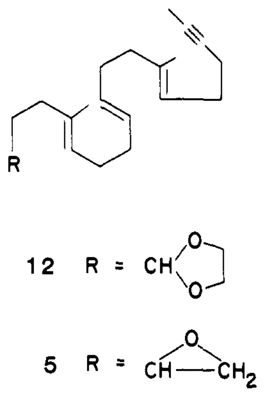

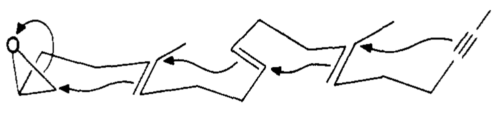
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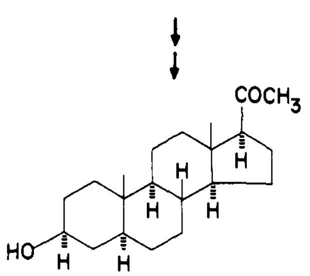

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treatment with $BF_3 \cdot Et_2O$ and ethylene carbonate in CH_2Cl_2 for 0.33 h at 0 °C.[13] After workup and preliminary chromatography of silica gel, cyclization product was separated and purified by HPLC (monitored by GC). Comparison using the standard criteria, including NMR and mass spectral properties as well as GC retention times, with authentic material indicated the steroidal fraction to be (±)-allopregnanolone (**14**), which assignment was corroborated by radioactivity experiments. The synthetic material was reduced with $NaBT_4$ (MeOH, 0 °C), and the resulting tritium-labeled diol was mixed with authentic, nonradioactive allopregnanediol prepared by $NaBH_4$ reduction under comparable conditions; three recrystallizations from aqueous MeOH sufficed to bring the radioactivity level of the recovered sterol to an immutable value.

Although transformation **13** is of distinct theoretical interest, the yield of (±)-allopregnanolone from oxide **5** so far is modest (~2%). However, in compensation, it should be noted that the cyclization process achieves, in one laboratory operation, generation not only of four new rings but also seven new asymmetric centers—one more than in the biological conversion of squalene oxide to lanosterol—all possessing the proper relative configuration characteristic of normal nonaromatic steroids. Further, in a related polyene cyclization approach that involves use of an epoxide initiator on a preformed A-ring, a yield of naturally occurring nonaromatic steroidal product in excess of 50% has been observed (these studies, which are still in progress, will be described in another publication).[14]

Acknowledgment. We acknowledge financial support from the National Science Foundation (CHE 80-02661).

Registry No. (*u*)-**5**, 81044-08-8; **6**, 81027-73-8; **7**, 41143-17-3; **8**, 81027-74-9; (±)-**9**, 81027-75-0; **10**, 81045-27-4; **11**, 81027-76-1; **12**, 81027-77-2; (±)-**14**, 81076-02-0; vi, 35334-60-2; vii, 35334-61-3; viii, 81027-78-3; geranyl acetate, 105-87-3; 4,12-dimethyl-4,8,12-trienoctadecan-16-ynal, 81027-79-4.

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[13] For related examples of ring formation through participation of acetylene bonds in solvolytic processes, see: Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521, and also ref 9 herein.

[14] Results obtained by J.-R. Hwu in this laboratory.

Delocalized π Radical Cations of Acetals

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Recent ESR studies have shown that the radical cations of many simple alkanes are σ radicals with extensive spin delocalization through C–C bonds to the axial hydrogens situated in the plane of the extended carbon chain.[1-4] In contrast, we now report cases where positive holes of *saturated* molecules can also be delocalized in π orbitals.

The existence of large angular-dependent β-hydrogen hyperfine couplings associated with oxygen-centered π radicals such as RCH_2O,[5,6] CH_3O,[7] and $(CH_3)_2O^+$[8,9] provides evidence of facile spin-density transfer in these radicals from the oxygen p orbital to the neighboring methylene or methyl group orbital of π symmetry. This observation of efficient hyperconjugation raised the possibility that in a radical cation containing two equivalent oxygen atoms separated by a bridging methylene group, the spin is delocalized in a three-centered [$-O-CH_2-O-$] π orbital. The examples presented below clearly illustrate this effect and suggest, moreover, that the concept can be extended to include multicentered π orbitals in poly(oxymethylene) systems.

The radical cations were generated in each case by γ irradiation of a solid solution of the parent compound in a Freon matrix, the mechanism occurring by positive charge transfer from the solvent to the solute.[2-4,8-10] As shown in Figure 1, the ESR spectrum of the 1,3-dioxacyclopentane (1,3-dioxolane) radical cation consists of a main triplet with a quintet substructure resulting from hyperfine interaction with two and four equivalent ^1H nuclei, respectively. This pattern is consistent with either a symmetrically delocalized radical cation or a localized species in which the spin is rapidly exchanged between the two oxygen atoms on the ESR timescale. However, an argument based on quantum mechanics (see below) shows unequivocally that the unusually large coupling, $a(2H) = 153.0$ G, to the hydrogens of the bridging methylene group is characteristic of the symmetrically delocalized radical cation. In fact, a triplet pattern with a hyperfine splitting in the range 135–160 G is a diagnostic feature of the class of radicals described here.

Assuming that each of the two C–H_β bonds in the bridging methylene group of the 1,3-dioxacyclopentane radical cation makes a dihedral angle θ of 30° with the y axis of the oxygen p orbitals perpendicular to the O–C–O plane, a coupling of 76 ± 10 G would be expected for the methylene hydrogens from the equation $a_\beta = B_0 + B_2 \cos^2 \theta$, where $B_0 = 0$ and $B_2 = 101 \pm 13$ G,[6] if the unpaired spin population resided on one oxygen atom. On the other hand, if the unpaired electron is distributed between the two oxygen atoms in the 1,3-dioxacyclopentane radical cation such that the coefficients of the oxygen p_y orbitals in the SOMO are equal and have the same sign, the situation governing the admixture of CH_2 group orbitals into the SOMO is closely analogous to that which applies for the cyclohexadienyl radical,[11] and the

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[1] (a) Symons, M. C. R.; Smith, I. G. *J. Chem. Res., Synop.* **1979**, 382. (b) Symons, M. C. R. *Chem. Phys. Lett.* **1980**, *69*, 198.

[2] (a) Wang, J. T.; Williams, F. *J. Phys. Chem.* **1980**, *84*, 3156. (b) Wang, J. T.; Williams, F. *Chem. Phys. Lett.* **1981**, *82*, 177.

[3] Shida, T.; Kubodera, H.; Egawa, Y. *Chem. Phys. Lett.* **1981**, *79*, 179.

[4] (a) Iwasaki, M.; Toriyama, K.; Nunome, K. *J. Am. Chem. Soc.* **1981**, *103*, 3591. (b) Toriyama, K.; Nunome, K.; Iwasaki, M. *J. Phys. Chem.* **1981**, *85*, 2149.

[5] (a) Lee, J. Y.; Box, H. C. *J. Chem. Phys.* **1973**, *59*, 2509. (b) Box, H. C.; Budzinski, E. E. *Ibid.* **1975**, *62*, 197.

[6] Bernhard, W. A.; Close, D. M.; Hutterman, J.; Zehner, H. *J. Chem. Phys.* **1977**, *67*, 1211.

[7] Iwasaki, M.; Toriyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 1964.

[8] Kubodera, H.; Shida, T.; Shimokoshi, K. *J. Phys. Chem.* **1981**, *85*, 2583.

[9] Wang, J. T.; Williams, F. *J. Am. Chem. Soc.* **1981**, *103*, 6994.

[10] Grimison, A.; Simpson, G. A. *J. Phys. Chem.* **1968**, *72*, 1176 and references therein.

[11] (a) Whiffen, D. H. *Mol. Phys.* **1963**, *6*, 223. (b) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *38*, 773; *39*, 2147.

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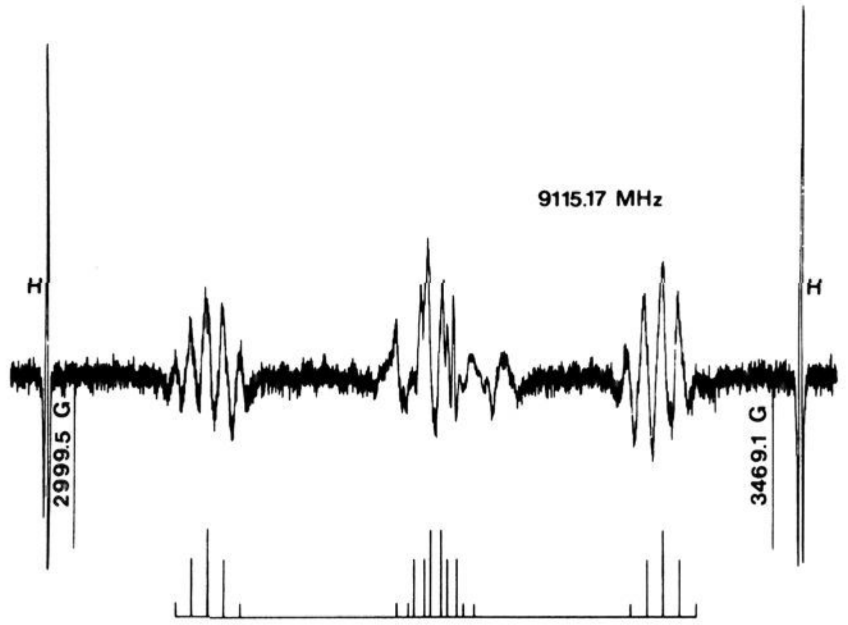

Figure 1. Second-derivative ESR spectrum from a γ-irradiated (dose, 0.8 Mrd) solid solution of 3 mol % 1,3-dioxacyclopentane in fluorotrichloromethane at 90 K. The stick diagram depicts a large triplet due to two equivalent acetal ^1H nuclei further split into a quintet by four equivalent β ^1H nuclei. Second-order splittings are shown for the center component of the triplet, but these features are obscured in the spectra by overlapping signals from extraneous radicals.

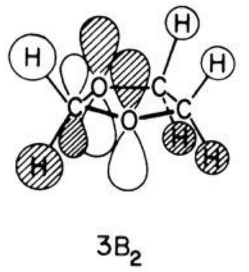

Figure 2. A schematic representation of the 3B$_2$ SOMO for the 1,3-dioxacyclopentane radical cation in C_{2v} symmetry. The molecular plane containing the C_2 (z) axis is designated the σ_v (xz) mirror plane.

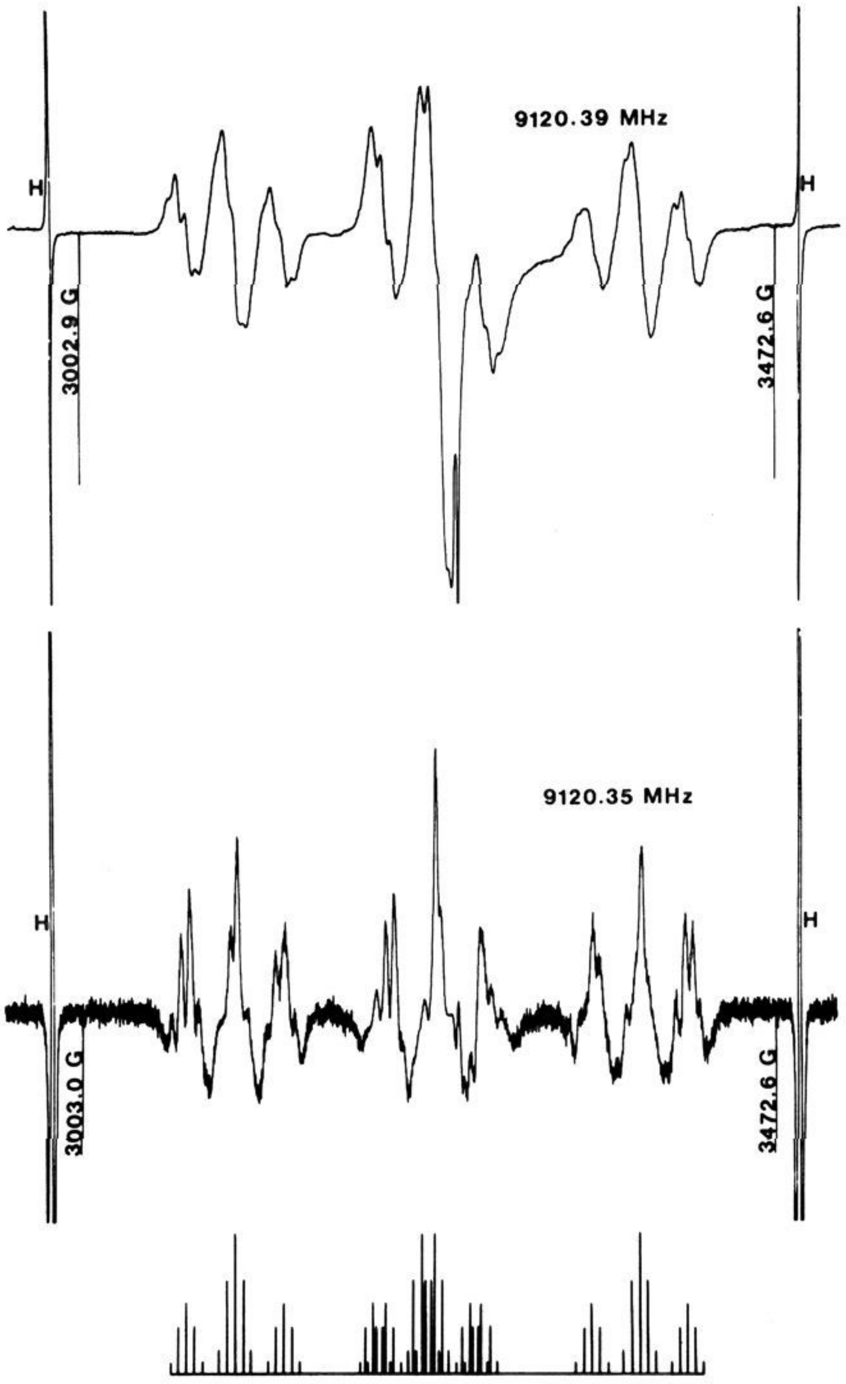

Figure 3. First-derivative and second-derivative ESR spectra from a γ-irradiated (dose, 0.8 Mrd) solid solution of 3 mol % dimethoxymethane in fluorotrichloromethane at 86 K. The stick diagram depicts a large triplet from two equivalent acetal ^1H nuclei, split into a smaller triplet by two equivalent "eclipsed" methyl ^1H nuclei and further split into a quintet by the other four equivalent methyl ^1H nuclei. Second-order splittings are shown for the center component of the triplet, but these features are obscured in the spectra by overlapping signals from extraneous radicals.

coupling to the methylene hydrogens should be approximately double the 76 G deduced for the spin on one adjacent oxygen. The experimental value of 153 G clearly shows that the latter case applies, and accordingly the unpaired electron can be assigned to the 3B$_2$ orbital (Figure 2) in time-averaged C_{2v} symmetry.

In terms of this assignment, the delocalization of the spin density can be viewed as occurring via the bridging CH_2 group. This is in contrast to a 1,3 π-interaction mechanism similar to that proposed for spin delocalization and electron transfer in substituted diphenylmethane radical anions[12,13] and analogous species.[13,14] In the present case, a through-space 1,3 π-interaction mechanism between the p_y orbitals of the oxygen atoms would be equivalent to placing the unpaired electron into the 2A$_2$ orbital. This choice is clearly unsatisfactory, however, since the 2A$_2$ orbital possesses a nodal plane between the two oxygens, and consequently the hyperfine coupling to the methylene hydrogens situated in this plane would be close to zero.

It is also of interest to consider the probable structure of the corresponding sulfur species, especially since radical cations containing two sulfur atoms in an open or cyclic carbon chain have a distinct tendency to form intramolecular σ complexes through interaction between the p orbitals of the sulfur atoms.[15,16] Although no ESR studies appear to have been reported, it has been argued[15] that the almost planar structure of the 1,3-dithiacyclopentane radical cation prevents a mutual p-orbital overlap of the type required to form a σ^* radical with an intramolecular three-electron bond between the two sulfur atoms. In support of this conclusion, no optical absorption identifiable with a $\sigma \rightarrow \sigma^*$ transition was observed for the 2-methyl-1,3-dithiacyclopentane radical cation,[15] and therefore it seems probable that these sulfur analogs are also π radicals.

Table I summarizes the ESR parameters for the 1,3-dioxacyclopentane radical cation and four other species in this class, the largest hyperfine couplings being assigned in each case to the β hydrogens of the bridging CH_2 or CH in the acetal groups. The smaller ^1H couplings originate from the other β hydrogens and, not surprisingly, the results appear to reflect conformational preferences. Also, the equivalence of the four nonacetal β hydrogens for the 1,3-dioxacyclopentane radical cation is not retained in going to the 1,3-dioxacyclohexane radical cation, presumably because of slower ring inversion in the latter case. The results for the *s*-trioxane radical cation show that the spin is not delocalized around the ring but is confined to a single acetal group; since the neutral molecule is highly puckered, this finding probably reflects stringent requirements in terms of a planar system for spin transmission rather than some intrinsic impediment to delocalization over more than two oxygen atoms. In fact, the results for the 2,5-dimethoxytetrahydrofuran radical cation provide clear evidence that the spin is delocalized over three oxygen atoms, the large couplings in this case coming from two equivalent methine hydrogens located on the bridging carbon atoms.

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[12] Young, J. D.; Stevenson, G. R.; Bauld, N. L. *J. Am. Chem. Soc.* **1972**, *94*, 8790.

[13] (a) Gerson, F. *Chimia* **1974**, *28*, 194. (b) Gerson, F.; Martin, W. B., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 1883. (c) McConnell, H. M. *J. Chem. Phys.* **1961**, *35*, 508. (d) Weissman, S. I. *J. Am. Chem. Soc.* **1958**, *80*, 6462.

[14] Jones, M. T.; LaLancette, E. A.; Benson, R. E. *J. Chem. Phys.* **1964**, *41*, 401.

[15] Asmus, K.-D. *Acc. Chem. Res.* **1979**, *12*, 436.

[16] Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200.

Table I. ESR Parameters for Acetal Radical Cations

radical cation	T/K	hyperfine couplings/G	g
1,3-dioxacyclopentane	96	153.0 (2 H)	2.0070
		11.2 (4 H)	
1,3-dioxacyclohexane	83	140.6 (2 H)	2.0086
		26.3 (2 H)	
		12.4 (2 H)	
s-trioxane	89	160.2 (2 H)	2.0065
2,5-dimethoxytetrahydrofuran	125	135.0 (2 H)	2.0066
		32.0 (2 H)	
dimethoxymethane	133	136.1 (2 H)	2.0072
		31.3 (2 H)	
		6.0 (4 H)	

Although the radical cations discussed above are derived from cyclic ethers, π delocalization in three-center [$-O-CH_2-O-$] orbitals is not limited to radical cations where the acetal group forms part of a ring system. Thus, the ESR spectrum of the dimethoxymethane radical cation (Figure 3) shows a characteristically large triplet splitting from the bridging methylene group, and the experimental value of 136.1 G (Table I) agrees very well with the value of 137.4 G derived from INDO calculations in C_{2v} symmetry. It is interesting that the methyl groups are not freely rotating in this radical cation at 133 K, the couplings to two and four equivalent methyl hydrogens indicating that each methyl group adopts an eclipsed conformation such that the methyl group orbital has pseudo-π-symmetry with respect to the C–O–C plane. Finally, the average g factor for these acetal radical cations (Table I) is somewhat lower than the corresponding value of 2.0085 for the dimethyl ether radical cation,[9] as expected since the net spin density on the oxygen atoms is reduced in forming the three-center [$-O-CH_2-O-$] orbital.

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Registry No. 1,3-Dioxacyclopentane radical cation, 81027-69-2; 1,3-dioxacyclohexane radical cation, 81027-70-5; *s*-trioxane radical cation, 81027-71-6; 2,5-dimethoxytetrahydrofuran radical cation, 81076-01-9; dimethoxymethane radical cation, 81027-72-7.

Triphase Catalytic Cyclization. Efficacious Macrolide Synthesis[1]

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In this communication we describe a new approach to the synthesis of large-ring lactones based on the internal esterification of hydroxy acids.[2] Our method is derived, conceptually, from the synergistic coupling of triphase catalysis[3] with the principle of "pseudodilution" within cross-linked polymers.[4] Macrolides prepared in this manner are obtained (1) in good to excellent yields, (2) under relatively mild conditions, and (3) without the use of conventional high-dilution techniques. To the best of our knowledge, the results described herein represent the first successful application of polymer supports to the synthesis of large-ring compounds.

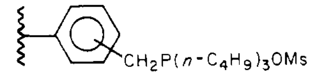
Table I. Triphase Synthesis of 12-Hydroxydodecanoic Acid Lactone[a]

catalyst	yield, %[b]	catalyst	yield, %[b]
none	0	1b	38
1a	66	1c	15
	62[c]	1d	0

[a] Reaction of 2.0 mL of 3×10^{-3} M 12-(methylsulfonyloxy)dodecanoic acid in toluene with 0.5 mL of 1.3×10^{-2} M $KHCO_3$ in water in the presence of 1.2×10^{-2} mmol of polymer-bound phosphonium salt for 20 h at 90 °C; yields were unchanged over an additional 24 h. [b] GLC yield based on 10^{-3} M *n*-hexadecane present as an internal standard. [c] Reused polymer.

Scheme I summarizes the synthetic design of *triphase macrolide synthesis*. A hydroxy acid is first activated by mesylation and then added to a toluene/aqueous bicarbonate/phosphonium mesylate resin (>1 equiv) three-phase system, i. Acid–base reaction ensues followed by ion exchange, ii. Upon being heated, intraresin nucleophilic displacement of "kinetically isolated"[5] pendant groups favors the formation of macrolide monomer over cyclic or acyclic oligomer or polymer and returns the resin to the mesylate form, iii.

So that the synthetic viability of this scheme could be tested, the lactonization of 12-hydroxydodecanoic acid was attempted.[6] 12-Methylsulfonate dodecanoic acid (50 mg, 0.17 mmol) was added in one portion to 60 mL of toluene, 1.0 g of **1a** and 14 mL of aqueous bicarbonate (0.17 mmol), and the resulting three-phase mixture was heated for 20 h at 90 °C.[7] The organic layer was then separated, combined with toluene extracts of the resin and aqueous phase, dried (Na_2SO_4), and concentrated under reduced pressure. Preparative layer chromatography of the residue on silica gel (10% ether in hexane for development) afforded 23 mg (68%) of 12-hydroxydodecanoic acid lactone having an infrared and mass spectrum identical with that of an authentic sample. Use of polymers with a higher loading of pendant methylenetri-*n*-butylphosphonium mesylate groups resulted in a substantial decrease in the yield of lactone (Table I). In the absence of resin or in the presence of unfunctionalized cross-linked polystyrene, no detectable lactone was produced.



1% cross-linked polystyrene gel (200–400 mesh)

1a, percent ring substitution (prs) = 4 (0.3 mequiv/g)
1b, prs = 17 (1.1 mequiv/g)
1c, prs = 52 (2.0 mequiv/g)
1d, prs = 0

Table II summarizes the results obtained for a series of related triphase lactonizations. For comparison, yields reported via the Corey–Nicolaou[8] (thermally induced cyclization of 2-pyridine thiol esters of hydroxy acids) and Kruizinga–Kellog[7] (Cs_2CO_3–DMF-promoted cyclization of ω-iodo acids) procedures are included. In general, triphase cyclization compares favorably with both methods, except for the preparation of a medium-sized ring (n = 7). We presume that in this case internal cyclization is sufficiently slow relative to the frequency with which pendant groups encounter one another that "kinetic isolation" within the polymer is not achieved.[9]

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(1) Supported by the Division of Basic Energy Sciences of the Department of Energy (Contract EG-77-S-02-4446).

(2) Reviews of macrolide synthesis: Nicolaou, K. C. *Tetrahedron* **1977**, *23*, 683. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Back, T. G. *Tetrahedron* **1977**, *33*, 3041. Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.

(3) Review of triphase catalysis: Regen, S. L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 421.

(4) For the concept of "pseudodilution" within cross-linked polymers, see: Mazur, S.; Jayalekshmy, P. *J. Am. Chem. Soc.* **1979**, *101*, 677. Rebek, J., Jr.; Trend, J. E. *Ibid.* **1979**, *101*, 737. Ford, W. T. *J. Org. Chem.* **1981**, *46*, 3756 and references cited therein.

(5) Regen, S. L.; Bolikal, D. *J. Am. Chem. Soc.* **1981**, *103*, 5248.

(6) Hydroxy acids used in this study were obtained by hydrolysis of the corresponding lactones, which were derived from Bayer–Villiger oxidation of commercially available cycloalkanones.

(7) Mesylation was carried out by using procedures similar to those previously described: Kruizinga, W. H.; Kellog, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183.

(8) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

0002-7863/82/1504-2064$01.25/0