Structure–Activity Relationships of C1 and C6 Side Chains of Zaragozic Acid A Derivatives

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Systematic modification of the C6 acyl side chain of zaragozic acid A, a potent squalene synthase inhibitor, was undertaken to improve its biological activity. Simplification of the C6 side chain to the octanoyl ester has deleterious effects; increasing the linear chain length improves the in vitro activity up to the tetradecanoyl ester. An ω-phenoxy group is a better activity enhancer than an ω-phenyl group. A number of C6 carbamates, ethers, and carbonates were prepared and found to have similar activity profiles as the C6 esters. In the preparation of C6 ethers, C4 and C4,6 bisethers were also isolated; their relative activity is: C6 > C4 > C4,6. These C6 long-chain derivatives are subnanomolar squalene synthase inhibitors; they are, however, only weakly active in inhibiting hepatic cholesterol synthesis in mice. The C6 short-chain derivatives are much less active in vitro, but they all have improved oral activity in mice. Modification of the C1 alkyl side chain of the *n*-butanoyl analogue (ED_{50} 4.5 mg/kg) did not improve the po activity further. A number of these C6 long-chain derivatives are also potent antifungal agents in vitro.

Squalene synthase (farnesyl-diphosphate:farnesyl-diphosphate farnesyltransferase, EC 2.5.1.21) is a microsomal protein that catalyzes the head-to-head reductive dimerization of farnesyl pyrophosphate (FPP) to squalene via the cyclopropane intermediate, presqualene pyrophosphate.[1-3] It is a key enzyme that lies strategically at the final branch point of the cholesterol biosynthetic pathway. Selective inhibition of this enzyme should not directly interfere with the production of the nonsterol isoprene metabolites such as dolichol, ubiquinone, the farnesyl group of heme A, the farnesyl and geranylgeranyl groups of prenylated proteins, and the isopentenyl side chain of isopentenyladenine. Thus specific and potent squalene synthase inhibitors may be useful cholesterol-lowering agents and not adversely affect the synthesis of other isoprenoids. Substrate analogues of FPP have been investigated as squalene synthase inhibitors.[4-6] A series of isoprenoid (phosphinylmethyl)phosphonates were prepared, and the most potent derivative was reported to have an IC_{50} value of 50 nM (K_i 37 nM, a competitive inhibitor with respect to FPP).[5] Putative transition-state analogues such as presqualene phosphonophosphates,[7] ammonium[8] and sulfonium[9] analogues of presqualene pyrophosphate, prenyl-substituted cyclobutanones,[10] and a series of amphiphilic polyisoprenoid compounds[11] were also investigated as squalene synthase inhibitors, but only modest activities were observed. A series of *N*-(arylalkyl)farnesylamines were investigated as squalene synthase inhibitors.[12] The most active compound in this series was *N*-(3-pyridylmethyl)farnesylamine, which had an IC_{50} value of 4 nM when tested in the presence of added inorganic pyrophosphate (PP_i). Recently, bisphosphonates such as YM 175 (cycloheptylaminomethylene-1,1-bisphosphonic acid)[13] and a number of lipophilic 1,1-bisphophonates[14] were reported to be potent squalene synthase inhibitors. The geranyl and biphenyl bisphosphonates had IC_{50} values of 0.7–0.95 nM and were active in vivo in rats and hamsters.[14]

The zaragozic acids A–C, characterized by a novel 4,6,7-trihydroxy-2,8-dioxabicylo[3.2.1]octane-3,4,5-tricarboxylic acid core, differ from each other in the structures of the C6 acyl and C1 alkyl side chains.[15] These three related fungal metabolites, A, B, and C, were produced from an unidentified sterile fungal culture, *Sporormiella intermedia* and *Leptodontium elatius*. They were potent competitive inhibitors of rat liver squalene synthase with apparent K_i values of 7.8×10^{-11}, 2.9×10^{-11}, and 4.5×10^{-11} M, respectively. They inhibited the incorporation of [^{3}H]mevalonate into cholesterol in Hep G2 cells. Each zaragozic acid gave a dose-dependent decrease in cholesterol synthesis with IC_{50} values for zaragozic acids A, B, and C of 6×10^{-6}, 6×10^{-7}, and 4×10^{-6} M, respectively. Zaragozic acid A, administered subcutaneously, inhibited hepatic cholesterol synthesis in the mouse with an ED_{50} value of 0.2 mg/kg.[15] The isolation, characterization, and structural elucidation of these natural products were described.[16-18] The biosynthesis of zaragozic acids was also delineated.[19] Squalestatin 1, reported to be the same structure as zaragozic acid A, was independently discovered by a group of researchers at Glaxo.[20-23] They showed that squalestatin 1 lowered serum cholesterol by up to 75% at an oral dose of 10–100 mg/kg/day in marmosets. The cholesterol lowering was apparent within 24 h and could be maintained for at least 8 weeks on prolonged dosing with no attenuation of the response. Apolipoprotein B, characteristic of low and very low density lipoproteins, was reduced by 45%, whereas apolipoprotein A1 levels (indicative of the high density lipoprotein fraction) were unchanged. In addition to being very potent squalene synthase inhibitors, the zaragozic acids (or squalestatins) also had broad spectrum in vitro antifungal activity against both yeast and filamentous fungi.[17,20] Modifications of the 4,6,7-trihy-

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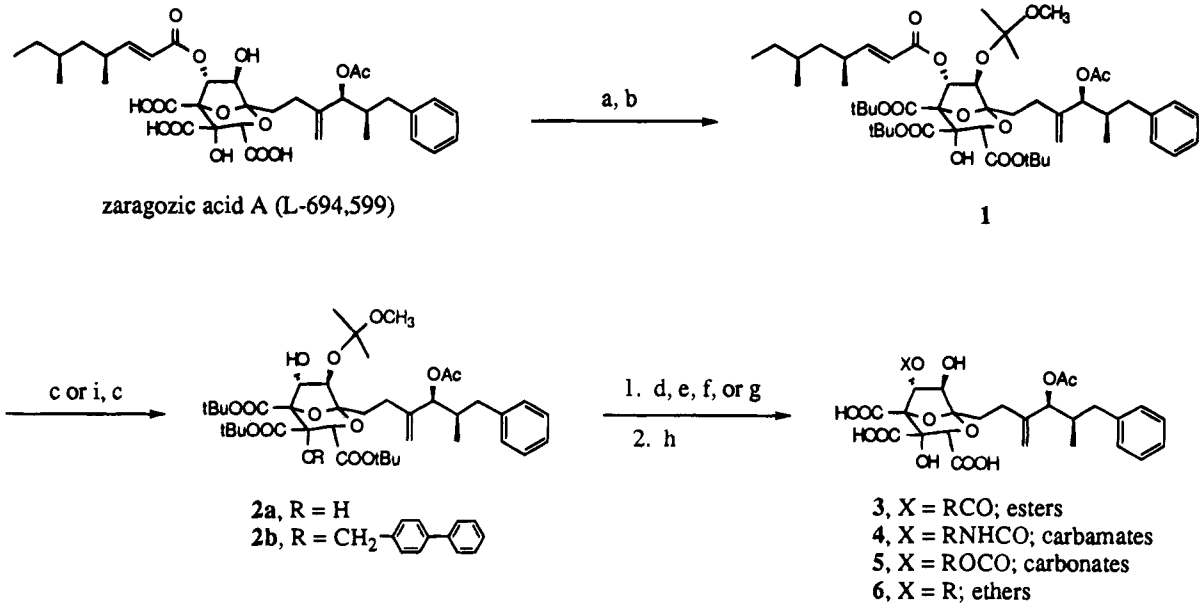
Scheme 1[a]



[a] (a) *i*PrN=C(OtBu)NH*i*Pr, $PhCH_3$, 65 °C, 16 h, 86%; (b) $CH_3C(OCH_3)=CH_2$, CH_2Cl_2, pyridinium *p*-toluenesulfonate, 100%; (c) $NH_2OH{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, CH_3OH, 90%; (d) RCOOH, DCC, DMAP, CH_2Cl_2, 76–95% (C6 esters); (e) 1,1′-carbonyldiimidazole, $PhCH_3$, 5 h, followed by RNH_2, 3 h, 66–90% (C6 carbamates); (f) 1,1′-carbonyldiimidazole, $PhCH_3$, 5 h followed by ROH, DBU, 66–90% (C6 carbonates); (g) RI or RBr/*n*-Bu4N$^+$I$^-$, NaH, DMF, 7–16 h, 18–40% (C6 ethers); (h) CF_3COOH, CH_2Cl_2, overnight, 85–100%; (i) 4-phenylbenzyl chloride, *n*-Bu4N$^+$I$^-$, NaH, 58%.

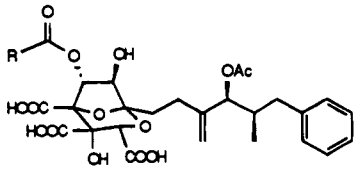
droxy-2,8-dioxabicylo[3.2.1]octane-3,4,5-tricarboxylic acid core of zaragozic acid A (squalestatin 1) have been reported by researchers at Glaxo[24,25] and by us.[26–29] The 6,7-unsubstituted analogue of zaragozic acid A was reported to have an IC_{50} value of 57 nM.[24] A number of 3,4-diesters of zaragozic acid A were prepared in our laboratories and found to have improved oral activity, e.g., 3-isopentyl-4-pivaloyloxymethyl and 3-isopentyl-4-acetoxymethyl diesters had ED_{50} values of 9 and 6 mg/kg, respectively.[28] The C3-decarboxy-C3-methyl-4-pivaloyloxymethyl derivative exhibits an ED_{50} value of 1.6 mg/kg in our oral mouse assay.[27] Recently, researchers at Glaxo also disclosed their efforts in the C1/C6 side chains modifications.[30–31] In this paper, we report the syntheses and structure–activity relationships of the C1 and C6 side chains of zaragozic acid A and its derivatives.

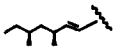
Chemistry

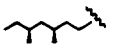
The important intermediate **2a** was prepared from zaragozic acid A (L-694,599) as outlined in Scheme 1. A preliminary account of this work has appeared.[32] Briefly, treatment of L-694,599 with *O-tert*-butyl-*N,N′*-diisopropylisourea[33] in toluene at 65 °C for 16 h afforded the tris-*tert*-butyl ester, which was ketalized with 2-methoxypropene to give 1 in 86% overall yield. Selective removal of the α,β-unsaturated C6 acyl side chain was effected with lithium hydroxide monohydrate and 30% hydrogen peroxide in THF (58%) or preferably with hydroxylamine hydrochloride and sodium acetate trihydrate in methanol (90–99%).[34] Reactions of **2a** with carboxylic acids (DCC, DMAP, CH_2Cl_2, 76–95%), acid anhydrides, or acid chlorides (Et_3N, DMAP, CH_2Cl_2, 63–95%) gave the protected C6 esters (**3**). Acylation of the C4 *tert*-hydroxyl group was also observed when acid chlorides were used as acylating agents. Treatment of **2a** with 1,1′-carbonyldiimidazole in toluene at room temperature for 6 h provided the C6 imidazolyl carbamate, which was reacted in situ with amines and alcohols/DBU to give the respective C6 carbamates and carbonates in 66–95% yields. The carbamates can also be prepared from **2a** and isocyanates in pyridine or toluene/Et_3N at 90 °C. Direct alkylation of **2a** gave a mixture of C6 and C4 ethers (18–40% for each ether) and C4,6 bisethers (10–20%), which were separated by preparative TLC. To selectively prepare the C6 ether, the intermediate 1 was first reacted with 4-phenylbenzyl chloride (tetra-*n*-butylammonium iodide, NaH, 58%) followed by removal of the C6 acyl side chain to give the intermediate **2b**, which can then be alkylated with alkyl and aralkyl halides in good yields. These protected C6 esters, carbamates, carbonates, and ethers were conveniently deprotected with CF_3COOH (TFA) in CH_2Cl_2 at room temperature overnight to give **3** (esters), **4** (carbamates), **5** (carbonates), and **6** (ethers) in high yields. The C4 ethers (**7**) and C4,6 bisethers (**8**) were similarly obtained from their respective protected precursors. These products were usually purified by reverse-phase HPLC. The C6 side chains used for the synthesis of **3a-6a** were prepared from 4*S*(2*E*,4*R**,6*R**)-4,6-dimethyl-2-octenoic acid[21] (see the Experimental Section).

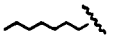
To modify the C1 alkyl side chain, the intermediate 1 was treated with ethylmagnesium chloride/cerium chloride in THF at −78 °C for 5 min to give the 4,4′-diol **9** and the two minor byproducts **10** and **11** (see Scheme 2). The intermediate **9** was selectively ozonolyzed at the C3′ *exo*-double bond to give the keto diol **12** in 31% overall yield from 1.[35] Sodium borohydride reduction ($NaBH_4$, EtOH, 72%) afforded the triol **13**, which was oxidized with sodium periodate in aqueous dioxane to give the propanal **14** in 89% yield. Propionylation of **9** followed by deprotection with TFA in CH_2Cl_2 afforded **15** in high yields (Chart 4). Compounds **16** and **17** were obtained from **9** (four steps) and **10** (two

Chart 1



L-694,599, R = 

3a, R = 

3b, R = 

3c, R = $CH_3(CH_2)_{10}$

3d, R = $CH_3(CH_2)_{12}$

3e, R = $CH_3(CH_2)_{14}$

3f, R = $PhO(CH_2)_{10}$

3g, R = $Ph(CH_2)_{10}$

3h, R = CH_3

3i, R = CH_3CH_2

3j, R = $CH_3CH_2CH_2$

3k, R = $CH_3CH_2CH_2CH_2$

3l, R = 

3m, R = 

3n, R = 

3o, R = 

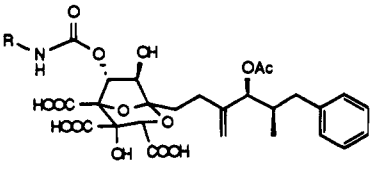
3p, R = 

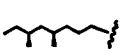
3q, R = 

3r, R = $CH_3OCH_2CH_2CH_2$

3s, R = $H_2NCHCCH_2CH_2$

3t, R = $HOOCCH_2CH_2$



4a, R = 

4b, R = $CH_3(CH_2)_9$

4c, R = $CH_3(CH_2)_{11}$

4d, R = $CH_3(CH_2)_{13}$

4e, R = $PhO(CH_2)_{11}$

4f, R = CH_3

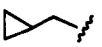
4g, R = CH_3CH_2

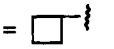
4h, X = $(CH_3)_2NCO$

4i, R = 

4j, X = 

4k, R = 

4l, R = 

4m, R = 

4n, R = 

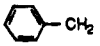
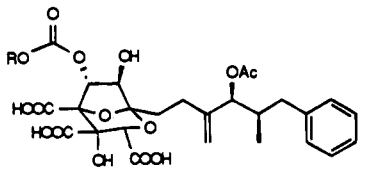
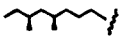
4o, R = 

Chart 2



5a, R = 

5b, R = $CH_3(CH_2)_9$

5c, R = $CH_3(CH_2)_{11}$

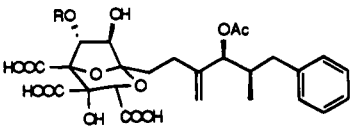
5d, R = $PhO(CH_2)_{11}$

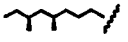
5e, R = CH_3

5f, R = CH_3CH_2

5g, R = 

5h, R = 



6a, R = 

6b, R = $CH_3(CH_2)_9$

6c, R = $CH_3(CH_2)_{11}$

6d, R = $CH_3(CH_2)_{13}$

6e, R = $CH_3(CH_2)_{15}$

6f, R = $PhO(CH_2)_8$

6g, R = $PhO(CH_2)_{11}$

6h, R = H

6i, R = CH_3

6j, R = $CH_3CH_2CH_2$

6k, R = $CH_3CH_2CH_2CH_2$

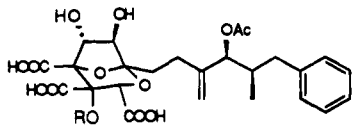
6l, R = 

steps), respectively, by standard manipulation (see the Experimental Section). Acetyloxy extrusion of L-694,-599 with bis(triphenylphosphine)palladium(II) chloride and ammonium formate at 110 °C for 4 h gave **18** in 48% yield.

Another target compound is the 1-[5(*S*)-methyl-6-phenylhexyl]-6-*O*-butyryl derivative **22** that requires the deoxygenation of the C1 side chain of **13** and the replacement of its C6 acyl moiety by a butyryl group (Scheme 3). Thus **13** was treated with 1,1′-thiocarbonyldiimidazole in toluene at room temperature to give the 3′,4′-cyclic thionocarbonate **19** (91%), which was heated under reflux in trimethyl phosphite for 28 h to afford the olefin **20** (51%). Several attempts to generate **20** from the 3′,4′-bismethyl sulfonates of **13** by the Tipson–Cohen reaction[36] (NaI–Zn in DMF) led to complex mixture. Removal of the C6 acyl side chain of **20** (NH_2OH·HCl, $NaOAc·3H_2O$, CH_3OH, 93%) followed by *n*-butyrylation (butyric anhydride, Et_3N, DMAP, 87%) gave **21**. Subsequent hydrogenation and deprotection with TFA in CH_2Cl_2 at room temperature overnight afforded **22** in high yields.

Wittig reactions of the propanal **14** with aralkyltriphenylphosphonium halides as outlined in Scheme 4 gave the olefins **23a** (78%; *trans:cis*, 84:16), **23b** (76%; *trans:cis*, 81:19), and **23c** (41%; *trans:cis*, 79:21). Compounds **23a** and **23b** were hydrogenated over 10% Pd/C in methanol and deprotected with TFA in CH_2Cl_2 to give **24a** and **24b**, respectively. Replacement of the C6 acyl side chains of **23a-c** by a *n*-butyryl group was effected in the usual manner (see the Experimental Section) to provide **25a-c**, which were hydrogenated over 10% Pd/C in MeOH and deprotected with TFA in CH_2Cl_2 to give the C1/C6 modified analogues, **26a-c**.

Chart 3



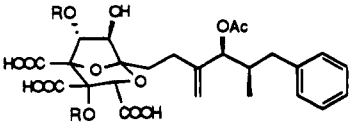
7c, R = $CH_3(CH_2)_{11}$

7d, R = $CH_3(CH_2)_{13}$

7f, R = $PhO(CH_2)_8$

7g, R = $PhO(CH_2)_{11}$

7j, R = $CH_3CH_2CH_2$



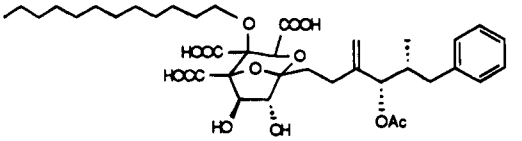
8c, R = $CH_3(CH_2)_{11}$

8d, R = $CH_3(CH_2)_{13}$

8f, R = $PhO(CH_2)_8$

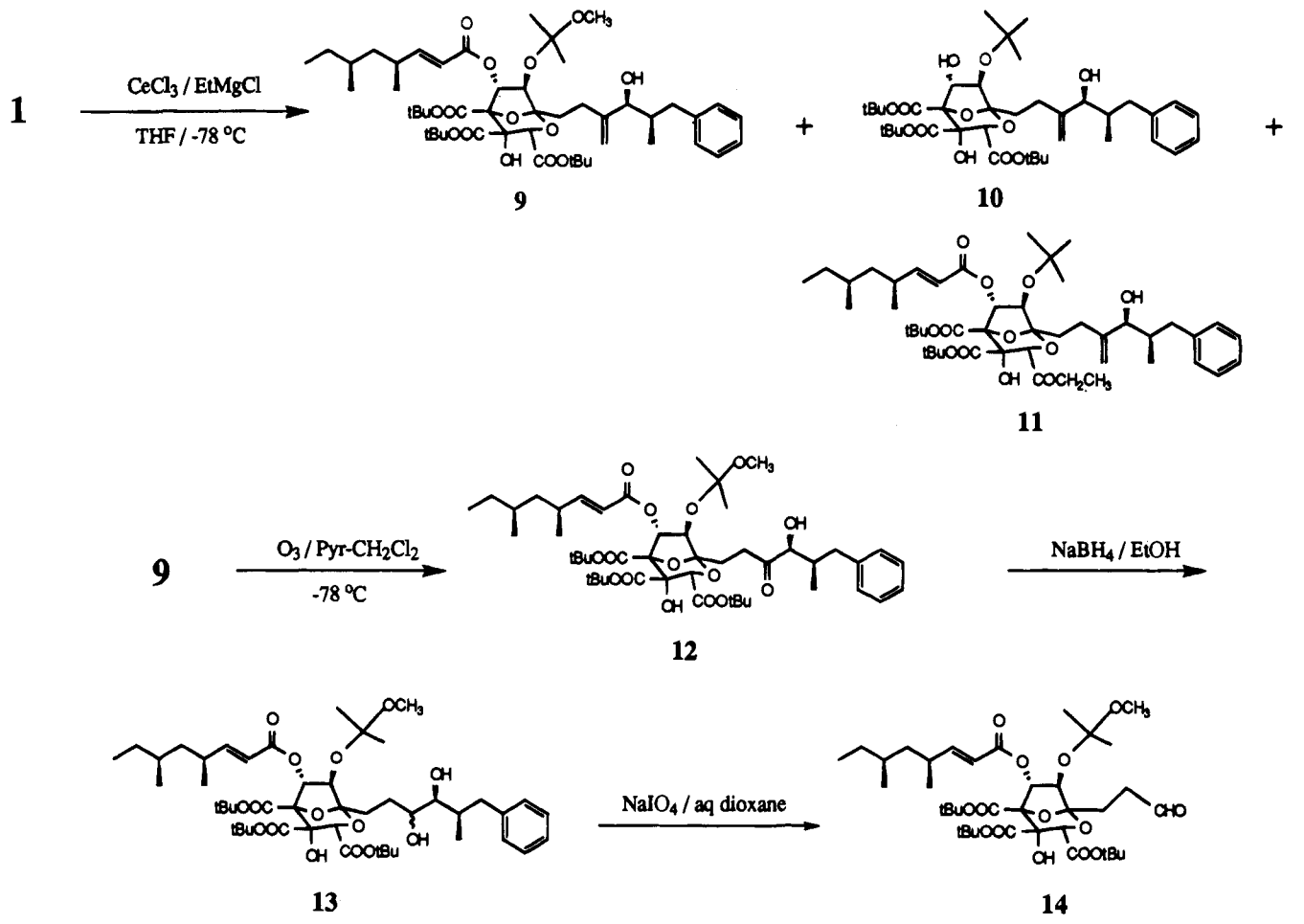
8g, R = $PhO(CH_2)_{11}$

8j, R = $CH_3CH_2CH_2$



7c

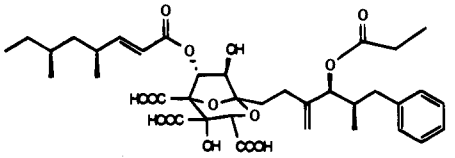
Scheme 2



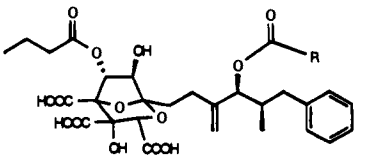
Results and Discussion

Zaragozic acid A is a subnanomolar squalene synthase inhibitor that blocks hepatic cholesterol synthesis when administered sc in mice and rats with an ED_{50} of 0.1–0.2 mg/kg.[15] It was also reported to be orally active in marmosets, achieving 50% reduction in serum cholesterol levels at a dose of 10 mg/kg/day.[23] However, it is only weakly active in blocking cholesterol synthesis when administered po in mice (ED_{50} 100 mg/kg; Table 1a). Lovastatin, simvastatin, and pravastatin, all HMG-CoA reductase inhibitors, are cholesterol-lowering agents that are used in humans at clinical doses of 0.1–1.0 mg/kg/day.[37] They are also orally active in blocking cholesterol synthesis in rats at these doses.[38] Our goal with the derivatization of zaragozic acid A was to produce compounds that would be orally active in animal models with doses comparable (i.e., ED_{50} < 1 mg/kg) to that used with the HMG-CoA reductase inhibitors in humans. The limited oral activity and absorption of zaragozic acid A is a major problem to be overcome in the development of this class of compounds into new therapies for elevated serum cholesterol in humans. Thus our initial objective was to improve the biological profile of zaragozic acid A by modification of its C6 side chain. Rat liver squalene synthase (RLSS), Hep G2, and oral mouse assays (see the Experimental Section) were used to guide our SAR studies. The C6 esters (**3a-t**), C6 carbamates (**4a-o**), C6 carbonates (**5a-h**), and C6 ethers (**6a-l**) were prepared (see Chemistry and the

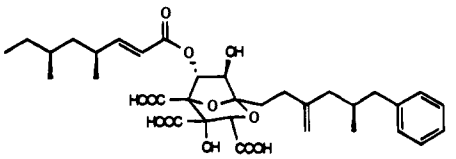
Chart 4



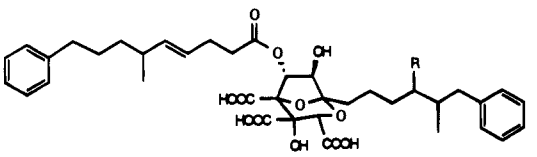
15



16, R = CH_3CH_2
17, R = $CH_3CH_2CH_2$

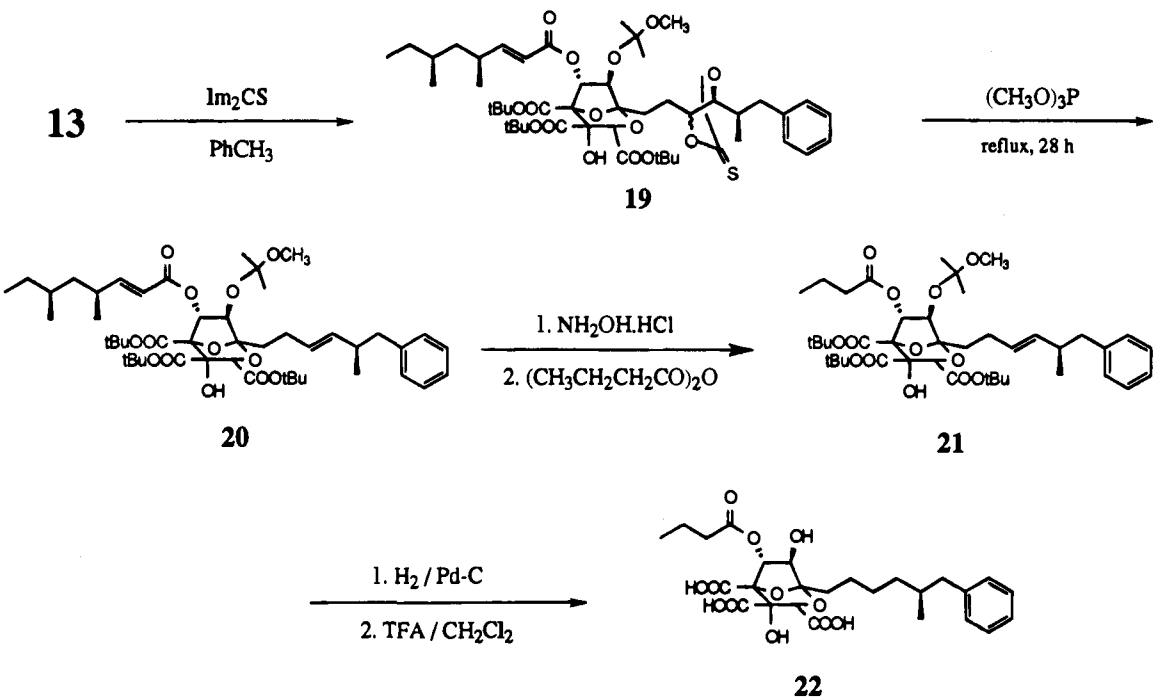


18



zaragozic acid C (L-697,350), R = OAc
L-735,021, R = H

Scheme 3



Experimental Section) and evaluated as squalene synthase inhibitors (Charts 1 and 2). The SAR of C6 long-chain derivatives will be discussed with reference to their inhibitory activities in RLSS (Tables 1a–4a). Hydrogenation of the α,β double bond of zaragozic acid A (L-694,599) (giving **3a**) lost about 30% of the enzyme inhibitory activity (see Table 1a). Removal of the two branched methyl groups (giving **3b**) diminished the activity further. In contrast, increasing the linear chain lengths (compounds **3b-d**) increased the inhibitory activity up to the tetradecanoyl **3d**, which is slightly more potent than L-694,599 in RLSS and about 6-fold more active in the Hep G2 assay. Further increase in linear chain lengths (to **3e**) diminished the inhibitory activity. Interestingly, ω-phenoxyundecanoyl **3f** is more active than ω-phenylundecanoyl **3g** in both the enzyme and Hep G2 assays. Although L-694,599 and its derivatives **3a-g** are very potent enzyme inhibitors, they are only moderately active in the cellular Hep G2 assay (IC_{50} values are about 3–4 orders of magnitude higher than those measured in the enzyme assay) and weakly active in the oral mouse assay. These data suggest possible problems with oral absorption, bioavailability, uptake, or stability of these compouds.

To eliminate the potential instability of C6 esters in vivo (due to esterases), we set out to prepare C6 derivatives having more stable linkages such as C6 carbamates **4** and C6 ethers **6** for biological evaluations. The SAR of C6 long chain carbamates **4** (Table 2a) is similar to that described for C6 esters **3**. The most active derivative in the linear long-chain alkyl series is the dodecyl carbamate **4c**, which is slightly more active than L-694,599 in both the enzyme and celluar assays. These analogues were all inactive in the oral mouse assay except **4e** (ω-phenoxyundecyl carbamate), which had ED_{50} value of about 24 mg/kg. For C6 long-chain ethers (Table 4a), it is noteworthy that **6a** (a C6 hydrogenated ether derivative of L-694,599) is equipotent to L-694,599. The optimal linear alkyl chain length in this series is the dodecyl ether **6c**, which is about

Scheme 4

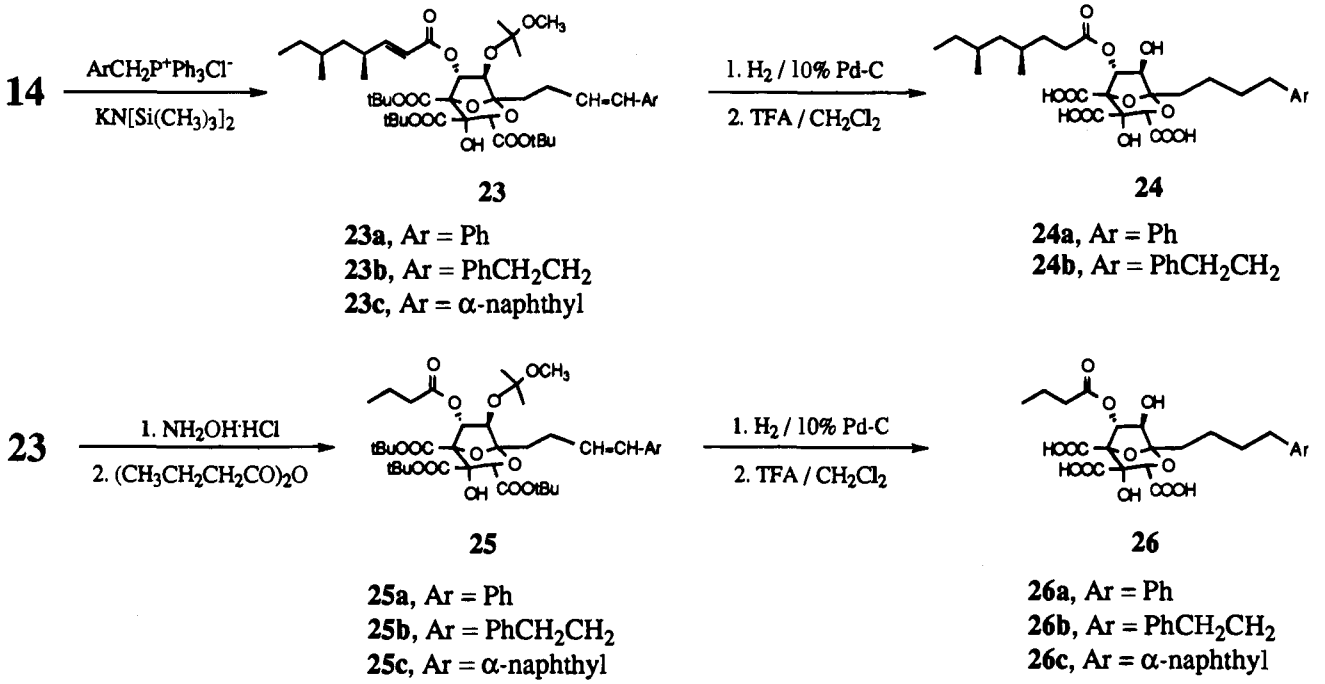
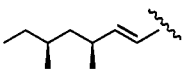
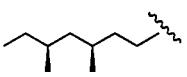
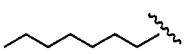


Table 1. Inhibitory Activity of C6 Long-Chain and Short-Chain Esters **3**

(a) C6 Long-Chain Esters **3**

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	Hep G2 (IC_{50}, μM)[a]	Hep G2 RA[b]	po mouse % inhibn (dose, mpk)
L-694,599		0.11–0.23	1.0	5.5–6.0	1.0	na[c] (40); 50 (100)
3a		0.19 (0.14)	0.74	7.5 (6.0)	0.80	nd[d]
3b		0.66 (0.11)	0.17	9.6 (5.5)	0.57	nd[d]
3c	$CH_3(CH_2)_{10}$	0.80 (0.23)	0.29	1.7 (5.5)	3.24	20 (40)
3d	$CH_3(CH_2)_{12}$	0.20 (0.22)	1.10	0.9 (5.5)	6.11	nd[d]
3e	$CH_3(CH_2)_{14}$	0.52 (0.14)	0.27	2.5 (5.5)	2.20	nd[d]
3f	$PhO(CH_2)_{10}$	0.13 (0.14)	1.08	2.0 (6.8)	3.40	11 (24)
3g	$Ph(CH_2)_{10}$	0.38 (0.17)	0.45	8.0 (11.0)	1.37	11 (24)

(b) C6 Short-Chain Esters **3**

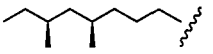
compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	po mouse ED_{50} (% inhibn (mpk))
3h	CH_3	36.1 (0.68)	0.02	18
3i	CH_3CH_2	11.0 (0.22)	0.02	12
3j	$CH_3CH_2CH_2$	9.2 (0.65)	0.07	4.5
3k	$CH_3CH_2CH_2CH_2$	9.6 (0.65)	0.07	>24 (40% at 24 mpk)
3l	$(CH_3)_2CH$	21.0 (0.36)	0.02	8
3m	$(CH_3)_3C$	na[c] at 161 nM		>12 (−2% at 12 mpk)
3n	$CH_3CH_2CHCH_3$	18.0 (0.65)	0.04	24
3o	$(CH_3)_2CHCH_2$	4.3 (0.58)	0.13	11
3p	$CH_2{=}C(CH_3)CH_2$	5.6 (0.36)	0.06	12
3q	$(CH_3)_3CCH_2$	2.0 (0.29)	0.15	>12 (25% at 12 mpk)
3r	$CH_3OCH_2CH_2CH_2$	25.0 (0.65)	0.03	20
3s	$H_2NCH_2CH_2CH_2$	na[c] at 161 nM		>12 (0% at 12 mpk)
3t	$HOOCCH_2CH_2$	na[c] at 161 nM		>12 (−20% at 12 mpk)

[a] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [b] Relative activity. [c] Not active. [d] Not done.

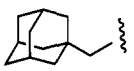
2.5- and 6-fold more active than L-694,599 in the respective enzyme and cellular assays. Again, the ω-phenoxyundecyl ether **6g** has enhanced potency. The corresponding C6 long-chain carbonates **5** were prepared and tabulated (Table 3a) to complete the studies. The decyl carbonate **5b** and ω-phenoxyundecyl carbonate **5d** were found to be about 3–4-fold more active than L-694,599 in both the enzyme and cellular assays. Again, these derivatives, including the more stable C6 long-chain carbamates **4** and ethers **6**, were all weakly active in the oral mouse assay, suggesting that the potential instability of the C6 ester linkage was not a major factor in the poor oral activity of zaragozic acid A and its C6 ester analogues.

Table 2. Inhibitory Activity of C6 Long-Chain and Short-Chain Carbamates 4

(a) C6 Long-Chain Carbamates 4

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	Hep G2 (IC_{50}, μM)[a]	Hep G2 RA[b]	po mouse % inhibn (dose, mpk)
4a		0.80 (0.20)	0.25	nd[c]		−2 (24)
4b	$CH_3(CH_2)_9$	1.00 (0.14)	0.14	3.6 (9.0)	2.5	4 (24)
4c	$CH_3(CH_2)_{11}$	0.17 (0.22)	1.29	8.8 (9.0)	1.02	0 (24)
4d	$CH_3(CH_2)_{13}$	0.28 (0.14)	0.50	nd[c]		12 (24)
4e	$PhO(CH_2)_{11}$	0.07 (0.12)	1.71	1.30 (8.3)	0.64	56 (24)

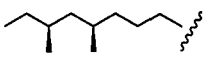
(b) C6 Short-Chain Carbamates 4

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	po mouse ED_{50} (% inhibn (mpk))
4f	CH_3	nd[c]		11
4g	CH_3CH_2	16.0 (0.36)	0.02	11
4h	$X=(CH_3)_2NCO$	nd[c]		>24 (12% at mpk)
4i	$(CH_3)_2CH$	8.0 (0.36)	0.05	6
4j	$X=(CH_3)_2CHNHCS$	14.0 (0.12)	0.01	>6 (9% at 6 mpk)
4k		3.2 (0.29)	0.09	11
4l		17.0 (0.75)	0.04	8
4m		14.0 (0.75)	0.05	6
4n		0.8 (0.36)	0.46	>24 (−5% at 24 mpk)
4o	$PhCH_2$	1.6 (0.22)	0.14	40

[a] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [b] Relative activity. [c] Not done.

Table 3. Inhibitory Activity of C6 Long-Chain and Short-Chain Carbonates 5

(a) C6 Long-Chain Carbonates 5

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	Hep G2 (IC_{50}, μM)[a]	Hep G2 RA[b]	po mouse % inhibn (dose, mpk)
5a		0.26 (0.20)	0.77	nd[c]		−4 (24)
5b	$CH_3(CH_2)_9$	0.04 (0.12)	3.00	2.4 (9.9)	4.12	28 (24)
5c	$CH_3(CH_2)_{11}$	0.19 (0.09)	0.47	1.9 (8.3)	4.36	5 (40)
5d	$PhO(CH_2)_{11}$	0.04 (0.12)	3.00	2.4 (8.3)	3.46	12 (40)

(b) C6 Short-Chain Carbonates 5

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	po mouse ED_{50}, mpk
5e	CH_3	3.5 (0.20)	0.06	9
5f	CH_3CH_2	9.2 (0.19)	0.02	9
5g	$(CH_3)_2CH$	3.0 (0.29)	0.10	10
5h	$X=(CH_3)_2CHSCO$	3.4 (0.19)	0.06	14

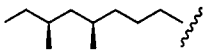
[a] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [b] Relative activity. [c] Not done.

In the direct alkylation of **2a**, the C4 ethers and C4,6 bisethers (**7** and **8** respectively, Chart 3) were also isolated and evaluated in the enzyme assay. Interestingly, the C4 long-chain ethers **7** (e.g., **7c**, **7d**, **7f**, and **7g**) are still nanomolar squalene synthase inhibitors (having 8−17% enzyme inhibitory activity of L-694,599; Table 5). The overlapping of the two long side chains of **7** (e.g., **7c**) with C1/C6 side chains of L-694,599 is readily seen when **7c** is viewed vertically flipped (180°) and compared with the natural product (see Chart 3 for **7c**). However, the C4 short-chain ethers (e.g., C4 methyl, *n*-propyl, *n*-butyl, isobutyl, and *n*-pentyl) are all inactive when tested up to 161 nM (exemplified by **7j** in Table 5). A number of C4,6 bisethers **8** (e.g., **8c** and **8f**) still retain 2% squalene synthase inhibitory activity of L-694,599 (Table 5). In general, the following order of enzyme inhibitory activity of ethers was observed: C6 > C4 > C4,6. These derivatives were only moderately or weakly active in the oral mouse assay (data not shown).

Since we did not have much success in improving the oral activity of zaragozic acid A with the C6 long-chain derivatives, we began to shorten the C6 side chain using the oral mouse assay to guide our SAR studies. The in vitro (RLSS) activities of almost all the C6 short-chain derivatives are about 2−15% of that of L-694,599 (Tables 1b−4b), but most of these compounds appear to have enhanced in vivo potency. This may be due to the findings (data not shown) that the C6 short-chain derivatives exert all of their biological effect over a much shorter time period (showed maximum effect at 15−30 min after dosing) than the C6 long-chain analogues (showed maximum effect at 30−60 min after dosing). For linear short-chain alkyl C6 esters **3** (**3h-k**, Table

Table 4. Inhibitory Activity of C6 Long-Chain and Short-Chain Ethers **6**

(a) C6 Long-Chain Ethers **6**

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	Hep G2 (IC_{50}, μM)[a]	Hep G2 RA[b]	po mouse % inhibn (dose, mpk)
6a		0.20 (0.20)	1.00	nd[c]		38 (24)
6b	$CH_3(CH_2)_9$	0.21 (0.30)	1.43	2.2 (9.0)	4.09	28 (40)
6c	$CH_3(CH_2)_{11}$	0.12 (0.30)	2.50	1.6 (9.0)	5.62	26 (40)
6d	$CH_3(CH_2)_{13}$	0.09 (0.12)	1.26	1.5 (9.0)	6.00	0 (40)
6e	$CH_3(CH_2)_{15}$	0.79 (0.12)	0.15	14.0 (6.8)	0.49	nd[c]
6f	$PhO(CH_2)_8$	0.16 (0.13)	0.81	nd[c]		4 (40)
6g	$PhO(CH_2)_{11}$	0.06 (0.12)	2.00	1.3 (8.3)	6.38	nd[c]

(b) C6 Short-Chain Ethers **6**

compd	R	RLSS (IC_{50}, nM)[a]	RLSS RA[b]	po mouse ED_{50} (% inhibn (mpk))
6h	H	30		>24 (34% at 24 mpk)
6i	CH_3	22.0 (0.09)	0.004	<12 (73% at 12 mpk)
6j	$CH_3CH_2CH_2$	10.0 (0.52)	0.05	8
6k	$CH_3CH_2CH_2CH_2$	2.0 (0.16)	0.08	12
6l	$(CH_3)_2CHCH_2CH_2$	2.3 (0.20)	0.09	9

[a] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [b] Relative activity. [c] Not done.

Table 5. Comparative Inhibitory Activity of C6, C4 Ethers (**6** and **7**) and C4,6 Bisethers (**8**)

compd	R	ether	RLSS (IC_{50}, nM)[a]	RLSS RA[b]
6c	$CH_3(CH_2)_{11}$	C6	0.12 (0.30)	2.50
7c	$CH_3(CH_2)_{11}$	C4	1.20 (0.09)	0.08
8c	$CH_3(CH_2)_{11}$	C4,6	17.0 (0.30)	0.02
6d	$CH_3(CH_2)_{13}$	C6	0.09 (0.12)	1.26
7d	$CH_3(CH_2)_{13}$	C4	0.75 (0.13)	0.17
8d	$CH_3(CH_2)_{13}$	C4,6	na[c] at 161 nM	
6f	$PhO(CH_2)_8$	C6	0.16 (0.13)	0.81
7f	$PhO(CH_2)_8$	C4	0.81 (0.13)	0.16
8f	$PhO(CH_2)_8$	C4,6	8.20 (0.13)	0.02
6g	$PhO(CH_2)_{11}$	C6	0.06 (0.12)	2.00
7g	$PhO(CH_2)_{11}$	C4	1.10 (0.12)	0.11
8g	$PhO(CH_2)_{11}$	C4,6	na[c] at 161 nM	
6j	$CH_3CH_2CH_2$	C6	10.00 (0.52)	0.05
7j	$CH_3CH_2CH_2$	C4	na[c] at 161 nM	
8j	$CH_3CH_2CH_2$	C4,6	na[c] at 161 nM	

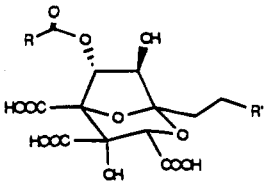
[a] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [b] Relative activity. [c] Not active.

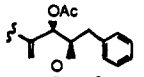
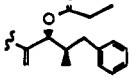
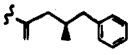
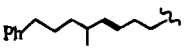
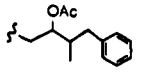
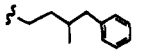
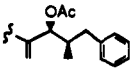
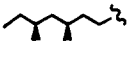
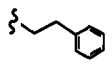
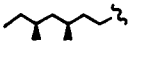
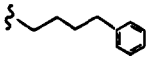
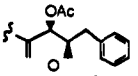
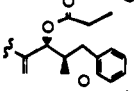
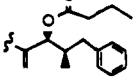
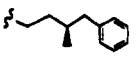
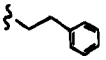
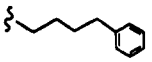
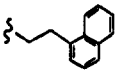
1b), the most active analogue is the *n*-butyryl **3j** (ED_{50} 4.5 mg/kg). Adding an α-methyl group to the propionyl **3i** (ED_{50} 12 mg/kg) improved the inhibitory activity by 1.5-fold (isobutyryl **3l**, ED_{50} 8 mg/kg). However, adding another α-methyl group (to **3l**) substantially reduced the activity (trimethylacetyl **3m** was inactive at 12 mg/kg). The (2*S*)-2-methylbutyryl derivative (**3n**, ED_{50} 24 mg/kg) was about 5-fold less active than **3j**. Moving the methyl group of **3n** to the β position enhanced the activity by 2-fold (isovaleryl **3o**, ED_{50} 11 mg/kg). Unsaturation did not affect the bioactivity (**3p**, ED_{50} 12 mg/kg). The *tert*-butyl group again had deleterious effects (*tert*-butylacetyl **3q**, 25% inhibition at 12 mg/kg). 4-Methoxybutyryl **3r** was moderately active (ED_{50} 20 mg/kg). Replacing the 4-methoxyl group by NH_2 or COOH moiety led to inactive compounds (**3s** and **3t**, inactive at 12 mg/kg). It seems that hydrophilic groups at the C6 position are less well tolerated.

For C6 short-chain carbamates (Table 2b), the in vivo activity of methyl, ethyl, *n*-propyl, and *n*-butyl carbamates are about the same with ED_{50} values of 11−12 mg/kg (data not shown for *n*-propyl and *n*-butyl carbamates). *N*-Methylation of the methyl carbamate **4f** greatly diminished the oral activity (**4h**, 12% inhibition at 24 mg/kg). Adding an α-methyl group to **4g** enhanced the potency by about 2-fold (**4i**, ED_{50} 6 mg/kg). Replacing the oxygen atom in the (isopropylamino)carbonyl group of **4i** by a sulfur atom diminished the oral activity (**4j**, 9% inhibition at 6 mg/kg). Cyclopropyl and cyclopropylmethyl carbamates (**4k** and **4l**) were about 1.5−2-fold less active than **4i** and **4m** (cyclobutyl carbamate, ED_{50} 6 mg/kg). Lipophilic adamantyl carbamate **4n**, as expected, had good in vitro activity, but it was inactive orally at 24 mg/kg. Aralkyl derivatives had moderate in vivo activity (e.g., ED_{50} value of **4o** = 40 mg/kg). For C6 short-chain carbonates (Table 3b), the methyl, ethyl, and isopropyl carbonates (**5e-g**) were equipotent with ED_{50} values of 9−10 mg/kg. Replacing the oxygen atom of isopropyloxy of **5g** by a sulfur atom diminished the activity by about 1.5-fold (**5h**, ED_{50} 14 mg/kg). For C6 short-chain ethers (Table 4b), the *n*-propyl ether **6j** is the most active one in this series (ED_{50} 8 mg/kg).

Comparing the in vitro activity of L-694,599, L-697,-350,[15] and L-735,021[37] (see Table 6 and Chart 4), the 3′-*exo*-double bond and the 4′-OAc group of L-694,599 appear to be not essential; L-694,599 and L-735,021 are equipotent with IC_{50} value of 0.14 nM. Replacing the 4′-OCOMe group of L-694,599 with an OCOEt moiety (**15**) diminished the enzyme inhibitory activity by 30%, yet complete extrusion of the 4′-OAc group enhanced the in vitro potency by 1.6-fold (**18**, Table 6). Removing all the C1 appendages and/or shortening the C1 chain length of **3a** led to compounds of diminished inhibitory activity (e.g., **24a** and **24b**). Since a number of C6 short-chain derivatives such as **3j** (ED_{50} 4.5 mg/kg, Tables 1b and 6), **4i** and **4m** (ED_{50} 6 mg/kg, Table 2b) have enhanced oral activity, we proceeded to modify the C1 alkyl side chain of one of these (e.g., **3j**) hoping to improve the oral activity further. Increasing the 4′-acyl chain length of **3j** diminished the in vivo activity (e.g., **16** and **17**; Table 6). Removing the 3′-*exo*-double bond and the 4′-OAc group of **3j** greatly diminished the enzyme inhibitory activity and completely abolished the oral activity (**22**, Table 6). Removing all the C1 appendages followed by shortening the C1 chain length of **3j** gave the respective 6′-phenylhexyl **26b** (IC_{50} 362 nM) and 4′-phenylbutyl **26a** (IC50 > 3 μM). The 4′-(α-

Table 6. Inhibitory Activity of C1 and C1/C6 Modified Derivatives



compd	R	R'	RLSS		po mouse
			(IC_{50}, nM)[a]	RA[b]	%Inhibn (dose, mpk)
L-649,599			0.10-0.23	1.0	na[c](40)
15			0.42(0.29)	0.69	-4(24)
18			0.24(0.40)	1.67	nd[d]
L-697,350			0.37(0.51)	1.38	20(40)
L-735,021			0.14(0.14)	1.0	8(24)
3a			0.19(0.14)	0.74	nd[d]
24a			137(0.26)	0.002	nd[d]
24b			1.8(0.26)	0.144	-2(24)
3j			9.2(0.65)	0.07	77(24)[e]
16			8.8(0.26)	0.03	67(24)
17			9.7(0.26)	0.027	1(24)
22			110(0.29)	0.0026	-3(12)
26a			>3000(0.29)	0	5(12)
26b			362(0.29)	0.0008	-6(24)
26c			1800(0.26)	0.00014	nd[d]

[a] L-694,599 was used as control. [b] RA = relative activity. [c] Not active. [d] Not done. [e] ED_{50} = 4.5 mg/kg.

naphthyl)butyl **26c** also had greatly diminished enzyme inhibitory activity (IC_{50} 1.8 μM). Compounds **26a-c** were all inactive in the oral mouse assay (Table 6).

In addition to being very potent squalene synthase inhibitors, the zaragozic acids (squalestatins) also had broad spectrum in vitro antifungal activity against both yeast and filamentous fungi.[17,20] Thus during our investigation of zaragozic acid A derivatives as mammalian squalene synthase inhibitors, we routinely tested our C1/C6-modified compounds in the yeast squalene synthase (YESS) and in the whole cell antifungal assays. The C6 long-chain analogues were generally much more potent antifungal agents than the C6 short-chain derivatives (data not shown). A set of four compounds with different linkages at C6 (**3c** ester, **4b** carbamate, **5b** carbonate, and **6c** ether), all having 12 atoms in length from the oxygen at the C6 position and **5d** (ω-phenoxyundecyl carbonate) were selected for in vivo antifungal studies. These compounds had previously been evaluated in the squalene synthase (RLSS/YESS) and the in vitro antifungal assays, and their data are shown in Tables 7 and 8. With the exception of **4b**, these analogues are about 3–9-fold more active than L-694,599 in the YESS assay (Table 7). They are all relatively more inhibitory in the yeast than in the mammalian squalene synthase assay (RLSS, Table 7).

Table 7. Squalene Synthase Inhibitory Activity[a]

compd	X	SQSYN (IC_{50}, nM)[b] RLSS	RA[c]	YESS	RA[c]	YESS/RLSS RA[c]
3c	$CH_3(CH_2)_{10}CO$	0.80 (0.23)	0.29	0.96 (3.00)	3.13	10.79
4b	$CH_3(CH_2)_9NHCO$	1.00 (0.14)	0.14	3.20 (2.88)	0.90	6.43
5b	$CH_3(CH_2)_9OCO$	0.04 (0.12)	3.00	0.64 (2.78)	4.35	1.45
6c	$CH_3(CH_2)_{11}$	0.12 (0.30)	2.50	0.30 (2.78)	9.26	3.71
5d	$PhO(CH_2)_{11}OCO$	0.04 (0.12)	3.00	0.28 (1.70)	6.07	2.02

[a] For C6 derivatives (ester, carbamate, carbonate, and ether) having 12 atoms in length from the oxygen at the C6 position and the phenoxy carbonate **5d**. [b] L-694,599 was used as a control; its IC_{50} values are given in parentheses. [c] Relative activity to the control.

Table 8. In Vitro Antifungal Activity of Zaragozic Acid Derivatives against Fungi[a]

fungas	L-694,599	**3c**	**4b**	**5b**	**6c**	**5d**
C. albicans						
MY 1055	16	4	8	8	4	>128
MY 1750	8	8	4	16	32	0.5
C. tropicalis						
MY 1012	2	8	16	2	64	0.5
C. parapsilosis						
MY 1010	8	8	8	2	8	4
Cry. neoformans						
MY 1051	1	2	4	8	0.5	8
MY 2061	1	0.12	0.5	0.25	0.12	16
A. fumigatus						
MF 4839	32	8	32	2	0.5	0.15
T. mentagrophytes						
MF 4864	4	4	2	<0.06	1	

[a] Minimum fungicidal concentrations (MFC, μg/mL) for C6 derivatives (ester, carbamate, carbonate, and ether) having 12 atoms in length from the oxygen at C6 position and the phenoxy carbonate **5d**.

Their in vitro efficacy against *Candida albicans*, *tropicalis*, and *parapsilosis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Trichophyton mentagrophytes* compares favorably with L-694,599 (Table 8). These compounds were tested ip against mice challenged iv with *Cryptococcus neoformans* MY2061 in a 7 day target organ assay. Only the carbamate **4b** and the ether **6c** (data not shown) showed in vivo efficacy against *Cryptococcus neoformans* in the spleens of challenged mice. The more active **4b** showed significant reductions of *C. neoformans* CFU/g spleens in a dose-dependent manner at 50 and 25 mg/kg (almost 2 $\log_{10}$ reduction in spleens from controls; Figure 1) and 12.5 mg/kg (1 $\log_{10}$ reduction in spleens from controls). Doses at 50 and 25 mg/kg were found to be statistically significant from sham-treated controls ($p < 0.5$). However, **4b** was not active when administered orally. It did not show (given ip or po) any efficacy against *C. neoformans* in the brains of challenged mice.

The present study, detailing the modification of C1 and/or C6 side chains, augments well the modification of the core structure of zaragozic acid A.[24-29] The C6 long-chain esters, carbamates, carbonates, and ethers all have similar biological profiles. They are subnanomolar squalene synthase inhibitors, but only weakly active po. The C4 long-chain ethers **7** are nanomolar squalene synthase inhibitors; they are substantially more potent than the C4,6 bisethers **8**. The C6 short-chain derivatives have much improved oral activity in mice. The most active analogue is the C6 *n*-butyryl ester **3j**, which has an ED_{50} value of 4.5 mg/kg. The isopropyl and cyclobutyl carbamates **4i** and **4m** are also quite potent with an ED_{50} value of 6 mg/kg. Modification of the C1 alkyl side chain of **3j** did not improve the po activity further. A number of the C6 long-chain derivatives are also potent antifungal agents in vitro.

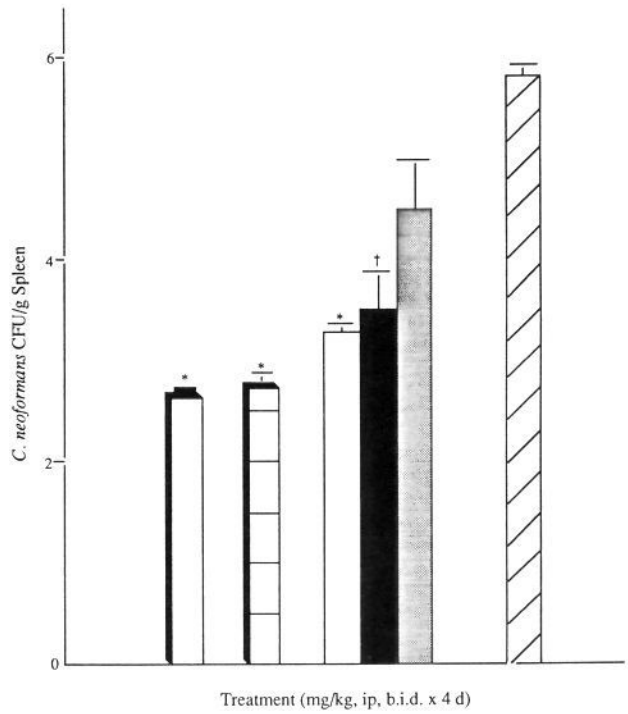


Figure 1. Compound **4b** *vs C. neoformans* in the spleen. Unshaded bar: amphotericin B administered at 6.25 mg/kg po, qd × 4 d. Horizontally hashed bar: Fluconazole given at 100 mg/kg po, qd × 4 d. Unshaded bar, black bar, stippled bar: Compound **4b** was administered ip, b.i.d × 4 d at 50, 25, and 12.5 mg/kg, respectively. Diagonally hashed bar: Vehicle treated controls spleen. *Statistically significant from infected vehicle-treated $p < 0.05$. †Statistically significant by Student's *t* test.

Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter at 27 °C. Thin-layer chromatography (TLC) was performed on silica gel GF254 (Analtech) plates, and the spots were detected by a ceric sulfate (1%)−sulfuric acid (10%) spray. Flash column chromatography was conducted on silica gel 60 (70−230 mesh ASTM). Preparative HPLC was performed on a Waters Prep LC-500A apparatus with Prep-PAK 500 silica gel cartridges. ^1H NMR spectra were recorded for solutions in deuterated chloroform or methanol on a Varian XL200 or 400 pulsed Fourier transformed instrument, with tetramethylsilane as the internal standard. High-resolution FAB and negative FAB mass spectra were recorded on the JEOL HX110A magnetic sector mass spectrometer. Analytical results for compounds followed by elemental symbols were within 0.4% of calculated values. Conventional processing consisted of drying organic solutions with anhydrous sodium sulfate or magnesium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

Rat Liver Squalene Synthase Assays (RLSS). Squalene synthase activity was monitored by the formation of [^{14}C]-

squalene from [4-^{14}C]FPP by a modified method.[15] The FPP concentration, 5 μM, that was used in the assays is approximately 10 times higher than the K_m of the enzyme for FPP. Thus the IC_{50} values of this class of competitive inhibitors[15] should be significantly greater than the actual K_i values of each of the compounds tested. Compounds were dissolved in DMSO and added to the assay mixture to give a final concentration of 0.3% DMSO in the assay. The IC_{50} values were determined from a plot of the percent inhibition vs the log of the inhibitor concentration. Serial dilutions of the inhibitor that differed by a factor of 3 were used. For most compounds, the highest concentration tested was 30 ng/mL (approximately 40 nM). Zaragozic acid A (L-694,599) was titrated and used as a relative standard in all assays. The IC_{50} values determined for zaragozic acid A have varied considerably from assay to assay with a range of 0.09–0.75 nM (0.30 ± 0.18 nM, n = 80). However, the activity of compounds relative to zaragozic acid A was found to be fairly constant when the compounds were tested multiple times; for example, the relative activity of zaragozic acid C (L-697,350) is 1.54 ± 0.28 (n = 4). Thus the activity of compounds relative to that of zaragozic acid A is a more meaningful number for use in comparing the enzyme inhibitory activity of this class of compounds.

Yeast Squalene Synthase Assays (YESS). The yeast squalene synthase assays were performed using microsomes prepared from *Candida albicans* MY 1055 and assayed with a procedure essentially as described for RLSS.[15] Modifications to this assay included the use of the fungal specific squalene epoxidase inhibitor, SF86-327, instead of the Banyu FW-439H and quenching the reaction with one volume of ethanol followed by extraction of the labeled squalene with two volumes of heptane.

Hep G2 Assay. Inhibition of cholesterol synthesis in Hep G2 cells (human transformed cells) was measured as reported previously.[15] Hep G2 cells were maintained in lipoprotein-depleted fetal bovine serum for 2 days to stimulate cholesterol synthesis. The cells were incubated with squalene synthase inhibitors in a serum-free medium for 2 h, and then 15 μCi of [5-^{3}H]mevalonate (0.2 mCi/mmol) was added. After 1 h, the cells were washed and saponified as reported previously,[15] and the radioactivities were measured in a Packard model 2200CA scintillation counter.

In Vivo Mouse Assay. The assay measured the incorporation of [5-^{3}H]mevalonolactone into cholesterol.[15] Female Swiss Webster mice (~25 g) were dosed po (by gavage) with squalene synthase inhibitors suspended in 5% emulphor with six animals per group. After 30 min, the animals were injected sc with [5-^{3}H]mevalonolactone (0.5 μCi/mouse) in saline (50 μL). Thirty minutes later, the animals were sacrificed, and the livers were removed and saponified in a mixture of 40% KOH (4 mL) and 95% EtOH (2 mL) overnight at 55 °C. The saponified livers were extracted with petroleum ether, and the total dpm in the nonsaponifiable fractions were determined. Compounds were first tested at one dose (typically 12 or 24 mg/kg) above the targeted potency level. If the compound was found to be significantly active (inhibition greater than 50%), the compound was then titrated to determine the ED_{50} values. The titrations were done with dosage groups (six mice per group) with serial dilutions that differed by a factor of 2 (typically 24, 12, 6, and 2 mg/kg). ED_{50} values were determined from a plot of percent inhibition vs the log dose. Analysis of the data from the titrations to determine the ED_{50} values and 95% confidence intervals were done on log–log plots using a least median of squares regression[40] and inverse prediction methodology.[41] The typical 95% confidence interval ranged from a value of 20–40% below the estimated ED_{50} values to a value of 30–50% above the estimated values.

In Vitro Antifungal Assay. Compounds were evaluated for antifungal spectrum and potency against a selected panel of clinically relevant and animal virulent fungi utilizing broth microdilution methodology for determination of minimum fungicidal concentration (MFC) in μg/mL as described previously.[42]

In Vivo Target Organ Assay. Female mice (DBA/2, 17–20 g) were challenged iv with 2 × 10^5 CFU (0.2 mL) of *Cryptococcus neoformans* MY2061/mouse. Squalene synthase inhibitors were administered ip, b.i.d × 4 d. Amphotericin B and fluconazole were administered po, qd × 4 d. Squalene synthase inhibitors were formulated in 5% EtOH/0.5 M phosphate buffer. Amphotericin B and fluconazole were formulated in desoxycholate and distilled water, respectively. Desoxycholate (10.5 mg/kg), distilled water, 5% EtOH/0.5 M phosphate buffer, and 5% DMSO/0.5 M phosphate buffer were administered to groups of infected mice ip, po, or ip b.i.d or po, qd × 4 d, as controls. At day 7 after challenge, brains and spleens from five mice/group were aseptically removed, homogenized and plated for enumeration of *C. neoformans* CFU/g. The limit of detection was approximately 50 CFU/organ sample. The Student's t-test was used to determine the significance from vehicle-treated controls.

[1*S*-[1α(4*R,5*S**),3α,4β,5α,6α(2*E*,4*R**,6*R**),7β]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) 3,4,5-Tris(1,1-dimethylethyl) Ester.** A solution of L-694,599 (40 g, 0.058 mol; 61% pure) and *O-tert*-butyl-*N,N'*-diisopropylisourea (116 g, 0.58 mol) in toluene (1.5 L) was heated at 65 °C for 16 h, cooled, and concentrated to dryness. The residue was chromatographed on a flash column of silica gel (hexanes–ethyl acetate, 2:1, v/v) to give the title compound (26 g, 86%): NMR ($CDCl_3$) δ 0.81–0.87 (m, 3 CH_3), 1.04 (d, J = 6.7 Hz, C=CCHC**H**$_3$), 1.45, 1.49 and 1.60 (3 s, 3 t-Bu), 2.10 (s, OAc), 2.88 (d, J = 3.2 Hz, C_6 OH), 4.02 (d, H-7), 4.09 (s, C_4 OH), 4.96 and 4.97 (2 s, =CH_2), 5.06 (s, H-3), 5.12 (d, J = 4.8 Hz, C**H**OAc), 5.82 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.01 (d, J = 2.0 Hz, H-6), 6.91 (m, H_β olefinic), 7.14–7.28 (m, ArH); MS (FAB) m/z 865 $(M + Li)^+$.

7-(1-Methoxy-1-methylethyl) Ether (1). Pyridinium p-toluenesulfonate (0.196 g, 0.78 mmol) was added to a stirred solution of the above diol (13.34 g, 15.55 mmol) and 2-methoxypropene (15 mL, 156 mmol) in CH_2Cl_2 (120 mL) at 0–5 °C. After 2 h at room temperature, the solution was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, and dried. The solid was filtered off, and the filtrate was concentrated to dryness. The residue was purified by flash column chromatography (hexanes–ethyl acetate, 4:1, v/v containing 0.1% Et_3N) to give **1** (14.5 g, quantitative yield): NMR ($CDCl_3$) δ 0.80–0.85 (m, 3 CH_3), 1.01 (d, J = 6.6 Hz, C=CCHC**H**$_3$), 1.29 and 1.37 [2 s, $(CH_3)_2C$], 1.40, 1.46, and 1.69 (3 s, 3 t-Bu), 2.10 (s, OAc), 3.22 (s, OCH_3), 4.07 (s, C_4 OH), 4.23 (d, J = 1.4 Hz, H-7), 4.96 and 4.97 (2 s, =CH_2), 5.06 (s, H-3), 5.15 (d, J = 5.1 Hz, C**H**OAc), 5.80 (d, H_α olefinic), 6.44 (d, J = 1.4 Hz, H-6), 6.91 (m, H_β olefinic), 7.16–7.29 (m, ArH); $[\alpha]_D$ −13.5 (c 2.0, $CHCl_3$). Anal. ($C_{51}H_{78}O_{15}$·0.5H_2O) C, H.

Des-C6-*O*-acylated Derivative 2a. Method A. A mixture of **1** (9.31 g, 10 mmol), hydroxylamine hydrochloride (6.95 g, 100 mmol), and sodium acetate trihydrate (30 g, 220 mmol) in methanol (100 mL) was stirred at room temperature for 20 h and filtered, and the filtrate was concentrated to dryness. The residue was partitioned between ethyl ether and brine. The aqueous layer was back-extracted with ethyl ether, and the combined organic extracts were dried and concentrated in vacuo. The residue was purified by flash column chromatography with hexanes–EtOAc (2:1, v/v containing 0.1% Et_3N) as the eluant. Compound **2a** was isolated in 90% yield (7.01 g): NMR ($CDCl_3$) δ 0.81 (d, J = 6.6 Hz, CH_3), 1.39 and 1.47 [2 s, $(CH_3)_2C$], 1.46, 1.50, and 1.60 (3 s, 3 t-Bu), 2.09 (s, OAc), 3.27 (s, OCH_3), 3.93 (s, C_4 OH), 4.07 (d, J = 1.9 Hz, H-7), 4.86 (s, H-3), 4.96–4.97 (br d, H-6 and =CH_2), 5.12 (d, J = 5.1 Hz, C**H**OAc), 7.14–7.28 (m, ArH); MS (FAB) m/z 785 $(M + Li)^+$; $[\alpha]_D$ −1.4 (c 2.0, $CHCl_3$). Anal. ($C_{41}H_{62}O_{14}$·0.5H_2O) C, H.

Method B. Hydrogen peroxide (30%) was added dropwise to a stirred solution of **1** (10 g, 10.8 mmol) in THF (153 mL). Lithium hydroxide monohydrate (4.5 g, 107 mmol) was then added, and the biphasic mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the product was extracted with ethyl ether. The organic layer was washed with brine, dried, and filtered, and the filtrate was concentrated in vacuo. The residue was purified by PrepPak 500/silica on a Waters Associates Prep LC/System 500 at 250 mL/min using hexanes-

EtOAc (2:1, v/v) as a liquid phase. Compound **2a** was isolated in 58% yield (4.85 g) and had identical physical properties to that prepared by Method A.

General Procedure for Preparation of C6 Esters (Protected 3). Method A. A mixture of **2a** (100 mg, 0.128 mmol), an appropriate carboxylic acid (0.256 mmol), dicyclohexylcarbodiimide (DCC; 53 mg, 0.257 mmol), and 4-(*N,N*-dimethylamino)pyridine (DMAP; 6 mg, 0.05 mmol) in dichloromethane (1 mL) was stirred at room temperature overnight. If the reaction was incomplete (monitored by TLC), additional reagents were added, and the reaction was allowed to proceed to completion. The mixture was diluted with hexanes and filtered, and the filtrate was evaporated to dryness. The residue was purified by preparative TLC (hexanes–ethyl acetate, 4:1, v/v containing 0.1% Et_3N). The yields were 76–95%.

Method B. The appropriate acid anhydride or acid chloride (0.256 mmol) was added to a solution of **2a** (100 mg, 0.128 mmol), triethylamine (71 μL, 0.52 mmol), and DMAP (2 mg, 0.016 mmol) in dry dichloromethane (1 mL). The reaction mixture was stirred at room temperature overnight and diluted with dichloromethane. The solution was washed with 1 N HCl, 5% aqueous $NaHCO_3$, and brine, dried, and evaporated to dryness. The product was purified by preparative TLC. The yields were 63–95%.

General Procedure for Preparation of C6 Carbamates (Protected 4). Method A. A solution of **2a** (100 mg, 0.128 mmol) and 1,1′-carbonyldiimidazole (42 mg, 0.256 mmol) in dry toluene (0.5 mL) was stirred at room temperature for 6 h. An appropriate amine (1.28 mmol) was added, the reaction mixture was stirred at room temperature for 3 h, diluted with hexanes, and filtered, and the filtrate was evaporated to dryness. The residue was purified by preparative TLC (hexanes–ethyl acetate, 4:1 or 3:1, v/v containing 0.1% Et_3N). The yields were 66–90%.

Method B. An appropriate isocyanate (0.192 mmol) was added to a solution of **2a** (100 mg, 0.128 mmol) in pyridine or toluene (1 mL) containing triethylamine (90 μL), and the mixture was heated at 90 °C for 2 h. If the reaction was incomplete (monitored by TLC), additional isocyanate was added, and the reaction was allowed to proceed to completion. The mixture was cooled, and the solid was filtered off and washed with dichloromethane. The combined filtrates were evaporated to a residue, which was purified by preparative TLC. The yields were 66–95%.

General Procedure for Preparation of C6 Carbonates (Protected 5). A solution of **2a** (100 mg, 0.128 mmol) and 1,1′-carbonyldiimidazole (42 mg, 0.256 mmol) in dry toluene (0.5 mL) was stirred at room temperature for 6 h. An appropriate alcohol (0.64 mmol) and DBU (96 μL, 0.64 mmol) were added, and the mixture was stirred at room temperature overnight. The product was purified by preparative TLC (hexanes–ethyl acetate, 7:3, v/v containing 0.1% Et_3N). The yields were 66–95%.

General Procedure for Preparation of C6 Ethers (Protected 6). Sodium hydride (19.3 mg, 0.48 mmol; 60% dispersion in mineral oil) was added to a solution of **2a** (300 mg, 0.384 mmol) in dry DMF (1.5 mL) containing an appropriate organic iodide (0.48 mmol) or an appropriate organic bromide (0.48 mmol) plus tetra-*n*-butylammonium iodide (15 mg, 0.038 mmol). The reaction mixture was stirred at room temperature for 7–16 h and partitioned between ethyl ether and water. The aqueous layer was back-extracted twice with ethyl ether, and the combined organic extracts were washed with brine, dried, and evaporated to dryness. The three products and the starting material were separated by preparative TLC (hexanes–ethyl acetate, 4:1; v/v containing 0.1% Et_3N). The C6 ethers (**6**, 18–40%), C4 ethers (**7**, 18–40%), and C4,6 bisethers (**8**, 10–20%) were isolated in yields as indicated, based on the recovered starting material.

General Procedure for Deprotection (3-8). A solution of the protected **3-8** (100 mg) in dry dichloromethane (3 mL) was treated with trifluoroacetic acid (TFA, 1 mL) at room temperature overnight. The solvent was evaporated to dryness, and traces of TFA was codistilled with toluene. The product was purified by reverse-phase HPLC and freeze-dried from benzene to give a white fluffy material (85–100% yields).

Selective Preparation of C6 Ethers (e.g., 6i). Intermediate 2b. Sodium hydride (240 mg, 5.97 mmol; 60% dispersion in mineral oil) was added to a stirred solution of 1 (3.73 g, 4.0 mmol), tetra-*n*-butylammonium iodide (0.15 g, 4.0 mmol), and 4-phenylbenyzyl chloride (1.62 g, 8.0 mmol) in dry DMF (15 mL) at 0 °C. After 30 min, the reaction mixture was stirred at room temperature for 7 h and quenched with ice–water, and the product was extracted with ethyl ether (3×). The organic layer was washed with brine, dried, and evaporated to a residue, which was purified by flash column chromatography (hexanes–ethyl acetate, 80:20, v/v containing 0.1% Et_3N) to give the 4-*O*-(4-phenylbenzyl) ether of 1 (2.55 g, 58%): NMR ($CDCl_3$) δ 0.78–0.82 (m, 3 CH_3), 0.96 (d, J = 6.7 Hz, C=CCHC**H**$_3$), 1.26, 1.35, and 1.63 (3 s, 3 *t*-Bu), 2.07 (s, OAc), 3.20 (s, OCH_3), 4.19 (br s, H-7), 4.98 (m , 3 H), 5.12 (m, 1 H), 5.30 (m, 2 H), 5.76 (d, J = 15.8 Hz, H_α olefinic), 6.56 (d, J = 1.0 Hz, H-6), 6.89 (m, H_β olefinic), 7.07–7.51 (m, ArH). The following signals were assigned to the C6 (6*S*)-4,6-dimethyl-3-octenoyl isomer (15%): δ 4.16 (br s, H-6), 6.53 (br s, H-7). Treatment of this material with hydroxylamine hydrochloride and sodium acetate trihydrate in methanol at room temperature overnight afforded **2b** in 72% yield: NMR ($CDCl_3$) δ 0.79 (d, J = 6.7 Hz, CHC**H**$_3$), 1.28, 1.43, and 1.54 (3 s, 3 *t*-Bu), 2.05 (s, OAc), 2.40 (d, J = 2.3 Hz, C_6 OH), 3.26 (s, OCH_3), 4.01 (d, J = 2.3 Hz, H-7), 4.87 and 5.08 (2 d, J = 10.6 Hz, OC**H**$_2$Ar), 4.93 and 4.94 (2 s, =CH_2), 4.9 (s, H-3), 5.10 (d, J = 5.5 Hz, C**H**OAc), 5.17 (2 d, J = 2.3 and 5.0 Hz, H-6), 7.06–7.51 (m, ArH).

C6 Methyl Ether 6i. Sodium hydride (16 mg, 0.40 mmol; 60% dispersion in mineral oil) was added to a stirred solution of **2b** (255 mg, 0.27 mmol) and methyl iodide (35 μL, 0.54 mmol) in DMF (1 mL) at 0 °C. After 1 h, the mixture was partitioned between ethyl ether and water. The organic layer was washed with brine, dried, and evaporated to a residue, which was purified by preparative TLC to give the 6-*O*-methyl ether of **2b** (246 mg, 95%): NMR ($CDCl_3$) δ 0.77 (d, J = 6.7 Hz, CHC**H**$_3$), 1.28, 1.45, and 1.58 (3 s, 3 *t*-Bu), 1.37 and 1.40 [2 s, $(CH_3)_2$C], 2.04 (s, OAc), 3.25 and 3.44 (2 s, 2 OCH_3), 4.11 (d, J = 2.3 Hz, H-7), 4.86 (m, 6 H), 5.09 (d, J = 5.4 Hz, C**H**OAc), 7.03–7.49 (m, ArH). A solution of this material (245 mg, 0.26 mmol) in dichloromethane (7.5 mL) was treated with TFA (2.5 mL) at room temperature overnight. The mixture was evaporated, and traces of TFA was codistilled with toluene. 4-Phenylbenzyl trifluroacetate was repeatedly extracted with hexanes. The hexanes–insoluble material was purified by reverse-phase HPLC to give **6i** (107 mg, 76%): NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 2.11 (s, OAc), 3.45 (s, OCH_3), 4.05 (d, J = 2.0 Hz, H-7), 4.76 (d, J = 2.0 Hz, H-6), 4.97 and 5.01 (2 s, =CH_2), 5.08 (d, J = 4.0 Hz, C**H**OAc), 5.10 (s, H-3), 7.10–7.28 (m, ArH); MS (neg FAB) m/z 551 $(M - H)^-$. Anal. ($C_{26}H_{32}O_{13}$·1.3H_2O) C, H.

C6 Side Chain Derivatives of L-694,599. (4*S*,6*S*)-4,6-Dimethyloctanoic Acid. A solution of [4*S*(2E,4*R**,6*R**)]-4,6-dimethyl-2-octenoic acid[21] (1.24 g, 7.3 mmol) in ethyl acetate (5 mL) was hydrogenated over 10% Pd/C (0.124 g) at room temperature for 3 h. The catalyst was filtered off and washed with ethyl acetate. The combined filtrates were evaporated to give the title compound in near quantitative yield (1.24 g): NMR (CD_3OD) δ 0.85–0.88 (m, 3 CH_3), 2.28 (m, C**H**$_2$COOH).

(4*S*,6*S*)-4,6-Dimethyloctanol. A solution of lithium aluminum hydride in THF (8 mL, 8 mmol; 1 M solution) was added dropwise to a stirred solution of (4*S*,6*S*)-4,6-dimethyloctanoic acid (1.1 g, 6.4 mmol) in THF (10 mL) at 0–5 °C. After 2.5 h, excess lithium aluminum hydride was quenched with ethyl acetate. Aqueous hydrochloric acid was added, and the product was extracted with hexanes (3×). The organic layer was washed with brine, dried, and evaportated to a residue, which was purified by flash column chromatography (hexanes–ethyl acetate, 95:5, v/v) to give the title compound (0.92 g, 91%) as a colorless oil: NMR ($CDCl_3$) δ 0.78–0.82 (m, 3 CH_3), 3.59 (m, C**H**$_2$OH).

(4*S*,6*S*)-4,6-dimethyloctylamine. A solution of (4*S*,6*S*)-4,6-dimethyloctanol (724 mg, 4.68 mmol) in pyridine (3 mL) was reacted with *p*-toluenesulfonyl chloride (1.07 g, 5.61 mmol)

at 0 °C for 4 h to give (4*S*,6*S*)-4,6-dimethyloctyl *p*-toluenesulfonate (1.36 g, 93%): NMR ($CDCl_3$) δ 0.74–0.80 (m, 3 CH_3), 2.40 (s, CH_3Ar), 3.95 (t, J = 6.6 Hz, CH_2O), 7.30 and 7.74 (2 d, J = 7.7 and 8.3 Hz, ArH). Nucleophilic displacement of the tosylate (0.52 g, 1.66 mmol) with sodium azide (2.16 g, 33.23 mmol) in DMF (5 mL) at 80 °C for 4 h gave (4*S*,6*S*)-4,6-dimethyloctyl azide (0.30 g, 98%): NMR ($CDCl_3$) δ 0.79–0.83 (m, 3 CH_3), 3.22 (m, CH_2N_3). Hydrogenation of the azide (175 mg, 0.96 mmol) in methanol (2 mL) over 10% Pd/C (35 mg) at room temperature for 2 h afforded the title compound (135 mg, 83%): NMR (CD_3OD) δ 0.84–0.89 (m, 3 CH_3), 2.67 (m, CH_2NH_2).

(4*S*,6*S*)-4,6-Dimethyloctyl Iodide. A mixture of (4*S*,6*S*)-4,6-dimethyloctyl *p*-toluenesulfonate (1.04 g, 3.31 mmol) and sodium iodide (2.48 g, 16.54 mmol) in methyl ethyl ketone (10 mL) was heated under reflux for 1 h. The solid was filtered off and washed with CH_2Cl_2. The combined filtrates were evaporated to a residue, which was partitioned between hexanes and water. The organic layer was washed with brine, dried, and evaporated to give the title compound (0.86 g, 97%): NMR ($CDCl_3$) δ 0.79–0.83 (m, 3 CH_3), 3.13 (m, CH_2I).

C6 Esters 3. C6 (4*S*,6*S*)-4,6-dimethyloctanoyl ester 3a: NMR (CD_3OD) δ 0.84–0.88 (m, 4 CH_3), 2.10 (s, OAc), 4.02 (d, J = 1.8 Hz, H-7), 4.97 and 5.02 (2 s, $=CH_2$), 5.07 (d, J = 5.0 Hz, CHOAc), 5.25 (s, H-3), 6.26 (d, J = 1.8 Hz, H-6), 7.14–7.27 (m, ArH). The deketalized precursor had NMR ($CDCl_3$) δ 0.81–0.88 (m, 4 CH_3), 1.45, 1.50, and 1.59 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 2.88 (d, J = 3.1 Hz, C_7 OH), 3.97 (2 d, J = 2.0 and 3.1 Hz, H-7), 4.09 (s, C_4 OH), 4.97 and 4.98 (2 s, $=CH_2$), 5.01 (s, H-3), 5.11 (d, J = 5.1 Hz, CHOAc), 5.92 (d, J = 2.0 Hz, H-6), 7.13–7.28 (m, ArH).

C6 octanoyl ester 3b: NMR (CD_3OD) δ 0.88–0.95 (m, 2 CH_3), 1.26–1.41 (m, 8 H), 1.58–1.70 (m, 2 H), 2.14 (s, OAc), 2.06–2.50 (m, 8 H), 2.70–2.76 (m, 1 H), 4.06 (d, J = 1.8 Hz, H-7), 5.02 and 5.06 (2 br s, $=CH_2$), 5.12 (d, J = 4.8 Hz, CHOAc), 5.30 (s, H-3), 6.32 (d, J = 1.8 Hz, H-6), 7.19–7.33 (m, ArH); MS (FAB) m/z 683 $(M + 3Li + H)^+$. The deketalized precursor had NMR ($CDCl_3$) δ 0.79 (d, J = 6.7 Hz, $CHCH_3$), 0.85 (t, CH_2CH_3), 1.20–1.37 (m, 8 H), 1.42, 1.47, and 1.56 (3 s, 3 *t*-Bu), 1.50–1.62 (m, 2 H), 2.08 (s, OAc), 2.04–2.50 (m, 9 H), 2.64–2.72 (m, 1 H), 3.94 (d, J = 1.8 Hz, H-7), 4.07 (br s, C_4 OH), 4.94 (br s, $=CH_2$), 4.98 (s, H-3), 5.08 (d, J = 4.5 Hz, CHOAc), 5.89 (d, J = 1.8 Hz, H-6), 7.10–7.25 (m, ArH).

C6 dodecanoyl ester 3c: NMR (CD_3OD) δ 0.88 (d, J = 7.0 Hz, $CHCH_3$), 0.95 (t, J = 7.0 Hz, CH_2CH_3), 1.30 [m, $(CH_2)_9$], 2.14 (s, OAc), 2.06–2.50 (m, 8 H), 2.70–2.76 (m, 1 H), 4.06 (d, J = 1.8 Hz, H-7), 5.02 and 5.06 (2 br s, $=CH_2$), 5.12 (d, J = 4.8 Hz, CHOAc), 5.30 (s, H-3), 6.32 (d, J = 1.8 Hz, H-6), 7.19–7.33 (m, ArH); MS (FAB) m/z 743 $(M + Na)^+$. Anal. ($C_{37}H_{52}O_{14}$·0.5H_2O) C, H.

C6 tetradecanoyl ester 3d: NMR (CD_3OD) δ 0.86 (m, 2 CH_3), 1.26 [br s, $(CH_2)_n$], 2.08 (s, OAc), 4.00 (br s, H-7), 4.96 and 5.01 (2 s, $=CH_2$), 5.07 (d, J = 5.0 Hz, CHOAc), 5.24 (s, H-3), 6.28 (br s, H-6), 7.06–7.30 (m, ArH); MS (FAB) m/z 771 $(M + Na)^+$, 793 $(M + 2Na - H)^+$, 816 $(M + 3Na - H)^+$; HRMS (neg FAB) calcd for ($C_{39}H_{56}O_{14}$ − H) 747.3591, found 747.3608. The protected precursor had NMR ($CDCl_3$) δ 0.80–0.96 (m, 2 CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.44, 1.46, and 1.68 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 3.22 (s, OCH_3), 4.10 (s, C_4 OH), 4.17 (d, J = 1.8 Hz, H-7), 5.00 (br s, $=CH_2$), 5.04 (*s*, H-3), 5.16 (d, J = 4.0, CHOAc), 6.38 (d, J = 1.8 Hz, H-6), 7.14–7.38 (m, ArH).

C6 hexadecanoyl ester 3e: NMR (CD_3OD) δ 0.85 (d, J = 6.5 Hz, $CHCH_3$), 0.89 (t, J = 7.0 Hz, CH_2CH_3), 1.27 [br s, $(CH_2)_n$], 2.11 (s, OAc), 4.02 (br s, H-7), 4.98 and 5.02 (2 s, $=CH_2$), 5.07 (d, J = 5.5 Hz, CHOAc), 5.26 (s, H-3), 6.27 (br s, H-6), 7.08–7.29 (m, ArH); MS (FAB) m/z 799 $(M + Na)^+$, 821 $(M + 2Na)^+$, 843 $(M + 3Na)^+$. Anal. ($C_{41}H_{60}O_{14}$·1.14H_2O) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, $CHCH_3$), 0.87 (t, J = 7.0 Hz, CH_2CH_3), 1.24 [br s, $(CH_2)_n$], 1.30 and 1.36 [2 s, $(CH_3)_2C$], 1.44, 1.45, and 1.66 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 3.23 (s, OCH_3), 4.07 (s, C_4 OH), 4.16 (br s, H-7), 4.97 (br s, $=CH_2$), 5.01 (s, H-3), 5.14 (d, J = 7.0 Hz, CHOAc), 6.36 (br s, H-6), 7.11–7.32 (m, ArH).

C6 11-phenoxyundecanoyl ester 3f: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 2.10 (s, OAc), 3.94 (t, J = 6.2 Hz, $PhOCH_2$), 4.02 (d, J = 1.5 Hz, H-7), 4.87 and 5.02 (2 s, $=CH_2$), 5.07 (d, J = 6.5 Hz, CHOAc), 5.27 (s, H-3), 6.28 (d, J = 1.5 Hz, H-6), 6.79–6.93 and 7.03–7.30 (2 m, ArH); MS (FAB) m/z 821 $(M + Na)^+$. Anal. ($C_{42}H_{54}O_{15}$·H_2O) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, $CHCH_3$), 1.29 [br s, $(CH_2)_n$], 1.44, 1.45 and 1.66 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 3.22 (s, OCH_3), 3.94 (t, J = 7.0 Hz, $PhOCH_2$), 4.07 (s, C_4 OH), 4.15 (d, J = 2.5 Hz, H-7), 4.96 (br s, $=CH_2$), 5.01 (s, H-3), 5.13 (d, J = 7.5 Hz, CHOAc), 6.36 (d, J = 2.5 Hz, H-6), 6.84–6.94 and 7.10–7.34 (2 m, ArH).

C6 11-phenylundecanoyl ester 3g: NMR (CD_3OD) δ 0.92 (d, J = 6.5 Hz, $CHCH_3$), 1.30 [br s, $(CH_2)_n$], 1.62 (m, 8 H), 2.14 (s, OAc), 2.07–2.77 (m, 13 H), 4.07 (d, J = 1.5, H-7), 5.00 and 5.06 (2 br s, $=CH_2$), 5.10 (d, J = 4.8 Hz, CHOAc), 5.32 (s, H-3), 6.33 (d, J = 1.5 Hz, H-6), 7.14–7.35 (m, ArH); MS (FAB) m/z 804 $(M + Na)^+$; HRMS (neg FAB) calcd for ($C_{42}H_{54}O_{14}$ − H) 781.3435, found 781.3410. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, $CHCH_3$), 1.11–1.20 [m, $(CH_2)_n$], 1.21 and 1.32 [2 s, $(CH_3)_2C$], 1.43, 1.45, and 1.65 (3 s, 3 *t*-Bu), 1.99 (s, OAc), 3.20 (s, OCH_3), 4.07 (s, C_4 OH), 4.14 (br s, H-7), 4.95 (br s, $=CH_2$), 5.00 (s, H-3), 5.12 (d, J = 6.0 Hz, CHOAc), 6.35 (br s, H-6), 7.08–7.30 (m, ArH).

C6 acetyl ester 3h: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 2.06 and 2.12 (2 s, 2 OAc), 4.06 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.26 (s, H-3), 6.28 (d, J = 2.0 Hz, H-6), 7.05–7.34 (m, ArH); MS (FAB) m/z 603 $(M + Na)^+$; HRMS (neg FAB) calcd for ($C_{27}H_{32}O_{14}$ − H) 579.1714, found 579.1729.

C6 propionyl ester 3i: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 1.12 (t, J = 7.0 Hz, CH_2CH_3), 2.11(s, OAc), 4.04 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.26 (s, H-3), 6.30 (d, J = 2.0 Hz, H-6), 7.05–7.36 (m, ArH); MS (neg FAB) m/z 593 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{28}H_{34}O_{14}$ − H) 593.1870, found 593.1881. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 7.0 Hz, $CHCH_3$), 1.15 (t, J = 7.0 Hz, CH_2CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.45, 1.47, and 1.67 (3 s , 3 *t*-Bu), 2.10 (s, OAc), 3.23 (s, OCH_3), 4.08 (s, C_4 OH), 4.18 (d, J = 2.0 Hz, H-7), 4.97 (br s, $=CH_2$) 5.02 (s, H-3), 5.14 (d, J = 5.0 Hz, CHOAc), 6.38 (d, J = 2.0 Hz, H-6), 7.10–7.32 (m, ArH).

C6 butyryl ester 3j: NMR (CD_3OD) δ 0.87 (d, J = 7.0 Hz, $CHCH_3$), 0.96 (t, J = 7.0 Hz, CH_2CH_3), 1.64 (m, $CH_2CH_2CH_3$), 2.12 (s, OAc), 4.04 (d, J = 2.0 Hz, H-7), 4.99 and 5.03 (2 s, $=CH_2$), 5.08 (d, J = 5.0 Hz, CHOAc), 5.26 (s, H-3), 6.30 (d, J = 2.0 Hz, H-6), 7.06–7.38 (m, ArH); MS (neg FAB) m/z 607 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{29}H_{36}O_{14}$ − H) 607.2026, found 607.2043. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 7.0 Hz, $CHCH_3$), 0.95 (t, J = 7.0 Hz, CH_2CH_3), 1.30 and 1.37 [2 s, $(CH_3)_2C$], 1.45, 1.47, and 1.68 (3 s , 3 *t*-Bu), 2.10 (s, OAc), 3.22 (s, OCH_3), 4.08 (s, C_4 OH), 4.16 (d, J = 2.0 Hz, H-7), 4.96 (br s, $=CH_2$), 5.01 (s, H-3), 5.14 (d, J = 5.0 Hz, CHOAc), 6.37 (d, J = 2.0 Hz, H-6), 7.09–7.31 (m, ArH).

C6 valeryl ester 3k: NMR (CD_3OD) δ 0.84 (d, J = 7.0 Hz, $CHCH_3$), 0.92 (t, J = 7.0 Hz, CH_2CH_3), 2.02–2.75 (m, 9 H), 2.10 (s, OAc), 4.04 (d, J = 2.0 Hz, H-7), 5.01 (2 s, $=CH_2$), 5.10 (d, J = 5.0 Hz, CHOAc), 5.27 (s, H-3), 6.20 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 621 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{30}H_{38}O_{14}$ − H) 621.2183, found 621.2173. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 7.0 Hz, $CHCH_3$), 0.89 (t, J = 7.0 Hz, CH_2CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.42, 1.43, and 1.66 (3 s , 3 *t*-Bu), 2.02–2.75 (m, 9 H), 2.08 (s, OAc), 4.07 (s, C_4 OH), 4.16 (d, J = 2.0 Hz, H-7), 4.96 (br s, $=CH_2$), 5.05 (s, H-3), 5.12 (d, J = 5.0 Hz, CHOAc), 6.37 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH).

C6 isobutyryl ester 3l: NMR (CD_3OD) δ 0.87 (d, J = 7.0 Hz, $CHCH_3$), 1.17 [d, J = 7.0 Hz, $CH(CH_3)_2$], 2.12 (s, OAc), 4.02 (d, J = 2.0 Hz, H-7), 4.99 and 5.04 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.27 (s, H-3), 6.29 (d, J = 2.0 Hz, H-6), 7.06–7.38 (m, ArH); MS (neg FAB) m/z 607 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{29}H_{36}O_{14}$ − H) 607.2026, found 607.2054. The protected precursor had NMR ($CDCl_3$) δ 0.82 (d, J = 7.0 Hz, $CHCH_3$), 1.15 and 1.22 [2 d, J = 7.0 Hz, $CH(CH_3)_2$], 1.29 and 1.37 [2 s, $(CH_3)_2C$], 1.45, 1.47, and 1.68 (3 s , 3 *t*-Bu), 2.10 (s, OAc), 3.22 (s, OCH_3), 4.09 (s, C_4 OH), 4.17 (d, J = 2 0 Hz, H-7), 4.98 (br s, $=CH_2$), 5.02 (s, H-3), 5.15 (d, J = 5.0 Hz, CHOAc), 6.37 (d, J = 2.0 Hz, H-6), 7.12–7.34 (m, ArH).

C6 trimethylacetyl ester 3m: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 1.19 [s, C(C**H**$_3$)$_3$], 2.10 (s, OAc), 3.98 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, =C**H**$_2$), 5.08 (d, J = 5.0 Hz, C**H**OAc), 5.27 (s, H-3), 6.25 (d, J = 2.0 Hz, H-6), 7.05–7.33 (m, ArH); MS (FAB) m/z 645 $(M + Na)^+$. Anal. ($C_{30}H_{38}O_{14}\cdot 2H_2O$) C, H.

C6 (2*S*)-2-methylbutyryl ester 3n: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 0.91 (t, J = 7.0 Hz, CH$_2$C**H**$_3$), 1.13 (d, J = 7.0 Hz, COCHC**H**$_3$), 2.10 (s, OAc), 4.0 (d, J = 2.0 Hz, H-7), 4.98 and 5.02 (2 s, =C**H**$_2$), 5.08 (d, J = 5.0 Hz, C**H**OAc), 5.26 (s, H-3), 6.28 (d, J = 2.0 Hz, H-6), 7.01–7.38 (m, ArH); MS (neg FAB) m/z 621 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{30}H_{38}O_{14}$ – H) 621.2183, found 621.2207. The protected precursor had NMR ($CDCl_3$) δ 0.82 (d, J = 7.0 Hz, CHC**H**$_3$), O.95 (t, J = 7.0 Hz, CH$_2$C**H**$_3$), 1.13 (d, J = 7.0 Hz, COCHC**H**$_3$), 1.32 and 1.38 [2 s, (CH$_3$)$_2$C], 1.48 and 1.68 (2 s, 2 *t*-Bu), 2.11 (s, OAc), 3.23 (s, OCH$_3$), 4.09 (s, C$_4$ OH), 4.17 (d, J = 2.0 Hz, H-7), 4.99 (br s, =C**H**$_2$), 5.04 (s, H-3), 5.15 (d, J = 5.0 Hz, C**H**OAc), 6.37 (d, J = 2.0 Hz, H-6), 7.12–7.34 (m, ArH).

C6 isovaleryl ester 3o: NMR (CD_3OD) δ 0.84 (d, CHC**H**$_3$), 1.10 [m, (C**H**$_3$)$_2$CH], 2.10 (s, OAc), 2.02–2.75 (m, 9 H), 3.70 [m, (CH$_3$)$_2$C**H**], 4.06 (d, J = 2.0 Hz, H-7), 4.96 (m, 3 H), 5.06 (d, C**H**OAc), 6.19 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 621 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{30}H_{38}O_{14}$ – H) 621.2183, found 621.2188. The deketalized precursor had NMR ($CDCl_3$) δ 0.82 (d, J = 7.0 Hz, CHC**H**$_3$), 0.97 [d, (C**H**$_3$)$_2$CH], 1.24, 1.30, and 1.58 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 2.02–2.75 (m, 9 H), 3.49 (d, J = 2.0 Hz, C$_7$ OH), 3.70 [m, (CH$_3$)$_2$C**H**], 3.97 (d, J = 2.0 Hz, H-7), 3.97 and 5.06 (2 br s, =C**H**$_2$), 5.00 (s, H-3), 5.90 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH).

C6 3-methyl-3-butenoyl ester 3p: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 1.80 (s, C**H**$_3$C=CH$_2$), 2.13 (s, OAc), 3.06 (br s, CH$_2$CO), 4.04 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, =C**H**$_2$), 5.09 (d, J = 5.0 Hz, C**H**OAc), 5.26 (s, H-3), 6.31 (d, J = 2.0 Hz, H-6), 7.06–7.34 (m, ArH); MS (neg FAB) m/z 619 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{30}H_{36}O_{14}$ – H) 619.2026, found 619.2045. The NMR spectrum also indicated the presence of the isomeric C6-(3,3 dimethyl)acrylic ester (ca. 20%) as shown by the following peaks: δ 1.92 [br s, =C(C**H**$_3$)] and 5.66 (br s, =C**H**CO).

C6 *tert*-butylacetyl ester 3q: NMR (CD_3OD) δ 0.84 (d, CHC**H**$_3$), 2.10 (s, OAc), 2.02–2.75 (m, 9 H), 4.01 (d, J = 2.0 Hz, H-7), 4.97 and 5.01 (2 s, =C**H**$_2$), 5.06 (d, J = 5.0 Hz, C**H**OAc), 5.25 (s, H-3), 6.22 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 635 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{31}H_{40}O_{14}$ – H) 635.2340, found 635.2307. The protected precursor had NMR ($CDCl_3$) δ 0.78 (d, J = 6.5 Hz, CHC**H**$_3$), 1.02 [s, (CH$_3$)$_3$C], 1.43 and 1.69 (2 s, 3 *t*Bu), 2.08 (s, OAc), 2.02–2.75 (m, 9 H), 3.20 (s, OCH$_3$), 4.05 (s, C$_4$ OH), 4.14 (d, J = 2.0, H-7), 4.94 (br s, =C**H**$_2$), 5.00 (s, H-3), 5.12 (d, J = 5.0 Hz, C**H**OAc), 6.34 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH).

C6 4-methoxybutyryl ester 3r: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, CHC**H**$_3$), 2.10 (s, OAc), 3.30 (s, OCH$_3$), 3.39 (t, CH$_3$OC**H**$_2$), 4.05 (d, J = 2.0 Hz, H-7), 4.98–5.02 (=C**H**$_2$), 5.08 (d, J = 5.0 Hz, C**H**OAc), 5.26 (s, H-3), 6.28 (d, J = 2.0 Hz, H-6), 7.14–7.30 (m, ArH); MS (neg FAB) m/z 637 $(M - H)^-$. Anal. ($C_{30}H_{38}O_{15}\cdot 0.6H_2O$) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.82 (d, CHC**H**$_3$), 1.30 and 1.37 [2 s, (CH$_3$)$_2$C], 1.46, 1.47 and 1.67 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 3.22 (s, OCH$_3$), 3.31 (s, C**H**$_3$OCH$_2$), 3.38 (t, CH$_3$OC**H**$_2$), 4.08 (s, C$_4$ OH), 4.16 (d, J = 2.0 Hz, H-7), 4.95 (br s, =C**H**$_2$), 4.99 (s, H-3), 5.14 (d, J = 5.0 Hz, C**H**OAc), 6.38 (d, J = 2.0 Hz, H-6), 7.14–7.30 (m, ArH).

C6 4-aminobutyryl ester 3s: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 2.11 (s, OAc), 4.08 (br s, H-7), 4.98 and 5.04 (2 s, =C**H**$_2$), 5.09 (br d, C**H**OAc), 5.26 (s, H-3), 6.36 (br s, H-6,), 7.06–7.37 (m, ArH); MS (neg FAB) m/z 622 $(M - H)^-$.

C6 3-carboxypropionyl ester 3t: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, CHC**H**$_3$), 2.11 (s, OAc), 4.09 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (=C**H**$_2$), 5.07 (d, J = 5.0 Hz, C**H**OAc), 5.25 (s, H-3), 6.27 (d, J = 2.0 Hz, H-6), 7.06–7.34 (m, ArH); MS (neg FAB) m/z 637 $(M - H)^-$. Anal. ($C_{29}H_{34}O_{16}\cdot 2.2H_2O$) C, H.

C6 Carbamates 4. Protected C6 imidazolyl carbamate: NMR ($CDCl_3$) δ 0.84 (d, J = 7.5 Hz, CHC**H**$_3$), 1.27, 1.47, and 1.69 (3 s, 3 *t*-Bu), 1.36 and 1.39 [2 s, (CH$_3$)$_2$C], 2.12 (s, OAc), 3.25 (s, OCH$_3$), 4.11 (s, C$_4$ OH), 4.34 (d, H-7), 5.0 (br s, =C**H**$_2$), 5.03 (s, H-3), 5.16 (d, J = 7.0 Hz, C**H**OAc), 6.54 (d, J = 2.5, H-6), 7.10, 7.43, and 8.15 (3 br s, imidazole), 7.13–7.31 (m, ArH).

C6 [((4*S*,6*S*)-4,6-dimethyloctyl)amino]carbonyl carbamate 4a: NMR (CD_3OD) δ 0.81–0.87 (m, 4 CH$_3$), 2.09 (s, OAc), 2.94–3.12 (m, C**H**$_2$NH), 4.04 (s , H-7), 4.97 and 5.01 (2 s, =C**H**$_2$), 5.06 (d, J = 5.0 Hz, C**H**OAc), 5.25 (s, H-3), 6.15 (s, H-6), 7.14–7.27 (m, ArH); HRMS (neg FAB) calcd for ($C_{36}H_{51}NO_{14}$ – H) 720.3231, found 720.3265. The protected precursor had NMR ($CDCl_3$) δ 0.74–0.82 (m, 4 CH$_3$), 1.29 and 1.32 [2 s, C(CH$_3$)$_2$], 1.40, 1.41, and 1.63 (3 s, 3 *t*-Bu), 2.04 (s, OAc), 3.00–3.20 (m, C**H**$_2$NH), 3.19 (s, OCH$_3$), 4.00 (s, C$_4$ OH), 4.15 (s, H-7), 4.62 (t, J = 5.8 Hz, NH), 4.91 and 4.93 (2 s, =C**H**$_2$), 5.00 (s, H-3), 5.09 (d, J = 5.1 C**H**OAc), 6.17 (s, H-6), 7.10–7.22 (m, ArH).

C6 (decylamino)carbonyl carbamate 4b: NMR (CD_3OD) δ 0.81–0.90 (m, 2 CH$_3$), 1.28 [br s, (CH$_2$)$_n$], 2.10 (s, OAc), 2.03–2.52 (m, 9 H), 3.08 (m, C**H**$_2$NH), 4.06 (d, J = 1.8 Hz, H-7), 5.00 (br s, =C**H**$_2$), 5.06 (br s, H-3), 5.14 (d, J = 4.0 Hz, C**H**OAc), 6.22 (d, J = 1.8 Hz, H-6), 7.18–7.33 (m, ArH); MS (FAB) m/z 728 $(M + Li)^+$. Anal. ($C_{36}H_{51}O_{14}N\cdot 2H_2O$) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 7.0 Hz, CHC**H**$_3$), 0.87 (t, J = 7.5 Hz, CH$_2$C**H**$_3$), 1.25 [s, (CH$_2$)$_n$], 1.34 and 1.36 [2 s, C(CH$_3$)$_2$], 1.44, 1.46, and 1.67 (3 s, 3 *t*-Bu), 2.09 (s, OAc), 2.03–2.52 (m, 9 H), 2.70 (2 d, J = 6.3 and 13.2 Hz, 1 H), 3.14 (t, J = 5.0 Hz, C**H**$_2$NH), 3.23 (s, OCH$_3$), 4.04 (s, C$_4$ OH), 4.19 (d, J = 1.8 Hz, H-7), 4.65 (t, J = 5.0 Hz, NH), 4.96 (br s, =C**H**$_2$), 5.05 (s, H-3), 5.24 (d, J = 5.0 C**H**OAc), 6.22 (d, J = 1.8 Hz, H-6), 7.14–7.30 (m, ArH).

C6 (dodecylamino)carbonyl carbamate 4c: NMR (CD_3OD) δ 0.82–0.94 (m, 2 CH$_3$), 1.28 [br s, (CH$_2$)$_n$], 2.08 (s, OAc), 3.07 (br t, C**H**$_2$NH), 4.04 (br s, H-7), 4.97 and 5.01 (2 s, =C**H**$_2$), 5.07 (d, J = 5.0 Hz, C**H**OAc), 5.25 (s, H-3), 6.17 (br s, H-6), 7.12–7.25 (m, ArH); MS (FAB) m/z 772 $(M + Na)^+$, 795 $(M + 2Na)^+$. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 7 Hz, C**H**$_3$CH), 0.90 (t, C**H**$_3$CH$_2$), 1.24, 1.44, and 1.68 (3 s, 3 *t*-Bu), 1.35 and 1.38 [2 s, (CH$_3$)$_2$], 2.10 (s, OAc), 3.16 (m, C**H**$_2$-NH), 3.26 (s, OCH$_3$), 4.07 (s, C$_4$ OH), 4.20 (d, J = 1.8 Hz, H-7), 4.66 (br t, NH), 4.98 (br s, =C**H**$_2$), 5.06 (s, H-3), 5.15 (d, J = 4.0, C**H**OAc), 6.22 (d, J = 1.8, H-6), 7.1–7.35 (m, ArH).

C6 (tetradecylamino)carbonyl carbamate 4d: NMR (CD_3OD) δ 0.81 (d, J = 7.0 Hz, CHC**H**$_3$), 0.89 (t, J = 7.5 Hz, CH$_2$C**H**$_3$), 1.28 [s, (CH$_2$)$_n$], 1.45 (m, 2 H), 2.10 (s, OAc), 2.03–2.52 (m, 9 H), 3.08 (t, CH$_2$N), 4.06 (d, J = 1.8 Hz, H-7), 4.96 and 5.01 (2 br s, =C**H**$_2$), 5.06 (d, J = 5.0 Hz, C**H**OAc), 5.24 (s, H-3), 6.15 (d, J = 1.8 Hz, H-6), 7.18–7.33 (m, ArH); MS (FAB) m/z 800 $(M + Na)^+$; HRMS (neg FAB) calcd for ($C_{40}H_{59}NO_{14}$ – H) 776.3857, found 776.3855.

C6 [(11-phenoxyundecyl)amino]carbonyl carbamate 4e: NMR (CD_3OD) δ 0.87 (d, J = 7.5 Hz, CHC**H**$_3$), 2.10 (s, OAc), 3.10 (m, C**H**$_2$NHCO), 3.97 (t, J = 6.5 Hz, PhOC**H**$_2$), 4.09 (d, J = 1.5 Hz, H-7), 5.01 and 5.05 (2 s, =C**H**$_2$), 5.11 (d, J = 5.0 Hz, C**H**OAc), 5.29 (s, H-3), 6.20 (d, J = 1.5 Hz, H-6), 6.87–6.94 and 7.15–7.32 (2 m, ArH); MS (FAB) m/z 849 $(M + Na)^+$, 871 $(M + 2Na)^+$, 893 $(M + 3Na)^+$. Anal. ($C_{43}H_{57}NO_{15}\cdot 2.3H_2O$) C, H, N. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 7.5 Hz, CHC**H**$_3$), 1.35 and 1.38 [2 s, (CH$_3$)$_2$C], 1.44, 1.46, and 1.68 (3 s, 3 *t*-Bu), 2.09 (s, OAc), 3.15 (m, C**H**$_2$NHCO), 3.24 (s, OCH$_3$), 3.96 (t, J = 6.5 Hz, PhOC**H**$_2$), 4.05 (s, C$_4$ OH), 4.21 (br s, H-7), 4.67 (t, NH), 4.98 (br s, =C**H**$_2$), 5.06 (s, H-3), 5.16 (d, J = 5.0 Hz, C**H**OAc), 6.24 (br s, H-6), 6.84–6.99 and 7.12–7.35 (2 m, ArH).

C6 (methylamino)carbonyl carbamate 4f: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, CHC**H**$_3$), 2.10 (s, OAc), 2.69 (s, C**H**$_3$-NH), 4.06 (d, H-7), 5.08 (d, C**H**OAc), 5.26 (s, H-3), 6.17 (d, H-6), 7.13–7.30 (m, ArH); MS (neg FAB) m/z 594 $(M - H)^-$. Anal. ($C_{27}H_{33}NO_{14}\cdot 1.2H_2O$) C, H, N. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, CHC**H**$_3$), 1.36 and 1.39 [2 s, (CH$_3$)$_2$C], 1.46, 1.48, and 1.70 (3 s, 3 *t*-Bu), 2.10 (s, OAc), 2.78 (d, C**H**$_3$NH), 3.24 (s, OCH$_3$), 4.05 (s, C$_4$ OH), 4.21 (br s, H-7), 4.66 (m, NH), 4.98 (br s, =C**H**$_2$), 5.06 (s, H-3), 5.14 (d, C**H**OAc), 6.24 (br s, H-6), 7.14–7.30 (m, ArH).

C6 (ethylamino)carbonyl carbamate 4g: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, CHC**H**$_3$), 1.10 (t, J = 7.0 Hz, C**H**$_3$CH$_2$),

2.09 (s, OAc), 3.12 (m, CH_3CH_2NH), 4.06 (br s, H-7), 5.08 (d, CHOAc), 5.26 (s, H-3), 6.19 (d, H-6), 7.14–7.31 (m, ArH); MS (neg FAB) m/z 608 $(M - H)^-$. Anal. ($C_{28}H_{35}NO_{14}\cdot 1.6H_2O$) C, H, N. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, $CHCH_3$), 1.12 (t, J = 7.0 Hz, CH_3CH_2), 1.36 and 1.38 [2 s, $(CH_3)_2C$], 1.46, 1.47, and 1.69 (3 s, 3 t-Bu), 2.09 (s, OAc), 3.25 (s, OCH_3), 4.05 (s, C_4 OH), 4.21 (br s, H-7), 4.68 (m, NH), 4.98 (br s, $=CH_2$), 5.06 (s, H-3), 5.14 (d, CHOAc), 6.24 (br s, H-6), 7.14–7.32 (m, ArH).

C6 (*N,N*-dimethylamino)carbonyl carbamate 4h: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, $CHCH_3$), 2.10 (s, OAc), 2.86 and 2.90 [2 s, $(CH_3)_2N$], 4.06 (d, J = 2.5 Hz, H-7), 5.08 (d, J = 5.0 Hz, CHOAc), 5.24 (s, H-3), 6.07 (d, J = 2.5 Hz, H-6), 7.13–7.30 (m, ArH); MS (neg FAB) m/z 608 $(M - H)^-$. Anal. ($C_{28}H_{35}NO_{14}\cdot 1.6H_2O$) C, H, N. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, $CHCH_3$), 1.34 and 1.39 [2 s, $(CH_3)_2C$], 1.44, 1.48, and 1.70 (3 s, 3 t-Bu), 2.10 (s, OAc), 2.87 and 2.91 [2 s, $(CH_3)_2N$], 3.24 (s, OCH_3), 4.06 (s, C_4 OH), 4.21 (d, H-7), 4.98 (br s, $=CH_2$), 5.08 (s, H-3), 5.15 (d, CHOAc), 6.28 (d, H-6), 7.14–7.30 (m, ArH).

C6 (isopropylamino)carbonyl carbamate 4i: NMR (CD_3OD) δ 0.84 (d, $CHCH_3$), 1.10 [m, $CH(CH_3)_2$], 2.10 (s, OAc), 2.02–2.75 (m, 9 H), 3.70 (m, $(CH_3)_2CH$), 4.06 (d, J = 2.0 Hz, H-7), 4.96 and 5.02 (2 s, $=CH_2$), 5.06 (d, J = 5.0 Hz, CHOAc), 5.25 (s, H-3), 6.19 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 622 $(M - H)^-$; $[\alpha]_D$ +5.1° (c = 1.0, CH_3OH). Anal. ($C_{29}H_{37}NO_{14}\cdot 0.5H_2O$) C, H, N. The protected precursor had NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, $CHCH_3$), 1.2 [m, $(CH_3)_2CH$)], 1.53 and 1.75 (2 s, 3 t-Bu), 2.16 (s, OAc), 2.02–2.85 (m, 9 H), 3.30 (s, OCH_3), 3.85 [m, $(CH_3)_2CH$], 4.11 (s, C_4 OH), 4.26 (br s, H-7), 4.61 (d, J = 8.0 Hz, NH), 5.03 and 5.05 (2 s, $=CH_2$), 5.13 (s, H-3), 5.20 (d, J = 5.0 Hz, CHOAc), 6.29 (br s, H-6), 7.15–7.27 (m, ArH); mp 165–168 °C (CH_2Cl_2/hexanes). Anal. ($C_{45}H_{69}NO_{15}$) C, H, N.

C6 (isopropylamino)thiocarbonyl Carbamate 4j. A solution of **2a** (210 mg, 0.27 mmol) and 1,1′-thiocarbonyldiimidazole (200 mg, 1.15 mmol) in toluene (1.5 mL) was stirred at 70 °C for 1 h, and isopropylamine (200 mg, 3.4 mmol) was added. After 96 h, the mixture was filtered, and the filtrate was concentrated to a residue, which was purified by preparative TLC (hexanes–ethyl acetate, 3:1, v/v containing 0.1% Et_3N) to give the protected carbamate intermediate: NMR ($CDCl_3$) δ 0.76 (d, J = 6.5 Hz, $CHCH_3$), 1.14 and 1.18 [2 d, $CH(CH_3)_2$], 1.40, 1.43, and 1.68 (3 s, 3 t-Bu), 2.07 (s, OAc), 2.02–2.85 (m, 9 H), 3.23 (s, OCH_3), 4.08 (s, C_4 OH), 4.19 (br s, H-7), 4.23 [m, $(CH_3)_2CH$], 4.61 (d, J = 8.0 Hz, NH), 4.94 and 4.95 (2 s, $=CH_2$), 5.13 (d, J = 5.0 Hz, CHOAc), 5.15 (s, H-3), 6.20 (d, NH), 6.79 (br s, H-6), 7.15–7.27 (m, ArH). The following signals were assigned to the rotomer (20%): δ 1.06 and 1.09 [2 d, $CH(CH_3)_2$], 3.92 [m, $(CH_3)_2CH$], 4.27 (br s, H-7), 6.32 (d, NH), 6.82 (br s, H-6). Deprotection with TFA in CH_2Cl_2 at room temperature overnight afforded **4j**: NMR (CD_3OD) δ 0.86 (d, $CHCH_3$), 1.18 [m, $(CH_3)_2CH$], 2.07 (s, OAc), 2.02–2.75 (m, 9 H), 4.05 (d, J = 2.0 Hz, H-7), 4.30 [m, $(CH_3)_2CH$], 4.96 and 5.02 (2 s, $=CH_2$), 5.08 (d, J = 5.0 Hz, CHOAc), 5.27 (s, H-3), 6.65 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 638 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{29}H_{37}NO_{13}S$ – H) 638.1907, found 638.1917. The following signals were assigned to the rotomer (40%): δ 3.93 [m, $(CH_3)_2CH$], 4.10 (d, J = 2.0 Hz, H-7), 6.50 (d, J = 2.0 Hz, H-6).

C6 (cyclopropylamino)carbonyl carbamate 4k: NMR (CD_3OD) δ 0.38–0.50 and 0.58–0.69 (2 m, CH_2CH_2 cyclic), 0.84 (d, J = 6.5 Hz, $CHCH_3$), 2.10 (s, OAc), 3.97 (s, C_4 OH), 4.05 (br s, H-7), 5.06 (d, CHOAc), 5.25 (s, H-3), 6.19 (br s, H-6), 7.15–7.30 (m, ArH); MS (neg FAB) m/z 620 $(M - H)^-$. Anal. ($C_{29}H_{35}NO_{14}\cdot 1.1H_2O$) C, H, N. The protected precursor had NMR ($CDCl_3$) δ 0.39–0.56 and 0.69–0.78 (2 m, CH_2CH_2 cyclic), 0.80 (d, J = 6.5 Hz, $CHCH_3$), 1.35 and 1.38 [2 s, $(CH_3)_2C$], 1.45, 1.46, and 1.69 (3 s, 3 t-Bu), 2.09 (s, OAc), 3.24 (s, OCH_3), 4.04 (s, C_4 OH), 4.19 (br s, H-7), 4.89 (br s, NH), 4.86–4.88 ($=CH_2$), 5.05 (s, H-3), 5.14 (d, CHOAc), 6.22 (br s, H-6), 7.12–7.32 (m, ArH).

C6 [(cyclopropylmethyl)amino]carbonyl carbamate 4l: NMR (CD_3OD) δ 0.12–0.21 and 0.40–0.48 (2 m, CH_2CH_2 cyclic), 0.85 (d, J = 6.5 Hz, $CHCH_3$), 2.10 (s, OAc), 2.95 (m, CH_2NHCO), 3.97 (s, C_4 OH), 4.07 (d, J = 1.0 Hz, H-7), 5.08 (d, J = 4.5 Hz, CHOAc), 5.26 (s, H-3), 6.18 (d, J = 1.0 Hz, H-6), 7.14–7.29 (m, ArH); MS (neg FAB) m/z 634 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{30}H_{37}NO_{14}$ – H) 634.2136, found 634.2153.

C6 (cyclobutylamino)carbonyl carbamate 4m: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 2.10 (s, OAc), 4.05 (m, CHNH), 4.05 (d, J = 2.0 Hz, H-7), 4.99 and 5.03 (2 s, $=CH_2$), 5.07 (d, J = 5.0 Hz, CHOAc), 5.25 (s, H-3), 6.17 (d, J = 2.0 Hz, H-6), 7.06–7.34 (m, ArH); MS (FAB) m/z 658 $(M + Na)^+$. Anal. ($C_{30}H_{37}NO_{14}\cdot 2H_2O$) C, H, N.

C6 [(adamantylmethyl)amino]carbonyl carbamate 4n: NMR ($CDCl_3$) δ 0.84 (d, $CHCH_3$), 1.43 (s, adamantyl CH_2), 2.10 (s, OAc), 2.02–2.75 (m, 9 H), 4.06 (d, J = 2.0 Hz, H-7), 4.96 and 5.02 (2 s, $=CH_2$), 5.06 (d, J = 5.0 Hz, CHOAc), 6.16 (d, J = 2.0 Hz, H-6), 7.15–7.27 (m, ArH); MS (neg FAB) m/z 728 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{37}H_{47}NO_{14}$ – H) 728.2918, found 728.2941. The protected precursor had NMR ($CDCl_3$) δ 0.80 (d, $CHCH_3$), 1.43 (s, adamantyl CH_2), 1.66 (s, 3 t-Bu), 2.07 (s, OAc), 3.23 (s, OCH_3), 4.05 (s, C_4 OH), 4.21 (d, J = 2 .0 Hz, H-7), 4.73 (t, J = 5.0, NH), 4.99 and 5.05 (2 s, $=CH_2$), 5.16 (d, CHOAc), 6.24 (d, J = 2.0 Hz, H-6), 7.2 (m, ArH).

C6 (benzylamino)carbonyl carbamate 4o: NMR (CD_3OD) δ 0.94 (d, J = 7.0 Hz, $CHCH_3$), 2.10 (s, OAc), 4.17 (br s, H-7), 5.13 (d, J = 5.0 Hz, CHOAc), 5.28 (s, H-3), 6.28 (br s, H-6), 7.0–7.50 (m, ArH); MS (FAB) m/z 694 $(M + Na)^+$, 717 $(M + 2Na)^+$; HRMS (neg FAB) calcd for ($C_{33}H_{37}NO_{14}$ – H) 670.2136, found 670.2164. The deketalized precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 7.0 Hz, CH_3CH), 1.42, 1.45, and 1.61 (3 s, 3 t-Bu), 2.10 (s, OAc), 4.06 (s, C_4 OH), 4.11 (d, J = 1.8 Hz, H-7), 4.39 (d, J = 6 Hz, CH_2NH), 4.98 (br s, $=CH_2$), 5.05 (s, H-3), 5.11 (d, J = 4.0 Hz, CHOAc), 5.94 (d, J = 1.8 Hz, H-6), 7.06–7.40 (m, ArH).

C6 Carbonates 5. C6 [[(4*S*,6*S*)-4,6-dimethyloctyl]oxy]carbonyl carbonate 5a: NMR (CD_3OD) δ 0.83–0.88 (m, 4 CH_3), 2.09 (s, OAc), 4.08 (d , J = 1.9 Hz, H-7), 4.13–4.19 (m, CH_2O), 4.95 and 5.00 (2 s, $=CH_2$), 5.06 (d, J = 4.2 Hz, CHOAc), 5.21 (s, H-3), 6.16 (d, J = 1.90 Hz, H-6), 7.13–7.27 (m, ArH); HRMS (neg FAB) calcd for ($C_{36}H_{50}O_{15}$ – H) 721.3071, found 721.3070. The protected precursor had NMR ($CDCl_3$) δ 0.75–0.81 (m, 4 CH_3), 1.29 and 1.32 [2 s, $C(CH_3)_2$], 1.40, 1.41, and 1.61 (3 s, 3 t-Bu), 2.04 (s, OAc), 3.18 (s, OCH_3), 4.03 (s, C_4 OH), 4.02–4.15 (m, CH_2O), 4.18 (d, J = 1.4 Hz, H-7), 4.91 (br s, H-3 and $=CH_2$), 5.08 (d, J = 5.1 CHOAc), 6.12 (d, J = 1.4 H-6), 7.10–7.23 (m, ArH).

C6 (decyloxy)carbonyl carbonate 5b: NMR (CD_3OD) δ 0.87 (d, J = 6.5 Hz, $CHCH_3$), 0.89 (t, CH_2CH_3), 2.10 (s, OAc), 4.12 (d, H-7), 4.15 (t, CH_2OCO), 4.97–5.02 ($=CH_2$), 5.25 (s, H-3), 6.19 (d, H-6), 7.14–7.29 (m, ArH); MS (FAB) m/z 745 $(M + Na)^+$, 767 $(M + 2Na)^+$, 789 $(M + 3Na)^+$. Anal. ($C_{36}H_{50}O_{15}\cdot 1.5H_2O$) C, H, N. The deketalized precursor had NMR ($CDCl_3$) δ 0.83 (d, J = 6.5 Hz, $CHCH_3$), 1.46, 1.49, and 1.63 (3 s, 3 t-Bu), 2.11 (s, OAc), 4.11 (d, J = 2.0 Hz, H-7), 4.18 (t, J = 6.5 Hz, CH_2OCO), 4.97–5.0 ($=CH_2$), 5.01 (s, H-3), 5.11 (d, CHOAc), 5.97 (d, H-6), 7.13–7.31 (m, ArH).

C6 (dodecyloxy)carbonyl carbonate 5c: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, $CHCH_3$), 0.88 (t, J = 6.5 Hz, CH_2CH_3), 2.10 (s, OAc), 4.09 (d, J = 1.5 Hz, H-7), 4.14 (t, J = 6.2 Hz, CH_2OCO), 4.96 and 5.01 (2 s, $=CH_2$), 5.08 (d, J = 4.5 Hz, CHOAc), 5.22 (s, H-3), 6.18 (d, J = 1.5 Hz, H-6), 7.14–7.30 (m, ArH); MS (FAB) m/z 773 $(M + Na)^+$, 795 $(M + 2Na)^+$, 817 $(M + 3Na)^+$. Anal. ($C_{38}H_{54}O_{15}\cdot 2.2H_2O$) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.82 (d, J = 6.5 Hz, $CHCH_3$), 0.88 (t, J = 6.0 Hz, CH_2CH_3), 1.26 [br s, $(CH_2)_n$], 1.34 and 1.36 [2 s, $(CH_3)_2C$], 1.45, 1.46, and 1.66 (3 s, t-Bu), 2.08 (s, OAc), 3.22 (s, OCH_3), 4.06 (s, C_4 OH), 4.11 (m, CH_2OCO), 4.23 (d, H-7), 4.96 (s, H-3 and $=CH_2$), 5.13 (d, J = 5.0 Hz, CHOAc), 6.18 (d, H-6), 7.14–7.31 (m, ArH).

C6 [(11-phenoxyundecyl)oxy]carbonyl carbonate 5d: NMR (CD_3OD) δ 0.86 (d, J = 6.0 Hz, $CHCH_3$), 2.09 (s, OAc), 3.93 (t, J = 6.2 Hz, $PhOCH_2$), 4.09–4.17 (m, H-7 and CH_2OCO), 4.95 and 5.01 (2 s, $=CH_2$), 5.07 (d, J = 4.5 Hz, CHOAc), 5.23 (s, H-3), 6.18 (br s, H-6), 6.84–6.91 and 7.13–7.29 (2 m, ArH); MS (FAB) m/z 850 $(M + Na)^+$, 872 $(M + 2Na)^+$, 894 $(M + 3Na)^+$. Anal. ($C_{43}H_{56}O_{16}\cdot 1.8H_2O$) C, H. The protected

precursor had NMR ($CDCl_3$) δ 0.82 (d, J = 7.5 Hz, $CHCH_3$), 1.28 [br s, $(CH_2)_n$], 1.34 and 1.36 [2 s, $(CH_3)_2C$], 1.45 and 1.66 (2 s, t-Bu), 2.08 (s, OAc), 3.22 (s, OCH_3), 3.94 (t, J = 6.2 Hz, $PhOCH_2$), 4.06 (s, C_4 OH), 4.12 (m, CH_2OCO), 4.23 (br s, H-7), 4.96 (s, H-3), 4.96 (br s, $=CH_2$), 5.13 (d, J = 4.5 Hz, CHOAc), 6.18 (br s, H-6), 6.87–6.96 and 7.14–7.32 (2 m, ArH).

C6 methoxycarbonyl carbonate 5e: NMR (CD_3OD) δ 0.84 (d, J = 6.5, $CHCH_3$), 2.09 (s, OAc), 2.02–2.75 (m, 9 H), 3.78 (s, OCH_3), 4.09 (d, J = 2.0 Hz, H-7), 4.94–4.98 (H-3 and $=CH_2$), 5.06 (d, J = 5.0 Hz, CHOAc), 6.17 (d, J = 2.0 Hz, H-6), 7.15–7.24 (m, ArH); MS (neg FAB) m/z 595 $(M - H)^-$. The protected precursor had NMR ($CDCl_3$) δ 0.78 (d, J = 6.5 Hz, $CHCH_3$), 1.40, 1.43, and 1.64 (3 s, 3 t-Bu), 2.06 (s, OAc), 3.75 (s, OCH_3), 4.05 (s, C_4 OH), 4.23 (br s, H-7), 4.93 (br s, $=CH_2$), 5.08 (d, CHOAc), 6.15 (br s, H-6), 7.15–7.23 (m, ArH).

C6 ethoxycarbonyl carbonate 5f: NMR (CD_3OD) δ 0.86 (d, J = 6.5, $CHCH_3$), 1.30 (t, J = 6.5 Hz, CH_2CH_3), 2.10 (s, OAc), 4.08 (d, J = 1.5 Hz, H-7), 4.20 (q, J = 6.5 Hz, CH_2CH_3), 4.93 and 5.01 (2 s, $=CH_2$), 5.06 (d, J = 5.0 Hz, CHOAc), 5.22 (s, H-3), 6.17 (d, H-6), 7.12–7.30 (m, ArH); MS (neg FAB) m/z 609 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{28}H_{34}O_{15}$ − H) 609.1819, found 609.1832. The deketalized precursor had NMR ($CDCl_3$) δ 0.79 (d, J = 6.5 Hz, $CHCH_3$), 1.31 (t, CH_2CH_3), 1.42, 1.45, and 1.58 (3 s, 3 t-Bu), 2.09 (s, OAc), 4.05 (s, C_4 OH), 4.08 (d, H-7), 4.22 (2 d, CH_2CH_3), 4.92 and 4.95 (2 s, $=CH_2$), 4.96 (s, H-3), 5.08 (d, J = 5.0 Hz, CHOAc), 5.92 (d, H-6), 7.15–7.29 (m, ArH).

C6 (isopropyloxy)carbonyl carbonate 5g: NMR (CD_3OD) δ 0.86 (d, J = 6.5 Hz, $CHCH_3$), 1.27 and 1.28 [2 d, J = 6.5 Hz, $(CH_3)_2CH$], 2.10 (s, OAc), 4.08 (d, J = 3.0 Hz, H-7), 5.06 (d, J = 5.0 Hz, CHOAc), 5.22 (s, H-3), 6.17 (d, J = 3.0 Hz, H-6), 7.12–7.30 (m, ArH); MS (neg FAB) m/z 623 $(M - H)^-$. Anal. ($C_{29}H_{36}O_{15}$·2.2H_2O) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, $CHCH_3$), 1.25 and 1.26 [2 d, J = 6.5 Hz, $(CH_3)_2CH$], 1.36 and 1.38 [2 s, $(CH_3)_2C$], 1.46 and 1.67 (2 s, 3 t-Bu), 2.09 (s, OAc), 3.23 (s, OCH_3), 4.09 (s, C_4 OH), 4.24 (d, H-7), 4.86 [m, $(CH_3)_2CH$], 4.96 (s, H-3), 4.96 (br s, $=CH_2$), 5.13 (d, J = 5.0 Hz, CHOAc), 6.19 (d, H-6), 7.15–7.29 (m, ArH).

C6 (isopropylthio)carbonyl carbonate 5h: NMR (CD_3OD) δ 0.86 (d, J = 6.6 Hz, $CHCH_3$), 1.33 and 1.34 [2 d, J = 6.9 Hz, $(CH_3)_2CH$], 2.10 (s, OAc), 3.52 (m, [$(CH_3)_2CH$], 4.05 (d, J = 1.8 Hz, H-7), 4.95 and 5.01 (2 s, $=CH_2$), 5.07 (d, J = 4.6 Hz, CHOAc), 5.21 (s, H-3), 6.42 (d, J = 1.8 Hz, H-6), 7.14–7.28 (m, ArH); MS (neg FAB) m/z 639 $(M - H)^-$; HRMS (neg FAB) calcd for ($C_{29}H_{36}O_{14}S$ − H) 639.1747, found 639.1760.

C6 Ethers 6. C6 (4*S*,6*S*)-4,6-Dimethyloctyl Ether (6a). Sodium hydride (6 mg, 0.15 mmol; 60% dispersion in mineral oil) was added to a stirred solution of **2b** (95 mg, 0.10 mmol) and (4*S*,6*S*)-4,6-dimethyloctyl iodide (65 μL, 0.45 mmol) in DMF (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 28 h and partitioned between hexanes and water. The organic layer was washed with brine, dried, and evaporated to a residue, which was purified by preparative TLC (hexanes–ethyl acetate, 80:20, v/v containing 0.1% triethylamine) to give the C6 (4*S*,6*S*)-4,6-dimethyloctyl ether of **2b** (89 mg, 82%): NMR ($CDCl_3$) δ 0.77–0.81 (m, 4 CH_3), 1.27, 1.43, and 1.57 (3 s, 3 t-Bu), 1.37 and 1.39 [2 s, $(CH_3)_2C$], 2.05 (s, OAc), 3.25 (s, OCH_3), 3.49 and 3.65 (2 m, CH_2O), 4.12 (d, J = 1.8 Hz, H-7), 4.84–5.04 (m, 6 H), 5.10 (d, J = 5.1 Hz, CHOAc), 7.05–7.14 (m, ArH). A solution of this material (89 mg, 0.08 mmol) in dichloromethane (3 mL) was treated with TFA (1 mL) at room temperature overnight. The mixture was evaporated, and traces of TFA was codistilled with toluene. 4-Phenylbenzyl trifluroacetate was repeatedly extracted with hexanes. The hexanes-insoluble material was purified by reverse-phase HPLC to give **6a** (36 mg, 65%): NMR (CD_3OD) δ 0.83–0.87 (m, 4 CH_3), 2.09 (s, OAc), 3.48–3.54 and 3.64–3.69 (2 m, OCH_2), 4.05 (d, J = 2.0 Hz, H-7), 4.86 (d, J = 2.0 Hz, H-6), 4.96 and 5.01 (2 s, $=CH_2$), 5.08 (d, J = 4.9 Hz, CHOAc), 5.10 (s, H-3), 7.12–7.26 (m, ArH). HRMS (neg FAB) calcd for ($C_{35}H_{50}O_{13}$ − H) 677.3172, found 677.3157.

C6 decyl ether 6b: NMR (CD_3OD) δ 0.82–0.91 (m, 2 CH_3), 1.28 [br s, $(CH_2)_n$], 2.09 (s, OAc), 3.42 and 3.62 (2 m, CH_2O), 4.01 (s, J = 2.0 Hz, H-7), 4.93 and 4.98 (2 s, $=CH_2$), 5.04 (m, 2 H), 7.04–7.30 (m, ArH); MS (FAB) m/z 701 $(M + Na)^+$; HRMS (neg FAB) calcd for ($C_{35}H_{50}O_{13}$ − H) 677.3173, found 677.3171.

C6 dodecyl ether 6c: NMR (CD_3OD) δ 0.83–0.93 (m, 2 CH_3), 1.29 [br s, $(CH_2)_n$], 2.11 (s, OAc), 3.53 and 3.69 (2 m, CH_2O), 4.06 (d, J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.12 (br s, H-6), 7.05–7.33 (m, ArH); MS (FAB) m/z 729 $(M + Na)^+$; HRMS (neg FAB) calcd for ($C_{37}H_{54}O_{13}$ − H) 705.3486, found 705.3502.

C6 tetradecyl ether 6d: NMR (CD_3OD) δ 0.83–0.91 (m, 2 CH_3), 1.27 [br s, $(CH_2)_n$], 2.09 (s, OAc), 3.54 and 3.67 (2 m, CH_2O), 4.06 (br s, H-7), 4.97 (s, 1 H), 5.02 (s, 1 H), 5.09 (m, 2 H), 7.11–7.31 (m, ArH); MS (FAB) m/z 757 $(M + Na)^+$, 780 $(M + 2Na)^+$; HRMS (neg FAB) calcd for ($C_{39}H_{58}O_{13}$ − H) 733.3799, found 733.3804. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 7.0 Hz, $CHCH_3$), 0.89 (t, J = 7.0 Hz, CH_2CH_3), 1.25 [br s, $(CH_2)_n$], 1.41 and 1.44 [2 s, $(CH_3)_2C$], 1.46 1.49 and 1.64 (3 s, 3 t-Bu), 2.09 (s, OAc), 3.28 (s, OCH_3), 3.56 and 3.72 (2 m, CH_2O), 3.99 (s, C_4 OH), 4.19 (d, J = 2.0 Hz, H-7), 4.72 (d, J = 2.0 Hz, H-6), 4.85 (s, H-3), 4.98 (s, $=CH_2$), 5.15 (d, J = 5.0 Hz, CHOAc), 7.10–7.34 (m, ArH).

C6 hexadecyl ether 6e: NMR (CD_3OD) δ 0.84–0.96 (m, 2 CH_3), 1.30 [br s, $(CH_2)_n$], 2.11 (s, OAc), 3.56 and 3.70 (2 m, CH_2O), 4.08 (br s, H-7), 4.98 and 5.04 (2 s, $=CH_2$), 5.12 (m, 2 H), 7.12–7.34 (m, ArH); MS (FAB) m/z 785 $(M + Na)^+$, 808 $(M + 2Na)^+$; HRMS (neg FAB) calcd for ($C_{41}H_{62}O_{13}$ − H) 761.4112, found 761.4129. The deketalized precursor had NMR ($CDCl_3$) δ 0.84 (d, J = 7.0 Hz, $CHCH_3$), 0.89 (t, J = 7.0 Hz, CH_2CH_3), 1.26 [br s, $(CH_2)_n$], 1.45, 1.49, and 1.63 (3 s, 3 t-Bu), 2.12.(s, OAc), 3.47 and 3.67 (2 m, CH_2O), 4.10 (s, C_4 OH), 4.10 (m, H-7), 4.75 (d, J = 2.0 Hz, H-6), 4.87 (s, H-3), 4.97 and 5.02 (2 s, $=CH_2$), 5.12 (d, J = 5.0 Hz, CHOAc), 7.11–7.35 (m, ArH).

C6 8-phenoxyoctyl ether 6f: NMR (CD_3OD) δ 0.85 (d, J = 7.5 Hz, $CHCH_3$), 1.37 [br s, $(CH_2)_n$], 2.09 (s, OAc), 3.35 and 3.68 (2 m, CH_2O), 3.94 (t, J = 6.5 Hz, $PhOCH_2$), 4.08 (d, J = 2.0 Hz, H-7), 4.89 (d, J = 2.0 Hz, H-6), 4.98 and 5.04 (2 s, $=CH_2$), 5.09 (d, J = 4.5 Hz, CHOAc), 5.13 (s, H-3), 6.85–6.91 and 7.12–7.30 (2 m, ArH); MS (FAB) m/z 765 $(M + Na)^+$. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 7.5 Hz, $CHCH_3$), 1.40 and 1.43 [2 s, $C(OCH_3)(CH_3)_2$], 1.45, 1.49, and 1.63 (3 s, t-Bu), 2.08 (s, OAc), 3.27 (s, OCH_3), 3.55 and 3.73 (2 m, CH_2O), 3.95 (t, J = 6.5 Hz, $PhOCH_2$), 3.99 (s, C_4-OH), 4.18 (d, J = 1.5 Hz, H-7), 4.72 (d, J = 1.5 Hz, H-6), 4.85 (s, H-3), 4.97 (br s, $=CH_2$), 5.15 (d, J = 5.0 Hz, CHOAc), 6.87–6.97 and 7.13–7.31 (2 m, ArH).

C6 11-phenoxyundecyl ether 6g: NMR (CD_3OD) δ 0.84 (d, J = 6.0 Hz, $CHCH_3$), 2.08 (s, OAc), 3.54 and 3.66 (2 m, CH_2O), 3.92 (t, J = 6.5 Hz, $PhOCH_2$), 4.05 (br s, H-7), 4.95 and 5.00 (2 s, $=CH_2$), 5.07 (d, J = 4.5 Hz, CHOAc), 6.84–6.90 and 7.12–7.30 (2 m, ArH); MS (FAB) m/z 806 $(M + Na)^+$, 828 $(M + 2Na)^+$. The deketalized precursor had NMR ($CDCl_3$) δ 0.83 (d, J = 7.0 Hz, $CHCH_3$), 1.29 [br s, $(CH_2)_n$], 1.44, 1.47, and 1.61 (3 s, 3 t-Bu), 2.10 (s, OAc), 3.46 and 3.66 (2 m, CH_2O), 3.94 (t, J = 6.2 Hz, $PhOCH_2$), 4.06 (s, C_4 OH), 4.07 (d, J = 2.5 Hz, H-7), 4.69 (d, J = 2.5 Hz, H-6), 4.84 (s, H-3), 4.95 and 5.00 (2 s, $=CH_2$), 5.09 (d, J = 4.5 Hz, CHOAc), 6.86–6.95 and 7.12–7.31 (2 m, ArH).

C6 hydroxy derivative 6h: NMR (CD_3OD) δ 0.85 (d, J = 6.5 Hz, $CHCH_3$), 2.10 (s, OAc), 4.07 (d, H-7), 4.98–5.02 ($=CH_2$), 5.08 (d, J = 5.0, CHOAc), 5.12 (d, J = 2.0 Hz, H-6), 5.14 (s, H-3), 7.12–7.29 (m, ArH); MS (neg FAB) m/z 537 $(M - H)^-$. Anal. ($C_{25}H_{30}O_{13}$·1.7H_2O) C, H.

C6 methyl ether 6i: see selective preparation of C6 ethers (e.g., **6i**).

C6 *n*-propyl ether 6j: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 0.94 (t, J = 7.0 Hz, CH_2CH_3), 1.58 (m, $CH_2CH_2CH_3$), 2.11 (s, OAc), 3.52 and 3.66 (2 m, CH_2O), 4.06 (d, J = 2.0 Hz, H-7), 4.98 and 5.02 (2 s, 2 H), 5.09 (d, J = 5.0 Hz, CHOAc), 5.12 (s, H-3), 7.04–7.38 (m, ArH); MS (neg FAB) m/z 579 $(M - H)^-$. Anal. ($C_{28}H_{36}O_{13}$·2H_2O) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.81 (d, J = 7.0 Hz, $CHCH_3$), 0.92 (t, J = 7.0 Hz, CH_2CH_3), 1.40 and 1.43 [2 s, $(CH_3)_2C$], 1.47, 1.50, and 1.65 (3 s, 3 t-Bu), 2.09 (s, OAc), 3.27 (s, OCH_3), 3.52 and 3.70 (2 m, CH_2O), 3.99 (s, C_4 OH), 4.19 (d, J = 2.0

Hz, H-7), 4.71 (d, J = 2.0 Hz, H-6), 4.85 (s, H-3), 4.97 (br s, $=CH_2$), 5.13 (d, J = 5.0 Hz, CHOAc), 7.10–7.34 (m, ArH).

C6 *n*-butyl ether 6k: NMR (CD_3OD) δ 0.86 (d, J = 7.0 Hz, $CHCH_3$), 0.92 (t, J = 7.0 Hz, CH_2CH_3), 1.38 (m, 2 H), 1.53 (m, 2 H), 2.10 (s, OAc), 3.54 and 3.69 (2 m, CH_2O), 4.06 (d, J = 2.0 Hz, H-7), 4.87 (d, J = 2.0 Hz, H-6), 4.97 and 5.02 (2 s, $=CH_2$), 5.08 (d, J = 5.0 Hz, CHOAc), 5.11 (s, H-3), 7.13–7.30 (m, ArH); MS (neg FAB) m/z 593 $(M - H)^-$. Anal. ($C_{29}H_{38}O_{13}\cdot 1.4H_2O$) C, H.

C6 isoamyl ether 6l: NMR (CD_3OD) δ 0.84–0.90 (m, 3 CH_3), 1.44 (m, 2 H), 1.71 (m, 1 H), 2.10 (s, OAc), 3.56 and 3.72 (2 m, CH_2O), 4.05 (d, J = 2.0 Hz, H-7), 4.86 (d, J = 2.0, H-6), 4.96 and 5.01 (2 s, $=CH_2$), 5.08 (d, J = 5.0 CHOAc), 5.10 (s, H-3), 7.14–7.27 (m, ArH); MS (neg FAB) m/z 608 $(M - H)^-$. Anal. ($C_{30}H_{40}O_{13}\cdot 1.2H_2O$) C, H.

C4 Ether 7. C4 dodecyl ether 7c: NMR (CD_3OD) δ 0.84–0.93 (m, 2 CH_3), 1.23 [br s, $(CH_2)_n$], 2.10 (s, OAc), 3.89 and 4.05 (2 m, CH_2O), 4.00 (d , J = 2.0 Hz, H-7), 4.98 and 5.03 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.17 (s, H-3), 5.22 (s, J = 2.0 Hz, H-6), 7.05–7.31 (m, ArH); MS (FAB) m/z 729 $(M + Na)^+$; HRMS (neg FAB) calcd for $(C_{37}H_{54}O_{13} - H)$ 705.3486, found 705.3486.

C4 tetradecyl ether 7d: NMR (CD_3OD) δ 0.81–0.93 (m, 2 CH_3), 1.21 [br s, $(CH_2)_n$], 2.10 (s, OAc), 3.78–4.14 (m, CH_2O), 4.01 (br s, H-7), 5.00 and 5.04 (2 s, $=CH_2$), 5.10 (d, J = 5.0 Hz, CHOAc), 5.18 (s, H-3), 5.23 (br s , H-6) 7.08–7.34 (m, ArH); MS (FAB) m/z 757 $(M + Na)^+$. The protected precursor had NMR ($CDCl_3$) δ 0.84 (d, J = 7.0 Hz, $CHCH_3$), 0.88 (t, J = 7.0 Hz, CH_2CH_3), 1.23 [br s, $(CH_2)_n$], 1.39 and 1.46 [2 s, $(CH_3)_2C$], 1.47, 1.49, and 1.56 (3 s, t-Bu), 2.13 (s, OAc), 3.28 (s, CH_3O), 3.70 and 3.86 (2 m, CH_2O), 4.0 (d, J = 2.0 Hz, H-7), 4.86 (s, H-3), 4.98 (s, $=CH_2$), 5.14–5.25 (m, CHOAc and H-6), 7.14–7.34 (m, ArH).

C4 8-phenoxyoctyl ether 7f: NMR (CD_3OD) δ 0.85 (d, J = 7.0 Hz, $CHCH_3$), 2.08 (s, OAc), 3.81 (t, J = 6.5 Hz, $PhOCH_2$), 4.04 (d, J = 2.0 Hz, H-7), 5.01 and 5.05 (2 s, $=CH_2$), 5.09 (d, J = 5.0 Hz, CHOAc), 5.20 (s, H-3), 5.23 (d, J = 2.0 Hz, H-6), 6.85–6.93 and 7.14–7.30 (2 m, ArH); MS (FAB) m/z 765 $(M + Na)^+$. The protected precursor had NMR ($CDCl_3$) δ 0.84 (d, J = 6.5 Hz, $CHCH_3$), 1.47, 1.49, and 1.56 (3 s, t-Bu), 2.10 (s, OAc), 3.28 (s, OCH_3), 3.93 (t, J = 6.5 Hz, $PhOCH_2$), 4.01 (d, J = 2.0 Hz, H-7), 4.85 (s, H-3), 4.98 (br s, $=CH_2$), 5.15 (d, J = 5.0 , CHOAc), 5.20 (d, J = 2.0 Hz, H-6), 6.86–6.97 and 7.13–7.31 (2 m, ArH).

C4 11-phenoxyundecyl ether 7g: NMR (CD_3OD) δ 0.85 (d, J = 6.5 Hz, $CHCH_3$), 2.09 (s, OAc), 3.92 and 4.06 (2 m, CH_2O), 3.93 (t, J = 6.0 Hz, $PhOCH_2$), 4.02 (d, J = 2.0 Hz, H-7), 5.00 and 5.04 (2 s, $=CH_2$), 5.11 (d, J = 5.0 Hz, CHOAc), 5.18 (s, H-3), 5.23 (d, J = 2.0 Hz, H-6), 6.86–6.93 and 7.14–7.30 (2 m, ArH); MS (FAB) m/z 806 $(M + Na)^+$, 828 $(M + 2Na)^+$, 850 $(M + 3Na)^+$. Anal. ($C_{42}H_{56}O_{14}\cdot 1.4H_2O$) C, H. The deketalized precursor had NMR ($CDCl_3$) δ 0.84 (d, J = 7.0 Hz $CHCH_3$), 1.24 [br s, $(CH_2)_n$], 1.45, 1.47, and 1.55 (3 s, t-Bu), 2.10 (s, OAc), 2.60 (d, J = 4.5 Hz, C_7-OH), 2.69 (d, J = 5.5 Hz, C_6-OH), 3.64 and 3.83 (2 q, J = 6.5 and 13.0 Hz, CH_2O), 3.94 (t, J = 6.5 Hz, $PhOCH_2$), 4.01 (2 d, J = 2.5 and 4.5 Hz, H-7), 4.87 (s, H-3), 4.97 and 4.99 (2 s, $=CH_2$), 5.10 (d, J = 4.5 Hz, CHOAc), 5.23 (2 d, J = 2.5 and 5.5 Hz, H-6), 6.87–6.96 and 7.11–7.31 (2 m, ArH).

C4 propyl ether 7j: NMR (CD_3OD) δ 0.79–0.95 (m, 2 CH_3), 1.57 (m, $CH_2CH_2CH_3$), 2.11 (s, OAc), 3.85 and 4.03 (2 m, CH_2O), 4.04 (d, J = 2.0 Hz, H-7), 4.99 (s, 1 H), 5.03 (s, 1 H), 5.09 (d, J = 5.0 Hz, CHOAc), 5.19 (s, H-3), 5.23 (d, J = 2.0 Hz, H-6), 7.09–7.37 (m, ArH); MS (neg FAB) m/z 579. The protected precursor had NMR ($CDCl_3$) δ 0.83 (d, J = 7.0 Hz, $CHCH_3$), 0.93 (t, J = 7.0 Hz, CH_2CH_3), 1.40 and 1.46 [2 s, $(CH_3)_2C$], 1.48, 1.51, and 1.58 (3 s, t-Bu), 2.12 (s, OAc), 3.28 (s, CH_3O), 3.64 and 3.85 (2 m, CH_2O), 4.01 (d, J = 2.0 Hz, H-7), 4.84 (s, H-3), 4.95 (br d, $=CH_2$), 5.14 (d, J = 5.0 Hz, CHOAc), 5.18 (m, H-6), 7.11–7.34 (m, ArH). Anal. ($C_{28}H_{36}O_{13}\cdot 2H_2O$) C, H.

C4,6 Bisether 8. C4,6 bisdodecyl ether 8c: NMR (CD_3OD) δ 0.83–0.93 (m, 3 CH_3), 1.24–1.30 [m, $(CH_2)_n$], 2.11 (s, OAc), 3.52, 3.65, 3.87, and 4.03 (4 m, CH_2O), 4.01 (br s, H-7), 4.98 (s, 2 H), 5.04 (s, 1 H), 5.11 (m, 2 H), 7.05–7.33 (m, ArH); MS (neg FAB) m/z 874 $(M - H)^-$; HRMS (neg FAB) calcd for $(C_{49}H_{78}O_{13} - H)$ 873.5364, found 873.5374.

C4,6 bistetradecyl ether 8d: NMR (CD_3OD) δ 0.84–0.96 (m, 3 CH_3), 1.30 [br s, $(CH_2)_n$], 2.12 (s, OAc), 3.56, 3.66, 3.90, and 4.06 (4 m, CH_2O), 4.02 (br s, H-7), 5.01 (s, 2 H), 5.06 (s, 1 H), 5.12 (m, 2 H), 7.10–7.36 (m, ArH); MS (FAB) m/z 953 $(M + Na)^+$. The protected precursor had NMR ($CDCl_3$) δ 0.83 (d, J = 7.0 Hz, $CHCH_3$), 0.89 (t, J = 7.0 Hz, CH_2CH_3), 1.27 [br s, $(CH_2)_n$], 1.40 and 1.42 [2 s, $(CH_3)_2C$], 1.48, 1.50, and 1.60 (3 s, t-Bu), 2.11 (s, OAc), 3.27 (s, CH_3O), 3.52, 3.69 and 3.86 (3 m, CH_2O), 4.11 (d, J = 2.0 Hz, H-7), 4.84 (s, H-3), 4.89 (d, J = 2.0 Hz, H-6), 4.98 (s, $=CH_2$), 5.15 (d, J = 5.0 Hz, CHOAc), 7.10–7.32 (m, ArH).

C4,6 bis(8-phenoxyoctyl) ether 8f: NMR (CD_3OD) δ 0.87 (d, J = 7.0 Hz, $CHCH_3$), 2.10 (s, OAc), 3.92 and 3.97 (2 t, J = 6.5 Hz, $PhOCH_2$), 4.05 (d, J = 2.0 Hz, H-7), 5.00 and 5.06 (2 br s, $=CH_2$), 5.02 (d, J = 2.0 Hz, H-6), 5.12 (d, J = 5.0 Hz, CHOAc), 5.17 (s, H-3), 6.87–6.94 and 7.14–7.32 (2 m, ArH); MS (FAB) m/z 969 $(M + Na)^+$. Anal. ($C_{53}H_{70}O_{15}$) C, H. The protected precursor had NMR ($CDCl_3$) δ 0.83 (d, J = 6.5 Hz, CHCH), 1.39 and 1.41 [2 s, $C(OCH_3)(CH_3)_2$], 1.46, 1.49, and 1.58 (3 s, t-Bu), 2.10 (s, OAc), 3.27 (s, OCH_3), 3.92 and 3.95 (2 t, J = 6.5 Hz, $PhOCH_2$), 4.11 (d, J = 2.0 Hz, H-7), 4.85 (s, H-3), 4.90 (d, J = 2.0 Hz, H-6), 4.97 (br s, $=CH_2$), 5.15 (d, J = 5.0 Hz, CHOAc), 6.86–6.96 and 7.14–7.31 (2 m, ArH).

C4,6 bis(11-phenoxyundecyl) ether 8g: MS (FAB) m/z 1052 $(M + Na)^+$, 1074 $(M + 2Na)^+$, 1096 $(M + 3Na)^+$. The deketalized precursor had NMR ($CDCl_3$) δ 0.84 (d, $CHCH_3$), 1.45 and 1.56 (2 s, t-Bu), 2.10 (s, OAc), 3.90–3.99 (m, H-7 and 2 $PhOCH_2$), 4.74 (br s, H-6), 4.86 (s, H-3), 4.96 and 4.98 (2 s, $=CH_2$), 5.11 (d, CHOAc).

C4,6 bispropyl ether 8j: NMR (CD_3OD) δ 0.82–0.96 (m, 3 CH_3), 1.56 (m, $CH_2CH_2CH_3$), 2.11 (s, OAc), 3.49, 3.64, 3.82, and 4.02 (4 m, CH_2O), 4.03 (d, J = 2.0 Hz, H-7), 4.98 (s, 1 H), 5.02 (s, 1 H), 5.0 (d, J = 2.0 Hz, H-6), 5.08 (d, J = 5.0 Hz, CHOAc), 5.12 (s, H-3), 7.10–7.37 (m, ArH); MS (neg FAB) m/z 621. The protected precursor had NMR ($CDCl_3$) δ 0.80–1.00 (m, 3 CH_3), 1.41 and 1.43 [2 s, $(CH_3)_2C$], 1.48, 1.51, and 1.61 (3 s , t-Bu), 2.12 (s, OAc), 3.27 (s, CH_3O), 3.36, 3.46, and 3.64 (3 m, CH_2O), 4.13 (d, J = 2.0 Hz, H-7), 4.84 (s, H-3), 4.90 (d, J = 2.0 Hz, H-6), 4.96 (br s, $=CH_2$), 5.14 (d, J = 5.0 Hz, CHOAc), 7.12–7.34 (m, ArH). Anal. ($C_{31}H_{42}O_{13}\cdot 1.5H_2O$) C, H.

[1*S*-[1α(*4R,*5S**),3α,4*β*,5α,6α(*2E*,*4R**,*6R**),7*β*]]-1-(4-Hydroxy-5-methyl-3-methylene-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) 7-(1-Methoxy-1-methylethyl ether) 3,4,5-Tris(1,1-dimethylethyl) Ester (9).** Cerium(III) chloride heptahydrate (50 g, 134.2 mmol) was heated with stirring at 145 °C under high vacuum overnight. Freshly distilled THF (420 mL) was added to the cooled anhydrous cerium(III) chloride, the suspension was stirred at room temperature under nitrogen overnight and cooled to −78 °C, and ethylmagnesium chloride (59 mL, 118 mmol; 2 M in THF) was added dropwise. The reaction mixture was then stirred at −78 °C for 45 min, kept at 0 °C for 1 h, and again cooled to −78 °C before adding 1 (25 g, 26.0 mmol). After 5 min, the mixture was warmed to 0 °C and quenched with saturated NH_4Cl. The solid was filtered off and washed with THF. The combined filtrates were evaporated to a small volume and was partitioned between CH_2Cl_2 and brine. The organic extracts were washed with water, dried, and evaporated to a syrup (25.1 g). A small sample was purified by preparative TLC for characterization. Compound **9**: NMR ($CDCl_3$) δ 0.81–0.85 (m, 3 CH_3), 1.00 (d, J = 6.7 Hz, $C{=}CHCH_3$), 1.29 and 1.37 [2 s, $(CH_3)_2C$], 1.39, 1.47, and 1.68 (3 s, 3 t-Bu), 2.41 (d, J = 3.6 Hz, $C_{4'}$ OH), 3.22 (s, OCH_3), 3.97 (s, C_4 OH), 4.14 (t, CHOH), 4.24 (d, J = 1.6 Hz, H-7), 5.02 and 5.14 (2 s, $=CH_2$), 5.05 (s, H-3), 5.77 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.42 (d, J = 1.6 Hz, H-6), 6.90 (m, H_β olefinic), 7.14–7.28 (m, ArH). Two minor byproducts **10** and **11** were also isolated. Compound **10**: NMR ($CDCl_3$) δ 0.84 (d, J = 6.7 Hz, CH_3), 1.48, 1.49, and 1.59 (3 s, 3 t-Bu), 2.52 (d, J = 6.3 Hz, C_6 OH), 2.85 (d, J = 3.1 Hz, $C_{4'}$ OH), 3.26 (s, OCH_3), 3.85 (s, C_4 OH), 4.12 (d, J = 1.8 Hz, H-7), 4.13 (m, CHOH), 4.89 (s, H-3), 4.91 (2 d, J = 1.8 and 3.1 Hz, H-6), 5.06 and 5.16 (2 br

s, $=CH_2$), 7.13–7.30 (m, ArH). Compound 11: NMR ($CDCl_3$) δ 0.80–0.87 and 0.97–1.10 (2 m, 5 CH_3), 1.28 and 1.36 [2 s, $(CH_3)_2C$], 1.37 and 1.68 (2 s, 2 *t*-Bu), 3.22 (s, OCH_3), 3.97 (s, C_4 OH), 4.11 (t, CHOH), 4.28 (d, J = 1.8 Hz, H-7), 4.99 (s, H-3), 5.00 and 5.15 (2 s, $=CH_2$), 5.78 (2 d, J = 0.9 and 15.7 Hz, H_α olefinic), 6.41 (d, J = 1.8 Hz, H-6), 6.91 (2 d , J = 8.1 and 15.7 Hz, H_β olefinic), 7.17–7.32 (m, ArH).

3′-Oxo 4,4′-Diol 12. A solution of crude **9** (23.2 g) in dichloromethane (100 mL) and pyridine (7 mL) was cooled to −78 °C, and ozone was bubbled into the solution. The progress of the reaction was monitored by TLC. After 3 h, excess ozone was quenched with dimethyl sulfide, and the solution was evaporated to a syrup. The crude material was purified by silica gel (1 kg) flash column chromatography with hexanes–ethyl acetate (90:10 to 80:20, v/v containing 0.1% Et_3N) as the eluant. The desired fractions were pooled and evaporated to give **12** (6.85 g, 31% overall yield): NMR ($CDCl_3$) δ 0.71 (d, J = 6.7 Hz, CH(OH)CH**CH$_3$**), 0.80–0.84 (m, 2 CH_3), 0.99 (d, J = 6.7 Hz, C=CCHC**H$_3$**), 1.28 and 1.38 [2 s, $(CH_3)_2C$], 1.37, 1.45, and 1.68 (3 s, 3 *t*-Bu), 3.25 (s, OCH_3), 3.58 (d, J = 4.5 Hz, C_4 OH), 4.08 (s, C_4 OH), 4.19 (m, CHOH), 4.21 (d, J = 1.6 Hz, H-7), 5.04 (s, H-3), 5.75 (2 d, J = 1.1 and 15.7 Hz, H_α olefinic), 6.42 (d, J = 1.6 Hz, H-6), 6.89 (m, H_β olefinic), 7.16–7.30 (m, ArH).

3′,4,4′-Triol 13. A solution of **12** (6.36 g, 7.14 mmol) in ethanol (40 mL) was treated with sodium borohydride (271 mg, 7.13 mmol) at room temperature for 2 h. The mixture was evaporated to a residue and was partitioned between dichloromethane and brine. The organic layer was washed with water, dried, and evaportated to a syrup (6.1 g). The crude material was purified by silica gel (400 g) flash column chromatograpy with hexanes–ethyl acetate (70:30 to 65:35, v/v containing 0.1% Et_3N) as the eluant. The desired fractions were pooled and evaporated to give **13** (4.59 g, 72%): NMR ($CDCl_3$) δ 0.81–0.85 (m, 2 CH_3), 0.90 (d, J = 6.7 Hz, CH(OH)-CH**CH$_3$**), 1.00 (d, J = 6.7 Hz, C=CCHC**H$_3$**), 1.38, 1.44, and 1.68 (3 s, 3 *t*-Bu), 3.23 (s, OCH_3), 3.44 and 3.89 (2 m, 2 CHOH), 4.03 (s, C_4 OH), 4.25 (d, J = 1.5 Hz, H-7), 5.05 (s, H-3), 5.76 (2 d, J = 1.1 and 15.7 Hz, H_α olefinic), 6.41 (d, J = 1.5 Hz, H-6), 6.89 (m, H_β olefinic), 7.15–7.28 (m, ArH).

3′-Propanal 14. Sodium periodate (0.59 g, 2.76 mmol) was added to a solution of **13** (1.22 g, 1.37 mmol) in dioxane–water (60 mL; 5:1, v/v), and the mixture was stirred at room temperature overnight. The solid was filtered off, and the filtrate was partitioned between dichloromethane and brine. The organic layer was dried and evaporated to a residue, which was purified by flash column chromatography with hexanes–ethyl acetate (80:20, v/v containing 0.1% Et_3N) as the eluant. The desired fractions were combined and evaporated to give **14** (0.9 g, 89%): NMR ($CDCl_3$) δ 0.81–0.85 (m, 2 CH_3), 1.00 (d, J = 6.7 Hz, C=CCHC**H$_3$**), 1.38, 1.47, and 1.68 (3 s, 3 *t*-Bu), 3.26 (s, OCH_3), 4.06 (s, C_4 OH), 4.24 (d, J = 1.5 Hz, H-7), 5.05 (s, H-3), 5.76 (d, J = 15.7 Hz, H_α olefinic), 6.43 (d, J = 1.5 Hz, H-6), 6.90 (2 d, J = 8.1 and 15.7 Hz, H_β olefinic), 9.90 (s, CHO).

[1*S*-[1α(4*R,5*S**),3α,4β,5α,6α(2*E*,4*R**,6*R**),7β]]-1-(5-Methyl-3-methylene-4-(*n*-propionyloxy)-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (15).** A solution of **9** (253 mg, 0.285 mmol), *n*-propionic anhydride (73 μL, 0.57 mmol), triethylamine (158 μL, 1.14 mmol), and DMAP (26 mg, 0.214 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The mixture was evaporated to a residue, which was purified by preparative TLC (hexanes–ethyl acetate, 80:20, v/v containing 0.1% Et_3N) to give the protected **15** (195 mg, 73%): NMR ($CDCl_3$) δ 0.80–0.85 (m, 3 CH_3), 1.01 (d, J = 6.6 Hz, C=CCHC**H$_3$**), 1.12 (t, J = 7.6 Hz, $COCH_2CH_3$), 1.29 and 1.37 [2 s, $(CH_3)_2C$], 1.40, 1.46, and 1.69 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.06 (s, C_4 OH), 4.22 (s, H-7), 4.95 and 4.96 (2 s, $=CH_2$), 5.05 (s, H-3), 5.17 (d, J = 5.0 Hz, CHOCO), 5.79 (d, J = 15.7 Hz, H_α olefinic), 6.44 (s, H-6), 6.91 (m, H_β olefinic), 7.16–7.28 (m, ArH). Deprotection with TFA in CH_2Cl_2 at room temperature overnight afforded **15** in 98% yield: NMR (CD_3OD) δ 0.85–0.88 (m, 3 CH_3), 1.02 (d, J = 6.7 Hz, C=CCHC**H$_3$**), 1.16 (t, J = 7.5 Hz, $COCH_2CH_3$), 4.04 (d, J = 1.8 Hz, H-7), 4.96 and 5.02 (2 s, $=CH_2$), 5.09 (d, J = 4.6 Hz, CHOCO), 5.26 (s, H-3), 5.80 (2 d, J = 0.8 and 15.8 Hz, H_α olefinic), 6.31 (d, J = 1.8 Hz, H-6), 6.85 (m, H_β olefinic), 7.12–7.27 (m, ArH); MS (neg FAB) m/z 703 ($M - H$)$^-$; HRMS (neg FAB) calcd for $(C_{36}H_{48}O_{14} - H)$ 703.2966, found 703.2984.

[1*S*-[1α(4*R,5*S**),3α,4β,5α,6α,7β]]-1-[5-Methyl-3-methylene-4-(*n*-propionyloxy)-6-phenylhexyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-Butyrate (16).** A mixture of the protected **15** (135 mg, 0.143 mmol), sodium acetate trihydrate (427 mg, 3.14 mmol), and hydroxylamine hydrochloride (100 mg, 1.44 mmol) in methanol (2.5 mL) was stirred at room temperature overnight. The solid was filtered off and washed with methanol. The combined filtrates were evaporated to a residue and partitioned between dichloromethane and aqueous $NaHCO_3$. The organic layer was washed with water, dried, and evaporated to dryness. The crude product was purified by preparative TLC (hexanes–ethyl acetate, 70:30, v/v containing 0.1% Et_3N) to give the des-C6-acyl intermediate (103 mg, 91%): NMR ($CDCl_3$) δ 0.81 (d, J = 6.7 Hz, CHC**H$_3$**), 1.17 (t, J = 7.6 Hz, CH_2CH_3), 1.39 and 1.47 [2 s, $(CH_3)_2C$], 1.46, 1.50, and 1.60 (3 s, 3 *t*-Bu), 3.27 (s, OCH_3), 3.92 (s, C_4 OH), 4.07 (d, J = 1.9 Hz, H-7), 4.86 (s, H-3), 4.96 and 4.98 (m, H-6 and $=CH_2$), 5.15 (d, J = 4.8 Hz, CHOCO), 7.13–7.29 (m, ArH). C6-*O*-*n*-Butyrylation of the above intermediate with *n*-butyric anhydride in dichloromethane containing triethylamie and DMAP at room temperature for 4 h afforded, after preparative TLC, the protected 6-*O*-*n*-butyryl intermediate of **16** in 85% yield: NMR ($CDCl_3$) δ 0.81 (d, J = 6.6 Hz, CHC**H$_3$**), 0.95 (t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.18 (t, J = 7.5 Hz, CH_2CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.45, 1.46, and 1.67 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.08 (s, C_4 OH), 4.17 (d, J = 1.6 Hz, H-7), 4.95 and 4.96 (2 s, $=CH_2$), 5.01 (s, H-3), 5.16 (d, J = 5.0 Hz, CHOCO), 6.37 (d, J = 1.6 Hz, H-6), 7.15–7.28 (m, ArH). Deprotection of this compound with TFA in CH_2Cl_2 at room temperature overnight gave **16** in 97% yield: NMR (CD_3OD) δ 0.86 (d, J = 6.7 Hz, CHC**H$_3$**), 0.94 (t, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.16 (t, J = 7.6 Hz, CH_2CH_3), 4.02 (d, J = 1.9 Hz, H-7), 4.96 and 5.02 (2 s, $=CH_2$), 5.09 (d, J = 4.5 Hz, CHOCO), 5.25 (s, H-3), 6.29 (d, J = 1.9 Hz, H-6), 7.13–7.27 (m, ArH); MS (neg FAB) m/z 621 ($M - H$)$^-$; HRMS (neg FAB) calcd for $(C_{30}H_{38}O_{14} - H)$ 621.2183, found 621.2155.

[1*S*-[1α(4*R,5*S**),3α,4β,5α,6α,7β]]-1-[4-(*n*-Butyryloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-*n*-Butyrate (17).** A mixture of **10** (200 mg, 0.27 mmol), *n*-butyric anhydride (177 μL, 1.08 mmol), triethylamine (301 μL, 2.17 mmol), and DMAP (50 mg, 0.41 mmol) in dichloromethane (2 mL) was stirred at room temperature overnight. The solution was evaporated to a residue, which was purified by preparative TLC (hexanes–ethyl acetate, 80:20, v/v containing 0.1% Et_3N) to give the protected **17** (210 mg, 88%): NMR ($CDCl_3$) δ 0.81 (d, J = 6.6 Hz, CHC**H$_3$**), 0.91–1.01 (m, 2 CH_2CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.45, 1.46, and 1.67 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.07 (s, C_4 OH), 4.16 (d, J = 1.6 Hz, H-7), 4.96 (br s, $=CH_2$), 5.01 (s, H-3), 5.19 (d, CHOCO), 6.38 (d, J = 1.6 Hz, H-6), 7.15–7.33 (m, ArH). Deprotection of this material with TFA in CH_2Cl_2 at room temperature overnight afforded **17** in 85% yield: NMR (CD_3OD) δ 0.86 (d, J = 6.7 Hz, CHC**H$_3$**), 0.94 and 0.99 (2 t, J = 7.4 Hz, 2 CH_2CH_3), 4.02 (d, J = 1.9 Hz, H-7), 4.97 and 5.02 (2 s, $=CH_2$), 5.09 (d, J = 4.9 Hz, CHOCO), 5.26 (s, H-3), 6.29 (d, J = 1.9 Hz, H-6), 7.13–7.28 (m, ArH); MS (neg FAB) m/z 635 ($M - H$)$^-$; HRMS (neg FAB) calcd for $(C_{31}H_{40}O_{14} - H)$ 635.2340, found 635.2327.

[1*S*-[1α(5*R),3α,4β,5α,6α(2*E*,4*R**,6*R**),7β]]-1-(5-Methyl-3-methylene-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (18).** A mixture of L-694,599 (209 mg, 0.30 mmol), ammonium formate (38 mg, 0.60 mmol), and bis(triphenylphosphine)palladium(II) chloride (21 mg, 0.03 mmol) was heated at 110 °C for 4 h. The reaction mixture was evaporated to a residue, which was purified by reverse-phase HPLC to give **18** in 48% yield (by HPLC): NMR (CD_3OD) δ 0.81–0.87 (m, 3 CH_3), 1.02 (d, J = 6.7 Hz, C=CCHC**H$_3$**), 4.07 (s, H-7), 4.75 and 4.86 (2 s, $=CH_2$), 5.25 (s, H-3), 5.80 (d, J = 15.7 Hz, H_α olefinic), 6.36 (s, H-6), 6.86 (2 d, J = 8.3 and 15.7 Hz, H_β olefinic), 7.10–7.24 (m, ArH); MS (FAB) m/z 655

(M + Na)$^+$; HRMS (neg FAB) calcd for ($C_{33}H_{44}O_{12}$ − H) 631.2754, found 631.2721.

3′,4′-Cyclic Thionocarbonate 19. A mixture of **13** (399 mg, 0.447 mmol) and 1,1′-thiocarbonyldiimidazole (167 mg, 0.938 mmol) in toluene (2.5 mL) was stirred at room temperature overnight. The solid was filtered off and washed with toluene. The combined filtrates were evaporated to a residue, which was purified by preparative TLC (hexanes−ethyl acetate, 80:20, v/v containing 0.1% Et_3N) to give **19** (380 mg, 91%): NMR ($CDCl_3$) δ 0.81−0.85 (m, 2 CH_3), 1.01 (d, J = 6.7 Hz, C=CCHC**H**$_3$), 1.06 [d, J = 6.5 Hz, CH(OCS)CHC**H**$_3$], 1.37, 1.40, and 1.68 (3 s, 3 t-Bu), 3.24 (s, OCH_3), 3.98 (s, C_4 OH), 4.20 (d, J = 1.6 Hz, H-7), 4.73 and 5.26 [2 m, 2 C**H**(OCS)], 5.03 (s, H-3), 5.77 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.41 (d, J = 1.6 Hz, H-6), 6.90 (m, H_β olefinic), 7.19−7.31 (m, ArH).

3′4′-Ene Derivative 20. A solution of **19** (410 mg, 0.439 mmol) in trimethyl phosphite (5 mL) was heated under reflux for 28 h, cooled, and poured into 5 N NaOH and ice−water. The product was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and evaporated to dryness. Preparative TLC (hexanes−ethyl acetate, 70:30, v/v containing 0.1% Et_3N) gave the deketalized product (182 mg) and the deketalized starting material (65 mg). The deketalized product (182 mg) in dichloromethane (3 mL) was treated with excess 2-methoxypropene and pyridinium p-toluenesulfonate (2.5 mg) to give **20** (194 mg, 51%): NMR ($CDCl_3$) δ 0.81−0.85 (m, 2 CH_3), 0.97 and 1.01 (2 d, J = 6.6 and 6.7 Hz, 2 C=CCHC**H**$_3$), 1.42, 1.46, and 1.68 (3 s, 3 t-Bu), 3.19 (s, OCH_3), 4.03 (s, C_4 OH), 4.11 (d, J = 1.6 Hz, H-7), 5.01 (s, H-3), 5.19 and 5.30 (2 m, $C_{3'}$=$C_{4'}$H), 5.80 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.42 (d, J = 1.6 Hz, H-6), 6.91 (m, H_β olefinic), 7.13−7.29 (m, ArH).

Intermediate 21. A mixture of **20** (194 mg, 0.226 mmol), sodium acetate trihydrate (675 mg, 4.96 mmol), and hydroxylamine hydrochloride (157 mg, 2.26 mmol) in methanol (3 mL) was stirred at room temperature overnight. The reaction mixture was filtered and washed with methanol. The combined filtrates were evaporated to dryness, and the residue was partitioned between dichloromethane and water. The organic layer was washed with water, dried, and evaporated to dryness. The crude material was purified by preparative TLC (hexanes−ethyl acetate, 70:30, v/v containing 0.1% Et_3N) to give the des-C6-O-acyl intermediate (146 mg, 93%): NMR ($CDCl_3$) δ 0.98 (d, J = 6.6 Hz, CH_3), 1.46, 1.52, and 1.59 (3 s, 3 t-Bu), 3.25 (s, OCH_3), 3.86 (s, C_4 OH), 3.95 (br s, H-7), 4.82 (s, H-3), 4.93 and 4.96 (2 br s, C_6 OH and H-6), 5.13−5.39 (m, $C_{3'}$=$C_{4'}$H), 7.14−7.31 (m, ArH). C6-O-n-Butyrylation of this intermediate with n-butyric anhydride in CH_2Cl_2 containing Et_3N and DMAP at room temperature for 4 h afforded **21** in 87% yield: NMR ($CDCl_3$) δ 0.93−0.98 (m, 2 CH_3), 1.29 and 1.33 [2 s, $(CH_3)_2$C], 1.45, 1.47, and 1.66 (3 s, 3 t-Bu), 3.19 (s, OCH_3), 4.04 (s, C_4 OH), 4.05 (d, J = 1.6 Hz, H-7), 4.96 (s, H-3), 5.17 and 5.28 (2 m, $C_{3'}$=$C_{4'}$H), 6.36 (d, J = 1.6 Hz, H-6), 7.12−7.28 (m, ArH).

[1*S*-[1α(5*R),3α,4β,5α,6α,7β]]-1-(5-Methyl-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-*n*-Butyrate (22).** A solution of **21** (102 mg) in methanol (2 mL) was hydrogenated over 10% Pd−C (20 mg) at 40 psi for 1 h. The catalyst was filtered off and washed with methanol. The combined filtrates were evaporated to a residue, which was treated with 2 N HCl in THF to give the deketalized intermediate in near quantitative yield: NMR ($CDCl_3$) δ 0.82 (d, J = 6.6 Hz, CHC**H**$_3$), 0.96 (t, J = 7.4 Hz, CH_2C**H**$_3$), 1.45, 1.49, and 1.58 (3 s, 3 t-Bu), 2.82 (d, C_7 OH), 3.99 (br s, H-7), 4.05 (s, C_4 OH), 5.00 (s, H-3), 5.91 (d, J = 2.1 Hz, H-6), 7.12−7.28 (m, ArH). Deprotection of this intermediate with TFA in CH_2Cl_2 at room temperature overnight afforded **22** in 87% yield: NMR (CD_3OD) δ 0.85 (d, J = 6.6 Hz, CHC**H**$_3$), 0.93 (t, J = 7.3 Hz, CH_2C**H**$_3$), 4.04 (d, J = 1.5 Hz, H-7), 5.23 (s, H-3), 6.28 (d, J = 1.5 Hz, H-6), 7.12−7.28 (m, ArH); MS (neg FAB) m/z 537 (M − H)$^-$; HRMS (neg FAB) calcd for ($C_{26}H_{34}O_{12}$ − H) 537.1972, found 537.1984.

Reactions of 14 with Phosphorus Ylides 23: Compound 23a. Potassium bis(trimethylsilyl)amide (0.42 mL, 0.315 mmol; 0.75 M in toluene) was added to a stirred suspension of benzyltriphenylphosphonium chloride (131 mg, 0.337 mmol) in dry THF (2 mL) under nitrogen at 0 °C. An orange-red color formed immediately. After 5 min, a solution of **14** (167 mg, 0.225 mmol) in dry THF (2 mL) was added under nitrogen. The orange-red color gradually dissipated and became yellow after 30 min at room temperature. The mixture was partitioned between dichloromethane and cold water. The organic layer was wahed with brine and evaporated to a residue, which was purified by preparative TLC (hexanes−ethyl acetate, 70:30, v/v containing 0.1% Et_3N) to give **23a** (144 mg, 78%): NMR ($CDCl_3$) δ 0.81−0.85 (m, 2 CH_3), 0.99 (d, J = 6.7 Hz, C=CCHC**H**$_3$), 1.39, 1.48, and 1.69 (3 s, 3 t-Bu), 3.25 (s, OCH_3), 4.02 (s, C_4 OH), 4.29 (d, J = 1.6 Hz, H-7), 5.07 (s, H-3), 5.73 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.27−6.47 (m, $C_{3'}$=$C_{4'}$H), 6.44 (d, J = 1.6 Hz, H-6), 6.89 (m, H_β olefinic), 7.16−7.36 (m, ArH). The following signals were assigned to the *cis* isomer (16%): δ 3.20 (s, OCH_3), 4.25 (d, H-7), 5.06 (s, H-3).

Compound 23b. Potassium bis(trimethylsilyl)amide (1.6 mL, 1.2 mmol; 0.75 M in toluene) was added to a stirred suspension of (3-phenylpropyl)triphenylphosphonium bromide (567 mg, 1.23 mmol) in dry THF (2 mL) under nitrogen at −78 °C. An orange-red color formed immediately. After 5 min, a solution of **14** (183 mg, 0.246 mmol) in dry THF (2 mL) was added at −78 °C under nitrogen. The temperature was allowed to warm to 0 °C, and the orange-red color gradually dissipated and became pale yellow. After 30 min, the mixture was worked up and purified as usual to give **23b** (158 mg, 76%): NMR ($CDCl_3$) δ 0.81−0.86 (m, 2 CH_3), 0.99 (d, J = 6.6 Hz, C=CCHC**H**$_3$), 1.38, 1.46, and 1.68 (3 s, 3 t-Bu), 3.22 (s, OCH_3), 4.02 (s, C_4 OH), 4.22 (d, J = 1.6 Hz, H-7), 5.05 (s, H-3), 5.38−5.49 (m, $C_{3'}$=$C_{4'}$H), 5.77 (2 d, J = 1.0 and 15.7 Hz, H_α olefinic), 6.43 (d, J = 1.6 Hz, H-6), 6.89 (m, H_β olefinic), 7.15−7.29 (m, ArH). The following signals were assigned to the *cis* isomer (19%): δ 4.03 (s, C_4 OH), 4.18 (d, J = 1.6 Hz, H-7), 5.00 (s, H-3), 6.35 (d, J = 1.6 Hz, H-6).

Compound 23c. Potassium bis(trimethylsilyl)amide (0.42 mL, 0.315 mmol; 0.75 M in toluene) was added to a stirred suspension of (1-naphthylmethyl)triphenylphosphonium chloride (147 mg, 0.334 mmol) in dry THF (2 mL) under nitrogen at 0 °C. An orange-red color formed immediately. After 5 min, a solution of **14** (165 mg, 0.223 mmol) in dry THF (2 mL) was added under nitrogen. The orange-red color gradually dissipated and became yellow after stirring at room temperature for 3 days. The mixture was worked up and purified as usual to give **23c** (78 mg, 41%): NMR ($CDCl_3$) δ 0.79−0.85 (m, 2 CH_3), 0.98 (d, J = 6.7 Hz, C=CCHC**H**$_3$), 1.40, 1.49, and 1.70 (3 s, 3 t-Bu), 3.28 (s, OCH_3), 4.04 (s, C_4 OH), 4.35 (d, J = 1.2 Hz, H-7), 5.10 (s, H-3), 5.73 (d, J = 15.7 Hz, H_α olefinic), 6.28−6.35 (m, $C_{3'}$=$C_{4'}$H), 6.47 (d, J = 0.9 Hz, H-6), 6.89 (m, H_β olefinic), 7.17−8.12 (m, ArH). The following signals were assigned to the *cis* isomer (21%): δ 3.09 (s, OCH_3), 4.31 (d, H-7), 6.07−6.14 (m, $C_{3'}$=$C_{4'}$H), 6.39 (d, H-6), 6.87 (m, H_β olefinic).

[1*S*-[1α,3α,4β,5α,6α(4*S,6*R**),7β]] 1-(4-Phenylbutyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyloctanoate) (24a).** Compound **23a** was hydrogenated over 10% Pd/C and deprotected with TFA in CH_2Cl_2 in the normal manner to give **24a**: NMR (CD_3OD) δ 0.85−0.89 (m, 3 CH_3), 4.02 (d, J = 1.7 Hz, H-7), 5.23 (s, H-3), 6.25 (br s, H-6), 7.10−7.24 (m, ArH); MS (neg FAB) m/z 579 (M − H)$^-$; HRMS (neg FAB) calcd for ($C_{29}H_{40}O_{12}$ − H) 579.2441, found 579.2445.

[1*S*-[1α,3α,4β,5α,6α(4*S,6*R**),7β]]-1-(6-Phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyloctanoate) (24b).** A solution **23b** (54 mg) in methanol (2 mL) was hydrogenated over 10% Pd/C (16 mg) at room temperature for 1 h. The solid was filtered off and washed with methanol. The combined filtrates were evaporated to give the protected **24b** (43 mg, 79%): NMR ($CDCl_3$) δ 0.81−0.87 (m, 3 CH_3), 1.43, 1.46, and 1.66 (3 s, 3 t-Bu), 3.22 (s, OCH_3), 4.01 (s, C_4 OH), 4.19 (d, J = 1.5 Hz, H-7), 5.00 (s, H-3), 6.34 (d, J = 1.5 Hz, H-6), 7.12−7.30 (m, ArH). Deprotection with TFA in CH_2Cl_2 at room temperature overnight afforded **24b** in 97%: NMR (CD_3OD) δ 0.85−0.89 (m, 3 CH_3), 4.04 (d, J = 1.7 Hz, H-7), 5.23 (s, H-3), 6.24 (d, H-6),

7.10–7.25 (m, ArH); MS (neg FAB) m/z 607 $(M - H)^-$; HRMS (neg FAB) calcd for $(C_{31}H_{44}O_{12} - H)$ 607.2754, found 607.2775.

Intermediates 25: Compound 25a. A mixture of **23a** (135 mg, 0.165 mmol), sodium acetate trihydrate (494 mg, 3.63 mmol), and hydroxylamine hydrochloride (115 mg, 1.65 mmol) in methanol (2 mL) was stirred at room temperature overnight. The solid was filtered off and washed with methanol. The combined filtrates were evaporated to dryness, and the residue was partitioned between dichloromethane and water. The organic layer was dried and evaporated to a residue, which was purified by preparative TLC (hexanes–ethyl acetate, 70:30, v/v containing 0.1% Et_3N) to give the 6-OH intermediate (88 mg, 80%): NMR ($CDCl_3$) δ 1.47, 1.48, and 1.60 (3 s, 3 *t*-Bu), 2.32 (d, J = 5.5 Hz, C_6 OH), 3.30 (s, OCH_3), 3.87 (s, C_4 OH), 4.13 (d, J = 1.8 Hz, H-7), 4.88 (s, H-3), 4.97 (d, J = 1.8 Hz, H-6), 6.27–6.46 (m, $C_{3'}$=$C_{4'}$H), 7.16–7.37 (m, ArH). The following signals were assigned to the *cis* isomer (16%): δ 3.23 (s, OCH_3), 3.86 (s, C_4 OH), 4.07 (d, J = 1.9 Hz, H-7), 4.86 (s, H-3). C_6-*O*-*n*-Butyrylation of the above intermediate with *n*-butyric anhydride in CH_2Cl_2 containing Et_3N and DMAP at room temperature for 4 h afforded **25a** in 93% yield: NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, CH_2CH_3), 1.45, 1.47, and 1.67 (3 s, 3 *t*-Bu), 3.25 (s, OCH_3), 4.04 (s, C_4 OH), 4.25 (d, J = 1.5 Hz, H-7), 5.02 (s, H-3), 6.27–6.47 (m, $C_{3'}$=$C_{4'}$H), 6.37 (d, J = 1.5 Hz, H-6), 7.17–7.36 (m, ArH). The following signals were assigned to the *cis* isomer (16%): δ 0.93 (t, J = 7.4 Hz, CH_2CH_3), 3.19 (s, OCH_3), 5.01 (s, H-3).

Compound 25b. Compound **25b** was prepared similarly from **23b** and had NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, CH_2CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.44, 1.45, and 1.66 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.03 (s, C_4 OH), 4.17 (d, J = 1.6 Hz, H-7), 5.00 (s, H-3), 5.38–5.48 (m, $C_{3'}$=$C_{4'}$H), 6.36 (d, J = 1.6 Hz, H-6), 7.15–7.29 (m, ArH).

Compound 25c. Compound **25c** was prepared similarly from **23c** and had NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, CH_3), 1.45, 1.48, and 1.68 (3 s, 3 *t*-Bu), 3.28 (s, OCH_3), 4.30 (d, J = 1.6 Hz, H-7), 5.05 (s, H-3), 6.28–6.35 (m, $C_{3'}$=$C_{4'}$H), 6.40 (d, J = 1.6 Hz, H-6), 7.17–8.13 (m, ArH). The following signals were assigned to the *cis* isomer (21%): δ 0.90 (t, J = 7.4 Hz, CH_3), 3.10 (s, OCH_3), 4.97 (s, H-3), 6.04–6.12 (m, $C_{3'}$=$C_{4'}$H).

[1*S*-[1α,3α,4β,5α,6α,7β]]-1-(4-Phenylbutyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-*n*-Butanoate (26a). A solution of **25a** (90 mg, 0.122 mmol) in methanol (2 mL) was hydrogenated over 10% Pd/C (18 mg) at room temperature for 2 h. The solid was filtered off and washed with methanol. The combined filtrates were evaporated to give the protected **26a** (86 mg, 95%): NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, CH_3), 1.29 and 1.36 [2 s, $(CH_3)_2C$], 1.43, 1.46, and 1.66 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.02 (s, C_4 OH), 4.19 (br s, H-7), 5.01 (s, H-3), 6.36 (br s, H-6), 7.13–7.28 (m, ArH). Deprotection of this intermediate with TFA in CH_2Cl_2 at room temperature overnight afforded **26a** in 90% yield: NMR (CD_3OD) δ 0.94 (t, J = 7.4 Hz, CH_3), 4.03 (d, J = 1.9 Hz, H-7), 5.24 (s, H-3), 6.27 (d, J = 1.9 Hz, H-6), 7.09–7.29 (m, ArH); MS (neg FAB) m/z 495 $(M - H)^-$; HRMS (neg FAB) calcd for $(C_{23}H_{28}O_{12} - H)$ 495.1502, found 495.1520.

[1*S*-[1α,3α,4β,5α,6α,7β]]-1-(6-Phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-*n*-Butanoate (26b). A solution of **25b** (54 mg) in methanol (1 mL) was hydrogenated over 10% Pd/C (16 mg) at room temperature for 2 h. The catalyst was filtered off and washed with methanol. The combined filtrates were evaporated to a residue that was partially deketalized as judged by TLC. The products were dissolved in THF (1 mL) and treated with 2 N HCl (2 drops). After 1 h, the solution was partitioned between dichloromethane and aqueous $NaHCO_3$. The organic layer was washed with water, dried, and evaporated to give the deketalized intermediate (46 mg, 96%): NMR ($CDCl_3$) δ 0.96 (t, J = 7.5 Hz, CH_3), 1.45, 1.48, and 1.58 (3 s, 3 *t*-Bu), 2.84 (br s, C_7 OH), 3.99 (br s, H-7), 4.05 (s, C_4 OH), 5.00 (s, H-3), 5.91 (d, J = 1.5 Hz, H-6), 7.14–7.28 (m, ArH). Deprotection of this intermediate with TFA in CH_2Cl_2 at room temperature overnight afforded **26b** in 99% yield: NMR (CD_3OD) δ 0.93 (t, J = 7.4 Hz, CH_3), 4.04 (d, J = 1.8 Hz, H-7), 5.23 (s, H-3), 6.27 (d, J = 1.8 Hz, H-6), 7.11–7.26 (m, ArH); MS (neg FAB) m/z 523 $(M - H)^-$; HRMS (neg FAB) calcd for $(C_{25}H_{32}O_{12} - H)$ 523.1815, found 523.1823.

[1*S*-[1α,3α,4β,5α,6α,7β]]-1-[4-(1-Naphthyl)butyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-*n*-Butanoate (26c). A solution of **25c** (55 mg) in methanol (2 mL) was hydrogenated over 10% Pd/C (11 mg) at room temperature for 1 h. The solid was filtered off and washed with methanol. The combined filtrates were evaporated to give the protected **26c** (55 mg, near quantitative yield): NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, CH_3), 1.30 and 1.37 [2 s, $(CH_3)_2$], 1.44, 1.47, and 1.67 (3 s, 3 *t*-Bu), 3.22 (s, OCH_3), 4.21 (d, J = 1.5 Hz, H-7), 5.03 (s, H-3), 6.38 (d, J = 1.5 Hz, H-6), 7.32–8.05 (m, ArH). Deprotection of this intermediate with TFA in CH_2Cl_2 at room temperature overnight afforded **26c** in 99% yield: NMR (CD_3OD) δ 0.94 (t, J = 7.4 Hz, CH_3), 4.06 (d, J = 1.9 Hz, H-7), 5.25 (s, H-3), 6.28 (d, J = 1.9 Hz, H-6), 7.36–8.10 (m, ArH); MS (neg FAB) m/z 545 $(M - H)^-$; HRMS (neg FAB) calcd for $(C_{27}H_{30}O_{12} - H)$ 545.1659, found 545.1651.

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References

(1) Poulter, C. D.; Rilling, H. C. Conversion of farnesyl pyrophosphate to squalene. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, Chapter 8, pp 414–441.
(2) Agnew, W. S. Squalene synthetase. In *Methods Enzymol.* **1985**, *110*, 359–373.
(3) Poulter, C. D. Biosynthesis of non-head-to-tail terpenes. Formation of 1′-1 and 1′-3 linkages. *Acc. Chem. Res.* **1990**, *23*, 70–77.
(4) Ortiz de Montellano, P. R.; Wei, J. S.; Castillo, R.; Hsu, C. K.; Boparai, A. Inhibition of squalene synthetase by farnesyl pyrophosphate analogues. *J. Med. Chem.* **1977**, *20*, 243–249.
(5) Biller, S. A.; Sofia, M. J.; DeLange, B.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Ciosek, C. P., Jr. The first potent inhibitor of squalene synthase: A profound contribution of an ether oxygen to inhibitor-enzyme interaction. *J. Am. Chem. Soc.* **1991**, *113*, 8522–8524.
(6) Biller, S. A.; Sofia, M. J.; Abt, J. W.; DeLange, B.; Dickson, J. K., Jr.; Forster, C.; Gordon, E. M.; Harrity, T.; Magnin, D. R.; Marretta, J.; Rich, L. C.; Ciosek, C. P., Jr. Potent, rationally designed inhibitors of squalene synthase. *Am. Chem. Soc. Symp.* **1992**, *497*, 65–80.
(7) Corey, E. J.; Volante R. P. Application of unreactive analogs of terpenoid pyrophosphates to studies of multistep biosynthesis. Demonstration that "Presqualene Pyrophosphate" is an esential intermediate on the path to squalene. *J. Am. Chem. Soc.* **1976**, *98*, 1291–1293.
(8) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. Squalene synthetase. Inhibition by ammonium analogues of carbocationic intermediates in the conversion of presqualene diphosphate to squalene. *J. Am. Chem. Soc.* **1989**, *111*, 3734–3739.
(9) Oehlschlager, A. C.; Singh, S. M.; Sharma, S. Squalene synthetase inhibitors: Synthesis of sulfonium ion mimics of the carbocationic intermediates. *J. Org. Chem.* **1991**, *56*, 3856–3861.
(10) Ortiz de Montellano, P. R.; Castillo, R. Prenyl substituted cyclobutanones as squalene synthetase inhibitors. *Tetrahedron Lett.* **1976**, 4115–4118.
(11) Bertolino, A.; Altman, L. J.; Vasak, J.; Rilling, H. C. Polyisoprenoid amphiphilic compounds as inhibitors of squalene synthesis and other microsomal enzymes. *Biochim. Biophys. Acta* **1978**, *530*, 17–23.
(12) Prashad, M.; Kathawala, F. G.; Scallen, T. *N*-(Arylalkyl)farnesylamines: New potent squalene synthetase inhibitors. *J. Med. Chem.* **1993**, *36*, 1501–1504.
(13) Amin, D.; Cornell, S. A.; Gustafson, S. K.; Needle, S. J.; Ullrich, J. W.; Bilder, G. E.; Perrone, M. H. Bisphosphonates used for the treatment of bone disorders inhibit squalene synthase and cholesterol biosynthesis. *J. Lipid Res.* **1992**, 1657–1663.
(14) Ciosek, C. P., Jr.; Magnin, D. R.; Harrity, T. W.; Logan, J. V. H.; Dickson, J. K., Jr.; Gordon, E. M.; Hamilton, K. A.; Jolibois, K. G.; Kunselman, L. K.; Lawrence, R. M.; Mookhtiar, K. A.; Rich, L. C.; Slusarchyk, D. A.; Sulsky, R. B.; Biller, S. A. Lipophilic 1,1-bisphosphonates are potent squalene synthase

inhibitors and orally active cholesterol lowering agents in vivo. *J. Biol. Chem.* **1993**, 24832–24837.
(15) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Omstead, M. N.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. Zaragozic acids: A family of fungal metabolites that are picomolar competitive inhibitors of squalene synthase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 80–84.
(16) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. The zaragozic acids: Structure elucidation of a new class of squalene synthase inhibitors. *Tetrahedron Lett.* **1993**, *34*, 399–402.
(17) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. The isolation and structure elucidation of zaragozic acid C, a novel potent squalene synthase inhibitor. *Tetrahedron* **1992**, *48*, 10221–10226.
(18) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. Zaragozic acid A, a potent inhibitor of squalene synthase: Initial chemistry and absolute stereochemistry. *J. Org. Chem.* **1992**, *57*, 7151–7158.
(19) Byrne, K. M.; Arison, B. H.; Nallin-Omstead, M.; Kaplan, L. Biosynthesis of the zaragozic acids. 1. Zaragozic acid A. *J. Org. Chem.* **1993**, *58*, 1019–1024.
(20) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tair, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. The squalestatins, novel inhibitors of squalene synthase produced by a species of *Phoma*. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activity. *J. Antibiot.* **1992**, *45*, 639–647.
(21) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. The squalestatins, novel inhibitors of squalene synthase produced by a species of *Phoma*. II. Structure elucidation. *J. Antibiot.* **1992**, *45*, 648–658.
(22) Jones, C. A.; Sidebottom, P. J.; Cannell, R. J. P.; Noble, D.; Rudd, B. A. M. The squalestatins, novel inhibitors of squalene synthase produced by a species of *Phoma*. III. Biosynthesis. *J. Antibiot.* **1992**, *45*, 1492–1498.
(23) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. Squalestatin 1, a potent inhibitor of squalene synthase, which lowers serum cholesterol in vivo. *J. Biol. Chem.* **1992**, *267*, 11705–11708.
(24) Lester, M. G.; Giblin, G. M. P.; Inglis, G. G. A.; Procopiou, P. A.; Ross, B. C.; Watson, N. S. Structurally simplified squalestatins: A convenient route to a 6,7-unsubstituted derivative. *Tetrahedron Lett.* **1993**, *34*, 4357–4360.
(25) Watson, N. S.; Bell, R.; Chan, C.; Cox, B.; Hutson, J. L.; Keeling, S. E.; Kirk, B. E.; Procopiou, P. A.; Steeples, I. P.; Widdowson, J. The squalestatins: Potent inhibitors of squalene synthase. The role of the tricarboxylic acid moiety. *BioMed. Chem. Lett.* **1993**, *3*, 2541–2546.
(26) Girotra, N. N.; Reamer, R. A.; Ponpipom, M. M. Rearrangement of zaragozic acid A deriviatives. *Tetrahedron Lett.* **1993**, *34*, 4293–4296; 206th ACS National Meeting in Chicago, August 22–27, 1993, Orgn-132.
(27) Kuo, C. H.; Plevyak, S. P.; Biftu, T.; Parsons, W. H.; Berger, G. D. The synthesis of C3-methyl, C3-decarboxy-zaragozic acid A—a potent squalene synthase inhibitor. *Tetrahedron Lett.* **1993**, *43*, 6863–6866.
(28) Chiang, Y.-C. P.; Biftu, T.; Doss, G. A.; Plevyak, S. P.; Marquis, R. W.; Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Berger, G. D. Diesters of zaragozic acid A: Synthesis and biological activity. *BioMed. Chem. Lett.* **1993**, *3*, 2029–2034.
(29) Biftu, T.; Acton, J. J.; Berger, G. D.; Bergstrom, J. D.; Dufresne, C.; Kurtz, M. M.; Marquis, R. W.; Parsons, W. H.; Rew, D. R.; Wilson, K. E. Selective protection and relative importance of the carboxylic acid groups of zaragozic acid A for squalene synthase inhibition. *J. Med. Chem.* In press.
(30) Procopiou, P. A.; Bailey, E. J.; Hutson, J. L.; Kirk, B. E.; Sharrattt, P. J.; Spooner, S. J.; Watson, N. S. The squalestatins: Novel inhibitors of squalene synthase. The optimal C1 chain-length requirements. *BioMed. Chem. Lett.* **1993**, *3*, 2527–2532.
(31) Giblin, G. M. P.; Bell, R.; Hancock, A. P.; Harley, C. D.; Inglis, G. G. A.; Payne, J. J.; Procopiou, P. A.; Shingler, A. H.; Smith, C.; Spooner, S. J. Semi-synthetic squalestatins: Squalene synthase inhibition and antifungal activity. The SAR of C6 and C7 modifications. *BioMed. Chem. Lett.* **1993**, *3*, 2605–2610.
(32) Burk, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. Chemoselective removal and replacement of the C-4′ and C-6′ acyl esters of zaragozic acid A. *Tetrahedron Lett.* **1993**, *34*, 975–978.
(33) Mathias, L. J. Esterification and alkylation reactions employing isourias. *Synthesis* **1979**, 561–576.
(34) Panfil, I.; Maciejewski, S.; Belzecki, C.; Chmielewski, M. Synthesis of enantiomerically pure 2,3-disubstituted isoxazolidin-5-ones. *Tetrahedron Lett.* **1989**, *30*, 1527–1528.
(35) Marquis, R. W.; Plevyak, S. P.; Berger, G. D.; Parsons, W. H. Degradation of the C1 side chain of zaragozic acid A. *Tetrahedron Lett.* **1994**, *35*, 2451–2454.
(36) Tipson, R. S.; Cohen, A. Action of zinc dust and sodium iodide in *N,N*-dimethylformamide on contiguous, secondary sulfonyloxy groups: A simple method for introducing nonterminal unsaturation. *Carbohydr. Res.* **1965**, *1*, 338–340.
(37) Maher, V. M. G.; Thompson, G. R. HMG-CoA reductase inhibitors as lipid-lowering agents: Five years experience with lovastatin and an appraisal of simvastatin and pravastatin. *Q. J. Med.* **1990**, *74*, 165–175.
(38) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957–3961.
(39) Dufresne, C.; et al. Unpublished results.
(40) Rousseeuw, P. J. Least Median of Squares Regression. *J. Am. Stat. Assoc.* **1984**, *79*, 871–880.
(41) Draper, N. R.; Smith, H. *Applied Regression Analysis*; Wiley: New York, 1981.
(42) Bartizal, K.; Abruzzo, G.; Trainor, C.; Krupa, D.; Nollstadt, K.; Schmatz, D.; Schwartz, R.; Hammond, M.; Balkovec, J.; Van-Middlesworth, F. In vitro antifungal activities and in vivo efficacies of 1,3-β-D-glucan synthesis inhibitors L-671,329, L-646,991, tetrahydroechinocandin B, and L-687,781, a papulacandin. *Antimicrob. Agents Chemother.* **1992**, *36*, 1648–1657.