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Total synthesis of *cis*-solamin and its inhibitory action with bovine heart mitochondrial complex I

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Abstract—A convergent total synthesis of *cis*-solamin (**1a**) and its diastereomer (**1b**) was accomplished. A key reaction of this approach was the use of $VO(acac)_2$-catalyzed diastereoselective epoxidation of (*Z*)-bis-homoallylic alcohol **3** followed by spontaneous cyclization for the *cis*-THF ring formation. By comparison of the optical rotation of the two possible diastereomers, it is suggested that the absolute configuration of natural *cis*-solamin is **1a**. Inhibitory action of synthetic **1a** and **1b** with bovine heart mitochondrial complex I are reported.

1. Introduction

Annonaceous acetogenins, which have been isolated from a number of plants of *Annonaceae*, have attracted much attention in recent years due to their broad spectrum of biological activities such as cytotoxic, antitumor, antimalarial, antimicrobial, immunosuppressive, pesticidal, and antifeedant effects. Since the first annonaceous acetogenin, uvaricin was found from the plant of *Uvaria accuminata* in 1982,[1] more than 350 related compounds have been isolated in the past of 20 years.[2] The common structural features of annonaceous acetogenins are characterized by a terminal α,β-unsaturated γ-lactone ring and a C-32 or 34 long aliphatic side chain connected with some oxygen containing moieties, such as THF, THP, and/or epoxide rings and several hydroxyl groups. Consequently, significant effort has been devoted toward the total synthesis of annonaceous acetogenins.[3]

cis-Solamin (**1**) is a mono-THF acetogenin, isolated from the roots of *Annona muricata* in 1998.[4] The relative stereochemistry of the THF-diol part of **1** was determined to be *threo–cis–threo* by Laurens et al.[4] and the (*S*)-configuration of the secondary methyl group of the γ-lactone moiety is well known, it follows that the absolute configuration of **1** is (15*R*, 16*R*, 19*S*, 20*S*, 34*S*) or (15*S*, 16*S*, 19*R*, 20*R*, 34*S*) (Fig. 1).

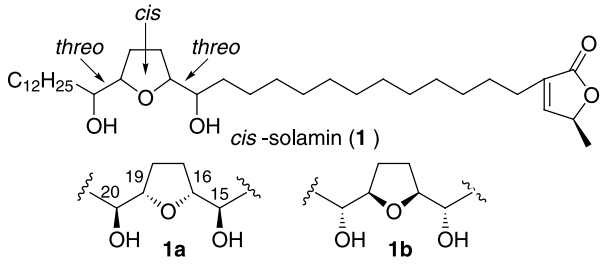

Figure 1. Structures of (15*R*, 16*R*, 19*S*, 20*S*, 34*S*)-*cis*-solamin (**1a**) and (15*S*, 16*S*, 19*R*, 20*R*, 34*S*)-*cis*-solamin (**1b**).

The two possible structures, **1a** and **1b**, would be difficult to distinguish by ^1H or ^{13}C NMR spectroscopic data, because the THF moiety and γ-lactone moiety are separated by 13 carbon long chain. X-ray analysis would be also very hard due to the waxy nature of this compound. To establish the absolute configuration and evaluate biological activity, we planned to synthesize the two candidates **1a** and **1b**, employing a $VO(acac)_2$ catalyzed diastereoselective

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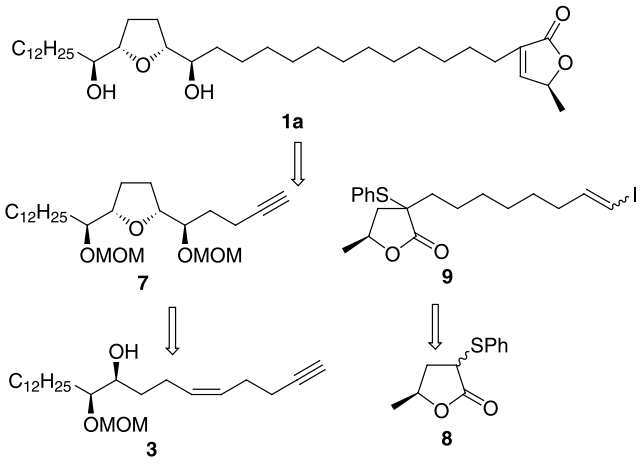
epoxidation in the presence of peroxide followed by a cyclization strategy.[5]

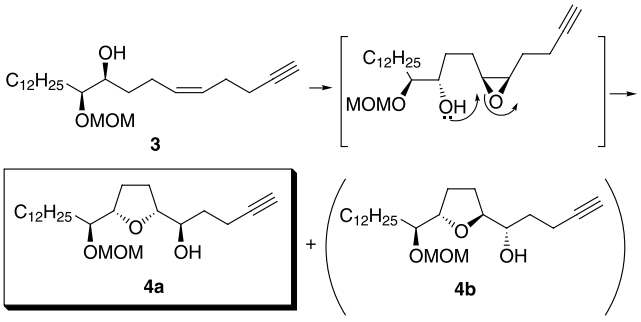
2. Results and discussion

Our synthetic strategy is outlined in Scheme 1. The key step for constructing THF ring formation is $VO(acac)_2$ catalyzed diastereoselective epoxidation[6,7] followed by spontaneous cyclization in the presence of molecular sieves 4 Å. The starting material is (*Z*)-bis-homoallylic alcohol **3**, whose enantiomer had been synthesized earlier by us.[7]



Scheme 1. Synthetic strategy of *cis*-solamin (**1a**).

The results of diastereoselective epoxidation of **3** (Scheme 2) and cyclization are summarized in Table 1.



Scheme 2. Diastereoselective epoxidation of **3** and cyclization.

The results shown indicate the following. TBHP-$VO(acac)_2$ in the presence of 4 Å molecular sieves can serve as the most effective system in the diastereoselective epoxidation. Cumene hydroperoxide also served as a good oxidant. On the other hand, Ti and Mo catalysts were ineffective. Halogenic solvents, especially 1,2-dichloroethane, gave a good stereoselectivity and yield.

Determination of the relative stereochemistry of **4a** and **4b** was performed by applying Cassady's method as we have previously reported (Fig. 2).[7,8]

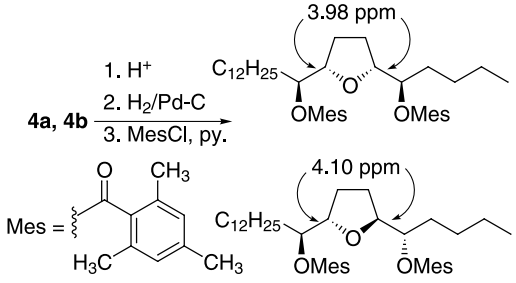


Figure 2. Determination of the relative stereochemistry of **4a** and **4b** by applying Cassady's method.[8]

Diastereomers **4a** and **4b** were separated by silica gel column chromatography (benzene–AcOEt=20:1) after hydroxyl group of **4a** and **4b** had been protected as a benzoate ester to give **5a** and **5b**. The differences of ^1H NMR chemical shifts of compounds **5a** and **5b** were shown in Figure 3. This indicates that the *threo–cis–threo* and the *threo–trans–threo* relationships of the THF core part can be differentiated by ^1H NMR (Fig. 3).

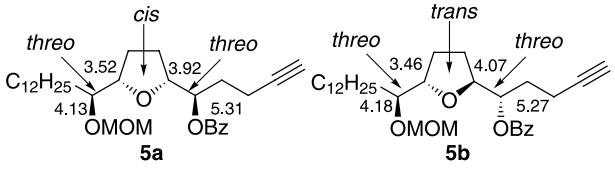


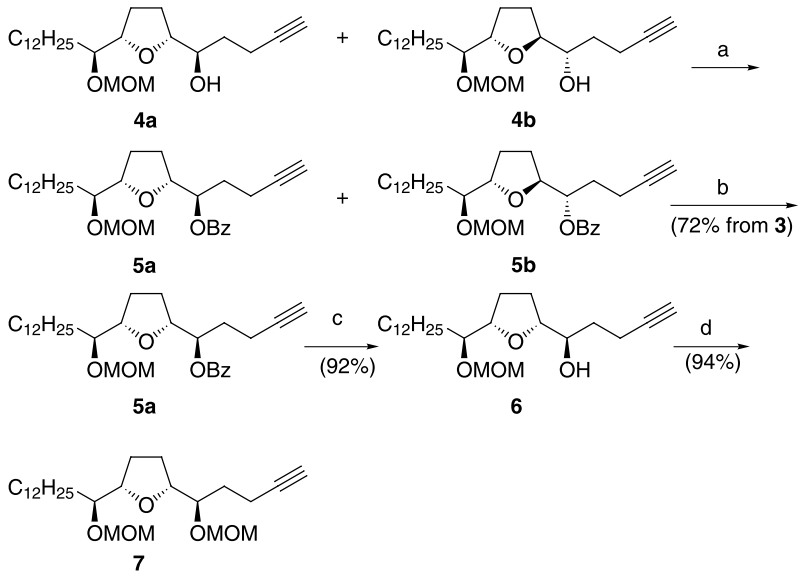
Figure 3. Differences between the characteristic chemical shifts of the oxymethine proton of compounds **5a** and **5b**.

Hydrolysis of the benzoate ester **5a** gave **6** and protection of the hydroxyl group as MOM ether afforded tetrahydrofuran moiety **7** (Scheme 3).

Table 1. Epoxidation and subsequent cyclization of bis-homoallyl alcohol **3**[a]

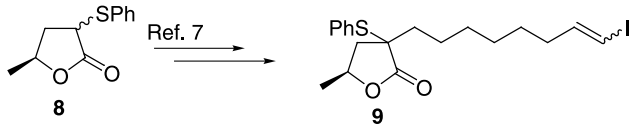
Reagent	Solvent	Additive	Yield (**4a**+**4b**)	**4a**:**4b**
*m*CPBA	CH_2Cl_2	—	83	37:63
TBHP–10 mol% $Ti(O\text{-}iPr)_4$	CH_2Cl_2	—	24	49:51
TBHP–10 mol% $MoO_2(acac)_2$	CH_2Cl_2	—	Trace	—
TBHP–5 mol% $VO(acac)_2$	C_6H_5Cl	—	Trace	—
TBHP–5 mol% $VO(acac)_2$	CH_2Cl_2	—	43	78:22
TBHP–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	—	51	87:13
Cummene hydroperoxide–5 mol% $VO(acac)_2$	CH_2Cl_2	—	78	83:17
Cummene hydroperoxide–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$		77	85:15
Cummene hydroperoxide–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	MS 4 Å	83	85:15
TBHP–5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	MS 4 Å	75	89:11

[a] Determination of the relative stereochemistry of **4a** and **4b** was performed by applying Cassady's methods as we have previously reported.[8]



Scheme 3. Reagents and conditions: (a) BzCl, pyridine; (b) separation; (c) NaOH, MeOH; (d) MOMCl, *i*-Pr_2NEt.

As shown in Scheme 4, the γ-lactone part **9** was constructed as we had reported earlier starting from γ-lactone **8**.[7,9]

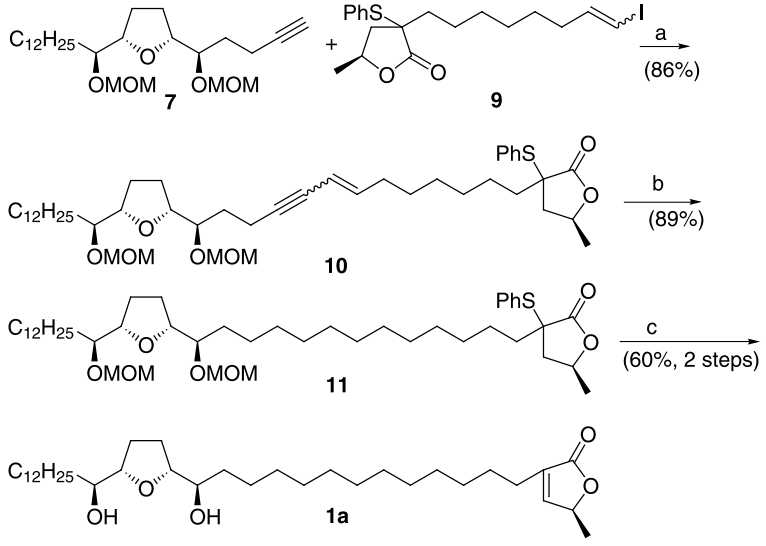


Scheme 4. Synthesis of γ-lactone part.

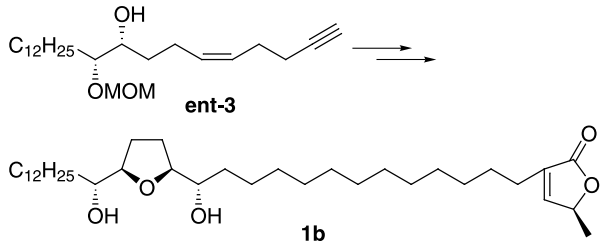
Both segments were coupled by Sonogashira cross-coupling reaction[10] mediated by $Cl_2Pd(PPh_3)_2$/CuI in the Et_3N solvent system to give compound **10**. When THF or benzene was used as a solvent the yield of coupled product got lower. Diimide reduction with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded saturated product **11** in good yield.[3g] When ethylene glycol dimethyl ether was used, some partially unsaturated compound was observed. Catalytic hydrogenation with $ClRh(PPh_3)_3$ under 1 atm of H_2 atmosphere in benzene–EtOH (4:1) also sometimes gave some minor amount of unsaturated product. Oxidation of the sulfur with *m*-CPBA followed by thermal elimination and deprotection of the MOM ethers with $BF_3 \cdot Et_2O$ in dimethyl sulfide afforded the candidate **1a** (Scheme 5).

The other candidate **1b** was also synthesized from the enantiomer of compound **3** using the same procedure as that employed for **1a** (Scheme 6).

The two synthetic samples (**1a**, **1b**) could not be differentiated by the spectral data (^1H, ^{13}C NMR). On the other hand, their specific rotation showed different values. While the specific rotation of synthetic **1a** ($[\alpha]_D^{21} = +26$, *c* 0.45, MeOH) is similar to the reported value of the naturally occurring *cis*-solamin ($[\alpha]_D = +22$, *c* 0.55, MeOH), that of **1b** ($[\alpha]_D^{21} = +42$, *c* 0.50, MeOH) showed a much higher value. As shown in Table 2, the ^1H NMR spectra of the



Scheme 5. Reagents and conditions: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N; (b) *p*-$TsNHNH_2$, ethylene glycol diethyl ether, NaOAc; (c) (i) *m*CPBA, toluene, (ii) reflux; (iii) $BF_3 \cdot Et_2O$/dimethyl sulfide.



Scheme 6.

Table 2. [1]H NMR chemical shifts of the bis-(*R*)- and (*S*)-MTPA esters of **1a** and **1b**[a]

MTPA ester	15-H	16-H	19-H	20-H
(*R*)-MTPA-**1a**	5.06	3.87	4.08	4.92
(*S*)-MTPA-**1a**	5.06	3.86	4.09	4.93
δ (*S*)-(*R*)-**1a**		−0.01	0.01	0.01
Abs. confign.	*R*	*R*	*S*	*S*
(*R*)-MTPA-**1b**	5.06	3.86	4.09	4.93
(*S*)-MTPA-**1b**	5.06	3.87	4.08	4.92
δ (*S*)-(*R*)-**1b**		0.01	−0.01	−0.01
Abs. confign.	*S*	*S*	*R*	*R*

[a] Proton chemical shifts are referenced to $CHCl_3$ (δ 7.25). Each proton was assigned by H–H COSY experiment.

carbinol centers of the corresponding bis-(*R*)- and (*S*)-MTPA esters of synthetic **1a** and **1b** showed a slight chemical shift difference. According to the sign of $\Delta\delta_H[=(\delta_S-\delta_R)]$ values of each carbinol center, the absolute configuration of **1a** was assigned as C-15*R*, C-16*R*, C-19*S*, and C-20*S*. Similarly, the absolute configuration of **1b** was assigned as C-15*S*, C-16*S*, C-19*R*, and C-20*R*.[11] This indicates that if natural **1** is available, we can determine stereochemistry of *cis*-solamin by applying advanced Mosher methodology.[12]

The inhibition of mitochondrial complex I was determined by NADH oxidase assay using bovine-heart submitochondrial particles (Table 3).

Table 3. Inhibition activity of mitochondrial complex I

Sample	IC_{50} (nM)
1a	2.2
1b	2.1
(10*R*)-corossoline	1.5
(10*S*)-corossoline	2.0
(17*R*, 18*R*, 21*R*, 22*S*)-reticulation-1	16
(17*S*, 18*S*, 21*S*, 22*R*)-reticulation-1	17
bullatacin	0.8

The inhibitory potency in terms of IC_{50} of bullatacin, one of the most potent natural acetogenins, was 0.8 nM as a control. Under the same experimental conditions, the IC_{50} of **1a** and **1b** were 2.2 and 2.1 nM, respectively. The inhibitory potencies were almost identical to those of (10*R*)- and (10*S*)-corossoline which had been synthesized by us.[13] This indicates that the stereochemistry around the hydroxylated THF rings and the presence of 10-OH group in the spacer region are not essential for the potent activity. This observation is consistent with the results of Miyoshi et al. who revealed that the stereochemistry around the hydroxylated THF rings and the presence of a polar substituent(s) in the spacer moiety were of minor importance for the activity.[14–17] The length of the spacer of compounds **1a**, **1b**, (10*R*)-, and (10*S*)-corossoline is 13 carbon atoms in common. Compared to both possible diastereomers of reticulatain-1, which has a spacer of 15 carbon atoms, the inhibitory activities of the four compounds are about eight-times stronger (Fig. 4).[14]

Thus, the length of spacer moiety is critically important for the inhibitory action. This observation is also consistent with the results of Takada et al. which demonstrated that an optimal length of the spacer is about 13 carbon atoms.[18]

In summary, the first total synthesis of *cis*-solamin (**1a**) and its diastereomer **1b** was accomplished using $VO(acac)_2$-catalyzed diastereselective epoxidation followed by spontaneous cyclization. On the basis of the present data, it is strongly suggested that the natural *cis*-solamin is **1a**.

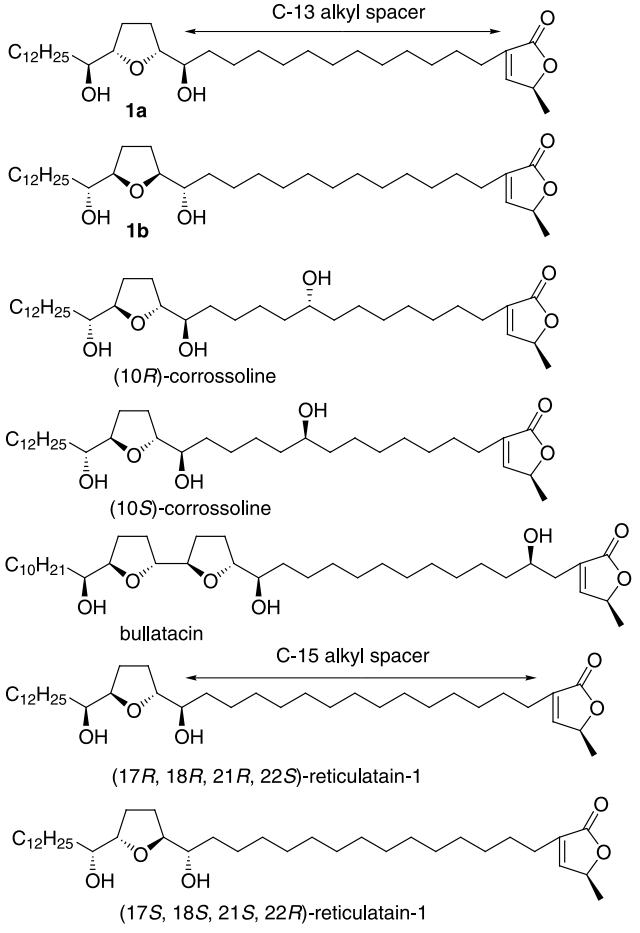


Figure 4. The structure of biological tested compounds.

Inhibitory action of these compounds was examined with bovine heart mitochondrial complex I. Both compounds showed almost same activity.

3. Experimental

3.1. General

All melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DR 500 FT NMR spectrometer in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hertz. Mass spectra were obtained on JEOL JMS 700 mass spectrometer. IR spectra were recorded with JASCO IR-810 infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

3.1.1. (*Z*,9*S*,10*S*)-10-(Methoxymethoxy)docos-5-en-1-yn-9-ol (3). This compound was prepared as we reported previously starting from (+)-muricatacin.[7] $[\alpha]_D^{27}=+9.3$ (*c* 1.5, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3450, 3300, 3000, 2920, 2850, 2100, 1650, 1470, 1455, 1100, 1040, 920, 720, 630; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.26–1.58 (24H, m), 1.94 (1H, t, $J=2.4$ Hz), 2.19–2.32 (6H, m), 2.40 (1H, br., –OH), 3.35 (1H, m), 3.41 (3H, s), 3.52 (1H, m), 4.70 (2H, s), 5.47 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 18.83, 22.71, 23.56, 25.22, 26.34, 29.37, 29.60, 29.63 (2×C), 29.67, 29.69, 29.84, 31.11, 31.94, 33.23, 55.85, 68.37, 72.25, 83.44, 84.20, 97.12, 128.19, 130.91 ppm; HREIMS calcd for $C_{24}H_{44}O_3$ [M^+] 380.3290, found 380.3286. Anal. Calcd for $C_{24}H_{44}O_3$: C, 75.74; H, 11.65. Found: C, 75.34; H, 11.60.

3.1.2. Determination of the ratio of 4a and 4b. This experiment was carried out as we reported previously.[7] The ^{1}H NMR showed that the ratio of **4a** and **4b** was 89:11.

3.1.3. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Benzoyloxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (5a). To a solution of mixture **4a** and **4b** (909 mg, 2.3 mmol) in pyridine (10 mL) was added benzoyl chloride (0.18 mL, 3.5 mmol) at 0 °C. After being stirred in an ice bath for 1 h and then at 23 °C for 5 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. Drying over $MgSO_4$ and subsequent evaporation of the extract afforded a crude product, which was purified by preparative TLC (benzene–AcOEt=20:1) furnished **5a** (828 mg, 72% from **3**) as a colorless oil. $[\alpha]_D^{27}=+4.1$ (*c* 0.95, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3300, 3060, 2920, 2850, 2100, 1720, 1600, 1450, 1270, 1170, 1040, 920, 720; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.7$ Hz), 1.20–1.65 (22H, m), 1.70–2.10 (6H, m), 1.93 (1H, t, $J=2.5$ Hz), 2.29 (2H, m), 3.36 (3H, s), 3.54 (1H, m), 3.92 (1H, m), 4.13 (1H, m), 4.65 (1H, d, $J=6.5$ Hz), 4.83 (1H, d, $J=6.5$ Hz), 5.31 (1H, m), 7.44 (2H, m), 7.56 (1H, m), 8.07 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 14.21, 15.10, 22.70, 25.36, 27.68, 27.94, 29.37, 29.64 (2×C), 29.65, 29.66, 29.68, 29.70, 29.83, 30.44, 31.30, 31.94, 55.68, 68.86, 74.51, 79.49, 79.96, 82.55, 83.37, 96.78, 128.39, 129.80, 130.22, 133.00, 166.21 ppm; HREIMS calcd for $C_{31}H_{48}O_5$ [M^+] 500.3502, found 500.3505. Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 73.90; H, 9.48.

3.1.4. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Hydroxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (6). To a solution of **5a** (219 mg, 0.44 mmol) in MeOH (10 mL) was added NaOH (50 mg). After the mixture had been stirred for 5 h, the solvent was evaporated and the mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and concentrated to afford crude product, which was chromatographed over silica gel with hexane–AcOEt (4:1) to give **6** as a colorless oil (169 mg, 92%). $[\alpha]_D^{24}=+12.0$ (*c* 1.70, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3450, 3320, 2950, 2930, 2850, 2120, 1460, 1070, 620; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.20–1.45 (21H, m), 1.45–2.00 (7H, m), 1.93 (1H, t, $J=2.4$ Hz), 2.30–2.40 (2H, m), 3.08 (1H, br., –OH), 3.37 (3H, s), 3.46 (1H, m), 3.54 (1H, m), 3.86 (1H, m), 4.00 (1H, m), 4.70 (1H, d, $J=6.5$ Hz), 4.73 (1H, d, $J=6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 15.04, 22.70, 25.44, 28.09, 28.15, 29.37, 29.62 (2×C), 29.66 (2×C), 29.69 (2×C), 29.85, 31.94, 33.59, 55.89, 68.31, 72.49, 80.36, 81.28, 82.09, 84.40, 96.50 ppm; HREIMS calcd for $C_{24}H_{44}O_4$ [M^+] 396.3240, found 396.3242. Anal. Calcd for $C_{24}H_{44}O_4$: C, 70.87; H, 10.98. Found: C, 70.73; H, 11.22.

3.1.5. (2*R*,5*S*,1′*R*,1″*S*)-2-(1′-Methoxymethoxy-4′-pentynyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (7). An ice-cooled mixture of alcohol **6** (169 mg, 0.43 mmol) and chloromethyl methyl ether (caution) (0.07 mL, 0.9 mmol) in CH_2Cl_2 (5 mL) was treated with *i*-Pr_2NEt (0.17 mL, 1.0 mmol) and the resulting mixture was allowed to warm to 24 °C and stirred for 24 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and saturated aqueous NH_4Cl was added to it. The mixture was extracted with ether and the extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexane–AcOEt=5:1) afforded **7** (176 mg, 94%) as a colorless oil. $[\alpha]_D^{17}=+9.1$ (*c* 0.84, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3320, 2930, 2850, 2120, 1470, 1150, 1100, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.6$ Hz), 1.20–1.55 (24H, m), 1.60–1.85 (4H, m), 1.95 (1H, t, $J=2.6$ Hz), 2.25–2.35 (2H, m), 3.38 (3H, s), 3.40 (3H, s), 3.49 (1H, m), 3.64 (1H, m), 3.89 (2H, m), 4.67 (1H, d, $J=6.5$ Hz), 4.69 (1H, d, $J=6.5$ Hz), 4.81 (1H, d, $J=6.5$ Hz), 4.82 (1H, d, $J=6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 14.79, 22.70, 25.42, 27.48, 27.69, 29.37, 29.62, 29.65, 29.66, 29.68, 29.70, 29.84, 30.32, 31.36, 31.94, 55.72, 55.88, 68.55, 78.63, 79.80, 81.48, 82.02, 84.19, 96.71, 97.10 ppm; HREIMS calcd for $C_{26}H_{48}O_5$ [M^+] 440.3502, found 440.3505. Anal. Calcd for $C_{26}H_{48}O_5$: C, 72.68; H, 11.18. Found: C, 72.39; H, 11.08.

3.1.6. (1‴*S*,2″*R*,3*RS*,5*S*,5″*S*,7′*E*,13′*R*)-3-{13′-Methoxymethoxy-13′-[5″-(1‴-methoxymethoxytridecyl)tetrahydrofuran-2″-yl]tridec-7′-en-9′-ynyl}-5-methyl-3-(phenylsulphanyl)tetrahydrofuran-2-one (10). To a solution of the vinyl iodide **9** (60 mg, 0.14 mmol) in Et_3N (0.5 mL) was added $Cl_2Pd(PPh_3)_2$ (2.8 mg, 0.007 mmol) and the resulting solution was stirred for 1 h. The acetylenic ether **7** (60 mg, 0.14 mmol) along with CuI (1.4 mg, 0.014 mmol) were then added to the mixture, which after

being stirred for a further 8 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane–AcOEt=4:1) to give **10** (87 mg, 86%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2920, 2850, 2200, 1765, 1460, 1430, 1150, 1100, 1040, 920, 745, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.19 (2.4H, d, J=6.2 Hz), 1.39 (0.6H, d, J=6.2 Hz), 1.20–1.95 (39H, m), 2.00–2.10 (2H, m), 2.20–2.55 (3H, m), 3.38 (3H, s), 3.39 (3H, s), 3.49 (1H, m), 3.62 (1H, m), 3.86–3.93 (2H, m), 4.46–4.65 (1H, m), 4.67 (1H, d, J=6.5 Hz), 4.69 (1H, d, J=6.5 Hz), 4.81 (1H, d, J=6.5 Hz), 4.82 (1H, d, J=6.5 Hz), 5.40–5.45 (1H, m), 5.96–6.05 (1H, m), 7.30–7.45 (3H, m), 7.50–7.60 (2H, m); HRFABMS calcd for $C_{45}H_{72}O_7SNa$ [$(M+Na)^+$] 779.4896, found 778.4894.

3.1.7. (1‴*S*,2″*R*,3*RS*,5*S*,5″*S*,13′*R*)-3-{13′-Methoxymethoxy-13′-[5″-(1‴-methoxymethoxytridecyl)tetrahydrofuran-2″-yl]tridecyl}-5-methyl-3-(phenylsulphanyl)-tetrahydrofuran-2-one (11). To a refluxing solution of **10** (15 mg, 0.2 mmol) and *p*-toluenesulfonylhydrazide (2.62 g, 13.4 mmol) in diethoxyethane (15 mL) was added sodium acetate (1.36 g, 16.6 mmol) in water (20 mL) over a 4 h period at 120 °C. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed over silica gel (hexane–AcOEt=4:1) to give **11** (13 mg, 89%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2920, 2850, 1765, 1460, 1430, 1150, 1100, 1040, 920, 740; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.19 (2.4H, d, J=6.2 Hz), 1.38 (0.6H, d, J=6.2 Hz), 1.20–1.90 (49H, m), 1.95–2.10 (2H, m), 2.32 (0.2H, dd, J=13.9, 5.5 Hz), 2.52 (0.8H, dd, J=13.9, 7.5 Hz), 3.38 (3H, s), 3.39 (3H, s), 3.49 (2H, m), 3.89 (2H, m), 4.46–4.65 (1H, m), 4.67 (1H, d, J=6.5 Hz), 4.69 (1H, d, J=6.5 Hz), 4.81 (1H, d, J=6.5 Hz), 4.82 (1H, d, J=6.5 Hz), 7.30–7.45 (3H, m), 7.50–7.60 (2H, m); HRFABMS calcd for $C_{45}H_{78}O_7SNa$ [$(M+Na)^+$] 785.5366, found 785.5368.

3.1.8. *cis*-Solamin (1a). To a solution of **11** (10 mg, 13.6 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (80%, 5.4 mg, 25 mmol) at 0 °C. After the mixture had been stirred at this temperature for 10 min, $Na_2S_2O_3$/$NaHCO_3$ (1:1, 1.0 mL) was added. After stirring at 23 °C for 1 h, the mixture was extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and subsequent concentration gave an oil, which was then dissolved in toluene (2.0 mL) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture gave an oil, which was dissolved in dimethyl sulfide (0.5 mL) at 0 °C and $BF_3{\cdot}Et_2O$ was added. After the mixture had been stirred for 10 min at this temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with AcOEt. The mixture was washed with water and brine. Drying over $MgSO_4$ and evaporation of the solvent gave a colorless solid, which was purified by silica gel chromatography (AcOEt) gave **1a** (3.4 mg, 60%) as a colorless solid. Mp 66–68 °C; $[\alpha]_D^{21}=+26$ (*c* 0.45, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 1320, 1110, 1080, 1030, 960, 840, 750, 715; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (48H, m), 1.41 (3H, d, J=6.6 Hz), 2.27 (2H, t, J=7.3 Hz), 2.39 (2H, br., –OH), 3.41 (2H, m), 3.81 (2H, m), 4.99 (1H, dq, J=6.7, 1.6 Hz), 6.98 (1H, d, J=1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.12, 19.23, 22.70, 25.20, 25.73, 27.43, 28.15 (2×C), 29.20, 29.31, 29.37, 29.51 (2×C), 29.61, 29.64, 29.66 (2×C), 29.68, 29.69, 29.84, 29.72 (2×C), 30.32, 31.94, 32.54, 34.00 (2×C), 34.16, 74.39, 77.40, 82.70, 134.40, 148.83, 173.89 ppm; HREIMS calcd for $C_{35}H_{64}O_5$ [M^+] 564.4753, found 564.4720.

3.1.8.1. Diastereomer of *cis*-solamin (1b). Mp 63–66 °C; $[\alpha]_D^{21}=+42$ (*c* 0.50, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 1320, 1110, 1080, 1030, 960, 840, 750, 715; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (48H, m), 1.41 (3H, d, J=6.6 Hz), 2.00 (1H, br., –OH), 2.27 (2H, t, J=7.3 Hz), 2.35 (1H, br., –OH), 3.42 (2H, m), 3.81 (2H, m), 4.99 (1H, dq, J=6.7, 1.6 Hz), 6.98 (1H, d, J=1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.11, 19.24, 22.70, 25.20, 25.73, 27.44, 28.16 (2×C), 29.20, 29.32, 29.37, 29.52 (2×C), 29.61, 29.63, 29.65 (2×C), 29.68, 29.70, 29.72 (2×C), 30.32, 31.94, 32.54, 34.00 (2×C), 34.16, 74.40, 77.40, 82.70, 134.41, 148.83, 173.90 ppm; HRFABMS calcd for $C_{35}H_{64}O_5Na$ [$M+Na^+$] 587.4651, found 587.4650.

3.1.9. Preparation of the bis-(*R*)-MTPA ester of 1a. To a stirred solution of **1a** (1.0 mg, 1.8 μmol) in CH_2Cl_2 (0.2 mL) was sequentially added Et_3N (0.4 mg, 2.5 μmol), DMAP (0.1 mg, 0.8 μmol), and (*S*)-MTPACl (~5 μL, 27 mmol) at room temperature. After the mixture was stirred for 8 h, saturated aqueous $NaHCO_3$ and Et_2O were added. This mixture was stirred vigorously for 1 h. The organic phase was extracted with Et_2O and the extract was washed with brine. Drying over $MgSO_4$ and the evaporation of the solvent gave an oil, which was purified with preparative TLC (hexane–AcOEt=4:1) to give bis-(*R*)-MTPA ester of **1a** (1.2 mg, 90%) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87 (1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.1. Bis-(*S*)-MTPA ester of 1a. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86 (1H, m), 4.09 (1H, m), 4.93 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.2. Bis-(*R*)-MTPA ester of 1b. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86 (1H, m), 4.09 (1H, m), 4.93 (1H, m), 4.98 (1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J=1.4 Hz), 7.35–7.65 (10H, m) ppm.

3.1.9.3. Bis-(*S*)-MTPA ester of 1b. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.20–2.05 (50H, m), 1.39 (3H, d, J=6.2 Hz), 2.26 (2H, t, J=7.6 Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87 (1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98

(1H, dq, J=6.2, 1.4 Hz), 5.06 (1H, m), 6.97 (1H, d, J= 1.4 Hz), 7.35–7.65 (10H, m) ppm.

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