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Total Synthesis and Preliminary Biological Evaluation of *cis*-Solamin Isomers

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An efficient total synthesis of *cis*-solamin (**1**) has been achieved in 21% overall yield and with a longest linear sequence of just 11 steps from aldehyde **8**. A key feature of the approach was the use of asymmetric permanganate-promoted oxidative cyclization to introduce four of the five required stereocenters in a single step. The use of robust and chemoselective methodology meant that the use of protecting groups could be avoided during the assembly of *cis*-solamin (**1**) from the three fragments **23**, **6**, and **4**. The methodology was also applied to the synthesis of three further *cis*-solamin isomers **2**, *ent*-**1**, and *ent*-**2**. Cytotoxicity and hemolytic properties of *cis*-solamin isomers and synthetic intermediates are reported.

Introduction

Annonaceous acetogenins, isolated from the species Annonaceae (custard apple family), are waxy substances usually characterized by the presence of one or more 2,5-disubstituted tetrahydrofuran (THF) rings connected to a butenolide via an alkyl spacer. Many examples of these fascinating natural products have now been reported, and their isolation, synthesis, and biological activities have been reviewed.[1,2] The annonaceous acetogenins have been the subject of considerable interest, primarily due to their potent cytotoxicity,[1,3] although a variety of other important properties including insecticidal activity have also been described.[1] Consequently, significant effort has been devoted toward the synthesis of acetogenins, and a number of total syntheses have appeared.[2,4] Most synthetic approaches to acetogenins have focused on natural products containing *trans*-2,5-disubstituted THF rings. In contrast, there has been relatively little published on the stereoselective synthesis of the corresponding *cis*-THF compounds.[5,6]

cis-Solamin (**1**, Figure 1) provides an example of a mono-*cis*-THF acetogenin, originally isolated from the roots of a tropical fruit tree *Annona muricata* (popularly known as "sour sop" or "guanabana").[7] The relative stereochemistry within the bis-hydroxyalkyl THF (THF-diol) unit of *cis*-solamin was assigned as *threo*/*cis*/*threo* (C15/C16, C16/C19, and C19/C20) on the basis of detailed 2D NMR data and correlation with NMR data from model compounds with known configuration. The absolute configuration of the THF−diol region present in *cis*-solamin

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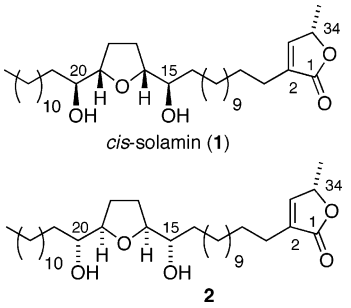


FIGURE 1. Structures of *threo*/*cis*/*threo* (C15/C16, C16/C19, and C19/C20) isomers of solamin.

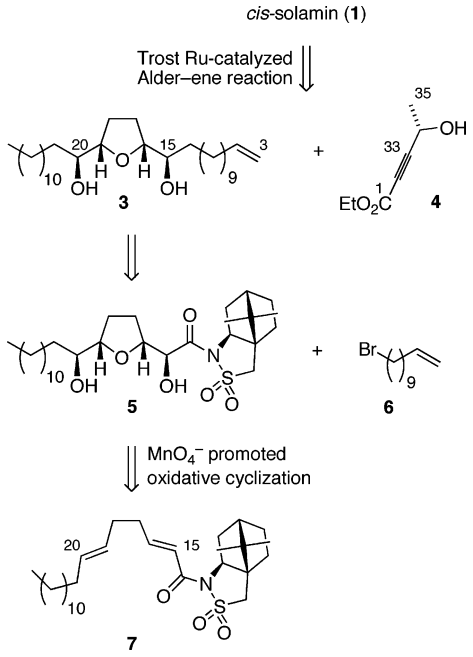
could not be established from the available data, leading the authors to conclude that its structure was either **1** or **2**. Subsequently, total syntheses of **1** and **2** were reported by Makabe et al.,[5c] and the structure of *cis*-solamin was tentatively assigned as **1** on the basis of optical rotation values. For the purpose of clarity we will refer to the structure **1** as *cis*-solamin.

cis-Solamin analogues have considerable potential as a new family of anticancer agents and may even be useful as the bioactive in polymer therapeutics;[8] therefore, it was important to develop a synthetic approach to give *cis*-solamin analogues and evaluate their biological properties in vitro (hemolysis and cytotoxicity). Here we report the total synthesis of *cis*-solamin and three stereoisomers along with preliminary in vitro cytotoxicity and hemolytic activity data.[5d]

Results and Discussion

Our retrosynthetic analysis of *cis*-solamin (**1**) was designed to take advantage of elegant ruthenium-catalyzed methodology developed by Trost to introduce the butenolide portion of the molecule (Scheme 1).[4n,9] Strategically, the use of the highly chemoselective transition-metal-catalyzed Alder-ene reaction would minimize the requirement for protecting groups during the final stages of the synthesis.[4n] After disconnection of the butenolide, it becomes apparent that the C3−C13 chain could be introduced by copper-promoted opening of an epoxide derived from the product **5** of permanganate oxidative cyclization of a diene **7**.[10−12] Asymmetric induction would be provided by a chiral auxiliary present in the 1,5-dienoate **7**,[10f−i] prepared from a commercially available aldehyde **8**.

SCHEME 1. Retrosynthetic Analysis of *cis*-Solamin (1)



Starting from the aldehyde **8**, addition of vinyl Grignard afforded allylic alcohol **9**, which underwent a Johnson−Claisen rearrangement to give enoate **10** in excellent overall yield (Scheme 2).[13,14] Elaboration of **10** to dienoate **12** was best achieved without isolation of the intermediate aldehyde **11**, in a one-pot reduction−olefination reaction,[15] although care was required during the

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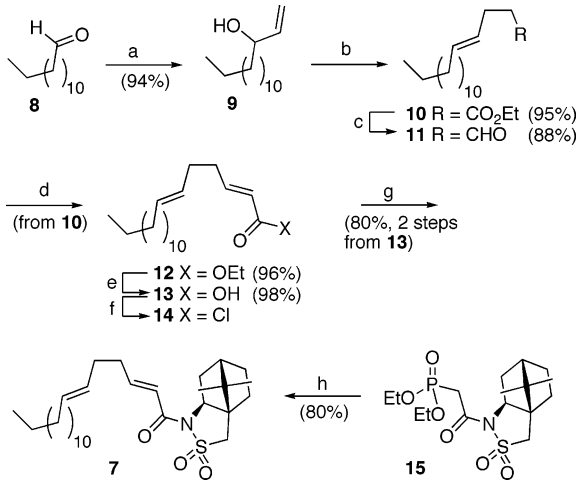
SCHEME 2 [a]

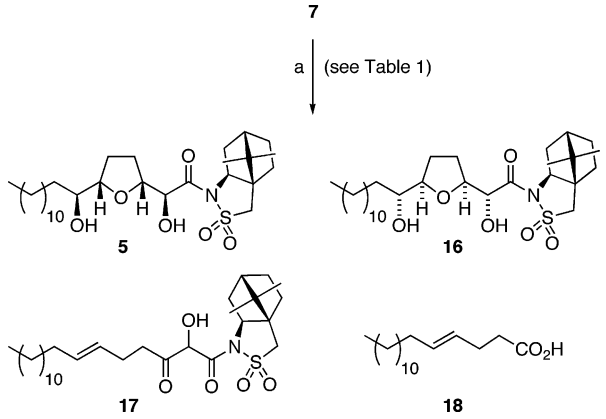


[a] Reagents and conditions: (a) CH_2=$CHMgBr$/THF; (b) $CH_3C(OEt)_3$, 145 °C, xylene; (c) DIBAL-H; toluene, −60 °C; (d) DIBAL-H; toluene, −60 °C then add to $(EtO)_2POCH_2CO_2Et$, NaH, THF, −40 °C to rt; (e) NaOH, $NaHCO_3$, MeOH−H_2O; (f) $(COCl)_2$, DMF, CH_2Cl_2; (g) (2*S*)-10,2-camphorsultam, *n*-BuLi, THF; (h) NaH, CH_2Cl_2, 0 °C to rt, then **11**.

reduction step as any remaining ester **10** coeluted with the desired dienoate **12**. The synthesis of the oxidative cyclization precursor **7** was originally completed by hydrolysis of **12** and activation of the resulting unsaturated acid **13** as its pentafluorophenol ester prior to substitution with the lithiated (2*S*)-10,2-camphorsultam. On a larger scale, the byproduct from acylation, pentafluorophenol, proved inconvenient to separate from **7** leading to the use of acid chloride **14** as the acylating agent. The sequence used to introduce the auxiliary proceeded in satisfactory yield, but at the expense of three extra synthetic steps in the overall linear sequence. Therefore a more convergent route from aldehyde **11** to 1,5-diene **7** was subsequently developed by making use of phosphonate **15** already carrying the sultam auxiliary.[16]

Prior to this work, the asymmetric oxidative cyclization of dienoates had been shown to provide an effective tool for the synthesis of polyether antibiotic fragments, where the starting olefins were trisubstituted.[10e−i] However, other reports on the permanganate-promoted oxidative cyclization of dienes containing mono- and disubstituted olefins were far less encouraging in terms of isolated yields (5−33%).[17] In fact, our first attempts to effect the oxidative cyclization of **7** gave similarly disappointing results (Scheme 3), isolating the desired product **5** in only 18% yield along with a major component that arose from mono-oxidation of the enoate olefin (entry 1, Table 1).[18] Other minor products included the diastereoisomeric THF-diol **16** and acid **18** that probably resulted from oxidative cleavage of the enol tautomer of **17**. The previously successful oxidative cyclization of a model

SCHEME 3 [a]



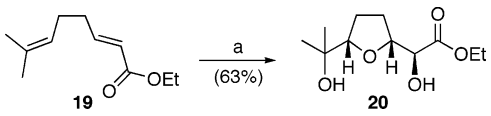
[a] Reagents and conditions: (a) $KMnO_4$, AcOH, solvent, additive (see Table 1).

TABLE 1. Results from the Oxidative Cyclization of Dienoate 7 (See Scheme 3)

entry	solvent	AcOH (equiv)	**5**/**16**[a] (%) (dr)[b]
1	acetone/H_2O/ pH 6.5 buffer	3	21 (6:1)
2[c]	CH_2Cl_2	8	31 (6:1)
3[c]	toluene	8	50 (nd)
4[c]	EtOAc	8	55 (6:1)
5[c]	acetone	16	62 (6:1)
6[c]	acetone	cosolvent[d]	75 (6:1)[e]

[a] Combined isolated yield of THF diols **5** and **16**. [b] Ratio of **5**/**16** estimated from ^{1}H NMR. [c] Reaction carried out with the addition of 10 mol % adogen 464. [d] Acetone/AcOH (3:2). [e] Reaction carried out without adogen 464 gave similar results.

SCHEME 4 [a]



[a] Reagents and conditions: (a) $KMnO_4$ (aq, 1.6 equiv), AcOH (3 equiv), acetone, pH 6.5 buffer, −20 °C.

dienoate **19** led us to speculate that the reluctance of **7** to undergo the cyclization reaction was related to poor solvation of the hydrophobic C21−C32 alkyl chain in acetone/water, causing aggregation in an aqueous environment (Scheme 4).[19]

To improve the solubility of the diene **7**, the oxidative cyclization reaction was investigated under phase-transfer conditions in a variety of solvents (Table 1, entries 2−5).[20] Improved yields of the desired THF product **5** were realized, with the best results occurring in acetone or EtOAc using adogen 464 as phase-transfer catalysts (entries 4 and 5). However, we ultimately found that addition of powdered $KMnO_4$ (1.3 equiv) to the substrate **7** dissolved in a mixed solvent system of acetone/AcOH (3:2) provided the conditions of choice for the oxidative cyclization of dienoate systems of this type. Furthermore, both the substrate and the oxidant were

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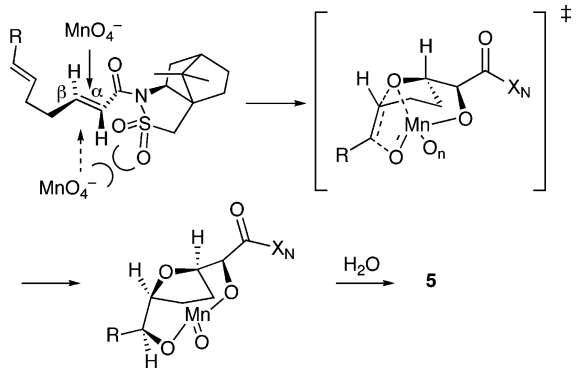


FIGURE 2. Diastereoselective oxidation of dienoyl sultam by MnO_4^-.

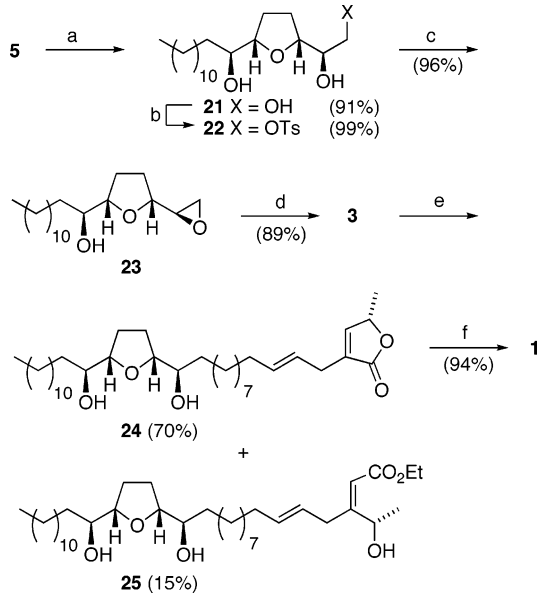
soluble in acetone/AcOH (3:2), avoiding the need for any phase-transfer agents.

Little change in diastereoselectivity was observed under the various conditions investigated, with a dr estimated as 6:1 in favor of **5**.[21] Considering the consistent dr values obtained from reactions run in solvents of very different polarity, it seems unlikely that chelation control is involved in determining the facial selectivity of the initial attack upon the enoate olefin.[22] Dipolar organization of the carbonyl and SO_2 groups and an s-*cis*-arrangement of the C=O and C(α)−C(*β*) bonds would give a conformer where approach of MnO_4^- from the C(*β*) *Re*-face would be favored (Figure 2).[23]

Following separation of the diastereoisomeric THF-diols **5** and **16** by column chromatography, the sultam was removed by reduction of **5** using $NaBH_4$ to afford diol **21** and the recovered auxiliary (Scheme 5). Closure of the epoxide **23** was carried out by DBU treatment of tosylate **22**, obtained by direct mono-tosylation of **21** or more efficiently via a stannylene derivative of the 1,2-diol. As anticipated, cuprate addition to epoxide **23** proceeded without the need for protection of the C20 hydroxyl group, affording the C3−C32 fragment **3** of *cis*-solamin in 89% yield. Formal Alder−ene reaction of the terminal olefin **3** with alkyne **4** was carried out by refluxing the reactants and a catalytic amount of the Ru(II) complex **26** in MeOH for 3 h,[4m,9] delivering a 6:1 (NMR) mixture of products derived from addition to either end of the alkyne. As noted previously by Trost, the undesired minor regioisomeric adduct **25** is reluctant to cyclize to the corresponding butenolide due to developing $A_{1,2}$ strain, facilitating chromatographic separation of the two products.

The final step in the synthesis required selective reduction of the C4−C5 double bond, a transformation that was well precedented in the literature using careful catalytic hydrogenation in the presence of Wilkinson's

SCHEME 5 [a]



[a] Reagents and conditions: (a) $NaBH_4$, THF, H_2O; (b) Bu_2SnO, C_6H_6 then TsCl, TBAB; (c) DBU, CH_2Cl_2; (d) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF, −60 to −20 °C; (e) **4**, CpRu(cod)Cl (**26**), MeOH, reflux; (f) $TsNHNH_2$, NaOAc, THF−H_2O, 60 °C.

catalyst.[2] Initial attempts conducted on a small scale led to some over reduction of the butenolide ring, and although we were able to achieve separation of *cis*-solmin (**1**) from the mixture by preparative HPLC, we were concerned to observe complete epimerisation of the C34 stereocenter in one of our synthetic samples.[24] We subsequently found that diimide reduction provided a convenient and reliable means of reducing **24** to *cis*-solamin, without any detectable epimerization at C34.[25]

Due to our interest in the relative cytotoxicity of *cis*-solamin diastereoisomers and the uncertainty regarding the absolute stereochemistry of the THF−diol unit present in the natural product, we also prepared the enantiomeric C3−C32 fragment *ent*-**3** either using the enantiomeric chiral auxiliary or from the minor diastereoisomer **16** obtained in the oxidative cyclization of dienoate **7** (Scheme 6). The enantiomers of **1** and **2** were also synthesized by combination of the (*R*)-alkyne *ent*-**4** with intermediates *ent*-**3** and **3**, respectively.[26]

The four synthetic solamin isomers were indistinguishable from each other and natural *cis*-solamin on the basis of their IR, MS, ^1H NMR, and ^{13}C NMR spectra, due to the length and flexiblity of the chain connecting the THF−diol and butenolide regions. Optical rotation values obtained for each of the pairs of diastereoisomers were also very similar and consistent with previous observations that the contribution from the butenolide ring dominates that from a pseudosymmetrical THF region in acetogenins.[27] Although all four isomers could be

(21) Diastereoselectivity was estimated by integration of the H15 and H16 signals from the major and minor diastereoisomers in the ^1H NMR spectrum of the crude reaction mixture. Determination of an accurate dr was complicated due to the incomplete resolution of the $H16_{minor}$ signal from the $H15/H16_{major}$ signals, leading us to initially report a higher value of 10:1. The dr value of 6:1 was confirmed from the isolated yields of **5** and **16**.

(22) The diastereofacial selectivity observed for the oxidative cyclization of enantiomerically enriched *N*-enoyl oxazolidinones was previously explained by dipolar organization of the substrate (see ref 10f).

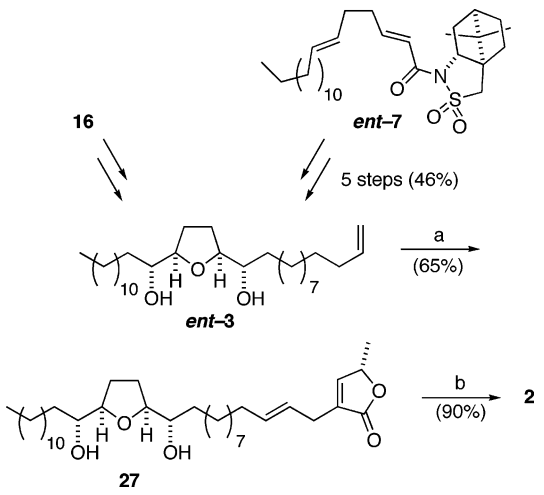
(23) Reiser, O. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH: Weinheim, 2000; pp 11−16.

(24) Evidence for epimerization of the C34 stereocentre was provided by chiral HPLC on a Chiralcel OD-H HPLC column, eluting with *i*-PrOH/hexane (5:95), which gave two peaks with a ratio of 1:1. The same sample only showed one set of signals in its ^1H and ^{13}C NMR spectra.

(25) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996−6000.

(26) *ent*-**4** was prepared from (*R*)-methyl lactate using the method described for the synthesis of **4** (see ref 9). $[\alpha]^{24}_D = +27.2$ (*c* 0.85, $CHCl_3$).

SCHEME 6 [a]



[a] Reagents and conditions: (a) **4**, CpRu(cod)Cl (**26**), MeOH, reflux; (b) $TsNHNH_2$, NaOAc, THF−H_2O, 60 °C.

separated by chiral HPLC and were shown to be isomerically pure,[28] we were unable to determine whether *cis*-solamin had the structure **1** or **2** due to the lack of an authentic sample of the natural product.

Biological Activity of *cis*-Solamin Analogues. To study the relative influence of the structural and stereochemical features on biological activity, the hemolytic activity and cytotoxicity were evaluated. Understanding the structure−activity relationship of these properties is important in relation to the selection of a potential candidate(s) for further development as anticancer agent(s). Cytotoxicity gives an indication of antitumor activity, and the hemolysis model relates to mechanism of action and also the potential for later intravenous administration.

In vitro cytotoxicity of acetogenin derivatives was evaluated using an MTT assay (72 h incubation) against B16F10 murine melanoma cell line.[29] Results are expressed as a percentage of viability of cells grown in the absence of drug, but also with 3% DMSO medium (Table 2 and Figure 3).

All acetogenin derivatives were active at μM concentrations except **3** and **25** (IC_{50} > 447 and 336 μM, respectively). These results are consistent with the previous observation that the terminal lactone ring is one of the main requirements for antitumoral activity in acetogenins.[1] The unsaturated precursor **24** to *cis*-solamin (**1**) was most potent ($IC_{50} = 0.27 \pm 0.01$ μM). In fact, **24** was at least 10 times more active than the rest of the acetogenins described and even 100 times more active than *ent*-**1** ($IC_{50} = 23.2 \pm 0.1$ μM).

Hemolytic properties of the acetogenin derivatives studied were also related to their chemical structures

TABLE 2. In Vitro Cytotoxicity and Hemolytic Properties of Acetogenin Derivatives

entry	compd	IC_{50}[a] (μM)	Hb[b](% control)
1	**24**	0.27 ± 0.01	84.0 ± 1.2
2	**27**	3.0 ± 0.8	20.4 ± 5.0
3	*ent*-**27**	2.2 ± 0.4	24.7 ± 4.8
4	*ent*-**24**	5.5 ± 0.8	92.1 ± 1.7
5	**1**	2.8 ± 0.2	7.0 ± 0.8
6	**2**	7.0 ± 1.6	3.6 ± 0.7
7	*ent*-**1**	23.2 ± 0.1	2.9 ± 0.8
8	*ent*-**2**	6.4 ± 0.8	5.6 ± 0.5
9	**3**	>447	1.5 ± 0.4
10	**25**	>336	1.0 ± 0.6

[a] IC_{50} values against B16F10 murine melanoma cell line (seeding density 5×10^4 cells/mL, 3% DMSO in medium) ($n = 3$, mean ± SD). [b] Hemolysis (% control 1% Triton X-100) at compound concentration of 0.3 mg/mL, 3% DMSO in PBS ($n = 3$, mean ± SE).

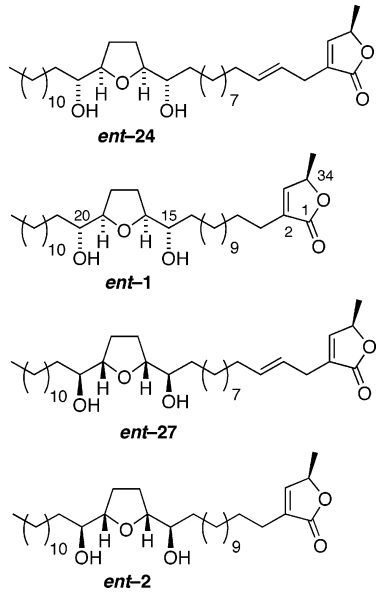


FIGURE 3. Structures of acetogenin derivatives for in vitro cytotoxicity and haemolysis studies.

(Table 2). For instance, comparison of the compounds containing C4−C5 unsaturation (entries 1−4, Table 2) with the corresponding saturated spacer compounds (entries 5−8, Table 2) shows that the presence of the double bond (reduced flexibility) leads to a marked increase in hemolysis. In addition, comparison of **24**/*ent*-**24** with the diastereoisomers **27**/*ent*-**27**, which display differences in the relative chirality between the central THF−diol and butenolide units, showed a decrease in hemolysis (going from 84 to 92% to approximately 20%). Further studies using other models are required to better understand structure−activity relationships of membrane interactions, but these are the first to investigate such membrane properties.

In summary, we have completed a short and efficient synthesis of *cis*-solamin (**1**) using an asymmetric oxidative cyclization of a 1,5-diene as the key step. It has been shown for the first time that permanganate-promoted oxidations of substrates containing disubstituted olefins can be achieved in high yield. The cytotoxicity and hemolytic activity of several isomers of *cis*-solamin indicated their potential for further investigation as antitumor agents.

(27) It has previously been observed that the optical rotation value of acetogenins is largely due to the stereochemistry of the butenolide, and to a lesser extent due to the stereochemistry of the THF diol portion: Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 8849−8852.

(28) Each of the four isomers (**1**, *ent*-**1**, **2**, and *ent*-**2**) gave a separate and single peak on a Chiral CD-Ph HPLC column, eluting with *i*-PrOH/hexane (15:85). Retention times: **1** (14.5 min), **2** (17.3 min), *ent*-**1** (18.7 min), *ent*-**2** (15.7 min). See the Supporting Information for an HPLC trace for a mixed sample of **1** and **2**.

(29) Sgouras, D.; Duncan, R. *J. Mater. Sci.: Mater. Med.* **1990**, *1*, 61−68.

Experimental Section

(2*S*)-*N*-((2*E*,6*E*)-2,6-Nonadecadienoyl)camphor-10,2-sultam (7). To a solution of phosphonate **15**[16] (409 mg 1.04 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added in one batch NaH (42 mg of a 60% dispersion in mineral oil, 1.04 mmol). The reaction was allowed to warm to rt and was stirred for 20 min. The solution was then cooled to 0 °C, and a solution of aldehyde **11** (250 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 16 h, a saturated aqueous solution of NH_4Cl (10 mL) was added, and the organic layer was separated, re-extracting with CH_2Cl_2 (2 × 10 mL). The combined organic solution was dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography (SiO_2) eluting with Et_2O/hexane (1:9 then 1:4) gave diene **7** (389 mg, 0.79 mmol, 80%) as a white solid. A sample was recrystallized from hexane to give colorless prisms: mp 41−44 °C; $[\alpha]^{24}_D$ +62.0 ($CHCl_3$, *c* 0.77); IR ν_{max} (neat) 1671, 1630, 1334, 1294, 1215, 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dt, *J* = 15.1, 7.0 Hz), 6.56 (1H, dt, *J* = 15.1, 1.5 Hz), 5.46 (1H, dt, *J* = 15.3, 6.3 Hz), 5.38 (1H, dt, *J* = 15.3, 6.3 Hz), 3.93 (1H, dd, *J* = 5.0, 7.5 Hz), 3.51 (1H, d, *J* = 13.6 Hz), 3.44 (1H, d, *J* = 13.6 Hz), 2.31 (2H, q, *J* = 7.0 Hz), 2.20−2.05 (4H, m), 2.00−1.84 (5H, m), 1.46−1.26 (22H, m), 1.18 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 150.5, 132.0, 128.3, 121.1, 65.3, 53.3, 48.5, 47.9, 44.8, 38.6, 33.0, 32.7, 32.6, 32.0, 31.1, 29.8, 29.6, 29.5, 29.3, 26.6, 22.8, 21.0, 20.0, 14.3; LRMS (ES^+) *m*/*z* 515 (100, $[M + Na]^+$). Anal. Calcd for $C_{29}H_{49}NO_3S$: C, 70.83; H, 10.01; N, 2.85. Found: C, 70.71; H, 9.96; N, 2.79.

(2*S*)-*N*-[(*S*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((*S*)-1-hydroxytridecyl)tetrahydro-2-furanyl)ethanoyl]camphor-10,2-sultam (5). To a rapidly stirred solution of diene **7** (500 mg, 1.0 mmol) and adogen 464 (10 mol %, 40 mg, 0.01 mmol) in AcOH/acetone (25 mL 2:3) at −30 °C was added powdered $KMnO_4$ (221 mg, 1.4 mmol) in one batch. The reaction mixture was allowed to warm to −10 °C over 1 h, whereupon an ice-cold solution of $Na_2S_2O_5$ (20 mL of satd aq) was added. The resulting aqueous mixture was extracted with EtOAc (3 × 20 mL). The combined organic solution was dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil (600 mg). Purification by column chromatography (SiO_2) eluting with Et_2O/hexane (gradient 3:7 to 6:4) gave three main fractions: major THF diastereoisomer **5** (355 mg, 0.63 mmol, 65%) as a gummy oil, minor THF diastereoisomer **16** as a white solid (58 mg, 0.11 mmol, 11%), and hydroxyketoester **17** (5 mg, 0.01 mmol, 10%) as a yellow solid. **Data for 5:** $[\alpha]^{20}_D$ +40.0 ($CHCl_3$, *c* 0.44); IR $\nu\nu_{max}$ (neat) 3524, 1699, 1467, 1304, 1295, 1214, 1131, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60−4.55 (2H, m), 3.96 (1H, dd, *J* = 5.0, 7.5 Hz), 3.87 (1H, dt, *J* = 4.5, 7.3 Hz), 3.52 (1H, d, *J* = 13.8 Hz), 3.48−3.43 (1H, m), 3.45 (1H, d, *J* = 13.8 Hz), 2.29−2.21 (3H, m), 2.13−2.03 (6H, m), 1.55−1.20 (24H, m), 1.16 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 83.3, 78.7, 74.1, 73.7, 65.9, 53.2, 49.1, 48.0, 44.7, 38.4, 34.7, 33.0, 32.0, 29.8, 29.7, 29.5, 28.5, 28.3, 26.5, 25.9 22.8, 21.0, 20.0, 14.2; LRMS (ES^+) *m*/*z* 1106 (5, $[2M + Na]^+$), 564 (100, $[M + Na]^+$), 542 (5, $[M + H]^+$); HRMS (ES^+) calcd for $C_{29}H_{51}NO_6SNa^+$ *m*/*z* 564.3329, found 564.3326. Anal. Calcd for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.24; H, 9.55; N, 2.56. **Data for compound 16:** mp 95−97 °C; $[\alpha]^{24}_D$ +102.8 (MeOH, *c* 0.38); ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, br s), 4.51 (1H, ddd, *J* = 2.3, 5.0, 7.5 Hz), 3.96 (1H, t, *J* = 6.5 Hz), 3.77 (1H, dt, *J* = 4.5, 7.3 Hz), 3.65 (1H, br), 3.50 (1H, d, *J* = 13.7 Hz), 3.49−3.39 (1H, m), 3.45 (1H, d, *J* = 13.7 Hz), 2.25−2.14 (1H, m), 2.10−1.83 (8H, m), 1.60 (1H, br), 1.51−1.20 (24H, m), 1.16 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 83.1, 80.3, 74.3, 73.8, 65.0, 53.1, 49.1, 48.1, 44.6, 37.8, 34.7, 32.7, 32.1, 29.9, 29.8, 29.7, 29.5, 28.3, 27.9, 26.7, 25.8 22.8, 20.5, 20.0, 14.2; LRMS (ES^+) *m*/*z* 564 (100, $[M + Na]^+$), 542 (5, $[M + H]^+$); HRMS (ES^+) calcd for $C_{29}H_{51}NO_6SNa^+$ *m*/*z* 564.3329, found 564.3328. Anal. Calcd for $C_{29}H_{51}NO_6S$: C, 64.29; H, 9.49; N, 2.58. Found: C, 64.20; H, 9.61; N, 2.57. **Data for compound 17:** (obtained as a 5:1 inseparable mixture of diastereoisomers, spectroscopic data for major isomer only) mp 66−69 °C; IR ν_{max} (neat) 3524, 1699, 1467, 1304, 1295, 1214, 1131, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, td, *J* = 6.5, 15.0 Hz), 5.35 (1H, td, 6.3, 15.3 Hz), 5.35 (1H, d, 7.5 Hz), 3.95 (1H, dd, *J* = 5.0, 7.5 Hz), 3.92 (1H, d, *J* = 7.5 Hz), 3.52 (1H, d, *J* = 13.6 Hz), 3.45 (1H, d, *J* = 13.6 Hz), 2.80 (1H, td, *J* = 7.3, 17.5 Hz), 2.64 (1H, td, *J* = 7.2, 17.5 Hz), 2.29 (2H, q, *J* = 6.8 Hz), 2.21−2.01 (2H, m), 1.94−1.86 (5H, m), 1.49−1.20 (22H, m), 1.16 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 168.3, 132.1, 127.6, 76.6, 65.2, 53.0, 49.2, 48.0, 44.7, 39.4, 37.9, 32.9, 32.6, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 26.6, 26.2, 22.8, 20.6, 20.1, 14.2; LRMS (ES^+) *m*/*z* 1069 (100, $[2M + Na]^+$), 546 (50, $[M + Na]^+$). Anal. Calcd for $C_{29}H_{49}NO_5S$: C, 66.50; H, 9.43; N, 2.67. Found: C, 66.23; H, 9.27; N, 2.55.

(*R*)-1-[(2*R*,5*S*)-5-((*S*)-1-Hydroxytridecyl)tetrahydrofuran-2-yl]ethane-1,2-diol (21). To a solution of the acylsultam **5** (1.39 g, 3.57 mmol) in a 3:1 mixture of THF/H_2O (40 mL) at −10 °C was added $NaBH_4$ (0.54 g, 14.3 mmol) in several batches. The mixture was allowed to warm to 0 °C over 2 h, whereupon HCl (2M, 10 mL) and EtOAc (20 mL) were added. The organic phase was separated, re-extracting the aqueous with EtOAc (2 × 20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil. Purification by column chromatography (SiO_2) eluting with MeOH/CH_2Cl_2 (3:97 then 5:95) gave triol **21** (0.771 g, 2.33 mmol, 91%) as a white solid: mp 47−48 °C; $[\alpha]^{25}_D$ −9.1 ($CHCl_3$, *c* 0.76); IR ν_{max} (neat) 3238 (br), 1460, 1415, 1327, 1118, 1078, 1056 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 4.02 (1H, dt, *J* = 3.7, 6.7 Hz), 3.84 (1H, br q, *J* = 6.0 Hz), 3.66 (1H, dd, *J* = 5.3, 11.0 Hz), 3.62 (1H, dd, *J* = 6.3, 11.0 Hz), 3.54 (1H, br q, *J* = 5.5 Hz), 3.45 (1H, br q, *J* = 5.3 Hz), 2.04−1.77 (4H, m), 1.58−1.47 (2H, m), 1.45−1.26 (20H, m), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, MeO-d_4) δ 83.8, 80.9, 75.3, 74.9, 65.2, 35.2, 33.1, 30.8, 30.5, 28.9, 28.6, 27.0, 23.8, 14.7; LRMS (ES^+) *m*/*z* 684 (40, $[2M + Na]^+$), 353 (100, $[M + Na]^+$); HRMS (ES^+) calcd for $C_{26}H_{44}O_4Na^+$ *m*/*z* 330.2770, found 330.2768. Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 68.82; H, 11.41.

(*R*)-2-Hydroxy-2-[(2*R*,5*S*)-5-((*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl]ethyl 4-Methylbenzenesulfonate (22). To a solution of the triol **21** (200 mg, 0.61 mmol) in benzene (12 mL) was added Bu_2SnO (181 mg, 0.73 mmol). The reaction mixture was heated at reflux for 3 h and then cooled to rt. TsCl (127 mg, 0.66 mmol) was added followed by TBAB (98 mg, 0.3 mmol). After 30 min, the reaction mixture was concentrated in vacuo. Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (1:4 then 2:3) afforded the title tosylate **22** (293 mg, 0.61 mmol, 99%) as a white solid: mp 70−72 °C; $[\alpha]^{25}_D$ −10.4 ($CHCl_3$, *c* 0.40); IR ν_{max} (neat) 3425, 3309 (br), 1596, 1469, 1365, 1171, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.3 Hz), 4.09 (2H, d, *J* = 6.0 Hz), 4.00 (1H, dt, *J* = 2.7, 6.8 Hz), 3.84 (1H, dt, *J* = 4.0, 7.0 Hz), 3.74 (1H, dt, *J* = 2.7, 6.0 Hz), 3.44−3.40 (1H, m), 2.78 (2H, br), 2.45 (3H, s), 2.02−1.81 (4H, m), 1.47−1.40 (2H, m), 1.34−1.20 (20H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 132.9, 130.0, 128.1, 82.7, 78.6, 74.2, 71.8, 71.6, 34.6, 32.0, 29.8, 29.5, 28.2, 27.9, 25.9, 22.8, 21.8, 14.2; LRMS (ES^+) *m*/*z* 991 (60, $[2M + Na]^+$), 507 (100, $[M + Na]^+$), 485 (30, $[M + H]^+$). Anal. Calcd for $C_{26}H_{44}O_6S$: C, 64.43; H, 9.15. Found: C, 64.39; H, 9.08.

(*S*)-1-[(2*S*,5*R*)-5-((*R*)-Oxiran-2-yl)tetrahydrofuran-2-yl]-tridecan-1-ol (23). To a solution of tosylate **22** (95 mg, 0.20 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added dropwise DBU (64 μL, 0.4 mmol). The solution was allowed to warm to rt, and after 2 h the solution was concentrated in vacuo to give a yellow oil that was purified by column chromatography (SiO_2) eluting with EtOAc/hexane (2:3) to give the title epoxide **23** (59 mg, 0.19 mmol, 96%) as a white solid: mp 36−40 °C; $[\alpha]^{24}_D$ −10.1 ($CHCl_3$, *c* 0.40); IR ν_{max} (neat) 3320 (br), 1465, 1418, 1321, 1122 cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4) δ 4.06 (1H, dt, *J* = 3.1, 6.6 Hz), 3.88 (1H, dt, *J* = 4.2, 7.2 Hz), 3.45−3.29

(1H, m), 3.03 (1H, td, J = 3.1, 4.0 Hz), 2.82 (1H, dd, J = 2.9, 5.1 Hz), 2.80 (1H, br), 2.78 (1H, dd, J = 4.0, 5.1 Hz), 2.20−1.80 (4H, m), 1.57−1.12 (22H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.1, 77.2, 74.3, 54.7, 44.5, 34.8, 32.1, 29.8, 29.5, 29.4, 28.2, 26.0, 22.8, 14.3; LRMS (ES^+) m/z 647 (100, $[2M + Na]^+$), 335 (10, $[M + Na]^+$). Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.95; H, 11.55.

(1*R*)-1-[(2*R*,5*S*)-5-((1*S*)-1-Hydroxytridecyl)tetrahydrofuran-2-yl]-12-tridecen-1-ol (3). To a rapidly stirring suspension of CuI (350 mg, 1.85 mmol) in THF (20 mL) at −60 °C was added dropwise a solution of undec-10-enylmagnesium bromide (9.2 mL of 0.4 M in THF, 3.65 mmol). The mixture was warmed to −30 °C, and after 20 min the resulting gray suspension was cooled to −60 °C whereupon a solution of epoxide **23** (228 mg, 0.73 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to −20 °C over 1 h before an aqueous solution of NH_4Cl/NH_3 (9:1, 15 mL) was added. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil. Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (1:9 then 3:17) afforded the title olefin **3** (304 mg, 0.65 mmol, 89%) as a white solid: mp 55−57 °C; $[\alpha]^{25}_D$ −0.9 ($CHCl_3$, c 1.1); IR ν_{max} (neat) 3380 (br), 1462, 1367, 1169, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, tdd, J = 6.8, 10.2, 17.0 Hz), 4.99 (1H, dd, J = 1.3, 17.0 Hz), 4.93 (1H, dd, J = 1.3, 10.2 Hz), 3.84−3.80 (2H, m), 3.42 (2H, br q, J = 5.5 Hz), 2.58 (2H, br s), 2.04 (2H, q, J = 7.2 Hz), 1.99−1.86 (2H, m), 1.81−1.69 (2H, m) 1.56−1.18 (40H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 114.2, 82.9, 74.5, 34.2, 33.9, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 28.2, 25.8, 22.8, 14.2; LRMS (ES^+) m/z 955 (90, $[2M + Na]^+$), 489 (100, $[M + Na]^+$). Anal. Calcd for $C_{30}H_{58}O_3$: C, 77.19; H, 12.52. Found: C, 77.15; H, 12.37.

(4*E*)-4,5-Didehydro-*cis*-solamin (24). To a stirred solution of olefin **3** (200 mg, 0.43 mmol) and alkyne **4**[9] (93 mg, 0.65 mmol) in degassed CH_3OH (4 mL) was added a bright orange solution of CpRu(COD)Cl[9] (**26**, 7 mg, 0.023 mmol) in degassed CH_3OH (2 mL) under an atmosphere of argon. The solution was heated at reflux for 3 h before cooling to rt and diluted with ether (10 mL). The solution was then concentrated in vacuo to give an orange gum which was filtered through a plug of SiO_2 eluting with acetone/hexane (2:5). Purification by column chromatography (SiO_2) eluting with MeOH/CH_2Cl_2 (1:99 then 2:98) afforded the title butenolide **24** (169 mg, 0.30 mmol, 70%) as a white solid and the enoate **25** (39 mg, 0.064 mmol, 15%) as a white solid. **Data for 24:** mp 60−62 °C; $[\alpha]^{20}_D$ +10.5 (MeOH, c 0.76); IR ν_{max} (neat) 3350 (br), 1758, 1462, 1365, 1171, 1115, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 1.8 Hz), 5.57 (1H, dt, J = 15.3, 6.5 Hz), 5.47 (1H, dt, J = 15.3, 6.5 Hz), 5.03 (1H, qq, J = 1.8, 6.8 Hz), 3.87−3.83 (2H, m), 3.47−3.39 (2H, m), 2.96 (2H, d, J = 6.5), 2.50 (2H, br s), 2.03 (2H, q, J = 7.1 Hz), 1.98−1.89 (2H, m), 1.81−1.71 (2H, m), 1.54−1.22 (38H, m), 1.42 (3H, d, J = 6.8 Hz), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 149.5, 134.3, 133.7, 124.4, 82.8, 77.7, 74.5 34.3, 32.6, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.9, 22.8, 19.3, 14.2; LRMS (ES^+) m/z 1148 (20, $[2M + Na]^+$), 1126 (10, $[2M + H]^+$), 586 (100, $[M + Na]^+$), 564 (100, $[M + H]^+$); HRMS (ES^+) $C_{35}H_{63}O_5^+$ calcd 563.4670, found 563.4662. Anal. Calcd for $C_{35}H_{62}O_5$: C, 74.68; H, 11.10. Found: C, 74.65; H, 11.09. **Data for (2*Z*,5*E*,16*R*)-16-hydroxy-3-((1*S*)-1-hydroxyethyl)-16-[(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl]hexadeca-2,5-dienoic acid ethyl ester (25):** mp 32−34 °C; IR ν_{max} (neat) 3333, 1730, 1462, 1365, 1171, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (1H, d, J = 1.1 Hz), 5.51 (1H, dt, J = 15.3, 6.5 Hz), 5.43 (1H, dt, J = 15.3, 6.5 Hz), 4.34 (1H, dq, J = 1.1, 6.5 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.86−3.78 (2H, m), 3.56 (1H, dd, J = 6.0, 13.8 Hz), 3.47−3.38 (2H, m), 3.07 (1H, dd, J = 6.7, 13.8 Hz), 2.39 (1H, br s), 2.02−1.89 (4H, m), 1.82−1.70 (2H, m), 1.53−1.19 (44H, m), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 163.4, 133.1, 126.7, 114.2, 82.8, 74.5, 70.8, 60.0, 34.3, 32.9, 32.6, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 25.8, 22.8, 22.4, 14.4, 14.2; LRMS (ES^+) m/z 631 (100, $[M + Na]^+$), 609 (100, $[M + H]^+$); HRMS (ES^+) $C_{37}H_{69}O_6^+$ calcd 609.5089, found 609.5085.

***cis*-Solamin (1).** A solution of 4,5-dihydro-*cis*-solamin (**24**) (20 mg, 0.036 mmol), $TsNHNH_2$ (40 mg, 0.22 mmol), and NaOAc (18 mg, 0.22 mmol) in THF−H_2O) (2 mL of 1:1) was heated at 80 °C for 18 h. K_2CO_3 (satd aq, 2 mL) was added and the mixture stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a white solid. Purification by column chromatography (SiO_2) eluting with EtOAc/hexane (2:3) afforded *cis*-solamin (**1**) (19 mg, 0.034 mmol, 94%) as a white solid: mp 67−69 °C (lit.[7] mp 63−66 °C, lit.[5c] mp 66−68 °C); $[\alpha]^{24}_D$ +11.3 (MeOH, c 0.87) [lit.[5c] $[\alpha]^{21}_D$ +26 (MeOH, c 0.45), lit.[7] $[\alpha]_D$ +22 (MeOH, c 0.55)]; IR ν_{max} (neat) 3390 (br), 1760, 1464, 1367, 1169, 1118, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 1.8 Hz), 5.00 (1H, dq, J = 1.8, 6.8 Hz), 3.87−3.83 (2H, m), 3.47−3.39 (2H, m), 2.26 (2H, t, J = 7.1), 2.00−1.88 (2H, m), 1.81−1.71 (2H, m), 1.62−1.10 (44H, m), 1.42 (3H, d, J = 6.8 Hz), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 148.9, 134.5, 82.8, 77.6, 74.5, 34.2, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.3, 25.9, 25.2, 22.8, 19.3, 14.2; LRMS (ES^+) m/z 1152 (20, $[2M + Na]^+$), 1130 (10, $[2M + H]^+$), 587 (80, $[M + Na]^+$), 565 (100, $[M + H]^+$); HRMS (ES^+) $C_{35}H_{65}O_5^+$ calcd 565.4827, found 565.4821. Anal. Calcd for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.72; H, 11.53.

***ent-cis*-Solamin (*ent*-1).** Following the procedure for the preparation of *cis*-solamin (**1**): compound *ent*-**24** (24 mg, 0.04 mmol) was reduced to afford the title compound *ent*-**1** (23 mg, 0.04, 92%) as a white solid: mp 71−72 °C; $[\alpha]^{24}_D$ −11.7 (MeOH, c 1.02). Anal. Calcd for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.68; H, 11.47. The ^{1}H NMR, ^{13}C NMR, IR, and MS data for compound *ent*-**1** were indistiguishable from that of *cis*-solamin (**1**).

(*S*)-3-((*S*)-13-Hydroxy-13-[(2*S*,5*R*)-5-((*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl)tridecyl]-5-methyl-2,5-dihydrofuran-2(5*H*)-one (2). Following the procedure for the preparation of *cis*-solamin (**1**): compound **27** (24 mg, 0.04 mmol) was reduced to afford the title compound **2** (23 mg, 0.04 mmol, 91%) as a white solid: mp 69−70 °C [lit.[5c] mp 61−63 °C]; $[\alpha]^{24}_D$ +11.8 (MeOH, c 0.85) [lit.[5c] $[\alpha]^{21}_D$ +42 (MeOH, c 0.50)]. Anal. Calcd for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.80; H, 11.63. The ^{1}H NMR, ^{13}C NMR, IR, and MS data for compound **2** were indistiguishable from that of *cis*-solamin (**1**).

(*R*)-3-((*R*)-13-Hydroxy-13-[(2*R*,5*S*)-5-((*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl)tridecyl]-5-methyl-2,5-dihydrofuran-2(5*H*)-one (*ent*-2). Following the procedure for the preparation of *cis*-solamin (**1**): compound *ent*-**27** (24 mg, 0.04 mmol) was reduced to afford the title compound *ent*-**2** (23 mg, 0.04, 90%) as a white solid: mp 68−70 °C; $[\alpha]^{24}_D$ −11.3 (MeOH, c 0.68). Anal. Calcd for $C_{34}H_{64}O_5$: C, 73.86; H, 11.67. Found: C, 73.78; H, 11.61. The ^{1}H NMR, ^{13}C NMR, IR, and MS data for compound *ent*-**2** were indistiguishable from that of *cis*-solamin (**1**).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **5**, **16**, and **25**. Experimental procedures and characterization data for *ent*-**3**, **7**, *ent*-**7**, **11**, **12**, **13**, **15**, *ent*-**21**, *ent*-**22**, *ent*-**23**, *ent*-**24**, **27**, and *ent*-**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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