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Enantioselective Syntheses of Pachastrissamine and Jaspine A *via* Hydroxylactonization of a Chiral Epoxy Ester

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A new enantioselective total synthesis of pachastrissamine (jaspine B) was achieved from a known α,β-unsaturated aldehyde by utilizing Córdova's asymmetric epoxidation as the chirality-inducing step. The 2,3-*cis* stereochemistry of pachastrissamine was established *via* intramolecular epoxide ring opening of a γ,δ-epoxy-α,β-unsaturated ester intermediate coupled with oxy-Michael cyclization. Treatment of pachastrissamine with tetrahydro-2-furanol under acidic conditions led to smooth oxazolidine ring formation, furnishing jaspine A in a high yield.

Key words: pachastrissamine; jaspine; heterocycle; phytosphingosine; cytotoxic

Pachastrissamine (**1**) was first discovered by Higa and co-workers from the marine sponge *Pachastrissa* sp. collected in Okinawa, Japan, and shown to exhibit significant cytotoxicity against P388, A549, HT29, and MEL28 cancer cell lines with an IC_{50} value of 10 ng/ml (Fig. 1).[1] Shortly after this discovery, Debitus *et al.* also isolated the same compound together with another anhydrophytosphingosine derivative from the marine sponge *Jaspis* sp., and named them jaspine B (**1**) and jaspine A (**2**); the hydrochloride of **1** was shown to display marked cytotoxicity ($IC_{50} = 0.24\,\mu M$) against the A549 human lung carcinoma cell line.[2] Prompted by the intriguing biological activity and unique molecular architecture featuring an all-*cis* 2,3,4-trisubstituted tetrahydrofuran structural motif, many studies have been made on the synthesis of **1** using various approaches.[3] As many as 17 syntheses of **1** have already been reported which can be categorized into 5 groups according to the source of chirality: i) chiral natural products (L-serine, carbohydrates, and tartaric acids);[4–12] ii) commercially available D-*ribo*-phytosphingosine;[13,14] iii) asymmetric conjugate addition of a chiral amide;[15] iv) Sharpless asymmetric epoxidation/dihydroxylation;[16–19] and v) asymmetric aldol reaction.[20] We describe here a new enantioselective synthesis of **1** and the first synthesis of **2** by using Córdova's asymmetric epoxidation of an α,β-unsaturated aldehyde as the chirality-inducing step and hydroxylactonization of a chiral epoxy ester intermediate coupled with oxy-Michael cyclization to establish their 2,3-*cis* stereochemical relationship.

Results and Discussion

Our retrosynthetic analysis of **1** and **2** is shown in Scheme 1. Heterobicyclic compound **2** would be readily accessible from **1** through thermodynamically controlled oxazolidine ring formation. We envisaged that the α-oriented amino group at the C4 position of **1** could be stereoselectively installed by reductive amination of ketone intermediate **3**. This dihydro-3(2*H*)-furanone derivative **3** was considered to be obtainable from bicyclic lactone **4** *via* reduction of the lactone moiety and subsequent chain elongation and oxidation of the C4 alcoholic functionality. The tetrahydrofuran ring of **4** would be constructed by an intramolecular oxy-Michael reaction of hydroxylactone **5**, which in turn would probably be prepared by the hydroxylactonization of γ,δ-epoxy-α,β-unsaturated ester **6**. To obtain **6**, we planned to utilize Córdova's asymmetric epoxidation of α,β-unsaturated aldehyde **7** and subsequent *Z*-selective Wittig olefination

According to the synthetic plan, known unsaturated aldehyde **8**[21] was subjected to Córdova's asymmetric epoxidation conditions by using D-proline-derived organocatalyst **9** to give epoxy aldehyde **10** in an 80% yield (Scheme 2).[22] The *Z*-selective olefination of **10** using Ando's protocol proceeded smoothly,[23] furnishing **11** in an 89% yield with high geometric selectivity ($Z/E =$ 18:1). The intramolecular epoxide ring opening of **11** could be induced with TFA in CH_2Cl_2,[24] affording hydroxylactone **12a** in a 76% yield. The enantiomeric excess of **12a** was determined to be 95% by analyzing the ^{1}H-NMR spectra of corresponding (*R*)- and (*S*)-MTPA esters **12b**.[25] The newly formed hydroxyl group of **12a** was protected as its PMB ether with PMBOC(=NH)CCl_3 and CSA to give **12c**, the TBS group of which was then removed under acidic conditions to afford alcohol **13** in an 84% yield for the two steps. The intramolecular oxy-Michael reaction of **13** to form the tetrahydrofuran ring was effected by treating **13** with saturated aqueous $NaHCO_3$ in EtOAc according to Datta's procedure,[5] delivering desired tetrahydrofuran derivative **14**, albeit in a moderate yield of 52% yield (69%, based on the recovered starting material).

With bicyclic lactone **14** in hand, we moved on to its elaboration into ketone intermediate **21**, the substrate for

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Abbreviations: TBS, *tert*-butyldimethylsilyl; KHMDS, potassium hexamethyldisilazide; TFA, trifluoroacetic acid; CSA, 10-camphorsulfonic acid; MTPA, α-methoxy-α-(trifluoromethyl)phenylacetyl; PMB, *p*-methoxybenzyl; DIBAL, diisobutylaluminum hydride; TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DMP, Dess-Martin periodinane; TBAF, tetrabutylammonium fluoride

reductive amination (Scheme 3). Reduction of lactone **14** with DIBAL afforded lactol **15** which was then subjected to the Wittig reaction to give **16** as a mixture of geometrical isomers in a 70% yield from **14** ($Z/E = ca.$ 3:1). TBS protection of the hydroxyl group of **16** gave **17** in an 82% yield which was then exposed to H_2 under two kinds of reaction condition (Pd/C in MeOH and $Pd(OH)_2/C$ in EtOAc) to effect both hydrogenation of the double bond and hydrogenolysis of the PMB ether. This conversion aimed at obtaining **18** was, however, found to be very difficult; not only the hydrogenolysis but also the hydrogenation did not proceed at all, resulting only in the recovery of starting material **17**. Faced with unexpected difficulty in the reduction of **17**, we tried to first hydrogenate the double bond of unprotected alcohol **16**. Fortunately, this reduction took place uneventfully to give **19** bearing the saturated side chain in an almost quantitative yield. After protecting the hydroxyl group of **19** as its TBS ether, resulting product **20** was exposed to DDQ in THF containing a phosphate buffer solution to give alcohol intermediate **18** which was then oxidized with Dess-Martin periodinane to furnish ketone **21** in an 84% overall yield from **19**.

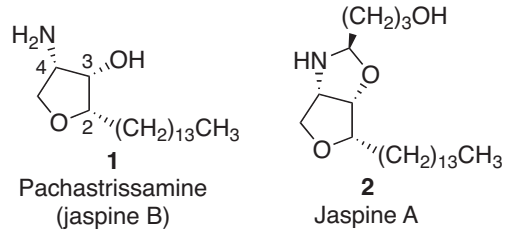
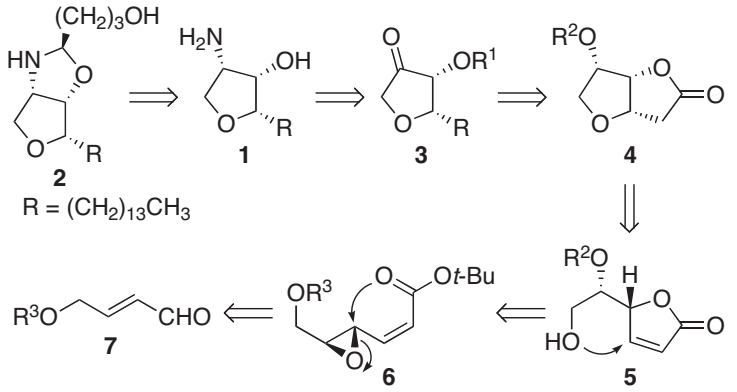
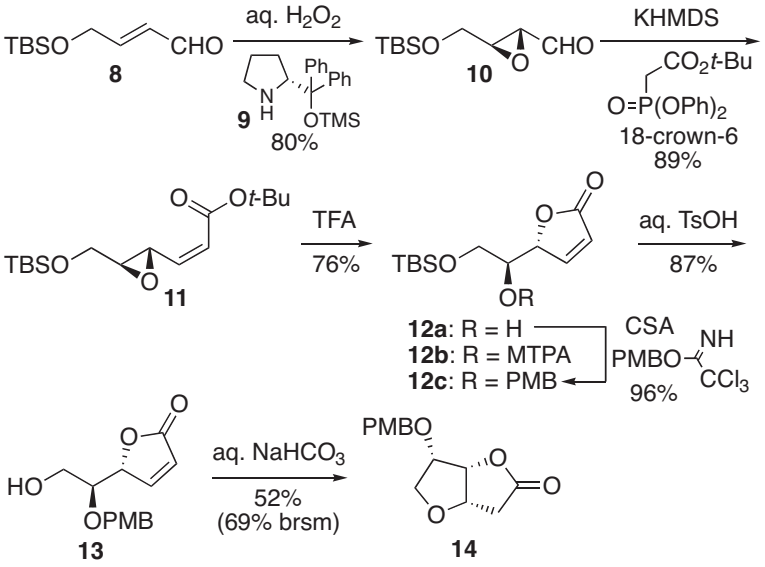


Fig. 1. Structures of Pachastrissamine (**1**) and Jaspine A (**2**).

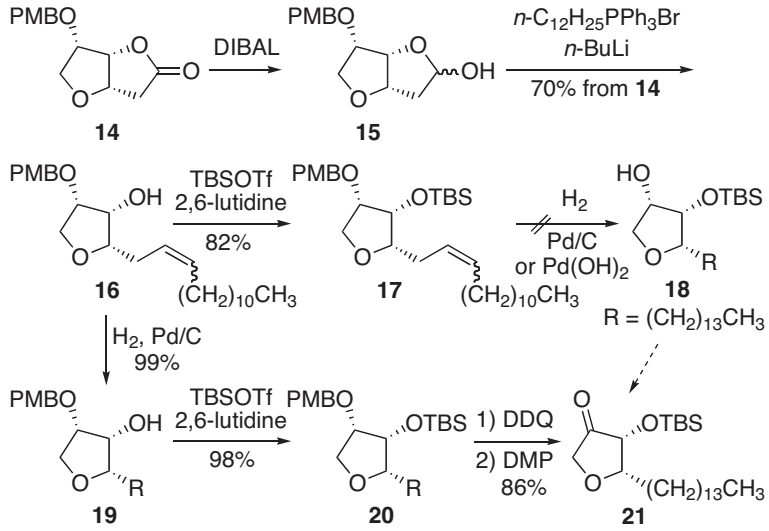
The final stage of the syntheses of **1** and **2** is depicted in Scheme 4. The stereoselective reductive amination of **21** to **22** was achieved by using Bhattacharyya's protocol ($NH_3/Ti(O\textit{i}\text{-}Pr)_4$ in EtOH, and then $NaBH_4$),[26] furnishing desired reductive amination product **22** as a single stereoisomer in a 60% yield; on the other hand, exposure of **21** to conventional reductive amination conditions ($NaCNBH_3/NH_4OAc$ in MeOH) gave none of the desired product, resulting only in reduction of the ketone functionality to give alcohol **18**. Finally, deprotection of the TBS group with TBAF gave pachastrissamine **1** in a 90% yield. The ^{1}H- and ^{13}C-NMR data, as well as the specific rotation value of **1**, matched those reported for the natural product.[1,2] The conversion of **1** to jaspine A (**2**) proceeded uneventfully in an 89% yield



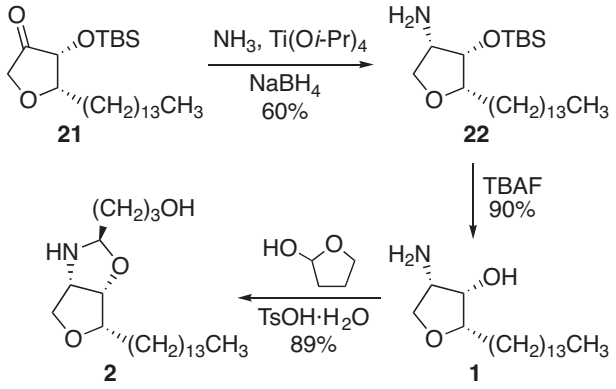
Scheme 1. Retrosynthetic Analysis of **1** and **2**.



Scheme 2. Preparation of Intermediate **14**.



Scheme 3. Preparation of Intermediate **21**.



Scheme 4. Completion of the Syntheses of **1** and **2**.

by treating **1** with tetrahydro-2-furanol in the presence of *p*-toluenesulfonic acid.[27] The ^{1}H- and ^{13}C-NMR spectral data and specific rotation value of **2** were in good agreement with those reported for natural jaspine A.[2] It is worth mentioning that, unlike its ^{1}H-NMR spectrum, the ^{13}C-NMR spectrum of **2** in $CDCl_3$, which required a prolonged measurement time as compared to ^{1}H-NMR, indicated gradual transformation of **2** into another compound. Although we could not identify the newly formed compound, this phenomenon seems to be ascribable to the slightly acidic nature of $CDCl_3$, since this transformation was substantially suppressed by recording the ^{13}C-NMR in C_5D_5N.

In conclusion, a new enantioselective total synthesis of pachastrissamine (**1**) was achieved in a 7.5% overall yield from known unsaturated aldehyde **8** *via* 14 steps. The new synthetic route utilized Córdova's asymmetric epoxidation as the chirality-inducing step and established the 2,3-*cis* stereochemistry of **1** by intramolecular epoxide ring opening of epoxy ester intermediate **11** coupled with oxy-Michael cyclization of ε-hydroxy-α,β-unsaturated γ-lactone intermediate **13**. The C4 amino group was stereoselectively installed by reductive amination of ketone intermediate **21** under Bhattacharyya's conditions. Jaspine A (**2**) was also synthesized for the first time by treating **1** with tetrahydro-2-furanol under acidic conditions.

Experimental

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment and are reported in cm^{-1}. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Unity plus-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) unless otherwise stated. Optical rotation values were measured with a Jasco DIP-371 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the EI or FAB mode. Melting point (mp) data were determined with a Yanaco MP-J3 apparatus and are uncorrected. Merck silica gel 60 (7–230 mesh) was used for column chromatography unless otherwise stated. The solvents used for the reactions were distilled prior to use: THF from Na and benzophenone; MeOH from Mg and I_2; and CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted in a nitrogen atmosphere.

*(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-2-oxiranecarbaldehyde (**10**).* To a stirred solution of **8** (1.59 g, 7.94 mmol) in $CHCl_3$ (60.0 ml) was added catalyst **9** (355 mg, 1.09 mmol) at room temperature. After 10 min, 30% aqueous H_2O_2 (1.08 g, 9.55 mmol) was added, and the resulting mixture was stirred vigorously for 3 h at room temperature. The mixture was quenched with solid $Na_2S_2O_3$, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 10:1) to give 1.38 g (80%) of **10** as a colorless oil. $[\alpha]^{24}_D$ +43.8° (*c* 1.33, $CHCl_3$); IR ν_{max}: 2955 (m), 1731 (s), 1131 (m), 836 (m); ^{1}H-NMR δ: 0.075 (3H, s), 0.085 (3H, s), 0.90 (9H, s), 3.37 (1H, dd, J = 2.0, 6.5 Hz), 3.37–3.42 (1H, m), 3.79 (1H, dd, J = 4.0, 12 Hz), 4.00 (1H, dd, J = 2.5, 12 Hz), 9.08 (1H, d, J = 6.5 Hz); ^{13}C-NMR δ: −5.5 (2C), 18.2, 25.7 (3C), 56.1, 56.7, 61.2, 198.1; HRMS (FAB) m/z ($[M+H]^+$): calcd. for $C_{10}H_{21}O_3Si$, 217.1260; found, 217.1264.

tert-*Butyl (*Z*)-3-[(2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)methyl-2-oxyranyl]-2-propenoate (**11**).* To a stirred solution of 18-crown-6 (438 mg, 1.66 mmol) and $(PhO)_2P(O)CH_2CO_2t$-Bu (578 mg, 1.66 mmol) in THF (14.5 ml) was added KHMDS (0.5 M in THF, 3.3 ml, 1.66 mmol) at −78 °C. After 35 min, a solution of **10** (276 mg, 1.28 mmol) in THF (14.5 ml) was added at −78 °C, and the mixture was gradually warmed to room temperature. After being stirred overnight at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 10:1) to give 358 mg (89%) of an 18:1 mixture of **11** and its *E*-isomer as a colorless oil. $[\alpha]^{28}_D$ +31.5° (*c* 1.2, $CHCl_3$); IR ν_{max}: 2958 (m), 2858 (m), 1716 (s), 1159 (m), 839 (m); ^{1}H-NMR δ: 0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.50 (9H, s), 3.06 (1H, m), 3.66 (1H, dd, J = 5.5, 12 Hz), 3.99 (1H, dd, J = 2.5, 12 Hz), 4.43 (1H, d, J = 8.5 Hz), 5.69

(1H, dd, $J = 8.5$, 11.5 Hz), 5.89 (1H, d, $J = 11.5$ Hz); ^{13}C-NMR δ: −5.3 (2C), 18.3, 25.8 (3C), 28.1 (3C), 51.7, 60.0, 63.4, 80.9, 125.8, 144.4, 165.1; HRMS (FAB) m/z ($[M + H]^+$): calcd. for $C_{16}H_{31}O_4Si$, 315.1992; found, 315.1998.

*(*R*)-5-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl]-5*H*-furan-2-one (**12a**).* To a stirred solution of **11** (697 mg, 2.22 mmol) in CH_2Cl_2 (22 ml) was added CF_3CO_2H (160 µl, 2.09 mmol) at room temperature. After being stirred overnight, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 3:1) to give 437 mg (76%) of **12a** as a colorless oil. $[\alpha]^{27}_D$ +78.2° (*c* 1.00, $CHCl_3$); IR ν_{max}: 3449 (m), 1752 (s), 1255 (m), 835 (m); ^{1}H-NMR δ: 0.115 (3H, s), 0.120 (3H, s), 0.92 (9H, s), 2.68 (1H, d, $J = 7.5$ Hz, OH), 3.55 (1H, m), 3.83 (1H, dd, $J = 3.5$, 10.5 Hz), 3.89 (1H, dd, $J = 3.5$, 10.5 Hz), 4.97 (1H, ddd, $J = 1.5$, 2.0, 8.0 Hz), 6.18 (1H, dd, $J = 2.0$, 6.0 Hz), 7.73 (1H, dd, $J = 1.5$, 6.0 Hz); ^{13}C-NMR δ: −5.5 (2C), 18.2, 25.8 (3C), 63.4, 72.3, 82.3, 121.8, 155.7, 172.9; HRMS (FAB) m/z ($[M + H]^+$): calcd. for $C_{12}H_{23}O_4Si$, 259.1366; found, 259.1366.

*Determination of the enantiomeric excess of **12a**.* According to the literature,[25] compound **12a** was treated with (*R*)- and (*S*)-MTPA chloride in pyridine to respectively give MTPA esters (*S*)-**12b** and (*R*)-**12b** which were analyzed as $CDCl_3$ solutions by ^{1}H-NMR. The signals for the two protons on the TBSO-bearing methylene carbon of (*R*)-**12b** were observed at δ 3.98 (1H, dd, $J = 3.9$, 11.7 Hz) and δ 4.02 (1H, dd, $J = 3.4$, 11.7 Hz), while those of (*S*)-**12b** appeared at δ 3.86 (1H, dd, $J = 4.6$, 11.5 Hz) and δ 3.94 (1H, dd, $J = 3.7$, 11.5 Hz). A comparison of the two ^{1}H-NMR spectra clearly showed the enantiomeric excess of **12a** to be *ca.* 95%.

*(*R*)-5-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)ethyl]-5*H*-furan-2-one (**12c**).* To a stirred solution of **12a** (100 mg, 0.39 mmol) and camphorsulfonic acid (13 mg, 0.06 mmol) in CH_2Cl_2 (1.0 ml) was added a solution of $PMBOC(=NH)CCl_3$ in CH_2Cl_2 (0.6 ml) at room temperature. After 20 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was triturated with hexane and then filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over SiO_2 (hexane/EtOAc = 20:1–2:1) to give 142 mg (96%) of **12c** as a colorless oil. $[\alpha]^{25}_D$ +99.3° (*c* 1.36, $CHCl_3$); IR ν_{max}: 1756 (s), 1613 (m), 1513 (m), 1249 (m), 833 (m); ^{1}H-NMR δ: 0.07 (6H, s), 0.90 (9H, s), 3.68 (1H, dt, $J = 5.5$, 4.8 Hz), 3.78 (2H, d, $J = 4.8$ Hz) 3.80 (3H, s), 4.50 (1H, d, $J = 11.2$ Hz), 4.58 (1H, d, $J = 11.2$ Hz), 5.20 (1H, ddd, $J = 1.5$, 1.5, 5.5 Hz), 6.14 (1H, dd, $J = 1.5$, 6.0 Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.57 (1H, dd, $J = 1.5$, 6.0 Hz); ^{13}C-NMR δ: −5.5 (2C), 18.2, 25.8 (3C), 55.2, 62.4, 73.0, 78.7, 82.9, 113.8 (2C), 122.2, 129.6 (3C), 154.4, 159.4, 173.0; HRMS (EI) m/z ($[M]^+$): calcd. for $C_{20}H_{30}O_5Si$, 378.1863; found, 378.1863.

*(*R*)-5-[(*S*)-2-Hydroxy-1-(4-methoxybenzyloxy)ethyl]-5*H*-furan-2-one (**13**).* To a stirred solution of **12c** (1.21 g, 3.20 mol) and water (0.6 ml) in THF (12 ml) was added $TsOH\cdot H_2O$ (183 mg, 0.96 mmol) at room temperature. After 12 h, the reaction mixture was quenched with solid $NaHCO_3$, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 1:1–0:1) to give 735 mg (87%) of **13** as a colorless oil. $[\alpha]^{23}_D$ +113° (*c* 1.06, $CHCl_3$); IR ν_{max}: 3474 (m), 1752 (s), 1613 (m), 1513 (m), 1250 (m); ^{1}H-NMR δ: 1.95 (1H, s, OH), 3.63 (1H, dt, $J = 6.0$, 3.5 Hz), 3.75 (1H, dd, $J = 3.5$, 11.0 Hz), 3.81 (3H, s), 3.87 (1H, dd, $J = 3.5$, 11.0 Hz), 4.55 (2H, s), 5.15 (1H, ddd, $J = 1.5$, 1.8, 6.0 Hz), 6.16 (1H, dd, $J = 1.8$, 5.8 Hz), 6.89 (2H, d, $J = 8.8$ Hz), 7.23 (2H, d, $J = 8.8$ Hz), 7.61 (1H, dd, $J = 1.5$, 5.8 Hz); ^{13}C-NMR δ: 55.2, 61.3, 72.9, 78.7, 82.6, 113.9 (2C), 122.1, 129.1, 129.6 (2C), 154.7, 159.5, 172.7; HRMS (EI) m/z ($[M]^+$): calcd. for $C_{14}H_{16}O_5$, 264.0998; found, 264.1001.

*(3a*S*,6*S*,6a*R*)-6-(4-Methoxybenzyloxy)tetrahydrofuro[3,2-*b*]furan-2-one (**14**).* To a stirred solution of **13** (414 mg, 1.57 mmol) in EtOAc (13 ml) was added saturated aqueous $NaHCO_3$ (50 ml) at room temperature. After 15 h, the reaction mixture was extracted with EtOAc, and the extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 5:1–4:1) to give 215 mg (52%) of **14** as a colorless oil together with 102 mg of recovered **13**. $[\alpha]^{27}_D$ −119° (*c* 1.00, $CHCl_3$); IR ν_{max}: 1780 (s), 1613 (m), 1513 (m), 1249 (m); ^{1}H-NMR δ: 2.67 (1H, dd, $J = 2.0$, 18.5 Hz), 2.78 (1H, dd, $J = 7.0$, 18.5 Hz), 3.77 (1H, dd, $J = 7.0$, 9.0 Hz), 3.81 (3H, s), 3.92 (1H, dd, $J = 6.0$, 9.0 Hz), 4.11–4.15 (1H, m), 4.51 (1H, d, $J = 11.5$ Hz), 4.69 (1H, d, $J = 11.5$ Hz), 4.75 (1H, ddd, $J = 2.0$, 5.0, 7.0 Hz), 4.94 (1H, dd, $J = 5.0$, 5.0 Hz), 6.89 (2H, d, $J = 8.8$ Hz), 7.30 (2H, d, $J = 8.8$ Hz); ^{13}C-NMR δ: 36.2, 55.2, 69.3, 72.2, 76.8, 77.4, 80.9, 113.8 (2C), 129.1, 129.6 (2C), 159.4, 175.4; HRMS (EI) m/z ($[M]^+$): calcd. for $C_{14}H_{16}O_5$, 264.0998; found, 264.0998.

*(2*S*,3*R*,4*S*)-4-(4-Methoxybenzyloxy)-2-[(*E*/*Z*)-2-tetradecenyl]tetrahydrofuran-3-ol (**16**).* To a stirred solution of **14** (385 mg, 1.46 mmol) in CH_2Cl_2 (13 ml) was added DIBAL (1.03 M in hexane, 1.84 ml, 1.89 mmol) at −78 °C. After 1 h, the reaction mixture was quenched with saturated aqueous Rochelle's salt and extracted with a mixture of CH_2Cl_2 and EtOAc. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give crude **15** (366 mg) which was then dissolved in THF (8 ml) and added at −78 °C to a solution of n-$C_{11}H_{23}CH{=}PPh_3$ [prepared by treating a solution of n-$C_{12}H_{25}PPh_3Br$ (3.16 g, 6.18 mmol) in THF (31 ml) with n-BuLi (1.6 M in hexane, 3.4 ml, 5.5 mmol) at −78 °C]. The mixture was gradually warmed to room temperature over 18 h and quenched with saturated aqueous NH_4Cl. The mixture was then extracted with EtOAc, and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 10:1) to give 423 mg (70% from **14**) of **16** (*E*/*Z* = *ca.* 1:3) as a white waxy solid. $[\alpha]^{25}_D$ +8.2° (*c* 1.40, $CHCl_3$); IR ν_{max}: 3366 (m), 2918 (s), 1614 (m), 1515 (m), 1251 (m); ^{1}H-NMR (3:1 mixture of *Z*/*E* isomer) δ: 0.88 (3H, t, $J = 6.5$ Hz), 1.20–1.36 (18H, m), 1.99 (0.25 × 2H, dt, $J = 7.0$, 7.0 Hz, 4′-H_2), 2.07 (0.75 × 2H, dt, $J = 7.0$, 7.0 Hz, 4′-H_2), 2.36 (0.25 × 1H, dt, $J = 14.2$, 7.0 Hz, 1′-H), 2.44 (0.25 × 1H, dt, $J = 14.2$, 7.0 Hz, 1′-H), 2.46 (0.75 × 2H, dd, $J = 7.1$, 7.1 Hz, 1′-H_2) 2.61 (1H, br s, OH), 3.65–3.70 (1H, m), 3.79–3.88 (2H, m), 3.81 (3H, s), 4.07–4.15 (1H, m), 4.14–4.19 (1H, m), 4.50 (1H, d, $J = 11.2$ Hz), 4.54 (1H, d, $J = 11.2$ Hz), 5.38–5.53 (0.75 × 2H + 0.25 × 1H, m, 2′-H + 3′-H), 5.56 (0.25 × 1H, dt, $J = 15.1$, 6.8 Hz, 2′-H), 6.89 (2H, d, $J = 8.3$ Hz), 7.27 (2H, d, $J = 8.3$ Hz); ^{13}C-NMR δ: 14.4, 22.9, 27.4/27.6, 29.5, 29.60/29.61, 29.67, 29.77, 29.82, 29.90, 29.93, 32.2, 32.6/32.9, 55.5, 69.87/69.89, 70.4, 72.56/72.58, 79.13/79.14, 82.34/82.58, 114.2 (2C), 125.2/125.9, 129.5 (2C), 129.8, 132.7/133.6, 159.8; HRMS (EI) m/z ($[M]^+$): calcd. for $C_{26}H_{42}O_4$, 418.3083; found, 418.3084.

*(2*S*,3*R*,4*S*)-4-(4-Methoxybenzyloxy)-2-tetradecyltetrahydrofuran-3-ol (**19**).* A mixture of **16** (264 mg, 0.63 mmol) and 10% Pd/C (50 mg) in EtOAc (25 ml) was stirred at room temperature under a hydrogen atmosphere. After 2.5 h, the mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 4:1) to give 261 mg (99%) of **19** as a white crystalline solid. Mp 80–81 °C; $[\alpha]^{26}_D$ +3.5° (*c* 1.64, $CHCl_3$); IR ν_{max} 3378 (m), 2916 (s), 1613 (m), 1515 (m), 1251 (m), 907 (m); ^{1}H-NMR δ: 0.88 (3H, t, $J = 6.5$ Hz), 1.20–1.44 (24H, m), 1.62–1.71 (2H, m), 2.59 (1H, d, $J = 4.5$ Hz, OH), 3.62–3.67 (1H, m), 3.81 (3H, s), 3.77–3.85 (2H, m), 4.04–4.09 (1H, m), 4.17 (1H, dd, $J = 6.0$, 12.0 Hz), 4.50 (1H, d, $J = 11.2$ Hz), 4.54 (1H, d, $J = 11.2$ Hz), 6.89 (2H, d, $J = 8.8$ Hz), 7.27 (2H, d, $J = 8.8$ Hz); ^{13}C-NMR δ: 14.1, 22.7, 26.1, 28.8, 29.3, 29.54, 29.56, 29.63 (2C), 29.64, 29.65, 29.72, 31.9, 55.2, 69.4, 70.3, 72.3, 79.0, 82.3, 82.4, 113.9 (2C), 129.2, 129.5 (2C), 159.5; HRMS (EI) m/z ($[M]^+$): calcd. for $C_{26}H_{44}O_4$, 420.3240; found, 420.3244.

*(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-2-tetradecyltetrahydrofuran (**20**).* To a stirred solution of **19** (238 mg, 0.566 mmol) in CH_2Cl_2 (8 ml) were added 2,6-lutidine (395 µl, 3.40 mmol) and TBSOTf (519 µl, 2.26 mmol) at 0 °C. After 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The

residue was chromatographed over SiO_2 (hexane/EtOAc = 30:1) to give 296 mg (98%) of **20** as a colorless oil. $[\alpha]^{25}_D$ −5.6° (*c* 1.18, $CHCl_3$); IR ν_{max}: 2926 (s), 1614 (m), 1514 (m), 1250 (m); ^{1}H-NMR δ: 0.072 (3H, s), 0.082 (3H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.91 (9H, s), 1.20–1.34 (22H, m), 1.34–1.42 (2H, m), 1.51–1.59 (1H, m), 1.59–1.68 (1H, m), 3.73–3.78 (2H, m), 3.81 (3H, s), 3.85 (1H, dd, *J* = 7.5, 7.5 Hz), 3.94–3.99 (1H, m), 4.12 (1H, dd, *J* = 4.0, 4.0 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.55 (1H, d, *J* = 11.7 Hz), 6.87 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR δ: −4.9, −4.2, 14.1, 18.5, 22.7, 25.9 (3C), 26.2, 29.4, 29.59, 29.62, 29.64 (2C), 29.67 (2C), 29.69, 29.73, 29.76, 31.9, 55.2, 68.5, 72.0, 73.0, 79.1, 81.3, 113.7 (2C), 129.3 (2C), 130.3, 159.2; HRMS (FAB) *m*/*z* ($[M + Na]^+$): calcd. for $C_{32}H_{58}O_4SiNa$, 557.4002; found, 557.4004.

*(4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-tetradecyldihydrofuran-3-one (**21**).* To a stirred solution of **20** (296 mg, 0.550 mmol) in CH_2Cl_2 (9.4 ml) containing a phosphate buffer (pH 7.0, 0.1 M, 0.47 ml) was added DDQ (151 mg, 0.660 mmol) at room temperature. After 4.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give 224 mg of crude **18** which was then dissolved in CH_2Cl_2 (12 ml). The solution was added to a suspension of Dess-Martin periodinane (687 mg, 1.62 mmol) and $NaHCO_3$ (136 mg, 1.62 mmol) in CH_2Cl_2 (6 ml) at room temperature. After 2 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc = 100:1) to give 196 mg (86% from **20**) of **21** as a colorless oil. $[\alpha]^{25}_D$ −22.1° (*c* 1.42, $CHCl_3$); IR ν_{max}: 2926 (s), 1773 (m), 1468 (m), 1254 (m); ^{1}H-NMR δ: 0.11 (3H, s), 0.14 (3H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.91 (9H, s), 1.23–1.40 (22H, m), 1.44–1.54 (2H, m), 1.52–1.65 (2H, m), 3.94 (1H, d, *J* = 17.8 Hz), 3.98 (1H, d, *J* = 17.8 Hz), 4.16–4.20 (1H, m), 4.24 (1H, d, *J* = 6.5 Hz); ^{13}C-NMR δ: −5.3, −4.6, 14.1, 18.3, 22.7, 25.4, 25.65, 25.67 (3C), 27.8, 29.3, 29.5 (2C), 29.64 (2C), 29.66, 29.68 (2C), 31.9, 67.6, 74.1, 80.6, 213.7; HRMS (FAB) *m*/*z* ($[M + H]^+$): calcd. for $C_{24}H_{49}O_3Si$, 413.3451; found, 413.3457.

*(3*S*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-tetradecyltetrahydrofuran-3-amine (**22**).* To a stirred solution of **21** (50 mg, 0.12 mmol) in 2.0 M NH_3/EtOH (1 ml) was added Ti(O*i*-Pr)$_4$ (72 µl, 0.24 mmol) at room temperature. After 5.5 h, $NaBH_4$ (9.1 mg, 0.24 mmol) was added, and the resulting mixture was stirred for 18.5 h, during which time 15 mg (0.39 mmol) of additional $NaBH_4$ was added to bring the reaction to completion. The reaction mixture was poured into 25% aqueous NH_3 and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kanto Kagaku silica gel 60N, hexane/EtOAc = 3:1–0:1) to give 30 mg (60%) of **22** as a colorless oil. $[\alpha]^{25}_D$ −2.6° (*c* 1.40, $CHCl_3$); IR ν_{max}: 3394 (w), 2925 (s), 1464 (m), 1255 (m); ^{1}H-NMR δ: 0.10 (3H, s), 0.12 (3H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.95 (9H, s), 1.20–1.34 (22H, m), 1.36–1.48 (4H, m), 1.54–1.62 (2H, m), 3.45–3.50 (2H, m), 3.80–3.85 (1H, m), 3.87–3.90 (1H, m), 3.92–3.95 (1H, m); ^{13}C-NMR δ: −4.5, −4.2, 14.1, 18.3, 22.7, 25.9 (3C), 26.5, 29.3, 29.58 (2C), 29.64 (3C), 29.67, 29.68 29.76, 30.6, 31.9, 55.9, 71.6, 74.6, 82.5; HRMS (FAB) *m*/*z* ($[M + H]^+$): calcd. for $C_{24}H_{52}NO_2Si$, 414.3767; found, 414.3762.

*(3*S*,4*S*,5*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (**1**).* To a stirred solution of **22** (20 mg, 0.048 mmol) in THF (5 ml) was added TBAF (1.0 M in THF, 190 µl, 0.19 mmol) at room temperature. After 20 h, 190 µl (0.19 mmol) of additional TBAF was added, and the mixture was stirred for 1.5 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed over SiO_2 (Kanto Kagaku silica gel 60N, EtOAc/MeOH/25% aqueous NH_3 = 90:5:1) to give 13 mg (90%) of **1** as a colorless powder. Mp 88–90 °C (lit.[10] 96–97 °C, lit.[12] 89–91 °C, lit.[13] 89–91 °C, lit.[14] 96.6–97.2 °C, lit.[15] 90–92 °C, lit.[19] 90–91 °C); $[\alpha]^{25}_D$ +18.2° (*c* 0.20, EtOH) (lit.[1] $[\alpha]_D$ +18° (*c* 0.1, EtOH), lit.[9] $[\alpha]_D$ +13.3° (*c* 0.03, EtOH), lit.[10] $[\alpha]_D$ +17.5° (*c* 0.4, EtOH), lit.[15] $[\alpha]^{23}_D$ +17.5° (*c* 0.3, EtOH), lit.[18] $[\alpha]^{25}_D$ +17.7° (*c* 0.40, EtOH)); IR ν_{max}: 3344 (m), 2921 (s), 1470 (w), 1036 (w); ^{1}H-NMR δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.23–1.46 (24H, m), 1.60–1.75 (2H, m), 1.91 (3H, br s, OH, NH_2), 3.52 (1H, dd, *J* = 6.8, 8.3 Hz), 3.66 (1H, ddd, *J* = 4.9, 6.8, 7.8 Hz), 3.71–3.76 (1H, m), 3.87 (1H, dd, *J* = 3.4, 4.9 Hz), 3.93 (1H, dd, *J* = 7.8, 8.3 Hz); ^{13}C-NMR δ: 14.1, 22.7, 26.3, 29.35, 29.39, 29.57, 29.60, 29.64, 29.66, 29.68, 29.69, 29.8, 31.9, 54.2, 71.7, 72.3 (2C), 83.2; HRMS (FAB) *m*/*z* ($[M + H]^+$): calcd. for $C_{18}H_{38}NO_2$, 300.2903; found, 300.2911.

*3-[(2*R*,3*aS*,6*S*,6*aS*)-6-Tetradecylhexahydrofuro[3,4-*d*]oxazol-2-yl]-1-propanol (**2**).* To a stirred solution of **1** (24 mg, 0.081 mmol) and tetrahydro-2-furanol (21 mg, 0.24 mmol) in MeOH (1.5 ml) was added $TsOH{\cdot}H_2O$ (4.6 mg, 0.024 mmol) at room temperature. After 17 h, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed over SiO_2 (Kanto Kagaku silica gel 60N, $CHCl_3$/MeOH = 30:1) to give 27 mg (89%) of **2** as a colorless powder. Mp 82–83 °C; $[\alpha]^{22}_D$ +26° (*c* 0.27, $CHCl_3$) (lit.[2] $[\alpha]^{20}_D$ +25° (*c* 1, $CHCl_3$)); IR ν_{max}: 3303 (w), 2921 (s), 2850 (s), 1468 (w), 1054 (w); ^{1}H-NMR δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.24–1.37 (22H, m), 1.37–1.46 (2H, m), 1.56 (2H, br s, OH, NH), 1.66–1.79 (6H, m), 3.39 (1H, dt, *J* = 3.5, 7.0 Hz), 3.63–3.72 (3H, m), 3.90 (1H, d, *J* = 10.3 Hz), 4.05 (1H, dd, *J* = 6.0, 6.0 Hz), 4.34 (1H, dd, *J* = 3.5, 5.6 Hz), 4.51 (1H, m); ^{13}C-NMR (pyridine-d_5) δ: 14.2, 22.9, 26.6, 29.5, 29.8–29.9 (8C), 30.0, 30.1, 31.3, 32.0, 61.8, 64.1, 74.4, 80.9, 84.1, 94.4; ^{13}C-NMR ($CDCl_3$) δ: 14.1, 22.7, 26.3, 28.6, 28.8, 29.2, 29.4, 29.6–29.8 (7C), 31.4, 31.9, 62.7, 63.4, 73.7, 80.8, 83.9, 93.7; HRMS (FAB) *m*/*z* ($[M + H]^+$): calcd. for $C_{22}H_{44}NO_3$, 370.3321; found, 370.3326.

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