Stereocontrolled Total Synthesis of an Annonacin A-Type Acetogenin: Pseudoannonacin A?†

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A stereocontrolled first total synthesis of a diastereomer of the presumed mono-tetrahydrofuran type acetogenin annonacin A, starting with enantiomerically pure precursors, is described. The absolute stereochemistry of the $C_{15}-C_{20}$ segment corresponding to the tetrahydrofuran ring of the natural product was secured by X-ray crystal structure analysis of an advanced intermediate. The synthetic product (a mixture of epimers at C_{10}) had spectroscopic data identical to that of the natural product, but a different optical rotation.

The polyketide-derived fatty acid natural products belonging to the acetogenin group were isolated from the Annonaceae family of tropical and subtropical trees.[1] They are characterized by the presence of a mono- or bis-tetrahydrofuran ring(s) as a part of a "central" core unit of a long-chain hydrocarbon that may also contain hydroxy groups. Usually the end unit in these intriguing natural products consists of a butenolide moiety. The acetogenins exhibit a broad range of potent biological activities that include antitumor, antiprotozoal, antimicrobial, immunosuppressant, antifeedant, and related effects to mention a few.[2] Despite such a plethora of biological and physiological activities in animals and insects, only a few structures have been elucidated beyond doubt through synthesis. Stereochemical assignments have been made by inference to known structures and by correlating biogenetic patterns and based on comparisons with material obtained by total synthesis.[3] Although, a number of crystalline acetogenins are known,[2] no X-ray structures of any of the mono-tetrahydrofuran types have been determined to the best of our knowledge.

The largest group of annonaceous acetogenins are characterized by the presence of a secondary hydroxy group at the α,α′-position of the hydrocarbon chains on each side of a tetrahydrofuran ring. Although they are fewer in number compared to the bis-tetrahydrofuran types,[3] they present a major challenge for synthesis in view of the presence of four stereogenic centers encompassing the central tetrahydrofuran ring and its flanking carbon atoms. In some analogues, the additional hydroxy groups are present on the hydrocarbon chain between the tetrahydrofuran ring and the chiral butenolide end group. The structures of solamin, corrosolone, and annonacin A are shown in Figure 1 as representative examples of mono-tetrahydrofuran type acetogenins.

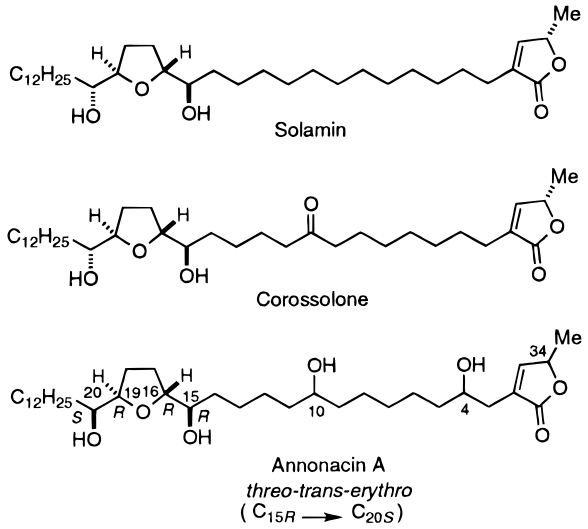

Figure 1.

The total synthesis of solamin was reported by Trost,[4] Keinan,[5] Oritani,[6] and their co-workers, utilizing different approaches. The synthesis of corossolone, starting with D-tartaric acid and L-lactic acid as chiral templates, was described by Wu and co-workers.[7] Although fragments of annonacin A have been synthesized,[8,9] its total synthesis has not been achieved to the best of our knowledge.

Annonacin A was isolated from seeds of *Annona squamosa* L. and obtained as an amorphous solid, $[\alpha]_D$ +23.8 (CH_2Cl_2).[10] It was characterized spectroscopically, and the relative configuration of the central tetrahydro-

† Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday, wishing him the best in life and in chemistry.

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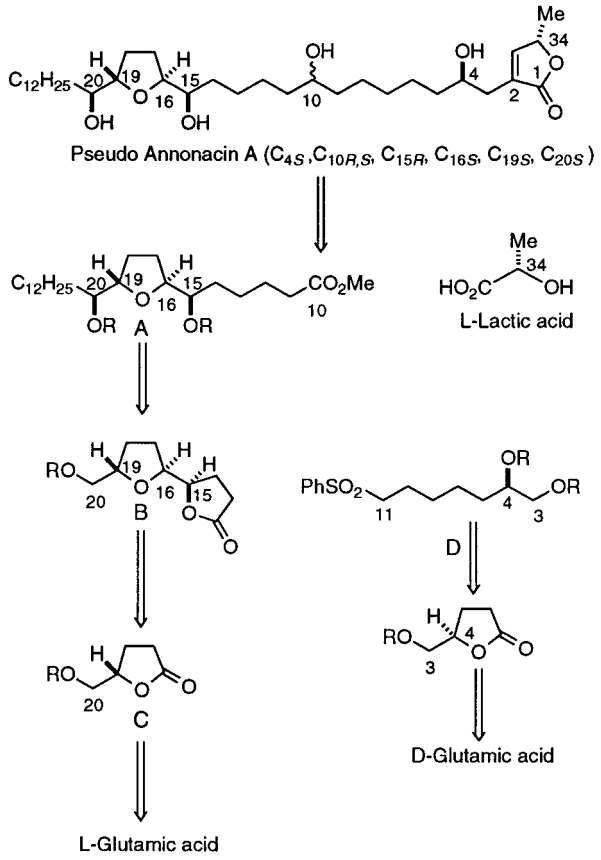


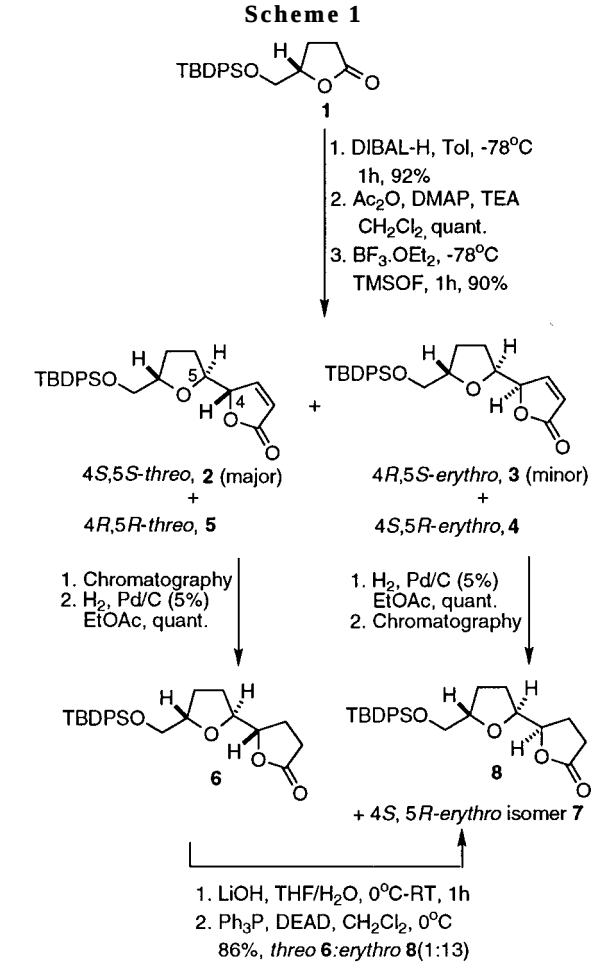
Figure 2.

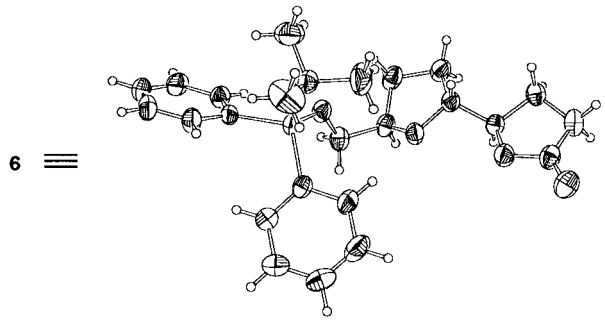
furan ring was assigned as being *threo-trans-erythro* (C_{16R},C_{19R})[1,2,10] as shown in Figure 1. The configurations at C_4 and C_{10} remain unknown. Since reference samples of known absolute (or relative) configuration are not available, it has not been possible to exclude the *erythro-trans-threo* (for C_{15R},C_{16S},C_{19S},C_{20S}) configuration for annonacin A, in which C_{16} and C_{19} would be epimeric to the commonly depicted *threo-trans-erythro* ($C_{15R} \rightarrow C_{20S}$) relationship shown in Figure 1.

Stereochemical features have been further complicated by the absence of a uniform way of depicting the structural representations of these compounds. Changes in perspective have often led to confusion in correlations and in synthesis planning.[11]

We describe in this paper our efforts toward a concise and stereocontrolled total synthesis of the *erythro-trans-threo* (C_{15R},C_{16S},C_{19S},C_{20S}) diastereomer of annonacin A utilizing the Chiron approach. A disconnective analysis shown in Figure 2 relates the stereochemistry of C_{19} and C_4 in the natural product to L-glutamic and D-glutamic acids, respectively, and C_{34} to that of L-lactic acid (C_{33}–C_{35}). The well-known lactone C[12] obtained from L-glutamic acid can be elaborated to a lactone intermediate B that secures the configuration of the tetrahydrofuran ring junctions as well as that of C_{15}. Further manipulation and chain elongation at both ends of B produces an advanced intermediate A, which is then elaborated to the intended natural product. The C_{11}–C_{34} subunit would come from L-lactic acid, and intermediate D can be prepared from D-glutamic acid. In such a strategy, only the configuration at C_{10} would remain uncertain, and in the worst of scenarios, it would consist of a mixture of epimers in the final product.

Scheme 1



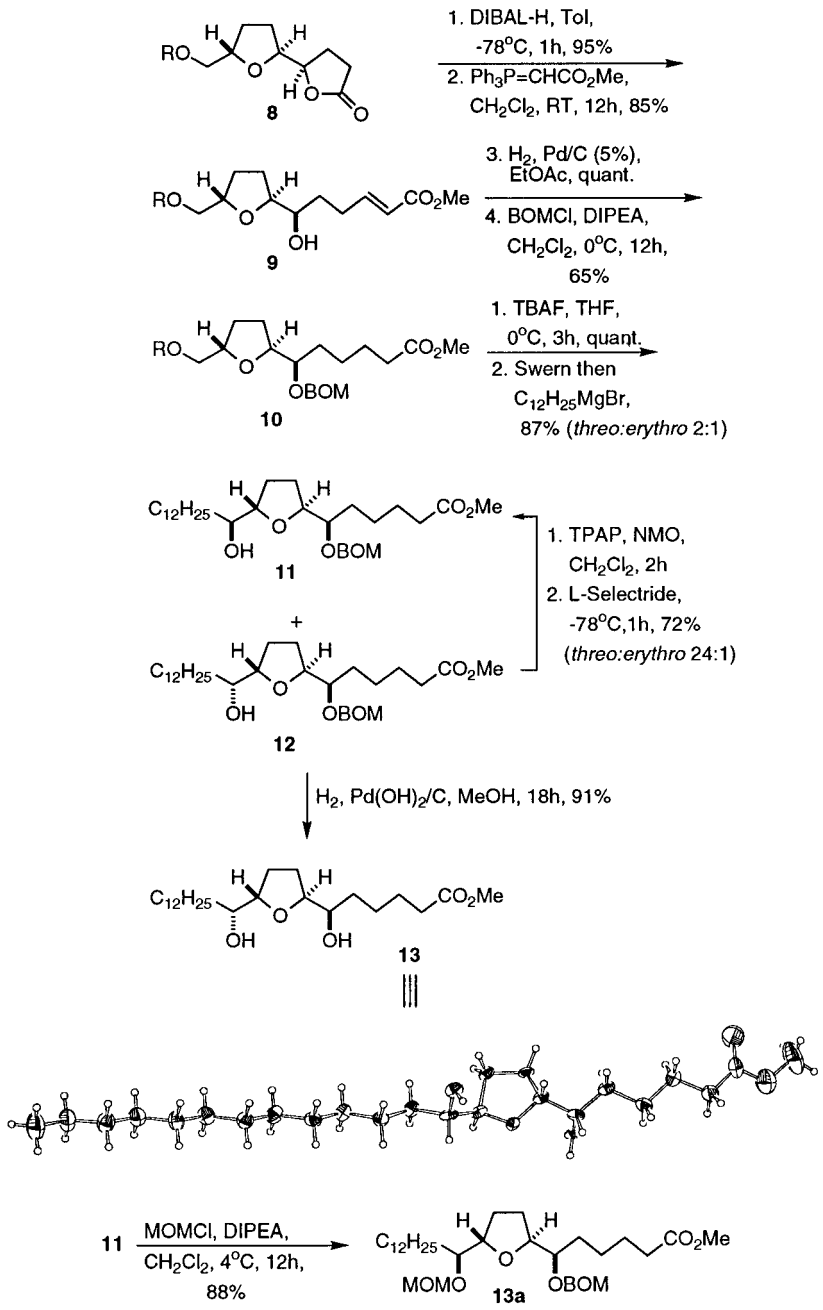


Results and Discussion

The synthesis started with the condensation of 2-((trimethylsilyl)oxy)furan with the lactol derived from the lactone **1**[12] (Scheme 1) under Lewis acid catalysis.[13,14] This reaction produced a mixture of four diastereomeric lactone adducts in which the 4*S*,5*S*-*threo* and the 4*R*,5*S*-

(10) Lieb, F.; Nonfon, M.; Wachendorff-Neumann, U.; Wendisch, D. *Planta Med.* **1990**, *56*, 317.
(11) Compare for example the representations of annonacin A and related analogues in refs 4–9.
(12) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055.
(13) (a) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037. (b) Rassu, G.; Spanu, P.; Casiraghi, G.; Pinna, L. *Tetrahedron* **1991**, *47*, 8025 and the references therein.
(14) Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.* **1993**, *34*, 2299. See also: Frigadère, B.; Chaboche, C.; Peyrat, J.-F.; Cavé, A. *Tetrahedron Lett.* **1993**, *34*, 8093. Frigadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428.

Scheme 2



erythro isomers **2** and **3** (1.14:1 ratio) were the major products which could be separated from the minor isomers by crystallization or chromatography. The absolute configuration of the *threo* isomer was determined unambiguously by a single-crystal X-ray analysis. The stereochemical identity of the 4*R*,5*S*-*erythro* isomer **3** was clearly established by a chemical correlation with **2**. Thus, catalytic reduction of **2** gave the saturated lactone **6** whose structure was also confirmed by X-ray analysis (Scheme 1). Hydrolysis to the lithium salt and careful acidification, followed by an intramolecular Mitsunobu inversion by lactone formation,[15] gave the 4*R*,5*S*-lactone **8** as the predominant product (13:1). Hydrogenation of **3** gave a product identical with that obtained from the intramolecular inversion sequence starting with **6** of known absolute configuration. It should be noted that the isomeric lactones **2** and **3** and their saturated derivatives **6** and **8** were easily separable by column chromatography or by fractional crystallization.

With three stereogenic centers corresponding to C_{15}, C_{16}, and C_{19} of the intended *erythro-trans-threo* annonacin A isomer secured in intermediate **8**, we proceeded to elaborate the chains flanking the tetrahydrofuran unit. Thus, reduction of **8** with DIBAL-H followed by a Wittig extension[16] led to **9**. Hydrogenation afforded the corresponding saturated ester which was protected as the BOM ether **10** (Scheme 2). Removal of the silyl protecting group, Swern oxidation, and a Grignard reaction with

(15) See, for example: (a) Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947. (b) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. (c) Hughes, D. L. In *Organic Reactions*; Paquette, L. A.; et al., Eds.; Wiley: New York, 1992; Vol. 42, Chapter 2. (d) Mitsunobu, O. *Synthesis* **1981**, 1.

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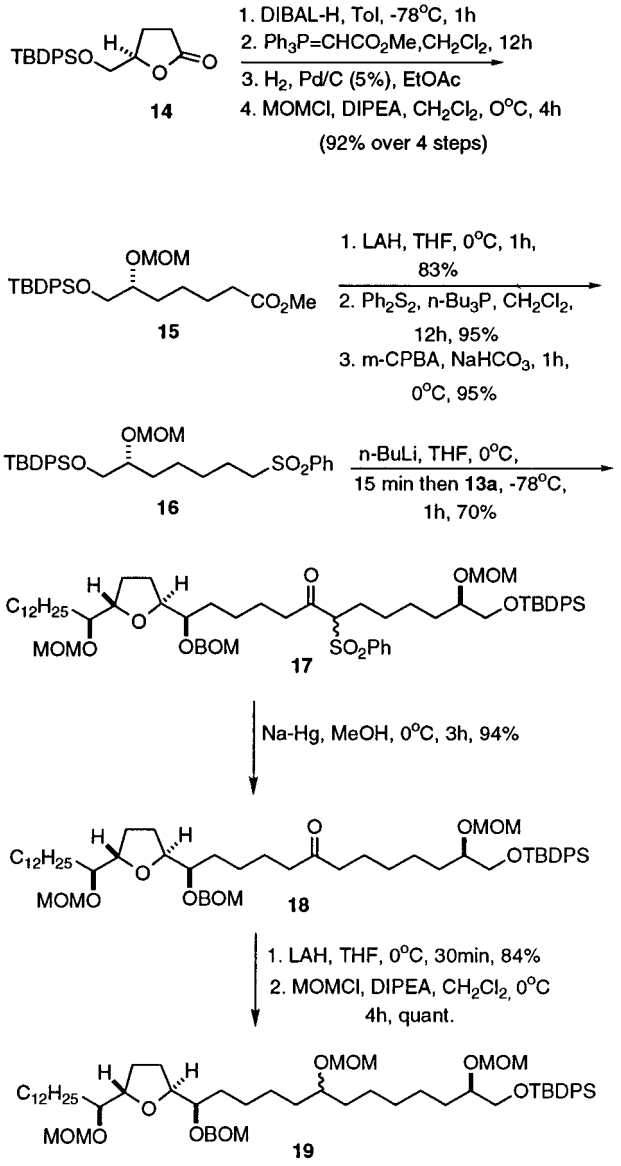
dodecylmagnesium bromide led to a 2:1 mixture of epimeric alcohols **11** and **12** in excellent yield. Upon deprotection, the minor crystalline *erythro* alcohol **13** was assigned the C_{20R} configuration (annonacin A numbering) as evidenced by single-crystal X-ray analysis. The major isomer **11** would thus be the required precursor to the intended target product. A chemical correlation with **12** was possible by an oxidation−reduction sequence. Thus, oxidation of **12** with TPAP,[17] followed by reduction of the resulting ketone with L-Selectride,[18] gave the desired alcohol **11** as the preponderant product (>24:1). Reduction with $NaBH_4$ in MeOH gave much lower ratios of the desired isomer. It is of interest to comment on the stereochemical outcome of the Grignard reaction. Normally, α-aldehydo tetrahydrofurans undergo a chelation-controlled addition by virtue of a favorable coordination of the organomagnesium reagent with the ring oxygen.[19] This should have led to a much higher ratio of **11** as the major isomer. Evidently, the presence of the α-OBOM group in the aldehyde derived from **10** interferes with the anticipated five-membered chelate, thus preventing a clean enantiofacial attack. Alternative methods using cuprate reagents ($C_{12}H_{25}MgBr/Li_2CuCl_4$ or $/CuBr{\cdot}SMe_2$) derived from the Grignard reagent led to higher ratios of **11** albeit in lower yields.

With the $C_{10}-C_{32}$ segment of the intended diastereomer of annonacin A in hand, and an absolute stereochemistry secured by X-ray crystal structure analysis, we proceeded to elaborate the remainder of the right-hand portion of the advanced intermediate **11** after protection to the MOM ether **13a** (Scheme 2). A sulfone anion coupling method was adopted as shown in Scheme 3. Thus, the anion of the phenyl sulfone chiron **16**, readily prepared from D-glutamic acid, was condensed[20] directly with the ester function in **13a** to give the α-keto sulfone **17**. Reductive desulfonylation with Na/Hg,[21] followed by reduction of the ketone group in **18** and protection, afforded the intermediate **19** as an epimeric mixture at C_{10} (annonacin A numbering). Unfortunately attempts to separate the diastereomers at this stage by derivatization (acetate, benzoate, esters) were unsuccessful. Also, no attempts were made to achieve stereoselective reduction of the ketone group in **18**.

It now remained to elaborate the chiral butenolide unit in order to complete the total synthesis of our intended target. Previous efforts in the synthesis of acetogenins have utilized the O-THP derivative of (*S*)-lactaldehyde as a source of the butenolide.[22] Thus, desilylation of **19** (Scheme 4) and oxidation to the aldehyde followed by a Wittig extension and reduction gave the saturated ester **20**. Condensation of the enolate derived from **20** with O-THP (*S*)-lactaldehyde,[22] followed by mesylation and elimination in the presence of DBU, gave the protected precursor **21**.

Finally, treatment with TMS-Br[23] at low temperature smoothly removed the MOM and BOM groups to afford

Scheme 3



22 as a microcrystalline solid, mp 100−102 °C, $[\alpha]_D$ +2.5. Due to the unavailability of annonacin A, a comparison of our synthetic sample with the authentic natural product was not possible. Table 1 lists comparisons of ^1H and ^{13}C NMR data at 400 and 100 MHz, respectively, which are in excellent agreement with published data for annonacin A itself.[10] Previous ^{13}C NMR correlations have also been made with synthetic fragments[8] and indicate a distinct difference between the chemical shifts for a *threo-trans-threo* pattern as in murisolin and those found in the proposed *threo-trans-erythro* ($C_{15} \rightarrow C_{20}$) configuration for annonacin A, or its *erythro-trans-threo* ($C_{15} \rightarrow C_{20}$) diastereovariant.[24]

In view of the stereocontrolled method of synthesis of our product, we can safely assign the *erythro-trans-threo* (C_{15R},C_{16S},C_{19S},C_{20S}) absolute configuration to the tetrahydrofuran unit and its flanking α,α′-carbon atoms bearing the secondary hydroxyl groups. The discrepancy with the optical rotation value of our synthetic product

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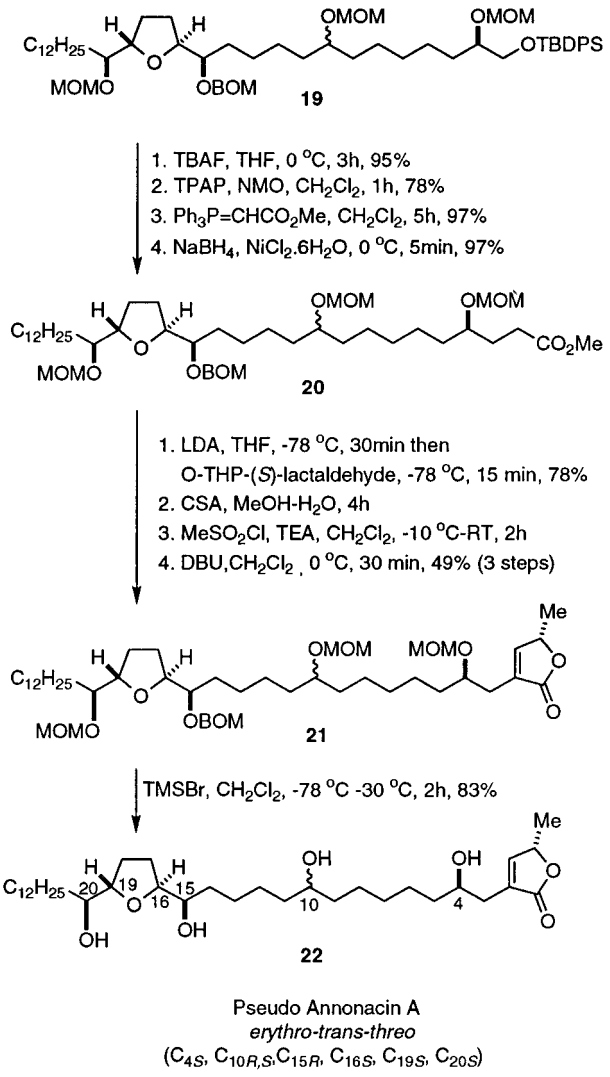
Scheme 4



Pseudo Annonacin A
erythro-trans-threo
(C_{4S}, $C_{10R,S}$,C_{15R}, C_{16S}, C_{19S}, C_{20S})

Table 1. Selected ^{1}H and ^{13}C NMR Data of Annonacin A[10] and 22

	annonacin A (ref 10)	**22**-Hδ	annonacin A (ref 10)	**22**-Cδ
1			174.68	174.51
2			131.14	131.06
3			37.41	37.18
4	3.82	3.84	69.77	69.83; 69.82[b]
5			31.94	31.81
9			37.30	37.18
10	3.60	3.58	71.69	71.66; 71.63[b]
11			37.30	37.18
14			33.36	33.29
15	3.40	3.38	74.36	74.26
16	3.82	3.84	82.31	82.01
19	3.82	3.84	83.32	83.16
20	3.82	3.84	71.62	71.41; 71.38[b]
21			33.12	33.15
32	0.88	0.88		
33	7.17	7.18	151.93	151.75
34	5.02	5.06	78.03	77.89
35	1.42	1.43	19.10	19.00

[a] Data were recorded in $CDCl_3$ at 400 MHz. [b] Split signal.

with that reported for the natural product and its undescribed physical state including a melting point remain unresolved issues which are subject to conjecture. The presence of two epimers differing in configuration at C_{10} in the synthetic sample is a minor issue that can be resolved on the basis of an alternative synthesis starting with an enantiopure precursor corresponding to that segment of the molecule. It is doubtful that the presence of two diastereomers differing in the configuration at C_{10} only accounts for the discrepancy in the physical constants reported for annonacin A.[10]

It is possible that coincidentally the ^{1}H and ^{13}C NMR chemical shifts of the proposed *threo-trans-erythro* (C_{15R},C_{16R},C_{19R},C_{20S}) configuration of annonacin A[10] and those of the synthetic diastereomer **22** are nearly identical. It is therefore clear that this particular *threo-trans-erythro* isomer should be synthesized also before an unambiguous assignment of absolute stereochemistry to annonacin A can be made. The unavailability of natural annonacin A will still present a problem in correlation, since only an optical rotation value can be compared with that of a synthetic sample. The unknown absolute configuration at C_4, C_{10}, and C_{34} in the natural product only heightens the challenge for the hunt in our laboratory and presumably elsewhere also. For the time being we shall designate the (C_{15R},C_{16S},C_{19S},C_{20S}) *erythro-trans-threo* isomer **22** as pseudo-annonacin A.

Experimental Section

General Experimental. ^{1}H and ^{13}C spectra were recorded at 300 and 400 MHz NMR in $CDCl_3$. IR spectra were recorded as solutions in $CHCl_3$. Optical rotations were recorded at ambient temperature. Mass spectra were obtained at low and high resolution. Organic solvents used were dried by standard methods. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Merck 60 F_{254} silica gel coated plates. Flash column chromatography was carried out using 230−400 mesh silica gel at increased pressure.

Isomers of 5-(5′-(((*tert*-Butyldiphenylsilylanyl)oxy)-methyl)tetrahydrofur-2′-yl)-5*H*-furan-2-one (2, 3, 5, and 4). A solution of DIBAL-H (45.9 mL, 1 M, 45.9 mmol) in toluene was added dropwise to a stirring solution of lactone **1** (12.5 g, 35.3 mmol) in toluene (176 mL) at −78 °C. After 1 h of stirring at −78 °C, methanol was added dropwise at −78 °C and the solution was stirred for 20 min before being allowed to warm to 0 °C. Ether was added followed by the addition of water (2 drops). On allowing the solution to warm to rt a slurry formed which was filtered under reduced pressure and washed repeatedly with hot EtOAc. The filtrates were collected, concentrated under reduced pressure, and passed through a short silica plug (hexane:EtOAc 4:1). Removal of the eluant under reduced pressure gave the product (11.56 g, 92%) as a colorless oil. The resulting lactol (11.5 g, 32.56 mmol) was acetylated by treatment with acetic anhydride (4.3 mL, 45.90 mmol), triethylamine (9.8 mL, 70.6 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (150 mL) at rt for 1 h. After removal of the solvent under reduced pressure, the remaining oil was rapidly passed through as short silica plug (hexane:EtOAc 4:1) to afford, after solvent removal, a colorless oil (12.9 g, 100%).

2-((Trimethylsilyl)oxy)furan (8.3 mL, 49.4 mmol) was added smoothly to a solution of the above product (12.9 g, 32.47 mmol) in CH_2Cl_2 (120 mL) at −78 °C, followed after 2 min by the dropwise addition of BF_3·OEt_2 (3 mL, 24.7 mmol). The resultant bright yellow solution was maintained at −78 °C for 1 h after which saturated aqueous NH_4Cl was added. The mixture was allowed to warm to rt whereupon the organic layer was separated, washed with water and brine, and dried (Na_2SO_4). Solvent removal followed by column chromatography (hexane:EtOAc 9:1) gave **2** (6.18 g, 40.7%) and **5** (0.86 g, 5.7%) which could be further separated by crystallization and an inseparable mixture of compounds **3** and **4** (4.56:1, 6.6 g, 43.5%) as a colorless oil. For **2**: $[\alpha]_D$ −53.6 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 1765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.42−7.37 (m, 7H), 6.16 (dd, J = 2.07, 5.7 Hz, 1H), 5.02 (m, 1H), 4.26 (m, 1H), 4.13 (m, 1H), 3.65 (dd, J = 10.7,

4.5 Hz, 1H), 3.64 (dd, J = 10.7, 4.5 Hz, 1H), 2.08−1.88 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 153.4, 135.5, 133.5, 129.6, 127.6, 122.5, 84.7, 80.7, 77.8, 66.1, 27.5, 26.8, 20.9, 19.2; EIMS (*m*/*z*) 421 (M − 1), 365, (M − ^{t}Bu); HRMS calcd for $C_{25}H_{29}O_4Si$ (M − 1) 421.18350, found 421.18450. **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.42−7.37 (m, 7H), 6.10 (dd, J = 5.7, 2.0 Hz, 1H), 5.05 (m, 1H), 4.20 (m, 1H), 4.06 (m, 1H), 3.65 (m, 2H), 2.10−1.70 (m, 4H), 1.04 (s, 9H).

(2*S*,2′*S*,5′*S*)-5-(5′-(((*tert*-Butyl-diphenyl-silylanyl)-oxy)methyl)tetrahydro[2,2′]bifuranyl-5-one (6). A mixture of **2** (6.18 g, 14.64 mmol) and Pd/C (0.5 g, 5%) in EtOAc (30 mL) was stirred under 1 atm of pressure of hydrogen for 5 h. Filtration of the mixture through Celite followed by solvent removal under reduced pressure gave the desired product **6** (6.20 g, quantitative) as a colorless oil, which crystallized on standing: mp 76−77 °C; $[\alpha]_D$ +4.0 (*c* 0.075, $CHCl_3$); IR ($CHCl_3$) 1775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.45−7.36 (m, 6H), 4.47 (m, 1H), 4.13 (m, 1H), 4.05 (m, 1H), 3.68 (dd, J = 10.7, 4.4 Hz, 1H), 3.64 (dd, J = 6.5, 4.4 Hz, 1H), 2.69 (m, 1H), 2.43 (m, 1H), 2.24 (m, 2H), 2.07−1.82 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 135.5, 135.6, 129.5, 127.5, 127.6, 81.0, 80.9, 80.4, 66.2, 28.0, 27.8, 27.7, 26.7, 24.6, 19.1; EIMS (*m*/*z*) 423 (M − 1), 367; HRMS calcd for $C_{25}H_{31}O_4Si$ (M − 1) 423.19916, found 423.19740.

(2*R*,2′*S*,5′*S*)-5′-(((*tert*-Butyldiphenylsilanyl)oxy)-methyl)tetrahydro[2,2′]bifuranyl-5-one (8). A mixture of **3** and **4** (4.56:1 ratio, 6.60 g, 15.64 mmol) and Pd/C (0.5 g, 5%) in EtOAc (30 mL) was stirred under 1 atm of pressure of hydrogen for 5 h. Filtration of the mixture through Celite followed by solvent removal under reduced pressure gave a mixture of **8** and its 4*S*,5*R*-*erythro* isomer **7** (6.63 g, quantitative). Column chromatography (10% EtOAc:hexane) gave the pure *trans*-*erythro* compound **8** (5.0 g, 92%) as a colorless oil and the *cis*-4*S*,5*R*-*erythro* compound **7** (1.04 g) as a colorless oil: For **8**: $[\alpha]_D$ −3.9 (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 1780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.70 (m, 4H), 7.43−7.36 (m, 6H), 4.41 (m, 4H), 4.14 (m, 1H), 3.68 (dd, J = 10.7, 4.5 Hz, 1H), 3.64 (dd, J = 10.7, 4.5 Hz, 1H), 2.53 (m, 2H), 2.30 (m, 1H), 2.20−1.80 (m, 3H), 1.73 (m, 1H), 1.06 (s, 9H); ^{13}C MNR (100 MHz, $CDCl_3$) δ 177.0, 135.5, 133.4, 129.5, 127.5, 81.6, 80.2, 80.1, 66.2, 28.2, 28.0, 27.5, 26.7, 23.8, 19.1; EIMS (*m*/*z*) 423 (M − 1), 367 (M − ^{t}Bu), for 347. For **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.45−7.36 (m, 6H), 4.48 (m, 1H), 4.11 (m, 1H), 4.05 (m, 1H), 3.68 (dd, J = 10.7, 4.4 Hz, 1H), 3.64 (dd, J = 6.5, 4.4 Hz, 1H), 2.70−2.52 (m, 1H), 2.50 (m, 2H), 2.49−2.35 (m, 1H), 1.85 (m, 4H), 1.05 (s, 9H).

Intramolecular Mitsunobu Reaction (8 from 6). To a stirring solution of **6** (100 mg, 0.235 mmol) in THF:H_2O (10:1, 11 mL) was added LiOH (13 mg, 0.54 mmol) in one portion at 0 °C. Stirring was continued for 1 h until TLC analysis indicated the absence of the starting material. Prewashed Amberlite IR-120 resin (H^+) was added to the aqueous phase until pH ∼4 was attained. The mixture was filtered, and the aqueous phase was repeatedly extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was further dried over P_2O_5 under reduced pressure for 1 h to afford the crude ω-hydroxy acid intermediate as a viscous oil (95.5 mg, 0.216 mmol). A solution of Ph_3P (170 mg, 0.648 mmol) in THF (1 mL) was added to a solution of this intermediate in THF (11.7 mL) at 0 °C followed by the dropwise addition of DEAD (0.1 mL, 2.97 mmol), and the yellow solution was stirred for a further 30 min. Evaporation of the solvent followed by column chromatography (hexane:EtOAc 9:1) gave a 13:1 inseparable mixture of **8** and **6** (80 mg, 86%).

(2′*S*,5′*S*,6*R*)-6-[5′-(((*tert*-Butyldiphenylsilanyl)oxy)-methyl)tetrahydrofuran-2′-yl]-6-hydroxyhex-2-enoic Acid Methyl Ester (9). A solution of DIBAL-H (4.18 mL, 1.5 M, 6.2 mmol) in toluene was added dropwise to a stirring solution of **8** (1.9 g, 4.48 mmol) in toluene (22 mL) at −78 °C. The solution was stirred at −78 °C for 1 h. Methanol (6 mL) was added dropwise at −78 °C, and the solution was stirred for 20 min before being allowed to warm to 0 °C. Ethyl acetate (10 mL) was added followed by the addition of water (2 drops). On allowing the solution to warm to rt, a slurry formed which was filtered under reduce pressure and washed repeatedly with hot EtOAc. The filtrates were concentrated under reduced pressure and passed through a short silica plug (hexane:EtOAc 4:1). Removal of the eluant under reduced pressure gave the lactol (1.79 g, 94%) as a colorless oil. To a solution of lactol (1.79 g, 4.2 mmol) in CH_2Cl_2 (42 mL) was added a catalytic amount of $PhCO_2H$ followed by $Ph_3P{=}CHCO_2$-Me (1.82 g, 5.46 mmol) in one portion. The reaction mixture was stirred for 12 h at rt, the solvent was evaporated, and the residue was purified by column chromatography (hexane: EtOAc 5:1) to give **9** (1.52 g, 85%) as a colorless oil: $[\alpha]_D$ +1.34 (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) 3600−3400, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.69 (m, 10H), 7.0 (dt, J = 15.6, 7.1, 6.7 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 4.15 (m, 1H), 3.85 (m, 1H), 3.71 (s, 3H), 3.67 (dd, J = 4.6, 2.0 Hz, 2H), 2.57 (brs, OH), 2.45 (m, 1H), 2.28 (m, 1H), 1.55 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.9, 135.5, 133.5, 129.5, 127.5, 121.1, 82.2, 79.8, 71.1, 66.4, 51.2, 31.0, 28.6, 27.9, 26.8, 26.7, 19.1; EIMS (*m*/*z*) 483 (M + 1), 460, 425, 405, 306, 153, (100.0); HRMS calcd for $C_{28}H_{39}O_5Si$ (M + 1) 483.2566, found 483.25510.

(2′*S*,5′*S*,6*R*)-6-((Benzyloxy)methoxy)-6-[5′-(((*tert*-butyl-diphenylsilanyl)oxy)methyl)tetrahydrofuran-2′-yl]-hexanoic Acid Methyl Ester (10). A mixture of 10% Pd/C (0.12 g) and **9** (1.52 g, 3.15 mmol) in EtOAc (3 mL) was stirred for 5 h at rt. The mixture was filtered through Celite, washed with EtOAc, and concentrated to afford the product (1.5 g, quantitative) as a colorless oil: $[\alpha]_D$ +33.3 (*c* 1.68, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.38−7.31 (m, 6H), 4.1 (m, 1H), 3.85 (m, 1H), 3.64 (m, 2H), 3.60 (m, 1H), 3.60 (s, 3H), 2.70 (brs OH), 2.28 (t, J = 7.4 Hz, 2H), 1.98−1.41 (m, 10H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 135.5, 133.5, 129.5, 127.5, 85.2, 79.8, 71.1, 66.4, 51.2, 34.0, 33.0, 27.9, 26.8, 26.7, 19.1; EIMS (*m*/*z*) 485 (M + 1), 467, 135 (100.0); HRMS calcd for $C_{28}H_{41}O_5Si$ (M + 1) 485.27234, found 485.27370.

BOMCl (4.39 mL, 31.5 mmol) was added to a solution of the above product (1.7 g, 3.51 mmol) and DIPEA (5.5 mL, 31.5 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The mixture was stirred for 48 h at 0 °C, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic layer was washed several times with water and brine and then dried (Na_2SO_4). Filtration and evaporation of the solvent afforded the crude mixture which was chromatographed on a silica gel column (hexane: EtOAc 6:1) to give **10** (1.37 g, 65%) as a colorless oil: $[\alpha]_D$ +10.68 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.76 (m, 4H), 7.48−7.31 (m, 6H), 4.94 (d, J = 6.88 Hz, 1H), 4.84 (d, J = 6.88 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.14 (m, 1H), 4.06 (m, 1H), 3.70 (m, 1H), 3.69 (m, 2H), 3.68 (s, 3H), 2.33 (t, J = 7.3 Hz, 2H), 2.15−1.85 (m, 4H), 1.84−1.31 (m, 6H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.9, 135.6, 133.6, 129.5, 128.3, 127.7, 127.6, 94.6, 81.4, 79.6, 78.7, 69.5, 66.5, 51.4, 33.9, 31.4, 28.2, 26.8, 25.2, 25.1, 19.2; HRMS calcd for $C_{36}H_{49}O_6$-SiNa 627.31177, found 627.31400.

(1′′*S*,2′*S*,5′*S*,6*R*)-6-((Benzyloxy)methoxy)-6-[5′-(1′′-hydroxytridecyl)tetrahydrofuran-2′-yl]hexanoic Acid Methyl Ester (11) and Isomer (12). To a solution of **10** (0.87 g, 1.45 mmol) in THF (29 mL) at 0 °C was added a solution of n-Bu_4NF (5.8 mL, 1.0M, 5.8 mmol) in THF, and the mixture was stirred for 3 h at rt, then quenched with saturated aqueous NH_4Cl, and diluted with ether and the organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography gave the expected alcohol (0.5 g, quantitative) as a colorless oil: $[\alpha]_D$ +19 (*c* 0.105, $CHCl_3$); IR ($CHCl_3$) 3695−3460, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 4.87 (d, J = 6.88 Hz, 1H), 4.6 (m, 2H), 4.04 (m, 1H), 3.99 (m, 1H), 3.73 (m, 1H), 3.62 (s, 3H), 3.61 (m, 1H), 3.50 (m, 1H), 2.27 (t, J = 7.4 Hz, 2H), 1.95−1.88 (m, 3H), 1.68−1.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 137.8, 128.2, 127.6, 127.5, 94.5, 81.2, 79.7, 78.4, 69.5, 64.7, 51.3, 33.8, 31.1, 27.5, 26.6, 25.0, 24.9; EIMS (*m*/*z*) 367 (M + 1), 338, 259 (100.0); HRMS calcd for $C_{20}H_{31}O_6$ (M +1) 367.21280, found 367.21207.

To a stirred solution of oxalyl chloride (1.89 mL, 0.162 mmol) in THF (2.95 mL) at −78 °C was added a solution of DMSO (2.52 mmol, 0.179 mL) in THF (1.26 mL). The solution was allowed to warm to −35 °C for 3 min and was then recooled to −78 °C. A solution of the above alcohol (461 mg, 1.26 mmol) in THF (2.37 mL) was then added to the reaction mixture. The resulting solution was allowed to warm to −35 °C, and after 15 min it was treated with DIPEA (1.09 mL). The reaction mixture was allowed to warm to rt, and an ethereal solution of dodecylmagnesium bromide (7.55 mL, 1.0M, 5.55 mmol) was then added dropwise to the vigorously stirred mixture at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl, diluted with ether, and the organic layer was washed with water and brine and then dried (Na_2SO_4). Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column (hexane:EtOAc 9:1), to give the *threo* isomer **11** (402.0 mg, 60%) and the *erythro* isomer **12** (184.0 mg, 27%) as a colorless oils.

Conversion of 12 to 11. TPAP (catalytic amount) was added as a single portion to a stirring mixture of the *erythro* alcohol **12** (138 mg, 0.258 mmol), NMO (*N*-methylmorpholine *N*-oxide) (60.5 mg, 0.512 mmol), and powdered 4 Å molecular sieves in CH_2Cl_2 (0.5 mL) at rt under argon. After 1 h of stirring, the reaction mixture was filtered through a pad of silica (EtOAc) and the solvent was removed under reduced pressure. L-Selectride (0.3 mL, 0.3 mmol) was added dropwise to a stirring solution of the freshly prepared ketone in THF (2.3 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h after which the reaction was quenched by the dropwise addition of methanol. Removal of the solvent followed by column chromatography (hexane:EtOAc 6:1) gave **11** (105 mg) and **12** (4 mg) (76%) as colorless oils. For **11**: $[\alpha]_D$ +5.56 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3584, 1735 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.34−7.26 (m, 5H), 4.89 (d, J = 6.8 Hz, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 11.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 3.98 (m, 1H), 3.76 (m, 1H), 3.64 (s, 3H), 3.35 (m, 1H), 2.34 (d, J = 3.8 Hz, OH), 2.29 (t, J = 7.4 Hz, 2H), 1.95−1.91 (m, 3H), 1.65−1.25 (m, 35H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 137.8, 128.3, 127.6, 127.5, 94.5, 82.7, 81.2, 78.2, 73.9, 69.5, 51.3, 33.8, 33.4, 31.8, 31.2, 29.6, 29.5, 29.4, 29.2, 28.3, 26.9, 25.5, 25.0, 24.9, 22.6, 14.0; EIMS (*m*/*z*) 533 (M + 1), 517, 427 (100.0); HRMS calcd for $C_{32}H_{53}O_6$ (M + 1) 533.38422, found 533.38190.

(1′′*R*,2′*S*,5′*S*,6*R*)-6-Hydroxy-6-[5′-(1′′-hydroxytridecyl)tetrahydrofuran-2′-yl]hexanoic Acid Methyl Ester (13). A mixture of **12** (10 mg, 0.019 mmol) and $Pd(OH)_2/C$ in dry methanol (1 mL) was stirred under 1 atm of pressure of hydrogen for 18 h. The resulting mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure to afford **13** (7.1 mg, 91%) as a colorless solid. Recrystallization (ether−diisopropyl ether) gave colorless plates that were used for X-ray analysis: mp 50−51 °C; $[\alpha]_D$ −8.1 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.93−3.89 (m, 2H), 3.81−3.77 (m, 2H), 3.67 (s, 3H), 2.33 (d, J = 7.4 Hz, 2H), 2.05−1.95 (brs, 2¥OH), 1.91−1.85 (m, 4H), 1.71−1.50 (m, 6H), 1.43−1.26 (m, 25H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 82.9, 82.8, 71.8, 71.6, 51.4, 33.8, 33.2, 32.4, 31.9, 31.8, 29.6, 29.5 (×2), 29.3, 28.5, 25.9, 25.4, 25.2, 25.1, 24.8, 22.6, 14.0; HRMS calcd for $C_{24}H_{47}O_5$ (M + 1) 415.3423, found 415.3401.

(1′′*S*,2′*S*,5′*S*,6*R*)-6-((Benzyloxy)methoxy)-6-[5′-(1′′-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl]hexanoic Acid Methyl Ester (13a). MOMCl (0.4 mL, 5.33 mmol) was added to a solution of **11** (190 mg, 0.35 mmol) and DIPEA (1.24 mL, 7.11 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred for 12 h at 4 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2, and the organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography (hexane:EtOAc 9:1) gave **13a** (181 mg, 88%) as a colorless oil: $[\alpha]_D$ −3.9 (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 4.89 (d, J = 6.8 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.78 (d, J = 6.7 Hz, 1H), 4.64 (m, 3H), 3.95 (m, 2H), 3.70 (m, 1H), 3.63 (s, 3H), 3.37 (m, 1H), 3.30 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.91−1.80 (m, 3H), 1.70−1.25 (m, 29H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 137.9, 128.2, 127.6, 127.5, 96.5, 94.5, 81.6, 81.2, 79.4, 78.5, 69.5, 55.5, 51.3, 33.8, 31.8, 31.3, 31.2, 29.7, 29.5, 29.4, 29.2, 28.4, 26.6, 25.4, 25.0, 24.9, 22.6, 14.0; EIMS (*m*/*z*) 577 (M − 1) 547, 471 (100.0); HRMS calcd for $C_{34}H_{57}O_7$ (M − 1) 577.41040, found 577.41280.

(6*R*)-7-((*tert*-Butyldiphenylsilanyl)oxy)-6-(methoxymethoxy)heptanoic Acid Methyl Ester (15). A solution of DIBAL-H (17.45 mL, 1.5 M, 26.1 mmol) in toluene was added dropwise to a stirring solution of lactone **14**[12] (7.13 g, 20.1 mmol) in toluene (100 mL) at −78 °C. The solution was stirred at −78 °C for 1 h, after which methanol was added dropwise at −78 °C and the solution was stirred for 20 min before being allowed to warm to 0 °C. EtOAc was added followed by the addition of water (2 drops). A slurry formed which was filtered under reduced pressure and washed repeatedly with hot EtOAc. The filtrates were collected, concentrated under reduced pressure, and passed through a short silica plug (hexane:EtOAc 4:1). Removal of the eluant under reduced pressure gave the expected lactol (6.5 g, 93%) as a colorless oil. To a solution of lactol (0.64 g, 1.8 mmol) in CH_2Cl_2 (18 mL) at rt was added a catalytic amount of $PhCO_2H$ followed by $Ph_3P{=}CHCO_2Me$ (0.78 g, 2.3 mmol) in one portion. The reaction mixture was stirred for 12 h at rt, the solvent was evaporated, and the residue was purified by column chromatography (hexane:EtOAc 5:1) to give the expected α,β-unsaturated ester (0.68 g, 92%) as a colorless oil: $[\alpha]_D$ + 2 (*c* 0.45, $CHCl_3$); HRMS calcd for $C_{24}H_{33}O_4Si$ (M + 1) 413.21481, found 413.21310.

A mixture of 10% Pd/C (100 mg) and the above product (0.686 g, 1.66 mmol) in EtOAc (1.6 mL) was stirred for 2 h at rt under 1 atm of pressure of hydrogen. The mixture was filtered through Celite, washed with EtOAc, and concentrated to afford the product (0.689 g, 100%) as a colorless oil: $[\alpha]_D$ +28 (*c* 1.05, $CHCl_3$); HRMS calcd for $C_{24}H_{34}O_4NaSi$ 437.21240, found 437.21020.

MOMCl (0.69 mL, 9.12 mmol) was added to a solution of the above-obtained product (630 mg, 1.52 mmol) and DIPEA (1.6 mL, 1.52 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 4 h at 0 °C → rt. The reaction mixture was quenched with saturated aqueous NH_4Cl extracted with CH_2Cl_2, and the organic layer was processed as usual. Column chromatography (hexane:EtOAc 9:1) gave **15** (695.0 mg, quantitative) as a colorless oil: $[\alpha]_D$ +23.86 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.30 (m, 10H), 4.77 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 3.71−3.60 (m, 3H), 3.67 (s, 3H), 3.36 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 1.70−1.20 (m, 6H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 135.6, 135.5, 133.4, 129.6, 127.6, 96.1, 77.6, 66.2, 55.4, 51.4, 33.9, 31.3, 26.7, 24.9, 24.8, 19.1; EIMS (*m*/*z*) 481 (M + Na), 457 (M − 1); HRMS calcd for $C_{26}H_{38}O_5NaSi$ 481.23862, found 481.23700.

(2*R*)-((7-(Benzenesulfonyl)-2-(methoxymethoxy)heptyl)oxy)*tert*-butyl-diphenylsilane (16). To a solution of **15** (695.0 mg, 1.5 mmol) in THF (15 mL) at 0 °C was added $LiAlH_4$ (86.5 mg, 2.25 mmol) in one portion. The reaction mixture was stirred at this temperature for 1 h, EtOAc (5 mL) was added dropwise, and the reaction was allowed to warm to rt. Water (10 mL) was added, and the organic layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated. Filtration and evaporation of the solvent afforded the crude mixture, which was purified by column chromatography (hexane:EtOAc 1:1) to give the corresponding alcohol (543.0 mg, 83%) as a colorless oil: $[\alpha]_D$ +26.13 (*c* 0.62, $CHCl_3$); EIMS (*m*/*z*) 453 (M + Na), 431 (M + 1); HRMS calcd for $C_{25}H_{39}O_4Si$ (M + 1) 431.26050, found 431.26175.

To a stirred solution of diphenyl disulfide (358 mg, 1.64 mmol) and tri-*n*-butylphosphine (0.4 mL, 1.64 mmol) in CH_2Cl_2 (12 mL) was added the above product (544.0 mg, 1.26 mmol) in CH_2Cl_2. The mixture reaction was stirred for 12 h at rt and then quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography (hexane:EtOAc 9:1) afforded the corresponding phenylthio deriva-

tive (627.0 mg, 95%) as a colorless oil: $[\alpha]_D$ +22.7 (*c* 0.185, $CHCl_3$); HRMS calcd for $C_{31}H_{41}O_3SiS$ (M + 1) 521.25220, found 521.25458.

To a solution of the sulfide (206.0 mg, 0.39 mmol) in CH_2Cl_2 (13 mL) was added $NaHCO_3$ (331.0 mg, 3.9 mmol) followed by 70−75% *m*-CPBA (204.0 mg, 1.18 mmol) at 0 °C. The reaction mixture was stirred for 1 h, saturated aqueous $NaHCO_3$ was added, and the organic layer was washed with water, brine, and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography (hexane:EtOAc 9:1) afforded **16** (627.0 mg, 95%) as a colorless oil: $[\alpha]_D$ +20.38 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 1310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.89 (m, 2H), 7.68−7.35 (m, 13H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 3.66−3.55 (m, 3H), 3.32 (s, 3H), 3.07 (m, 2H), 1.66 (m, 2H), 1.66 (m, 2H), 1.48−1.06 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.5, 133.5, 133.3, 129.6, 129.3, 128.5, 127.9, 127.6, 96.0, 77.5, 66.1, 56.2, 55.4, 31.3, 28.3, 26.7, 24.7, 22.6, 19.1; EIMS (*m*/*z*) 523 (M − OMe), 493 (M − MOMO), 435 (M − OMe − ^{t}Bu); HRMS calcd for $C_{31}H_{42}O_5SiSNa$ 577.24200, found 577.24293.

(1*R*,1′′*S*,2′*S*,5′*S*,7*R*,*S*,12*R*)-7-(Benzenesulfonyl-1-((benzyloxy)methoxy)-13-((*tert*-butyldiphenylsilanyl)oxy)-12-(methoxymethoxy)-1-[5′-(1′′-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl]tridecan-6-one (17). To a solution of **16** (97.4 mg, 0.17 mmol) in THF (0.32 mL) was added a solution of *n*-BuLi in hexanes (134.8 mL, 2.5 M, 0.337 mmol) dropwise at 0 °C. The solution was stirred at this temperature for 15 min, and then was added to a solution of **13a** (46 mg, 79.5 mmol) in THF (0.23 mL) at −40 °C. The mixture was stirred for 1 h at −40 °C → 0 °C and then quenched with saturated aqueous NH_4Cl and diluted with ether. The organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column (hexane:EtOAc 9:1) to give **17** (58.0 mg, 66%) as a colorless oil: IR ($CHCl_3$) 1730, 1315 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.65 (m, 4H), 7.53 (t, *J* = 8.0 Hz, 2H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.72 (dd, *J* = 6.8, 1 Hz, 1H), 4.65 (m, 3H), 4.58 (d, *J* = 6.8 Hz, 1H), 3.98 (m, 3H), 3.65 (m, 1H), 3.58 (m, 3H), 3.48 (m, 3H), 3.39 (s, 3H), 3.31 (s, 3H), 2.85 (m, 1H), 2.55 (m, 2H), 2.29 (m, 1H), 1.94−0.89 (m, 43H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0 (×2), 137.9, 136.4, 136.3, 135.5 (×3), 135.4 (×2), 134.1, 133.3 (×2), 129.6 (×2), 129.3, 128.9, 128.3 (×2), 127.7, 127.6, 127.5, 96.6, 96.1 (×2), 94.6 (×2), 81.7, 81.2, 79.5, 78.5 (×2), 77.5, 77.4, 77.3, 76.9, 76.6, 74.9 (×2), 69.5 (×2), 66.1, 55.6, 55.4, 44.9, 31.8 (×3), 31.4, 31.2, 31.1, 29.7, 29.5 (×4), 29.2 (×2), 28.5, 26.9, 26.7, 26.6 (×2), 25.4, 24.8 (×2), 23.1, 22.5, 20.9, 19.0, 14.1, 14.0; EIMS (*m*/*z*) 1123 (M + Na); HRMS calcd for $C_{64}H_{96}O_{11}SiSNa$ 1123.634035, found 1123.641.

(1*R*,1′′*S*,2′*S*,5′*S*,12*R*)-1-((Benzyloxymethoxy)-13-((*tert*-butyldiphenylsilanyl)oxy)-12-(methoxymethoxy)-1-[5′-(1′′-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl]tridecan-6-one (18). To a solution of **17** (279.0 mg, 0.25 mmol) in dry MeOH (5 mL) at 0 °C was added Na_2HPO_4 (144.0 mg, 1.01 mmol) followed by an Na−Hg amalgam (2.80 g). The suspension was stirred for 3 h at 0 °C and then diluted with saturated aqueous NH_4Cl and ether. The organic layer was washed with water and brine and then dried (Na_2SO_4). Filtration and solvent removal afforded the crude mixture, which was purified by column chromatography (hexane:EtOAc 8:2) to give **18** (230.0 mg, 94%) as a colorless oil: $[\alpha]_D$ +8 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.44−7.29 (m, 11H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.70−4.60 (m, 4H), 3.99 (m, 2H), 3.78 (m, 1H), 3.65 (m, 3H), 3.47 (m, 1H), 3.40 (s, 3H); 3.36 (s, 3H), 2.35 (t, *J* = 7.1 Hz, 4H), 1.93 (m, 3H), 1.59−1.24 (m, 40H), 1.06 (s, 9H), 0.89 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 137.9, 135.6, 135.5 (×4), 133.4, 129.6 (×2), 128.3 (×2), 127.6 (×5), 127.5 (×2), 96.5, 96.0, 94.6, 81.7, 81.2, 79.5, 78.5, 77.7, 77.2, 69.5, 66.3, 55.6 (×2), 55.4 (×2), 42.6, 42.5, 31.8, 31.5, 31.2, 29.7, 29.6 (×3), 29.5, 29.3 (×2), 28.5, 26.7, 26.6, 25.4, 25.2, 25.1, 23.8, 23.6, 22.6, 19.1, 14.0; EIMS (*m*/*z*) 983 (M + Na), 899 (M − MOMO), 777 (M − 3MOMO); HRMS calcd for $C_{58}H_{92}O_9SiNa$ 983.640834, found 983.6351.

(1′′*S*,2*R*,2′*S*,5′*S*,8*R*,*S*,13*R*)-{13-((Benzyloxy)methoxy)-2,8-bis(methoxymethoxy)-13-[[5′-(1′′-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl]tridecyl]oxy}-*tert*-butyldiphenylsilane (19). To a solution of **18** (212.0 mg, 0.22 mmol) in THF (2 mL) at 0 °C was added $LiAlH_4$ (25 mg, 0.66 mmol) in one portion. The reaction was stirred at this temperature for 30 min, EtOAc was added dropwise, and the reaction was allowed to warm to rt. Water (5 mL) was added, and the organic layer was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), and concentrated. Filtration and evaporation of the solvent afforded the crude mixture, which was purified by column chromatography (hexane:EtOAc 6:4) to give a mixture of C-10 alcohols (178 mg, 84%) as a colorless oil.

MOMCl (209.6 mL, 2.76 mmol) and DIPEA (0.64 mL, 3.68 mmol) in CH_2Cl_2 (2.62 mL) were added to the above solution at 0 °C, and the mixture was stirred for 4 h at 4 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography (hexane:EtOAc 8:2) gave **19** (186.0 mg, 100%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.76 (m, 4H), 7.45−7.25 (m, 11H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.7 Hz, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.69−4.61 (m, 6H), 4.03−3.95 (m, 2H), 3.79 (m, 1H), 3.70−3.61 (m, 3H), 3.53−3.44 (m, 2H), 3.39 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 1.96−1.78 (m, 3H), 1.68−1.27 (m, 41H), 1.06 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.5, 133.4, 129.5, 128.2, 127.5 (×2), 127.4, 96.5, 96.0, 95.2, 94.5, 81.6, 81.2, 79.4, 78.6, 77.7, 77.3, 69.4, 66.3, 55.6, 55.3, 34.3, 34.2, 31.8, 31.7, 31.2, 29.9, 29.8, 29.7, 29.6, 29.5, 29.2, 26.7, 25.8, 25.5, 15.5, 25.4, 25.3, 25.2, 22.6, 19.1, 14.0; EIMS (*m*/*z*) 1029 (M + Na), 823 (M − 3MOMO); HRMS calcd for $C_{60}H_{98}O_{10}SiNa$ 1029.68274, found 1029.67800.

(1′′*S*,2′*S*,4*R*,5′*S*,8*R*,*S*,15*R*)-15-((Benzyloxy)methoxy)-4,-10-bis(methoxymethoxy)-15-[5′-(1′′-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl]pentadecanoic Acid Methyl Ester (20). To a solution of **19** (192.0 mg, 0.19 mmol) in THF (3.8 mL) at 0 °C was added a solution of *n*-Bu_4NF (0.57 mL, 1.0M, 0.57 mmol) in THF, and the mixture was stirred for 3 h at rt and then quenched with saturated aqueous NH_4Cl and diluted with ether, and the organic layer was washed with water and brine and dried (Na_2SO_4). Filtration and evaporation of the solvent followed by column chromatography (hexane:EtOAc 1:1) gave the corresponding alcohol (139.0 mg, 95%) as a colorless oil: HRMS calcd for $C_{44}H_{80}O_{10}Na$ 791.5694, found 791.5685.

Solid TPAP (5 mol %) was added in one portion to a stirred mixture of the above product (31.4 mg, 0.04 mmol), followed by *N*-methylmorpholine *N*-oxide (7.18 mg, 0.06 mmol) and powdered 4 Å molecular sieves (500 mg/mmol) in CH_2Cl_2 (0.5 mL) at rt under argon. After 1 h the reaction mixture was filtered through a pad of silica (EtOAc), the filtrate was evaporated, and the residue was used in the next step without further purification.

To a solution of the above aldehyde (18 mg, 0.023 mmol) in CH_2Cl_2 (0.2 mL) at rt was added $Ph_3P{=}CHCO_2Me$ (10.2 mg, 0.03 mmol). The reaction mixture was stirred for 5 h at rt. Evaporation of the solvent followed by column chromatography (hexane:EtOAc 4:1) gave the Wittig adduct (18.8 mg, 97%) as a colorless oil: HRMS calcd for $C_{47}H_{82}O_{11}Na$ 845.57550, found 845.57710.

To a stirred solution of the above product (61.0 mg, 0.074 mmol) and $NiCl_2{\cdot}6H_2O$ (catalytic amount) in MeOH (0.7 mL) at 0 °C was added $NaBH_4$ (5.6 mg, 0.148 mmol) in one portion. The reaction mixture was stirred at 0 °C for 5 min and then filtered through Celite. The filtrate was evaporated, water was added to the residue, and the aqueous phase was extracted several times with ether and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (hexane:EtOAc 4:1) afforded **20** (60.0 mg, 97%) as a colorless oil: IR ($CHCl_3$): 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* =

6.8 Hz, 1H), 4.64 (m, 7H), 3.97 (m, 2H), 3.76 (m, 1H), 3.67 (s, 3H), 3.50 (m, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 2.40 (m, 2H), 1.95−1.26 (m, 46H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 138.0, 128.2, 127.6, 127.4, 96.6, 95.4, 95.3, 94.6, 81.6, 81.3, 79.5, 78.6, 77.4, 76.4, 69.5, 55.6, 55.5, 55.4, 51.4, 34.2, 34.1, 31.8 (×2), 31.3, 29.9, 29.8, 29.7, 29.6, 29.5 (×3), 29.2 (×2), 28.5, 26.5, 25.8, 25.4, 25.2, 22.6, 14.0; EIMS (*m*/*z*) 847 (M + Na), 641 (M − 3MOMO); HRMS calcd for $C_{47}H_{84}O_{11}Na$ 847.59113, found 847.58855.

(1‴*S*,2′*R*,2″*S*,5*S*,5″*S*,8*R*,*S*,13′*R*)-3-{13′-((Benzyloxy)methoxy)-2′,8′-bis(methoxymethoxy)-13′-[5″-(1‴-(methoxymethoxy)tridecyl)tetrahydrofuran-2″-yl]tridecyl}-5-methyl-5*H*-furan-2-one (21). A solution of *n*-BuLi (78.0 mL, 2.5 M in hexane, 0.195 mmol) was added to a solution of DIPEA (35.06 mL, 0.257 mmol) in anhydrous THF (0.5 mL) at −78 °C, and the mixture was stirred for 15 min at −78 °C. A solution of **20** (100 mg, 0.121 mmol) in THF (0.6 mL) was added to the above mixture. After 30 min, a solution of O-THP-(*S*)-lactaldehyde (38.0 mg, 0.24 mmol) in THF (0.3 mL) was introduced and the reaction mixture was stirred for 25 min at −78 °C before being quenched with saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was washed with water and brine and dried (Na_2SO_4). Evaporation of the solvents afforded the crude mixture which after column chromatography (hexane:EtOAc 9:1) gave the product (92.7 mg, 78%) as a mixture of diastereomers (^{1}H NMR analysis). The mixture was treated with CSA (catalytic amount in 10 mL of methanol:water 9:1) for 4 h at rt and was then diluted with ether, washed with a saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. To a solution of the crude product (64.2 mg, 0.074 mmol) in CH_2Cl_2 (0.7 mL) was added TEA (30.9 mL, 0.221 mmol) followed by MsCl (17.2 mL, 0.22 mmol) at 0 °C, and the mixture was allowed to warm to rt over 2 h. The reaction mixture was diluted with ether, washed with a saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. Finally, DBU (30.16 mL, 0.2 mmol) was added to a solution of the crude product (95.2 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the mixture was stirred at this temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layers were extracted with CH_2Cl_2, washed with water and brine, and dried (Na_2SO_4). Solvent removal followed by column chromatography (hexane:EtOAc 4:1) afforded **21** (34.0 mg, 49%, for three steps) as a colorless oil: IR ($CHCl_3$) 1540 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 7.16 (d, J = 1.4 Hz, 1H), 5.02 (dq, J = 6.8, 1.5 Hz, 1H), 4.90 (d, J = 6.8 Hz, 1H), 4.81 (d, J = 6.8 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.68−4.60 (m, 7H), 3.99 (m, 2H), 3.83−3.76 (m, 2H), 3.50−3.44 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 2.49 (d, J = 5.8 Hz, 2H), 1.94−1.87 (m, 3H), 1.67−1.25 (m, 38H), 1.41 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 151.3, 138.0, 130.5, 128.3 (×2), 127.7, 127.5, 96.6, 95.6, 95.3, 94.6, 81.7, 81.3, 79.5, 78.6, 77.4, 77.3, 75.5, 69.5, 55.6 (×2), 55.4, 34.3, 34.2, 31.8 (×2), 31.3, 29.9, 29.8, 29.7, 29.6 (×2), 29.5, 29.3, 28.5, 26.5, 25.8, 25.5, 25.2, 22.6, 19.0, 14.1; EIMS (*m*/*z*) 871 (M + Na), 787 (M − MOMO), 665 (M − 3MOMO); HRMS calcd for $C_{49}H_{84}O_{11}Na$ 871.59113, found 871.59260.

(1‴*S*,2′*R*,2″*S*,5*S*,5″*S*,8*R*,*S*,13′*R*)-5-Methyl-3-{2′,8′,13′-trihydroxy-13′-[5″-(1‴-hydroxytridecyl)tetrahydrofuran-2″-yl]tridecyl}-5*H*-furan-2-one (22). To a solution of **21** (34.0 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added $TMSBr$[21] (52.9 mL, 0.4 mmol), and the mixture was allowed to warm to −30 °C over 2 h. The reaction mixture was diluted with EtOAc (10 mL), washed with a saturated $NaHCO_3$ solution and then brine, and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (EtOAc) afforded **22** (20.0 mg, 83%) as a white solid: mp 100−102 °C; $[\alpha]_D$ +2.5 (*c* 0.2, CH_2Cl_2); IR ($CHCl_3$) 3450−3750, 1755 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.18 (d, J = 1.3 Hz, 1H), 5.06 (dq, J = 6.8, 1.4 Hz, 1H), 3.84 (m, 4H), 3.58 (m, 1H), 3.38 (m, 1H), 2.52 (ddt, J = 15.1, 3.4, 1.7 Hz, 1H), 2.39 (dd, J = 15.1, 8.2 Hz, 1H), 2.03−1.81 (m, 4H), 1.68−1.21 (m, 37H), 1.43 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 151.7, 131.1, 83.1, 82.0, 77.9, 74.2, 71.7, 71.6, 71.4 (×2), 69.8 (×2), 37.2 (×3), 33.3, 33.1, 32.3, 31.8, 29.6, 29.5 (×2), 29.5 (×5), 29.4, 29.2, 29.1, 28.5, 25.9, 25.8, 25.5 (×2), 25.4 (×2), 25.2, 22.6, 19.0, 14.0; EIMS (*m*/*z*) 619 (M + Na), 597 (M + 1), 578 (M − H_2O); HRMS calcd for $C_{35}H_{64}O_7Na$ 619.45496, found 619.45340.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for intermediates and X-ray ORTEP diagrams for compound **6** and **13a** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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