

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 Synthesis¹

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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 catalysis³ 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

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

(2) Reviews of macrolide syntheses: 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.

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

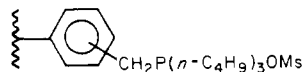
catalyst	yield, % ^b	catalyst	yield, % ^b
none	0	1b	38
1a	66	1c	15
	62 ^c	1d	0

^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.

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.

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-Methylsulfonyl 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



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

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.

Table II summarizes the results obtained for a series of related triphase lactonizations. For comparison, yields reported via the Corey-Nicolaou⁸ (thermally induced cyclization of 2-pyridine thiol esters of hydroxy acids) and Kruizinga-Kellogg⁷ (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

(5) Regen, S. L.; Bollkal, 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.; Kellogg, R. M. *J. Am. Chem. Soc.* 1981, 103, 5183.

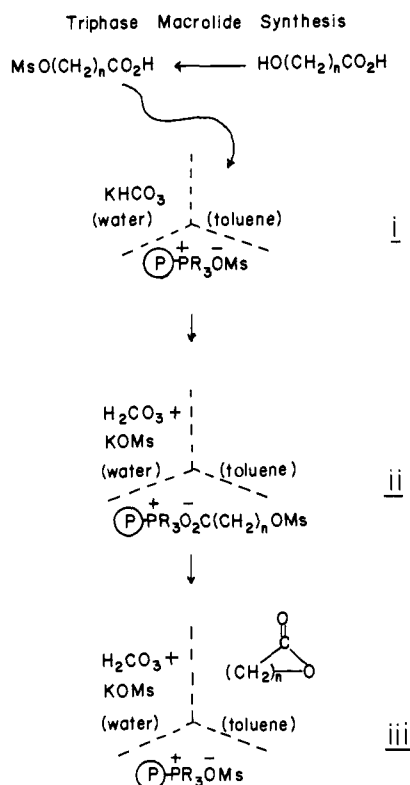
(8) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* 1974, 96, 5614.

Table II. Yields of Lactone (%)^a

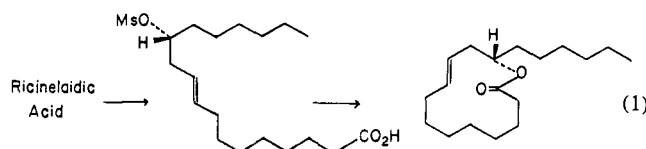
<i>n</i>	ring size	Corey-Nicolaou ^c		
		triphasic cyclization ^b (R = OH, X = OMs)	R = , X = OH	Kruizinga-Kellogg ^d (R = OH, X = I)
7	9	0	25	
10	12	47	64	33
11	13	66	76	62
		68 ^e	66 ^e	
12	14	76	79	77
14	16	72	88	83

^a Yields determined by GLC. ^b Same reaction conditions as described in Table I. ^c Reference 8. ^d Reference 7. ^e Isolated Yield.

Scheme I



Since naturally occurring macrolides are often closed at a secondary hydroxyl group, it was of interest to evaluate the effectiveness and stereochemistry of a triphase cyclization taking place at a secondary carbon. For this purpose, ricinelaidic acid was converted to the corresponding mesylate and subjected to the cyclization conditions described above (see eq 1).^{7,10} Preparative



layer chromatography afforded a 40% isolated yield of ricinelaidic acid lactone having $[\alpha]_D^{21} -38^\circ$. Comparison with the optically pure *R* form of the macrolide having $[\alpha]_D^{20} +42^\circ$ indicates that the displacement proceeds with predominate inversion of configuration.⁷

(9) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* 1981, 14, 95.

(10) Sigma Chemical Co., $[\alpha]_D^{20} +6.6^\circ$ (*c* 1, C₂H₅OH), mp 50.5–52 °C.

Further applications of this new methodology to macrocyclic synthesis are in progress.

Registry No. 11-(Methylsulfonyloxy)undecanoic acid, 80907-73-9; 12-(methylsulfonyloxy)dodecanoic acid, 80907-74-0; 13-(methylsulfonyloxy)tridecanoic acid, 80907-75-1; 15-(methylsulfonyloxy)tetradecanoic acid, 80907-76-2; 11-hydroxyundecanoic acid lactone, 1725-03-7; 12-hydroxydodecanoic acid lactone, 947-05-7; 13-hydroxytridecanoic acid lactone, 1725-04-8; 15-hydroxytetradecanoic acid lactone, 106-02-5; ricinelaidic acid, 540-12-5; ricinelaidic acid mesylate, 78773-30-5; ricinelaidic acid lactone, 69651-29-2.

Lifetime of Singlet Oxygen in Solution Directly Determined by Laser Spectroscopy

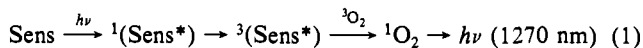
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The properties of singlet oxygen (¹Δ_g, ¹O₂) are of profound importance to the understanding of its role in physical, chemical, and biological transformations.^{1,2} In consideration of its important position there have been numerous studies of this reactant in the gaseous and in the condensed phases. Until recently these studies have been hampered by the unavailability of suitable methods for unambiguously detecting ¹O₂ or for directly measuring its lifetime in solution. Recently phosphorescence characteristic of ¹O₂ at 1270 and 1580 nm has been observed in solution³⁻⁶ and has been used to determine directly its lifetime in a variety of solvents.^{7,8} We have also been engaged in an effort to determine directly the properties of ¹O₂ generated through dye sensitization by monitoring the phosphorescent emission characteristic of this state (eq 1).



(1) (a) "Singlet Molecular Oxygen"; Schaap, A. P., Ed.; Dowden, Hutchinson and Ross, Stroudsburg, Pa., 1976. (b) "Singlet Oxygen, Reactions with Organic Compounds and Polymers"; Ranby, B., Rabek, J. F., Eds.; Wiley: New York, 1978. (c) "Singlet Oxygen"; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979.

(2) Stephenson, L. M.; Gridna, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* 1980, 13, 419.

(3) Peters, J. W.; Pitts, J. N., Jr.; Rosenthal, I.; Fuhr, H. *J. Am. Chem. Soc.* 1972, 94, 4348. Peters, J. W.; Bekowies, P. J.; Winer, A. M.; Pitts, J. N., Jr. *Ibid.* 1975, 97, 3299. This emission may actually have originated within O₂ bubbles in the solution.

(4) Krasnovsky, A. A., Jr. *Photochem. Photobiol.* 1979, 29, 29.

(5) Krasnovsky, A. A., Jr. *Chem. Phys. Lett.* 1981, 81, 443. Krasnovsky, A. A., Jr. *Zh. Prikl. Spektrosk.* 1980, 32, 852.

(6) Khan, A. U.; Kasha, M. *Proc. Natl. Acad. Sci. U.S.A.* 1979, 76, 6047. Khan, A. U. *Chem. Phys. Lett.* 1980, 72, 112.

(7) Salokhiddinov, K. I.; Byteva, I. M.; Gurinovich, G. P. *Zh. Prikl. Spektrosk.* 1981, 34, 892.

(8) Salokhiddinov, K. I.; Dzhagarov, B. M.; Byteva, I. M.; Gurinovich, G. P. *Chem. Phys. Lett.* 1980, 76, 85.