Template Macrolactonization of Trichloroethyl Ester Derivatives Catalyzed by Potassium Salts

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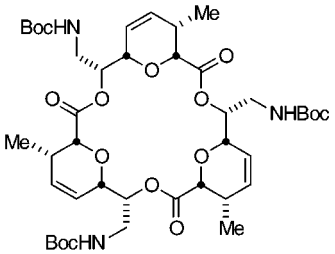
Introduction

We have initiated a program involving the synthesis and study of a variety of unnatural hydropyran-containing macrocycles[1−4] for applications to alkali metal ion sequestration and transport.[5−7] We have recently reported syntheses,[1,2] solid-state structures,[3,4] variable-temperature NMR behavior, and alkali metal binding affinity[4] of a number of hydropyran-containing cyclic oligolides. Macrocycles **1** and **2** are examples of this class of ionophores, both available from the corresponding ω-hydroxy acids.



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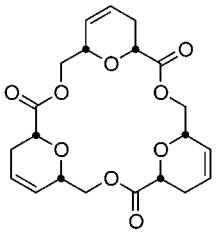

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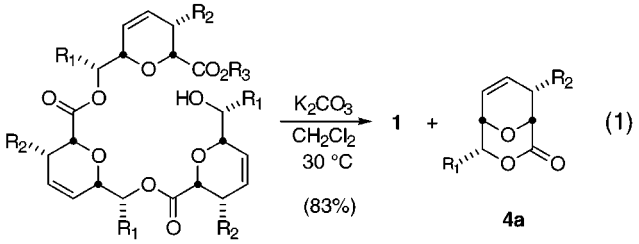
The methods we have used in the past for formation of the 18-membered ring employed high dilution conditions, with carboxylate activation using a carbodiimide−DMAP protocol (Keck−Steglich coupling)[8,9] or involvement of the 2,4,6-trichlorobenzoyl mixed anhydride (Yamaguchi coupling).[10] Although these macrolactonization methods are generally successful, they are complicated by the formation of side products, the necessity to activate the carboxylic acid group, and the requirement of high dilution or syringe-pump methods.

Alkali metal binding studies and molecular modeling indicate that macrolides such as **1** and **2** are well-suited to bind potassium ions;[4] thus, one might expect alkali metal salts to facilitate macrocyclization via a substrate templating effect. As precedent, the templating effect of alkali metal hydroxides in the formation of crown ethers is well-established,[11] and high yields in macrolactonizations of cesium ω-halocarboxylates are thought to be the result of the templating ability of cesium.[12] However, there have been no reports of the templating effect of alkali metal ions on the lactonization of ω-hydroxy acid derivatives.[5] We wish to report here that a variety of alkali metal salts promote macrolactonizations to give **1** or **2** under very mild conditions.

Results and Discussion

During the synthesis of the second-generation trisaminomethyl-appended macrolide **1**, a serendipitous result revealed the ability of alkali metal salts to promote macrolactonization. Acyclic trimer alcohol **3a** ($R_1 = CH_2NHBoc$, $R_2 = Me$, $R_3 = CH_2CCl_3$) was allowed to stand in methylene chloride over a small amount of aqueous K_2CO_3 during workup. After several hours, the sample had been converted to material that was identified as macrocycle **1**, isolated in 83% yield, along with a small, undetermined amount of the bicyclic lactone **4a** ($R_1 = CH_2NHBoc$, $R_2 = Me$, eq 1).



3a
$R_1 = CH_2NHBoc$
$R_2 = Me$
$R_3 = CH_2CCl_3$

4a
$R_1 = CH_2NHBoc$
$R_2 = Me$

Although the inadvertent conditions for this first cyclization were difficult to reproduce, further investigation was indicated. Ester **3a** ($R_1 = CH_2NHBoc$, $R_2 = Me$, $R_3 = CH_2CCl_3$) was thus subjected to a variety of cyclization conditions as summarized in Table 1. Treatment of the trichloroethyl ester **3a** with excess solid alkali metal salt (used without prior purification or drying) was found to give the most reliable results. A survey of common solvents indicated that tetrahydrofuran (THF) is best suited for this reaction (Table 1, entries 1−4). The cyclizations gave decreasing yields of **1** as the concentration was increased (Table 1, entries 4−7), and significantly more side products were observed. It is noteworthy that the use of the smaller alkali metal cations, Na_2CO_3 and Li_2CO_3 (Table 1, entries 8 and 9), gave no detectable cyclization product, while the use of the larger

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Table 1. Cyclization of 3a (R_1 = CH_2NHBoc, R_2 = Me, R_3 = CH_2CCl_3) To Give Macrocycle 1[a]

entry	salt[b]	solvent[c]	concn (M)	time (d)	% yield of **1**[d,e]
1	K_2CO_3[f]	CH_2Cl_2	0.002	5	74 (10)
2	K_2CO_3	PhH	0.002	1	64 (11)
3	K_2CO_3	CH_3CN[g]	0.002	1	38 (62)
4	K_2CO_3	THF[h]	0.002	1	88 (12)
5	K_2CO_3[f]	THF	0.005	2	69 (7)[i]
6	K_2CO_3	THF	0.01	1	60 (10)[j]
7	K_2CO_3	THF	0.1	1	24 (26)[j]
8	Li_2CO_3[f]	THF	0.002	4	0[k]
9	Na_2CO_3	THF	0.002	4	0[k]
10	Cs_2CO_3	THF	0.002	8 h	52 (20)
11	KOAc	THF	0.002	3	47 (0)
12	KI	THF	0.002	3 h	65 (0)
13	NaI	THF	0.002	4	0[k]
14	$KBPh_4$	THF	0.002	3	0[l]

[a] All reactions were carried out at 30 °C. [b] 10 equiv of solid salt was used without prior purification, unless otherwise noted. [c] Solvents were dried in the normal way unless otherwise noted. [d] Isolated yield of macrocycle **1**. [e] Numbers in parentheses indicate isolated yield of bicyclic lactone **4a**. [f] 20 equiv of solid salt used. [g] Used without prior drying. [h] Tetrahydrofuran. [i] Seco acid observed by TLC. [j] Trichloroethyl ester hydrolysis products isolated. [k] Starting material only. [l] No macrocycle present by TLC after 3 days.

alkali metal cation, Cs_2CO_3 (Table 1, entry 10), led to decreased yield. Finally, the effect of the anion was briefly investigated. The use of the less basic KOAc and KI (Table 1, entries 11 and 12) resulted in diminished yield of macrocycle. However, it should be noted that none of the bicyclic lactone side product **4a** was detected in these cases. The use of NaI (Table 1, entry 13) resulted in complete recovery of starting material, and the use of a potassium salt with a nonbasic counterion, $KBPh_4$, resulted in no cyclization after 3 days (Table 1, entry 14). It should be noted that, with the exception of NaI, all of the salts used are essentially insoluble in THF and are thus present in solution in catalytic amounts.

Some additional comment is necessary about the effect of concentration on the cyclization reaction. A cyclization that truly proceeds by the templating effect of a cation would be expected to tolerate higher concentrations.[13] This is clearly not the case here (Table 1, entries 4−7). As the concentration of the reaction increases, the isolated yield of macrocycle **1** decreases, due principally to competing formation of bicyclic lactone **4a** or hydrolysis of the trichloroethyl ester. The low solubility of potassium carbonate in THF ensures a low and constant concentration relative to that of the substrate in these entries. The side reaction leading to **4a**, involving base-induced intramolecular transacylation, would be accelerated by increased substrate concentration, whereas the templated cyclization would not. It is noteworthy that increased substrate concentration does not lead to higher order oligomer formation, further supporting the assertion that a template effect is operative.[13]

Another issue raised by the data in Table 1 is that of cation selectivity. Alkali metal picrate extraction studies[4,14,15] were carried out to determine the cation binding affinity of hydroxy ester **3a** and macrolide **1** (Table 2).

Table 2. Alkali Metal Binding Affinity of Trichloroethyl Ester 3a (R_1 = CH_2NHBoc, R_2 = Me, R_3 = CH_2CCl_3) and Macrolide 1

	K_a (M^{-1})[a], $-\Delta G°$[b] (kcal/mol)			
host[c]	Li^+	Na^+	K^+	Cs^+
3a	3.9×10^4; 6.2	2.4×10^4; 6.0	5.5×10^4; 6.4	1.2×10^4; 5.5
1	3.5×10^4; 6.2	7.1×10^4; 6.6	2.2×10^6; 8.6	1.5×10^4; 5.7

[a] Association constant. [b] Free energy of association. [c] There was no evidence of macrolide formation upon exposure of **3a** to alkali metal picrate salts.

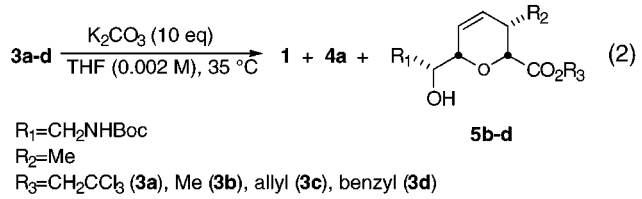
Table 3. Cyclization of Esters 3a−d (R_1 = CH_2NHBoc, R_2 = Me, R_3 = Trichloroethyl, Me, Allyl, Benzyl)

			% yield[a]		
entry	R_3	time (d)	**1**	**4**	**5**
1	CH_2CCl_3 (**3a**)	1	88	12	
2	Me (**3b**)	2[b]	18	50	20
3	allyl (**3c**)	5	39	28	17
4	benzyl (**3d**)	5	37	16	17

[a] Isolated yields. [b] 24 h at 35 °C, 24 h at reflux.

As was the case in earlier picrate binding studies,[4] macrolide **1** selectively binds potassium over the other alkali metal cations tested. The trichloroethyl ester **3a** has a relatively weak affinity for and little selectivity between alkali metal cations. Not all complexes between **3a** and metal cations are likely to have structures that place the ester and hydroxyl groups in proximity. Templated transesterification via a productive binding conformation between **3a** and K^+ is most likely because of the substantial preference (>2 kcal/mol) for K^+·**1** over the other M^+·**1** complexes. In addition, the product macrocycle will more effectively solubilize K^+ salts over those of Li^+, Na^+, or Cs^+. In general, potassium salts gave the highest yields of macrolide product (Table 1).

We next studied the effect of different esters on the cyclization reaction. A series of esters **3b**−**d** (R_1 = CH_2-NHBoc, R_2 = Me, R_3 = Me, allyl, benzyl) were prepared and exposed to the optimized cyclization conditions for trichloroethyl ester **3a** (eq 2 and Table 3). Esters **3b**−**d**



(2)

were less reactive, requiring higher temperatures or longer reaction times for complete consumption of starting material. In addition to macrolide **1** and bicyclic lactone **4a**, the monomer hydroxy esters **5b**−**d** (R_1 = CH_2-NHBoc, R_2 = Me) were isolated from the reaction mixtures. A competition experiment between **3a** (R_3 = CH_2CCl_3) and **3b** (R_3 = Me) in the presence of phenanthrene as an internal standard demonstrated the different rates of cyclization for these esters. Treatment of the mixture with K_2CO_3 in THF at 30 °C for 39 h resulted in complete conversion of **3a** to macrocycle **1**, while leaving **3b** unchanged by ^1H NMR analysis (85% recovery after purification).[16]

The possibility exists that the alkali metal cations are simply acting as Lewis acids and thus promoting trans-

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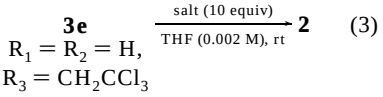
Table 4. Cyclization of 3e ($R_1 = R_2 = H$, $R_3 = CH_2CCl_3$) to Macrocycle 2 (Eq 3)



(3)

entry	salt[a]	time (h)	yield[b] (%)
1	K_2CO_3	2	90
2	Na_2CO_3	36	73[c]
3	Cs_2CO_3	1	93
4	KOAc	1	96
5	KI	2	81
6	NaI[d]	10 min	90
7	LiI[d]	18	10[e]
8	KBF_4	24	0[e]
9	$NaBF_4$	24	0[e]
10	$KBPh_4$	24	0[e]
11	$NaBPh_4$[d]	25	0[e,f]
12	KPF_6	22	0[e]

[a] Used without prior purification or drying. [b] Isolated yield of macrocycle **2**. [c] Starting material and bicyclic lactone **4e** ($R_1 = R_2 = H$) were observed by crude NMR. [d] Completely soluble in THF. [e] Unreacted starting material was recovered. [f] Unidentified decomposition product was noted by TLC.

esterification, as has been demonstrated for a different system.[18] If the cation's only function was as a Lewis acid and the templating effect was unnecessary, interas well as intramolecular transesterifications should be facilitated.[13] However, attempts to promote intermolecular transesterifications under similar conditions, even in the presence of excess methanol, were unsuccessful.

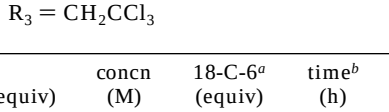
Formation of the unsubstituted oligolide **2** ($R_1 = R_2 = H$) from the corresponding trichloroethyl ester **3e** ($R_1 = R_2 = H$, $R_3 = CH_2CCl_3$) was then investigated, as summarized in Table 4 (eq 3). The optimal conditions for macrocycle **1** also gave an excellent yield of macrocycle **2** (Table 4, entry 1). The reaction time necessary for consumption of starting material was considerably shorter for the unsubstituted case. The use of the smaller sodium cation, Na_2CO_3, resulted in a sluggish reaction, giving 73% of **2** after 36 h, along with bicyclic lactone **4e** ($R_1 = R_2 = H$) and unreacted starting material (Table 4, entry 2). The larger cesium cation, Cs_2CO_3, showed reactivity similar to that of K_2CO_3 (Table 4, entry 3). The use of the less basic KOAc (Table 4, entry 4) gave fast, clean conversion to the desired macrolide. The use of alkali metal iodides (Table 4, entries 5−7) gave unexpected results. KI behaved similarly to potassium salts in earlier entries, giving macrocycle **2** in good yield after about 2 h, and NaI gave a 90% yield of macrolide **2** in 10 min. Our prior experience was that sodium salts were less effective than the corresponding potassium salts. However, this discrepancy may be partially explained (see below) by the fact that NaI is completely soluble in THF at the concentration of the reaction, where KI is much less soluble. Solubility of the alkali metal salt is not sufficient to guarantee success, as evidenced by the fact that LiI results in only 10% conversion to macrocycle after 18 h and $NaBPh_4$ results in no reaction after 25 h (Table 4, entry 11). A series of potassium and sodium salts with nonbasic counterions (Table 4, entries 8−12) routinely returned starting material after 24 h. The reaction conditions that typically gave the highest yield of macrocycle **2** in the shortest amount of time with a simple filtration workup were excess KOAc in THF at room temperature for about 1 h (Table 4, entry 4).

Table 5. Alkali Metal Binding Affinity

host[c]	K_a (M^{-1})[a]; $-\Delta G°$[b] (kcal/mol)	
	Na^+	K^+
3e	4.9×10^4; 6.4	3.6×10^4; 6.2
2	4.6×10^4; 6.3	7.2×10^5; 8.0
cis-dicyclohexano-18-crown-6[d]		2.0×10^8; 11.3

[a] Association constant. [b] Free energy of association. [c] There was no evidence of macrolide formation upon exposure of **3e** to potassium or sodium picrate. [d] See ref 15.

Table 6. Cyclization of 3e ($R_1 = R_2 = H$, $R_3 = CH_2CCl_3$) with a Catalytic Amount of Acetate Salt



(4)

entry	M^+ (equiv)	concn (M)	18-C-6[a] (equiv)	time[b] (h)	% yield of **2**[c]
1	K (0.5)	0.002		1	100
2	K (0.5)	0.002	1	24	97
3[d]	K (0.05)	0.05[e]		1	87
4	Bu_4N (0.5)	0.002		8	trace[f]
5	Bu_4N (0.5)	0.002	1	18	trace[f]

[a] *cis*-Dicyclohexano-18-crown-6. [b] The reactions were allowed to proceed until starting material was gone by TLC. [c] Isolated yield of macrolide **2**. [d] This experiment was carried out on 1.2 mmol (0.68 g) of trimer alcohol **3e**. [e] This was the highest concentration at which trimer alcohol **3e** was completely soluble in THF. [f] NMR analysis of the crude reaction mixture showed a small amount of macrolide **2** along with bicyclic lactone **4e** and unidentified degradation products.

Table 5 lists the sodium and potassium picrate binding affinities of unsubstituted ester **3e** ($R_1 = R_2 = H$, $R_3 = CH_2CCl_3$) and macrolide **2** and the potassium picrate binding affinity of *cis*-dicyclohexano-18-crown-6.[15] The lack of substitution in **2** removes one of the major conformational control elements present in macrolide **1**, resulting in a less preorganized binding array.[4] The lower overall binding affinity for K^+ and selectivity for K^+/Na^+ (compare Tables 2 and 5) is a reflection of the increased flexibility of macrolide **2** relative to macrolide **1**.[4] Presumably, this increased flexibility applies as well to the substrate **3e**, allowing productive template complexes with a range of cation sizes.

On the basis of the optimized conditions from Table 4, the experiments presented in Table 6 (eq 4) provide informative data regarding the cyclization reaction. First, the cyclization proceeds to completion with substoichiometric amounts of the potassium salt (Table 6, entries 1 and 3), indicating that the macrocycle, while selective for binding potassium (see Table 5), is not a sufficiently strong binder to effectively remove it from the reaction mixture. In the presence of *cis*-dicyclohexano-18-crown-6, a more effective potassium binder,[15] the reaction is substantially inhibited (Table 6, entry 2). The cyclization reaction was found to tolerate higher concentration and less catalyst (Table 6, entry 3); e.g., 680 mg of trimer alcohol **3e** was converted to macrocycle **2** in 87% yield using 6 mg of KOAc in 24 mL of THF. Replacement

(16) The details of the competition experiment are available with the Supporting Information for this paper.

(17) Koskikallio, J. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; Interscience: New York, 1969; pp 103−136.

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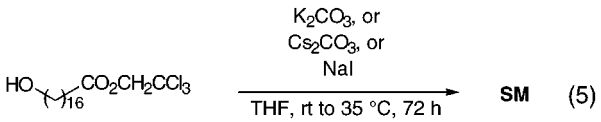
of K^+ with a nontemplating cation (Table 6, entries 4 and 5) provided only a small amount of macrocycle **2**, along with bicyclic lactone **4e** and other degradation products.

To determine whether the polydentate coordinating ability of the substrates **3a** and **3e** is necessary for successful cyclization, trichloroethyl 17-hydroxyheptadecanoate (**6**) was prepared[19] and subjected to several lactonization attempts. In all cases, NMR analysis of the crude reaction mixtures showed only starting material after heating for extended periods (eq 5). These experiments indicate that the trichloroethyl ester group is not sufficiently activated to under go an intra- or intermolecular transesterification reaction under these conditions.



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Summary and Conclusion

We have described macrolactone formation from a hydroxy ester utilizing the templating effect of alkali metal cations to facilitate an intramolecular transesterification reaction. In most cases, the rate-limiting step of a transesterification is the addition of the alcohol or alkoxide fragment to the carbonyl carbon, followed by fast breakdown of the resulting tetrahedral intermediate.[17] The data presented herein suggest that the conversions of **3a** to **1** and **3e** to **2** are M^+-templated cyclizations wherein the collapse of the tetrahedral intermediate is the slow step.[20] With the proximity of the hydroxyl and ester moieties enforced and the associated entropic costs paid by the template effect, the formation of the tetrahedral intermediate would be facilitated for all substrates **3a**−**d**. The rate of the productive collapse of this intermediate would be dependent upon the departing alkoxide nucleofuge, thus the superiority of the trichloroethyl esters. Macrolactonization of ester **3e** was successful with a catalytic amount of KOAc and was inhibited by the addition of *cis*-dicyclohexano-18-crown-6. Unfunctionalized hydroxy trichloroethyl ester **6**, incapable of being templated, was completely inert to the cyclization conditions. All of these observations are consistent with a templated cyclization mechanism.

Experimental Section

General Methods. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and benzene were distilled from sodium/benzophenone immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 immediately prior to use. Silica gel chromatography was performed according to the method of Still.[21] Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00), and coupling constants (J) are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz. Where indicated, distortionless enhancement by polarization transfer (DEPT) was used to assign carbon resonances as CH_3, CH_2, CH, or C. Chemical shifts are reported in ppm relative to Me_4Si (δ 0.00). Elemental analyses were performed by Desert Analytics Laboratories (Phoenix, AZ).

General Procedure for Macrolactonization. To a solution of acyclic trimer alcohol **3** in THF (0.002 M) was added the alkali metal salt (10 equiv). The reaction flask was flushed with N_2 and capped, and the mixture was stirred at the indicated temperature. The progress of the reaction was followed by TLC analysis until the starting material was consumed. The mixture was filtered and the solid washed with ether or CH_2Cl_2 and concentrated. The crude reaction mixture was purified by silica gel chromatography.

Macrolide 1: R_f 0.45 (5% MeOH in CH_2Cl_2); ^{1}H NMR (CD_3OD, 250 MHz, 85 °C) δ 6.08 (ddd, 3H, J = 10.3, 5.7, 2.4 Hz), 5.71 (br d, 3H, J = 10.1 Hz), 5.35−5.29 (m, 3H), 4.55−4.52 (m, 3H), 4.41 (d, 3H, J = 3.4 Hz), 3.66−3.55 (m, 3H), 3.40 (dd, 3H, J = 14.5, 2.9 Hz), 2.58−2.48 (m, 3H), 1.42 (s, 27H), 1.05 (d, 9H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 171.1 (C), 158.4 (C), 134.0 (CH), 124.6 (CH), 80.6 (C), 77.8 (CH), 77.5 (CH), 75.4 (CH), 39.0 (CH_2), 33.3(CH), 28.8(CH_3 × 3), 15.3(CH_3); IR (thin film) 3408 (br), 2976, 1741, 1709, 1506, 1367, 1286, 1170 cm^{-1}; MS (FAB) *m/e* (relative intensity, assignment) 982.3 (60, M + Cs^+), 888.4 (90, M + K^+), 872.4 (75, M + Na^+), 850.4 (10, M + H^+), 750.4 (100, M + H^+ − C_4H_8 − CO_2), 694.3 (30, M + H^+ − 2C_4H_8 − CO_2); $[\alpha]^{22}_D$ +218.0 (c=3.9, CH_2Cl_2).

Bicyclic lactone 4a (R_1 = CH_2NHBoc, R_2 = Me): mp 110−112 °C; R_f 0.26 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89 (br d, 1H, J = 10.3 Hz), 5.72 (ddd, 1H, J = 10.3, 3.7, 2.6 Hz), 5.00−4.95 (m, 1H), 4.72 (ddd, 1H, J = 8.1, 4.0, 4.0 Hz), 4.43 (d, 1H, J = 5.9 Hz), 4.35−4.33 (m, 1H), 3.58−3.49 (m, 1H), 2.97−2.82 (m, 2H), 1.40 (s, 9H), 1.04 (d, 3H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5 (C), 155.8 (C), 134.6 (CH), 120.9 (CH), 81.5 (CH), 80.0 (C), 73.6 (CH), 66.3 (CH), 41.3 (CH_2), 32.7 (CH), 28.3 (CH_3), 15.2 (CH_3); IR (thin film) 3256 (br), 2978, 1745, 1711, 1514, 1367, 1229, 1170 cm^{-1}; MS (FAB) *m/e* (relative intensity, assignment) 306.2 (100, M + Na^+), 250.1 (40, M + Na^+ − C_4H_8), 228.2 (45, M + H^+ − C_4H_8); $[\alpha]^{22}_D$ +70.6 (c = 0.6, CH_2Cl_2).

Macrolide 2: mp 80−87 °C; R_f 0.25 (2% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02−5.94 (m, 1H), 5.58−5.51 (m, 1H), 4.60−4.52 (m, 2H), 4.25 (dd, J = 10.7, 3.7 Hz, 1H), 3.95 (dd, J = 12.1, 9.2 Hz, 1H), 2.47−2.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C), 127.0 (CH), 124.8 (CH), 73.6 (CH), 72.5 (CH), 66.6 (CH_2), 27.7 (CH_2); IR (neat) 2947, 1734, 1298, 1184, 1099, 727 cm^{-1}; MS (FAB) *m/e* 420.1 (M + H^+), 443.1 (M + Na^+), 460.1 (M+K^+); $[\alpha]^{20}_D$ +181° (c = 1.53, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}O_9$: C, 60.00; H, 5.75. Found: C, 59.48; H, 5.95.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **3a**, **3e**, and **4e**; details of the syntheses of ester derivatives **3b**−**d** (Table 3); and details of competition experiment between **3a** and **3b** are presented (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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