Template-Driven Macrolide Closures

William H. Rastetter*[1] and Dennis P. Phillion

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received February 4, 1981

Thiol-functionalized crown ethers serve as reagents for macrolide closures. The thioesters derived from these crown ethers and ω-hydroxy carboxylic acids yield macrolides when treated with potassium *tert*-butoxide. The cyclization reaction proceeds via a templated conformation in which the ω-alkoxide is held proximate to the thioester through ionic bonding to the crown-bound potassium cation. Variations in crown ether structure in the series 1–4 show that the criterion of proximate binding is necessary but not sufficient to ensure efficient macrolide closure. The optimal crown ether reagent is thought to provide transition-state stabilization for the attack of the alkoxide on the thioester carbonyl by situating the carbonyl oxygen immediately adjacent to the crown-bound potassium cation.

The accompanying paper[2] describes the syntheses of four thiol-substituted crown ethers which differ in the spatial relationship of the thiol to the crown ether binding site. ω-Alkoxy thioesters derived from the crown ethers (e.g., **10**, Scheme I) have been used[3] in macrolide forming reactions. Herein we detail our study of the influence of crown ether structure on the efficiency of the macrolide closure process. The alkoxides derived from methano crown thioester **1**, ethano crown thioester **2**, convergent cyclopentano crown thioester **3**, and divergent cyclopentano crown thioester **4** (Chart I) have been examined. The efficiency of the macrolide closure process appears related to the ability of the crown ether to bind (stabilize) the transition state for the closure reaction (e.g., **10** → **11**, Scheme I).

Closure Method. The general approach to crown template macrolide closures is shown for convergent cyclopentano crown thioester **3** in Scheme I. The coupling of crown ether thiol[2] (e.g., **7**) and ω-silyloxy carboxylic acid **8** is achieved with a carbodiimide (R = R′ = C_6H_{11} or R = CH_2CH_3, R′ = $(CH_2)_3N(CH_3)_2$·HCl; see Experimental Section) and 4-(dimethylamino)pyridine (DMAP).[4] Hydrolytic cleavage of the silyl group of, e.g., ω-silyloxy thioester **9** provides the corresponding ω-hydroxy thioester **3**. Details of the preparation of representative ω-hydroxy thioesters from each crown ether series (**1**–**4**) are given in the Experimental Section.

Closure of the ω-hydroxy thioesters (e.g., **3**, Scheme I) is achieved upon mixing the thioesters with potassium *tert*-butoxide in aprotic media. The ω-alkoxide so produced is thought to adopt a templated conformation (**10**) with the potassium counterion in the host binding site. The entropic disadvantage of macrolide closure is not manifested in **10** where appreciable enthalpic advantage is associated with templated preclosure conformations having small separations of the potassium cation and alkoxide anion. Alkoxide **10** reacts via the putative tetrahedral intermediate **11**, giving crown ether thiolate salt **12** and macrolide **13**.

Testing the Method. Initial experiments with crown-mediated macrolide closures[3a] were performed with ethano crown thioester **2a** under conditions of both medium and high dilution of the reactants (**2a** + *t*-BuOK, Scheme II). These closure experiments, yielding the 12-membered lactone 11-undecanolide (**13a**), are summarized in Table I.

Scheme I

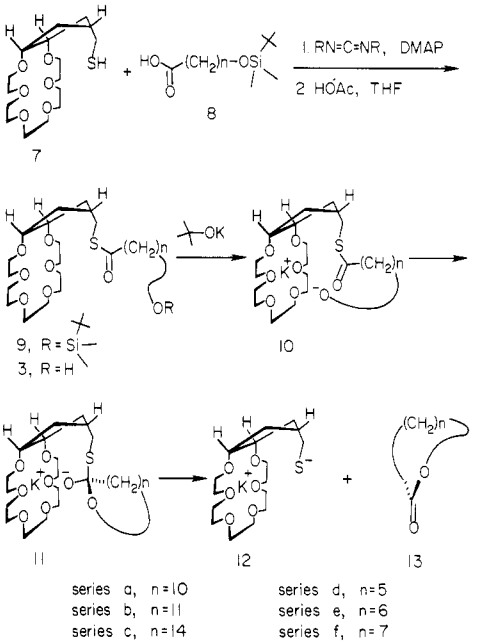
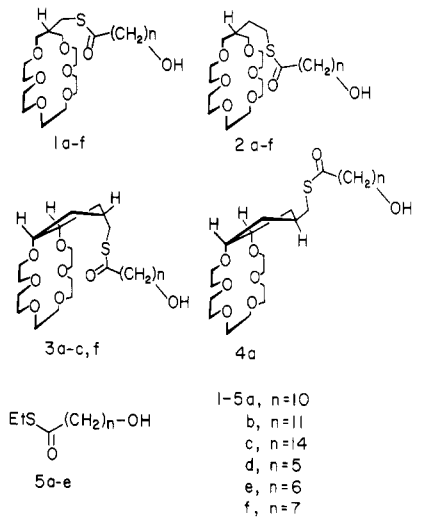


Chart I



Medium-dilution closure (entry 1, Table I) is achieved at ambient temperature over a 10-h period by simultaneous injection of ω-hydroxy thioester **2a** in dry benzene and *t*-BuOK in dry tetrahydrofuran (THF) into dry THF. In this fashion 11-undecanolide (**13a**) is produced in 44% yield. The macrolide product is stable to the closure conditions (entry 2). Thus, when starting materials are injected into THF containing 1.0 equiv (vs. **2a**) of ma-

(1) Firmenich Career Development Assistant Professor of Natural Products Chemistry, Alfred P. Sloan Fellow, 1980–1982.
(2) Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.*, previous paper in this issue.
(3) (a) Rastetter, W. H.; Phillion, D. P. *Tetrahedron Lett.* **1979**, 1469. (b) *J. Org. Chem.* **1980**, *45*, 1535.
(4) Neises, B. and Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

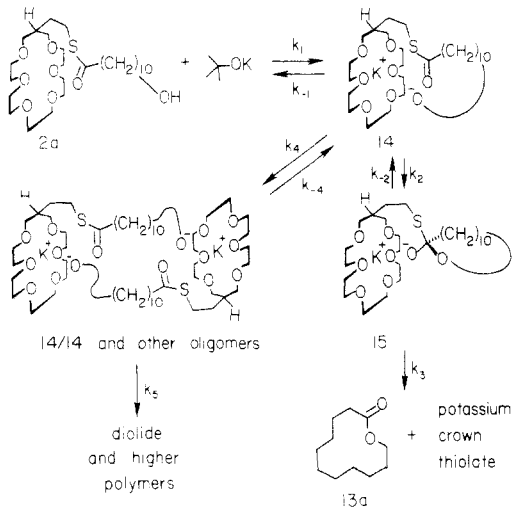
0022-3263/81/1946-3209$01.25/0

Table I. Closure Reactions of Thioester 2a and Control Thioester 5a

entry	thioester (amt, mmol; PhH solvent, mL)	amt t-BuOK,[a] mmol (in THF,[e] mL)	vessel (solvent THF, mL)	additive	addition time,[b] h	yield[c] of lactone 13a, %
1	2a (0.51; 16)	0.53 (16)	round bottom (20)		10	44
2	2a (0.48; 15.5)	0.50 (15.5)	round bottom (20)	0.48 mmol of lactone 13a in round bottom	10	148
3	2a (0.51; 18.5)	0.53 (18.5)	dilution head,[f] (30)		3.4	72, isolated: 68 plus 14 diolide
4	5a (0.60; 22)	0.63 (22)	round bottom (20)		10	~1
5	5a (0.50; 16)	0.52 (16)	round bottom (20)	0.50 mmol of crown ether 6 mixed with 5a	10	5
6	5a (0.60; 16)	0.63 (16)	dilution head,[f] (30)		4	57

[a] Sublimed. [b] Mechanical syringe drive used. [c] GLC yield unless indicated. [d] Benzene, 4-Å molecular sieve dried. [e] Tetrahydrofuran, Na/benzophenone ketyl dried. [f] The dilution head described in ref 3a was used.

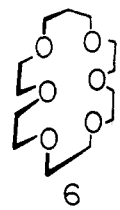
Scheme II



crolide **13a**, 148% of product (**13a**) can be recovered after the reaction (48% closure yield).

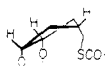
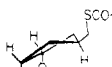
To achieve high-dilution closure of **2a** a high-dilution head (pictured in ref 3a) is utilized. The dilution head is a short-path distilling head modified to allow condensed solvent to drain from the filled collection flask back into the distillation pot. In this fashion, solvent is rapidly cycled between the two chambers of the reaction vessel. The templated alkoxide **14** (Scheme II) is generated at medium dilution in cooled solvent in the collection flask and then is diluted further as it is swept into refluxing solvent in the distillation pot. In principle, in the refluxing solvent the unimolecular cyclization of **14** is rapid and the alkoxide **14** does not accumulate. In this way, bimolecular reactions of **14** are minimized (see **14**/**14**, Scheme II).

The effect of dilution on the closure yield of thioester **2a** is seen by comparison of entries 1 and 3 of Table I. With increased dilution the yield of 11-undecanolide (**13a**) rises from 44% to 72%. In contrast, the effect of dilution on the closure of a control ethyl thioester (**5a**) is more dramatic. Under conditions of medium dilution (entry 4) thioester **5a** gives only a trace (~1%) of macrolide; in the presence of unfunctionalized 19-crown-6 (**6**) the yield increases only to 5% (entry 5, cf. entry 1). The ethyl thioester becomes a viable macrolide precursor *only at high dilution*, closing in 57% yield to macrolide **13a** (entry 6, cf. entry 4).



6

Table II. Yields for Closures of Large Rings[a,b]

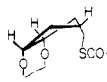
thioester	11-undecanolide (13a) medium dilution	11-undecanolide (13a) high dilution	12-dodecanolide (13b) medium dilution	12-dodecanolide (13b) high dilution	15-pentadecanolide (13c) medium dilution	15-pentadecanolide (13c) high dilution
 series 1	9-10		4-6		38-45	
 series 2	44	72 (68 plus 14 diolide)	37-47	64-74 (71-74 plus 6 diolide)	57-58	73-76 (73-74 plus 6 diolide)
 series 3	60-63	68-77 (75 plus 2 diolide)	58		61-69	72-76 (81 plus trace diolide)
 series 4	11-12	54 (52 plus 11 diolide)				
EtSCO-, 19-crown-6 series 5	5, ~1[c]	57[c]	9		40-43	

[a] Yields (in percent) determined by GLC vs. an internal standard; isolated yields (in percent) appear in parentheses. In all cases the yields of macrolide and diolide were determined after consumption of all starting material (TLC). [b] Macrolides and diolides were identified by their GLC and/or TLC behavior vs. that of authentic samples and displayed satisfactory spectral data (see Experimental Section). [c] Yield without added 19-crown-6.

Structural Studies. The success of the crown template in facilitating cyclization of ethano crown thioester **2a** led us to examine structurally different crown template systems. Methano crown thioester **1** is readily available in large quantities.[2] We found,[3b] however, a marked difference in its behavior as compared to the successful ethano crown **2**; viz., the template effect is not manifested in methano crown **1**. A full account of the studies with **1** and **2** is presented below. In addition, the results from two new crown thioester series (**3** and **4**) are presented. The former series has been designed on the basis of ethano crown thioester **2** to incorporate features which promote macrocyclization of ω-alkoxy thioesters. Epimeric series **4**, lacking these features, serves as a control.

ω-Alkoxy thioesters generated from crown thioesters **1a**, **3a**, and **4a** produce 11-undecanolide (**13a**). These cyclizations and the pertinent cyclizations of thioesters **2a** and **5a** are summarized in columns 1 and 2 of Table II. Methano crown thioester **1a**, divergent cyclopentano crown thioester **4a**, and ethyl thioester **5a** produce macrolide **13a**

Table III. Yields for Closures of Medium Rings[a,b]

thioester	6-hexanolide (13d) medium dilution	6-hexanolide (13d) high dilution	7-heptanolide (13e) medium dilution	7-heptanolide (13e) high dilution	8-octanolide (13f) medium dilution	8-octanolide (13f) high dilution
 series 1	23-24		< 1		0	
 series 2	25	19-23 plus 19 diolide (14 diolide)	0-1	0-1 plus 37-41 diolide (23 diolide)	4	35 (27 diolide)
 series 3					19-24	
EtSCO-, 19-crown-6 series 5	27		0			

a Yields (in percent) determined by GLC vs. an internal standard; isolated yields (in percent) appear in parentheses. In all cases the yields of macrolide and diolide were determined after consumption of all starting material (TLC). b Macrolides and diolides were identified by their GLC and/or TLC behavior vs. that of authentic samples and displayed satisfactory spectral data (see Experimental Section).

in low yield at medium dilution. Under these conditions, however, ethano crown thioester **2a** and convergent cyclopentano crown thioester **3a** close in significantly better yields. At high dilution the closure yields are increased. The relative advantage of the template effect, however, is most strongly manifested at medium dilution. In principle, *at the limit of infinite dilution* all five thioesters (**1a–5a**) will close quantitatively to macrolide, albeit at different rates (vide infra).

The crown template approach to macrolides has also been tested for the 13- and 16-membered lactones (12-dodecanolide (**13b**) and 15-pentadecanolide (**13c**), respectively). Table II shows inefficient closures of 12-dodecanolide (column 3) from methano crown thioester **1b** and from control ethyl thioester **5b**. The closure yields from ethano crown thioester **2b** and convergent cyclopentano thioester **3b** are significantly higher. 15-Pentadecanolide (**13c**, column 5) is formed in moderate yield even from the ethyl thioester **5c**. Methano crown thioester **1c**, however, shows no advantage over control **5c**. A modest but reproducible advantage is seen for medium dilution closures of crown thioesters **2c** and **3c**. In those cases examined (**2c,b**, **3c**), higher dilution increases the yields of the 13- and 16-membered lactones (columns 4 and 6). Thus, crown ether thioester series **2** and **3** appear to facilitate formation of 12-, 13-, and 16-membered macrolides; series 1 and 4, however, are only as effective as the simple control ethyl thioesters (series **5**).

Successful macrolide production by the crown template strategy appears to be limited to large ring sizes (e.g., ≥12-membered ring). The crown ether reagents are not effective in high-yield formation of 7-, 8-, or 9-membered macrolides (Table III). The failure of the template approach for these ring sizes, in part, may be due to product instability to closure conditions. In control experiments the 7-, 8-, 9-, and 12-membered macrolides were stirred with potassium ethyl thiolate and unfunctionalized 19-crown-6 (**6**) under conditions of medium-dilution closures (see Table I). Only 11-undecanolide (**13a**) was entirely stable to these conditions. Strained 7-heptanolide was completely destroyed by crown-bound ethyl thiolate overnight at ambient temperature; 6-hexanolide and 8-octanolide were 29%[5] and 83% recovered (GLC vs. internal standard), respectively, under these conditions. Thus, the failure of the template approach to medium ring sizes may be attributed, in part, to crown-catalyzed oligomerization of formed macrolides. However, it is also possible that the reactions of monomeric templated alkoxides leading to medium-sized lactones are slow and the polyesters produced (e.g., the diolides) are largely kinetic products.

Discussion

Proximate binding of thioester and alkoxide is necessary but not sufficient to ensure efficient macrolide closures from templated alkoxides (e.g., **10**, Scheme I, and **14**, Scheme II). Proximate binding is achieved in thioester series **1–3** by the ionic anchoring of alkoxide against the potassium–crown template. In control series **4** a template is provided, but the divergent crown stereochemistry holds the alkoxide and thioester away from each other. In series **5** the alkoxide and the ethyl thioester are allowed to randomly coil in solution. Despite the apparent similarity of the preclosure conformations of alkoxides in series **1–3**, no template effect is manifested in methano crown thioester **1**. The advantage seen in series **2** and **3**, thus, cannot be due entirely to the proximate binding of the thioesters and alkoxides in the preclosure intermediates (**10**, Scheme I, and **14**, Scheme II).

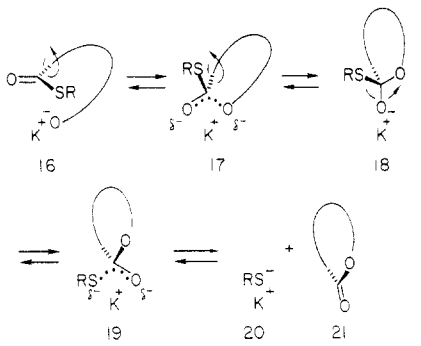
Rate/Yield Relationship. The entire ring-closure process must be examined to understand the benefit of the template effect in crown thioesters **2** and **3**. The process leading to macrolide **13a** and the competing processes leading to diolide and other polymeric materials are represented for ethano crown thioester **2a** in Scheme II.[6] At the limit of infinite dilution, all of templated alkoxide **14** will react unimolecularly (processes k_2 and k_3), giving macrolide. In practice, however, the yield of macrolide is diminished by polymerization. Most, if not all, polymerization of **14** (process k_5) likely occurs via ionic oligomers such as **14/14**, in which the reactive ends of indidual ω-alkoxy thioesters have become separated, owing to intermolecular association. Having lost the internally templated conformation of monomeric alkoxide **14**, ionic oligomers such as **14/14** will lead readily to polyesters (process k_5). The extent of intermolecular association (equilibrium k_4/k_{-4}) will be concentration dependent, this dependence being responsible for the effect of dilution on macrolide yield (Table II). Clearly, to retard polymerization of **14**, the concentration of the alkoxide should be kept as low as possible *throughout the closure process.*

An examination of Scheme II reveals the factors which determine the concentration of **14** in the reaction medium. The generation of the preclosure alkoxide **14** is achieved by the slow addition (see Table I) of ω-hydroxy thioester **2a** and *t*-BuOK to the reaction vessel. The rate of formation of **14** is governed by the injection rate of the reactants, not by the rate of the rapid proton-transfer process k_1. The concentration of ω-alkoxy thioester which exists during the closure process can be determined by applying a steady-state argument; i.e., the concentration of **14** at the beginning of the closure reaction increases until its rate of reaction exactly equals its rate of formation. From this point the concentration of **14** remains constant

(5) 6-Hexanolide was completely destroyed by further stirring (1 additional day) with the crown–potassium thiolate complex; the corresponding diolide was stable to these conditions. The yields for 6-hexanolide in Table III presumably reflect partial destruction of the product by the product thiolate salts (yields not optimized).

(6) In Scheme II it is assumed that the macrolide is stable to the potassium crown thiolate, i.e., that equilibrium of macrolide, diolide, and other polymers does not occur under conditions of the cyclization. For macrolide **13a** this assumption seems valid (see discussion earlier in text).

Scheme III



until the reactants are depleted (injection of reactants ceases). Thus, the determinants of the steady-state concentration of the macrolide precursor (14) are the injection rate and the combined rate of cyclization (k_2, k_3) and polymerization (k_4, k_5) of the ω-alkoxy thioester. When the reactions of 14 are rapid, the alkoxide does not reach a high steady-state concentration, and bimolecular reactions (e.g., k_5) are rare as compared to the unimolecular reaction (k_2, k_3). In this way, *the yield of macrolide 13a is directly linked to the lifetime of the preclosure intermediate 14 in the cyclization medium.*

Template Catalysis. The relative advantage in achieving macrolide closure of ethano crown **2a** (cf. **1a** and **5a**) seems related to an accelerated consumption of the alkoxide precursor (14, Scheme II) in this crown thioester series. Under identical closure conditions the steady-state concentration of 14 is apparently lower than that of the corresponding alkoxides in the methano crown (1) or ethyl thioester (5) series. For effective reduction of the steady-state concentration of 14, the crown template must function to lower the *rate determining* activation barrier in the macrolide-forming process (Scheme II). In principle, either the actual ring closure (k_2, Scheme II) or the breakdown (k_3) of the tetrahedral intermediate 15 might be rate determining. At least for the large-sized rings (≥12-membered), however, we have assumed that the rate of formation of macrolide is determined by process k_2. By analogy to the alkaline hydrolysis of thioesters,[7] tetrahedral intermediate 15 is likely short-lived, collapsing rapidly to products (process k_3). The breakdown of the tetrahedral intermediate probably becomes rate determining only when the antiperiplanar alignment of the breaking C–S bond with one lone pair on each oxygen atom is prevented by ring size or conformation.[8,9] In the absence of such adverse stereoelectronic effects, process k_2 rather than k_3 is expected to be the primary determinant of the steady-state concentration of the preclosure alkoxide 14.

Scheme III depicts the closure of a generalized ω-alkoxy thioester. As applied to the ethano crown series, 17 and 19 represent the transition states for processes k_2 and k_3 (Scheme II), respectively. As the alkoxide oxygen of 16 approaches the thioester carbonyl carbon (see 16 → 17), negative charge density begins to appear on the carbonyl oxygen. The activation barrier for the assumed rate-determining ring closure 16 → 18 (cf. k_2, Scheme II) will depend directly on the amount of ionic stabilization in 17. The transition state is characterized by negative charge density on both the alkoxide and carbonyl oxygens—both oxygens must be capable of close approach to the potassium cation to optimize transition-state stabilization and enhance the rate of ring closure.

Corey–Pauling–Koltun (CPK or space-filling) models of the intermediates from ethano crown 2 show the relationship of the two oxygen atoms to the bound potassium cation during the ring closure reaction, 16 → 17 → 18 (photographs of the models appear in ref 3b). In the ethano crown series the reactants are held close together at stage 16, and during ring closure both oxygens are able to tightly straddle the bound potassium cation (see 17). At stage 18 the negative charge is fully developed on the oxygen which occupied the carbonyl position in 16. The new alkoxide in the CPK model of 18[3b] can be seen centered directly over the host binding site. Thus, in ethano crown thioester 2 attack of alkoxide at the carbonyl carbon (16 → 18) occurs with a smooth transfer of charge from oxygen to oxygen; at no point in the closure process are anion and bound cation separated.

Further examination of CPK models in the ethano crown series shows that the crown template should also facilitate transfer of charge to the leaving thiolate in the process 18 → 19 → 20 + 21 (k_3, Scheme II). In 19, as in 17, the atoms sharing the negative charge are able to tightly straddle the bound potassium cation. As a consequence, tetrahedral intermediate 18 should not accumulate; thiolate expulsion should rapidly follow the assumed rate-determining formation of 18.[9]

Similar analysis for the methano crown thioester shows the deficiency of series 1 as a crown template. Methano crown thioester 1 meets the requirement of proximate binding of reactants at stage 16 (Scheme III). However, a CPK model of intermediate 18 in the methano crown series shows that the one carbon chain connecting the sulfur atom to the crown ether is too short to allow placement of the alkoxide of the tetrahedral intermediate over the potassium binding site without pushing the collar of crown ether oxygens away from the bound cation. Closures in series 1 will proceed, disrupting the geometry of the crown ether–potassium complex or, alternatively, with increasing charge separation between developing alkoxide and the counterion. In series 1, intermediate 18, and the transition state leading to it (17), are destabilized relative to series 2.

Closure experiments with the homologous crown thioesters 1 and 2 indicated the sensitivity of the closure process to small changes in ionophore structure. To further test the concepts represented in Scheme II, we designed convergent cyclopentano crown thioester 3 with the aid of CPK models. On the basis of this scheme two design features were sought. First, a convergent crown template (3) was chosen to enforce the proximity of reactants at preclosure stage 16 (Scheme III). Second, the spacing of the thiol and binding site was selected to allow tight ionic bonds at stages 18 and 20. Close contact of anion and cation in 18 also ensures ionic stabilization of the developing negative charge at the carbonyl oxygen in transition-state 17. Analogously, tight ionic pairing in 20 allows facile breakdown of intermediate 18 via transition-state 19.[9] Incorporating these features, crown template 3 is designed to minimize both the entropic and enthalpic demands of the macrolide closure process. In essence, this is achieved by constructing a template to bind the closure transition state 17 (presumably the rate-determining barrier) and the subsequent transition-state 19. The success of the design process is shown in Table II.

(7) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; pp 517–523, and references therein.
(8) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463.
(9) For the 7-, 8- and 9-membered rings (see Table III) it is possible that the stereoelectronic requirements[8] for thiolate expulsion cannot be met readily. Were this the case, process k_3 would become rate limiting, and the preclosure alkoxide would accumulate and ultimately polymerize.
(10) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

The synthetic scheme used to assemble crown ether **3** also provided its epimer, divergent crown thioester **4**. Epimer **4** fails to meet the requirements of proximate reactant binding or transition-state binding (stabilization). Closures in series **4** were expected to be impeded by the structure of the crown template. This prediction is borne out (Table II).

The rational design process leading to the selection of crown template **3** and the yield data from this series provide good evidence of a catalytic role for the crown–potassium template during the macrocyclization process. Yield data alone, however, do not suffice to prove catalysis. The demonstration of a template catalytic effect ultimately must be based on rate data. On the basis of the assumed entropic and enthalpic requirements of macrolide closure and the observed efficiency of the closure processes in thioester series **1–4**, we expect that the rates of crown thioester ring closure should follow the sequence $3 \geq 2 > 1 \geq 4$. The measurement of these rates will be performed in the near future and reported in due course.

Experimental Section

General Methods. Abbreviations used in this section plus details of general experimental procedures, instrumentation, and materials are given in the corresponding section of the accompanying paper.[2]

1,4,7,10,13,16-Hexaoxacyclononadecane (19-crown-6, 6). A solution of bromoacetic acid (32.35 g, 230 mmol) in THF (60 mL) was added dropwise to a stirred mixture of 1,3-propanediol (7.61 g, 100 mmol) and *t*-BuOK (57.95 g, 520 mmol) in THF (240 mL). The resulting thick, white suspension was refluxed for 3 h, cooled to ambient temperature, and concentrated under reduced pressure. The residual oily solid was diluted with CH_3OH (400 mL) and carefully acidified with H_2SO_4 (8.7 mL). The mixture was refluxed overnight, concentrated under reduced pressure, and purified by extraction (H_2O/Et_2O, $NaHCO_3$(satd, aq) wash). Distillation in vacuo afforded 14.67 g (67%) of diester (dimethyl 3,7-dioxanonane-1,9-dicarboxylate): ^1H NMR (60 MHz, $CDCl_3$) 1.87 (2 H, quintet), 3.60 (4 H, t), 3.75 (6 H, s), 4.00 (4 H, s); exact mass calcd for $C_9H_{16}O_6$ (M^+) m/e 220.094 69, found 220.094 98.

A solution of the diester (14.67 g, 66.6 mmol) in Et_2O (35 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (5.10 g, 134 mmol) in Et_2O (100 mL) cooled with an ice–water bath. The mixture was stirred overnight at ambient temperature then quenched carefully by addition of excess $Na_2SO_4 \cdot 10H_2O$. After being stirred several hours, the suspension was filtered, and the collected salts were washed thoroughly with hot THF. The combined filtrates were concentrated under reduced pressure, and the residual oil was distilled in vacuo, affording 9.80 g (90%) of diol (3,7-dioxanonane-1,9-diol): ^1H NMR (60 MHz, $CDCl_3$) 1.83 (2 H, quintet), 3.00 (2 H, t, D_2O exchangeable), 3.57 (m, 12 H); exact mass calcd for $C_6H_{13}O_3$ ($M^+ - CH_2OH$) 133.086 47, found 133.086 53.

A solution of triethylene glycol ditosylate (30.8 g, 67.2 mmol) in THF (120 mL) was added rapidly to a stirred solution of *t*-BuOK (15.25 g, 135.9 mmol) and 3,7-dioxanonane-1,9-diol (10.03 g, 61.1 mmol) in THF (1.05 L). The mixture was heated at 35 °C for 3 days, cooled, and filtered, and the collected solid was washed with THF. The combined filtrates were concentrated under reduced pressure and the residue filtered through alumina (5:1 by weight vs. crude crown ether **6**, THF), affording 17.3 g of yellow oil. Distillation (115 °C, ca. 0.01 mmHg) yielded 5.94 g (35%) of crown ether **6**: ^1H NMR (60 MHz, CCl_4) 1.70 (2 H, quintet), 3.55 (24 H, m); IR (neat, NaCl) 2900 (br), 1448, 1350, 1298, 1250, 1120 (br), 990, 943, 872 cm^{-1}; exact mass calcd for $C_{13}H_{26}O_6$ (M^+) m/e 278.172 94, found 278.175 58.

ω-Silyloxy Carboxylic Acids. Acids **8a–f** were prepared either from the corresponding ω-hydroxy acids or lactones (**13**). 11-Hydroxy undecanoic acid and 15-hydroxypentadecanoic acid (Farchan Division, Chemical Samples Co.) were converted by the general procedure given below into acids **8a** and **8c**, respectively. Baeyer–Villiger oxidation of the appropriate ketones[10] (Aldrich Chemical Co.) produced lactones **13b** and **13e,f**. These and **13d** (Aldrich) also were converted by the general procedure (below) into acids **8b**, **8e**, **f**, and **8d**, respectively. Fischer esterification (acids) or acid-catalyzed methanolysis (lactones) transformed the starting materials into the corresponding ω-hydroxy carboxylic acid methyl esters. The procedure given for the synthesis of ω-silyloxy carboxylic acid **8a** from 11-hydroxyundecanoic acid is general for all hydroxy acids and lactones.

A solution of 11-hydroxyundecanoic acid (2.62 g, 13.0 mmol) and concentrated HCl(aq, several drops) in CH_3OH (50 mL) was refluxed overnight. After the mixture cooled, the solvent was removed under reduced pressure. The residue was dissolved in toluene, and the solvent was again removed under reduced pressure, affording oily hydroxy ester: 2.80 g (or 100% of methyl 11-hydroxyundecanoate): ^1H NMR (60 MHz, $CDCl_3$) 1.29 (17 H, br s), 2.27 (2 H, t, J = 6 Hz), 3.61 (5 H, m).

A mixture of hydroxy ester (2.80 g, 13.0 mmol), *tert*-butyldimethylsilyl chloride (2.35 g, 15.6 mmol), and imidazole (2.21 g, 32.5 mmol) in DMF (7 mL) was stirred overnight. Extractive workup (2% HCl(aq)/benzene, $NaHCO_3$(aq) and H_2O washes), drying ($MgSO_4$), and removal of the solvent at reduced pressure afforded 4.32 g (100%) of oily ω-silyloxy carboxylic acid methyl ester. Traces of hydroxylic impurities in the product were routinely removed by distillation of the silyloxy methyl ester under high vacuum (oil-diffusion line). Data for methyl 11-[(*tert*-butyldimethylsilyl)oxy]undecanoate: ^1H NMR (60 MHz, $CDCl_3$) $(CH_3)_2Si$ absorption set at δ 0.00 (6 H, s), 0.83 (9 H, s), 1.23 (16 H, br s), 2.21 (2 H, t, J = 6 Hz), 3.47 (2 H, t, J = 6 Hz), 3.54 (3 H, s); IR (neat, NaCl) 2930, 2855, 1740, 1460, 1433, 1385, 1359, 1250, 1193, 1168, 1090, 1000, 933, 830, 770, 715, 654 cm^{-1}; exact mass calcd for $C_{14}H_{29}O_3Si$ ($M^+ - C_4H_9$) m/e 273.188 60, found 273.186 77.

Saponification of the ω-silyloxy carboxylic acid methyl ester (0.905 g, 2.74 mmol) was achieved with NaOH (5.0 M solution, 0.56 mL, 2.8 mmol) in rapidly stirred THF–CH_3OH–H_2O (2:2:1, 2.0 mL). After the mixture became homogeneous (7 h), extractive workup (benzene/10% HCl(aq)), drying ($MgSO_4$), and concentration under reduced pressure afforded 0.850 g (98%) of oily acid **8a**: ^1H NMR (250 MHz, $CDCl_3$) 0.03 (6 H, s), 0.87 (9 H, s), 1.26 (12 H, br s), 1.48 (2 H, m), 1.61 (2 H, m), 2.32 (2 H, t, J = 7.7 Hz), 3.57 (2 H, t, J = 6.6 Hz); IR (neat, NaCl) 3700–2300 (br), 2925, 2855, 1708, 1469, 1460, 1409, 1385, 1359, 1283, 1250, 1092, 1000, 932, 830, 805, 769, 715, 653 cm^{-1}; exact mass calcd for $C_{13}H_{27}O_3Si$ ($M^+ - C_4H_9$) m/e 259.172 95, found 259.174 08.

ω-Hydroxy Thioester 1. The procedure for thioester **1b** is representative. A solution of mercaptomethyl crown ether (**1** in the accompanying paper;[2] 1.03 g, 3.19 mmol), carboxylic acid **8b** (985.4 mg, 2.98 mmol), DCC (708 mg, 3.44 mmol), and DMAP (22 mg, 0.18 mmol) in THF (12 mL) was kept at −25 °C for 4 days. The mixture was warmed to ambient temperature, filtered, concentrated under reduced pressure, and triturated with pentane to remove most of the DCU. Removal of the solvent under reduced pressure and flash chromatography (silica gel, EtOAc) gave 1.58 g (83%) of pure, oily ω-silyloxy thioester: ^1H NMR (60 MHz, $CDCl_3$) $(CH_3)_2Si$ absorption set at δ 0.00 (6 H, s), 0.85 (9 H, s), 1.23 (18 H, br s), 2.04 (1 H, m), 2.51 (2 H, t, J = 7 Hz), 2.95 (2 H, d, J = 7 Hz), 3.54 (26 H, m); IR (neat, NaCl) 2930, 2860, 1690, 1463, 1352, 1297, 1256, 1120 (br), 838, 778 cm^{-1}; exact mass calcd for $C_{32}H_{64}O_8SSi$ (M^+) m/e 636.409 12, found 636.409 11.

Hydrolysis of the ω-silyl protective group was achieved by stirring the ω-*tert*-butyldimethylsilyloxy thioester (1.58 g, 2.47 mmol) in CH_3COOH–H_2O (2:1, 25 mL) for 8 h. The solvent and silanol were removed under reduced pressure. The residue was dissolved in xylenes and reconcentrated, affording ω-hydroxy thioester **1b** in quantitative yield: ^1H NMR (60 MHz, $CDCl_3$) 1.27 (18 H, br s), 2.02 (2 H, complex m), 2.52 (2 H, t, J = 7 Hz), 2.95 (2 H, d, J = 7 Hz), 3.55 (26 H, m); IR (neat, NaCl) 3470 (br), 2890, 1690, 1468, 1354, 1298, 1250, 1100 (br) cm^{-1}; exact mass calcd for $C_{26}H_{50}O_8S$ (M^+) m/e 522.322 64, found 522.320 86.

ω-Hydroxy Thioester 2. The procedure for thioester **2f** is representative. A solution of mercaptoethyl crown ether (**2** in the accompanying paper;[2] 1.04 g, 3.08 mmol), carboxylic acid **8f** (832 mg, 3.03 mmol), DCC (686 mg, 3.32 mmol), and DMAP (20.2 mg, 0.170 mmol) in THF (12 mL) was reacted and purified by following the protocol for thioester **1** (vide supra). Data for the ω-silyloxy thioester: yield 1.47 g (81%) of pure, oily thioester; ^1H NMR (60 MHz, $CDCl_3$) $(CH_3)_2Si$ absorption set at δ 0.00 (6

H, s), 0.86 (9 H, s), 1.49 (13 H, m), 2.49 (2 H, t, J = 7 Hz), 2.90 (2 H, t, J = 7 Hz), 3.52 (26 H, m); IR (neat, NaCl) 2940, 2870, 1690, 1465, 1358, 1300, 1260, 1115 (br), 840, 780 cm^{-1}; exact mass calcd for $C_{29}H_{58}O_8SSi$ (M^+) m/e 594.362 17, found 594.359 78.

Hydrolysis of the ω-silyl protective group was achieved by treating the ω-*tert*-butyldimethylsilyloxy thioester (1.47 g, 3.06 mmol) as detailed above for thioester series **1**. ω-Hydroxy thioester **2f**, produced in quantitative yield, displayed the following: ^1H NMR (60 MHz, $CDCl_3$) 1.52 (13 H, m), 2.52 (2 H, t, J = 7 Hz), 2.83 (1 H, s), 2.90 (2 H, t, J = 7 Hz), 3.52 (26 H, m); IR (neat, NaCl) 3470 (br), 2935, 2870, 1690, 1453, 1357, 1300, 1255, 1120 (br) cm^{-1}; exact mass calcd for $C_{23}H_{44}O_8S$ (M^+) m/e 480.275 69, found 480.275 19.

ω-Hydroxy Thioester 3. The procedure for thioester **3a** is representative. A solution of convergent cyclopentano crown thiol **7** (1.03 g, 2.94 mmol), carboxylic acid **8a** (933 mg, 2.95 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (704 mg, 4.00 mmol), and DMAP (19.9 mg, 0.16 mmol) in DMF (15 mL) was stirred for 1 day. Extractive workup (H_2O/Et_2O, $NaHCO_3$(satd, aq) and H_2O washes), drying ($MgSO_4$), concentration under reduced pressure, and flash chromatography (silicic acid, eluted sequentially with 3–5 column volumes of 1:1 Et_2O–pentane, EtOAc, and THF) afforded 1.30 g (68%) of pure ω-silyloxy thioester **9a**: ^1H NMR (250 MHz, $CDCl_3$) 0.02 (6 H, s), 0.87 (9 H, s), 1.24 (12 H, br s), 1.54 (6 H, m), 2.00 (3 H, m), 2.49 (2 H, t, J = 7.5 Hz), 2.93 (2 H, d, J = 6.6 Hz), 3.57 (2 H, t, J = 6.6 Hz), 3.66 (20 H, m), 3.77 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 2925, 2850, 1689, 1458, 1349, 1120 (br), 1066, 933, 907, 830, 770 cm^{-1}; exact mass calcd for $C_{33}H_{64}O_8SSi$ (M^+) m/e 648.409 12, found 648.412 52.

Hydrolysis of the ω-silyl protective group of **9a** (1.30 g, 2.00 mmol) was achieved over a 12-h period as detailed above for thioester series **1**. ω-Hydroxy thioester **3a** produced in quantitative yield displayed the following: ^1H NMR (250 MHz, $CDCl_3$) 1.24 (12 H, br s), 1.55 (6 H, m), 1.94–2.02 (4 H, m), 2.49 (2 H, t, J = 7.4 Hz), 2.93 (2 H, d, J = 7.0 Hz), 3.64 (22 H, m), 3.76 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 3450 (br), 2920, 2850, 1683, 1455, 1345, 1290, 1243, 1120 (br), 940, 740 cm^{-1}; exact mass calcd for $C_{27}H_{50}O_8S$ (M^+) m/e 534.322 64, found 534.320 87.

ω-Hydroxy Thioester 4. The procedure for thioester **4a** is representative. A solution of divergent cyclopentano crown thiol (**4** in the accompanying paper;[2] 622 mg, 1.77 mmol), carboxylic acid **8a** (568 mg, 1.79 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (440 mg, 2.50 mmol), and DMAP (11.9 mg, 0.10 mmol) in DMF (9 mL) was stirred for 2 days. Workup by use of the procedure for series **3** above afforded 795 mg (69%) of pure, oily ω-silyloxy thioester: ^1H NMR (250 MHz, $CDCl_3$) 0.02 (6 H, s), 0.87 (9 H, s), 1.24 (12 H, br s), 1.41 (4 H, m), 1.61 (2 H, m), 2.00 (2 H, m), 2.48 (1 H, m), 2.51 (2 H, t, J = 7.5 Hz), 2.87 (2 H, d, J = 7.0 Hz), 3.57 (2 H, t, J = 6.6 Hz), 3.65 (20 H, m), 3.88 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 2930, 2850, 1683, 1458, 1408, 1383, 1348, 1290, 1248, 1116 (br), 934, 830, 770 cm^{-1}; exact mass calcd for $C_{33}H_{64}O_8SSi$ (M^+) m/e 648.409 12, found 648.408 11.

Hydrolysis of the ω-silyl protective group was achieved by stirring the ω-silyloxy thioester (795 mg, 1.22 mmol) in CH_3CO-OH–H_2O (2:1, 12 mL) for 8 h. Solvent and silanol were removed under reduced pressure, and the oily residue was dissolved in Et_2O and washed sequentially with 10% HCl(aq), $NaHCO_3$(satd, aq), and H_2O. Drying and removal of Et_2O under reduced pressure yielded 601 mg (92%) of pure, oily ω-hydroxy thioester **4a**: ^1H NMR (250 MHz, $CDCl_3$) 1.25 (12 H, br s), 1.38 (2 H, m), 1.57 (4 H, m), 1.94 (1 H, s), 2.00 (2 H, m), 2.44 (1 H, m), 2.50 (2 H, t, J = 7.5 Hz), 2.87 (2 H, d, J = 7.0 Hz), 3.64 (22 H, m), 3.88 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 3450 (br), 2890, 1684, 1450, 1346, 1290, 1243, 1110 (br), 940 cm^{-1}; exact mass calcd for $C_{27}H_{50}O_8S$ (M^+) m/e 534.322 64, found 534.321 74.

ω-Hydroxy Thioester 5. The procedure for thioester **5b** is representative. A solution of carboxylic acid **8b** (662 mg, 2.00 mmol), EtSH (0.60 mL, 8.03 mmol), DCC (467 mg, 2.26 mmol), and DMAP (13.8 mg, 0.11 mmol) in THF (8 mL) was kept at −25 °C for 5 days. The mixture was warmed to ambient temperature, filtered, concentrated under reduced pressure, and triturated with pentane to remove most of the DCU. Removal of solvent and flash chromatography (silica gel, CH_2Cl_2) afforded 537 mg (72%) of pure, oily ω-silyloxy thioester: ^1H NMR (60 MHz, $CDCl_3$) $(CH_3)_2Si$ absorption set at δ 0.00 (6 H, s), 0.86 (9 H, s), 1.20 (3 H, t, J = 7 Hz), 1.25 (18 H, br s), 2.49 (2 H, t, J = 7 Hz), 2.82 (2 H, q, J = 7 Hz), 3.55 (2 H, t, J = 7 Hz); IR (neat, NaCl) 2925, 2850, 1691, 1462, 1256, 1095, 835, 775 cm^{-1}; exact mass calcd for $C_{16}H_{33}O_2SSi$ ($M^+ - C_4H_9$) m/e 317.197 06, found 317.199 07.

Hydrolysis of the ω-silyl protective group was achieved by stirring the ω-silyloxy ethyl thioester (573 mg, 1.43 mmol) in CH_3COOH–THF–H_2O (2:1:1, 19 mL) for 20 h. Solvent and silanol were removed at reduced pressure. The residue was dissolved in xylenes and reconcentrated affording ω-hydroxy thioester **5b** in quantitative yield: mp 40.5–41.5 °C; ^1H NMR (60 MHz, $CDCl_3$) 1.12–1.60 (22 H, m), 2.53 (2 H, t, J = 7 Hz), 2.86 (2 H, q, J = 7 Hz), 3.64 (2 H, t, J = 7 Hz); exact mass calcd for $C_{14}H_{28}O_2S$ (M^+) m/e 260.181 00, found 260.181 47.

Medium Dilution Macrolide Closure. The procedure for convergent cyclopentano crown thioester **3a** is representative. A solution of ω-hydroxy thioester **3a** (270 mg, 0.506 mmol) in benzene (55 mL) was azeotropically dried to a volume of 14.7 mL and then drawn into a gas-tight syringe. A second gas-tight syringe was loaded with a solution of *t*-BuOK (59.6 mg, 0.53 mmol) in THF (14.7 mL). The two solutions were simultaneously injected over a 10-h period (syringe pump) into stirred THF (20 mL). The resulting mixture was quenched with CH_3COOH, affording macrolide **13a** in 63% yield (GLC, 4.2% SE-30, vs. internal standard, product coelutes with authentic sample). Full characterization was obtained on isolated **13a** (vide infra).

High Dilution Macrolide Closure. The procedure for convergent cyclopentano crown **3a** is representative. A solution of ω-hydroxy thioester **3a** (256 mg, 0.480 mmol) in benzene (55 mL) was azeotropically dried to a volume of 17.2 mL and then drawn into a gas-tight syringe. A second gas-tight syringe was loaded with a solution of *t*-BuOK (56.5 mg, 0.503 mmol) in THF (17.2 mL). The high-dilution vessel pictured in ref 3a was charged with THF (30 mL) and the solvent brought to reflux. The two reactant solutions were simultaneously injected over 3.2 h (syringe pump) into the high-dilution-vessel collection flask charged with several activated 4-Å molecular sieves. Over the period of injection the solvent in the collection flask was rapidly stirred magnetically and cooled with a bath of cold tap water. After the injection of reactants was completed, the mixture was cooled to ambient temperature and quenched with CH_3COOH, affording macrolide **13a** in 77% yield (GLC, 4.2% SE-30, vs. internal standard). Concentration of the reaction mixture and chromatography (2000-μm silica gel plate eluted with 1:9 Et_2O–pentane) gave 66 mg (75%) of pure macrolide **13a** and 1.7 mg (2%) of diolide (cyclic dimer). Data for **13a**: ^1H NMR (250 MHz, $CDCl_3$) 1.33 (10 H, m), 1.51 (2 H, m), 1.66 (4 H, m), 2.34 (2 H, half an AA′BB′ pattern), 4.17 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 2930, 2860, 1730, 1462, 1441, 1377, 1345, 1323, 1238, 1215, 1169, 1135, 1088, 1042, 959 cm^{-1}; exact mass calcd for $C_{11}H_{20}O_2$ (M^+) m/e 184.146 33, found 184.144 30. Data for diolide: ^1H NMR (250 MHz, $CDCl_3$) 1.26 (24 H, br s), 1.62 (8 H, br m), 2.29 (4 H, t, J = 6.8 Hz), 4.07 (4 H, t, J = 5.9 Hz); IR (CCl_4) 2925, 2855, 1730, 1455, 1242, 1170, 1100 cm^{-1}; exact mass calcd for $C_{22}H_{40}O_4$ (M^+) m/e 368.292 66, found 368.292 05.

Registry No. 1a, 73177-56-7; **1b**, 73177-57-8; **1c**, 73177-58-9; **1d**, 73177-59-0; **2a**, 72037-28-6; **2b**, 73177-52-3; **2c**, 73192-74-2; **2d**, 73177-53-4; **2e**, 73177-54-5; **2f**, 73177-55-6; **3a**, 77744-37-7; **3b**, 77744-38-8; **3c**, 77744-39-9; **3f**, 77744-40-2; **4a**, 77744-41-3; **5a**, 72037-29-7; **5b**, 73177-62-5; **5c**, 73177-63-6; **5d**, 73177-64-7; **6**, 55471-27-7; *cis*-**7**, 77714-59-1; **8a**, 72037-31-1; **8b**, 77744-42-4; **8c**, 77744-43-5; **8d**, 77744-44-6; **8e**, 77744-45-7; **8f**, 77744-46-8; **9a**, 77744-47-9; **13a**, 1725-03-7; **13b**, 947-05-7; **13c**, 106-02-5; **13d**, 502-44-3; **13e**, 539-87-7; **13f**, 5698-29-3; bromoacetic acid, 79-08-3; 1,3-propanediol, 504-63-2; dimethyl 3,7-dioxanonane-1,9-dicarboxylate, 77744-48-0; 3,7-dioxanonane-1,9-diol, 67439-82-1; triethylene glycol ditosylate, 19249-03-7; 15-hydroxypentadecanoic acid, 4617-33-8; 11-hydroxyundecanoic acid, 3669-80-5; methyl 11-hydroxyundecanoate, 24724-07-0; methyl 11-[(*tert*-butyldimethylsilyl)oxy]undecanoate, 77773-56-9; mercaptomethyl 19-crown-6 ether, 77661-77-9; 12-[[(*tert*-butyldimethylsilyl)oxy]-1-oxododecanylthiomethyl] 19-crown-6 ether, 77744-49-1; mercaptoethyl 19-crown-6 ether, 72037-30-0; 12-[(*tert*-butyldimethylsilyl)oxy]-1-oxododecanylthioethylene] 19-crown-6 ether, 77773-57-0; *cis*-7/8a ω-silyloxy thioester, 77842-82-1; *trans*-7, 77661-78-0; ethanethiol, 75-08-1; 12-[(*tert*-butyldimethylsilyl)oxy]-1-oxododecanylthioethane, 77744-50-4.