(s, 6 H), 3.82 (s, 3 H), 3.93 (br d, $J = 6.2$ Hz, 1 H), 4.50 (d, $J = 6.2$ Hz, 1 H), 4.58 (br d, $J = 1.5$ Hz), 4.80 (d, $J = 7.9$ Hz, 1 H), 5.95 (s, 1 H), 5.97 (s, 1 H), 6.37 (s, 2 H), 6.48 (s, 1 H), 6.93 (s, 1 H).

(−)-Podophyllotoxin (1). A solution of 4.7 mg (0.009 06 mmol) of silyl ether (−)-**22** in 0.45 mL of acetonitrile was treated at room temperature under argon with 27 μL (0.054 mmol) of a 2.0 M solution of triethylammonium fluoride in acetonitrile. The mixture was stirred at room temperature for 3 days, at which time the mixture was concentrated under reduced pressure. Chromatography of the residue on 3 g of silica gel (elution with 30% ethyl acetate–hexane followed by 70% ethyl acetate–hexane) gave 2.9 mg (79%) of crystalline (−)-podophyllotoxin (**1**): mp 157–160 °C; $[\alpha]^{22}_{D}$ −85° (c 0.29, EtOH); IR (KBr) ν 3450, 2900, 1769, 1580, 1472, 1225, 1112 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.80 (m, 2 H), 3.76 (s, 6 H), 3.82 (s, 3 H), 4.10 (br t, $J = 9.4$ Hz, 1 H), 4.61 (m, 2 H), 4.79 (br d, $J = 6.6$ Hz, 1 H), 5.97 (d, $J = 1.1$ Hz, 1 H), 5.99 (d, $J = 1.1$ Hz, 1 H), 6.37 (s, 2 H), 6.52 (s, 1 H), 7.12 (s, 1 H).

Recrystallization of a sample of 5.2 mg of synthetic (−)-podophyllotoxin from 1:5 CH_2Cl_2–hexanes gave 4.4 mg of crystalline (−)-**1**: mp 158–159.5 °C; $[\alpha]^{21}_{D}$ −97° (c 0.33, EtOH).

A sample of authentic (−)-podophyllotoxin recrystallized in the same manner gave crystalline (−)-**1**: mp 158.5–159.5 °C; $[\alpha]^{22}_{D}$ −104° (c 0.36, EtOH).

Acknowledgment. We are grateful to the National Institutes of Health for their support of this study. An NIH (NRSA) Postdoctoral Fellowship (to R.C.A.) and an SERC Postdoctoral Fellowship (to S.J.T.) are also gratefully acknowledged. Finally, we are grateful to Professor Andrew S. Kende for providing spectra and details from his own studies and Drs. Terrance W. Doyle and T. Kaneko of Bristol-Myers for authentic samples of podophyllotoxin and other technical information.

Conformational Analysis of 14-Membered Macrolides Using X-ray Crystallography and Molecular Mechanics Calculations

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Abstract: The solid-state conformations of nine 14-membered-ring macrolides were determined by X-ray crystallography. In each conformation, the geometry of the lactone group was s-trans and the lactone C–O–C–H torsional angle was within a 0–40° arc. Geminally disubstituted atoms were found to occupy the corner positions. These trends greatly simplified the conformational analysis of the large-ring lactones. Two macrolides crystallized in a previously unreported low-energy conformation for 14-membered lactones. A modified nomenclature for the conformations of large rings is proposed which is based upon the number of bonds separating corner and pseudocorner atoms.

For the last 30 years chemists have shown that the conformational analysis of small ring compounds can be a powerful tool in understanding the physical and chemical properties of these systems. Simple pictorial representations, such as the cyclohexane chair, have demonstrated the potential of graphical representations of molecular conformation to rationalize known results and suggest new reactions.

Recently, Still and Galynker[1] described the profound effects of conformational control on the reactivity of medium and large rings. Following this pioneering work, several other research groups[2] have elegantly used conformational control to introduce new asymmetric centers on medium and large rings. Since the stereochemical outcome of a reaction in a large ring compound is usually not obvious, the planning of a synthesis of complex large rings must include a careful conformational analysis. Invariably researchers have relied on the use of computer calculations[2] to determine the important conformations controlling these reactions.

For some time we have been intrigued with the possibility of developing a simple pictorial model for the conformation of large rings with the hope that this model might be useful in understanding the chemistry of these systems. Some of these chemical findings have been published.[3] In this paper, we outline our efforts to determine the principles of conformational analysis governing the stereochemistry of reactions in 14-membered lactones. The macrolide antibiotics[4] are well represented by 14-membered lactones, and these compounds have been popular targets for synthetic chemists over the past decade.[5]

At first glance, the conformational analysis of 14-membered rings seems to be overwhelmingly complex. Although large rings can exist in a number of stable conformations, only a few of these are of low enough energy to be appreciably populated at room temperature. In his pioneering work, Dale[6] showed that conformations of 14-membered rings that are superimposable on a diamond lattice framework are of lower energy. He found that the minimum energy conformation was the [3434][7] conformation.[6] Later calculations on cyclotetradecane, however, revealed two low-energy conformations that were not superimposable on the diamond lattice.[8] These were the [3344] conformation, with a strain energy of 1.1 kcal/mol relative to the [3434] conformation, and the [3335] conformation, with a strain energy of 2.4 kcal/mol relative to the [3434] conformation. These two nondiamond lattice

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[4] (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) Masamune, S.; Bates, G. S.;Corocan, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

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[6] (a) Dale, J. *J. Chem. Soc.* **1963**, 93. (b) Dale, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 1000.

[7] The number of bonds found between corner atoms is indicated in the square brackets.[8]

[8] Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115.

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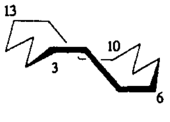
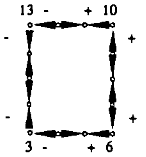
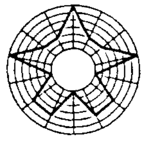
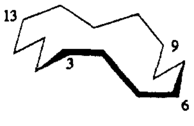
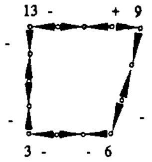
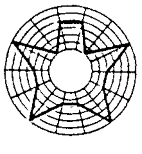
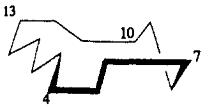
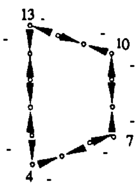
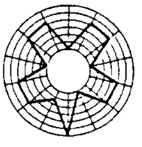
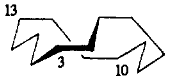
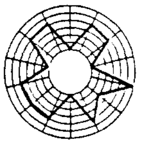
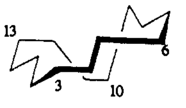
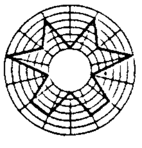
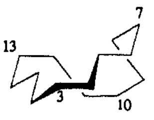
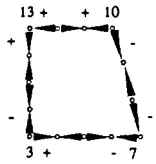
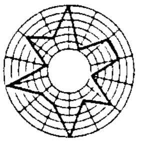
Table I. Six Lowest Energy Conformations of Cyclotetradecane

conformation	side view	top view	polar map	strain energy, kcal/mol
[3434][a,b]				0.0
[3344][b]				1.1
[3335][b]				2.3
D[a,c] [311][a,b] [347][a,d]				3.0
twist [311][b] [343′4′][d]				3.4
C[a,c] [68][a,b] [3′3′4′4′][a,d]				5.0

[a] Diamond lattice conformations. [b] Dale nomenclature.[6] [c] Ogura nomenclature.[20] [d] Modified Dale nomenclature (see text).

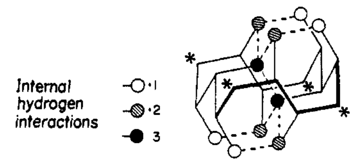


Figure 1. [3434] conformation of cyclotetradecane.

conformations were found to be lower in energy than every diamond lattice conformation with the exception of the [3434] conformation.[8] According to Dale's analysis, the 14-membered-ring compounds should exist predominantly in the [3434] conformation, and indeed, X-ray crystal structures of cyclotetradecane[9] and the structurally equivalent 1,8-diazacyclotetradecane dihydrobromide[10] support this prediction. NMR data on cyclotetradecane[11] and cyclotetradecanone[12] also show that in solution these 14-membered-ring compounds adopt the [3434] conformation.

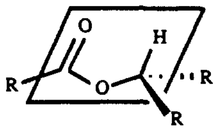


Figure 2. C–O–C–H dihedral angle of esters of secondary alcohols.

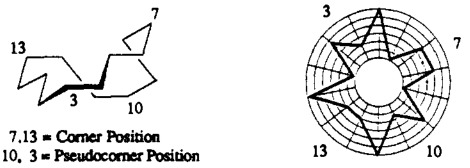


Figure 3. Comparison of the two corner positions in the C conformation of cyclotetradecane.

The substituents of a macrolide can only occupy exterior positions; otherwise the transannular interactions are prohibitively large.[13] The introduction of a geminally substituted atom should force the molecule to adopt a conformation in which the fully substituted atom occupies a corner position[14] (vide infra). The corner position (starred atoms in Figure 1) is the only position in the [3434] conformation where both substituents are exterior to the ring and do not experience severe transannular interactions.

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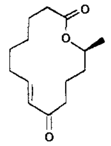
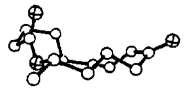
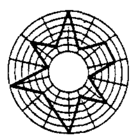
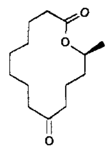
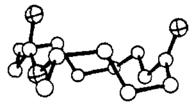
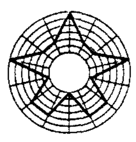
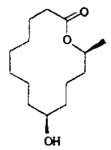
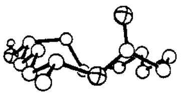
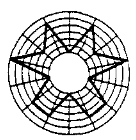
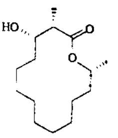
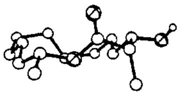
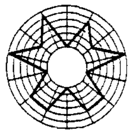
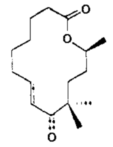
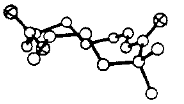
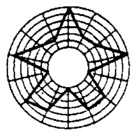
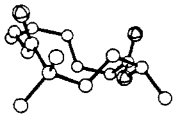
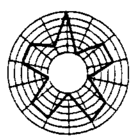
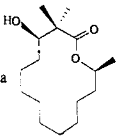
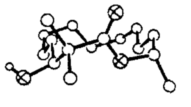
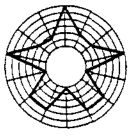
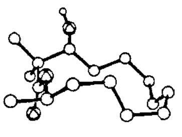
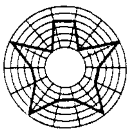
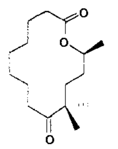
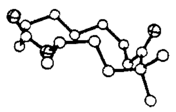
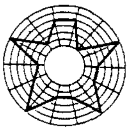
(14) (a) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1149. (b) Björnstad, S. L.; Borgen, G.; Dale, J.; Gaupset, G. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 320.

Table II. ORTEP Diagram and Polar Maps of Macrolides **1**–**4**

macrolide	ORTEP diagram	polar map	conformation
1 			[3′3′4′4′][a]
2 			[3434][a]
3 			[34′3′4′]
4 			[34′3′4′]

[a] Diamond lattice conformations.

Table III. ORTEP Diagram and Polar Maps of Geminally Disubstituted Macrolides **5**–**7**

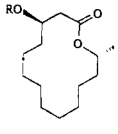
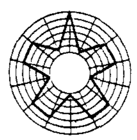
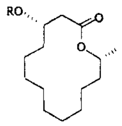
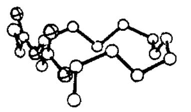
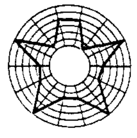
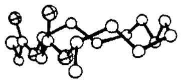
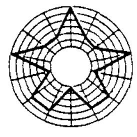
macrolide	ORTEP diagram	polar map	conformation
5a 			[3434][a]
5b			[3335]
6a 			[3434][a]
6b			[3344]
7 			[3344]

[a] Diamond lattice conformations.

Results and Discussion

General. Dale's findings considerably simplified the conformational analysis of 14-membered-ring compounds. Many large-ring natural products contain a lactone group, frequently a lactone of a secondary alcohol (e.g., erythromycin, pikromycin, methymycin).[5] The introduction of a lactone functionality into a large ring should further reduce the number of possible conformations. It is well-known that the s-trans geometry in esters is ~3.0 kcal/mol more stable than the s-cis isomer.[15] The 14-membered ring is large enough to accommodate an s-trans linkage, and therefore, conformations that contain s-cis lactones are energetically disfavored and can usually be ignored. Moreover, Schweizer and Dunitz[16a] observed a preference for the esters of secondary alcohols to exist in a conformation where the C–O–C–H dihedral angle is within the range 0–40° (Figure 2). It was anticipated that this finding might also apply to large-ring lactones.[16b]

Table IV. ORTEP Diagram and Polar Maps of Macrolides **8** and **9**[23] [a]

macrolide	ORTEP diagram	polar map	conformation
8 			[3335]
9a 			[3344]
9b			[3434][b]

[a] $R = BrCH_2CO$. [b] Diamond lattice conformations.

Efforts to probe the conformations of large rings have included the use of ^{13}C and ^{1}H NMR spectroscopy,[17] NOEDS,[18] and IR.[14b,19,20a] But the most successful technique has been X-ray crystallography.[21] Dunitz has concluded that "any conformation observed in a molecular crystal cannot be far from an equilibrium structure of the isolated molecule. X-ray analysis thus provides information about the preferred conformations of molecules although it has nothing to say about the energy differences between them."[22]

To aid in the conformational analysis of the 13-tetradecanolide series, we therefore employed X-ray crystallography studies in conjunction with molecular mechanics calculations. The crystal structures of nine compounds were determined.[23] We were interested in determining whether the conformational preferences calculated by Dale could be applied to our modestly substituted lactones. Furthermore, this was a welcome opportunity to investigate if the Schweizer–Dunitz observation applied to lactones, namely, that in s-trans lactones the C–O–C–H angle is limited to 0–40°, and to examine the suggestion that substituents will

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(15) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Permagon: New York, 1983. (b) Pinkus, A. G.; Lin, E. Y. *J. Mol. Struct.* **1975**, *24*, 9.

(16) (a) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547. (b) Dale, J.; Groth, P.; Schwartz, J. E. *Acta Chem. Scand., Ser. B* **1986**, *B40*, 568.

(17) (a) Egan, R. S.; Perun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525. (b) Egan, R. S.; Martin, J. R.; Perun, T. J.; Mitscher, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 4578. (c) Nourse, J. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 4584.

(18) Quinkert, G.; Heim, N.; Bats, J. W.; Oschkinat, H.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 987.

(19) (a) Borgen, G.; Dale, J. *Chem. Soc., Chem. Commun.* **1970**, 1340. (b) Meyer, W. L.; Schweizer, W. B.; Beck, A. K.; Scheifele, W.; Seebach, D.; Schreiber, S. L.; Kelly, S. E. *Helv. Chim. Acta* **1987**, *70*, 281.

(20) (a) Ogura, H.; Furuhata, K.; Kuwano, H.; Suzuki, M. *Tetrahedron* **1981**, *37*, 165. (b) Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6733. (c) Ogura, H.; Furuhata, K.; Kuwano, H.; Harada, N. *J. Am. Chem. Soc.* **1975**, *97*, 1930. (d) Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2385.

(21) Hauske, J. R.; Gaudliana, M.; Kostek, G.; Schulte, G. *J. Org. Chem.* **1987**, *52*, 4622.

(22) Dunitz, J. D. *X-Ray Analysis and the Structure of Organic Molecules*; Cornell University Press: Ithaca, New York, 1979.

(23) The crystal structures of two of these macrolides have been reported previously. See: Ponnuswamy, M. N.; Trotter, J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *C41*, 1109.

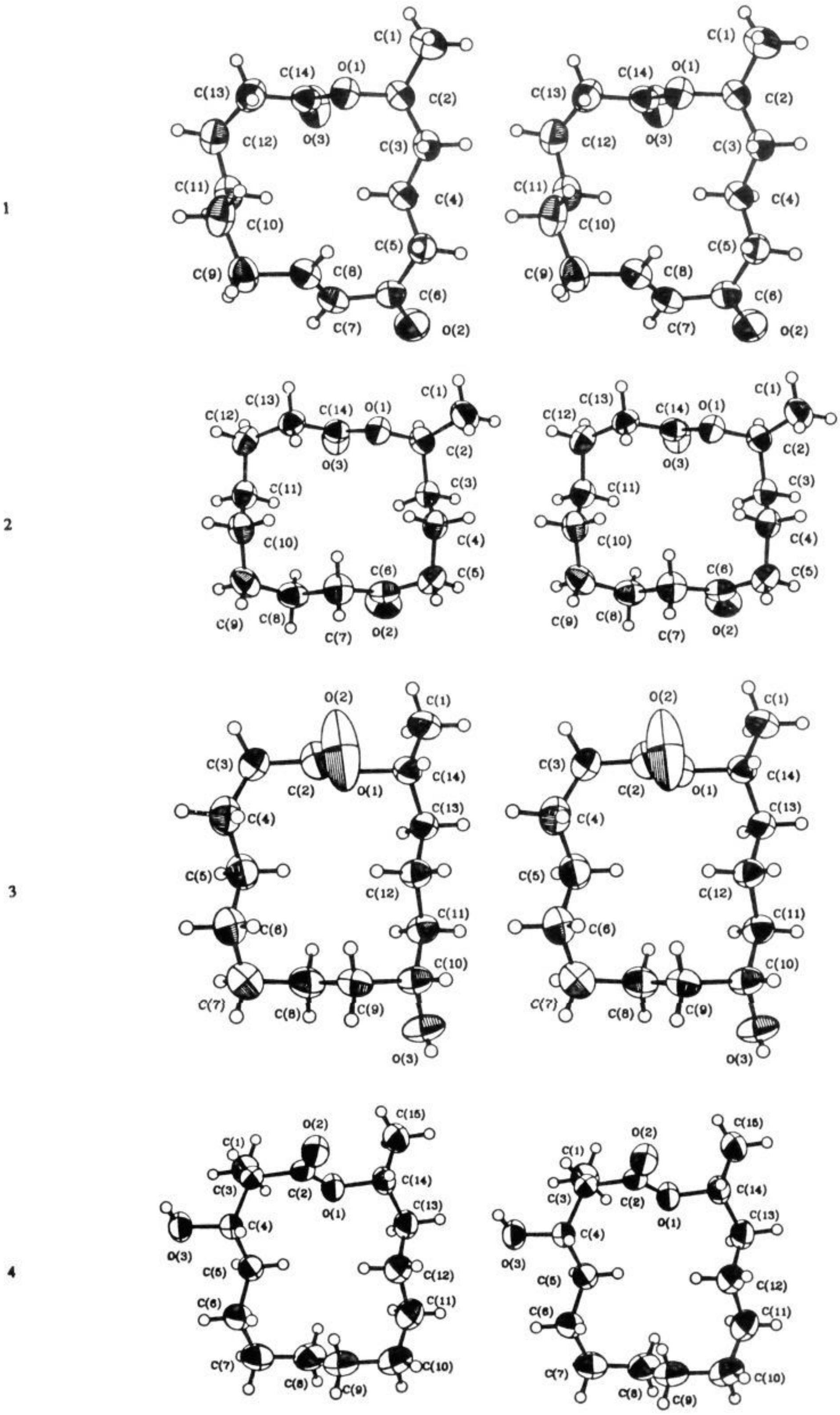

Figure 4. Stereoscopic view of compounds **1**–**4**.

prefer to be outside of the ring and geminal substituents on corner positions.

During the early stages of this work, the recognition and comparison of conformations was time consuming and prone to error. This task was greatly simplified by the use of polar maps.[20,24] A polar map is a graph of the sign and magnitude of the dihedral angles versus the bond number in a conformation plotted in polar coordinates. A polar map, which is unique for each conformation, can then be generated,[25] and the comparison of polar maps allows for the facile identification of a conformation.[24]

In our studies, we found that the (*E*)-9-oxo-7-tetradecen-13-olide (**1**) adopted a C conformation[20] in solid state and the two alcohols, 2-methyl-3-hydroxy-13-tetradecanolide (**4**) and 9-

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[24] Ounsworth, J. P.; Weiler, L. *J. Chem. Educ.* **1987**, *64*, 568.

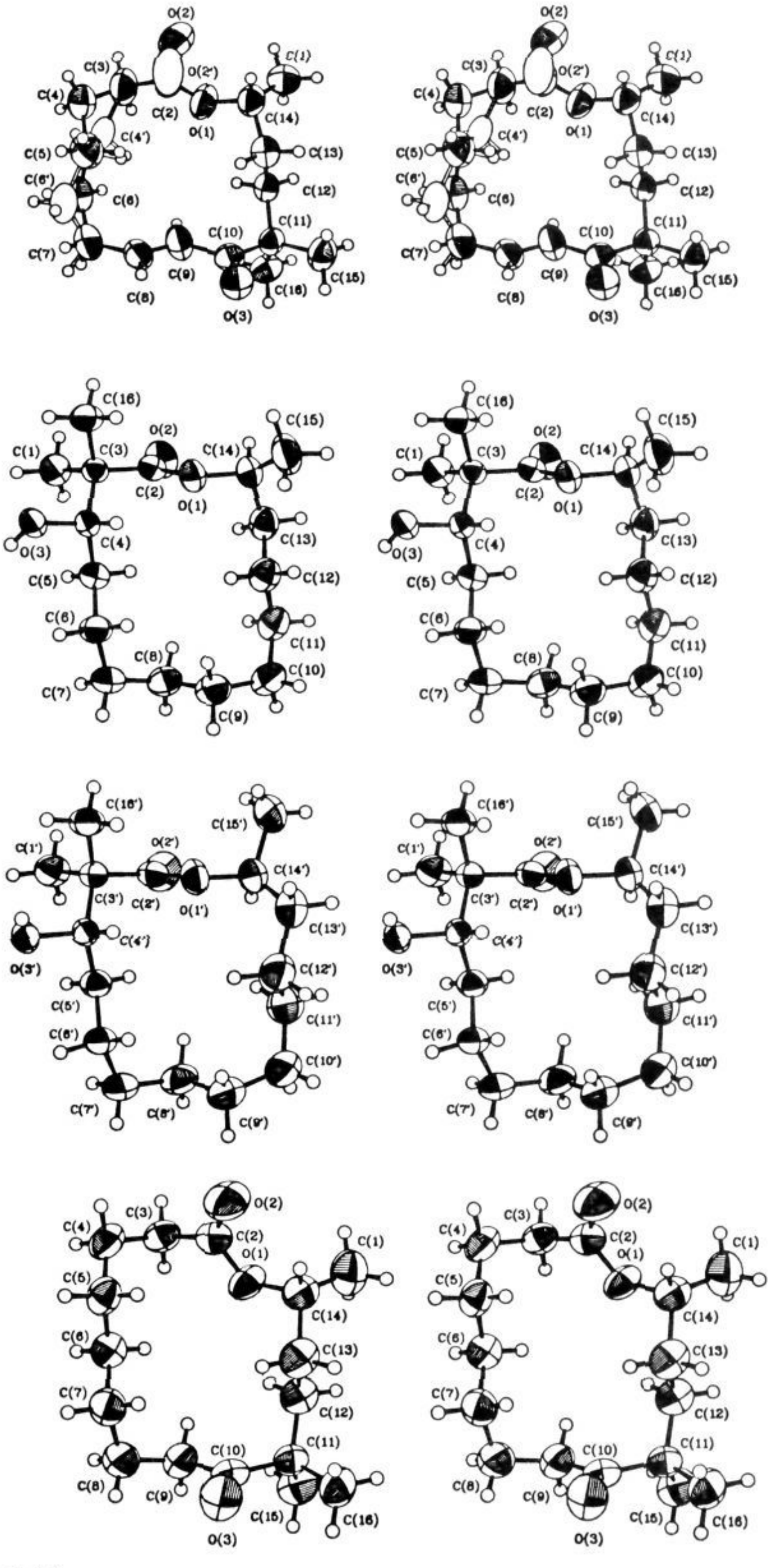

Figure 5. Stereoscopic view of compounds **5**–**7**.

hydroxy-13-tetradecanolide (**3**), crystallized in a previously unrecognized "twist" conformation. During this work, Schreiber and Liew published the crystal structure of a 14-membered macrolide, (*E*)-5,9-dimethoxy-6-oxo-10-tridecen-13-olide (**1**),[26] and we also obtained unpublished crystallographic data on one of the intermediates II in the Woodward synthesis of erythromycin.[27] From the ORTEP diagrams we suspected that both macrolides crystallized in the same twist conformation as **3** and **4**, and this was confirmed by a comparison of their polar maps.

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(25) To generate the characteristic polar map of a conformation the anti dihedral angles, which are derived from X-ray or MM2 data, must be formed within the ring.[24] If not, the sign of the anti dihedral angle is to be reversed and this value used. We realize this method introduces a slight error in the value of the dihedral angle, e.g., a value of 178.5° formed outside the ring becomes −178.5° when in fact it should be −181.5°. The resulting polar map however is not significantly different.

(26) Schreiber, S. L.; Liew, W. *J. Am. Chem. Soc.* **1985**, *107*, 2980.

(27) Bothner-By, A. A., Carnegie Mellon University, personal communication, 1987.

Table V. Intraannular Torsion Angles[a]

atoms	value, deg	atoms	value, deg	atoms	value, deg
		1			
C(14)-O(1)-C(2)—C(3)	-113.2 (3)	C(5)-C(6)-C(7)-C(8)	-15.6 (5)	C(10)-C(11)-C(12)-C(13)	69.1 (4)
O(1)-C(2)-C(3)-C(4)	68.7 (3)	C(6)-C(7)-C(8)-C(9)	174.3 (3)	C(11)-C(12)-C(13)-C(14)	63.1 (4)
C(2)-C(3)-C(4)-C(5)	-169.1 (2)	C(7)-C(8)-C(9)-C(10)	-122.6 (3)	C(12)-C(13)-C(14)-O(1)	-137.4 (3)
C(3)-C(4)-C(5)-C(6)	170.3 (3)	C(8)-C(9)-C(10)-C(11)	68.3 (3)	C(2)-O(1)-C(14)-C(13)	179.5 (2)
C(4)-C(5)-C(6)-C(7)	-66.6 (3)	C(9)-C(10)-C(11)-C(12)	-172.4 (3)		
		2			
C(14)-O(1)-C(2)-C(3)	-81.5 (2)	C(5)-C(6)-C(7)-C(8)	172.10 (15)	C(10)-C(11)-C(12)-C(13)	65.3 (2)
O(1)-C(2)-C(3)-C(4)	-62.4 (2)	C(6)-C(7)-C(8)-C(9)	-168.77 (15)	C(11)-C(12)-C(13)-C(14)	64.0 (2)
C(2)-C(3)-C(4)-C(5)	170.15 (13)	C(7)-C(8)-C(9)-C(10)	62.3 (2)	C(12)-C(13)-C(14)-O(1)	-159.47 (14)
C(3)-C(4)-C(5)-C(6)	-57.8 (2)	C(8)-C(9)-C(10)-C(11)	61.4 (2)	C(2)-O(1)-C(14)-C(13)	177.02 (12)
C(4)-C(5)-C(6)-C(7)	-66.9 (2)	C(9)-C(10)-C(11)-C(12)	-174.34 (14)		
		3			
C(14)-O(1)-C(2)-C(3)	-179.6 (5)	C(5)-C(6)-C(7)-C(8)	56.0 (9)	C(10)-C(11)-C(12)-C(13)	-178.3 (5)
O(1)-C(2)-C(3)-C(4)	112.5 (7)	C(6)-C(7)-C(8)-C(9)	60.1 (8)	C(11)-C(12)-C(13)-C(14)	170.3 (5)
C(2)-C(3)-C(4)-C(5)	-73.1 (7)	C(7)-C(8)-C(9)-C(10)	-175.9 (5)	C(12)-C(13)-C(14)-O(1)	-71.2 (6)
C(3)-C(4)-C(5)-C(6)	162.9 (6)	C(8)-C(9)-C(10)-C(11)	58.4 (7)	C(2)-O(1)-C(14)-C(13)	123.0 (5)
C(4)-C(5)-C(6)-C(7)	-178.8 (6)	C(9)-C(10)-C(11)-C(12)	58.4 (7)		
C(14′)-O(1′)-C(2′)-C(3′)	-179.5 (5)	C(5′)-C(6′)-C(7′)-C(8′)	56.1 (11)	C(10′)-C(11′)-C(12′)-C(13′)	-179.8 (5)
O(1′)-C(2′)-C(3′)-C(4′)	109.7 (7)	C(6′)-C(7′)-C(8′)-C(9′)	63.7 (10)	C(11′)-C(12′)-C(13′)-C(14′)	170.0 (5)
C(2′)-C(3′)-C(4′)-C(5′)	-72.9 (7)	C(7′)-C(8′)-C(9′)-C(10′)	-174.1 (6)	C(12′)-C(13′)-C(14′)-O(1′)	-71.2 (6)
C(3′)-C(4′)-C(5′)-C(6′)	163.0 (6)	C(8′)-C(9′)-C(10′)-C(11′)	55.4 (7)	C(2′)-O(1′)-C(14′)-C(13′)	125.3 (5)
C(4′)-C(5′)-C(6′)-C(7′)	-179.1 (7)	C(9′)-C(10′)-C(11′)-C(12′)	57.5 (7)		
		4			
C(14)-O(1)-C(2)-C(3)	176.13 (13)	C(5)-C(6)-C(7)-C(8)	58.2 (3)	C(10)-C(11)-C(12)-C(13)	-172.2 (2)
O(1)-C(2)-C(3)-C(4)	89.00 (15)	C(6)-C(7)-C(8)-C(9)	60.4 (3)	C(11)-C(12)-C(13)-C(14)	166.8 (2)
C(2)-C(3)-C(4)-C(5)	-75.0 (2)	C(7)-C(8)-C(9)-C(10)	-176.3 (2)	C(12)-C(13)-C(14)-O(1)	-68.9 (2)
C(3)-C(4)-C(5)-C(6)	168.37 (15)	C(8)-C(9)-C(10)-C(11)	58.3 (3)	C(2)-O(1)-C(14)-C(13)	142.78 (14)
C(4)-C(5)-C(6)-C(7)	-179.5 (2)	C(9)-C(10)-C(11)-C(12)	56.6 (3)		
		5			
C(14)-O(1)-C(2)-C(3)	-178.1 (4)	C(5)-C(6)-C(7)-C(8)	-62.0 (9)	C(10)-C(11)-C(12)-C(13)	57.1 (4)
O(1)-C(2)-C(3)-C(4)	127.9 (7)	C(6)-C(7)-C(8)-C(9)	-41.7 (9)	C(11)-C(12)-C(13)-C(14)	-170.2 (3)
C(2)-C(3)-C(4)-C(5)	-50.3 (9)	C(7)-C(8)-C(9)-C(10)	178.9 (4)	C(12)-C(13)-C(14)-O(1)	61.1 (4)
C(3)-C(4)-C(5)-C(6)	-90.2 (8)	C(8)-C(9)-C(10)-C(11)	-179.0 (4)	C(2)-O(1)-C(14)-C(13)	113.6 (4)
C(4)-C(5)-C(6)-C(7)	173.5 (6)	C(9)-C(10)-C(11)-C(12)	51.6 (4)		
C(14)-O(1)-C(2)-C(3)	-178.1 (4)	C(5)-C(6′)-C(7)-C(8)	54.7 (14)	C(10)-C(11)-C(12)-C(13)	57.1 (4)
O(1)-C(2)-C(3)-C(4′)	75.9 (7)	C(6′)-C(7)-C(8)-C(9)	-97.3 (10)	C(11)-C(12)-C(13)-C(14)	-170.2 (3)
C(2)-C(3)-C(4′)-C(5)	58.3 (8)	C(7)-C(8)-C(9)-C(10)	178.9 (4)	C(12)-C(13)-C(14)-O(1)	61.1 (4)
C(3)-C(4′)-C(5)-C(6′)	-179.2 (6)	C(8)-C(9)-C(10)-C(11)	-179.0 (4)	C(2)-O(1)-C(14)-C(13)	113.6 (4)
C(4′)-C(5)-C(6′)-C(7)	56.3 (13)	C(9)-C(10)-C(11)-C(12)	51.6 (4)		
		6			
C(14)-O(1)-C(2)-C(3)	176.2 (2)	C(5)-C(6)-C(7)-C(8)	67.7 (4)	C(10)-C(11)-C(12)-C(13)	-173.3 (3)
O(1)-C(2)-C(3)-C(4)	-49.3 (3)	C(6)-C(7)-C(8)-C(9)	66.1 (4)	C(11)-C(12)-C(13)-C(14)	172.8 (3)
C(2)-C(3)-C(4)-C(5)	-63.1 (3)	C(7)-C(8)-C(9)-C(10)	-167.1 (3)	C(12)-C(13)-C(14)-O(1)	-60.2 (4)
C(3)-C(4)-C(5)-C(6)	172.0 (2)	C(8)-C(9)-C(10)-C(11)	58.0 (5)	C(2)-O(1)-C(14)-C(13)	-82.1 (3)
C(4)-C(5)-C(6)-C(7)	-174.3 (3)	C(9)-C(10)-C(11)-C(12)	55.8 (5)		
C(14′)-O(1′)-C(2′)-C(3′)	-177.8 (2)	C(5′)-C(6′)-C(7′)-C(8′)	-67.8 (4)	C(10′)-C(11′)-C(12′)-C(13′)	169.5 (4)
O(1′)-C(2′)-C(3′)-C(4′)	60.0 (3)	C(6′)-C(7′)-C(8′)-C(9′)	-70.6 (5)	C(11′)-C(12′)-C(13′)-C(14′)	-64.1 (5)
C(2′)-C(3′)-C(4′)-C(5′)	57.0 (3)	C(7′)-C(8′)-C(9′)-C(10′)	161.8 (3)	C(12′)-C(13′)-C(14′)-O(1′)	-63.9 (5)
C(3′)-C(4′)-C(5′)-C(6′)	-168.4 (3)	C(8′)-C(9′)-C(10′)-C(11′)	-66.4 (6)	C(2′)-O(1′)-C(14′)-C(13′)	153.2 (3)
C(4′)-C(5′)-C(6′)-C(7′)	171.0 (3)	C(9′)-C(10′)-C(11′)-C(12′)	-61.5 (7)		
		7			
C(14)-O(1)-C(2)-C(3)	-174.5 (5)	C(5)-C(6)-C(7)-C(8)	-171.5 (5)	C(10)-C(11)-C(12)-C(13)	64.3 (6)
O(1)-C(2)-C(3)-C(4)	116.9 (5)	C(6)-C(7)-C(8)-C(9)	66.1 (7)	C(11)-C(12)-C(13)-C(14)	-173.2 (5)
C(2)-C(3)-C(4)-C(5)	-54.2 (6)	C(7)-C(8)-C(9)-C(10)	71.1 (6)	C(12)-C(13)-C(14)-O(1)	64.9 (6)
C(3)-C(4)-C(5)-C(6)	-62.3 (6)	C(8)-C(9)-C(10)-C(11)	-163.7 (4)	C(2)-O(1)-C(14)-C(13)	129.4 (5)
C(4)-C(5)-C(6)-C(7)	177.3 (4)	C(9)-C(10)-C(11)-C(12)	66.7 (6)		

[a] Standard deviations in parentheses.

With the discovery of these additional twist conformations, we became interested in determining the energy of the twist and C conformations relative to the low-energy conformations calculated by Dale. With cyclotetradecane as a model, MM2 calculations were carried out on the twist, [3344], and [3335] conformations and the 13 possible[28] diamond lattice conformations. The six lowest energy conformations from these calculations are shown in Table I. It is interesting to note that the twist conformation was found to be lower in energy than every diamond lattice conformation except for the [3434] and the D conformations.

The pattern of a polar map (Figure 3) can be used to locate the corner positions of a conformation by recognizing its characteristic sequence of dihedral angles. Initially, the corner position was defined as an atom having two contiguous gauche dihedral angles each followed by an anti dihedral angle.[6a] As can easily be seen from the polar map of the C conformation (Figure 3), two types of corner atoms can exist in a macrolide that satisfy this definition. Both corner positions can be differentiated in the sign of their respective dihedral angles. Originally, Dale defined the corner (classical corner) position as having gauche angles of equal sign and an anti dihedral angle on each side[14] (e.g., 180, +60, +60, 180). The other possible corner position (pseudo-

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[28] Saunders, M. *Tetrahedron* **1967**, *23*, 2105.

Table VI. Hydrogen Bond and C-H···O Interaction (H···O ≤ 2.50 Å) Data

atoms (D-H···A)[a]	H···A, Å	D···A, Å	D-H···A, deg	compd
C(5)-H(5b)···O(3)^a	2.47	3.436 (4)	167	**1**
O(3)-H(O3)···O(3′)^b	2.11 (7)	2.820 (8)	168 (8)	**3**
O(3′)-H(O3′)···O(3)^c	1.91 (9)	2.795 (8)	177 (8)	**3**
O(3)-H(O3)···O(2)^d	1.92 (2)	2.799 (2)	175 (2)	**4**
O(3)-H(O3)···O(3′)^e	1.98 (3)	2.766 (3)	164 (3)	**6**
O(3′)-H(O3′)···O(3)^c	1.92 (4)	2.770 (3)	170 (4)	**6**
C(13)-H(13b)···O(3)^f	2.49	3.373 (7)	149	**7**

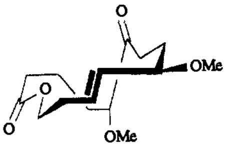
[a] Superscripts refer to symmetry operations: $^a x, {}^1/_2 - y, z - {}^1/_2$; $^b {}^1/_2 + x\ {}^1/_2 - y, z$; $^c x, y, z$; $^d 1 - x, 1 - y, 1 - z$; $^e -x, -y, 1 - z$; $^f 1 - x, {}^1/_2 + y, {}^1/_2 - z$.

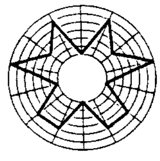
Table VII. Geometry of the Lactone Linkages in **1**-**7**[a]

compd	O···H, Å	C-H···O, deg	C=O···H, deg	C-O-C-H, deg	C···O, Å
1	2.31	105	82	6.3	2.727 (4)
2	2.40	96	80	37.5	2.686 (2)
3a	2.28	104	84	4.5	2.685 (7)
3b	2.29	103	84	6.5	2.691 (8)
4	2.27 (2)	107 (1)	81.5 (4)	22.5 (11)	2.712 (2)
5a	2.30	104	80	4.2	2.716 (9)
5b	2.27	102	83	4.2	2.647 (9)
6a	2.42 (3)	96 (2)	79.4 (6)	38 (2)	2.694 (4)
6b	2.39 (2)	97 (2)	79.4 (6)	38.1 (15)	2.707 (5)
7	2.28	104	82	14.1	2.696 (7)
av	2.32	102	82	18.0	2.696

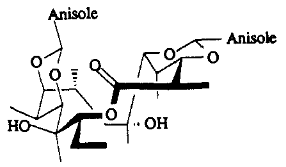
[a] O(3),C(14),O(1),C(2),H(2) for **1** and **2**; O(2),C(2),O(1),C(14),H(14) for **3**-**7**.

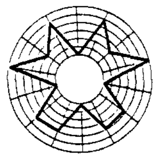
Chart I





I



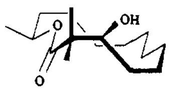
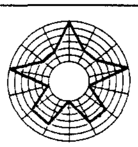
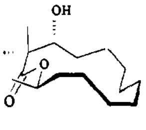
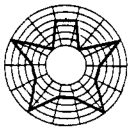
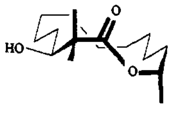
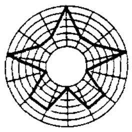
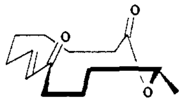
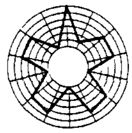
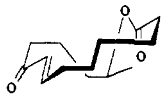
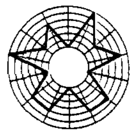
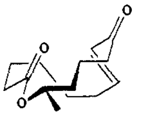
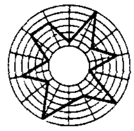


II

corner[29]) exists with the same anti-gauche-gauche-anti arrangement, but having gauche bonds with opposite signs. No mention was made regarding the signs of the 180° angles on either side of the gauche angles in the original definition by Dale.[6a] With our modification,[24,25] these anti angles consistently possessed torsional angles of opposite sign relative to the gauche angles, for example, a −180, +60, −60, +180 arrangement for the pseudocorner.

The corner position can accommodate a geminally substituted atom with the least amount of steric crowding within the macrolide.[14] Using MM2 calculations,[30] we investigated the effect of geminal dimethyl substitution on these two types of corner positions and compared the results with substitution at a noncorner position. Calculations on both the C and D conformations show geminal substitution of the corner to be the lowest energy, followed by substitution of the pseudocorner (0.6 kcal/mol). Predictably, geminal substitution of the noncorner position was a high-energy situation and disfavored. Therefore, in geminally substituted systems, the quaternary carbon atom should greatly favor the corner position over a noncorner position. This result agrees with Dale's qualitative prediction.[14] However, if the corner position cannot be geminally substituted, for whatever reasons, then geminal substitution at the pseudocorner position should be the next lowest energy situation (Figure 3).

Table VIII. Example of Molecular Mechanics Calculations for **6** and **1**

conformation	side view	polar map	strain energy, kcal/mol
[3434][a]			0.0
[3344]			0.7
[3434][a]			1.3
[3335]			0.0
[34′3′4′]			0.1
[3′3′4′4′][a]			0.7

[a] Diamond lattice conformations.

Dale's system for naming conformations is based on the number of bonds between corner atoms,[6] but it is impossible to describe a conformation adequately that has only one or two corner positions by using this convention. Ogura[20b] recognized this and turned to an arbitrary system which designates each conformational type with a letter. However, the use of the A, C, or D classifications for naming conformations is not a general one that could be applied to other ring systems. Ogura designated two of the 14-membered conformations as the D and C conformations which, under Dale's system, are classified as the [311] and [68] conformations, respectively. Neither of these designations are as informative as, for example, the [3434] conformation, and as a possible solution, the pseudocorners could be included. Maintaining the spirit of Dale's nomenclature, we suggest that it be extended to include pseudocorners as the basis for naming conformations. With polar maps, both corner and pseudocorner positions can be identified with ease. The number of bonds between a corner and pseudocorner atom or between two pseudocorner atoms shall be denoted with a primed number. As before, the smallest number of bonds should begin the sequence in the square brackets, but unprimed numbers shall have priority over primed ones, i.e., the starting value should represent the smallest number of bonds between two corner atoms, if possible. The combination of unprimed and primed numbers provides a more informative definition of a conformation. The C conformation would be renamed the [3′3′4′4′] conformation and the D the [34′7′] conformation. With Dale's system, the newly discovered twist conformation and Ogura's D conformation would both be designated as the [311] conformation.[31] Under this new proposed

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[29] Borgen, B.; Dale, J.; Teien, G. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 15.

[30] Strain energies were calculated by using W. C. Still's MACROMODEL (1986) or N. L. Allinger's MMP2 (1982) computer program.

Table IX. Crystallographic Data[a]

compd	**1**	**2**	**3**	**4**	**5**	**6**	**7**
formula	$C_{14}H_{22}O_3$	$C_{14}H_{24}O_3$	$C_{14}H_{26}O_3$	$C_{15}H_{28}O_3$	$C_{16}H_{26}O_3$	$C_{16}H_{30}O_3$	$C_{16}H_{28}O_3$
fw	238.33	240.34	242.36	256.38	266.38	270.41	268.40
cryst syst	monoclinic	monoclinic	orthorhombic	triclinic	monoclinic	triclinic	orthorhombic
space group	$P2_1/c$	$P2_1/n$	$Pna2_1$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$
a, Å	10.465 (1)	10.723 (2)	10.1909 (6)	9.0281 (4)	14.4318 (8)	11.8391 (6)	9.6077 (5)
b, Å	13.322 (1)	25.707 (3)	8.2033 (4)	15.4752 (6)	5.7145 (3)	13.0018 (8)	10.9778 (8)
c, Å	10.005 (1)	5.0807 (7)	34.425 (1)	6.0162 (3)	19.339 (1)	11.4904 (5)	15.2503 (9)
α, deg	90	90	90	95.563 (4)	90	95.913 (4)	90
β, deg	90.957 (6)	96.144 (7)	90	109.424 (4)	99.568 (4)	91.869 (4)	90
γ, deg	90	90	90	91.751 (4)	90	107.492 (4)	90
V, Å^3	1394.6 (3)	1392.4 (3)	2877.9 (2)	787.19 (6)	1572.7 (2)	1674.2 (2)	1608.5 (2)
Z	4	4	8	2	4	4	4
D_{calcd}, g/cm^3	1.135	1.148	1.119	1.082	1.125	1.073	1.108
F (000)	520	528	1072	284	584	600	592
radiation	Mo	Mo	Cu	Cu	Cu	Cu	Cu
μ, cm^{-1}	0.73	0.74	5.77	5.49	5.70	5.36	5.58
crystal dimens, mm	0.08 × 0.19 × 0.60	0.50 × 0.50 × 0.56	0.20 × 0.43 × 0.55	0.25 × 0.43 × 0.48	0.13 × 0.23 × 0.40	0.30 × 0.38 × 0.40	0.25 × 0.34 × 0.38
transmsn factors			0.771–0.896	0.816–0.908	0.836–0.936		
scan type	$\omega-2\theta$	$\omega-\theta$	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$
scan range, deg in ω	0.60 + 0.35 tan θ	0.65 + 0.35 tan θ	0.70 + 0.14 tan θ	0.65 + 0.14 tan θ	0.70 + 0.14 tan θ	0.65 + 0.14 tan θ	0.85 + 0.14 tan θ
scan speed, deg/min	0.8–6.7	0.8–10.0	1.2–10.0	1.3–10.0	1.1–10.0	1.2–10.0	1.3–10.0
data collected	$\pm h,+k,+l$	$\pm h,+k,+l$	$+h,+k,+l$	$+h,\pm k,\pm l$	$\pm h,+k,+l$	$-h,\pm k,\pm l$	$+h,+k,+l$
$2\theta_{max}$, deg	55	55	150	150	150	150	150
crystal decay, %	3.3	4.0	negligible	4.3	0–4.4, nonuniform	negligible	negligible
no. of unique reflcns	3185	3180	3007	3268	3212	6882	1890
no. of obsd. reflcns, $I \geq 3\sigma(I)$	1011	1606	1892	2249	1348	3192	1083
no. of variables	154	154	315	276	200	584	173
R	0.040	0.041	0.048	0.039	0.050	0.040	0.051
R_w	0.042	0.045	0.054	0.044	0.062	0.043	0.057
S	1.534	1.832	1.048	2.428	2.276	1.669	1.058
mean Δ/σ (final cycle)	0.04	0.003	0.04	0.008	0.002	0.04	0.001
max Δ/σ (final cycle)	0.16	0.02	0.20	0.10	0.01	0.42	0.006
resid density, e/Å^3	0.16	0.15	0.34	0.15	0.16	0.16	0.35

[a] Temperature 295 K, Enraf-Nonius CAD4-F diffractometer, graphite monochromatized Mo Kα radiation ($\lambda_{K_{\alpha1}} = 0.709\,30$, $\lambda_{K_{\alpha2}} = 0.713\,59$ Å), or nickel-filtered Cu Kα radiation ($\lambda_{K_{\alpha1}} = 1.540\,562$, $\lambda_{K_{\alpha2}} = 1.544\,390$ Å), takeoff angle 2.7°, aperture (2.0 + tan θ) × 4.0 mm at a distance of 173 mm from the crystal, scan range extended by 25% on both sides for background measurement, $\sigma^2(I) = C + 2B + [0.04(C - B)]^2$ (C = scan count, B = normalized background count), function minimized: $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F)$, $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = \sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$, $S = (\sum w(|F_o| - |F_c|)^2/(m - n))^{1/2}$. Values given for R, R_w, and S are based on those reflections with $I \geq 3\sigma(I)$.

nomenclature, the twist conformation is uniquely described as the [34′3′4′] conformation.

In keeping with Dale's system, this new naming procedure remains descriptive and is not dependent on memorizing a letter with a corresponding conformation. This system of naming could prove useful in other ring systems and shall be followed from this point on throughout this paper.

X-ray Data. The results of the X-ray crystallographic study of **1**–**7** are summarized in Tables II–V and Figures 4 and 5. In some cases (see Table VI), molecules are associated by hydrogen bonds or weak C–H···O interactions. All other intermolecular distances correspond to normal van der Waals contacts. In compounds **3** and **6**, there are two molecules in the asymmetric unit; these are virtually identical in the former but have different conformations in the latter. Compound **5** was found to be conformationally disordered. Bond lengths and angles in **1**–**7** are normal with the exception of the disordered portion of compound **5**. Departures from normal geometry in **5** are most likely a result of imperfect modeling of the disorder.

Not unexpectedly, the geometry of the lactone linkage was s-trans in every molecule. In addition, the C–O–C–H dihedral angle was consistently within a 0–40° arc (see Table VII), which agrees with the range reported for the open chain ester counterpart.[16]

Weak C–H···O interactions involving the carbonyl oxygen atom may be at least partially responsible for the stability of this particular arrangement of the lactone linkage. Details of the geometry of these interactions in compounds **1**–**7** are summarized in Table VII. The H···O distances are at least 0.18 Å less than the sum of the van der Waals radii. The C=O···H angles (which average 82°) are smaller than the "ideal" 120°, but this does not preclude a net attractive interaction. It should be pointed out that use of a C–H distance of 1.08 Å rather than the X-ray distance of 0.98 Å would result in shorter H···O distances and larger C=O···H angles.

Without exception, the geminal methyls were found occupying the corner positions in structures **5**–**7**, and these compounds represent one of the first examples confirming Dale's predictions for geminally substituted carbon atoms occupying a corner position.[32] The future use of these constraints should considerably simplify the conformational analysis in these systems.

Suitable crystals of compounds **1**–**7** were obtained by slow evaporation of hexane or heptane solutions of the purified compounds.

Molecular Mechanics Calculations. The plethora of conformations from the X-ray studies was unexpected. Of the 12 crystal structures determined, only four were [3434] conformations. The remainder crystallized in the [3344] (three structures), the [3335] (two structures), the [3′3′4′4′] (one structure), and the previously unknown [34′3′4′] conformation (two structures). In order to determine whether conformations found in the solid state would be significantly populated in solution, the nine molecules were analyzed by MM2/MMP2 calculations.[30]

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(31) Note that these conformations are 3-11 conformations not 3-1-1 conformations. The sum of the numbers in the square brackets must equal the number of bonds in the ring.

(32) Previously, the only reported examples were Groth's[33] crystal structure of 1,1,9,9-tetramethylcyclohexadecane and a few organometallic compounds with either geminally substituted nitrogen or phosphorus atoms.[34]

(33) Groth, P. *Acta Chem. Scand., Ser. A* **1974**, *A28*, 808.

(34) Al-Salem, N. A.; McDonald, W. S; Markham, R.; Norton, M. C.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1980**, 59, and references therein.

Table X. Final Positional (Fractional × 10^4) and Isotropic Thermal Parameters ($U \times 10^3$ Å^2)

atom	*x*	*y*	*z*	U_{eq}	atom	*x*	*y*	*z*	U_{eq}
1									
O(1)	4703 (2)	1467 (1)	3429 (2)	57	C(7)	1132 (3)	4146 (2)	3621 (3)	53
O(2)	1973 (2)	5484 (2)	4870 (2)	86	C(8)	1217 (3)	3498 (2)	2624 (3)	54
O(3)	3839 (2)	988 (2)	5358 (2)	85	C(9)	212 (3)	2774 (3)	2182 (3)	66
C(1)	6929 (3)	1836 (3)	3649 (4)	87	C(10)	722 (3)	1699 (3)	2230 (3)	75
C(2)	5610 (3)	2138 (2)	4105 (3)	56	C(11)	985 (3)	1316 (3)	3630 (3)	70
C(3)	5260 (3)	3201 (2)	3721 (3)	54	C(12)	1650 (3)	307 (3)	3733 (3)	74
C(4)	4005 (3)	3553 (2)	4295 (3)	55	C(13)	3039 (3)	290 (2)	3299 (3)	70
C(5)	3532 (3)	4545 (2)	3698 (3)	56	C(14)	3886 (3)	943 (2)	4154 (4)	56
C(6)	2193 (3)	4789 (3)	4104 (3)	56					
2									
O(1)	4823 (1)	796 (<1)	2860 (2)	53	C(7)	7934 (2)	1827 (1)	6207 (4)	67
O(2)	7542 (1)	2473 (1)	2909 (3)	88	C(8)	9134 (2)	1677 (1)	5096 (4)	65
O(3)	6023 (1)	740 (<1)	−457 (2)	72	C(9)	9742 (2)	1191 (1)	6352 (4)	69
C(1)	2826 (2)	1204 (1)	2503 (4)	75	C(10)	8958 (2)	698 (1)	5950 (3)	59
C(2)	4112 (2)	1223 (1)	1536 (3)	53	C(11)	8657 (2)	543 (1)	3087 (3)	57
C(3)	4813 (2)	1728 (1)	2123 (3)	49	C(12)	7772 (2)	83 (1)	2606 (3)	62
C(4)	4989 (2)	1881 (1)	5029 (3)	53	C(13)	6450 (2)	184 (1)	3333 (3)	54
C(5)	5890 (2)	2341 (1)	5584 (3)	61	C(14)	5770 (2)	598 (1)	1681 (3)	49
C(6)	7161 (2)	2237 (1)	4735 (4)	57					
3									
O(1)	4732 (4)	−280 (4)	7399	53	O(1′)	2507 (4)	5273 (4)	3635 (1)	56
O(2)	6684 (6)	−589 (7)	7653 (3)	169	O(2′)	4424 (6)	5573 (7)	3360 (3)	164
O(3)	6537 (5)	2149 (7)	5689 (2)	73	O(3′)	4082 (5)	2845 (7)	5368 (2)	77
C(1)	3766 (7)	2092 (9)	7693 (2)	69	C(1′)	1534 (7)	2933 (10)	3334 (3)	72
C(2)	5712 (7)	−1165 (9)	7528 (2)	69	C(2′)	3457 (7)	6168 (9)	3503 (2)	68
C(3)	5481 (6)	−2950 (9)	7481 (2)	65	C(3′)	3248 (6)	7968 (9)	3545 (2)	67
C(4)	6421 (6)	−3687 (8)	7183 (2)	71	C(4′)	4168 (6)	8655 (8)	3848 (3)	74
C(5)	6092 (7)	−3230 (8)	6768 (3)	69	C(5′)	3798 (7)	8203 (8)	4259 (2)	69
C(6)	7200 (7)	−3512 (8)	6486 (2)	79	C(6′)	4896 (8)	8445 (9)	4552 (3)	93
C(7)	6872 (8)	−3088 (13)	6064 (3)	96	C(7′)	4534 (10)	8022 (12)	4967 (3)	111
C(8)	6393 (7)	−1330 (10)	6002 (2)	74	C(8′)	4030 (8)	6329 (11)	5033 (3)	87
C(9)	7359 (6)	−11 (7)	6120 (2)	57	C(9′)	4984 (7)	4970 (9)	4949 (2)	68
C(10)	6853 (5)	1735 (8)	6086 (2)	55	C(10′)	4456 (5)	3241 (8)	4974 (2)	57
C(11)	5624 (6)	2075 (8)	6325 (2)	55	C(11′)	3266 (5)	2882 (8)	4722 (2)	55
C(12)	5825 (5)	1749 (7)	6755 (2)	53	C(12′)	3531 (5)	3220 (8)	4290 (2)	54
C(13)	4641 (5)	2114 (8)	7010 (2)	50	C(13′)	2368 (5)	2872 (8)	4028 (2)	51
C(14)	4814 (5)	1503 (7)	7423 (2)	50	C(14′)	2577 (5)	3491 (7)	3617 (2)	52
4									
O(1)	1288 (1)	3449 (1)	3643 (2)	59	C(7)	5299 (3)	1065 (1)	3158 (5)	85
O(2)	2141 (1)	4660 (1)	2651 (2)	67	C(8)	3611 (3)	772 (1)	1635 (4)	77
O(3)	6539 (1)	3654 (1)	7046 (2)	64	C(9)	3087 (3)	1052 (1)	−804 (4)	78
C(1)	3522 (3)	3755 (2)	8182 (3)	72	C(10)	1357 (3)	807 (2)	−2278 (4)	93
C(2)	2341 (2)	4096 (1)	3942 (2)	47	C(11)	173 (3)	1160 (1)	−1193 (5)	90
C(3)	3822 (2)	4044 (1)	6027 (2)	50	C(12)	317 (2)	2144 (1)	−621 (4)	69
C(4)	5032 (2)	3508 (1)	5265 (3)	49	C(13)	−707 (2)	2502 (1)	760 (4)	66
C(5)	4648 (2)	2531 (1)	4841 (3)	58	C(14)	−266 (2)	3440 (1)	1765 (3)	59
C(6)	5665 (2)	2050 (1)	3631 (4)	72	C(15)	−1367 (3)	3853 (2)	2887 (5)	82
5									
O(1)	8576 (2)	5626 (5)	1671 (1)	95	C(6′)^b	5211 (7)	3867 (25)	1727 (6)	101
O(2)^b	8873 (6)	5252 (18)	2826 (5)	102	C(7)	5075 (3)	3496 (11)	1030 (3)	110
O(2′)^b	8361 (7)	4055 (19)	2637 (6)	120	C(8)	5687 (3)	1870 (7)	717 (2)	75
O(3)	6819 (2)	−1425 (5)	158 (1)	84	C(9)	6419 (3)	2394 (7)	428 (2)	83
C(1)	10102 (3)	5212 (8)	1354 (2)	97	C(10)	7003 (3)	645 (7)	138 (2)	66
C(2)	8291 (3)	5787 (9)	2264 (3)	84	C(11)	7822 (2)	1519 (6)	−193 (2)	57
C(3)	7539 (4)	7579 (8)	2278 (3)	102	C(12)	8437 (2)	3180 (6)	316 (2)	57
C(4)^b	6705 (6)	7012 (16)	2505 (5)	86	C(13)	8824 (2)	2132 (7)	1033 (2)	67
C(4′)^b	6616 (6)	6793 (17)	1914 (4)	75	C(14)	9288 (3)	3904 (8)	1566 (2)	75
C(5)	6191 (3)	4674 (10)	2133 (2)	99	C(15)	8393 (3)	−539 (7)	−394 (2)	81
C(6)^b	5505 (6)	5392 (17)	1458 (6)	79	C(16)	7398 (3)	2892 (7)	−861 (2)	80
6									
O(1)	4901 (1)	2798 (1)	5458 (2)	54	C(8)	3385 (3)	109 (3)	8510 (3)	67
O(2)	5806 (2)	1718 (2)	4508 (2)	73	C(9)	3472 (3)	1162 (3)	9275 (3)	71
O(3)	1592 (1)	780 (2)	4374 (2)	49	C(10)	4707 (3)	1777 (4)	9829 (3)	78
C(1)	3742 (4)	350 (3)	3328 (3)	65	C(11)	5661 (3)	2091 (3)	8962 (3)	74
C(2)	4922 (2)	1955 (2)	4684 (2)	47	C(12)	5403 (3)	2754 (3)	8031 (3)	67
C(3)	3707 (2)	1389 (2)	4056 (2)	43	C(13)	6306 (3)	2934 (3)	7110 (3)	65
C(4)	2755 (2)	1150 (2)	4967 (2)	41	C(14)	6026 (3)	3467 (2)	6076 (3)	60
C(5)	2903 (3)	381 (2)	5823 (3)	51	C(15)	5892 (4)	4576 (3)	6362 (5)	88
C(6)	2054 (3)	298 (3)	6796 (3)	60	C(16)	3446 (3)	2168 (3)	3244 (3)	61
C(7)	2239 (3)	−375 (3)	7749 (3)	71	O(1′)	1774 (2)	4423 (1)	7223 (2)	63

Table X (Continued)

atom	x	y	z	U_{eq}	atom	x	y	z	U_{eq}
O(2′)	123 (2)	4898 (2)	6992 (2)	87	C(8′)	−518 (4)	2263 (3)	10204 (3)	75
O(3′)	−156 (2)	1333 (1)	5604 (2)	51	C(9′)	981 (4)	2363 (3)	10780 (4)	86
C(1′)	−931 (3)	3209 (3)	5261 (4)	70	C(10′)	1368 (6)	3492 (3)	11354 (3)	100
C(2′)	696 (3)	4301 (2)	6733 (2)	55	C(11′)	1758 (5)	4331 (3)	10492 (4)	96
C(3′)	290 (2)	3307 (2)	5809 (2)	45	C(12′)	2590 (4)	4098 (3)	9595 (4)	90
C(4′)	257 (2)	2293 (2)	6426 (2)	43	C(13′)	3150 (4)	5030 (3)	8885 (4)	90
C(5′)	−528 (3)	2132 (2)	7449 (3)	54	C(14′)	2303 (4)	5361 (2)	8094 (3)	77
C(6′)	−372 (3)	1286 (3)	8197 (3)	59	C(15′)	2931 (7)	6313 (4)	7456 (5)	128
C(7′)	−1024 (4)	1259 (3)	9327 (3)	73	C(16′)	1192 (3)	3448 (3)	4870 (3)	61
					7				
O(1)	2434 (3)	4038 (4)	4708 (2)	72	C(8)	2445 (7)	−399 (6)	3714 (3)	85
O(2)	3804 (4)	4590 (4)	5811 (3)	103	C(9)	1832 (6)	578 (5)	3130 (3)	76
O(3)	4026 (4)	769 (4)	2422 (2)	94	C(10)	2888 (6)	1227 (5)	2551 (3)	64
C(1)	2676 (8)	5854 (7)	3862 (4)	102	C(11)	2480 (6)	2439 (5)	2124 (3)	64
C(2)	2814 (6)	4016 (5)	5538 (3)	64	C(12)	2274 (6)	3447 (5)	2811 (3)	76
C(3)	1905 (6)	3236 (6)	6089 (3)	68	C(13)	3561 (6)	3783 (6)	3310 (4)	81
C(4)	2693 (6)	2174 (6)	6481 (3)	77	C(14)	3315 (6)	4685 (6)	4071 (3)	72
C(5)	3468 (6)	1391 (5)	5800 (4)	72	C(15)	1077 (6)	2302 (6)	1652 (4)	93
C(6)	2532 (6)	793 (5)	5150 (3)	72	C(16)	3601 (7)	2789 (6)	1447 (4)	90
C(7)	3314 (6)	69 (5)	4455 (4)	77					

[a] Estimated standard deviations in parentheses. [b] Occupancy factor 0.5.

The inherent high-strain energy of most conformations allowed us to focus on the six structures in Table I. To avoid any bias toward the X-ray crystal structure, we used the coordinates of the carbon skeletons in Table I as starting points with the appropriate functional groups and substituents.

By use of the constraints of an s-trans lactone linkage, a C–O–C–H dihedral angle of 0–40° and, where applicable, geminal substituents occupying corner positions, all possible combinations of each molecule were calculated. The results in every case showed the conformation found in the crystal to be one of the three lowest energy conformations,[35] except in alcohols **3** and **4** which exhibited strong intermolecular H bonding.

These calculations show that the order of stability calculated for cyclotetradecane, i.e., [3434] < [3344] < [3335] < [34′7′] < [34′3′4′] < [3′3′4′4′], is not maintained in molecules of higher complexity. We should also note that more than one substitution pattern can exist for the same conformation; for example, compound **6** can exist in two different [3434] conformations (see Table VIII). The calculations show that the [3434] arrangement is the major conformation for saturated macrolides. In seven out of nine molecules, the [3434] is the lowest energy calculated conformation. Of the two exceptions, **2** and **4**, all possible [3434] conformations in **4** have unfavorable transannular interactions (i.e., OH or Me pointing into the ring) and the keto lactone **2** has three [3434] conformations within a 0.7 kcal/mol spread of the lowest energy conformation, in this case the [3344].

The two α,β-unsaturated ketones **1** and **5** behave very differently. The lowest energy conformation for both compounds is the [3335] (see Table VIII) with distorted [34′3′4′] and [3′3′4′4′] conformations becoming much more important according to MMP2 calculations. The [3434] conformation of these unsaturated lactones is considerably higher energy than the above-mentioned conformations. The conformational analysis for these systems is less clear cut, and investigation into this area is continuing.

Therefore, we conclude that X-ray crystallography is useful in finding low-energy structures, but our calculations show that the crystal structures may not be the major conformation in solution. We have successfully used the [3434] conformation as a model to rationalize the stereochemical outcome of reactions in 14-membered rings,[3] and our calculations support this approach.

Conclusion. Our results show that the use of X-ray crystallography and molecular mechanics calculations on 14-membered macrolides provides a detailed analysis of the low-energy conformations available to these macrolides. The X-ray data suggest that the conformational analysis of macrolides can be simplified considerably by applying two principles that are well-known for open-chain esters, namely, the lactone group exists in the s-trans geometry, and the C–O–C–H dihedral angle of a secondary lactone is within a 0–40° arc. Furthermore, sterically bulky substituents are most easily accommodated outside the ring in monosubstituted macrolides or corner positions for geminal substitution. As a general trend, it seems that a [3434] conformation having exterior substituents should be the lowest energy conformation of a 14-membered macrolide. Consequently, the [3434] conformation by itself may be sufficient to understand the regio- and stereochemical outcome of many reactions in 14-membered-ring lactones. The conformational analysis of α,β-unsaturated lactones seems to be more complex. In both examples, the [3434] conformation exhibits a higher strain energy than the [3335], [34′3′4′], or the [3′3′4′4′] conformation.

It is noteworthy that a new twisted conformation [34′3′4′] is seen in four separate instances of 14-membered lactones. Very recently, the crystal structure of an erythromycin A derivative was reported[21] which we recognized as a fifth example of a [34′3′4′] conformation. The [34′3′4′] conformation undoubtedly reflects a low-energy situation in the crystal lattice and may have greater significance in solution for highly substituted macrolides.

Experimental Section

X-ray Crystallographic Analyses. Crystallographic data for compounds **1**–**7** are presented in Table IX. The final unit-cell parameters were obtained by least squares on 2 sin θ/λ values for 25 reflections with $2\theta = 25 - 40°$ (Mo Kα radiation) for **1** and **2** and $2\theta = 50 - 95°$ (Cu Kα radiation) for **3**–**7**. The intensities of three check reflections were measured each hour of X-ray exposure time throughout the data collections. For **3**, **6**, and **7** only small random variations in intensity were noted, while a small linear decay occurred for compounds **1**, **2**, and **4**. Compound **5** exhibited a small but nonuniform crystal decay, the three approximately orthogonal check reflections decaying by 0, 4.2, and 4.4%. Data were processed,[36] scaled for crystal decay[37] where appropriate and, for compounds **3**–**5**, corrected for absorption (numerical integration).

For compounds **3**, **4**, and **6**, the choice between centrosymmetric and noncentrosymmetric space groups having the same systematic absences was based on the E statistics and verified by subsequent calculations. All seven structures were solved by direct methods, the coordinates of all non-hydrogen atoms being determined from E maps. Conformational disorder was found for compound **5**; with atoms O(2), C(4), and C(6) being well resolved. Other atoms in this portion of the molecule are

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(35) Similarly, if two conformations cocrystallized in the unit cell, both conformations were within the three lowest energy conformations as well.

(36) The computer programs used include locally written programs for data processing and locally modified versions of the following: ORFLS, full-matrix least-squares, and ORFFE, function and errors, by W. R. Busing, K. O. Martin, and H. A. Levy; FORDAP, Patterson and Fourier syntheses, by A. Zalkin; ORTEP II, illustrations, by C. K. Johnson; AGNOST, absorption corrections by J. A. Ibers; MULTAN 80, multisolution program by P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson.

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probably subject to minor, unresolvable disorder [in particular: O(1), C(3), C(5), and C(7)] which results in some anomalous bond lengths and angles. Fourier peak heights indicated 1:1 disordering in **5**. Occupancy factors were fixed at 0.5 for the resolved atoms.

In the final stages of full matrix least-squares refinement, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were refined (isotropic thermal parameters) for **4** and **6** and were fixed in positions idealized from observed positions [C(sp^3)-H = 0.98 Å, C(sp^2)-H = 0.97 Å, thermal parameters proportional to that of the bound atom] for the remaining compounds with the exception of the hydroxyl hydrogen atoms in **3** which were refined. Neutral atom scattering factors and anomalous scattering corrections (O and C for those structures solved with Cu radiation) were taken from ref 38. Parallel refinements of mirror-image structures were carried out for compounds **3** and **7**, which crystallize in noncentrosymmetric space groups. In each case, the model with the lower value of R_w was retained (R_w ratios are 1.0005 for **3** and 1.0023 for **7**). Isotropic type I extinction corrections[39-41] were applied for compounds **3**-**7**, the final values of g being 0.33 (6), 0.22 (9), 1.6 (2), 0.49 (9), and 0.32 (6) (all × 10^4), respectively.

Final positional and equivalent isotropic thermal parameters (U_{eq} = $^1/_3$ trace diagonalized U) for the non-hydrogen atoms are given in Table X.

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Registry No. 1, 116503-90-3; **2**, 116503-91-4; **3**, 116503-92-5; **4**, 116561-05-8; **5a**, 116531-32-9; **6a**, 116503-93-6; **7**, 116503-94-7; **8**, 116561-06-9; **9a**, 116561-07-0.

Supplementary Material Available: Tables (S1-S6) of hydrogen atom parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, and bond lengths and angles involving hydrogen atoms (30 pages); observed and calculated structure factors (Tables S7-S13) (109 pages). Ordering information is given on any current masthead page.

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Communications to the Editor

Synthesis of $Os_2(CO)_8(\mu\text{-}CHCH_3)$ from a Geminal Ditriflate and Its Reversible Carbonylation to a Ketene-Bridged Diosmacycle

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A number of reactions[1] may be explained by the insertion of CO into the M-C bonds of dimetallacyclopropanes,[2-5] but the formation of a dimetallacyclobutanone by such a process has never been directly observed.[6,7] In view of (1) the suggestion[8-12] that CO and C_2H_4 compete for the M-C bonds of surface alkylidenes in the Fischer-Tropsch reaction and (2) our previous success in observing the insertion of ethylene into the Os-C bonds of $Os_2(CO)_8(\mu\text{-}CH_2)$ (**1**),[3b] we have investigated the reactivity of **1** and other diosmacyclopropanes toward CO. We now report the preparation of $Os_2(CO)_8(\mu\text{-}CHCH_3)$ (**2**) from ethylidene ditriflate and the reversible carbonylation of **2** to a dimetallacyclobutanone.

Our earlier success in preparing $Os_2(CO)_8(\mu\text{-}CH_2CH_2)$ from $TfOCH_2CH_2OTf$[13] suggested alkylidene ditriflates as precursors to alkylidene-bridged $Os_2(CO)_8$ derivatives. However, acylic geminal ditriflates containing α-hydrogens are thermally unstable and have not previously been isolated.[14,15] We have now found

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