# Synthesis and Study of $C_3$-Symmetric Hydropyran Cyclooligolides with Oriented Aryl and Alcohol Appendages at 10 Å Spacing

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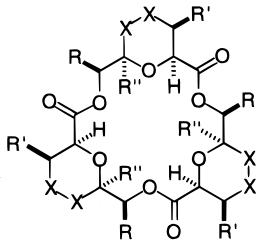
Modular syntheses of $C_3$-symmetric macrocycles with pendant aryl and hydroxymethyl groups are described. These functional groups, amenable to further elaboration, were installed early in each synthesis and carried through an iterative sequence of module coupling and macrolactonization. Association constants for macrolides **1a**−**c** with alkali metal cation guests were determined, and sandwich-type complexes with $Ba^{2+}$ were confirmed for these macrocycles based on $^1$H NMR studies, including Job plots. X-ray crystallographic data for macrolides **1a** and **1c** were obtained and are discussed in detail. These data provide support that the macrolides are structurally well-defined and preorganized for binding the potassium cation. Preparation of the tris(bromoacetylated) macrotriolide **43** exemplifies a functionalized platform suitable for elaboration with peptide or carbohydrate residues.

## Introduction

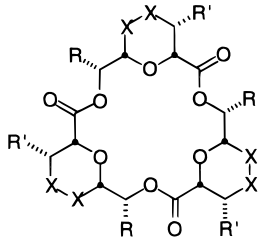
We have recently reported the synthesis and study of 18- to 72-membered cyclic hydropyran oligolides bearing methyl and phenyl appendages.[1] Further studies have led to the elucidation of structural elements important for control of the shape and cation-binding efficacy of these unnatural ionophores.[2] The data presented in these studies verify the rigid and preorganized nature of the 18-membered ligand arrays, enforced by the cooperative action of several conformational control elements. We have also reported the synthesis and study of a series of second-generation triolides, bearing aminomethyl (**2b**), (dimethylphosphono)methyl (**2c**), and 2-furyl (**1e**, **1f**) substituents.[3] The availability of these conformationally homogeneous macrocycles with appendages oriented perpendicular to the macrocycle suggests their employment as templates for oligosaccharide displays, ion channel helical peptide bundles,[4] or collagen-like triple-helix[5] mimics. Such applications require more functionalized pendant groups with appropriate spacings.

Described herein are synthetic routes leading to triphenyl triolide **1a** and tris(hydroxymethyl) derivatives **1b**, **1c**, and **1d** (Chart 1), where these R′ substituents occupy axial orientations on each hydropyran, more widely dispersed than if the substituents were directly on the 18-membered ring (R in **2a**−**c**). It was of interest to prepare **1a**, the regioisomer of **2a**, to determine whether the location and spacing of the phenyl groups would affect the overall shape and binding efficacy of the macrolides.

**Chart 1**



**1a**, R = Me, R' = Ph, R'' = H, X-X = CH=CH
**1b**, R = Me, R' = $CH_2OPMB$, R'' = H, X-X = CH=CH
**1c**, R = Me, R' = $CH_2OBn$, R'' = H, X-X = CH=CH
**1d**, R = Me, R' = $CH_2OH$, R'' = H, X-X = $CH_2CH_2$
**1e**, R = 2-furyl, R' = $CH_3$, R'' = H, X-X = $CH_2CH_2$
**1f**, R = 2-furyl, R' = $CH_3$, R'' = 2-furyl, X-X = $CH_2CH_2$



**2a**, R = Ph, R' = Me, X-X = CH=CH
**2b**, R = $CH_2NH_3Cl$, R' = Me, X-X = CH=CH
**2c**, R = $CH_2PO(OMe)_2$, R' = Me, X-X = CH=CH

Additionally, when compared to an average distance of 6 Å between the polar functional groups R in macrolides **2b** and **2c**, the distance between hydroxymethyl groups R′ of **1d** would be about 10 Å, which is comparable with the estimated interhelical distance for four helix peptide bundles described by DeGrado and Eisenberg.[6] Thus, preparation of **1a**−**d** was expected to provide additional

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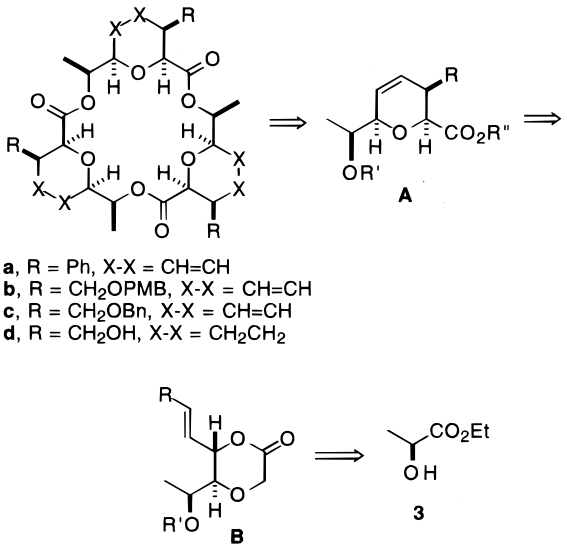
**Scheme 1**



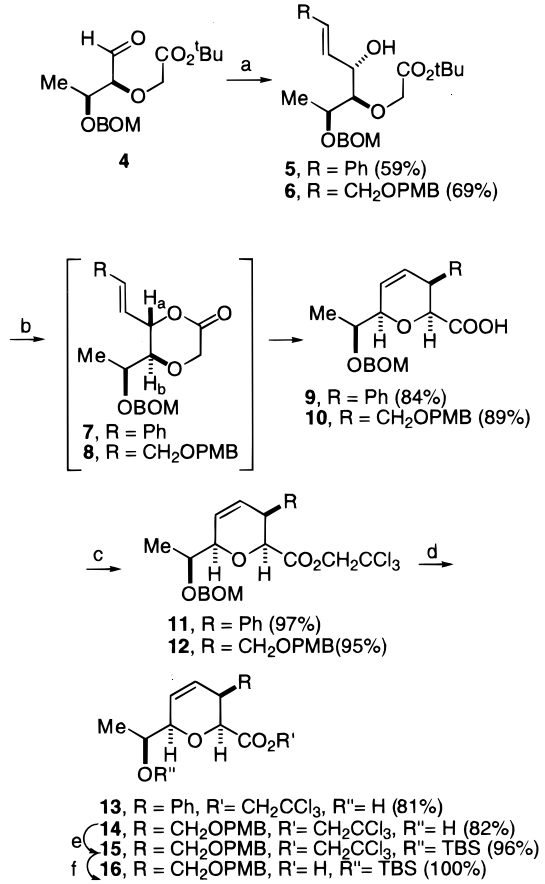

diversity in the nature and spacing of functionality pendant to the macrocycle scaffold for this class of macrocycles.

## Results and Discussion

Retrosynthetic analysis for macrolides **1a**−**d** is shown in Scheme 1. Reductive removal of hydroxyl protecting groups in **1b** or **1c** would afford **1d**. Macrolides **1a**−**c** were envisioned to come from iterative esterification couplings of three properly functionalized dihydropyran subunits **A** (R′ or R″ = H), followed by macrolactonization of the resulting seco acids. Dihydropyrans of general structure **A** could be obtained via an ester enolate Ireland−Claisen rearrangement[7] of the silyl ketene acetals derived from the trans-substituted dioxanones **B**. A sequence of chelation controlled additions to a protected derivative of (*S*)-(−)-ethyl lactate (**3**) followed by lactonization would result in the enantiomerically pure dioxanones generalized as **B**.

Synthetically (Scheme 2),conversion of (*S*)-ethyl lactate to aldehyde **4**[8] was followed by cuprate additions,[9,10] yielding allylic alcohols **5** and **6**. Trifluoroacetic acid-induced lactonization[11] of **5** and **6** proceeded without incident, supplying the trans-substituted dioxanones **7** and **8** ($J_{ab}$ = 9 Hz) in quantitative yield by $^1$H NMR analysis of the crude products. Conversion of the dioxanones to the corresponding silyl ketene acetals and thermolysis effected the Ireland−Claisen rearrangements[7] to afford carboxylic acids **9** (suitable for modular coupling) and **10**, respectively, after acidic workup. Protection of **9** and **10** as their trichloroethyl esters[12] **11**

**Scheme 2**[a]




[a] Reagents: (a) **4** to **5**, *trans*-$Ph_3SnCHCHPh$, PhLi, $Et_2O$, CuI·P*n*-$Bu_3$, −78 °C; **4** to **6**, *trans*-$Bu_3SnCHCHCH_2OPMB$, BuLi, CuI·P*n*-$Bu_3$, $Et_2O$, THF, −78 °C; (b) TFA, PhH, reflux; LHMDS, TMSCl-$Et_3N$, THF, −78 °C; reflux; (c) $HOCH_2CCl_3$, DIC, DMAP, DMAP·TFA, $CH_2Cl_2$, 40 °C; (d) $Me_2S$, $BF_3$·$Et_2O$, $CH_2Cl_2$, 0 °C; (e) imidazole, TBSCl, DMF; (f) LiOH, *t*-BuOH, 45 °C.

and **12** was followed by benzyloxymethyl ether removal,[13] yielding alcohol coupling modules **13** and **14**. Protection of **14** as its silyl ether **15** was followed by basic hydrolysis to give acid coupling partner **16**.

Preparation of modular coupling partners for assembling **1c** is shown in Scheme 3. Protection of (*S*)-ethyl lactate as its *p*-methoxybenzyloxymethyl ether **18**[14,15] was followed by a stereoselective, one-pot addition−reduction sequence[8b] to afford **19** (*β*-OH), which was then converted in three steps (O-alkylation,[16] ozonolysis, and cuprate addition[9,10]) to allylic alcohol **21**. Dihydropyran acid **22** was generated analogously to the sequence described for **9** and **10** in Scheme 2. Protection of the acid as its trichloroethyl ester, **23**, followed by removal of the *p*-methoxybenzyloxymethyl ether[17] gave alcohol coupling module **24**. Acid coupling module **26** was then prepared in two steps from **24** by a sequence similar to that described for **16** in Scheme 2.

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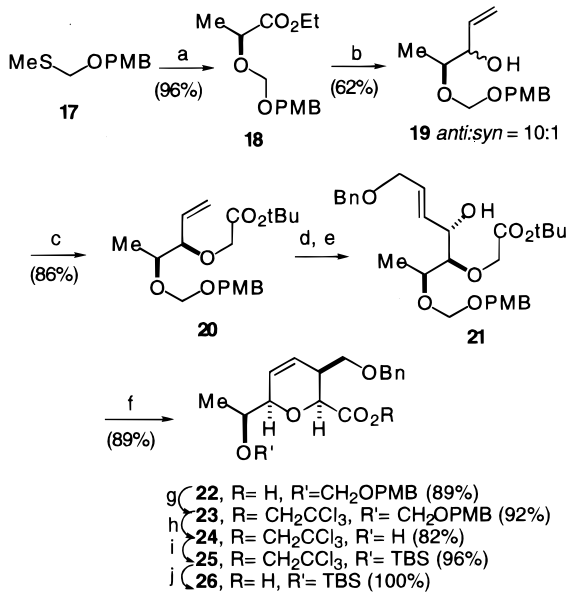
**Scheme 3**[a]



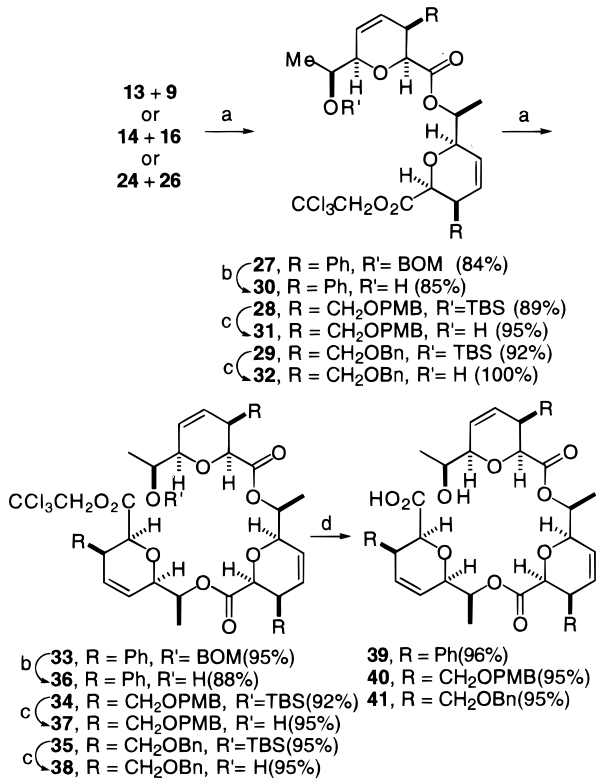

[a] Reagents: (a) $SO_2Cl_2$, $CH_2Cl_2$, −78 °C; (*S*)-ethyl lactate, $iPr_2NEt$, $CH_2Cl_2$; (b) $CH_2CHMgBr$, $LiBH_4$, THF, −20 °C; (c) $BrCH_2CO_2{}^tBu$, 50% NaOH, PhH, $Bu_4NHSO_4$, 0 °C; (d) $O_3$, $CH_2Cl_2$, −78 °C; $Ph_3P$, −78 °C to rt; (e) *trans*-$Bu_3SnCHCHCH_2OBn$, BuLi, CuI·P*n*-$Bu_3$, $Et_2O$, THF, −78 °C, 65%; (f) TFA, PhH, reflux; LHMDS, TMSCl−$Et_3N$, THF, −78 °C; reflux; (g) $HOCH_2CCl_3$, DIC, DMAP, DMAP·TFA, $CH_2Cl_2$, 40 °C; (h) DDQ, 1:8 $H_2O$/$CH_2Cl_2$; (i) Imidazole, TBSCl, DMF; (j) LiOH, *t*-BuOH, 45 °C.

With the acquisition of three sets of alcohol and acid coupling partners, the stage was set to implement the iterative esterification strategy (Scheme 4). Module coupling via the Yamaguchi esterification protocol[18] provided pseudodimers **27**−**29**. Cleavage of benzyloxymethyl or *tert*-butyldimethylsilyl groups (R′) effected deprotection of **27**−**29** to afford secondary alcohols **30**−**32**. Coupling of these alcohols with matched monomer acid units **9**, **16,** or **26**, again using the Yamaguchi esterification conditions, proceeded uneventfully to yield the fully protected acyclic pseudo trimers **33**−**35**. Removal of the secondary hydroxyl protecting group under the aforementioned conditions yielded trimer alcohols **36**−**38**, and reductive cleavage of the trichloroethyl esters[19] gave seco acids **39**−**41** without incident.

Macrolactonizations under Keck−Steglich high dilution conditions[20] gave **1a**−**c** (Scheme 5), and catalytic hydrogenation[21] provided **42** (from **1a**) and **1d** (from **1b** and **1c**). Macrolide triol **1d** was further elaborated to the tris(bromoacetylated) macrotriolide template **43** for attachment of α-helical peptides through a chemical ligation strategy.[22,23]

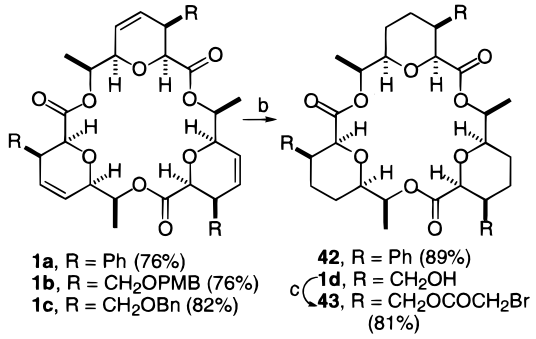
The solid-state conformations of **1a** and **1c** were determined by X-ray crystallographic analysis (Figure 1, H atoms omitted). In both structures, solvent molecules ($H_2O$ and MeOH, respectively) are trapped in the lattice,

**Scheme 4**[a]




[a] Reagents: (a) acid (**9**, **16** or **26**), $Et_3N$, 2,4,6-trichlorobenzoyl chloride, THF; alcohol (**13**, **14**, **26**, or **30**−**32**), DMAP, $Et_3N$, PhH; (b) $Me_2S$, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 0 °C; (c) HF, $CH_3CN$, 0 °C; (d) Zn, THF, $K_2HPO_3/KH_2PO_3$ buffer.

**Scheme 5**[a]




[a] Reagents: (a) DIC, DMAP, DMAP·TFA, $CHCl_3$, reflux; (b) $H_2$, $Pd(OH)_2$ on C, EtOH: **1b** to **1d**, 81%; **1c** to **1d**, 92%; (c) $BrCH_2COBr$, DMAP, $CH_2Cl_2$, −78 °C.

forming hydrogen-bonded arrays with macrolides **1a** and **1c**, respectively. Both **1a** and **1c** have pseudo-$C_3$ symmetry with well-defined cavities, lined with six oxygen atoms with convergent lone pairs. The cavity-defining oxygen atoms (O2a, O2b, O2c, O3a, O3b, O3c) of **1a** are nearly coplanar, with the three carbinol ester oxygens directed slightly up (O2a, 0.0578 Å; O2b, 0.1405 Å; O2c, 0.2458 Å) and the three dihydropyran oxygens directed slightly down (O3a, −0.042 Å; O3b, −0.2416 Å; O3c, −0.1604 Å) with respect to the mean plane defined by these six atoms. A similar arrangement is found in **1c**, where the three carbinol ester oxygens are directed up (O1a, 0.2355 Å; O1b, 0.2029 Å; O1c, 0.2181 Å) and the three dihydropyran oxygens are directed down (O5a, −0.2192 Å; O5b, −0.2035 Å; O5c, −0.2338 Å) with respect

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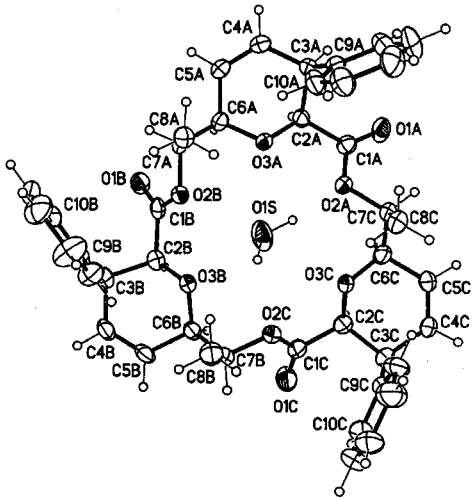
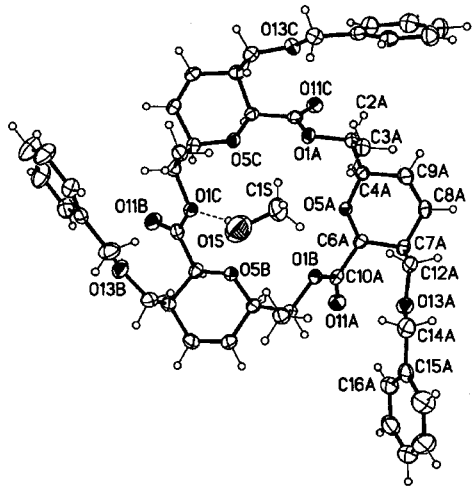



**1a**




**1c**

**Figure 1.** X-ray crystal structures of **1a** and **1c** (top view), showing the atom-labeling scheme.

to the mean plane formed by these oxygens. This alternating up and down ligand directionality and magnitude of deviation from planarity is similar to that determined for [18]crown-6 derivatives.[24] For **1a**, the average of the distances from dihydropyran oxygens to the carbinol ester oxygens across the macrocyclic ring (i.e., O3a−O2c, 5.463 Å; O3b−O2a, 5.241 Å; O3c−O2b, 5.355 Å) is approximately 5.353 Å, whereas that for **1c** is approximately 5.396 Å. This distance in **1a** and **1c** is close to the sum of twice the van der Waal radius of oxygen (1.4 Å) and twice the ionic radius of $K^+$ (1.38 Å), suggesting **1a**, **1c** and their derivatives should selectively bind potassium ions (vide infra). The cavity radii for **1a** and **1c** are nearly identical to the cavity radius of approximately 1.37 Å in tartrate-derived 18-C-6 hexacid templates described by Fyles.[25] The phenyl groups in **1a** and benzyloxymethyl groups in **1c** are oriented nearly perpendicular to the mean planes of the macrocyclic rings, as was predicted

**Table 1. Comparative Association Constants ($K_a$, $M^{-1}$) and Association Free Energies ($-\Delta G°$, kcal·mol$^{-1}$) of Macrocyclic Hosts for Picrate Salt Guests in $CDCl_3$ Saturated with $H_2O$ at 23−25 °C**

| host | $Li^+$ | $Na^+$ | $K^+$ |
|---|---|---|---|
| **1a** | <5000; <5 | $1.5 \times 10^4$; 5.7 | $2.4 \times 10^5$; 7.3 |
| **1b** | $1.3 \times 10^5$; 7.0 | $1.9 \times 10^5$; 7.2 | $7.7 \times 10^6$; 9.4 |
| **1c** | $1.3 \times 10^4$; 5.9 | $4.4 \times 10^4$; 6.3 | $5.7 \times 10^6$; 9.2 |
| **2a** | $<5.0 \times 10^3$; <5.0 | $<5.0 \times 10^3$; <5.0 | $1.4 \times 10^4$; 5.7 |
| dicyclohexano-18-C-6 | $1.9 \times 10^5$; 7.2 | $2.3 \times 10^6$; 8.7 | $2.0 \times 10^8$; 11.3 |

from the cooperative conformational constraints within these macrocycles.[2] The average distance between benzyl ether oxygen atoms in **1c** is 9.6 Å.

The association constants ($K_a$) and binding free energies of macrocyclic hosts **1a**−**c** in $CDCl_3$ saturated with $H_2O$ at 23−25 °C were determined by measurements from the $CDCl_3$ layer using Cram's picrate extraction method (Table 1).[26] The absorption maxima ($348 < \lambda_{max} < 362$ nm) of the picrate salts are indicative of 1:1 complexes between metal picrate and macrocyclic hosts.[27] Triolide **1a** has an association constant for $K^+$ 17-fold greater than its regioisomer **2a**.[2] The phenyl groups in **1a** are on the pyran rings, further from the cavity defined by ligating oxygen atoms. This would allow the binding cavity of macrocycle **1a** to be more accessible to cations and would render the final cation complex of macrocycles more stable because of less steric hindrance compared to **2a**. Moreover, **1a**, **1b**, and **1c** exhibit selectivity (as determined by $\Delta\Delta G$) for $K^+$ over $Na^+$ and $Li^+$. Triolides **1a**, **1b**, and **1c** display similar selectivities for $K^+$ over $Na^+$ as the previously prepared triolides[1,2] ($[\Delta\Delta G] = 1.6$, 2.2, 2.9 kcal/mol for **1a**, **1b**, and **1c,** respectively) as expected. This supports the contention that **1a**, **1b**, and **1c** are preorganized for binding $K^+$ in preference to the other cations investigated. Triolides **1b** and **1c** exhibit the highest association constants for $K^+$ of any of the triolide ionophores yet studied in our laboratories. These findings are attributed to the additional alkoxy ligations that could facilitate cation binding. Although the ester linkages are synthetically expedient and conformationally defining, they are less basic sites than the ether oxygens. The consequence of this is illustrated by comparison of the cation association constants for **1a**, **1b**, **1c**, and **2a** to those for *cis*-dicyclohexano-18-C-6.

During the cation-binding studies, a second set of $^1H$ NMR signals, in addition to those from the free macrolide, was observed when $Ba(OTf)_2$ was added to a $CD_3CN$ solution of macrolide **1b** (Figure 2). The new set of signals maintained the simplicity, coupling, and splitting pattern found in the corresponding free macrolide, suggesting a symmetrical structure of the new species. The intensity of the new set of signals increased while the intensity of the free macrolide decreased as $Ba(OTf)_2$ was added. On the basis of these results, the new set of signals was assigned to that of $Ba^{2+}$-complexed macrolide. Slow exchange of the $Ba^{2+}$ is inferred from the clear appearance of two states, complexed and uncomplexed.

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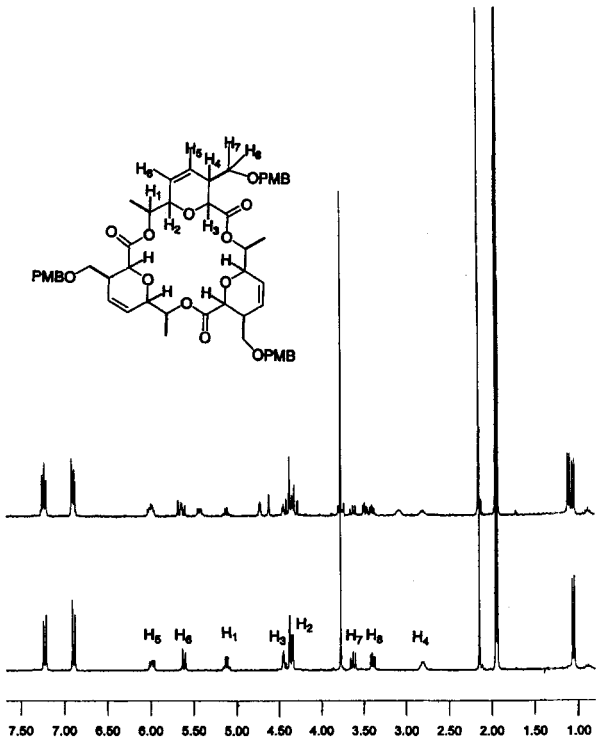


**Figure 2.** $^1$H NMR spectra of free macrolide **1b** (bottom) and a mixture of free macrolide **1b** and its $Ba^{2+}$ complex (top).

The proton resonances of complexed macrolide exhibit large downfield shifts relative to the free macrolide, reflecting the electron-withdrawing nature of the $Ba^{2+}$ cation. Similar data have been acquired for macrocycles **42** and **1c** (see the Supporting Information).

As shown above and in previous studies, the 18-membered macrocycles made in our laboratory are known to form 1:1 complexes with alkali metal ions. To determine the binding mode and stoichiometry of the barium complex, the method of continuous variation, also known as a Job plot,[28] was applied. In this method, the total molar concentration of barium salt and ligand macrocycle is held constant, but their mole fractions are varied. A measurable parameter that is proportional to complex formation is plotted against the mole fractions of the macrocycle ligand. In this case, the concentration of the complex was calculated from integration of $^1$H NMR signals characteristic of complexed and free macrocycle. A special point, the highest concentration of the assumed complex, is determined from the plot, and the binding stoichiometry is calculated from the ratio of mole fractions at that point. As shown in Job plots (Figure 3) for macrocycles **42** and **1b**, the highest concentration of the complex corresponds to a host mole percent of 67.5%, indicating formation of 2:1 host/guest complexes. The Job plot for macrocycles **1c** (see the Supporting Information) also indicates formation of a 2:1 host/guest complex.

Natural ionophores have been shown to form stable, lipophilic "sandwich"-type complexes with $Ba^{2+}$.[29,30] More systematic investigations show that, though the cavity-metal ion size relationship[31] is very plausible, it should be emphasized that this concept is an oversimplification. Other important factors affecting the complex structures, such as ligand substituents,[32] charge density of cation,[33] and counteranion[34] are involved. For an alkali metal ion as a spherical guest, the optimum complementary structural feature is a cavity of corresponding size, lined with polar groups in order to provide maximum interaction through ion−dipole forces. An arrangement of this type was shown by X-ray crystallography to exist in the complex of $K^+SCN^-$ (Figure 4) and host **44**,[2] the solid-state conformation of which is very similar to that of **1a** and **1c**. The pyran oxygens (O3a,b,c) and carbinol ester oxygens (O2a,b,c) to $K^+$ distances (2.799−2.806 Å and 2.699−2.745 Å, respectively) are all close to the sum of the van der Waals radii of oxygen (1.40 Å) and $K^+$ (1.38 Å).[35] Comparison of the solid-state conformations of host **44** and the **44**·$K^+$ complex reveals a nearly perfect overlap of the macrocycle in the free and complexed states. It should be noted that $K^+$ sits in the center of the cavity and is 0.6365 Å away from the average plane of the six coordinating oxygens. The $K^+$ is not very well shielded, and there are direct interactions with the $^-$SCN counteranion. Since the ionic radius of $Ba^{2+}$ (1.42 Å)[35] is slightly greater than that of $K^+$, $Ba^{2+}$ would occupy a site

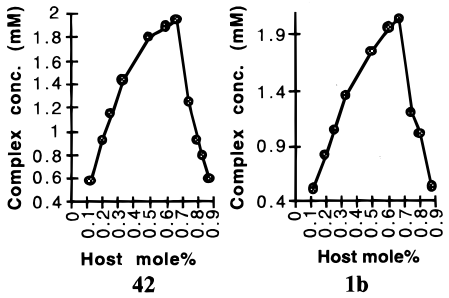


**Figure 3.** Job plots for complexes from macrocycles **42** and **1b** and $Ba(OTf)_2$. Total concentration of host and guest is 5.17 and 4.1 mM, respectively.

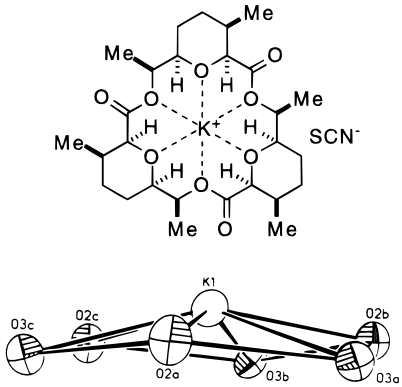


**Figure 4.** $K^+$ complex of macrocycle **44**.

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further above the plane of the macrocycle, which leads to a less favorable interaction with ligand donor atoms. In addition, $Ba^{2+}$ would prefer a high coordination environment because of its higher charge density as compared to $K^+$ and dominant ion−dipole effect.[36] Therefore, formation of "sandwich" dimeric complexes of stoichiometry $Ba^{2+}L_2$ better satisfies the coordination demands of divalent barium.

## Summary

Synthetic macrotriolides **1a**−**d**, **42**, and **43**, with $C_3$ symmetry and pendant functionality oriented normal to the macrocyclic plane, have been prepared and characterized. An iterative, modular synthetic strategy has been demonstrated, and the recognition and binding properties of the ionophores **1a**−**c** and **42** have been delineated. X-ray crystallographic analyses for macrotriolides **1a** and **1c** are fully described, and the formation of 2:1 complexes between macrocyclic ligands **1b**, **1c**, and **42** and $Ba^{2+}$ has been confirmed by Job plot analyses of $^1$H NMR data. Conversion of triol **42** to tris(bromoacetyl) derivative **43** illustrates the potential of these functionalized macrocycles to serve as scaffolds for oriented attachment of recognition elements such as carbohydrates or peptides. For example, a trivalent display of mannose residues on template **1d** has been prepared and found to have unusual lectin binding properties.[37]

## Experimental Section

**General Methods.** Optical rotations were measured on a digital polarimeter at room temperature (22−23 °C). Concentrations (*c*) are reported in g/100 mL. Infrared spectral (IR) signals are reported in wavenumbers ($cm^{-1}$) with the designation (br) signifying a broad signal. Melting points (mp) are uncorrected. Proton nuclear magnetic resonance (***$^1$H NMR***) spectra were recorded in deuterated solvents ($CDCl_3$, $CD_3OD$) at 300 MHz or at 250 MHz, as indicated. Chemical shifts are reported in parts per million (ppm, $\delta$). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sext), septet (sep), multiplet (m), apparent (ap), and broad (br) with the coupling constants reported in hertz (Hz). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded in deuterated solvents ($CDCl_3$, $CD_3OD$) at 75.4 MHz. Chemical shifts are reported in parts per million (ppm, $\delta$). Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with a phase angle of 135°: (C) not observed; (CH) positive; ($CH_2$) negative; ($CH_3$) positive. Due to magnetically and chemically equivalent carbons, the number of carbon resonances reported may not match the actual number of carbons in the molecule. Coincidental magnetically equivalent carbons were noted when relative signal intensity allowed. High-resolution mass spectra (HRMS) were recorded using electron impact (EI, 70 eV) ionization with peak matching. High- and low-resolution fast-atom bombardment (FAB) mass spectra were obtained on a VG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas).

All moisture-sensitive reactions were performed in flame- or oven-dried glassware under a stream of nitrogen unless otherwise noted. External bath temperatures were used to record all reaction temperatures. Concentrated in vacuo refers to the removal of volatile solvents via distillation using a rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (<1 Torr). Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silica gel 60 $F_{254}$ (250 $\mu$m layer thickness). Visualization was accomplished using UV light, a *p*-anisaldehyde (PAA) charring solution (18 mL of *p*-anisaldehyde, 7.5 mL of glacial acetic acid, 25 mL of 12.0 M $H_2SO_4$, 675 mL of absolute EtOH) and/or phosphomolybdic acid solution (10% PMA in EtOH). Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230−400 mesh). Solvent mixtures for TLC and FCC are reported in either $v_1/v_2$ ratios or $V_1/V_{total} \times 100\%$.

Tetrahydrofuran (THF), diethyl ether ($Et_2O$), and benzene (PhH) were distilled from sodium/benzophenone ketyl immediately prior to use. *N*,*N*-Dimethylformamide (DMF) was distilled under reduced pressure from magnesium sulfate and stored over 4 Å molecular sieves. Methanol (MeOH) was distilled from magnesium methoxide. Dichloromethane ($CH_2Cl_2$) and triethylamine ($Et_3N$) were distilled from calcium hydride immediately prior to use. Acetonitrile ($CH_3CN$), collidine, and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were distilled at reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Chloroform ($CHCl_3$) was passed through activated alumina, distilled from $P_2O_5$, and stored over 4 Å molecular sieves. Chlorotrimethylsilane ($Me_3SiCl$, TMSCl) was distilled from calcium hydride and stored over poly(4-vinylpyridine). 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) was recrystallized from toluene. All other commercially obtained reagents and solvents were used as received without further purification unless otherwise indicated.

**(2*S*)-2-(*p*-Methoxybenzyloxymethoxy)propanoic Acid Ethyl Ester (18).** To a cooled (−78 °C) solution of *p*-methoxybenzyloxymethyl methyl sulfide (**17**) (15.962 g, 80.5 mmol) in 100 mL of $CH_2Cl_2$ was added a solution of sulfuryl chloride (6.43 mL, 80 mmol) in 50 mL of $CH_2Cl_2$ dropwise over a 45 min period under $N_2$. The reaction mixture was stirred at −78 °C for 1.5 h and was then concentrated under reduced pressure. The resulting crude product, *p*-methoxybenzyloxymethyl chloride, was used directly in the subsequent reaction.

To a cooled (0 °C) solution of (*S*)-(−)-ethyl lactate (**3**) (9.89 mL, 87.2 mmol) and diisopropylethylamine (19 mL, 109.11 mmol) in 110 mL of $CH_2Cl_2$ was added a solution of crude *p*-methoxybenzyloxy methyl chloride in 50 mL of $CH_2Cl_2$ dropwise in a 45 min period. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The dark orange solution was washed with a saturated aqueous solution of $CuSO_4$ (2 × 100 mL) and NaCl (2 × 100 mL). Flash chromatography (10% ethyl acetate in hexanes) afforded 20.712 g (96%) of the product as a light yellow oil. Data for **18**: $R_f$ 0.2 (10% ether in hexanes); $[\alpha]^{23}_D$ −28.5 (*c* 0.778, $CHCl_3$); IR (thin film) 1737 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.24−7.30 (m, 2H), 6.86−6.90 (m, 2H), 4.81 (s, 2 H), 4.58 (s, 2 H), 4.28 (q, 1 H, $J$ = 7.2 Hz), 4.18 (q, 2 H, $J$ = 7.5 Hz), 3.81 (s, 3 H), 1.43 (d, 3 H, $J$ = 7.5 Hz), 1.26 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 mHz) $\delta$ 172.9, 159.1, 129.5, 129.4, 93.4, 71.4, 69.4, 60.7, 55.1, 18.4, 14.1; HRMS (EI, 70 eV) *m*/*e* 268.1321 ($C_{14}H_{20}O_5$ requires 268.1311).

**(3*R*,4*S*)-4-(*p*-Methoxybenzyloxymethoxy)-3-hydroxy-1-pentene (19).** To ester **18** (9.782 g, 36.5 mmol) in THF (110 mL) at −78 °C was added a 2.0 M THF solution of lithium borohydride ($LiBH_4$, 55 mL, 110 mmol). The reaction mixture was warmed to −30 °C, and vinylmagnesium bromide solution (54.8 mL, 1 M in THF) was slowly added to the reaction over 3 h. After the addition was complete, the reaction was allowed to react for another 30 min at −15 °C and then warmed to 0 °C and stirred for 30 min. The reaction was then quenched with saturated ammonium chloride solution (200 mL) at 0 °C. Aqueous HCl (5%, 100 mL) was added until a clear solution appeared. The aqueous layer was extracted with ether (3 × 250 mL), and the combined organic layers were washed with saturated NaCl solution (300 mL), dried ($MgSO_4$), and filtered. The organic solvent was removed via rotary evaporation. Flash chromatography (10% ether in hexanes) gave 5.703 g (62%, ds = 10:1) of the product as a colorless oil. Data for **19**: $R_f$ 0.2 (40% ether in hexanes); $[\alpha]^{23}_D$ −46.2 (*c* 0.865, $CHCl_3$); IR (thin film) 3300 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.22−7.29 (m, 2H), 6.84−6.89 (m, 2H), 5.88 (ddd, 1 H, $J$ = 18, 10.5, 6 Hz),

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5.32 (dt, 1 H, $J$ = 18, 1 Hz), 5.22 (dt, 1 H, $J$ = 10.5, 1 Hz), 4.79 (ABq, 2 H, $J_{AB}$= 7.5 Hz, $\Delta\upsilon_{AB}$ = 9.4 Hz), 4.56 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 19.6 Hz), 4.13 (m, 1 H), 3.82 (qd, 1 H, $J$ = 6.2, 3 Hz), 3.77 (s, 3 H), 2.98 (br s, 1 H), 1.17 (d, 3 H, $J$ = 6.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 159.1, 136.3, 129.3, 116.38, 113.6, 93.3, 77.2, 74.9, 69.2, 55.0, 15.1; HRMS (EI, 70 eV) *m/e* 252.1356 ($C_{14}H_{20}O_4$ requires 252.1362).

**(1*R*,2*S*)-[2-(*p*-Methoxybenzyloxymethoxy)-1-ethenylpropoxy]acetic Acid *tert*-Butyl Ester (20).** To a solution of a mixture of alcohol **19** (6.309 g, 25 mmol) in benzene (60 mL) at 0 °C were added tetrabutylammonium hydrogen sulfate (4.21 g, 1.24 mmol) and saturated NaOH aqueous solution (50 mL). The mixture was stirred for 5 min, and *tert*-butyl bromoacetate (6.04 mL, 37.4 mmol) was added. The reaction was rapidly stirred by means of mechanical stirrer for 2.5 h. Hexanes (50 mL) and water (50 mL) were then added, and the aqueous phase was extracted with ether (3 × 100 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (25% ether in hexanes) gave 7.848 g (86%) of desired product as a colorless oil. Data for **20**: $R_f$ 0.50 (25% ether in hexanes); $[\alpha]^{23}_D$ +25.7 (*c* 0.765, $CHCl_3$); IR (thin film): 3030, 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25−7.31 (m, 2H), 6.84−6.89 (m, 2H), 5.88 (ddd, 1 H, $J$ = 18, 11, 6 Hz), 5.36 (br d, 1 H, $J$ = 11 Hz), 5.29 (br d, 1 H, $J$ = 18 Hz), 4.83 (ABq, 2 H, $J_{AB}$= 7.5 Hz, $\Delta\upsilon_{AB}$ = 6.6 Hz), 4.57 (s, 2 H), 4.13 (m, 1 H), 3.82 (qd, 1 H, $J$ = 6.2, 3 Hz), 3.98 (ABq, 2 H, $J_{AB}$= 16.5 Hz, $\Delta\upsilon_{AB}$ = 21.4 Hz), 3.95 (dd,1 H, $J$ = 6.4, 5 Hz), 3.81 (qd, 1 H, $J$ = 8, 4.5 Hz), 3.79 (s, 3 H), 1.17 (d, 3 H, $J$ = 6.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.4, 158.8,134.3, 129.2, 119.8, 113.5, 92.8, 84.2, 80.9, 74.3, 68.6, 65.7, 54.9, 27.8, 16.1, −0.3; HRMS (FAB) *m/e* 389.1924 ($M^+$ + H + Na, $C_{20}H_{30}O_6Na$ requires 389.1941).

**(1*S*,2*S*,3*E*)-1-[(1*S*)-1-*p*-Methoxybenzyloxymethoxyethyl]-2-hydroxy-5-(benzyloxypent-3-enyloxy)acetic Acid *tert*-Butyl Ester (21).** To a cooled (−5 °C) of *trans*-$Ph_3SnCHCHPh$ (12.642 g, 28.93 mmol) in 58 mL of THF was added dropwise *n*-butyllithium (15.41 mL, 1.87 M in hexanes). The reaction was stirred at −5 °C for 2 h. The resulting vinyllithium solution was used in the next step reaction.

Through a cooled solution (−78 °C) of **20** (3.345 g, 9.556 mmol) in $CH_2Cl_2$ (95 mL) was passed a stream of ozone until a distinct blue color persisted. The excess ozone was dissipated by passing a stream of nitrogen through the solution for 15 min. $Ph_3P$ (2.746 g, 10.512 mmol) was then added, and the cooling bath was removed. The solution was warmed to room temperature, stirred for 2.5 h, and then concentrated by rotary evaporation followed by vacuum pump evacuation. The solid was removed by filtration through Celite while washing with hexanes. The filtrate was concentrated to an oil and diluted with diethyl ether (25 mL). The aldehyde was used for the next step without further purification. To a cooled solution (−45 °C) of CuI·*n*-$Bu_3P$ (5.672 g, 14.469 mmol) in $Et_2O$ (100 mL) was added dropwise 58 mL (28.817 mmol) of vinyllithium solution in THF. The bright yellow solution was stirred at −45 °C for 30 min and then cooled to −78 °C. The aldehyde solution in 25 mL of $Et_2O$ was then cannula transferred dropwise. The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to 0 °C. The reaction was quenched with a 1:1 solution of saturated aqueous ammonium chloride and 3% aqueous ammonium hydroxide solution (100 mL). After being stirred for 15 min at 0 °C, the blue aqueous phase was extracted with $Et_2O$ (2 × 100 mL). The combined organic extracts were combined, dried over $MgSO_4$, and concentrated. Flash chromatography (25% ether in hexanes) yielded 3.21 g (65% for two steps) of desired product as a light yellow oil. Data for **21**: $R_f$ 0.23 (50% ether in hexanes); $[\alpha]^{23}_D$ +28.8 (*c* 0.825, $CHCl_3$); IR (thin film) 3446, 1727 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.16−7.33 (m, 7 H), 6.8−6.86 (m, 2 H), 5.94 (dt, 1 H, $J$ = 15, 6 Hz), 5.7 (dd, 1 H, $J$ = 15, 7.5 Hz), 4.72 (ABq, 2 H, $J_{AB}$ = 7.5 Hz, $\Delta\upsilon_{AB}$ = 6.6 Hz), 4.66 (d, 1 H, $J$ = 3 Hz), 4.5 (s, 2 H), 4.47 (s, 2 H), 4.25 (ABq, 2 H, $J$ = 16.5 Hz, $\Delta\upsilon_{AB}$ = 29 Hz), 4.06 (br t, 1 H, $J$ = 6.8 Hz), 4.01 (br d, 2 H, $J$ = 6 Hz), 3.88 (qd, 1 H, $J$ = 6.2, 3 Hz), 3.72 (s, 3 H), 3.35 (dd, 1 H, $J$ = 7.5, 3.0 Hz), 1.46 (s, 9 H), 1.19 (d, 3 H, $J$ = 6.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.4, 159.2, 138.2, 130.5, 130.1, 129.7, 129.3, 128.2, 127.5, 127.4, 113.8, 92.6, 87.9, 82.2, 73.3, 71.9, 71.8, 69.8, 69.6, 69.2, 55.1, 28.1, 14.0; HRMS (FAB) *m/e* 539.2651 ($M^+$ + Na, $C_{29}H_{40}O_8Na$ requires 539.2621).

**(1*S*,2*S*,3*E*)-1-[(1*S*)-1-Benzyloxymethoxyethyl]-2-hydroxy-4-phenylbut-3-enyloxy)acetic Acid *tert*-Butyl Ester (5) and (1*S*,2*S*,3*E*)-1-[(1*S*)-1-Benzyloxymethoxyethyl]-2-hydroxy-5-(*p*-methoxybenzyloxypent-3-enyloxy)acetic Acid *tert*-Butyl Ester (6).** Refer to preparation of **21**. Data for **5**: $R_f$ 0.32 (75% ether in hexanes); $[\alpha]^{23}_D$ +28.8 (*c* 0.825, $CHCl_3$); IR (thin film) 3450, 1720 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25−7.45 (m, 10 H), 6.71 (d, 1 H, $J$ = 17.5 Hz), 6.13 (dd, 1 H, $J$ = 17.5, 7.0 Hz), 4.76 (ABq, 2 H, $J$ = 4.76 Hz, $\Delta\upsilon_{AB}$ = 2 Hz), 4.56 (s, 2 H), 4.26 (ABq, 2 H, $J$ = 16.6 Hz, $\Delta\upsilon_{AB}$ = 84.8 Hz), 4.16−4.26 (m, 1 H), 3.95 (qd, 1 H, $J$ = 6.5, 3.0 Hz), 3.44 (dd, 1 H, $J$ = 8.1, 3.0 Hz), 1.48 (s, 9 H), 1.23 (d, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR ($CDCl_3$, 300 MHz) $\delta$ 171.2, 137.3, 136.2, 132.5, 128.1, 128.0, 127.4, 126.9, 126.2, 92.5, 87.9, 82.1, 73.1, 72.1, 69.4, 27.7, 13.7; MS (FAB) *m/e* 443.2 ($M^+$ + H, $C_{26}H_{35}O_6$ requires 443.2).

Data for **6**: $R_f$ 0.34 (75% ether in hexanes); $[\alpha]^{23}_D$ +28.8 (*c* 0.825, $CHCl_3$); IR (thin film) 3300, 1728 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.16−7.36 (m, 7 H), 6.86 (m, 2 H), 5.94 (dtd, 1 H, $J$ = 16.5, 5.8, 1 Hz), 5.68 (ddt, 1 H, $J$ = 1.5, 7.0, 1 Hz), 4.76 (ABq, 2 H, $J$ = 7.5 Hz, $\Delta\upsilon_{AB}$ = 7.3 Hz), 4.62 (d, 1 H, $J$ = 3 Hz), 4.59 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 9 Hz), 4.43 (s, 2 H), 4.25 (ABq, 2 H, $J_{AB}$ = 15.8 Hz, $\Delta\upsilon_{AB}$ = 34.6 Hz), 4.06 (br t, 1 H, $J$ = 7.5 Hz), 3.88 (qd, 1 H, $J$ = 6, 3 Hz), 3.79 (s, 3 H), 3.33 (dd, 1 H, $J$ = 8.2, 3.0 Hz), 1.48 (s, 9 H), 1.19 (d, 3 H, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.4, 159.1, 137.6, 130.4, 130.3, 129.1, 128.3, 127.7, 113.6, 92.8, 87.9, 82.3, 73.5, 71.8, 71.6, 69.6, 69.5, 55.1, 27.9, 13.9; HRMS (FAB) *m/e* 539.2651 ($M^+$ + Na, $C_{29}H_{40}O_8Na$ requires 539.2621).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Benzyloxymethoxyethyl]-3-phenyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid (9).** To a solution of alcohol **5** (101 mg, 0.229 mmol) in benzene (2.5 mL) at 55 °C was added trifluoroacetic acid (6.5 mL). The resulting yellow solution was stirred for 0.5 h and then concentrated to a yellow oil. The trifluoroacetic acid was removed with benzene on a rotary evaporator. The dioxanone was used in the next step without further purification: $R_f$ 0.32 (50% ether in hexanes); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25−7.45 (m, 10 H), 6.76 (d, 1 H, $J$ = 17.6 Hz), 6.39 (dd, 1 H, $J$ = 17.6, 8.6 Hz), 5.20 (t, 1 H, $J$ = 8.6 Hz), 4.81 (ABq, 2 H, $J_{AB}$ = 7.18, $\Delta\upsilon_{AB}$ = 24.54 Hz), 4.61 (s, 2 H), 4.43 (ABq, 2 H, $J_{AB}$ = 17.5 Hz, $\Delta\upsilon_{AB}$ = 63.9 Hz), 3.97 (qd, 1 H, $J$ = 6.8, 3.1 Hz), 3.64 (dd, 1 H, $J$ = 8.6, 3.1 Hz), 1.28 (d, 3 H, $J$ = 6.8 Hz).

To a solution of hexamethyldisilazane (HMDS, 0.16 mL) in THF (2 mL) at 0 °C was added *n*-butyllithium solution in hexanes (0.28 mL, 2.45 M). After being stirred for 30 min, the solution was cooled to −78 °C, and the supernatant from centrifugation of a 1:1 (v:v, 0.4 mL:0.4 mL) mixture of $Me_3SiCl$ and $Et_3N$ was added. This solution was stirred for 15 min. Dioxanone prepared as above (85 mg, 0.23 mmol) in 1 mL of THF was then added dropwise. The reaction was stirred at −78 °C for 2 h, the cooling bath was removed, and the reaction was warmed to room temperature. The flask was submerged in an oil bath and heated to reflux for 12 h. The solution was cooled to 0 °C and treated with 5% HCl until acidic (pH = 2). The aqueous phase was extracted with chloroform (2 × 5 mL), and then the combined organic layers were concentrated. The residual was taken up in 5 mL of ether and treated with 5% NaOH solution until basic (pH = 12). The organic phase was washed with water (3 × 5 mL), and the combined aqueous phases were acidified with 5% HCl solution until acidic (pH = 2) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were dried and concentrated to give 70 mg desired product (84%) as a yellow oil in two steps. Data for **9**: $R_f$ 0.24 (1:4 hexanes/ether containing 3% acetic acid); $[\alpha]^{23}_D$ −25.8 (*c* 0.547, $CHCl_3$); IR (thin film) 3440, 1716 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.05 (br, 1 H), 7.2−7.4 (m, 10 H), 5.9−6.3 (m, 2 H), 4.88 (s, 2 H), 4.64 (ABq, 2 H, $J$ = 4.78 Hz, $\Delta\upsilon_{AB}$ = 6.18 Hz), 4.49 (d, 1 H, $J$ = 4.5 Hz), 4.28 (br, 1 H), 4.04 (m, 1 H), 3.65 (m, 1 H), 1.33 (d, 3 H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.8, 137.8, 137.5, 129.4, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.2, 125.6, 93.2, 78.6,

76.4, 74.2, 69.6, 42.5, 15.9; HSMS (FAB) *m/e* 413.1321 ($M^+ - H + 2Na$, $C_{22}H_{23}O_5Na_2$ requires 413.1341).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Benzyloxymethoxyethyl]-3-*p*-methoxybenzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid (10) and (2*S*,3*S*,6*R*)-6-[(1*S*)-1-*p*-Methoxybenzyloxymethoxyethyl]-3-benzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid (22).** Refer to preparation of **9**. Data for **10**: $R_f$ 0.25 (1:4 hexanes/ether containing 3% acetic acid); $[\alpha]^{23}_D$ −16.8 (*c* 0.685, $CHCl_3$); IR (thin film) 3430, 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 8.75 (br, 1 H), 7.15−7.4 (m, 7 H), 6.8 (m, 2 H), 6.02 (dd, 1 H, $J$ = 10, 6 Hz), 5.82 (d, 1 H, $J$ = 10 Hz), 4.64 (ABq, 2 H, $J$ = 6.2 Hz, $\Delta\upsilon_{AB}$ = 7.8 Hz), 4.62 (s, 2 H), 4.2−4.4 (m, 3 H), 3.9 (qd, 1 H, $J$ = 7, 3 Hz), 3.77 (m, 1 H), 3.74 (s, 3 H), 3.55 (A of ABX, 1 H, $J_{AB}$=$J_{AB}$= 6.5 Hz), 3.45 (B of ABX, 1 H, $J_{AB}$= 6.5 Hz, $J_{BX}$ = 4.5 Hz), 2.85 (br, 1 H), 1.23 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 172.5, 158.9, 137.6, 129.8, 129.1, 128.3, 127.7, 127.6, 127.3, 127.1, 113.7, 113.5, 93.2, 80.2, 74.0, 73.2, 72.0, 69.5, 68.7, 55.0, 37.0, 15.3; HRMS (FAB) *m/e* 465.1897 ($M^+$ + Na, $C_{25}H_{30}O_7Na$ requires 465.1889).

Data for **22**: $R_f$ 0.28 (1:4 hexanes/ether containing 3% acetic acid); $[\alpha]^{23}_D$ −35.8 (*c* 0.365, $CHCl_3$); IR (thin film) 3440, 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 8.75 (br, 1 H), 7.15−7.4 (m, 7 H), 6.8 (m, 2 H), 6.04 (dd, 1 H, $J$ = 10, 6 Hz), 5.80 (d, 1 H, $J$ = 10 Hz), 4.66 (ABq, 2 H, $J$ = 6.0 Hz, $\Delta\upsilon_{AB}$ = 7.6 Hz), 4.64 (s, 2 H), 4.2−4.4 (m, 3 H), 3.92 (qd, 1 H, $J$ = 7, 3 Hz), 3.78 (m, 1 H), 3.74 (s, 3 H), 3.55 (A of ABX, 1 H, $J_{AB}$=$J_{AB}$= 6.5 Hz), 3.46 (B of ABX, 1 H, $J_{AB}$= 6.5 Hz, $J_{BX}$ = 4.5 Hz), 2.86 (br, 1 H), 1.25 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 173.6, 159.6, 137.8, 129.9, 129.1, 128.4, 127.8, 127.7, 127.6, 127.1, 114.8, 114.1, 93.8, 80.5, 74.8, 73.6, 72.5, 70.4, 68.9, 55.5, 37.2, 15.0; HRMS (FAB) *m/e* 465.1887 ($M^+$ + Na, $C_{25}H_{30}O_7Na$ requires 465.1889).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Benzyloxymethoxyethyl]-3-phenyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (11).** To a solution of acid **9** (120 mg, 0.326 mmol), 2,2,2-trichloroethanol (0.063 mL, 0.652 mmol), DMAP (40 mg, 0.326 mmol), and DMAP−TFA (73.4 mg, 0.359 mmol) in $CH_2Cl_2$ (2 mL) was added DIC (0.062 mL, 0.358 mmol). The reaction was stirred at 40 °C overnight and then was diluted with 3 mL of ether and washed with 3 mL of 2% HCl solution and 3 mL of water. The combined aqueous layers were extracted with $CH_2Cl_2$ (2 × 5 mL). The organic phases was dried ($MgSO_4$) and concentrated. Flash chromatography (33% ether in hexanes) gave 160 mg (97%) desired product. Data for **11**: $R_f$ 0.72 (50% ether in hexanes); $[\alpha]^{23}_D$ −27.8 (*c* 0.758, $CHCl_3$); IR (thin film) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.45 (m, 10 H), 5.9−6.1 (m, 2 H), 4.95 (s, 2 H), 4.74 (d, 1 H, $J$ = 4.5 Hz), 4.69 (ABq, 2 H, $J$ = 6.5 Hz, $\Delta\upsilon_{AB}$ = 5.4 Hz), 4.45 (ABq, 2 H, $J$ = 11.9 Hz, $\Delta\upsilon_{AB}$ = 17.6 Hz), 4.24−4.29 (m, 1 H), 4.10 (m, 1 H), 3.72 (m, 1 H), 1.39 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 167.7, 138.1, 137.9, 129.4, 128.5, 128.4, 128.2, 127.9, 127.6, 127.4, 125.9, 93.7, 93.1, 78.5, 76.5, 74.3, 74.1, 69.6, 43.2, 16.5; MS (FAB) *m/e* 523.2 ($M^+$ + H + Na, $C_{24}H_{26}O_5Cl_3Na$ requires 523.2).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Benzyloxymethoxyethyl]-3-*p*-methoxybenzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (12) and (2*S*,3*S*,6*R*)-6-[(1*S*)-1-*p*-Methoxybenzyloxymethoxyethyl]-3-benzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (23).** Refer to preparation of **11**. Data for **12**: $R_f$ 0.68 (50% ether in hexanes); $[\alpha]^{23}_D$ −16.8 (*c* 0.578, $CHCl_3$); IR (thin film) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.1−7.5 (m, 7 H), 6.75−6.9 (m, 2 H), 5.90 (ddd, 1 H, $J$ = 11, 5.8, 2 Hz), 5.84 (br d, 1 H, $J$ = 11 Hz), 4.87 (ABq, 2 H, $J_{AB}$ = 7.5 Hz, $\Delta\upsilon_{AB}$ = 10 Hz), 4.65 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 9 Hz), 4.28 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 244 Hz), 4.2−4.25 (m, 1 H), 3.96 (qd, 1 H, $J$ = 6, 4.5 Hz), 4.42 (d, 1 H, $J$ = 3 Hz), 3.58 (A of ABX, 1 H, $J_{AB}$ = $J_{AX}$ = 9 Hz), 3.45 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4 Hz), 2.87 (m, 1 H), 1.25 (d, 3 H, $J$ = 6 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 168.8, 159.5, 137.4, 129.8, 129.4, 128.5, 128.3, 127.9, 127.5, 125.8, 113.8, 94.9, 93.5, 78.1, 74.6, 74.1, 73.2, 72.8, 69.6, 68.8, 55.2, 38.4, 16.3; HRMS (FAB) *m/e* 595.1039 ($M^+$ + Na, $C_{27}H_{33}O_7Cl_3Na$ requires 595.1033).

Data for **23**: $R_f$ 0.66 (50% ether in hexanes); $[\alpha]^{23}_D$ −12.8 (*c* 0.457, $CHCl_3$); IR (thin film) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25−7.37 (m, 7 H), 6.75−6.9 (m, 2 H), 5.92 (ddd, 1 H, $J$ = 11, 5.8, 2 Hz), 5.86, (br d, 1 H, $J$ = 11 Hz), 4.86 (ABq, 2 H, $J_{AB}$ = 7.5 Hz, $\Delta\upsilon_{AB}$ = 10 Hz), 4.66 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 9 Hz), 4.26 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 244 Hz), 4.2−4.25 (m, 1 H), 3.93 (qd, 1 H, $J$ = 6, 4.5 Hz), 4.4 (d, 1 H, $J$ = 3 Hz), 3.56 (A of ABX, 1 H, $J_{AB}$ = $J_{AX}$ = 9 Hz), 3.46 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4 Hz), 2.85 (m, 1 H), 1.28 (d, 3 H, $J$ = 6 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 168.5, 159.2, 137.8, 129.8, 129.7, 128.3, 128.1, 127.8, 127.5, 125.8, 113.6, 94.6, 93.4, 78.7, 74.2, 74.1, 72.9, 72.8, 69.4, 68.5, 55.1, 38.4, 16.1; HRMS (FAB) *m/e* 595.1047 ($M^+$ + Na, $C_{27}H_{33}O_7Cl_3Na$ requires 595.1033).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Hydroxyethyl]-3-phenyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (13).** To a solution of ester **11** (105 mg, 0.21 mmol) and $Me_2S$ (1.1 mL) in $CH_2Cl_2$ (2.2 mL) at 0 °C was added $BF_3$·$Et_2O$ (0.07 mL, 0.57 mmol). Saturated $NaHCO_3$ (2 mL) was added after 10 min, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (50% ether in hexanes) gave 64.8 mg (81%) of desired product. Data for **13**: $R_f$ 0.2 (50% ether in hexanes); $[\alpha]^{23}_D$ −58.8 (*c* 0.708, $CHCl_3$); IR (thin film) 3438, 1731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.4 (m, 5 H), 5.9−6.1 (m, 2 H), 4.78 (d, 1 H, $J$ = 4.3 Hz), 4.49 (ABq, 2 H, $J$ = 11.98 Hz, $\Delta\upsilon_{AB}$ = 18.5 Hz), 4.26 (m, 1 H), 4.11 (m, 1 H), 3.78 (m, 1 H), 2.67 (br, 1 H), 1.38 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 167.7, 137.7, 129.1, 128.7, 128.1, 127.3, 125.3, 94.1, 79.1, 76.4, 74.1, 68.9, 43.1, 18.0; MS (FAB) *m/e* 379.2 ($M^+$, $C_{16}H_{17}O_4Cl_3$ requires 379.2).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Hydroxyethyl]-3-*p*-methoxybenzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (14), Hydroxy 2,2,2-Trichloroethyl Ester Bis(hydropyran) 30, and Hydroxy 2,2,2-Trichloroethyl Ester Tris(hydropyran) 36.** Refer to preparation of **13**. Data for **14**: $R_f$ 0.21 (50% ether in hexanes); $[\alpha]^{23}_D$ −58.8 (*c* 0.708, $CHCl_3$); IR (thin film) 3430, 1731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.26 (m, 2 H), 6.83−6.91 (m, 2 H), 5.92 (ddd, 1 H, $J$ = 11, 5.8, 2 Hz), 5.86, (br d, 1 H, $J$ = 11 Hz), 4.68 (d, 1 H, $J$ = 9 Hz), 4.44 (d, 1 H, $J$ = 3 Hz), 4.30 (ABq, 2 H, $J$ = 10.5 Hz, $\Delta\upsilon_{AB}$ = 13.4 Hz), 4.22 (m, 1H), 3.98 (qd, 1 H, $J$ = 6, 3.5 Hz), 3.82 (d, 1 H, $J$ = 9 Hz), 3.78 (s, 3 H), 3.54 (A of ABX, 1 H, $J_{AB}$ = $J_{AX}$ = 9 Hz), 3.48 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.07 (br s, 1 H), 2.85 (m, 1 H), 1.25 (d, 3 H, $J$ = 6.2 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 169.1, 159.3, 130.0, 129.7, 126.1, 113.7, 94.5, 79.6, 74.1, 73.0, 72.8, 68.7, 68.5, 55.2, 38.5, 17.8; HRMS (FAB) *m/e* 475.0476 ($M^+$ + Na, $C_{19}H_{23}O_6Cl_3Na$ requires 475.0458).

Data for **30**: $R_f$ 0.21 (75% hexanes in ether); $[\alpha]^{23}_D$ −26.6 (*c* 0.526, $CHCl_3$); IR (thin film) 3440, 1731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.1−7.4 (m, 10 H), 5.88−6.08 (m, 3 H), 5.62 (br d, 1 H, $J$ = 10 Hz), 4.94 (m, 1 H), 4.60−4.73 (m, 4 H), 4.20−4.40 (m, 2 H), 3.95−4.15 (m, 2 H), 3.66−3.80 (m, 2 H), 2.41 (d, 1 H, $J$ = 7.2 Hz), 1.33 (d, 3 H, $J$ = 7.1 Hz), 1.21 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 169.1, 167.5, 138.4, 137.8, 129.4, 129.2, 129.1, 129.0, 128.2, 128.0, 127.4, 127.1, 125.4, 125.2, 94.2, 79.2, 76.7, 76.6, 76.3, 74.1, 72.2, 69.1, 43.2, 42.9, 18.1, 14.6; HSMS (FAB) *m/e* 631.1046 ($M^+$ + Na, $C_{30}H_{31}O_7Cl_3Na$ requires 631.1033).

Data for **36**: $R_f$ 0.2 (75% hexanes in ether); $[\alpha]^{23}_D$ 43.8 (*c* 0.816, $CHCl_3$); IR (thin film) 3400, 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.1−7.4 (m, 15 H), 5.85−6.08 (m, 4 H), 5.56 (br t, 2 H, $J$ = 10 Hz), 4.86−5.01 (m, 2 H), 4.66 (d, 1 H, $J$ = 4.3 Hz), 4.56 (d, 1 H, $J$ = 4.5 Hz), 4.53 (d, 1 H, $J$ = 4.5 Hz), 4.49 (AB, 2 H, $J$ = 1.9 Hz, $\Delta\upsilon_{AB}$ = 17.6 Hz), 4.26−4.30 (m, 1 H), 4.08−4.13 (m, 2 H), 3.83−3.90 (m, 1 H), 3.63−3.80 (m, 3 H), 1.33 (d, 3 H, $J$ = 7.2 Hz), 1.24 (d, 3 H, $J$ = 7.1 Hz), 1.11 (d, 3 H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 168.9, 168.7, 167.2, 138.2, 138.0, 137.6, 129.6, 129.3, 128.9, 128.8, 128.7, 128.1, 127.8, 127.2, 127.0, 126.9, 125.3, 125.2, 124.5, 94.0, 79.3, 77.1, 76.3, 76.1, 73.9, 72.1, 72.0, 68.6, 43.0, 42.7, 42.5, 17.4, 14.3, 13.8; MS (FAB) *m/e* 841.3 ($M^+$ + H, $C_{44}H_{46}O_{10}Cl_3$ requires 841.3).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-Hydroxyethyl]-3-benzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (24).** To a solution of ester **23** (1.20 g, 2.09 mmol) in $H_2O$ (2.2 mL) and $CH_2Cl_2$ (22 mL) was added DDQ (0.712 g, 3.135 mmol). Saturated $NaHCO_3$ (20 mL) was added after 1 h, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (50% ether in hexanes) gave 724 mg (82%) desired product. Data for **24**: $R_f$ 0.25 (50% ether in hexanes); $[\alpha]^{23}_D$ −58.8 (*c* 0.708, $CHCl_3$); IR (thin film) 3430, 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.24−7.38 (m, 5 H), 5.92 (ddd, 1 H, $J$ = 10.5, 5.8, 3 Hz), 5.86, (br d, 1 H, $J$ = 10.5 Hz), 4.68 (d, 1 H, $J$ = 12 Hz), 4.45 (d, 1 H, $J$ = 3 Hz), 4.37 (ABq, 2 H, $J_{AB}$ = 11 Hz, $\Delta\upsilon_{AB}$ = 11.6 Hz), 4.22 (m, 1H), 3.98 (qd, 1 H, $J$ = 6, 3.5 Hz), 3.9 (d, 1 H, $J$ = 12 Hz), 3.57 (A of ABX, 1 H, $J_{AB}$ = $J_{AX}$ = 10 Hz), 3.51 (B of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{BX}$ = 4.5 Hz), 2.82−3.0 (m, 1 H), 1.25 (d, 3 H, $J$ = 6 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.8, 137.4, 128.1, 127.7, 127.4, 126.1, 94.3, 79.5, 74.0, 73.2, 72.7, 68.6, 68.5, 38.2, 17.6; HRMS (FAB) *m/e* 445.036 ($M^+$ + Na, $C_{18}H_{21}O_5Cl_3Na$ requires 445.0352).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-*p*-methoxybenzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (15).** To a solution of alcohol **14** (1.448 g, 3.211 mmol) in 10 mL of DMF were added imidazole (2.171 g, 31.93 mmol) and *tert*-butyldimethylsilyl chloride (2.409 g, 15.982 mmol). The reaction mixture was stirred at ambient temperature for 8 h. A solution of 30 mL of $CH_2Cl_2$, 30 mL of $H_2O$, and 10 mL of MeOH was added. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined extracts were combined, dried ($MgSO_4$), and concentrated. Flash chromatography (10% hexanes in ether) afforded 1.747 g (96%) desired product. Data for **15**: $R_f$ 0.61 (50% ether in hexanes); $[\alpha]^{23}_D$ −28.8 (*c* 0.748, $CHCl_3$); IR (thin film) 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.26 (m, 2 H), 6.83−6.91 (m, 2 H), 6.01 (d, 1 H, $J$ = 10.5, 1 Hz), 5.82, (ddd, 1 H, $J$ = 10.5, 6, 2 Hz), 4.38 (d, 1 H, $J$ = 3 Hz), 4.29 (ABq, 2 H, $J$ = 11 Hz, $\Delta\upsilon_{AB}$ = 14.2 Hz), 4.23 (ABq, 2 H, $J$ = 9 Hz, $\Delta\upsilon_{AB}$ = 240 Hz), 3.93 (m, 1H), 3.77 (quint, 1 H, $J$ = 6 Hz), 2.81 (m, 1 H), 1.28 (d, 3 H, $J$ = 6 Hz), 0.9 (s, 9 H), 0.1 (s, 3 H), 0.09 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.7, 159.1, 129.8, 129.2, 124.5, 113.5, 94.5, 80.1, 74.0, 72.9, 72.7, 70.5, 68.6, 55.1, 38.4, 25.6, 20.8, 17.9, −4.5, −4.8; HRMS (FAB) *m/e* 589.1338 ($M^+$ + Na, $C_{25}H_{37}O_6Cl_3SiNa$ requires 589.1323).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-benzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid 2,2,2-Trichloroethyl Ester (25).** Refer to preparation of **15**. Data for **25**: $R_f$ 0.68 (50% ether in hexanes); $[\alpha]^{23}_D$ −35.6 (*c* 0.578, $CHCl_3$); IR (thin film) 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25−7.37 (m, 5 H), 6.01 (dt, 1 H, $J$ = 11, 2 Hz), 5.82, (ddd, 1 H, $J$ = 11, 6, 3 Hz), 4.29 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 222 Hz), 3.93 (m, 1H), 3.77 (quint, 1 H, $J$ = 6.2 Hz), 3.59 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.47 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.3 Hz), 2.81 (m, 1 H), 1.28 (d, 3 H, $J$ = 6.2 Hz), 0.9 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.9, 137.7, 124.3, 128.3, 128.2, 127.8, 124.7, 94.8, 80.2, 74.1, 73.2, 73.1, 70.6, 69.1, 35.5, 25.8, 20.9, 18.1, −4.3, −4.6; HRMS *m/e* (FAB) 559.1243 ($M^+$ + Na, $C_{24}H_{35}O_5Cl_3SiNa$ requires 559.1217).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-*p*-methoxybenzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid (16).** To a solution of ester **15** (1.515 g, 2.672 mmol) in 54 mL of *t*-BuOH at 40 °C was added 2 M aqueous lithium hydroxide solution (13.5 mL). The mixture was stirred for 2 h. A buffer solution (pH = 4, 35 mL, prepared from a mixture of 4 mL of 1 M $NaHSO_4$ aqueous solution and 40 mL of 1 M $NaH_2PO_4$ aqueous solution) was added until acidic (pH = 4). The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined extracts were combined, dried ($MgSO_4$), and concentrated without further purification to afford 1.165 g (100%) acid **16**. Data for **16**: $R_f$ 0.31 (50% ether in hexanes with 3% AcOH); $[\alpha]^{23}_D$ 23.6 (*c* 0.148, $CHCl_3$); IR (thin film) 3440, 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.13−7.2 (m, 2 H), 6.75−6.82 (m, 2 H), 5.8−5.9 (m, 2 H), 4.32 (ABq, 2 H, $J$ = 12 Hz, $\Delta\upsilon_{AB}$ = 14.7 Hz), 4.21 (d, 1 H, $J$ = 3 Hz), 3.72 (s, 3 H), 3.69 (quint, 1 H, $J$ = 6.5 Hz), 3.48 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 7.8 Hz), 3.34 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 6 Hz), 2.78 (m, 1 H), 1.16 (d, 3 H, $J$ = 6 Hz), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.0 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 172.1, 158.9, 129.9, 129.0, 128.0, 126.1, 113.5, 80.5, 73.4, 72.4, 70.2, 68.7, 55.0, 36.9, 31.3, 25.6, 19.9, 17.8, 13.9, −4.6, −4.8; HRMS (FAB) *m/e* 459.2195 ($M^+$ + Na, $C_{23}H_{36}O_6SiNa$ requires 459.2179).

**(2*S*,3*S*,6*R*)-6-[(1*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-benzyloxymethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid (26).** Refer to preparation of **16**. Data for **26**: $R_f$ 0.26 (50% ether in hexanes with 3% AcOH); $[\alpha]^{23}_D$ 24.8 (*c* 0.255, $CHCl_3$); IR (thin film) 3448, 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 10.75 (br, 1 H), 7.13−7.34 (m, 5 H), 5.94 (br d, 1 H, $J$ = 10.5 Hz), 5.88 (ddd, 1 H, $J$ = 10.5, 4.7, 2 Hz), 4.42 (ABq, 2 H, $J$ = 12 Hz, $\Delta\upsilon_{AB}$ = 24.2 Hz), 4.21 (d, 1 H, $J$ = 3 Hz), 3.98 (m, 1 H), 3.75 (quint, 1 H, $J$ = 6 Hz), 3.57 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.42 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 5 Hz), 2.82 (m, 1 H), 1.25 (d, 3 H, $J$ = 6 Hz), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 174.3, 137.9, 128.4, 128.0, 125.7, 80.3, 73.3, 72.7, 70.3, 69.1, 37.3, 25.6, 20.4, 17.9, −4.5, −4.8; HRMS *m/e* (FAB) 429.2082 ($M^+$ + Na, $C_{22}H_{34}O_5SiNa$ requires 429.2073).

**Bis(dihydropyran) 2,2,2-Trichloroethyl Ester 27.** To a mixture of carboxylic acid **9** (300 mg, 0.815 mmol) and $Et_3N$ (0.12 mL, 0.897 mmol) in 8 mL of THF was added 2,4,6-trichlorobenzoyl chloride (0.14 mL, 0.897 mmol). The reaction was stirred for 3 h. The white precipitate that had formed was removed by filtration under $N_2$ via cannula transfer to a glass pipet equipped with a septum and a plug of glasswool. The THF in the filtrate was evaporated by a stream of $N_2$. The residual was diluted with benzene (4 mL) and DMAP (96 mg, 0.815 mmol) was added. To this mixture was added alcohol **13** (300 mg, 0.792 mmol) in benzene (4 mL). The reaction was stirred for 2 h, diluted with ether (50 mL), and quenched with 50 mL water. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried and concentrated. Flash chromatography (50% ether in hexanes) gave 486 mg (84%) of the desired product as a colorless oil. Data for **27**: $R_f$ 0.3 (50% ether in hexanes); $[\alpha]^{23}_D$ −35.8 (*c* 0.458, $CHCl_3$); IR (thin film) 1725 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.4 (m, 15 H), 5.96−6.08 (m, 2 H), 5.89 (ddd, 2 H, $J$ = 10.0, 5.9, 3.2 Hz), 5.58 (br d, 2 H, $J$ = 10.0 Hz), 4.94 (s, 1 H), 4.88−4.92 (m, 1 H), 4.69 (ABq, 2 H, $J_{AB}$ = 6.8 Hz, $\Delta\upsilon_{AB}$ = 16.7 Hz), 4.63 (d, 1 H, $J$ = 4.5 Hz), 4.58 (d, 1 H, $J$ = 4.5 Hz), 4.45 (ABq, 2 H, $J_{AB}$ = 11.9 Hz, $\Delta\upsilon_{AB}$ = 17.6 Hz), 4.23−4.28 (m, 1 H), 4.02−4.12 (m, 1 H), 3.88−3.94 (m, 1 H), 3.63−3.76 (m, 2 H), 1.36 (d, 3 H, $J$ = 6.8 Hz), 1.11 (d, 3 H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.7, 167.3, 138.4, 137.9, 137.8, 129.5, 129.1, 128.9, 128.6, 128.3, 128.2, 128.1, 127.8, 127.7, 127.4, 127.32, 127.0, 125.5, 125.3, 94.2, 93.4, 78.3, 76.5, 76.2, 74.2, 74.1, 71.8, 69.3, 43.1, 42.9, 16.4, 14.7; MS (FAB) *m/e* 731.2 ($M^+$ + H, $C_{38}H_{40}O_8Cl_3$ requires 731.2).

**Bis(dihydropyran) 2,2,2-Trichloroethyl Esters 28 and 29 and Tris(dihydropyran) 2,2,2-Trichloroethyl Esters 33, 34, and 35.** Refer to preparation of **27**. Data for **28**: $R_f$ 0.24 (50% ether in hexanes); $[\alpha]^{23}_D$ −23.8 (*c* 0.508, $CHCl_3$); IR (thin film) 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.16−7.25 (m, 4 H), 6.8−6.88 (m, 4 H), 5.96 (br d, 1 H, $J$ = 10.5 Hz), 5.83 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.67 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.37 (br d, 1 H, $J$ = 10.5 Hz), 4.69 (qd, 1 H, $J$ = 6, 4.5 Hz), 4.61 (d, 1 H, $J$ = 3 Hz), 4.27 (ABq, 2 H, $J$ = 11 Hz, $\Delta\upsilon_{AB}$ = 28 Hz), 4.26 (ABq, 2 H, $J$ = 11 Hz, $\Delta\upsilon_{AB}$ = 12.7 Hz), 4.25 (d, 1 H, $J$ = 3 Hz), 4.17 (d, 1 H, $J$ = 3 Hz), 4.02 (m, 1 H), 3.91 (m, 1 H), 3.8 (d, 1 H, $J$ = 123 Hz), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.55 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.44 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.38 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.36 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 2.75 (m, 2 H), 1.27 (d, 3 H, $J$ = 6.5 Hz), 1.25 (d, 3 H, $J$ = 6.5 Hz), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.09 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.6, 168.2, 159.1, 158.9, 130.1, 129.7, 129.6, 128.8, 128.2, 125.3, 125.1, 113.5, 94.5, 80.1, 76.7, 73.9, 73.5, 72.8, 72.4, 71.8, 70.4, 68.9, 68.4, 55.0, 38.1, 25.6, 20.8, 17.9, 14.4, −4.5, −4.8; MS (FAB) *m/e* 895.2 ($M^+$ + Na $C_{42}H_{59}O_{11}Cl_3SiNa$ requires 895.3).

Data for **29**: $R_f$ 0.2 (50% ether in hexanes); $[\alpha]^{23}_D$ −24.7 (*c* 0.485, $CHCl_3$); IR (thin film) 1718 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300

MHz) $\delta$ 7.16−7.35 (m, 10 H), 5.96 (br d, 1 H, $J$ = 10.5 Hz), 5.83 (ddd, 1 H, $J$ = 10.5, 6, 2 Hz), 5.67 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.37 (br d, 1 H, $J$ = 10.5 Hz), 4.69 (qd, 1 H, $J$ = 6, 4.5 Hz), 4.62 (d, 1 H, $J$ = 12 Hz), 4.36 (ABq, 2 H, $J_{AB}$ = 11 Hz, $\Delta\upsilon_{AB}$ = 21.3 Hz), 4.33 (s, 2 H), 4.25 (d, 1 H, $J$ = 3 Hz), 4.26 (d, 1 H, $J$ = 3 Hz), 4.21 (d, 1 H, $J$ = 3 Hz), 3.58 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.47 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.41 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.37 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 2.75 (m, 2 H), 1.27 (d, 3 H, $J$ = 6 Hz), 1.25 (d, 3 H, $J$ = 6 Hz), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.6, 168.2, 137.9, 137.5, 128.9, 128.1, 128.1, 127.7, 127.4, 125.5, 125.2, 94.4, 80.1, 76.9, 74.1, 73.5, 73.2, 73.0, 72.5, 71.9, 70.4, 69.2, 68.6, 38.01, 25.6, 20.8, 17.9, 14.4, −4.5, −4.8, MS (FAB) *m/e* 835.2 ($M^+$ + Na, $C_{40}H_{55}O_9Cl_3SiNa$ requires 835.2).

Data for **33**: $R_f$ 0.21 (50% ether in hexanes); $[\alpha]^{23}_D$ 24.6 (*c* 0.766, $CHCl_3$); IR (thin film) 1716 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.2−7.4 (m, 20 H), 5.96−6.08 (m, 2 H), 5.82−5.93 (m, 2 H), 5.58 (br d, 2 H, $J$ = 10.0 Hz), 4.94 (s, 1 H), 4.86−4.96 (m, 2 H), 4.69 (ABq, 2 H, $J$ = 6.8 Hz, $\Delta\upsilon_{AB}$ = 16.7 Hz), 4.63 (d, 1 H, $J$ = 4.5 Hz), 4.58 (d, 1 H, $J$ = 4.5 Hz), 4.49 (d, 1 H, $J$ = 4.3 Hz), 4.45 (ABq, 2 H, $J$ = 11.9 Hz, $\Delta\upsilon_{AB}$ = 17.6 Hz), 4.21−4.28 (m, 1 H), 4.0−4.1 (m, 1 H), 3.88−3.96 (m, 2 H), 3.63−3.76 (m, 3 H), 1.36 (d, 3 H, $J$ = 6.8 Hz), 1.21 (d, 3 H, $J$ = 7.1 Hz), 0.98 (d, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) d 168.9, 168.6, 167.5, 138.4, 137.9, 137.8, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 127.5, 127.1, 125.7, 125.5, 125.1, 94.3, 93.6, 78.5, 77.2, 77.1, 76.7, 76.6, 76.5, 76.3, 74.3, 74.1, 72.2, 72.1, 69.5, 43.3, 43.1, 43.0, 16.5, 15.0, 14.89; MS (FAB) *m/e* 961.3 ($M^+$ + H, $C_{52}H_{54}O_{11}Cl_3$ requires 961.3).

Data for **34**: $R_f$ 0.31 (60% ether in hexanes); $[\alpha]^{23}_D$ 23.8 (*c* 0.576, $CHCl_3$); IR (thin film) 1715 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.25 (m, 6 H), 6.8−6.88 (m, 6 H), 5.96 (br d, 1 H, $J$ = 10.5 Hz), 5.83 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.68 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.67 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.29−5.37 (m, 2 H), 4.62 (d, 1 H, $J$ = 12 Hz), 4.62−4.72 (m, 2 H), 4.29 (ABq, 2 H, $J$ = 11 Hz, $\Delta\upsilon_{AB}$ = 19 Hz), 4.17−4.32 (m, 4 H), 3.99 (m, 2 H), 3.86−3.94 (m, 1 H), 3.8 (d, 1 H, $J$ = 12 Hz), 3.74−3.8 (m, 10 H), 3.54 (A of ABX, 1 H, $J_{AB}$ = 10.5 Hz, $J_{AX}$ = 10.5 Hz), 3.45 (A of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{AX}$ = 10 Hz), 3.44 (A of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{AX}$ = 10 Hz), 3.38 (B of ABX, 1 H, $J_{AB}$ = 10.5 Hz, $J_{BX}$ = 4 Hz), 3.37 (B of ABX, 1 H, $J_{AB}$ = 10.5 Hz, $J_{BX}$ = 4 Hz), 3.31 (B of ABX, 1 H, $J_{AB}$ = 10.5 Hz, $J_{BX}$ = 4 Hz), 2.6−2.85 (m, 3 H), 1.27 (d, 3 H, $J$ = 6.5 Hz), 1.25 (d, 3 H, $J$ = 6.5 Hz), 1.24 (d, 3 H, $J$ = 6.5 Hz), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.6, 169.1, 168.2, 159.1, 158.9, 130.2, 130.1, 129.7, 129.7, 129.6, 128.7, 128.1 127.9, 126.1, 125.4, 113.4, 94.5, 80.1, 77.1, 76.8, 73.9, 73.5, 73.0, 72.7, 72.6, 72.4, 72.0, 71.7, 70.4, 68.9, 68.7, 68.4, 55.0, 38.1, 38.0, 37.8, 25.7, 20.8, 17.9, 14.5, 14.3, −4.6, −4.8; MS (FAB) *m/e* 1199.1 ($M^+$ + H +Na, $C_{59}H_{78}O_{16}Cl_3SiNa$ requires 1198.4).

Data for **35**: $R_f$ 0.36 (75% ether in hexanes); $[\alpha]^{23}_D$ 35.7 (*c* 0.548, $CHCl_3$); IR (thin film) 1718 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.35 (m, 15 H), 5.96 (br d, 1 H, $J$ = 10.5 Hz), 5.84 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.63−5.73 (m, 2 H), 5.34 (br d, 2 H, $J$ = 10.5 Hz), 5.62 (d, 2 H), 5.6−5.74 (m, 2 H), 4.36 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 26.4 Hz), 4.34 (s, 2 H), 4.32 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 24.2 Hz), 4.19 (d, 1 H, $J$ = 3 Hz), 4.13 (d, 1 H,$J$ = 3 Hz), 4.04 (m, 2 H), 3.89 (d, 1 H, $J$ = 12 Hz), 3.88 (m, 1 H), 3.77 (quint, 1 H, $J$ = 6 Hz), 3.58 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.47 (A of ABX, 2 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.41 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.38 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.32 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 2.66−2.85 (m, 3 H), 1.27 (d, 3 H, $J$ = 6 Hz), 1.25 (d, 6 H, $J$ = 6 Hz), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.5, 169.1, 168.2, 137.9, 137.8, 137.4, 128.81, 128.8, 128.1, 127.9, 127.7, 127.5, 127.4, 126.2, 125.6, 125.4, 94.4, 80.1, 77.1, 76.9, 74.0, 73.5, 73.3, 73.2, 73.1, 72.4, 72.1, 71.9, 70.4, 69.2, 68.9, 68.6, 38.1, 37.8, 25.6, 20.8, 17.9, 14.6, 14.4, −4.6, −4.7; HRMS (FAB) *m/e* 1107.3681 ($M^+$ + Na, $C_{56}H_{71}O_{13}Cl_3SiNa$ requires 1107.3627).

**Bis(dihydropyran) Hydroxy 2,2,2-Trichloroethyl Ester 31**. To a solution of dimer **28** (830 mg, 0.951 mmol) in $CH_3CN$ (10 mL) at 0 °C was added 52% aqueous HF solution (1.5 mL). The reaction was quenched after 30 min with 20 mL of $CH_2Cl_2$, 20 mL of $H_2O$, and 10 mL of saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (33% hexanes in $Et_2O$) afforded 690 mg (95%) desired product as a colorless oil. Data for **31**: $R_f$ 0.26 (50% hexanes in ether); $[\alpha]^{23}_D$ −25.6 (*c* 0.626, $CHCl_3$); IR (thin film) 3358, 1726 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.25 (m, 4 H), 6.8−6.88 (m, 4 H), 5.94 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.81 (br d, 1 H, $J$ = 10.5 Hz), 5.7 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.35 (br d, 1 H, $J$ = 10.5 Hz), 4.72 (qd, 1 H, $J$ = 6.7, 4.5 Hz), 4.63 (d, 1 H, $J$ = 12 Hz), 4.33 (d, 1 H, $J$ = 3 Hz), 4.29 (ABq, 2 H, $J$ = 11 Hz, $\Delta\upsilon_{AB}$ = 34.3 Hz), 4.26 (ABq, 2 H, $J$ = 10.5 Hz, $\Delta\upsilon_{AB}$ = 19 Hz), 4.14 (d, 1 H, $J$ = 3 Hz), 4.18−4.23 (br, 1 H), 3.96−4.07 (m, 2 H), 3.75−3.82 (m, 7 H), 2.67−2.88 (m, 3 H), 1.24 (d, 3 H, $J$ = 7.5 Hz), 1.22 (d, 3 H, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.5, 168.2, 159.2, 159.1, 129.8, 129.7, 127.9, 127.1, 126.8, 125.6, 113.5, 94.4, 79.4, 76.7, 73.9, 73.3, 72.8, 72.4, 72.0, 68.5, 68.5, 68.3, 55.0, 38.2, 38.1, 17.5, 14.1; HRMS (FAB) *m/e* 779.1794 ($M^+$ + Na, $C_{36}H_{43}O_{11}Cl_3Na$ requires 779.1769).

**Bis(dihydropyran) Hydroxy 2,2,2-Trichloroethyl Ester 32 and Tris(dihydropyran) Hydroxy 2,2,2-Trichloroethyl Esters 37 and 38**. Refer to preparation of **31**. Data for **32**: $R_f$ 0.2 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −23.8 (*c* 0.508, $CHCl_3$); IR (thin film) 3440, 1726 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.38 (m, 10 H), 5.94 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.81 (br d, 1 H, $J$ = 10.5 Hz), 5.72 (ddd, 1 H, $J$ = 10.5, 6, 3 Hz), 5.35 (br d, 1 H, $J$ = 10.5 Hz), 4.73 (qd, 1 H, $J$ = 6.2, 4.5 Hz), 4.63 (d, 1 H, $J$ = 12 Hz), 4.36 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 32.3 Hz), 4.34 (ABq, 2 H, $J_{AB}$ = 12 Hz, $\Delta\upsilon_{AB}$ = 9 Hz), 4.32 (d, 1 H, $J$ = 3 Hz), 4.21 (m, 1 H), 4.16 (d, 1 H, $J$ = 3 Hz), 4.06 (m, 1 H), 4.02 (qd, 1 H, $J$ = 6.2, 4.5 Hz), 3.89 (d, 1 H, $J$ = 12 Hz), 3.54 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.47 (A of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{AX}$ = 9 Hz), 3.46 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 3.38 (B of ABX, 1 H, $J_{AB}$ = 9 Hz, $J_{BX}$ = 4.5 Hz), 2.7−2.87 (m, 3 H), 1.24 (d, 3 H, $J$ = 6.2 Hz), 1.21 (d, 3 H, $J$ = 6.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.5, 168.2, 137.7, 137.5, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.2, 126.9, 125.7, 94.4, 79.5, 76.7, 74.0, 73.4, 73.1, 72.4, 72.1, 68.9, 68.5, 38.0, 17.5, 17.9, 14.1; HRMS (FAB) *m/e* 719.1539 ($M^+$ + Na, $C_{34}H_{39}O_9Cl_3Na$ requires 719.1557).

Data for **37**: $R_f$ 0.25 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ 33.8 (*c* 0.816, $CHCl_3$); IR (thin film) 3456, 1716 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.25 (m, 6 H), 6.8−6.88 (m, 6 H), 5.93 (ddd, 1 H, $J$ = 10.5, 6, 2 Hz), 5.82 (br d, 1 H, $J$ = 10.5 Hz), 5.72 (ddd, 1 H, $J$ = 10.5, 6, 2 Hz), 5.67 (ddd, 1 H, $J$ = 10.5, 6, 2 Hz), 5.34 (br d, 1 H, $J$ = 10.5 Hz), 5.32 (br d, 1 H, $J$ = 10.5 Hz), 4.71 (qd, 1 H, $J$ = 6.8, 4.5 Hz), 4.66 (qd, 1 H, $J$ = 6.8, 4.5 Hz), 4.61 (d, 1 H, $J$ = 12 Hz), 4.33 (ABq, 2 H, $J$ = 12 Hz, $\Delta\upsilon_{AB}$ = 13.4 Hz), 4.32 (d, 1 H, $J$ = 3 Hz), 4.26 (ABq, 2 H, $J$ = 10.5 Hz, $\Delta\upsilon_{AB}$ = 20 Hz), 4.17 (m, 1 H), 4.16 (d, 1 H, $J$ = 3 Hz), 4.07 (d, 1 H, $J$ = 3 Hz), 3.99 (br, 2 H), 3.8 (d, 1 H, $J$ = 12 Hz), 3.77 (s, 9 H), 3.51 (A of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{AX}$ = 9 Hz), 3.4−3.5 (m, A of ABX, 2 H; B of ABX, 1 H), 3.37 (B of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{BX}$ = 4.5 Hz), 3.32 (B of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{BX}$ = 4.5 Hz), 2.96 (d, 1 H, $J$ = 5.8 Hz), 2.64−2.84 (m, 3 H), 1.24 (d, 3 H, $J$ = 6.5 Hz), 1.23 (d, 3 H, $J$ = 6.5 Hz), 1.22 (d, 3 H, $J$ = 6.5 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.6, 169.1, 168.2, 159.1, 158.9, 129.9, 129.8, 129.8, 129.7, 129.6, 128.1, 127.7, 127.1, 126.3, 125.5, 113.5, 94.5, 79.4, 76.8, 73.9, 73.3, 73.1, 72.7, 72.5, 72.2, 71.8, 68.7, 68.6, 68.5, 68.4, 55.0, 38.1, 38.0 37.8, 17.6, 14.3, 14.0; HRMS (FAB) *m/e* 1083.3106 ($M^+$ + Na, $C_{53}H_{63}O_{16}Cl_3Na$ requires 1083.3079).

Data for **38**: $R_f$ 0.28 (50% ethyl acetate in hexanes); $[\alpha]^{23}_D$ 25.8 (*c* 0.536, $CHCl_3$); IR (thin film) 3420, 1715 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.1−7.4 (m, 15 H), 5.85−6.08 (m, 4 H), 5.56 (br t, 2 H, $J$ = 10 Hz), 4.86−5.01 (m, 2 H), 4.66 (d, 1 H, $J$ = 4.3 Hz), 4.56 (d, 1 H, $J$ = 4.5 Hz), 4.53 (d, 1 H, $J$ = 4.5 Hz), 4.49 (ABq, 2 H, $J_{AB}$ = 1.9 Hz, $\Delta\upsilon_{AB}$ = 17.6 Hz), 4.26−4.30 (m, 1 H), 4.08−4.13 (m, 2 H), 3.83−3.90 (m, 1 H), 3.63−3.80 (m, 3 H), 1.33 (d, 3 H, $J$ = 7.2 Hz), 1.24 (d, 3 H, $J$ = 7.1 Hz), 1.11 (d, 3 H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.8, 168.7, 167.2, 138.2, 138.0, 137.6, 129.6, 129.3, 128.9, 128.8,

128.7, 128.0, 127.8, 127.2, 127.0, 126.9, 125.3, 125.2, 124.5, 94.0, 79.3, 77.1, 76.3, 76.1, 73.9, 72.1, 72.0, 68.6, 43.0, 42.7, 42.6, 17.4, 14.4, 13.8; HRMS (FAB) *m/e* 993.2734 ($M^+ + Na$, $C_{50}H_{57}O_{13}Cl_3Na$ requires 993.2763).

**Tris(dihydropyran) Seco Acid 39**. To a solution of alcohol **36** (160 mg, 0.19 mmol) in a mixture of 5:1 (v/v) THF/1 M $K_2HPO_3/KH_2PO_3$ solution (12 mL) was added zinc dust (330 mg, 5.08 mmol). The mixture was vigorously stirred for 2 h, and another portion of zinc dust (300 mg, 4.61 mmol) was added. The reaction was stirred for another 2 h and acidified with 5% HCl until acidic (pH = 2). The mixture was filtered through Celite, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic phases were concentrated. Flash chromatography (60% ether, 30% hexanes and 10% HOAc) gave 130 mg (96%) of the desired product as a colorless oil. Data for **39**: $R_f$ 0.35 (60% ether, 30% hexanes and 10% HOAc); $[\alpha]^{23}_D$ −25.7 (*c* 0.468, $CHCl_3$); IR (thin film) 3430, 1715 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 300 MHz) $\delta$ 7.1−7.5 (m, 15 H), 5.70−5.90 (m, 4 H), 5.40−5.55 (br d, 2 H, *J* = 9.8 Hz), 4.70−4.90 (m, 2 H), 4.55 (d, 1 H, *J* = 4.5 Hz), 4.45 (d, 1 H, *J* = 4,0.5 Hz), 4.16−4.26 (m, 1 H), 4.02−4.12 (m, 1 H), 3.7−3.92 (m, 3 H), 3.45−3.65 (m, 3 H), 1.33 (d, 3 H, *J* = 7.2 Hz), 1.24 (d, 3 H, *J* = 7.1 Hz), 1.11 (d, 3 H, *J* = 6.8 Hz); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 171.6, 171.4, 171.0, 140.5, 140.1, 139.9, 131.3, 130.9, 130.8, 130.7, 129.9, 129.3, 129.1, 129.0, 128.94, 128.9, 128.3, 128.2, 127.1, 126.4, 126.1, 80.8, 78.3, 78.0, 77.9, 77.8, 74.1, 73.9, 70.2, 44.5, 44.3, 44.2, 18.8, 15.1, 15.0; HRMS (FAB) *m/e* 731.2837 ($M^+ + Na$, $C_{42}H_{44}O_{10}Na$ requires 731.2832)

**Tris(dihydropyran) Seco Acids 40 and 41**. Refer to preparation of **39**. Data for **40**: $R_f$ 0.31 (60% ether, 30% hexanes and 10% HOAc); $[\alpha]^{23}_D$ 43.8 (*c* 0.816, $CHCl_3$); IR (thin film) 3400, 1716 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 300 MHz) $\delta$ 7.1−7.17 (m, 6 H), 6.73−6.83 (m, 6 H), 5.7−5.78 (m, 2 H), 5.65 (ddd, 1 H, *J* = 10.5, 6, 2 Hz), 5.27 (d, 2 H, *J* = 11 Hz), 4.86 (s, 2 H), 4.26 (qd, 1 H, *J* = 6.8, 4.2 Hz), 4.57 (qd, 1 H, *J* = 6.8, 4.2 Hz), 4.26 (ABq, 2 H, *J* = 12 Hz, $\Delta\upsilon_{AB}$ = 17.2 Hz), 4.21 (d, 1 H, *J* = 3 Hz), 4.2 (s, 2 H), 4.17 (ABq, 2 H, *J* = 12 Hz, $\Delta\upsilon_{AB}$ = 0 Hz), 3.98 (d, 1 H, *J* = 3 Hz), 3.95 (d, 1 H, *J* = 3 Hz), 3.93 (br, 2 H), 3.72 (qd, 1 H, *J* = 6.8, 4.2 Hz), 3.67 (s, 9 H), 3.2−3.5 (m, 6 H), 2.68 (br, 1 H), 2.59 (br, 2 H), 1.14 (d, 3 H, *J* = 6.5 Hz), 1.13 (d, 3 H, *J* = 6.5 Hz), 1.1 (d, 3 H, *J* = 6.5 Hz); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 173.6, 172.4, 171.1, 160.7, 160.5, 131.5, 131.3, 131.1, 131.0, 130.3, 129.3, 128.9, 128.7, 128.5, 128.4, 127.8, 127.4, 114.8, 114.7, 114.5, 81.0, 78.3, 78.2, 74.5, 74.44, 74.4, 74.0, 73.9, 73.7, 73.6, 70.3, 70.0, 55.7, 55.7, 55.6, 43.3, 43.1, 38.5, 18.2, 14.7, 14.6; HRMS (FAB) *m/e* 975.3723 ($M^+ - H + 2Na$, $C_{51}H_{61}O_{16}Na_2$ requires 975.3755).

Data for **41**: $R_f$ 0.32 (60% ether, 30% hexanes and 10% HOAc); $[\alpha]^{23}_D$ −25.7 (*c* 0.468, $CHCl_3$); IR (thin film) 3446, 1721 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 300 MHz) $\delta$ 7.1−7.5 (m, 15 H), 5.70−5.90 (m, 4 H), 5.40−5.55 (br d, 2 H, *J* = 9.8 Hz), 4.70−4.90 (m, 2 H), 4.55 (d, 1 H, *J* = 4.5 Hz), 4.45 (d, 1 H, *J* = 4.5 Hz), 4.16−4.26 (m, 1 H), 4.02−4.12 (m, 1 H), 3.7−3.92 (m, 3 H), 3.45−3.65 (m, 3 H), 1.33 (d, 3 H, *J* = 7.2 Hz), 1.24 (d, 3 H, *J* = 7.1 Hz), 1.11 (d, 3 H, *J* = 6.8 Hz); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 171.6, 171.4, 171.0, 140.4, 140.0, 139.9, 131.3, 130.9, 130.8, 130.7, 129.9, 129.3, 129.1, 129.0, 128.9, 128.9, 128.2, 128.1, 127.0, 126.4, 126.0, 80.8, 78.2, 78.0, 77.9, 77.8, 74.0, 73.9, 70.2, 44.4, 44.3, 44.2, 18.8, 15.1, 15.0; MS (FAB) *m/e* 885.3 ($M^+ - H + 2Na$, $C_{48}H_{55}O_{13}Na_2$ requires 885.3).

**Macrotriolide 1a**. To a refluxing mixture of DMAP (20 mg, 0.169 mmol) and DMAP−TFA (37 mg, 0.183 mmol) in $CH_3Cl$ (15 mL) was added DIC (0.3 mL, 0.196 mmol). To this mixture was added seco acid **39** (100 mg, 0.141 mmol) in $CH_3Cl$ (10 mL) via syringe pump over a period of 6 h. The heat was turned off after 3 h. The reaction was stirred overnight and then washed with $H_2O$ (2 × 30 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 30 mL). The organic phase was concentrated, and flash chromatography (75% ethyl acetate in hexanes) gave 75 mg (76%) desired product. Data for **1a**: mp 224−226 °C dec; $R_f$ 0.28 (75% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −15.8 (*c* 0.376, $CHCl_3$); IR (thin film) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20−7.33 (m, 15 H), 5.92−6.02 (ddd, 3 H, *J* = 11.8, 6.1, 3.1 Hz), 5.63 (br d, 3 H, *J* = 12 Hz), 4.75 (qd, 3 H, *J* = 7.1, 3.1 Hz), 4.52 (d, 3 H, *J* = 4.5 Hz), 4.42−4.49 (br, 3 H), 3.62 (br, 3 H), 0.91 (d, 9 H, *J* = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 169.4, 138.3, 129.3, 129.1, 127.8, 126.9, 125.7, 77.4, 75.6, 71.6, 43.0, 12.4; single crystals of **1a** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 $CH_2Cl_2$/hexane solution of **1a** (complete crystallographic data can be found in the Supporting Information); MS (FAB) *m/e* 691.3 ($M^+ + H$, $C_{42}H_{43}O_9$ requires 691.3).

**Macrotriolides 1b and 1c**. Refer to preparation of **1a**. Data for **1b**: $R_f$ 0.21 (75% ethyl acetate in hexanes); $[\alpha]^{23}_D$ 23.8 (*c* 0.236, $CHCl_3$); IR (thin film) 1726 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.1−7.18 (m, 6 H), 6.75−6.82 (m, 6 H), 5.88 (ddd, 3 H, *J* = 10.5, 6, 2 Hz), 5.49 (br d, 3 H, *J* = 10.5 Hz), 4.91 (qd, 3 H, *J* = 6.2, 2 Hz), 4.45 (br, 3 H), 4.31 (ABq, 6 H, *J* = 12 Hz, $\Delta\upsilon_{AB}$ = 10.6 Hz), 4.22 (d, 3 H, *J* = 3 Hz), 3.73 (s, 9 H), 3.54 (A of ABX, 3 H, $J_{AB}$ = 10 Hz, $J_{AX}$ = 9 Hz), 3.4−3.5 (m, A of ABX, 2 H; B of ABX, 1 H), 3.37 (B of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{BX}$ = 4.5 Hz), 3.3 (B of ABX, 1 H, $J_{AB}$ = 10 Hz, $J_{BX}$ = 6 Hz), 2.55 (m, 3 H), 1.05 (d, 9 H, *J* = 6 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 170.1, 158.8, 130.0, 128.6, 127.8, 127.3, 113.3, 76.1, 73.9, 72.0, 71.7, 68.7, 55.0, 37.1, 12.4; HRMS (FAB) *m/e* 935.3793 ($M^+ + Na$, $C_{51}H_{60}O_{15}Na$ requires 935.383).

Data for **1c**: mp 234−235 °C dec; $R_f$ 0.24 (75% ethyl acetate in hexanes); $[\alpha]^{23}D$ −18.8 (*c* 0.256, $CHCl_3$); IR (thin film) 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20−7.33 (m, 15 H), 5.92−6.02 (ddd, 3 H, *J* = 11.8, 6.1, 3.1 Hz), 5.63 (br d, 3 H, *J* = 12 Hz), 4.75 (qd, 3 H, *J* = 7.1, 3.1 Hz), 4.52 (d, 3 H, *J* = 4.5 Hz), 4.42−4.49 (br, 3 H), 3.62 (br, 3 H), 0.91 (d, 9 H, *J* = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 169.4, 138.3, 129.3, 129.1, 127.7, 126.9, 125.7, 77.4, 75.6, 71.6, 43.0, 12.4. Single crystals of **1c** suitable for X-ray structure determination were obtained by slowly cooling a saturated boiling methanol solution to 45 °C (complete crystallographic data can be found in the Supporting Information).

**Tris(tetrahydropyran) Macrotriolide 42.** Catalytic palladium(II) hydroxide (20 w/w % on carbon, 20 mg, 0.029 mmol) was added to **1a** (85 mg, 0.123 mmol) in 3 mL of ethyl acetate. The system was placed under 1 atm of hydrogen. The reaction was stirred for 12 h. The resulting mixture was then filtered through a plug of Celite. The plug was flushed with ethyl acetate, and the solution was concentrated. Flash chromatography (75% ethyl acetate in hexanes) gave 77 mg (89%) of desired product. Data for **42**: mp 225−227 °C dec; $R_f$ 0.22 (75% ethyl acetate in hexanes); $[\alpha]^{23}_D$ −20.8 (*c* 0.226, $CHCl_3$); IR (thin film) 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20−7.33 (m, 9 H), 7.4−7.6 (m, 6 H), 4.84 (qd, 3 H, *J* = 7.1, 3.1 Hz), 4.48 (d, 3 H, *J* = 4.5 Hz), 3.76 (brd, 3 H, *J* = 8.1 Hz), 3.42 (br, 3 H), 1.9−2.2 (br, 6 H), 1.36 (d, 9 H, *J* = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 170.2, 141.3, 128.7, 128.1, 127.6, 125.9, 78.3, 77.9, 72.2, 40.0, 31.2, 21.0, 12.7; single crystals of **42** suitable for X-ray structure determination were obtained by slowly evaporating a saturated 5:2 $CH_2Cl_2$/hexane solution of **42** (complete crystallographic data can be found in the Supporting Information); MS (FAB) *m/e* 697.3 ($M^+ + H$, $C_{42}H_{49}O_9$ requires 697.3).

**Tris(hydroxymethyl)-Substituted Macrocycle 1d.** Refer to preparation of **42**. Data for **1d**: $R_f$ 0.42 (25% $CH_3OH$ in $CH_2Cl_2$); $[\alpha]^{23}_D$ 43.8 (*c* 0.816, $CHCl_3$); IR (thin film) 3456, 1726 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 300 MHz) $\delta$ 5.06 (qd, 3 H, *J* = 6.2, 2 Hz), 4.35 (d, 3 H, *J* = 1 Hz), 3.79 (br d, 3 H, *J* = 12 Hz), 3.68 (A of ABX, 3 H, $J_{AB}$ = 12 Hz, $J_{AX}$ = 6.8 Hz), 3.62 (B of ABX, 3 H, $J_{AB}$ = 12 Hz, $J_{BX}$ = 6.8 Hz), 2.25 (m, 3 H), 2.08 (br d, 3 H, *J* = 12 Hz), 1.84 (m, 3 H), 1.62 (m, 3 H), 1.43 (br d, 3 H, *J* = 12 Hz), 1.39 (d, 9 H, *J* = 6.8 Hz); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 171.2, 80.1, 79.4, 74.6, 60.4, 39.1, 25.5, 22.3, 13.1; HRMS (FAB) *m/e* 581.2560 ($M^+ + Na$ $C_{27}H_{42}O_{12}Na$ requires 581.2574).

**Tris(bromoacetate) Macrocycle Derivative 43.** To a cooled (−78 °C) solution of triol **1d** (20 mg, 0.0358 mmol) and DMAP (19.7 mg, 0.161 mmol) in 1 mL of $CH_2Cl_2$ was added bromoacetyl bromide (14 mL, 0.161 mmol). The reaction mixture was stirred at −78 °C for 30 min. Two millilters of $CH_2Cl_2$ and 2 mL of $H_2O$ were added, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (10% MeOH in $CH_2Cl_2$) afforded 26.7 mg (81%) of product. Data for **43**: $R_f$ 0.25 (15% $CH_3OH$ in $CH_2Cl_2$); $[\alpha]^{23}_D$ −43.8 (*c* 0.116, $CHCl_3$); IR (thin film) 1735 $cm^{-1}$; $^1H$ NMR

($CDCl_3$, 300 MHz) $\delta$ 4.93 (qd, 3 H, $J$ = 6.8, 2 Hz), 4.37 (A of ABX, 3 H, $J_{AB}$ = 12 Hz, $J_{AX}$ = 9 Hz), 4.25 (B of ABX, 3 H, $J_{AB}$=12 Hz, $J_{BX}$=16 Hz), 4.16 (d, 3 H, $J$ = 3 Hz), 3.81 (s, 9 H), 3.69 (m, 3 H), 2.48 (m, 3 H), 2.05 (br d, 3 H, $J$ = 12 Hz), 1.77 (m, 3 H), 1.4−1.55(m, 6 H), 1.35 (d, 9 H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.6, 166.7, 78.1, 77.1, 72.7, 63.0, 34.16, 25.2, 21.1, 12.5; MS (FAB) *m/e* 941.0211 ($M^+$ + H + Na, $C_{33}H_{45}O_{15}Na$ requires 941.0206).

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**Supporting Information Available:** Characterization data including $^1$H and $^{13}$C NMR spectra of all new compounds; $^1$H NMR spectra of barium complexes of **1a** and **1c**; determination of spectra, association constants ($K_a$), and free energies of association ($-\Delta G°$) of host−guest complexes by ultraviolet spectroscopy; experimental procedures for Job plots; crystallographic data for **1a**, **42** and **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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