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A CROWN ETHER, TEMPLATE-DRIVEN, MACROLIDE CLOSURE

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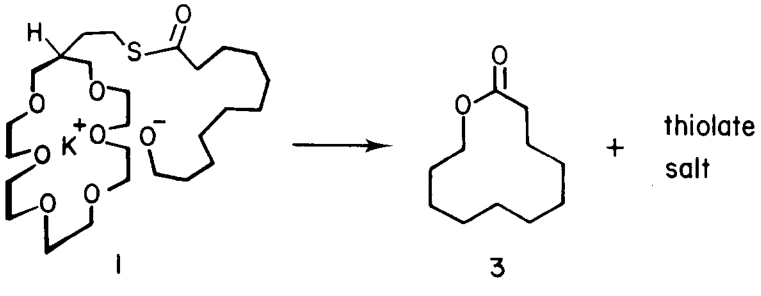
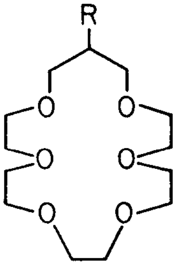
Summary: Macrolide formation from reactive crown ether 1 is driven by the proximate binding of alkoxide and thioester functionalities.

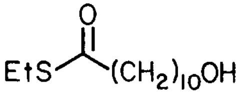
The closure of macrocycles, particularly by ester bond formation, has received intense attention.[1] Random tumbling of the long molecular chain of an ω-hydroxy carboxylic acid makes the closure of macrolides entropically demanding. A macrolide-forming reagent must render mutual reactivity to the ends of a closure intermediate--this criterion is fairly easily met. Ideally, the reagent must be capable as well of drawing the ends of the long molecular chain together prior to the closure reaction. The entropic disadvantage of macrolide closure will not be manifested if sufficient enthalpic advantage is associated with the pre-closure conformation--this second criterion is harder to meet.[2] Herein we report a macrolide closure which is driven by the proximate binding of alkoxide and thioester functionalities in intermediate 1.

Treatment of hydroxy thioester crown 2[3] with potassium tert-butoxide (tert-BuOK) leads via templated alkoxide 1 to macrolide (3).[3] As a control we have performed cyclizations of ethyl thioester 4[3] which lacks the crown ether binding site for the potassium cation. The yield of macrolide formed from thioesters 2 and 4 varies dramatically according to conditions (Table). When crown thioester 2 and tert-BuOK are syringed simultaneously into tetrahydrofuran (THF) at ambient temperature (Table, entry 1) a 44% yield of macrolide results. The macrolide product is stable to the closure conditions (entry 2). Thus when starting materials are injected into THF containing 1.0 equivalent (vs. 2) of macrolide a 148% "yield" of macrolide is obtained (48% yield for the closure reaction). When ethyl thioester 4 and tert-BuOK are injected into THF





2, R=$CH_2CH_2SCO(CH_2)_{10}OH$
5, R=H
6, R=CH_2CH_2SH



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(entry 3) approximately 1% of macrolide is formed; cyclization of 4 in the presence of the unfunctionalized 19-crown-6, 5,[4] is also ineffective for the production of macrolide (entry 4).

A more efficient procedure for macrolide closure utilizes the high dilution head[5] depicted in the *Figure*. Pot A containing THF is maintained at reflux; solvent returned by a reflux condenser fills the high dilution vessel B. Macrolide closure is achieved by simultaneous injection of thioester (2 or 4) and *tert*-BuOK through the sidearms on vessel B. Slowly injected thioester and *tert*-BuOK can react at high dilution in vessel B; at a high reflux rate the starting materials are injected into essentially pure THF, *throughout the entire course of the closure reaction*.[6] By this procedure crown thioester 2 closes to macrolide in 72% yield (entry 5); ethyl thioester 4 closes in 57% yield (entry 6, cf. entry 3). Thus, the advantage of the crown ether template is strongly manifested at medium dilution (cf. entries 1, 3 and 4) and is diminished at high dilution. In principle, in the limit of infinitely dilute solution, thioesters 2 and 4 will close to equal yields of macrolide.

The higher yield obtained by use of the high dilution head for closure of crown thioester 2 apparently reflects some degree of *inter*molecular complexation of the alkoxide of intermediate 1. The complexation of two crown alkoxides (1) may lead to dimeric macrolide product (diolide). Even with use of the high dilution head we have isolated 14% diolide[3] (entry 5) from the closure reaction of crown thioester 2. Interestingly, injection of 2 and *tert*-BuOK into THF containing an excess of unfunctionalized crown 5 (entry 7) does not lead to an appreciably diminished yield of macrolide. Although complexation of 1 and 5 will disrupt the enforced proximity of alkoxide and thioester functionalities, the alkoxide cannot react with the unfunctionalized crown ether (cf. dimer of 1). Complexation/decomplexation of 1 and 5 should be rapid and reversible; apparently any complexation which exists does not significantly reduce the tendency of 1 to react via its internally complexed conformation (see structure 1).

Crown ethers 2 and 5 were dried prior to the *tert*-BuOK initiated closure reactions. To determine the water content of dried 2 and 5 we have scintillation-counted solutions of the crown ethers which were doped with tritiated water prior to drying.[7] Azeotropic drying of a benzene solution of crown ether 5 followed by refluxing the solution over 4Å molecular sieves leaves 0.1 mole % water (vs. crown ether 5) in the benzene solution. Crown thioester 2, how-

Table.

	Thioester	tert-BuOK[a]	Vessel/Solvent	Additive	Addition Time[b]	Yield[c]	Estimated H_2O Content[d]
1	2,0.51 mmol in 16mL ϕH^e	0.53 mmol in 16mL THF^f	Round bottom/ 20mL THF^f	-	10h	44%	-
2	2,0.48 mmol in 15.5mL ϕH^e	0.50 mmol in 15.5mL THF^f	"	0.48 mmol 3	"	148%	-
3	4,0.60 mmol in 22mL ϕH^e	0.63 mmol in 22mL THF^f	"	-	"	~1%	-
4	4,0.50 mmol in 16mL ϕH^e	0.52 mmol in 16mL THF^f	"	0.50 mmol 5	"	5%	-
5	2,0.51 mmol in 18.5mL ϕH^e	0.53 mmol in 18.5mL THF^f	Dilution head[g]/ 30 mL THF^f	-	3.4h	72% (68% macrolide, 14% diolide)[h]	16%
6	4,0.60 mmol in 16mL ϕH^e	0.63 mmol in 16mL THF^f	"	-	4.0h	57%	-
7	2,0.50 mmol in 15.7mL ϕH^e	0.53 mmol in 15.7mL THF^f	Round bottom/ 15mL THF^f + 5 mL ϕH^e	1.3 mmol 5	10h	40%	0.1%

[a] Sublimed. [b] Mechanical syringe drive used. [c] GLC yield unless indicated. [d] ^3H_2O counted, see ref. 7. [e] 4Å molecular sieve dried. [f] Na/benzophenone ketyl dried. [g] Vessel B charged with 4Å molecular sieves. [h] Isolated yields from a similar reaction.

ever is destroyed by prolonged heating. Simple distillation of the benzene/water azeotrope as a forerun from a solution of 2 leaves 16 mole % water (vs. crown ether 2) associated with the pre-closure solution. Association of water with crown thioester 2 undoubtedly leads to destruction of thioester and macrolide. Each diprotic water molecule may reduce the yield of macrolide by as much as two molecules. The data in entry 5 (Table) suggests that the yield of macrolide obtained by our crown template method may be limited primarily by our ability to dry hydroxy thioester crown ether 2.

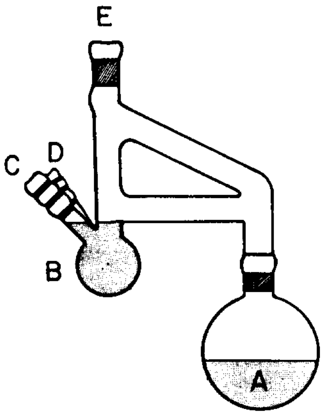

Figure. The dilution head used for macrolide closure. A: refluxing solvent; B: high dilution vessel; C and D: sidearms for injection of tert-BuOK and hydroxy thioester; E: to reflux condenser.

Crown ether 2 was produced for these studies by coupling[8] 11-(*tert*-butyldimethylsilyloxy)-undecanoic acid with thiol crown ether 6, followed by hydrolytic removal of the silyl protective group (H_2O/HOAc).[9] Crown 6 is available in large quantities by a conventional route in which the functionalized crown unit is assembled by malonate alkylation.[4]

We will continue the study of crown template-driven macrolide closures. In particular, we will extend our method to the closure of other ring sizes, and will seek more efficient means of drying the crown ether intermediate and shorter synthetic routes to thiol-substituted crown ethers.

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