crystallized from 95% EtOH to afford **19c** as a bright yellow solid: 63% yield; mp 138–140 °C; IR (KBr) 1605, 1420, 1385, 1350, 875, 810, 760, 685 cm^{-1}; UV (95% EtOH) λ_{max} 397 nm (log ϵ 3.19), 376 (3.38), 355 (3.28), 350 (3.16), 338 (2.96), 315 (3.99), 296 (4.46), 292 (4.45), 238 (4.55).

Anal. Calcd for $C_{20}H_{12}Cl_2F_2$: C, 66.50; H, 3.35; Cl, 19.63. Found: C, 66.46; H, 3.38; Cl, 19.62.

Benz[*a*]anthracene (19d). The usual procedure using **17c** and *m*-CPBA gave after chromatography **19d** as colorless flakes: 90% yield; mp 165 °C; identical with an authentic sample (IR, UV, TLC, ^{1}H NMR, mmp = 165 °C).

1,2,3,4,8,9,10,11-Octafluorobenz[*a*]anthracene (19e). To a magnetically stirred solution of **16** (0.700 g, 1.56 mmol) and **7b** (0.292 g, 1.56 mmol) in dry THF (50 mL) under N_2 at −78 °C was added dropwise via syringe phenyllithium (1.46 M in cyclohexane; 1.068 mL, 1.56 mmol). The solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 3 h. The mixture was concentrated in vacuo and the residue dissolved in Et_2O (250 mL). The Et_2O solution was washed with H_2O (5 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford crude 13-methyl-1,2,3,4,8,9,10,11-octafluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (**18a**) as a brown paste. This material exhibited appropriate ^{1}H NMR and mass spectra. A solution of crude **18a** and *m*-chloroperbenzoic acid (1 g, 5 mmol) in $CHCl_3$ (50 mL) was stirred under N_2 at 20 °C for 24 h. The solution was concentrated in vacuo and the residue was chromatographed over activity III basic alumina with hexane elution to afford 0.22 g (38% from **7b**) of **19e** as a yellow solid: mp 173–174 °C; UV (95% EtOH) λ_{max} 387 nm (log ϵ 3.20), 368 (3.38), 356 (3.69), 3.48 (3.73), 340 (3.85), 332 (3.80), 325 (3.81), 298 (4.27), 274 (4.76), 270 (4.76), 220 (4.48); mass spectrum, *m/e* 372 (M^+, 100), 352, 341, 321, 303, 186.

Anal. Calcd for $C_{18}H_4F_8$: C, 58.08; H, 1.08. Found: C, 58.16; H, 1.58.

1,2,3,4-Tetrafluorobenz[*a*]anthracene (5). The same procedure as described above for the preparation of **19e** but employing **7a**, **14b**, and LTMP followed by oxidation with *m*-CPBA gave **5** (ca. 25% overall yield) as yellow needles from benzene: mp 220–225 °C.

Anal. Calcd for $C_{18}H_8F_4$: C, 72.00; H, 2.69. Found: C, 72.10; H, 2.72.

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Registry No. **3**, 62209-62-5; **5**, 95785-05-0; **7a**, 33804-84-1; **7b**, 38053-09-7; **7c**, 95785-06-1; **7d**, 95785-07-2; **7e**, 95785-08-3; **7f**, 95785-09-4; **8a**, 344-07-0; **10a**, 5875-75-2; **10b**, 76137-28-5; **10c**, 86909-51-5; **10d**, 54989-05-8; **10e**, 86909-55-9; **11a**, 342-55-2; **11b**, 90948-03-1; **11c**, 42768-98-9; **12**, 715-44-6; **13**, 715-32-2; **14a**, 95785-10-7; **14b**, 31322-32-4; **15**, 95785-11-8; **16**, 95785-12-9; **17a**, 62209-95-4; **17a**·HCl, 95785-13-0; **17b**, 95785-14-1; **17c**, 95785-15-2; **17d** (isomer 1), 95785-16-3; **17d** (isomer 2), 95785-17-4; **17e** (isomer 1), 95785-18-5; **17e** (isomer 2), 95785-19-6; **18a**, 95785-20-9; **19a**, 95785-21-0; **19b** (isomer 1), 95785-22-1; **19b** (isomer 2), 95785-23-2; **19c** (isomer 1), 95785-24-3; **19c** (isomer 2), 95785-25-4; **19d**, 56-55-3; **19e**, 95785-26-5; 1-bromo-2-naphthylamine hydrochloride, 80413-60-1; α,α'-dibromo-*o*-xylene, 91-13-4; methylhydrazine, 60-34-4; 1-bromo-2-naphthol, 573-97-7; furan, 110-00-9.

Synthesis and Cyclization of Polymer-Supported 12-Hydroxydodecanoic Thiol Esters

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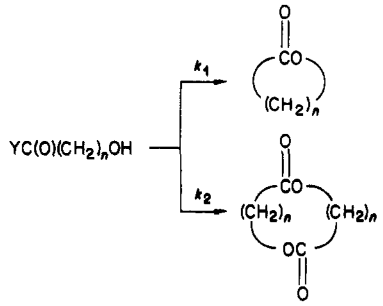
12-Hydroxydodecanoic thiol esters were synthesized on 2% cross-linked polystyrene supports to test the ability of the support to improve yields of intramolecular cyclization to lactone. With mercuric trifluoroacetate in dichloromethane, 0.03 M polymer-supported 12-hydroxydodecanoic thiol ester cyclized to 13% 12-dodecanolide and 19% of the corresponding diolide. Under otherwise similar conditions, 0.01 M model thiol ester gave <2% each of monolide and diolide. In acetonitrile, 0.01 M model thiol ester gave 26% and 35% yields of monolide and diolide.

Many methods of synthesis of macrocyclic lactones have been developed recently because of the importance of macrolide antibiotics.[1-3] The most generally useful methods, such as thermal transesterifications of 2-pyridinethiol esters[4,5] and cyclizations of less activated thiol esters promoted by thiophilic metal salts,[2,6] effect closure of an ω-hydroxy carboxylic acid under neutral conditions. The cyclizations must be performed by a high dilution method to minimize formation of dimeric and higher oligomeric byproducts which arise from intermolecular rather than intramolecular transesterification (eq 1).



(1)

Typically the thiol ester is added dropwise with a syringe

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[1] Nicolau, K. C. *Tetrahedron* **1977**, *33*, 683–710.

[2] Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew, Chem., Int. Ed. Engl.* **1977**, *16*, 585–607.

[3] Back, T. G. *Tetrahedron* **1977**, *33*, 3041–3059.

[4] Corey, E. J.; Nicolau, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616.

[5] Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, *31*, 2875–2878.

[6] Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513–3515.

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Table I. Degrees of Functionalization of Polymer-Bound Reagents

polymer[a]	mesh size	mequiv functional group/g[b] (% of rings substituted) 1	2	3	4
2–25	100/200	1.67 (19)	1.67 (19)	1.10 (19)	1.26 (19)
2–6	60/100	0.41 (4.4)	0.32 (3.4)	0.29 (3.4)	0.26 (3.0)
20–10	100/200	0.66[c] (7.6)	0.50 (5.7)	0.17 (2.0)	0.15 (1.8)

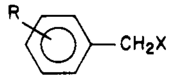
[a] % DVB – % (chloromethyl)styrene in copolymer 1. [b] Based on Cl, S, and Si elemental analyses. [c] 35% toluene was used as diluent in the organic phase during polymerization.

pump over many hours to a large volume of solvent. Usual concentrations of lactone at the end of the reaction are 1–10 mM. The large volume of solvent required makes high dilution syntheses impractical for all but small-scale reactions.

The competition between unimolecular and bimolecular esterification of ω-hydroxy carboxylic acids (at rate constants k_1 and k_2) has been described by the cyclization constant $C = k_1/k_2$.[7,8] At reactant concentration C the rates of intra- and intermolecular esterification are equal. More recently, C has been called EM (effective molarity), and EM values for numerous syntheses of medium and large rings have been summarized.[9] In principle either acceleration of the unimolecular reaction or retardation of the bimolecular reaction could be used to overcome the requirement for high dilution in synthesis of medium and large rings. The former has been accomplished in some crown ether syntheses by carrying out the synthesis in the presence of a metal ion which stabilizes the transition state for cyclization.[10] Template syntheses, however, are not general. The bimolecular reaction leading to dimers and oligomers should be retarded if the reactant is immobilized. This paper describes the use of cross-linked polystyrene supports to immobilize 12-hydroxydodecanoic thiol esters for lactonization at much higher concentrations than those used in high dilution syntheses. Other polymer-supported methods for medium and large ring lactonization have been reported.[12–15]

Results

Syntheses of the polymer-supported thiol esters were carried out by conversion of poly(styrene-*co*-(chloromethyl)styrene) (1) to thiol 2 via basic hydrolysis of the thiouronium salt, *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling of *O*-*tert*-butyldimethylsilyl-protected 12-hydroxydodecanoic acid with 2 to give thiol ester 3 and deprotection with aqueous trifluoroacetic acid to give 4. Results are in Table I. Three different copolymers were used: 2 wt % divinylbenzene (DVB) and 25 wt % (chloromethyl)styrene (2–25); 2% DVB and 6% (chloromethyl)styrene (2–6); and macroporous 20% DVB and 10% chloromethylstyrene (20–10). Repeated washings with swelling and shrinking solvents were necessary to remove byproducts after the thiouronium salt hydrolyses and the DCC couplings. Attempted deprotection of the *O*-*tert*-butyldimethylsilyl ethers 3 with tetra-*n*-butylammonium fluoride in tetrahydrofuran (THF) cleaved the thiol ester linkage also. The times and concentration of aqueous trifluoroacetic acid for conversion of 3 to 4 reported in the Experimental Section were critical. The polymer-supported reagents were characterized by elemental analysis and by IR and ^{13}C NMR spectral analyses. The NMR data are in Table II. Sample spectra are published elsewhere.[16]



1–4, R = polystyryl, **1**; X = Cl
2; X = SH
3; X = $SC(O)(CH_2)_{11}OSi(CH_3)_2C(CH_3)_3$
4; X = $SC(O)(CH_2)_{11}OH$

5–7, R = H, **5**; X = SH
6; X = $SC(O)(CH_2)_{11}OSi(CH_3)_2C(CH_3)_3$
7; X = $SC(O)(CH_2)_{11}OH$

The model benzyl thiol ester 7 was synthesized by the same method. Cyclizations of 0.01 M 7 are reported in Table III. The reactant concentration was deliberately chosen too high for high yield syntheses for purposes of comparison with the polymer-supported cyclizations. Potassium *tert*-butoxide in THF and mercuric trifluoroacetate in acetonitrile were the most effective cyclizing reagents, and both produced more of diolide 9 than of monolide 8. Products 8 and 9 were isolated by flash chromatography and distinguished by the greater chromatographic mobility and the longer ^{13}C NMR spin–lattice relaxation times of the monolide. The ^{13}C NMR data are in Table IV. Electron impact mass spectra did not reveal molecular ions for 8 and 9, but field desorption and field ionization mass spectra did.

All conditions that gave significant yields of lactones from polymer-supported thiol esters 4 are reported in Table V. The thiol ester concentrations in the entire reaction mixtures were 0.03 to 0.10 M, even higher than that used with the model thiol ester 7. The thiol ester concentrations within the polymer beads were higher still, because the concentrations in Table V include the external solvent. The cyclizations promoted by potassium *tert*-butoxide also produced 1–7% yields of *tert*-butyl 12-hydroxydodecanoate. The cyclizations promoted by mercuric trifluoroacetate also gave 12-(trifluoroacetoxy)dodecanoic acid (10), which was identified by IR, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectral analyses (see Table IV and the Experimental Section). After every experiment the recovered polymer beads were analyzed by ^{13}C NMR spectroscopy. In some cases residual starting thiol ester was detected as reported in Table V. In all cases an unidentified polymer-bound byproduct having a CH_2O peak at 64.3 ppm was detected. At shorter reaction times than those in Table V for mercuric trifluoroacetate promoted cyclization in dichloromethane, lower yields and residual polymer-bound thiol ester were observed.

Acetonitrile was the most effective solvent for mercuric trifluoroacetate promoted cyclization of model thiol ester 7, but it did not swell the polymer and gave <1% of either monolide 8 or diolide 9 with the polymer-supported thiol esters 4. Dichloromethane was the only effective solvent found for mercuric trifluoroacetate promoted lactonization of 4. A variety of other solvents, all of which swelled the polymer 4 (2–25) to at least 3 times its dry volume, were tried with mercuric trifluoroacetate. Use of THF, benzonitrile, trichloroacetonitrile, 4-morpholinecarbonitrile,

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[7] Stoll, M.; Rouve, A.; Stoll-Comte, G. *Helv. Chim. Acta* **1934**, *17*, 1289–1308.

[8] Stoll, M.; Rouve, A. *Helv. Chim. Acta* **1935**, *18*, 1087–1125.

[9] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.

[10] Gokel, G. W.; Korzeniowski, S. H. "Macrocyclic Polyether Syntheses"; Springer-Verlag: Berlin, 1982.

[11] Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.* **1981**, *46*, 3209–3214.

[12] Scott, L. T.; Naples, J. O. *Synthesis* **1976**, 738–739.

[13] Regen, S. L.; Kimura, Y. *J. Am. Chem. Soc.* **1982**, *104*, 2064–2065.

[14] Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940–5942.

[15] Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598–3600.

[16] Ford, W. T.; Mohanraj, S.; Periyasamy, M. *Brit. Polym. J.* **1984**, *16*, 179–187.

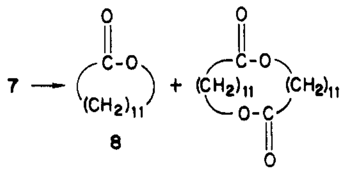
Table II. ^{13}C NMR Spectral Data

$$\overset{g}{\text{R-CO}}\text{-}\overset{f}{\text{CH}_2}\text{-}\overset{e}{\text{CH}_2}\text{-}\overset{d}{(\text{CH}_2)_6}\text{-}\overset{c}{\text{CH}_2}\text{-}\overset{b}{\text{CH}_2}\text{-}\overset{a}{\text{CH}_2}\text{-OX}$$

carbon	X = H, R = OH	X = SiMe$_2$-*t*-Bu, R = OH	X = SiMe$_2$-*t*-Bu, R = SCH$_2$Ph (6)	X = H, R = SCH$_2$Ph (7)	X = SiMe$_2$-*t*-Bu, R = SCH$_2$-PS[a] (3)	X = H, R = SCH$_2$-PS[a] (4)
a	62.85	63.36	63.31	62.86	63.26	62.78
b, f	32.55	32.93	32.87	32.72	32.86	32.68
	34.06	34.16	33.10	33.06		
c, e	25.67	25.88	25.78	25.68	25.99	25.67
	24.68	24.77	25.60	25.54		
d	29.34	29.50	29.57	29.47	29.45	29.36
	29.13	29.32	29.48	29.34		
	29.00	29.14	29.41	29.13		
			29.21	28.86		
			28.93			
g	179.10	180.00	198.87	198.61	*b*	*b*
Si(*C*H$_3$)$_2$		−5.12	−5.26		−5.21	
SiC(*C*H$_3$)$_3$		26.05	25.98		25.99	
Si*C*(CH$_3$)$_3$		18.46	18.36		18.38	
*C*H$_2$S			43.83	43.75	43.79[c]	43.70[c]
aryl ortho, meta			128.56	128.37		
			128.76	128.55		
aryl para			127.16	126.97		
aryl ipso			137.73	137.50		

[a] 3(2–25) and 4(2–25); PS = polystyryl. Spectra were obtained with 5-mm tubes in CDCl$_3$ at 75.43 MHz, spectral width 16000 Hz, 90° pulse, acquisition time 0.5 s. No delay between pulses was used with polymer samples; a 6-s delay was used otherwise. [b] Not observed since there was no delay between pulses. [c] Broadened due to overlapping with CH$_2$ of polymer backbone.

Table III. Cyclizations of Thiol Ester 7



concn of 7, M	reagent[a]	solvent	time, h	yield,[b] % 7	8	9
0.0098	*t*-BuOK	THF	0.4	0	8	51
0.0100	AgOCOCF$_3$	THF	30	70	0	0
0.0100	AgOSO$_2$CF$_3$	THF	120	35	<2	28
0.0098	Cu(OSO$_2$CF$_3$)$_2$	CH$_3$CN	192	75	0	0
0.0093	Hg(OCOCF$_3$)$_2$	THF	1.6	0	<2	0
0.0094	Hg(OCOCF$_3$)$_2$	CH$_3$CN	15	0	26	35
0.0098	Hg(OCOCF$_3$)$_2$	CH$_3$CN	0.6	0	23	30
0.0096	Hg(OCOCF$_3$)$_2$	CH$_2$Cl$_2$	0.8	0	2	2

[a] 0.02 M except for *t*-BuOK, 0.01 M. [b] Isolated yields after flash chromatography.

Table IV. ^{13}C NMR Spectra of Macrolide 8, Diolide 9, and HOOC(CH$_2$)$_{11}$OCOCF$_3$ (10)[a]

8		9		10	
ppm	T_1, s	ppm	T_1, s	ppm	T_1, s
24.19	3.04	25.32	1.02	24.71	1.21
24.51	2.68	26.08	1.10	25.54	1.61
24.93	2.76	28.62	0.96	28.15	1.82
25.37	2.85	28.93	0.64	29.08	1.33
26.40	3.01	29.14	1.25	29.24	1.24
26.60	3.05	29.40	1.16	29.40	1.24
27.41	2.75	29.47		29.45	
34.67	2.78	29.52		34.16	0.91
64.58	2.65	29.70		68.36	1.80
174.18	*b*	34.75	0.93	114.64 q, J = 286	*b*
		64.13	0.89	157.63 q, J = 41	*b*
		173.96	*b*	180.56	*b*

[a] CDCl$_3$, 24 °C, 75.43 MHz. [b] Not determined; T_1 > 10 s.

nitrobenzene, 3-methylsulfolane, and 1,1,2-trichloro-2,2,1-trifluoroethane containing 2 molar equiv of mercuric trifluoroacetate in >16 h at room temperature all resulted in complete loss of thiol ester from 0.08–0.10 M polymer 4(2–25) and 0.03 M polymer 4(2–6) but <1% yields of either 8 or 9. The major product isolated was trifluoroacetate 10 in a highest yield of 86% from 4(2–25) in THF.

Discussion

All of the functional group transformations (Table I) of the 19% ring-substituted polymers 1(2–25) to 4(2–25) proceeded in quantitative yield. With the more lipophilic 1(2–6) conversion to thiol 2(2–6) and cleavage of the *tert*-butyldimethylsilyl ether of 3(2–6) in aqueous trifluoroacetic acid proceeded in 78% and 88% yields. With the more rigid 20% cross-linked macroporous 1(20–10) and 3(20–10) those reactions gave 76% and 88% yields, respectively. The DCC coupling of *tert*-butyldimethylsilyl-protected 12-hydroxydodecanoic acid with the 20% cross-linked thiol 2(20–10) gave only 35% yield because the bulky reagent could not penetrate to many of the thiol sites in the more highly cross-linked network.

The ^{13}C NMR spin–lattice relaxation times in Table IV provide qualitative information on the rotational mobility of 8, 9, and 10. The T_1's of monolide 8 are longer than those of diolide 9 because of faster overall rotational diffusion of the monolide. The T_1's of monolide 8 are all almost equal, which indicates that rotation about single bonds in the 13-membered ring does not effect dipolar relaxation. The T_1's of diolide 9 vary from carbon to carbon, which indicates that the single bonds in the 26-membered ring have rotational freedom. There is an increase in T_1's from 0.91 s for HO$_2$CCH$_2$ to 1.80 s for *C*H$_2$O$_2$CCF$_3$ of 10, as expected for increased rotational mobility about C–C bonds away from the hydrogen-bonded carboxylic acid group.

Mercuric trifluoroacetate in acetonitrile provided by far the best cyclizations of 0.01 M *S*-benzyl 12-hydroxythiododecanoate (7) to dodecanolide 8. The yields of 8 correspond with a cyclization constant *C* of 1.1 × 10^{-3} M, calculated according to Stoll.[8] This *C* is a minimum value because isolated rather than GC yields were used in the calculation. In contrast, acid-catalyzed cyclization of 12-hydroxydodecanoic acid to 8 gave *C* = 2.7 × 10^{-4} M.[8] THF and dichloromethane were poor solvents for the mercuric

Table V. Cyclizations of Polymer-Supported 12-Hydroxydodecanoic Thiol Esters 4

polymer[a]	solvent	thiol ester, M	reagent, M	time, h	yield isolated, % 8	9	other
2–25	THF	0.10	*t*-BuOK, 0.10	2.2	0	18	*b*
2–6	THF	0.04	*t*-BuOK, 0.04	0.6	0	8	*c*
20–10[g]	THF	0.03	*t*-BuOK, 0.03	2.1	0	10	*d*
2–25	THF	0.06	$AgOSO_2CF_3$, 0.12	23.5	0	5	*e*
2–25	CH_2Cl_2	0.08	$Hg(O_2CCF_3)_2$, 0.16	29	7	9	*f*
2–6	CH_2Cl_2	0.03	$Hg(O_2CCF_3)_2$, 0.07	31	13	19	
20–10[g]	CH_2Cl_2	0.03	$Hg(O_2CCF_3)_2$, 0.06	29	<2	<2	

[a] % DVB − % (chloromethyl)styrene in copolymer 1. [b] 18% of trimer and higher oligomers and 7% of *tert*-butyl 12-hydroxydodecanoate. Recovered polymer showed in the CH_2O region of the ^{13}C NMR spectrum a 1:3 ratio of starting material (62.8 ppm) to side product (64.3 ppm). [c] 2% of trimer and higher oligomers and 2% of *tert*-butyl 12-hydroxydodecanoate. ^{13}C NMR of recovered polymer showed 5:2 starting material to side product. [d] 3% of trimer and higher oligomers and 7% of *tert*-butyl 12-hydroxydodecanoate. ^{13}C NMR of recovered polymer showed 1:5 starting material to side product. [e] 2% of trimer and higher oligomers. ^{13}C NMR of recovered polymer showed 1:4 starting material to side product. [f] No starting thiol ester remained on recovered polymer by ^{13}C NMR analysis. [g] Polymer swelled <1.5 times dry volume.

trifluoroacetate promoted cyclization of the model thiol ester 7.

The isolated yields of 8% of macrolide 8 and 51% of diolide 9 from 0.01 M thiol ester 7 and potassium *tert*-butoxide in THF may be compared with GC yields by the syringe pump method of (a) 58% of 8 from a 12-hydroxydodecanoic thiol ester in which the thiol fragment contained a crown-6 ether to act as a template for cyclization and (b) 9% of 8 from the thioethyl ester analogue of 7 with added 19-crown-6 ether.[11] In the syringe pump experiments the substrate concentration could never have exceeded 0.001 M and was certainly ≪0.001 M during most of the experiment. Our yield of 8 from 0.01 M 7 is lower than in the syringe pump experiments, but the high dilution method deliberately was not employed.

Since acetonitrile worked best for the mercuric trifluoroacetate promoted cyclization of model compound 7, it was the first solvent tried with the polymer-supported thiol esters 4. It failed to swell the 2% cross-linked polymers and to produce 8. However, cyclization yields using 0.08 M polymer 4(2–25) and 0.03 M polymer 4(2–6) with mercuric trifluoroacetate in dichloromethane were markedly higher than with 0.01 M of model thiol ester 7 in dichloromethane (Tables III and V). The minimum value of C for cyclization of 4(2–6) is 1.2×10^{-3} M. The improved yield with the polymer support may be attributed to (a) the ability of the polymer to retard bimolecular side reactions leading to oligomers and/or (b) a solvent effect of the polystyrene. Since a wide variety of swelling solvents proved inferior to dichloromethane for cyclization of 4, the reduced mobility of the polymer-supported species most likely is responsible for the higher yield of 8.

Data in Tables III and V and in the Results section show unpredictable solvent effects on yields of cyclization of 4 and 7 promoted by thiophilic metal salts. A good swelling solvent, such as dichloromethane, is one requirement for cyclization of the polymer-supported thiol ester, but numerous other swelling solvents and the nonswelling solvent acetonitrile failed. Yet acetonitrile was the most effective solvent for cyclization of the model thiol ester 7. Similar unpredictable solvent effects on transesterifications of thiol esters promoted by metal salts are well-known.[17]

Four other groups have carried out macrolide syntheses with insoluble reagents or catalysts. Cyclization of 0.1 to 0.5 M bis-benzenesulfonyl carbanion with a polymer-bound (π-allyl)palladium complex derived from a polymer-bound palladium catalyst and a vinyl epoxide proceeded in 70–87% yield to a 17-membered lactone.[14] Lactonization of 0.15 M 12-hydroxydodecanoic acid in THF with diethyl azodicarboxylate and polymer-bound triarylphosphine gave a 10% yield,[15] which probably could be improved by use of a lower phosphine concentration in the polymer and a modest reduction in overall substrate concentration. Cyclization of 2.3×10^{-3} M potassium 12[(methylsulfonyl)oxy]dodecanoate by triphase catalysis[13] and BF_3-catalyzed lactonization of 7.7×10^{-3} M ω-hydroxy carboxylic acids in the presence of unsubstituted polystyrene beads[12] do not overcome the problem of high dilution. Solid–liquid phase-transfer-catalyzed cyclization of potassium 12-bromododecanoate gave up to 95% GC yield of lactone with 0.1 mmol of substrate suspended in 1 mL of toluene.[18] Our cyclizations of 4 with mercuric trifluoroacetate in dichloromethane support the principle of improved intramolecular cyclization with an immobilized reactant, but the yields are unsatisfactory. None of these methods has been applied so far to the synthesis of a macrolide antibiotic.

Experimental Section

The cross-linked copolymers of (chloromethyl)styrene (Dow Chemical Co. vinylbenzyl chloride, a 70/30 meta/para mixture) were prepared as before.[19] Mercuric trifluoroacetate (Aldrich, 98%) was dried at 65 °C under vacuum over KOH for 16 h. Tetrahydrofuran (THF) was freshly distilled from potassium under argon. Acetonitrile was freshly distilled from calcium hydride under argon. Benzonitrile, trichloroacetonitrile, nitrobenzene, dichloromethane, 1,1,2-trichlorotrifluoroethane (Freon 113), and 3-methylsulfolane were distilled from P_2O_5 under argon or vacuum. 4-Morpholinecarbonitrile was passed through 3-Å molecular sieves and distilled at 64 °C (0.4 mm). All experiments were done under an atmosphere of argon.

IR spectra of thin films of liquids or of KBr wafers of polymers were recorded on a Perkin-Elmer 681 spectrophotometer. ^1H NMR spectra at 300 MHz and ^{13}C NMR spectra at 75.43 MHz were recorded in $CDCl_3$ on a Varian XL-300 spectrometer. ^{13}C NMR spectra of polymer gels swollen in $CDCl_3$ were obtained at 25.2 MHz on a Varian XL-100(15) instrument equipped with a Nicolet TT-100 PFT accessory. Elemental analyses were carried out by Galbraith Laboratories (Knoxville, TN) or MicAnal (Tucson, AZ). GC analyses were performed on a Hewlett Packard Model 5840A gas chromatograph with a 6 ft × 0.125 in. o.d. column of 20% SE-30 on 80/100-mesh Chromosorb W and a thermal conductivity detector. Analtech uniplates (silica gel GHLF, 250 μm) were used for analytical TLC. Silica gel, 10 ± 4 μm (Analtech), was used for flash chromatography. A wrist-action shaker was used for polymeric reactions.

12-[(*tert*-Butyldimethylsilyl)oxy]dodecanoic Acid. A solution of 10 g of 12-hydroxydodecanoic acid (Aldrich) in 200

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(17) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

(18) Kimura, Y.; Regen, S. L. *J. Org. Chem.* **1983**, *48*, 1533–1534.

(19) Balakrishnan, T.; Ford, W. T. *J. Appl. Polym. Sci.* **1982**, *27*, 133–138.

mL of methanol was refluxed with 1 mL of concentrated HCl for 18 h. Usual workup of the reaction mixture gave 10.33 g (97%) of methyl 12-hydroxydodecanoate: IR 3370, 2930, 2855, 1745 cm^{-1}; ^{1}H NMR (60 MHz) δ 3.63 (3 H, s), 3.57 (2 H, t, *J* = 6), 2.75 (1 H, br), 2.30 (2 H, t, *J* = 7), and 1.27 (18 H, s, br).

A mixture of 10.325 g of methyl 12-hydroxydodecanoate, 8.18 g of *tert*-butyldimethylsilyl chloride, and 7.66 g of imidazole in 40 mL of DMF was stirred for 19 h. Usual workup of the reaction mixture followed by distillation (160–165 °C, 0.25 mm) afforded 12.7 g (82%) of methyl 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoate: IR 2930, 2855, 1745, 1255, 1100, 835, 775 cm^{-1}; ^{1}H NMR (60 MHz) δ 3.64 (3 H, s), 3.59 (2 H, t, *J* = 6), 2.30 (2 H, t, *J* = 7), 1.27 (18 H, s, br), 0.89 (9 H, s), 0.05 (6 H, s).

A solution of 12.7 g of methyl 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoate in 12 mL of THF and 12 mL of methanol was stirred with 1.82 g of NaOH in 14 mL of H_2O at room temperature for 24 h. The reaction mixture was cooled to 0 °C, acidified with 10% aqueous HCl, and extracted with ether. The ether extract was washed with water, dried, and evaporated to furnish 11.89 g (98%) of 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid: IR 3600–2400, 2940, 2865, 1715, 1260, 1100, 835, 775 cm^{-1}; ^{1}H NMR δ 9.9 (1 H, br), 3.61 (2 H, t, *J* = 6.7), 2.34 (2 H, t, *J* = 7.2), 1.63 (2 H, t, br), 1.51 (2 H, t, br), 1.27 (14 H, s, br), 0.89 (9 H, s), 0.05 (6 H, s); ^{13}C NMR data are in Table II.

***S*-Benzyl 12-Hydroxythiododecanoate (7).** A mixture of 2.9 g of 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid, 2.28 g of *N*,*N*′-dicyclohexylcarbodiimide, and 100 mg of 4-(dimethylamino)pyridine in 40 mL of THF was stirred with 1.1 mL of benzyl mercaptan at room temperature for 22 h. The reaction mixture was filtered; the filtrate after rotary evaporation and chromatography over silica gel gave 3.82 g (99.8%) of thiol ester **6**: IR 2930, 2855, 1695, 1255, 1095, 835, 770, 695 cm^{-1}; ^{1}H NMR δ 7.30 (5 H, m), 4.13 (2 H, s), 3.60 (2 H, t, *J* = 6.7), 2.56 (2 H, t, *J* = 7.2), 1.66 (2 H, t, br), 1.50 (2 H, t, br), 1.27 (14 H, s, br), 0.90 (9 H, s), 0.05 (6 H, s); ^{13}C NMR data are in Table II.

A solution of 3.36 g of **6** in 50 mL of THF was stirred with 6 mL of CF_3COOH and 2 mL of water at room temperature for 1 h. The reaction mixture was diluted with ether and washed with water, sodium bicarbonate solution, and water. The organic layer was dried and rotary evaporated. Recrystallization of the residue from ether furnished 2.11 g (85%) of **7**: mp 67–69 °C; IR 3230, 2930, 2920, 2850, 1690, 1455, 1405, 1065, 705, 695 cm^{-1}; ^{1}H NMR δ 7.29 (5 H, m), 4.13 (2 H, s), 3.64 (2 H, t, *J* = 6.3), 2.56 (2 H, t, *J* = 7.2), 1.71 (1 H, br), 1.67 (2 H, t, br), 1.56 (2 H, t, br), 1.26 (14 H, s, br); ^{13}C NMR data are in Table II.

Polymer-supported thiol 2(2–25) was prepared from 20 g of 2% divinylbenzene (DVB) cross-linked poly(styrene-*co*-(chloromethyl)styrene) (1.665 mequiv of Cl/g) and thiourea to give a thiouronium salt,[20] followed by phase-transfer-catalyzed basic hydrolysis of the thiouronium salt[20] to 15.55 g of **2**(2–25): 1.67 mequiv S/g by S analysis; IR 3060, 3025, 2920, 2565 (weak), 1601, 1495, 1450, 755, 695 cm^{-1}; ^{13}C NMR 145.41, 127.46, 125.62, 123.46, 43.51, 40.39, 28.92 ppm.

Thiol Ester 3(2–25). A mixture of 6.006 g of **2**(2–25) (1.67 mequiv S/g), 4.146 g of 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid, 2.594 g of *N*,*N*′′-dicyclohexylcarbodiimide, and 85 mg of 4-(dimethylamino)pyridine ether 45 mL of THF was shaken at room temperature for 48 h. The reaction mixture was filtered and washed with THF 5 times, [THF/water (3/1 v/v) 2 times, water 2 times] 5 times, dichloromethane 2 times, ether 2 times, acetone 2 times, and methanol 3 times. The polymer beads were dried at 65 °C under vacuum for 14 h to give 8.068 g of **3**(2–25): 1.10 mequiv of S and 1.10 mequiv of Si/g by elemental analyses; IR 3030, 2930, 2855, 1695, 1601, 1490, 1450, 1255, 1095, 835, 770, 700 cm^{-1}; ^{13}C NMR data are in Table II.

Polymer-Supported 12-Hydroxydodecanoic Thiol Ester 4(2–25). A mixture of 6.174 g of **3** (1.10 mequiv S/g and 1.10 mequiv Si/g), 37 mL of THF, 6 mL of CF_3COOH, and 1.8 mL of water was shaken at room temperature for 3 h. The mixture was filtered and washed with THF 4 times, [THF/water (3/1 v/v) 2 times, water 2 times] 6 times, dichloromethane 2 times, acetone 3 times, and methanol 3 times. The polymer beads were dried at 65 °C under vacuum for 9 h to furnish 5.238 g of **4**(2–25): 1.26 mequiv S/g; IR 3420, 3030, 2925, 2855, 1690, 1601, 1495, 1455, 1030, 760, 700 cm^{-1}; ^{13}C NMR data are in Table II.

Cyclization of *S*-Benzyl 12-Hydroxythiododecanoate (7). A solution of 189 mg (0.586 mmol) of **7** in 60 mL of acetonitrile was stirred with 475 mg (1.12 mmol) of mercuric trifluoroacetate at room temperature for 34 min. Rotary evaporation of the reaction mixture followed by flash chromatography over silica gel gave 27 mg (23%) of macrolide **8** and 35 mg (30%) of diolide **9**. Data for **8**: IR 2930, 2860, 1740, 1250, 1145 cm^{-1}; ^{1}H NMR δ 4.18 (2 H, t, *J* = 5.3), 2.37 (2 H, t, *J* = 5.8), 1.66 (4 H, m), 1.40 (m) and 1.34 (s) [14 H]; ^{13}C NMR data are in Table IV; MS (field ionization), *m*/*z* 198 (M^+, 100%). Data for diolide **9**: mp 97–99 °C; IR 2920, 2850, 1730, 1260 cm^{-1}; ^{1}H NMR δ 4.13 (2 h, t, *J* = 6.2), 2.33 (2 H, t, *J* = 6.7), 1.62 (4 H, m), 1.28 (14 H, s, br); ^{13}C NMR data are in Table IV; MS (field desorption), *m*/*z* 397 (M + 1, 100%), 396 (M^+, 43%).

Cyclization of 4. A mixture of 619 mg (0.162 mmol) of **4**(2–6), 150 mg (0.35 mmol) of mercuric trifluoroacetate, and 5 mL of dichloromethane was shaken at room temperature for 31 h. The reaction mixture was filtered, and the polymeric beads were washed with [dichloromethane 2 times, and ether 3 times] 4 times. Rotary evaporation of the filtrate and flash chromatography furnished 4 mg (13%) of the macrolide **8** (identical with authentic sample in GC, IR, ^{1}H, and ^{13}C NMR) and 6 mg (19%) of the diolide **9** (identical with authentic sample in IR, ^{1}H, and ^{13}C NMR).

Characterization of 12-(Trifluoroacetoxy)dodecanoic Acid (10). Reaction of **4** with mercuric trifluoroacetate in solvents such as THF and CH_3CN gave **10** (see Results section): IR 3500–2400, 2925, 2855, 1790, 1715, 1350, 1220, 1160 cm^{-1}; ^{1}H NMR δ 10.64 (1 H, br), 4.38 (2 H, t, *J* = 7.5), 2.37 (2 H, t, *J* = 7.7), 1.76 (2 H, t, br), 1.64 (2 H, t, br), 1.29 (14 H, s, br); ^{13}C NMR data are in Table IV; ^{19}F NMR ($CDCl_3$, 282 MHz, vs. external trifluoroacetic acid at 0 ppm) 2.67 ppm.

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Registry No. 8, 947-05-7; 9, 807-04-5; 10, 95841-30-8; (DVB)·(styrene)·((chloromethyl)styrene) (copolymer), 55844-94-5; 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid, 77744-42-4; 12-hydroxydodecanoic acid, 505-95-3; methyl 12-hydroxydodecanoate, 71655-36-2; methyl 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoate, 95841-29-5.

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[20] Frechet, J. M. J.; de Smet, M. D.; Farrall, M. J. *Polymer* **1979**, *20*, 675–680.