, D. N. J.; Bovill, M. J. *Tetrahedron Lett.* **1975**, 2239. (f) Ermer, O.; Lifson, S. *J. Am. Chem. Soc.* **1973**, *95*, 4121. (g) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734. (h) Allinger, N. L.; Tribble, M. T.; Sprague, J. T. *J. Org. Chem.* **1972**, *37*, 2423.

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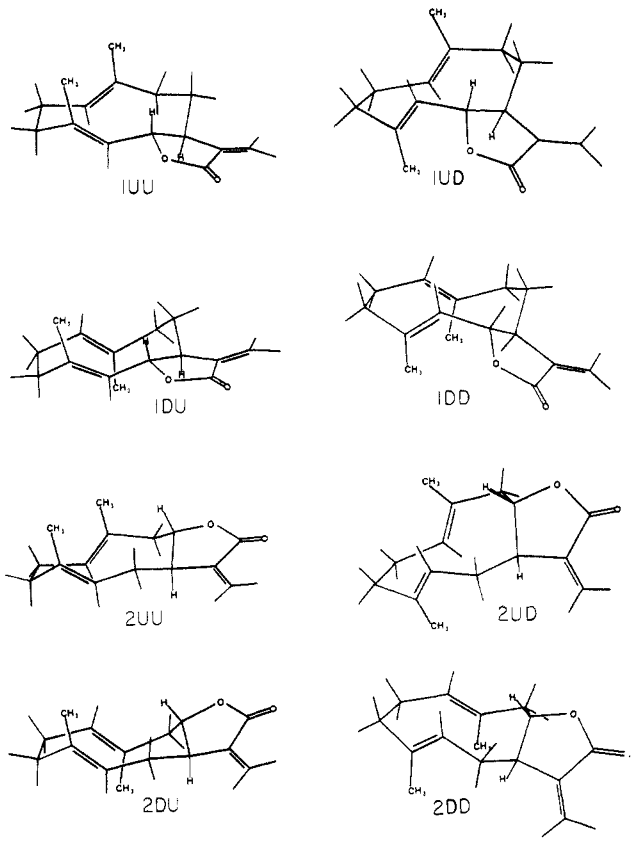


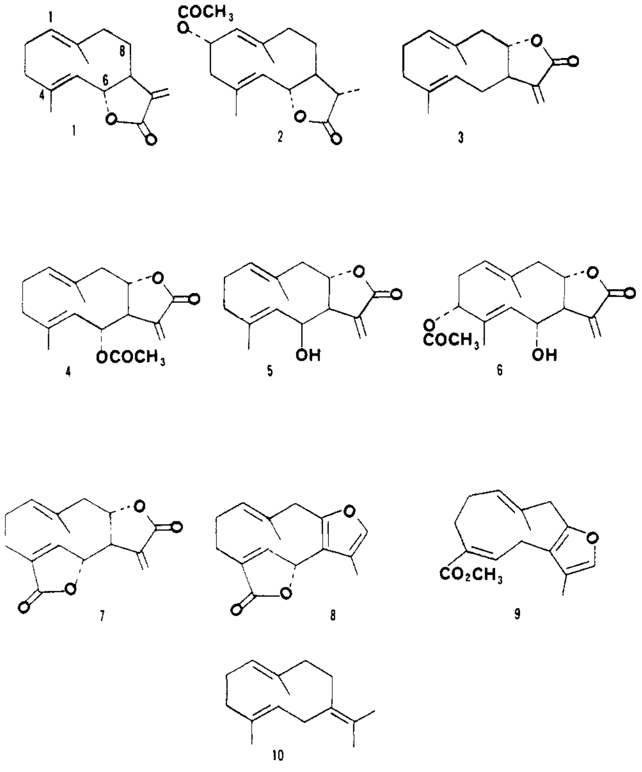
Figure 1. Four basic conformations for germacra-1(10),4-dien-6,12-olides (type 1) and germacra-1(10),4-dien-8,12-olides (type 2). UU, UD, DU, and DD notations refer to the orientation of the methyl groups attached at C(10) and C(4), respectively.

Table I. Relative Energies (kcal/mol) of Conformers Calculated by Molecular Mechanics (MM2)

compd	type 1			
	1UU[a]	1UD	1DU	1DD
1	0.00	3.55	4.41	4.46
2	0.00	3.22	5.25	3.62
	type 2			
compd	2UU	2UD	2DU	2DD
3	1.25	0.00	1.40	0.01
4	4.20	1.06	1.97	0.00 (1.17)[b]
5	5.52	0.00	4.10	2.14
6	3.68	1.05	2.04	0.00
7		0.04		0.00
	others			
8		2.69		0.00
9	0.00	2.11	2.19	0.00
10	0.00	1.82	1.12	0.06

[a] The labels are identified in Figure 1. [b] A second 2DD low energy conformation.

Chart I



sponding to these designations have been calculated for most compounds; however, it should be noted that several conformations may exist for each designation, and in some cases a second conformation is energetically more favorable than one of the four basic types. The UU and DD conformations have crossed double bonds while UD and DU exhibit parallel double bonds. The crossed conformations lead to transannular interactions of the π-orbitals and a strong end absorption in the UV spectra.[4]

X-ray structural data on type 1 germacradienolides show the most common conformation to be the 1UU.[1,5] NMR studies of costunolide[6] (**1**) and of dihydrotamaulipin A acetate[7] (**2**) led to the assignment of 1UU as the solution conformation. As indicated in Table I, MM calculations predict the 1UU conformation to be lower in energy by more than 3 kcal/mol. Torsional interactions are primarily responsible for the differences in conformer stability with van der Waals interactions making a significant contribution. The interactions between hydrogen atoms at C(2) and C(3) are unfavorable in 1UD and 1DU. The methyl hydrogen atoms in the down orientation lead to more severe intramolecular contacts. The presence or absence of an exocyclic double bond on the lactone ring has no effect on the ten-membered ring conformation unless bulky substituents interact with the C(13) methyl group.

Figure 2 gives the calculated barrier energies between the various conformers of **1**. In these calculations the —CC(CH_3)=C(H)C— moieties are maintained planar. One unit is rotated until the ethylenic hydrogen passes through the center of the ten-membered ring, see Figure 2. The methyl group cannot pass through the center of the ring and must traverse a path around the exterior. The molecular structure was refined by MM techniques at small fixed rotation increments as the energy passed through a maximum. At the maximum the refined positional parameters for C_{10}, C_1, C_4, C_5, H_1, and H_5 were held fixed while other atoms were allowed to move. A slight decrease in energy was achieved by permitting movement of methyl groups C_{14} and C_{15}. While this does not prove

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(3) Samek, Z.; Harmantha, J. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2779. These authors introduce a more extensive notation to identify conformers and the equivalence is shown below: UU = ${}_1D^{14}\,{}^{15}D_5$; UD = ${}_1D^{14}\,{}_{15}D^5$, etc.

(4) (a) Sorm, F. In *Fortschritte der Chemie organischer Naturstoffe*; Zechmeister, L., Ed.; Springer: Wienheim, 1961; Vol. 19, p 1.

(5) Watson, W. H. "A Comparison of Crystallographic Data and Molecular Mechanics Calculations on Some Germacranolide-type Sesquiterpenes", IUPAC 14th International Symposium on the Chemistry of Natural Products, Poznan, Poland, July, 1984.

(6) Tori, K.; Horibe, I.; Tamura, Y.; Tada, H. *J. Chem. Soc., Chem. Commun.* **1973**, 620.

(7) Bhacca, N. S.; Fischer, N. H. *J. Chem. Soc., Chem. Commun.* **1969**, 68.

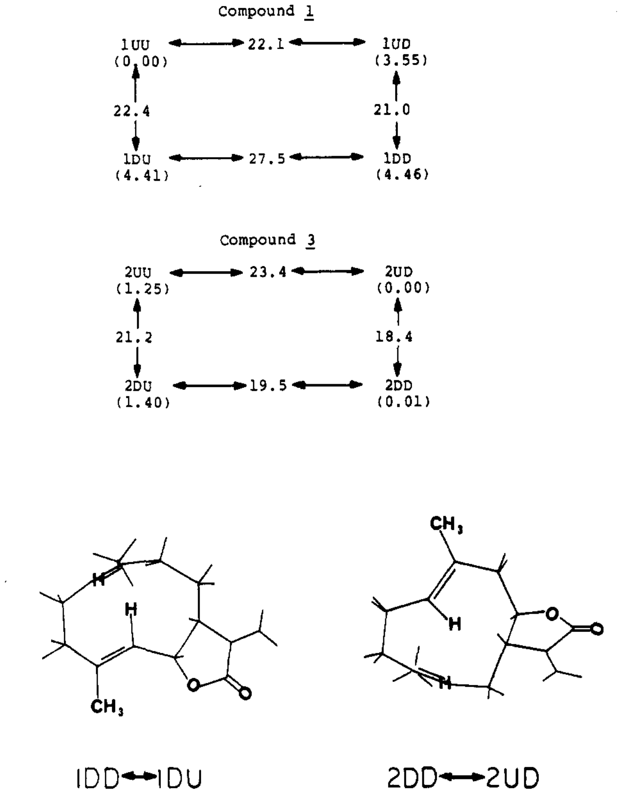

Figure 2. Relative conformer energies and barriers between conformations for the type 1 and type 2 germacranolides. The molecular mechanics calculations for compounds 1 and 3 are shown. Two barrier geometries are shown in the lower part of the figure. In each diagram one trans H–CH_3 pair lies in the plane of the paper while the other H–CH_3 pair is perpendicular to the plane of the paper.

conclusively that this is the lowest energy pathway between conformers, it probably provides a reasonable estimate of relative energies. Because the lactone ring is fused to one end of the planar system, C(6) in the type 1 germacratrienes (6,12-olides), there is a steeper rise in the barrier energy as the planar moiety containing the methyl group attached to C(4) begins to rotate. A lower energy conformational barrier and a higher energy conformer are encountered before the ethylenic hydrogen reaches the center of the ring.

X-ray structural studies on type 2 germacradienolides indicate that the solid state conformations differ from that observed for type 1 compounds. 6-Epidesacetyllaurenobiolide[8] (**5**) was found to exist in the solid state as the 2UD conformer. MM calculations predict the 2UD conformation to be 2.14 kcal/mol more stable than the 2DD conformer and 5.52 kcal/mol more stable than 2UU. Structure **6**, reported in this paper, exists in the solid state as the 2DD conformer, see Figure 3. MM calculations predict the 2DD conformer of **6** to be 1.05 kcal/mol more stable than the 2UD conformer and 3.68 kcal/mol more stable than 2UU. Although the differences in solid state conformation might be attributed to differences in packing or hydrogen bonding, the agreement between the solid state conformations and the isolated molecule MM calculations suggests the conformational preferences are inherent in the molecular structure. The differences can be attributed to different steric requirements associated with the change in stereochemistry at C(6) and the α-acetate present at C(3) in **6**. The NMR spectrum exhibits broadened lines indicative of equilibrating conformers.[9] MM calculations predict these to be 2DD and 2UD.

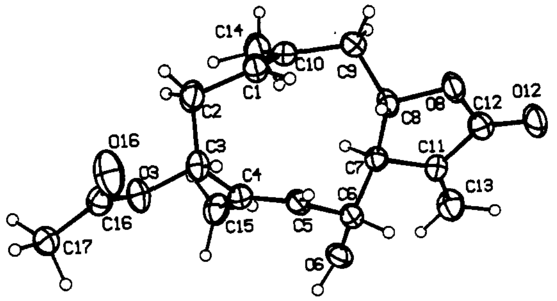

Figure 3. An Ortep drawing of 3-acetoxy-6-hydroxygermacra-1(10),4-dien-8,12-olide. The thermal ellipsoids are drawn at the 50% probability level while H atoms are shown as spheres of arbitrary size. This structure corresponds to the 2DD conformation.

Isabelin (**7**) is a type 2 compound with an additional lactone ring formed between C(4) and C(6). MM calculations predict the 2DD and the 2UD conformers differ in energy by only 0.04 kcal/mol. Low temperature NMR and NOE investigations are consistent with the existence of two equilibrating conformers (2DD and 2UD) in a 10:7 ratio.[10] An NMR investigation of linderalactone **8** indicated only the 2DD conformation in solution.[11] This is consistent with the MM calculation which predicts the 2UD conformer to be 2.59 kcal/mol higher in energy.

MM calculations on the parent type 2 compound **3** show the 2UD and the 2DD conformers to be essentially isoenergetic. The 2UU conformation has a significantly lower torsional energy as did 1UU; however, there is a significant increase in the van der Waals and bending energy contributions. 2UD has a high torsional component due to the hydrogen interactions at C(2) and C(3) but much lower van der Waals and bending components. Although 2UD and 2DD are essentially isoenergetic, the strain eneregies are distributed differently. Changes in substituents and/or stereochemistry around the ring produce differing steric requirements for the two conformers which can lead to either form being of lower energy. Figure 2 gives the calculated barrier energies between the four conformers of **3**. Not only are 2DD and 2UD lower in energy but the barrier between the conformers is calculated to be lower than that between the other conformers of **3** or those of type 1. The 18.4 kcal/mol barrier is just on the borderline for rapid room-temperature equilibration of conformers. Slight changes in barrier height due to substituent or solvent effects can lead to the observation of broadened lines or if the barrier is high enough to separate lines for each low energy conformer.

All X-ray and NMR data are consistent with the above observations except for compound 4. MM calculations predict that the 2DD conformer is of lowest energy and 1.06 kcal/mol more stable than 2UD. MM calculations predict the 2UU and 2DU conformers to be higher in energy by 4.20 and 1.97 kcal/mol, respectively. NOE and low temperature NMR studies of laurenobiolide **4** indicate the existence of equilibrating conformers. These were initially identified as 2UU and 2UD in a 8:2 ratio;[12] however, a later study suggested an equilibrating mixture of

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(10) Yoshioka, H.; Mabry, T. J.; Miller, H. E. *J. Chem. Soc. D.* **1971**, 1084.

(11) Takeda, K.; Tori, K.; Horibe, I.; Otsuru, M.; Minato, H. *J. Chem. Soc. C.* **1970**, 2697.

(12) Tori, K.; Horibe, I.; Kuriyama, K.; Tada, H.; Takeda, K. *J. Chem. Soc., Chem. Commun.* **1971**, 1393.

2UU, 2DU, 2DD, and 2UD in a 5:4:3:1 ratio.[13] Since MM calculations agree rather well with the NMR and X-ray data of other compounds and 2UU is calculated to 4.20 kcal/mol higher in energy than 2DD, the conformational assignments for laurenobiolide might be questioned. MM calculations predict the existence of a second 2DD conformation 1.17 kcal/mol higher in energy.

Germacratriene **10** should be the most reliable MM calculation since no constants need be added for the lactone ring. The UU and DD conformations are essentially isoenergetic with DU and UD being 1.12 and 1.92 kcal/mol higher in energy. The calculation gives H_f = 7.36 kcal/mol and E(strain) = 20.06 kcal/mol. Application of MM to the trans,cis compound **9** suggests the UU and DD conformations to be isoenergetic with UD and DU being 2.11 and 2.19 kcal/mol less stable. Room-temperature NMR spectra show broadened lines, but NOE measurements of −10 °C indicated the presence of the UU conformer.

Conclusion

Molecular mechanics calculations and X-ray and NMR studies indicate that trans,trans terpenes of type 1 exist primarily as the 1UU conformer. The energy difference in favor of the 1UU conformer is large enough that conformer mixtures are rarely observed. MM calculations on type 2 terpenes predict the 2DD and 2UD conformations to be approximately isoenergetic and mixtures of conformers should be common. Substitutional or stereochemical changes can favor either conformation. It should be noted that unlike type 1 terpenes, the least favorable conformers frequently differ from the one of lowest energy by less than 2 kcal/mol. Substitution patterns or significant solvent interactions might favor any of the conformers.

Experimental Section

Compound **6** was isolated from *Viguiera deltoidea* and characterized by NMR, MS, and IR spectroscopy.[9] A sample of **6** was recrystallized from EtOAc, yielding transparent well-formed crystals.

Crystallographic data: $C_{17}H_{22}O_5$, M_r 206.36; space group $p2_1$, a = 17.806 (5), b = 14.170 (6), and c = 6.914 (3) Å, β = 112.91 (2)°, V = 1606.9 (1) Å^3, Z = 4, d_{calcd} = 1.266 g cm^{-3}, d_m(flotation) = 1.263 g cm^{-3}, λ(Cu Kα) = 1.54178 Å, μ(Cu Kα) = 7.715 cm^{-1}, 2293 unique reflections with 2101 having $I \geq 3\sigma(I)$, R = 0.044, R_w = 0.043, $(\Delta/\sigma)_{avg}$ = 0.08, $(\Delta/\sigma)_{max}$ = 0.71, S = 2.76, with the largest peak in the final difference Fourier map being 0.18 e Å^{-3}.

X-ray Crystal Structure Analysis. All data were collected on a Syntex P2$_1$ diffractometer system using a θ–2θ scan with a variable scan rate and with $2\theta_{max}$ = 120°. Lattice parameters were obtained from a least-squares refinement of 15 reflections whose angles were measured by a centering routine associated with the diffractometer system. Reference reflections indicated no significant changes in intensity. Lorentz and polarization corrections were applied but no absorption corrections were made. The application of direct methods techniques[15] yielded the positions of all non-hydrogen atoms. After several cycles of least-squares refinement hydrogen atoms were located in a difference Fourier synthesis. A full-matrix least-squares refinement with H atom parameters fixed yielded the final structure. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o)$ was derived from counting statistics. Locally written programs were used for data reduction while XRAY76[16] was used for all other calculations.

Molecular Mechanics Calculations

The updated MM2 program as supplied by Serena Software[17] for the IBMXT PC was used for all computations. Several calculations were checked on an IBM 4301 utilizing MM2 supplied by the QCPE.[18] All computations were made with the parameters provided by the MM2 program or with special parameters developed for the lactone rings. The added parameters gave better distance, angle, and torsion angle agreement with X-ray data; however the relative strain energies did not change significantly. Only in the case of compound **7** did a change in order occur; however, these energies are so close to being isoenergetic that a 0.06 kcal/mol shift is not significant.

The modified lactone ring parameters are given below (1 = C(sp^3); 2 = C(sp^2); 3 = C(carbonyl); 6 = –O–):

atom types			
		k_s	L
2	3	9.0	1.480
2	2	12.5	1.333
1	6	5.3	1.460

atom types				
			k_s	angle
2	3	6	0.50	113.0

atom types						
				V_1	V_2	V_3
2	1	6	3	0.00	0.00	0.403
2	3	6	1	−2.50	1.39	0.000
1	2	3	6	0.00	0.00	−0.417
2	2	3	6	0.00	0.00	−0.417

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Registry No. 1, 553-21-9; 2, 19888-17-6; 3, 62928-84-1; 4, 35001-25-3; 5, 93236-19-2; 6, 101527-96-2; 7, 22391-22-6; 8, 728-61-0; 9, 21678-22-8; 10, 15423-57-1.

Supplementary Material Available: Tables of crystallographic data for **6** (8 pages). Ordering information is given on any current masthead page.

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