HETEROCYCLES, Vol. 78, No. 9, 2009, pp. 2369 - 2376. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd April, 2009, Accepted, 21st May, 2009, Published online, 21st May, 2009.
DOI: 10.3987/COM-09-11741

A CONCISE SYNTHESIS OF SOLAMIN AND *CIS*-SOLAMIN, MONO-THF ACETOGENINS FROM *ANNONA MURICATA*

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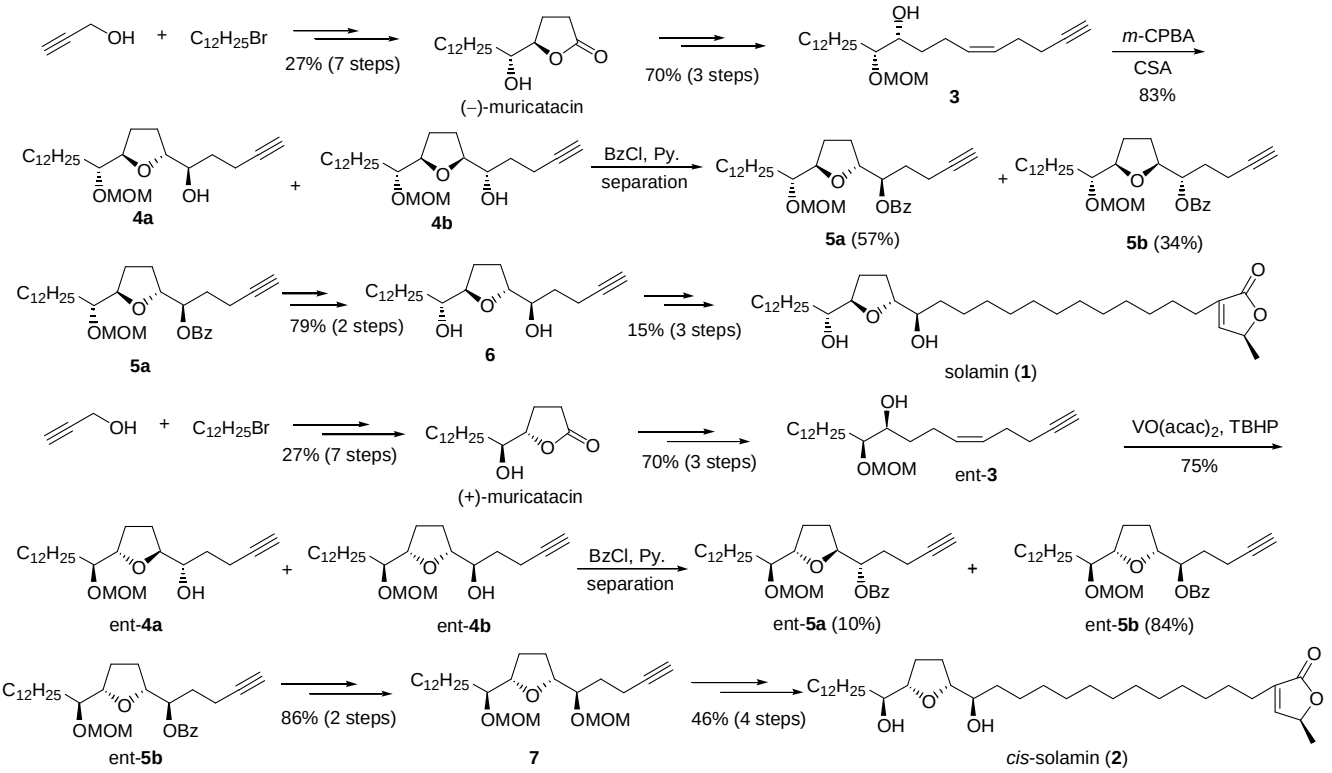
Abstract – A concise total synthesis of solamin (**1**) and *cis*-solamin (**2**) was performed using an epoxy alcohol (**11**) as a versatile chiral building block for synthesizing the stereoisomers of the mono-THF annonaceous acetogenins.

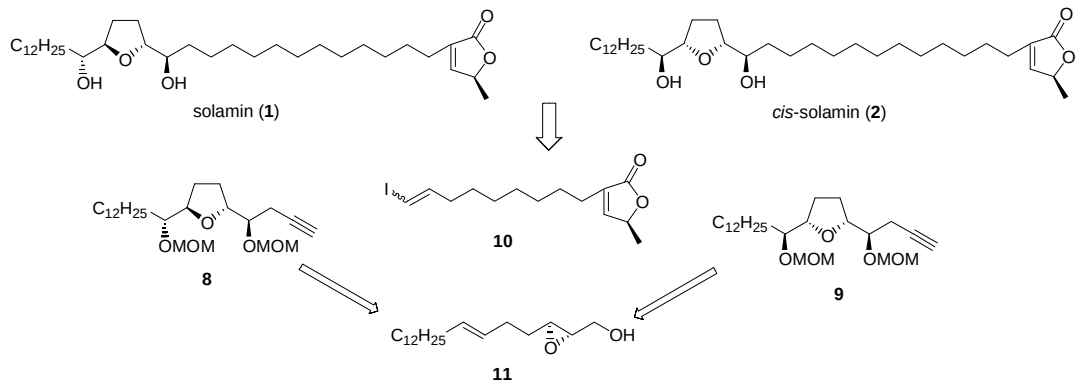
The annonaceous acetogenins, which are endemic to certain plants of the *Annonaceae*, are of much interest especially due to their unique structural features and significant biological activities such as cytotoxic, antitumoral, pesticidal, antiinfective, and antifeedant ones. Biochemical studies have shown that acetogenins are the most potent inhibitors of the mitochondrial respiratory enzyme complex I (NADH-ubiquinone oxidoreductase). More than 430 compounds belonging to this family have been isolated to date, and most of them possess tetrahydrofuran (THF) or tetrahydropyran (THP) rings, hydroxyl, keto and epoxy group, double and triple bonds together with a terminal α,β-unsaturated γ-lactone unit on a C-35 or C-37 long carbon chain.[1] Consequently, significant effort has been devoted toward the total synthesis of annonaceous acetogenins.[2] Solamin (**1**) is a mono-THF acetogenin, isolated from *Annona muricata* in 1991.[3] *cis*-Solamin (**2**) is a diastereomer of **1** and it was isolated in 1998 from same plants.[4] Several syntheses of **1** and **2** were reported including our previous syntheses.[5,6] In our previous syntheses, it was necessary to get rid of undesired diastereomer of the THF part. As to the synthesis of **1**, low stereoselectivity of the epoxidation of **3** and the difficulty to separate **4a** and **4b** caused serious problem. To separate undesired product **4b**, benzoylation of the hydroxyl group followed

by careful purification with preparative TLC was necessary.[5c] For the synthesis of **2**, although the stereoselectivity to construct ent-**4b** was improved using TBHP in the presence of $VO(acac)_2$ as a catalyst, it was still necessary to introduce benzoyl group for careful separation.[6a] Thus it was difficult to synthesize mono-THF moiety in large scale (Scheme 1).



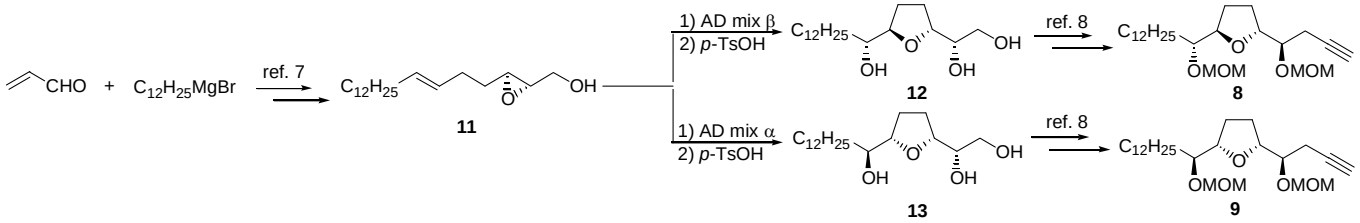
Scheme 1. Previous synthesis of solamin (**1**) and *cis*-solamin (**2**).

To solve these problems, we have developed a concise synthesis of solamin (**1**) and *cis*-solamin (**2**) using systematic and stereoselective construction of the mono-THF moieties without separating undesired diastereomers from chiral epoxy alcohol **11**.[8] The synthetic strategy of **1** and **2** is shown in Scheme 2. The mono-THF moieties were synthesized from epoxy alcohol **11** using Sharpless AD mix β for *threo-trans-threo* moiety **8** and AD mix α for *threo-cis-threo* THF moiety **9** (Scheme 2).



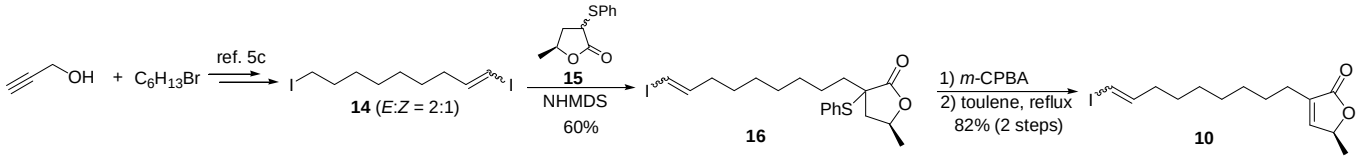
Scheme 2. Synthetic strategy of **1** and **2**.

As shown in Scheme 3, the THF part **8** and **9** were synthesized from acrolein and laurylmagnesium bromide as we prepared before through 8 steps in 50 and 52 % yield, respectively (Scheme 3).[7,8]



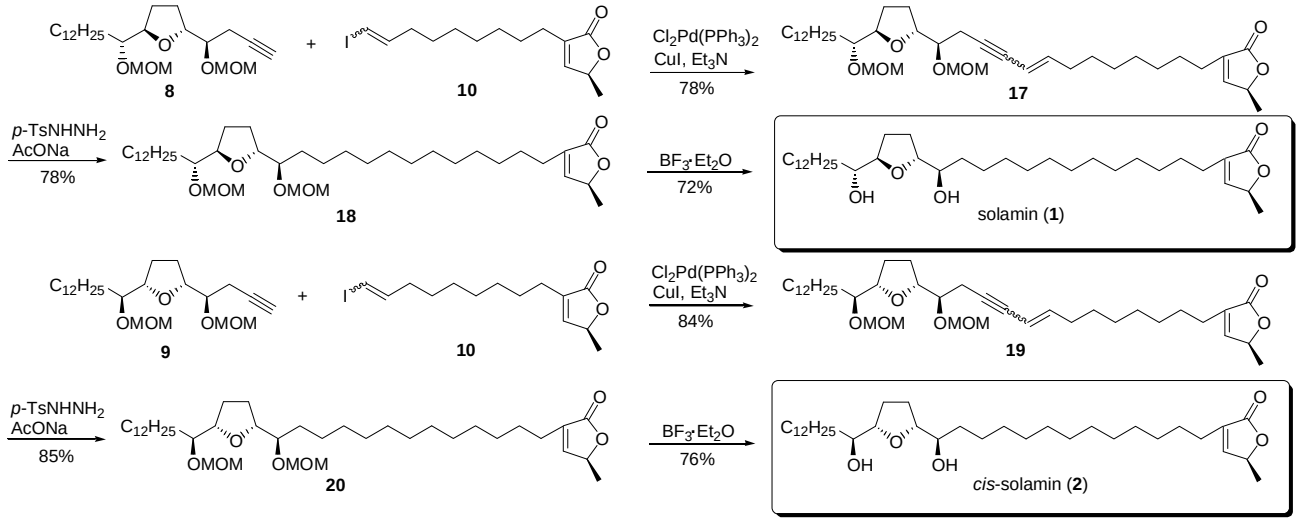
Scheme 3. Synthesis of the tetrahydrofuran moieties of **1** and **2**.

The α, β-unsaturated γ-lactone segment was synthesized as shown in Scheme 4. We selected vinyl iodide **14** as the coupling partner. Vinyl iodide **14** was derived from 1-bromohexane and propargyl alcohol as we reported before.[5c] We examined the alkylation of γ-lactone **15** (prepared by the method of White *et al.*[9]) with diiodide **14** using LDA, LHMDS, NHMDS, and KHMDS as a base. In the case of LDA and/or LHMDS, yield of product was very poor. On the other hand, NHMDS and KHMDS resulted in moderate yield. The counter cation of the base was extremely important for the alkylation of **15**. Oxidation with *m*-CPBA following thermal elimination of sulfoxide gave γ-lactone moiety **10** (Scheme 4).



Scheme 4. Synthesis of γ-lactone moiety **5**.

The THF moiety **8** and γ-lactone **10** were coupled by the Sonogashira cross-coupling reaction to give **17** in 78% yield. Diimide reduction with *p*-$TsNHNH_2$ and AcONa in ethylene glycol diethyl ether under reflux afforded saturated product **18**. Finally, deprotection of the MOM-protected ethers with $BF_3{\cdot}Et_2O$ afforded **1** in 72% yield. The synthesis of **2** was also carried out as described for **1**. The spectral and physical data of the synthetic **1** and **2** were in good agreement of those of reported values (Scheme 5).[3,4]



Scheme 5. Synthesis of solamin (**1**) and *cis*-solamin (**2**).

In conclusion, a concise synthesis of **1** and **2** was accomplished through 18 steps in 15% and 18% yield, respectively. The overall yields of **1** and **2** were much higher than those of our previous synthesis (19 steps, 0.86% yield for **1**,[5c] 20 steps, 3.5% for **2**[6a,6b]).

EXPERIMENTAL

General. All melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance DRX 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 Hz. Mass spectra were obtained on JEOL JMS-700 mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

(8'*EZ*)-3-(Iodonon-9'-enyl)-5-methyl-2,5-dihydrofuran-2-one (10). To an ice-cooled solution of compound **15** (200 mg, 1.0 mmol) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 1.0 mL). After the mixture had been stirred for 30 min at 0 ^{o}C, the diiodide **14** (396 mg, 1.0 mmol) in HMPA (2 mL) was added to it and the whole was allowed to warm to rt. The reaction mixture was then poured into saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was roughly purified with silica gel column chromatography (hexane/AcOEt = 8:1) to afford **16** (274 mg, 60%) as a colorless oil. This compound was used for the next step without further purification. Compound **16** (114 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL) and *m*-CPBA (65%, 66 mg, 0.25 mmol) was added at 0^{o}C. After the mixture was stirred for 20 min at this temperature, saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 5 mL) were added. The mixture was stirred for 1 h and extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with preparative TLC (toluene/AcOEt = 15:1) to afford **10** (71 mg, 82%) as a colorless oil. IR(film)ν_{max}: 3073, 2978, 2927, 2854, 1752, 1653, 1607, 1453, 1318, 1199, 1118, 1100, 1085, 1069, 1026, 949, 860 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20-1.55 (10H, m), 1.41 (3H, d, J = 7.0 Hz), 2.05-2.20 (2H, m), 2.26 (2H, t, J = 7.0 Hz), 5.00 (1H, qd, J = 7.0, 1.5 Hz), 5.98 (0.67H, dt, J = 15.8, 1.5 Hz), 6.18 (0.67H, m), 6.50 (0.67H, dt, J = 15.8, 6.8 Hz), 7.00 (1H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.19, 25.11, 27.30, 27.33, 27.83, 28.24, 28.35, 28.54, 28.71, 28.89, 28.97, 28.99, 29.02, 29.03, 29.05, 29.62, 34.59, 35.95, 74.35, 77.39, 82.23, 134.20, 141.32, 146.63, 148.90, 173.84 ppm. HREIMS Calcd for $C_{14}H_{21}IO_2$ $[M]^+$ 348.0586, found 348.0590.

(1'''*R*,2"*R*,5*S*,5"*R*,13'*R*)-3-{13'-Methoxymethoxy-13'-[5"-(1'''-methoxymethoxytridecyl)tetrahydr-

ofuran-2”-yl]tetradec-8’-en-10’-ynyl}-5-methyl-2,5-dihydrofuran-2-one (17). $Cl_2Pd(PPh_3)_2$ (2.5 mg, 3.5 μmol) was added to a solution of **10** (25 mg, 0.07 mmol) in Et_3N (0.15 mL). After the solution had been stirred for 30 min, a solution of **8** (30 mg, 0.07 mmol) in Et_3N (0.15 mL) and CuI (1.5 mg, 8 μmol) was added. After the mixture had been stirred for 12 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL), and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with preparative TLC (toluene/AcOEt = 10:1) to afford **17** (35 mg, 78%) as a colorless oil. IR(film)ν_{max}: 3052, 2924, 2853, 1758, 1654, 1465, 1318, 1205, 1150, 1102, 1035, 955, 918 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.25-1.80 (34H, m), 1.41 (3H, d, *J* = 6.8 Hz), 1.95-2.10 (4H, m), 2.26 (2H, t, *J* = 7.2 Hz), 2.45-2.65 (2H, m), 3.38 (3H, s), 3.39 (2H, s), 3.40 (1H, s), 3.46 (1H, m), 3.64 (1H, m), 3.98 (1H, m), 4.12 (1H, m), 4.67 (1H, d, *J* = 6.8 Hz), 4.73-4.78 (2H, m), 4.84 (1H, m), 5.00 (1H, qd, *J* = 6.8, 1.5 Hz), 5.42 (0.67H, dd, *J* = 15.8, 1.8 Hz), 5.81 (0.67H, m), 6.03 (0.67H, dt, *J* = 15.8, 7.4 Hz), 6.99 (1H, d, *J* = 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.11, 19.19, 22.42, 22.50, 22.66, 25.12, 25.46, 25.49, 27.33, 28.03, 28.10, 28.44, 28.69, 28.73, 28.92, 29.07, 29.33, 29.60, 29.62, 29.65, 29.79, 31.16, 31.89, 55.77, 66.64, 74.03, 77.65, 79.56, 80.09, 80.21, 81.70, 81.79, 96.37, 96.47, 96.65, 109.64, 134.21, 143.77, 148.89, 173.89 ppm. HRFABMS Calcd for $C_{39}H_{67}O_7$ $[M+H]^+$ 647.4886, found 647.4890.

(1’’’*R*,2”*R*,5*S*,5”*R*,13’*R*)-3-{13’-Methoxymethoxy-13’-[5”-(1’’’-methoxymethoxytridecyl)tetrahydr-ofuran-2”-yl]tetradecyl}-5-methyl-2,5-dihydrofuran-2-one (18). A solution of sodium acetate (371 mg, 4.52 mmol) in H_2O (12 mL) was added to a solution of **17** (16 mg, 0.025 mmol) and *p*-toluenesulfonylhydrazide (733 mg, 3.73 mmol) in diethoxyethane (8 mL) under reflux over 5 h. After being cooled to rt, the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified with preparative TLC (hexane/AcOEt = 4:1) to afford **18** (13 mg, 78%) as a colorless oil. $[\alpha]^{25}_D$ +28 (*c* 0.30, $CHCl_3$), IR(film)ν_{max}: 3052, 2925, 2854, 1759, 1654, 1466, 1373, 1318, 1203, 1149, 1102, 1033, 919, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.7 Hz), 1.25-1.50 (46H, m), 1.41 (3H, d, *J* = 6.8 Hz), 1.92 (2H, m), 2.26 (2H, t, *J* = 6.7 Hz), 3.39 (6H, s), 3.46 (2H, m), 3.98 (2H, m), 4.67 (2H, d, *J* = 6.8 Hz), 4.84 (2H, d, *J* = 6.8 Hz), 5.00 (1H, qd, *J* = 6.8, 1.5 Hz), 6.99 (1H, d, *J* = 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.13, 19.21, 22.69, 25.16, 25.52, 27.38, 28.44, 29.18, 29.31, 29.35, 29.52, 29.61, 29.64, 29.80, 31.22, 31.91, 55.71, 77.41, 79.60, 81.49, 96.67, 134.31, 148.86, 173.93 ppm. HREIMS Calcd for $C_{38}H_{69}O_6$ $[M–OMe]^+$ 621.5094, found 621.5086.

Solamin (1). $BF_3 \cdot Et_2O$ (0.02 mL) was added to a solution of **18** (5 mg, 0.076 mmol) in dimethyl sulfide (0.4 mL) at 0°C. After the mixture was stirred for 10 min at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified with preparative TLC (hexane/AcOEt = 1:2) to afford **1** (3.0 mg, 72%) as a colorless waxy solid. Mp 67-69 °C, $[\alpha]^{25}_D$ +22 (*c* 0.20, MeOH), IR(KBr)ν_{max}: 3438, 3052, 2918, 2850, 1737, 1653, 1468, 1374, 1203, 1115, 1082, 1028, 961, 890, 721 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.1 Hz), 1.21-1.58 (44H, m), 1.41 (3H, d, *J* = 6.8 Hz), 1.68 (2H, m), 2.00 (2H, m), 2.25-2.31 (4H, m), 3.40 (2H, m), 3.80 (2H, m), 5.00 (1H, dd, *J* = 6.8, 1.4 Hz), 6.99 (1H, d, *J* = 1.4 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.09, 19.22, 22.68, 25.19, 25.61, 27.43, 28.73, 29.18, 29.30, 29.35, 29.50, 29.59, 29.62, 29.64, 29.72, 31.92, 33.56, 74.04, 77.36, 81.83, 134.40, 148.79, 173.84 ppm. HRFABMS Calcd for $C_{35}H_{64}O_5Na$ $[M+Na]^+$ 587.4651, found 587.4650.

(1'''*S*,2"*R*,5*S*,5"*S*,13'*R*)-3-{13'-Methoxymethoxy-13'-[5"-(1'''-methoxymethoxytridecyl)tetrahydr-ofuran-2"-yl]tetradec-8'-en-10'-ynyl}-5-methyl-2,5-dihydrofuran-2-one (19). The procedure was the same as that used for the preparation of **17**. Compound **19** (97 mg, 84%) was prepared from **10** (75 mg, 0.45 mmol) and **9** (90 mg, 0.21 mmol) as a colorless oil. IR(film)ν_{max}: 3052, 2925, 2853, 1758, 1654, 1466, 1318, 1204, 1150, 1102, 1041, 955, 918 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.25-1.95 (39H, m), 2.07 (2H, m), 2.26 (2H, t, *J* = 7.0 Hz), 2.48-2.74 (2H, m), 3.39 (3H, s), 3.40 (1H, s), 3.41 (2H, s), 3.51 (1H, m), 3.68 (1H, m), 3.92 (1H, m), 4.08 (1H, m), 4.67 (1H, d, *J* = 6.8 Hz), 4.73-4.78 (3H, m), 5.00 (1H, qd, *J* = 7.0, 1.5 Hz), 5.42 (0.67H, dd, *J* = 15.5, 1.5 Hz), 5.81 (0.67H, m), 6.03 (0.67H, dt, *J* = 15.5, 7.0 Hz), 6.99 (1H, d, *J* = 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.09, 19.18, 22.39, 22.56, 22.65, 25.12, 25.14, 25.40, 27.33, 27.46, 27.73, 28.69, 28.85, 28.90, 29.06, 29.15, 29.32, 29.59, 29.60, 29.63, 29.78, 30.10, 31.20, 31.88, 32.87, 55.67, 66.64, 77.80, 77.89, 79.76, 80.33, 80.58, 82.01, 84.85, 96.39, 96.67, 109.16, 109.68, 134.22, 142.94, 143.71, 148.87, 173.84 ppm. HREIMS Calcd for $C_{39}H_{67}O_7$ $[M]^+$ 646.4809, found 646.4793.

(1'''*S*,2"*R*,5*S*,5"*S*,13'*R*)-3-{13'-Methoxymethoxy-13'-[5"-(1'''-methoxymethoxytridecyl)tetrahydro-furan-2"-yl]tetradecyl}-5-methyl-2,5-dihydrofuran-2-one (20). The procedure was the same as that used for the preparation of **18**. Compound **20** (85 mg, 85%) was prepared from **19** (96 mg, 0.15 mmol) as a colorless oil. $[\alpha]^{19}_D$ +4.5 (*c* 0.87, $CHCl_3$), IR(film)ν_{max}: 3052, 2924, 2853, 1760, 1654, 1466, 1318, 1149, 1102, 1078, 1041, 918 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.25-1.50 (46H, m), 1.41 (3H, d, *J* = 7.0 Hz), 1.86 (2H, m), 2.26 (2H, t, *J* = 7.5 Hz), 3.39 (6H, s), 3.50 (2H, m), 3.89

(2H, m), 4.67 (2H, d, *J* = 7.0 Hz), 4.83 (2H, d, *J* = 6.5 Hz), 5.00 (1H, qd, *J* = 7.0, 1.5 Hz), 6.99 (1H, d, *J* = 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.10, 19.21, 22.67, 25.17, 25.44, 27.39, 27.60, 29.25, 29.34, 29.52, 29.61, 29.65, 29.66, 29.81, 31.23, 31.91, 55.68, 77.38, 79.81, 81.83, 96.70, 134.33, 148.82, 173.88 ppm. HREIMS Calcd for $C_{38}H_{69}O_6$ $[M–OMe]^+$ 621.5094, found 621.5090.

***cis*-Solamin (2).** The procedure was the same as that used for the preparation of **1**. Compound **2** (36 mg, 76%) was prepared from **20** (55 mg, 0.84 mmol) as a colorless waxy solid. Mp. 70-72 °C, $[\alpha]^{19}_D$ +21 (*c* 0.34, MeOH), IR(KBr)ν_{max}: 3422, 3052, 2918, 2849, 1739, 1653, 1469, 1081, 1029, 969, 721 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.21-1.58 (44H, m), 1.41 (3H, d, *J* = 6.8 Hz), 1.75 (2H, m), 1.94 (2H, m), 2.26 (2H, t, *J* = 7.0 Hz), 2.55 (2H, brs. –OH), 3.42 (2H, m), 3.82 (2H, m), 5.00 (1H, dd, *J* = 6.8, 1.5 Hz), 6.99 (1H, d, *J* = 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ:14.10, 19.19, 22.66, 25.14, 25.69, 27.36, 28.09, 29.05, 29.15, 29.21, 29.27, 29.33, 29.39, 29.47, 29.57, 29.60, 29.62, 29.64, 29.65, 29.66, 29.68, 31.89, 34.07, 74.33, 77.39, 82.69, 134.30, 148.84, 173.89 ppm. HREIMS Calcd for $C_{35}H_{64}O_5$ $[M]^+$ 564.4753, found 564.4720.

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