The Squalestatins: Decarboxy and 4-Deoxy Analogues as Potent Squalene Synthase Inhibitors[1]

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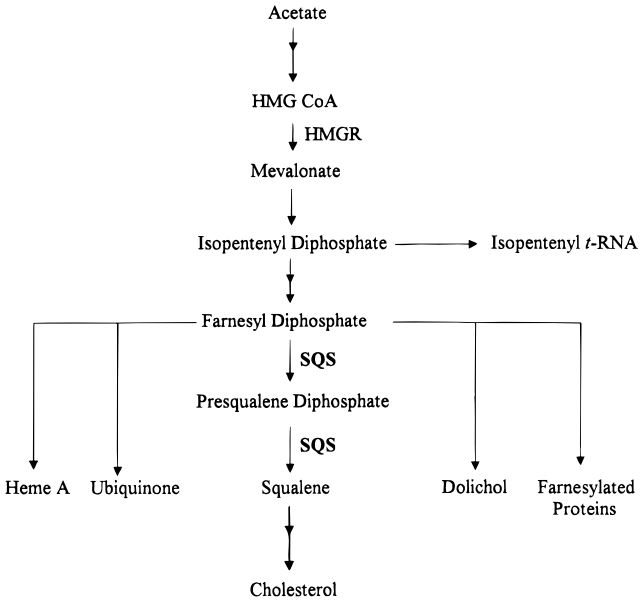
Squalestatins without either the hydroxy group at C-4 or the carboxylic acid at C-3 or C-4 were prepared and evaluated for their ability to inhibit rat liver microsomal squalene synthase (SQS) *in vitro*. These modifications were well tolerated for compounds with the 4,6-dimethyloctenoate ester at C-6 (S1 series). However in analogues without the C-6 ester (H1 series), removal of the C-4 hydroxy group gave compounds with reduced potency, whereas decarboxylation at C-3 resulted in a dramatic loss of SQS inhibitory activity. In comparison with S1 **1**, C-4 deoxyS1 **3** and C-3 decarboxyS1 **10** have shorter *in vivo* durations of action on the inhibition of hepatic cholesterol biosynthesis in rats. C-4 deoxyS1 **3** retains good serum cholesterol-lowering ability in marmosets, while C-3 decarboxyS1 **10** showed only a marginal effect even at high dose.

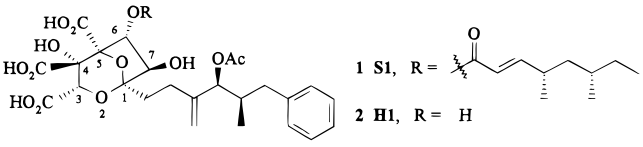
Atherosclerosis is a complex and progressive, multifactorial vascular disease[2] that leads to narrowing and occulsion of arterial vessels. Its clinical manifestations include angina, hemorrhage, thrombosis, and cerebral and myocardial infarction. Hypercholesterolemia and hyperlipoproteinemia are major risk factors[3,4] in the progression of the disease, and a direct correlation between low-density lipoprotein−cholesterol (LDL-C) and the incidence of coronary heart disease has been demonstrated.[5] Over 70% of cholesterol in the body is derived from *de novo* cholesterol biosynthesis, inhibition of which is currently the most effective clinical means of reducing plasma LDL-C levels.[6] 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) inhibitors[7] are currently the most effective therapeutic agents for the control of hypercholesterolemia. Although no major toxic effects are associated with this class of agents, mevalonate, the product of HMGR catalysis, is a common precursor to all isoprenoids such as dolichol and ubiquinone (Scheme 1). Squalene synthase (SQS) (farnesyl-diphosphate:farnesyl-diphosphate farnesyltransferase, EC 2.5.1.21), an enzyme that catalyzes the head to head condensation of farnesyl diphosphate (FPP) to presqualene diphosphate (PSPP) and its subsequent rearrangement to squalene, is the first enzyme committed to sterol biosynthesis.[8] Inhibitors of SQS are therefore attractive in the regulation of steroidal genesis as nonsterol pathways should be minimally affected.

Recently we reported the isolation[9] and structural elucidation[10] of the squalestatins, a novel class of highly potent SQS inhibitors; squalestatin (S1, **1**)[11,12] possesses an IC_{50} value of 12 nM against the rat enzyme and lowers serum cholesterol levels by up to 75% when administered 100 mg/kg/day for 7 days po to marmosets[13] and up to 86% at 1 mg/kg/day iv.[14] We have also reported on the biological activities of H1 (**2**), which has

Scheme 1



an IC_{50} value of 26 nM against rat SQS and lowers serum cholesterol level by 56% in marmosets when adminstered iv for 7 days at 1 mg/kg/day.[14] As part of



our medicinal chemistry program to identify the requisite structural features for biological activity, we have reported on modifications to both the C-1 side chain[14,15] and the substituents at C-6 and C-7[16] and the role of the 2,8-dioxabicyclo[3.2.1]octane moiety.[17] The group at Merck have also reported on modifications to C-1 and C-6 side chains.[18] In our recent communication[19] describing a series of methyl esters of both S1 (**1**) and H1 (**2**), we reported that the C-5 carboxylic acid is essential

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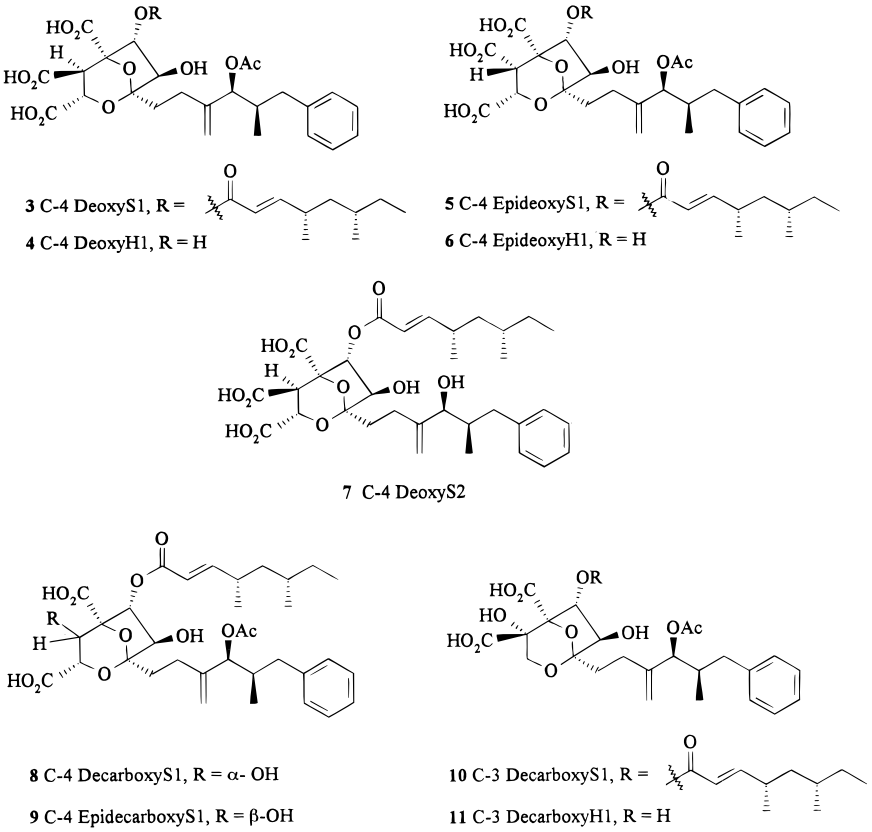
Chart 1



for SQS inhibitory activity and that, in the S1 series, carboxylic acid groups are not required at C-3 or C-4 for potent SQS inhibitory activity to be retained. In contrast C-3 and C-4 monomethyl esters of H1 show reduced enzyme inhibitory activity compared with that for the parent tricarboxylic acid H1 (**2**). Moreover C-3 hydroxymethyl analogues in the S1 series have been shown to retain potent SQS inhibitory activities, whereas the corresponding C-3 hydroxymethylH1 analogue possesses reduced enzyme inhibitory activity.[20] Herein we report on the synthesis of C-4 deoxy (**3**−**7**) and C-4 decarboxy (**8** and **9**) analogues together with their biological evaluation and that of the corresponding C-3 decarboxy analogues[21] (**10** and **11**). Differences in structure−activity relationships (SAR) between the C-6 acyl and C-6 desacyl analogues derived for inhibition of SQS and the *in vivo* activities of 4-deoxyS1 **3** and 3-decarboxyS1 **10** in comparison with S1 **1** are highlighted.

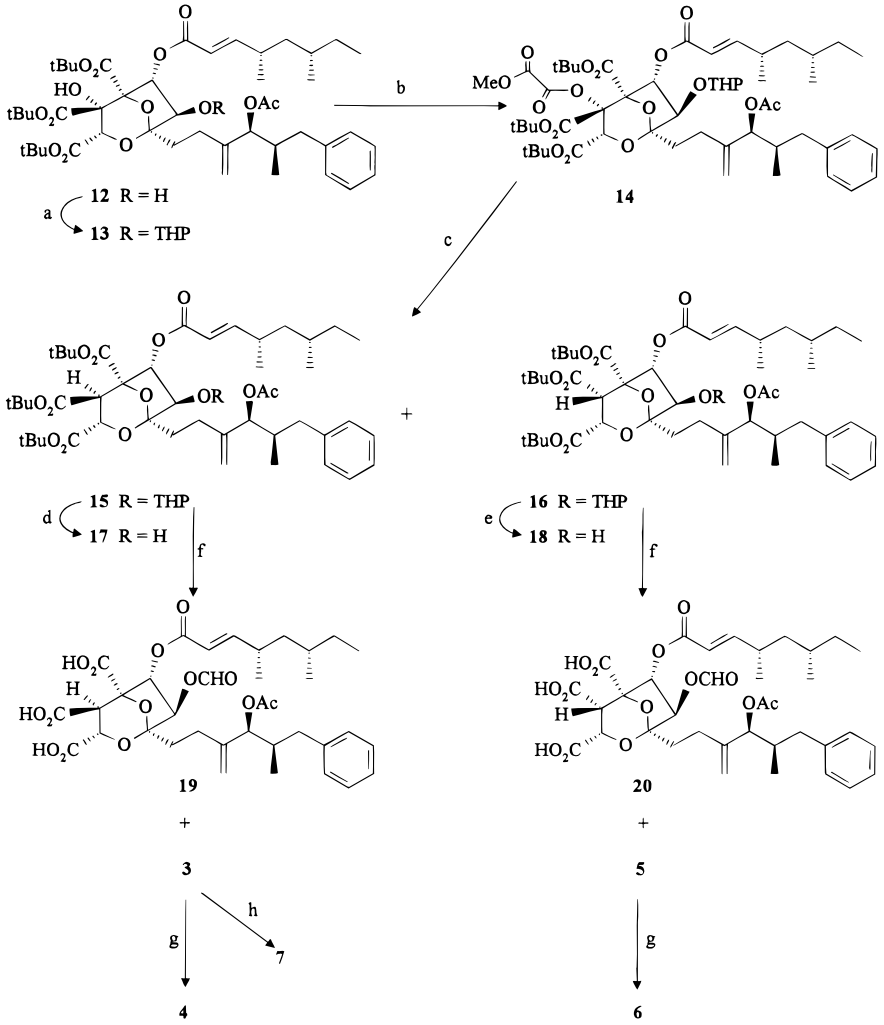
Chemistry

The syntheses of C-3 decarboxysqualestatins **10** and **11** have been reported previously.[21] In the preparation of C-4 deoxysqualestatins **3**−**7** (Scheme 2), the readily available S1 tri-*tert*-butyl ester **12**[14] was protected as its C-7 THP ether **13** (85%). Deprotonation with NaH followed by acylation with methyl oxalyl chloride gave the C-4 methyl oxalate **14** in excellent yield (95%). Free radical reduction[22] with tri-*n*-butylstannane in the presence of AIBN gave an epimeric mixture of C-4 deoxyS1 tri-*tert*-butyl esters **15** and **16** in the ratio of 4:1[23] in a total yield of 40% which were separable by flash column chromatography. To avoid complications from the diastereoisomeric pairs derived from the THP protecting group, the identities of these epimers were determined as their C-7 hydroxy derivatives **17** and **18**, which were obtained by cleavage of the C-7 THP ether with methanol in the presence of PPTS or Amberlyst-15. Coupling constants from ^{1}H-NMR spectroscopy clearly established the identities of C-4 deoxyS1 (major) and C-4 epideoxyS1 (minor) tri-*tert*-butyl esters **17** and **18**, respectively. In the major isomer, the coupling constant (11 Hz) between H-3 (δ 4.90) and H-4 (δ 2.95) clearly indicated their diaxial (*anti*) relationship, thereby establishing its structural identity as C-4 deoxyS1 tri-*tert*-butyl ester **17**. In the spectrum for the minor isomer, the coupling constant of 4 Hz between H-3 (δ 4.67) and H-4 (δ 3.30) protons established their *syn* relationship and confirmed the structure as C-4 epideoxyS1 tri-*tert*-butyl ester **18**.

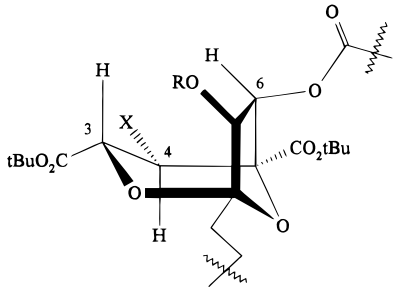
Acid hydrolysis of **17** with formic acid gave C-4 deoxyS1 **3**. A minor byproduct was also isolated which was identified as C-7 formyl C-4 deoxyS1 **19**. Removal of the C-6 side chain in **3** with *N*-methylhydroxylamine[16b] gave C-4 deoxyH1 **4**. The minor epimer **18** was similarly treated to give C-4 epideoxyS1 **5**, C-7 formyl C-4 epideoxyS1 **20**, and C-4 epideoxyH1 **6**. Deacetylation of C-4 deoxyS1 **3** with concentrated HCl in methanol[14] gave C-4 deoxyS2 **7**.

For the synthesis of C-4 decarboxysqualestatins **8** and **9** (Scheme 3), C-7 TBDMS-S1 tri-*tert*-butyl ester **21** was employed which was readily prepared by silylation of S1 tri-*tert*-butyl ester **12**[14] in quantitative yield. Selective acid hydrolysis[19a] gave the corresponding C-4 acid **22** (51%). Oxidative decarboxylation of **22** using *N*-ethyl-2-chlorobenzoxazolium tetrafluoroborate and triethylamine[24] followed by reduction with sodium borohydride provided access to the C-4 decarboxyS1 di-*tert*-butyl ester **23** and its C-4 epi derivative **24** in overall yields of 26% and 13%, respectively.[25] The stereochemistry

Scheme 2. Synthesis of C-4 Deoxysqualestatins[a]

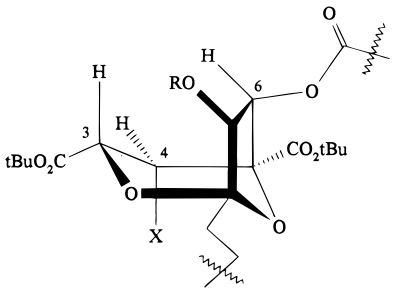


[a] Conditions: (a) DHP, PPTS, CH_2Cl_2; (b) NaH, MeOCOCOCl, THF, room temperature; (c) *n*-Bu_3SnH, AIBN, xylene, 90 °C; (d) PPTS, MeOH, 60 °C; (e) Amberlyst-15, MeOH, room temperature; (f) HCO_2H, room temperature; (g) Et_3N, MeNHOH·HCl, DMF, room temperature; (h) concentrated HCl, MeOH.



17 (X = *t*BuO_2C, R = H)

24 (X = OH, R = TBDMS)



18 (X = *t*BuO_2C, R = H)

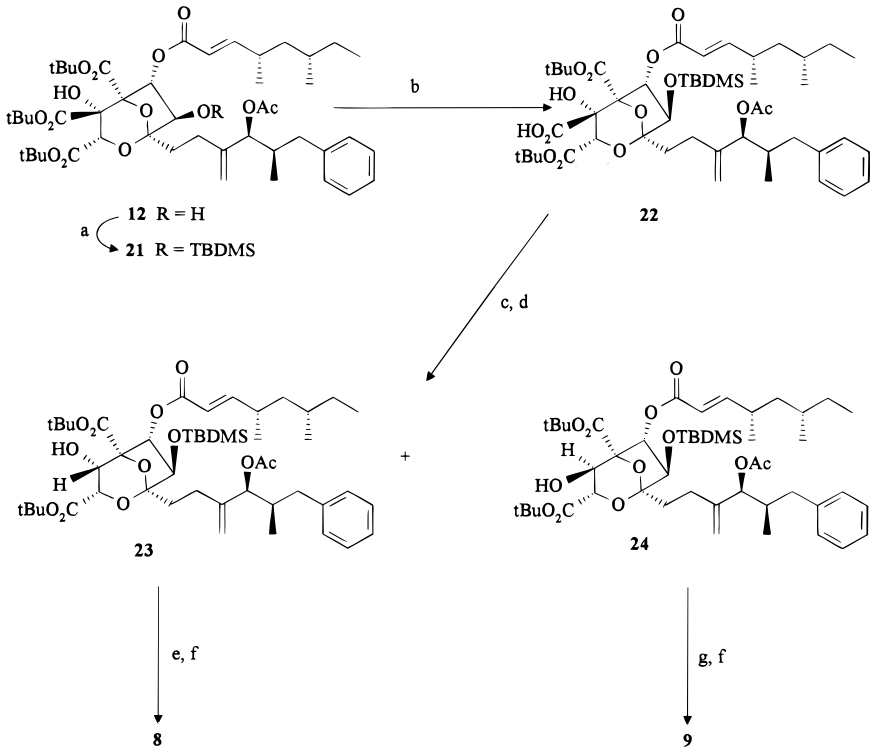
23 (X = OH, R = TBDMS)

of these epimeric alcohols was established by NMR spectroscopy. NOE experiments on the isomer in which H-6 resonates at δ 5.65 showed signal enhancement to H-3 (δ 4.36) on irradiation of H-6 indicating their close spatial proximity. The coupling constant of 10 Hz between H-3 and H-4 (δ 3.88) confirmed their *trans* diaxial relationship, thereby establishing its structure as the C-4 epidecarboxyS1 di-*tert*-butyl ester **24**. A similar NOE experiment on the other isomer showed signal enhancements to H-3 (δ 4.72) and H-4 (δ 4.17) on irradiation of H-6 (δ 5.45). These data together with their coupling constant of 2 Hz confirmed the axial−equatorial relationship of H-3 and H-4, thereby establishing its identity as the C-4 decarboxy isomer **23**. Fluoride-induced desilylation and hydrolysis with formic acid thereby gave C-4 decarboxyS1 **8** and its epimer **9**.

Biological Results and Discussion

The abilities of C-3 decarboxy-, C-4 deoxy-, and C-4 decarboxysqualestatins to inhibit the conversion of [2-^{14}C]farnesyl diphosphate (FPP) to [^{14}C]squalene by rat liver microsomal SQS were determined using our published assay procedures (Table 1).[13,26] As reported previously,[9,13,14] both S1 (**1**) and H1 (**2**) are highly potent inhibitors of SQS. In the S1 series, compounds without the carboxylic acid moieties at C-3 or C-4 (**8**−**10**) retain

Scheme 3. Synthesis of C-4 Decarboxysqualestatins[a]



[a] Conditions: (a) TBDMSCl, imidazole, DMF, 65 °C; (b) HCl−dioxane; (c) 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, Et_3N, CH_2Cl_2; (d) $NaBH_4$, EtOH; (e) aqueous HF−MeCN; (f) HCO_2H, room temperature; (g) TBAF, THF.

Table 1. *In Vitro* Rat SQS Inhibitory Activities of Squalestatins[a]

compd no.	trivial name	formula[b]	relative potency[c]
	S1 Series		
1	S1	$C_{35}H_{46}O_{14}$	1
3	C-4 deoxyS1	$C_{35}H_{46}O_{13}\cdot H_2O$	1
5	C-4 epideoxyS1	$C_{35}H_{46}O_{13}\cdot 2H_2O$	0.1
7	C-4 deoxyS2	$C_{33}H_{44}O_{12}\cdot 1.5H_2O$	2
8	C-4 decarboxyS1	$C_{34}H_{46}O_{12}\cdot H_2O$	0.2
9	C-4 epidecarboxyS1	$C_{34}H_{46}O_{12}\cdot 1.3H_2O$	0.2
10	C-3 decarboxyS1	$C_{34}H_{46}O_{12}$[d]	0.5
	H1 Series		
2	H1	$C_{25}H_{30}O_{13}$	0.5
4	C-4 deoxyH1	$C_{25}H_{30}O_{12}\cdot 2.5H_2O$	0.04
6	C-4 epideoxyH1	$C_{25}H_{30}O_{12}\cdot 2.5H_2O$	0.02
11	C-3 decarboxyH1	$C_{24}H_{30}O_{11}$[d]	0.0005

[a] Squalestatins were tested for their ability to inhibit the conversion of [2-^{14}C]farnesyl pyrophosphate (FPP) to [^{14}C]squalene by rat liver microsomal SQS using our published procedure.[13,26] [b] Unless otherwise stated, all compounds gave satisfactory microanalysis. [c] The concentration of test compounds required to inhibit the FPP−squalene conversion by 50% was expressed as an IC_{50} value which was determined on at least two different occasions in duplicate with a minimum of five and a maximum of eight dose levels. The relative potency of the test compound is expressed as the quotient of the IC_{50} determined for S1 (typical $IC_{50} = 12 \pm 5$ nM) divided by the IC_{50} for the test compound. [d] Syntheses of these compounds have been reported.[21]

good inhibitory activities, consistent with our previous findings[19a] for the C-3 and C-4 monomethyl esters of S1. In compounds retaining the tricarboxylic acid moiety, removal of the C-4 hydroxy group to give **3** did not diminish SQS inhibitory activity, while the corresponding epimer **5** showed 10-fold lower potency. The corresponding C-1 modified allylic alcohol **7** retains potent enzyme inhibitory activity; a similar finding has been reported with the C-3 hydroxymethyl series.[20]

However, in the H1 series, C-3 decarboxyH1 **11** is without significant SQS inhibitory activity, supporting our view that an acidic group at C-3 is essential for maximal enzyme inhibitory activity in this series.[19a] Removal of the C-4 hydroxyl in H1, to provide C-4 deoxyH1 **4** and C-4 epideoxyH1 **6**, also resulted in a significant loss of enzyme inhibitory activity, consistent with our previous observations[14,19a,20] that modifications to the C-1 side chain and tricarboxylic acid moiety in H1 substantially reduce biological activity. These differences in SAR between S1 and H1 series show that the C-6 dimethyloctenoate side chain critically affects the *in vitro* SQS inhibitory activity for modifications made in other parts of the squalestatin molecule. We have suggested previously[19a] that analogues of S1 mimic the biosynthetic intermediate PSPP while the related H1 derivatives are FPP mimetics; in both series the highly functionalized 2,8-dioxabicyclo[3.2.1]octane ring system acts as a diphosphate mimetic.

Having demonstrated their potent SQS inhibitory activities, the potassium salts of C-4 deoxyS1 **3** and C-3 decarboxyS1 **10** were evaluated *in vivo* in rats and marmosets. Their abilities to inhibit hepatic [^{14}C]-cholesterol biosynthesis from [^{14}C]acetate in rats at 1 h iv postdosing were studied. We reported previously[13] that **1** possesses an ED_{50} of 0.1 mg/kg for inhibition of cholesterol biosynthesis when administered iv in this model. The relative potencies of C-4 deoxyS1 **3** and C-3 decarboxyS1 **10** compared with **1** are shown in Figures 1 and 2. The potency of C-4 deoxyS1 **3** was found to be the same as that for **1**, whereas C-3 decarboxyS1 **10** was one-half as potent as **1**. The duration of action of C-4 deoxyS1 **3** relative to **1** was examined at an equipotent dose of 1 mg/kg iv (Figure 3). Both compounds showed maximal inhibition at 1 h postdose. Significant inhibition was observed for at least 7 h with S1 (**1**) and up to

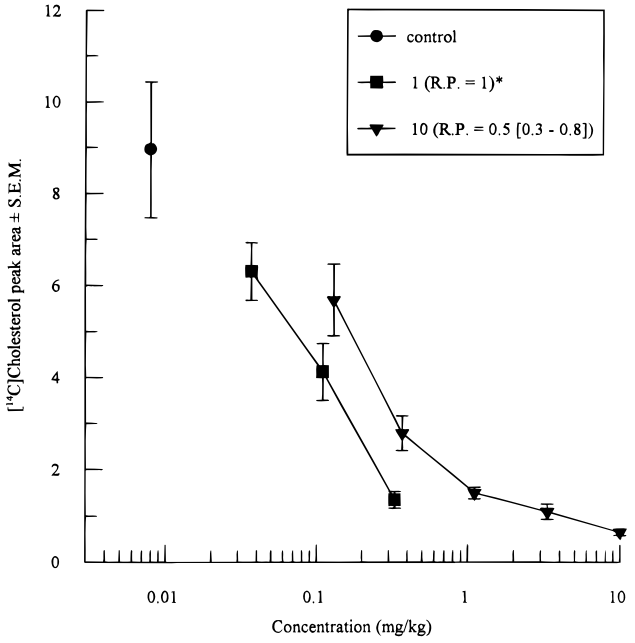


Figure 1. Effect of S1 (**1**) and C-3 decarboxyS1 **10** on cholesterol biosynthesis in rats (n = 8) at 1 h after iv administration. *RP = relative potency compared to **1**. Figures in brackets are fiducial ranges at p = 0.95.

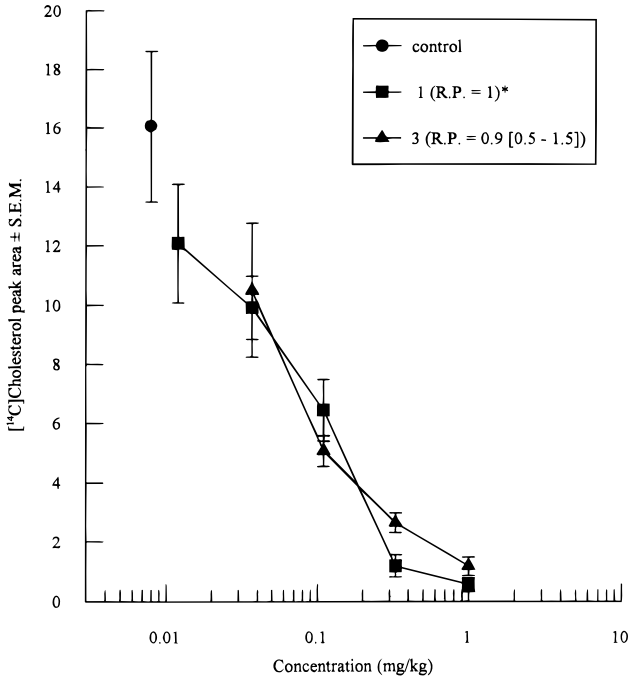
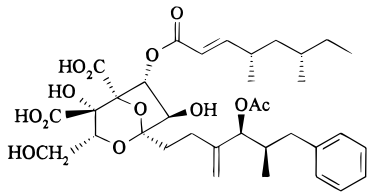


Figure 2. Effect of S1 (**1**) and C-4 deoxyS1 **3** on cholesterol biosynthesis in rats (n = 8) at 1 h after iv administration. *RP = relative potency compared to **1**. Figures in brackets are fiducial ranges at p = 0.95.

4 h with C-4 deoxyS1 **3**. Studies with C-3 decarboxyS1 **10** relative to **1** (1 mg/kg) at 6 h iv postdosing showed no significant effect on cholesterol biosynthesis in rats at doses up to 10 mg/kg (data not shown). The related C-3 hydroxymethylS1 **25** has been shown similarly to possess a short *in vivo* duration of action compared to S1 **1** due to rapid excretion through the biliary duct.[27]



25 3-HydroxymethylS1

We have reported previously[14] that **1** lowers serum cholesterol levels in marmosets by up to 60% during 7 days after a single iv dose of 1 mg/kg. In the present studies the serum cholesterol-lowering effects of C-4 deoxyS1 **3** (10 mg/kg) and C-3 decarboxyS1 **10** (50 mg/kg) in marmosets were similarly compared with **1** (1 mg/kg) (Figure 4). These results again demonstrated the profound and extended cholesterol-lowering effect of **1** in marmosets. C-4 deoxyS1 **3** retains good lipid lowering ability, while C-3 decarboxyS1 **10** has only a marginal effect on cholesterol levels even when dosed at 50 mg/kg.

Conclusion

C-4 deoxy- and C-3 and C-4 decarboxysqualestatins were prepared and evaluated for their abilities to inhibit rat microsomal SQS *in vitro*. These modifications were well tolerated in the S1 series, and potent SQS inhibitory activities were retained. However in the H1 series removal of the hydroxy group at C-4 significantly reduced their enzyme inhibitory activities, while the removal of carboxylic acid at C-3 resulted in a dramatic loss in its enzyme inhibitory activities. Both C-4 deoxyS1 **3** and C-3 decarboxyS1 **10** have shorter *in vivo* durations of action in the inhibition of cholesterol biosynthesis in rats compared with **1**. In comparison with **1**, which shows an excellent and extended reduction of serum cholesterol levels in marmosets following administration of a single iv dose, C-4 deoxyS1 **3** retained good lipid-lowering activity, whereas removal of C-3 carboxylic acid in S1, **10**, resulted in a dramatic loss in its ability to lower serum cholesterol levels.

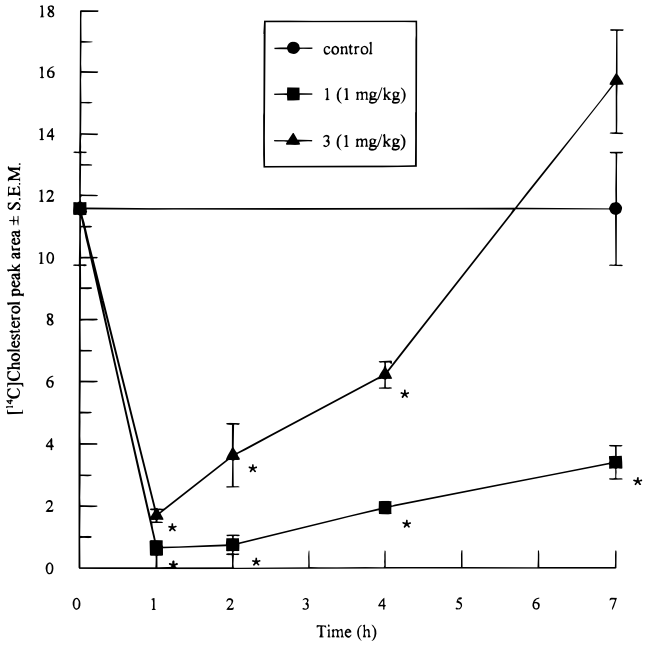


Figure 3. Duration of effect of S1 (**1**) and C-4 deoxyS1 **3** on cholesterol biosynthesis in rats (n = 8) after iv administration. An asterisk indicates significantly (p < 0.05) below control.

Experimental Section

Organic solutions were dried over $MgSO_4$, and column chromatography was performed on silica gel 60 (Merck, Art

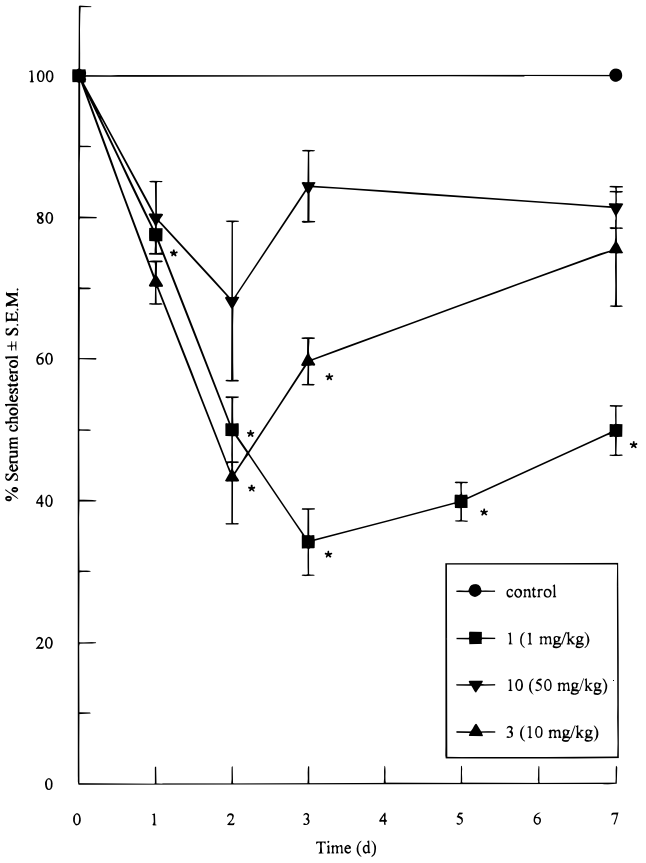


Figure 4. Effect of S1 (**1**), C-4 deoxyS1 **3**, and C-3 decarboxyS1 **10** on serum cholesterol levels of marmosets ($n = 6$) after a single iv dose. An asterisk indicates significantly ($p < 0.05$) below control.

no. 9385). Analytical HPLC was performed on a Spherisorb ODS-2 column (20 cm × 0.4 cm) using CH_3CN/H_2O containing 0.15 mL/L concentrated H_2SO_4 or 0.1% TFA as eluent, at a flow rate of 1.5 mL/min and detecting at 210 nm. Preparative HPLC was conducted on either a Spherisorb ODS-2 column (25 cm × 2.5 cm i.d.) at a flow rate of 10 mL/min (column A) or Spherisorb ODS-2 column (25 cm × 5 cm i.d.) at a flow rate of 40 mL/min (column B) using CH_3CN/H_2O containing 0.15 mL/L concentrated H_2SO_4 or 0.1% TFA as eluent and detecting at 210 nm. The appropriate fractions from each run were combined, the CH_3CN was removed *in vacuo* (bath temperature < 40 °C), and the remainder was extracted with EtOAc. The combined extracts were washed with brine and evaporated; the residue was dissolved in H_2O/dioxane and freeze-dried. IR spectra were recorded on a Nicolet 5SXC FTIR spectrometer. NMR spectra were recorded on a Bruker AM 500 or AM 250 or Varian VXR 400 spectrometer using standard pulse sequences. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Desorption chemical ionization mass spectrometry using NH_3 (DCI, NH_3, +ve) and negative ion FAB mass spectrometry (−ve FAB) were performed on Finnigan 4600 and 8400 spectrometers, respectively. Positive ion thermospray mass spectrometry (thermospray, +ve) was carried out with an HP 5989A engine, and high-resolution LSI mass spectrometry [HRMS (LSI, +ve)] was performed on a VG Autospec S spectrometer. Elemental analyses were determined with a Perkin-Elmer 240C or Carlo-Erba 1106 elemental analyzer.

Biological Tests. Squalestatins were tested for their ability to inhibit the conversion of [2-^{14}C]farnesyl pyrophosphate (FPP) to [^{14}C]squalene by rat liver microsomal SQS using our published procedure.[13,26] Effects of iv administration of **1**, C-4 deoxyS1 **3**, and C-3 decarboxyS1 **10** on cholesterol biosynthesis in rats and on serum cholesterol levels in marmosets were carried out according to our published methods.[13,14]

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*(2*R***S**)]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6-dihydroxy-7-[(2-tetrahydropyranyl)oxy]-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 (13).** A solution of **12**[14] (6.60 g, 7.70 mmol) in CH_2Cl_2 (150 mL) was treated with 3,4-dihydro-2*H*-pyran (15 mL, 161 mmol) and pyridinium *p*-toluenesulfonate (1 g, 4 mmol). After 20 h of stirring at room temperature, the mixture was diluted with CH_2Cl_2 (220 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and a saturated aqueous solution of NH_4Cl (100 mL). The organic phase was dried and concentrated to give a brown oil. This was purified by flash column chromatography on silica gel eluting with EtOAc: cyclohexane (2:8) to give **13** (6.10 g, 85%): NMR ($CDCl_3$) δ 1.02 (d, 3H, $J = 7$ Hz, CH═CHCHCH_3), 1.40, 1.42, 1.45, 1.65, and 1.70 (5s, 27H, 3 *t*-*Bu*O_2C), 2.1 (s, 3H, CH_3CO_2), 2.75 (2dd, 1H, $J = 5$, 13 Hz for both, one proton of PhCH_2), 3.45 and 3.80 (2m, 2H, CH_2O of THP), 4.05 and 4.08 (s, 1H, O*H*), 4.08 and 4.21 (d, 1H, $J = 2$ Hz, H-7), 4.70 and 4.90 (2bt, 1H, OC*H*O of THP), 4.98 (bs, 2H, C═CH_2), 5.07 and 5.10 (s, 1H, H-3), 5.15 (d, 1H, $J = 5$ Hz, C*H*OAc), 5.75 (d, 1H, $J = 15.5$ Hz, CH═C*H*CO), 6.45 and 6.60 (d, 1H, $J = 2$ Hz, H-6), 6.90 (dd, 1H, $J = 8$, 15.5 Hz, C*H*═CHCO), 7.1−7.3 (m, 5H, C_6H_5); MS (DCI, NH_3, +ve) m/z 960 $(M + NH_4)^+$, 943 $(M + H)^+$. Anal. ($C_{52}H_{78}O_{15}$) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*(2*R***S**)]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6-dihydroxy-7-[(2-tetrahydropyranyl)oxy]-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), 4-(Methoxy-2-oxoacetate), 3,4,5-Tris(1,1-dimethylethyl) Ester (14), [1*S*-[1α(4*R**,5*S**),3α,4*β*,5α,6α-(2*E*,4*R**,6*R**),7*β*(2*R***S**)]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-hydroxy-7-[(2-tetrahydropyranyl)oxy]-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 (15), and [1*S*-[1α(4*R**,5*S**),-3α,4α,5α,6α(2*E*,4*R**,6*R**),7*β*(2*R***S**)]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6-hydroxy-7-[(2-tetrahydropyranyl)oxy]-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 (16).** A solution of **13** (5.20 g, 5.6 mmol) in dry THF (80 mL) was treated with NaH (60% oil dispersion, 1.7 equiv, 0.38 g, 9.5 mmol) at room temperature. After 10 min, methyl oxalyl chloride (1.3 mL, 14 mmol) was added. After 10 min, saturated aqueous NH_4Cl solution (100 mL) and Et_2O (200 mL) were added. The organic phase was dried and evaporated to give **14** (5.2 g, 95%): NMR ($CDCl_3$) δ 1.02 (d, 3H, $J = 7$ Hz, CH═CHCHCH_3), 1.42, 1.45, 1.55, and 1.60 (4s, 27H, 3 *t*-*Bu*O_2C), 2.1 (s, 3H, CH_3CO_2), 3.8 (s, 3H, CH_3OCOCOO), 4.70 and 4.82 (bt, 1H, OC*H*O of THP), 4.95 (bs, 2H, C═CH_2), 5.21 (d, 1H, $J = 5$ Hz, C*H*OAc), 5.80 (d, 1H, $J = 15.5$ Hz, CH═C*H*CO), 6.40 and 6.52 (d, 1H, $J = 2$ Hz, H-6), 6.90 (dd, 1H, $J = 8$, 15.5 Hz, C*H*═CHCO), 7.10−7.30 (m, 5H, C_6H_5); MS (DCI, NH_3, +ve) m/z 1028 $(M + NH_4)^+$ for $C_{55}H_{80}O_{18}$.

A solution of **14** (5.1 g, 5.5 mmol) in dry xylene (80 mL) at 90 °C was treated with tributyltin hydride (2.2 mL, 8 mmol) and AIBN (50 mg). Further portions of AIBN (50 mg) and tributyltin hydride (0.7 mL, 2.5 mmol) were added after 3 h with continued heating at 90 °C. After a total of 16 h, heating was stopped, and the reaction mixture was allowed to cool and then purified by flash column chromatography on silica gel eluting with EtOAc:cyclohexane (5:95,1:9,1:4) to give **15** (1.56 g, 32%): NMR ($CDCl_3$) δ 1.02 (2d, 3H, $J = 6.5$ Hz for both, CH═CHCHCH_3), 2.1 (2s, 3H, CH_3CO_2), 2.95 and 2.96 (2d, 1H, $J = 12$ Hz for both, H-4), 3.45 and 3.80 (2m, 2H, CH_2O of THP), 4.02 and 4.20 (2d, 1H, $J = 2$ Hz for both, H-7), 4.75 and 4.90 (2t, 1H, OC*H*O of THP), 4.92 and 4.95 (bs, 2H, C═CH_2), 4.94 and 4.98 (2d, 1H, $J = 12$ Hz for both, H-3), 5.10 and 5.15 (2d, 1H, $J = 5$ Hz for both, C*H*OAc), 5.75 and 5.80 (2d, 1H, $J = 15$ Hz for both, CH═C*H*CO), 6.23 and 6.38 (2d, 1H, $J = 2$ Hz for both, H-6), 6.90 (2dd, 1H, $J = 7.5$, 15 Hz for both, C*H*═CHCO),

7.1−7.3 (m, 5H, C_6H_5); MS (DCI, NH_3, +ve) *m/z* 944 $(M + NH_4)^+$. Anal. ($C_{52}H_{78}O_{14}$) C, H.

16 (0.4 g, 8%): NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 2.1 (s, 3H, CH_3CO_2), 2.7 (bdd, 1H, one proton of PhCH_2), 3.28 and 3.32 (d, 1H, J = 3.5 Hz, H-4), 3.95 and 4.11 (d, 1H, J = 1.5 Hz, H-7), 4.62 and 4.66 (d, 1H, J = 3.5 Hz, H-3), 4.95 and 4.98 (bs, 2H, C=CH_2), 5.51 and 5.71 (d, 1H, J = 1.5 Hz, H-6), 5.80 and 5.81 (d, 1H, J = 15 Hz, CH=C*H*CO), 6.91 (dd, 1H, J = 7, 15 Hz, C*H*=CHCO), 7.1−7.3 (m, 5H, C_6H_5).

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6-hydroxy-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 (17).** A solution of **15** (1.34 g, 1.44 mmol) in MeOH (100 mL) at 60 °C was treated with pyridinium *p*-toluenesulfonate (0.1 g, 0.4 mmol). After 16 h of stirring at 60 °C, the solvent was evaporated and EtOAc (150 mL) was added. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and a saturated aqueous solution of NH_4Cl (30 mL). The organic phase was dried and evaporated to give **17** (1.15 g, 94%): NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 1.44, 1.45, and 1.47 (s, 27H, 3 *t*-BuO_2C), 2.10 (s, 3H, CH_3CO_2), 2.70 (dd, 1H, J = 5, 13 Hz, one proton of PhCH_2), 2.95 (d, 1H, J = 11 Hz, H-4), 3.07 (bd, 1H, O*H*), 3.98 (bs, 1H, H-7), 4.90 (d, 1H, J = 11 Hz, H-3), 4.93 and 4.95 (bs, 2H, C=CH_2), 5.10 (d, 1H, J = 5 Hz, C*H*OAc), 5.72 (d, 1H, J = 2 Hz, H-6), 5.75 (d, 1H, J = 15 Hz, CH=C*H*CO), 6.9 (dd, 1H, J = 7, 15 Hz, C*H*=CHCO), 7.10−7.30 (m, 5H, C_6H_5); MS (DCI, NH_3, +ve) *m/z* 860 $(M + NH_4)^+$. Anal. ($C_{47}H_{70}O_{13}$·1.5H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (3) and [1*S*-[1α(4*R**,5*S**),-3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), 7-Methanoate (19).** A solution of **17** (1.1 g, 1.32 mmol) in formic acid (10 mL) was stirred at room temperature. After 16 h, the formic acid was evaporated; the residue was purified by reverse-phase HPLC (column B) eluting with 68% MeCN−H_2O and acidified with 0.15 mL/L concentrated H_2SO_4 to give **3** (0.385 g, 43%): NMR (CD_3OD) δ 0.83−0.91 (m, 9H, 3 CH_3), 1.03 (d, 3H, J = 6.5 Hz, CH=CHCHCH_3), 2.09 (s, 3H, CH_3CO_2), 2.67 (dd, 1H, J = 13.5, 6.5 Hz, one proton of PhCH_2), 3.08 (d, 1H, J = 10.5 Hz, H-4), 4.01 (d, 1H, J = 2 Hz, H-7), 4.98 and 5.01 (2s, 2H, C=CH_2), 5.06 (d, 1H, J = 5 Hz, C*H*OAc), 5.82 (d, 1H, J = 16 Hz, CH=C*H*CO), 5.86 (d, 1H, J = 2 Hz, H-6), 6.87 (dd, 1H, J = 16, 8 Hz, C*H*=CHCO), 7.09−7.30 (m, 5H, C_6H_5); MS (−ve FAB) *m/z* 673 $(M - H)^-$. Anal. ($C_{35}H_{46}O_{13}$·H_2O) C, H.

19 (0.121 g, 13%): NMR (CD_3OD) δ 2.1 (s, 3H, CH_3CO_2), 2.66 (dd, 1H, J = 6, 14 Hz, one proton of PhCH_2), 3.02 (d, 1H, J = 11 Hz, H-4), 4.93 (d, 1H, J = 11 Hz, H-3), 5.05 (d, 1H, J = 5 Hz, C*H*OAc), 5.27 (d, 1H, J = 2 Hz, H-7), 5.80 (d, 1H, J = 15 Hz, CH=C*H*CO), 6.20 (d, 1H, J = 2 Hz, H-6), 6.85 (dd, 1H, J = 9, 15 Hz, C*H*=CHCO), 7.10−7.30 (m, 5H, C_6H_5), 8.25 (s, 1H, OC*H*O); MS (−ve FAB) *m/z* 701 $(M - H)^-$. Anal. ($C_{36}H_{46}O_{14}$·1.3H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), Tripotassium Salt (Tripotassium Salt of 3).** $KHCO_3$ (3 equiv, 170 mg, 1.7 mmol) in H_2O (5 mL) was added slowly to a stirring solution of **3** (380 mg, 0.56 mmol) in a mixture of dioxane (20 mL) and H_2O (2 mL). Stirring was continued until the cloudy solution became clear. The resultant solution was freeze-dried to give the potassium salt of **3** as a white solid (quantitative): NMR (D_2O) δ 0.80 (t, 3H, J = 9 Hz, CH_2CH_3), 0.81 (d, 3H, J = 7 Hz, $CHCH_3$), 0.91 (d, 3H, J = 7 Hz, $CHCH_3$), 1.01 (d, 3H, J = 6.5 Hz, CH=CHCHCH_3), 2.18 (s, 3H, CH_3CO_2), 2.60 (d, 2H, J = 7 Hz, PhCH_2CH), 2.69 (d, 1H, J = 11 Hz, H-4), 3.90 (s, 1H, H-7), 4.72 (d, 1H, J = 11 Hz, H-3), 4.89 (d, 1H, J = 5 Hz, C*H*OAc), 4.97 and 5.03 (2s, 2H, C=CH_2), 5.93 (d, 1H, J = 15 Hz, CH=C*H*CO), 5.94 (s, 1H, H-6), 6.95 (dd, 1H, J = 15, 8 Hz, C*H*=CHCO), 7.20−7.38 (m, 5H, C_6H_5).

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α,7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid (4).** A solution of **3** (70 mg, 0.105 mmol) in dry DMF (2 mL) was treated with Et_3N (63 μL, 0.47 mmol) and *N*-methylhydroxylamine hydrochloride (26 mg, 0.311 mmol) at room temperature. After stirring for 16 h, the solvent was evaporated under reduced pressure. The residue was purified by reverse-phase HPLC (column A) eluting with 43% MeCN−H_2O and acidified with 0.15 mL/L concentrated H_2SO_4 to give **4** (30 mg, 55%): NMR (CD_3OD) δ 0.85 (d, 3H, J = 7 Hz, CH_3CH), 2.10 (s, 3H, CH_3CO_2), 2.7 (dd, 1H, J = 6, 14 Hz, one proton of PhCH_2), 2.95 (d, 1H, J = 12 Hz, H-4), 4.0 (d, 1H, J = 1 Hz, H-7), 7.1−7.3 (m, 5H, C_6H_5); MS (−ve FAB) *m/z* 521 $(M - H)^-$. Anal. ($C_{25}H_{30}O_{12}$·2.5H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-(4-Hydroxy-5-methyl-3-methylene-6-phenylhexyl)-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (7).** A solution of **3** (25 mg, 0.037 mmol) in acetone:H_2O (3:1, 1 mL) at room temperature was treated with concentrated H_2SO_4 (0.05 mL, 0.92 mmol). After stirring for 14 days, the organic solvent was evaporated and the residue was purified by reverse-phase HPLC (column A) eluting with 60% MeCN−H_2O acidified with 0.15 mL/L concentrated H_2SO_4 to give **7** (17 mg, 70%): NMR (CD_3OD) δ 1.0 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 2.75 (dd, 1H, J = 6, 12.5 Hz, one proton of PhCH_2), 3.05 (d, 1H, J = 11 Hz, H-4), 3.90 (d, 1H, J = 5 Hz, C*H*(OH)C=CH_2), 4.03 (d, 1H, J = 1.5 Hz, H-6), 5.80 (d, 1H, J = 15.5 Hz, CH=C*H*CO), 6.85 (dd, 1H, J = 8.5, 15.5 Hz, C*H*=CHCO), 7.1−7.3 (m, 5H, C_6H_5). Anal. ($C_{33}H_{44}O_{12}$·1.5H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4α,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6-hydroxy-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 (18).** A mixture of **16** (450 mg, 0.486 mmol) and Amberlyst-15 (1 g) in MeOH (20 mL) was stirred at room temperature for 3 days. The methanolic solution was evaporated to give a residue which was purified by flash column chromatography to afford **18** (200 mg, 49%): NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 6.5 Hz, CH=CHCHCH_3), 1.42−1.55 (3s, 27H, 3 *t*-BuO_2C), 2.1 (s, 3H, CH_3CO_2), 2.7 (dd, 1H, J = 13, 5 Hz, one proton of PhCH_2), 2.93 (d, 1H, J = 2.5 Hz, CHO*H*), 3.3 (d, 1H, J = 4 Hz, H-4), 3.95 (t, 1H, J = 2.5 Hz, H-7), 4.67 (d, 1H, J = 4 Hz, H-3), 4.95 (s, 2H, C=CH_2), 5.02 (d, 1H, J = 2.5 Hz, H-6), 5.1 (d, 1H, J = 5 Hz, C*H*OAc), 5.8 (d, 1H, J = 15 Hz, CH=C*H*CO), 6.9 (dd, 1H, J = 15, 8 Hz, C*H*=CHCO), 7.1−7.3 (m, 5H, C_6H_5); MS (DCI, NH_3, +ve) *m/z* 860 $(M + NH_4)^+$ for $C_{47}H_{70}O_{13}$; analytical HPLC (90% MeCN−H_2O) showed 85% purity (t_R = 5.9 min).

[1*S*-[1α(4*R,5*S**),3α,4α,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (5) and [1*S*-[1α(4*R**,5*S**),-3α,4α,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), 7-Methanoate (20). 18** (200 mg, 0.237 mmol) was dissolved in formic acid (5 mL) and stirred at room temperature overnight. Removal of solvent gave a foam which was purified by preparative HPLC (column A) eluting with 60% MeCN−H_2O and acidified with 0.15 mL/L concentrated H_2SO_4 (t_R = 10.69 min) to give **5** (108 mg, 67%): NMR (CD_3OD) δ 0.82−0.92 (m, 9H, 3 CH_3), 1.06 (d, 3H, J = 7.2 Hz, CH=CHCHCH_3), 2.09 (s, 3H, CH_3CO_2), 2.67 (dd, 1H, J = 13.5, 6.5 Hz, one proton of PhCH_2), 3.61 (d, 1H, J = 3.5 Hz, H-4), 3.99 (d, 1H, J = 2.5 Hz, H-7), 4.94 and 5.01 (2s, 2H, C=CH_2), 5.06 (d, 1H, J = 5 Hz, C*H*OAc), 5.43 (d, 1H, J = 2.5 Hz, H-6), 5.85 (d, 1H, J = 15.5 Hz, CH=C*H*CO), 6.90 (dd, 1H, J = 15.5, 8 Hz, C*H*=CHCO), 7.09−7.30 (m, 5H, C_6H_5); MS (−ve FAB) *m/z* 673 $(M - H)^-$, 629 $(M - CO_2H)^-$. Anal. ($C_{35}H_{46}O_{13}$·2H_2O) C, H.

20 (20 mg, 8%): NMR (CD_3OD) δ 0.81−0.92 (m, 9H, 3 CH_3), 1.05 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 2.09 (s, 3H, CH_3CO_2),

2.68 (dd, 1H, J = 14, 6 Hz, one proton of PhCH_2), 3.69 (d, 1H, J = 3.5 Hz, H-4), 5.05 (d, 1H, J = 5 Hz, CHOAc), 5.19 (d, 1H, J = 2 Hz, H-7), 5.64 (d, 1H, J = 2 Hz, H-6), 5.86 (d, 1H, J = 15 Hz, CH=CHCO), 6.90 (dd, 1H, J = 15, 9 Hz, CH=CHCO), 7.12−7.30 (m, 5H, C_6H_5), 8.19 (s, 1H, OCHO); MS (−ve FAB) m/z 701 $(M - H)^-$ for $C_{36}H_{46}O_{14}$.

[1*S*-[1α(4*R,5*S**),3α,4α,5α,6α,7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid (6).** Et_3N (6 equiv, 63 μL, 0.66 mmol) followed by *N*-methylhydroxylamine (3 equiv, 24 mg, 0.33 mmol) was added to a solution of **5** (75 mg, 0.111 mmol) in dry DMF (2 mL). The mixture was stirred at room temperature overnight. Removal of volatile components under high vacuum gave a residue which was purified by preparative HPLC (column A) eluting with 40% MeCN−H_2O and acidified with 0.15 mL/L concentrated H_2SO_4 (t_R = 4.41 min) to give **6** (42 mg, 72%): NMR (CD_3OD) δ 0.85 (d, 3H, J = 7 Hz, CH_3), 2.1 (s, 3H, CH_3CO_2), 2.7 (dd, 1H, J = 13, 5 Hz, one proton of PhCH_2), 3.51 (d, 1H, J = 3.5 Hz, H-4), 3.98 and 4.17 (2s, 2H, J = 2 Hz, H-6, H-7), 4.65 (d, 1H, J = 3.5 Hz, H-3), 4.95 and 5.0 (2s, 2H, C=CH_2), 5.1 (d, 1H, J = 5 Hz, CHOAc), 7.1−7.3 (m, 5H, C_6H_5); MS (−ve FAB) m/z 521 $(M - H)^-$ for $C_{25}H_{30}O_{12}$. Anal. ($C_{25}H_{30}O_{12}$·2.5H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6-dihydroxy-7-[[(1,1-dimethylethyl)dimethylsilanyl]oxy]-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 (21).** To a solution of **12**[14] (9.84 g, 11.45 mmol) in dry DMF (30 mL) under nitrogen at 50 °C was added imidazole (18 equiv, 14 g, 206 mmol) and *tert*-butyldimethylchlorosilane (9 equiv, 15.46 g, 102.6 mmol). After heating at 80 °C for 5 h, the mixture was cooled to room temperature and stirred for a further 17 h. The mixture was diluted with Et_2O (500 mL), washed with H_2O (100 mL), aqueous HCl (1 M, 100 mL), and saturated aqueous NH_4Cl solution (2 × 100 mL), dried, and concentrated to an orange gummy oil (19.26 g) which was purified by flash column chromatography eluting with EtOAc:cyclohexane (1:9−3:7) to give **21** as a pale orange gum (11.5 g, quantitative): R_f = 0.47 (SiO_2, 25% EtOAc:cyclohexane); IR (KBr) 1729 cm^{-1}; NMR ($CDCl_3$) δ 0.05 and 0.10 (2s, 6H, (CH_3)$_2$Si), 0.75−0.97 (m, 18H, *t*-*Bu*Si, 3 CH_3), 1.02 (d, 3H, J = 6 Hz, CH=CHCHCH_3), 1.41, 1.44, and 1.56 (3s, 27H, 3 *t*-*Bu*O_2C), 2.09 (s, 3H, CH_3CO_2), 2.72 (dd, 1H, J = 13, 5.5 Hz, one proton of PhCH_2), 4.06 (s, 1H, 4-OH), 4.07 (d, 1H, J = 1.5 Hz, H-7), 4.96 and 4.98 (2s, 2H, C=CH_2), 5.09 (s, 1H, H-3), 5.13 (d, 1H, J = 5 Hz, CHOAc), 5.79 (d, 1H, J = 15.5 Hz, CH=CHCO), 6.34 (d, 1H, J = 1.5 Hz, H-6), 6.92 (dd, 1H, J = 15.5, 8 Hz, CH=CHCO), 7.1−7.3 (m, 5H, C_6H_5); MS (thermospray, +ve) m/z 990 $(M + NH_4)^+$. Anal. ($C_{53}H_{84}O_{14}Si$·2H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6-dihydroxy-7-[[(1,1-dimethylethyl)dimethylsilanyl]oxy]-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), 3,5-Bis(1,1-dimethylethyl) Ester (22).** To an ice-cold solution of **21** (2.37 g, 2.44 mmol) in dioxane (10 mL) was added dropwise a solution of HCl (6.4 M in dioxane, 3.8 mL). After 2 h, the mixture was warmed to 10 °C and a further aliquot of HCl (6.4 M in dioxane, 3.8 mL) was added. After another 1.5 h, the mixture was warmed to room temperature and concentrated *in vacuo* to give a pale yellow gummy foam (1.9 g) which was purified by gravity column chromatography eluting with $CHCl_3$:MeOH (9:1) to give **22** as an off-white foam (1.15 g, 51%): R_f = 0.54 (SiO_2/$CHCl_3$:MeOH, 5:1); IR (KBr) 3566, 1724 cm^{-1}; NMR (CD_3OD) δ 0.0 and 0.1 (2s, 6H, (CH_3)$_2$Si), 0.70−0.95 (m, 18H, *t*-*Bu*Si, 3 CH_3), 1.00 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 1.40 and 1.43 (2s, 18H, 2 *t*-*Bu*O_2C), 2.07 (s, 3H, CH_3CO_2), 2.65 (dd, 1H, J = 13, 5 Hz, one proton of PhCH_2), 4.02 (d, 1H, J = 1 Hz, H-7), 4.93 and 4.97 (2s, 2H, C=CH_2), 5.05 (d, 1H, J = 5 Hz, CHOAc), 5.22 (s, 1H, H-3), 5.8 (d, 1H, J = 15.5 Hz, CH=CHCO), 6.67 (d, 1H, J = 1 Hz, H-6), 6.88 (dd, 1H, J = 15.5, 8 Hz, CH=CHCO), 7.05−7.25 (m, 5H, C_6H_5); MS (thermospray, +ve) m/z 934 $(M + NH_4)^+$. Anal. ($C_{49}H_{76}O_{14}Si$·2H_2O) C, H.

[1*S*-[1α(4*R,5*S**),3α,4α,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,5-dicarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (8) and [1*S*-[1α(4*R**,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6-dihydroxy-7-[[(1,1-dimethylethyl)dimethylsilanyl]oxy]-2,8-dioxabicyclo[3.2.1]octane-3,5-dicarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate), 3,5-Bis(1,1-dimethylethyl) Ester (24).** To a stirring solid mixture of **22** (1.046 g, 1.14 mmol) and 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (1.5 equiv, 0.476 g, 1.71 mmol) under nitrogen at room temperature was added a solution of Et_3N (3 equiv, 0.48 mL, 3.43 mmol) in CH_2Cl_2 (2 mL).[24] After 1 h, the mixture was cooled to 0 °C and sodium borohydride (130 mg, 3.42 mmol) in EtOH (10 mL) was added. After a further 2 h, the reaction was quenched with 10% citric acid (9 mL) and the mixture diluted with H_2O (50 mL) and extracted with Et_2O (3 × 50 mL). Combined ethereal extracts were washed with brine, dried, and concentrated to a light brown oil (1.316 g) which was purified by flash column chromatography eluting with EtOAc:cyclohexane (1:9−1:4) and then MeOH:$CHCl_3$ (1:4) to give initially an isomeric mixture containing **24** (0.139 g): R_f = 0.34 (SiO_2/15% EtOAc:cyclohexane). This material was further purified by preparative HPLC (column A) eluting with 90% MeCN−H_2O/0.1% TFA (t_R = 35.9 min) to give **24** as a colorless gum (65 mg, 12% based on the recovery of **22**): NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 1.41 and 1.45 (2s, 18H, 2 *t*-*Bu*O_2C), 2.05 (s, 3H, CH_3CO_2), 2.62 (dd, 1H, J = 14, 6 Hz, one proton of PhCH_2), 3.88 (d, 1H, J = 10 Hz, H-4), 4.07 (d, 1H, J = 2 Hz, H-7), 4.36 (d, 1H, J = 10 Hz, H-3), 5.01 (d, 1H, J = 5 Hz, CHOAc), 5.65 (d, 1H, J = 2 Hz, H-6), 5.83 (d, 1H, J = 16 Hz, CH=CHCO), 6.89 (dd, 1H, J = 16, 9 Hz, CH=CHCO), 7.01−7.27 (m, 5H, C_6H_5); HRMS ($C_{48}H_{76}O_{12}Si$ + Na)$^+$ calcd 895.5059, found 895.5063.

A second component from the flash column chromatography was **23** (0.159 g, 30% based on the recovery of **22**): R_f = 0.20 (SiO_2/EtOAc:cyclohexane, 3:17); NMR ($CDCl_3$) δ −0.03 and 0.0 (2H, 6H, (CH_3)$_2$Si), 0.76−0.91 (m, 18H, 3 CH_3, *t*-*Bu*Si), 1.02 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 1.41 and 1.49 (2s, 18H, 2 *t*-*Bu*O_2C), 2.08 (s, 3H, CH_3CO_2), 2.70 (dd, 1H, J = 13, 5 Hz, one proton of PhCH_2), 2.73−2.85 (bm, 1H, OH), 4.06 (d, 1H, J = 2.5 Hz, H-7), 4.1−4.2 (m, 1H, H-4), 4.72 (d, 1H, J = 2.5 Hz, H-3), 4.94 and 4.98 (2s, 2H, C=CH_2), 5.1 (d, 1H, J = 5 Hz, CHOAc), 5.45 (d, 1H, J = 2.5 Hz, H-6), 5.8 (d, 1H, J = 15.5 Hz, CH=CHCO), 6.95 (dd, 1H, J = 15.5, 8 Hz, CH=CHCO), 7.1−7.3 (m, 5H, C_6H_5).

23 (101 mg, 0.116 mmol) was dissolved in formic acid (10 mL) and allowed to stand at room temperature for 17 h. Removal of solvent gave a light brown oil which was dissolved in MeCN (5 mL). To this solution was added dropwise aqueous hydrofluoric acid (40%, 2.12 mL). After 41 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture extracted with EtOAc, dried, and evaporated to give a gummy residue (63 mg). Preparative HPLC (column A) eluting with 40% MeCN−H_2O/0.1% TFA rising to 95% MeCN−H_2O/0.1% TFA over 25 min (t_R = 17.5 min) gave **8** as an off-white solid (15 mg, 20%): NMR (CD_3OD) δ 0.81−0.91 (m, 9H, 3 CH_3), 1.04 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 2.10 (s, 3H, CH_3CO_2), 2.69 (dd, 1H, J = 13, 6 Hz, one proton of PhCH_2), 4.01 (d, 1H, J = 2 Hz, H-7), 4.29 (d, 1H, J = 3 Hz, H-4), 4.96 and 5.08 (2s, 2H, C=CH_2), 5.08 (d, 1H, J = 5 Hz, CHOAc), 5.27 (d, 1H, J = 2 Hz, H-6), 5.83 (d, 1H, J = 15.5 Hz, CH=CHCO), 6.88 (dd, 1H, J = 15.5, 8.5 Hz, CH=CHCO), 7.07−7.29 (m, 5H, C_6H_5); MS (thermospray, +ve) m/z 664 $(M + NH_4)^+$. Anal. ($C_{34}H_{46}O_{12}$·H_2O) C, H.

The starting material **22** (0.49 g, 49%) was also recovered from the reaction mixture.

[1*S*-[1α(4*R,5*S**),3α,4*β*,5α,6α(2*E*,4*R**,6*R**),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,5-dicarboxylic Acid, 6-(4,6-Dimethyl-2-octenoate) (9).** To a solution of **24** (47 mg, 0.054 mmol) in THF (1 mL) was added tetra-*n*-butylammonium fluoride (1 M solution in THF, 60 mL, 60 mmol). After stirring at room temperature for 0.5 h, the mixture was diluted with EtOAc (10 mL), washed with 2 M HCl (5 mL) and brine

(2 × 5 mL), dried, and concentrated to a colorless gum (40 mg). Flash column chromatography (SiO_2/EtOAc:cyclohexane, 1:3) gave the desilylated product as a colorless gum (33 mg, 81%): NMR ($CDCl_3$) δ 0.75−0.90 (m, 9H, 3 CH_3), 1.05 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 1.51 and 1.55 (2s, 18H, 2 *t*-*Bu*O_2C), 2.09 (s, 3H, CH_3CO_2), 2.70 (1H, dd, J = 14, 5 Hz, one proton of PhCH_2), 3.15 (s, 1H, O*H*), 3.71 (s, 1H, O*H*), 4.01 (d, 1H, J = 2.5 Hz, H-7), 4.07 (d, 1H, J = 9.5 Hz, H-4), 4.34 (d, 1H, J = 9.5 Hz, H-3), 4.93 and 4.96 (2s, 2H, C=CH_2), 5.09 (d, 1H, J = 5 Hz, C*H*OAc), 5.24 (d, 1H, J = 2.5 Hz, H-6), 5.77 (d, 1H, J = 16 Hz, CH=C*H*CO), 6.92 (dd, 1H, J = 16, 9 Hz, C*H*=CHCO), 7.1−7.3 (bm, 5H, C_6H_5); MS (thermospray, +ve) *m*/*z* 776 (M + NH_4)$^+$. Anal. ($C_{42}H_{62}O_{12}$) H; C: calcd, 66.47; found, C 67.17.

This desilylated compound (12 mg, 0.016 mmol) was dissolved in formic acid (1 mL). After stirring at room temperature for 2 h, the solvent was evaporated. The residue was purified by preparative HPLC (column A) eluting with 60% MeCN−H_2O/0.1% TFA (t_R = 23 min) to give **9** as a colorless gum (6 mg, 59%): NMR (CD_3OD) δ 1.04 (d, 3H, J = 7 Hz, CH=CHCHCH_3), 2.09 (s, 3H, CH_3CO_2), 2.66 (dd, 1H, J = 14, 6 Hz, one proton of PhCH_2), 3.96 (d, 1H, J = 10 Hz, H-4), 4.05 (d, 1H, J = 2 Hz, H-7), 4.45 (d, 1H, J = 10 Hz, H-3), 4.93 and 4.97 (2s, 2H, C=CH_2), 5.04 (d, 1H, J = 5 Hz, C*H*OAc), 5.59 (d, 1H, J = 2 Hz, H-6), 5.83 (d, 1H, J = 16 Hz, CH=C*H*CO), 6.87 (dd, 1H, J = 16, 9 Hz, C*H*=CHCO), 7.1−7.3 (m, 5H, C_6H_5); HRMS ($C_{34}H_{45}O_{12}$)$^+$ calcd 645.2911, found 645.2889; analytical HPLC (60% MeCN−H_2O/0.1% TFA) showed 99.6% purity (t_R = 9.58 min). Anal. ($C_{34}H_{46}O_{12}$·1.3H_2O) C, H.

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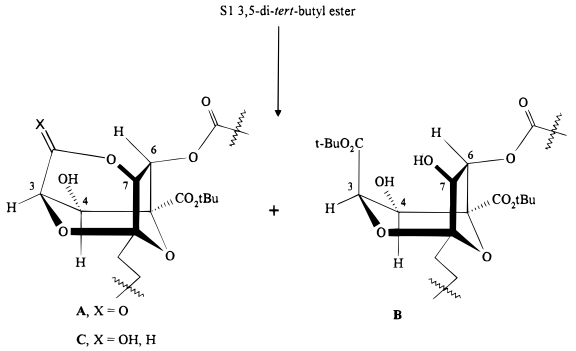

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