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Total synthesis of virgineone aglycone and stereochemical assignment of natural virgineone

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ABSTRACT

The first total synthesis of virgineone aglycone has been achieved employing the tandem *O*-acylation–migration reaction and the olefin cross-metathesis as key steps for fragment couplings. The left-hand segment of virgineone was also synthesized. The absolute configuration of the reported virgineone aglycone was determined to be (2*S*,7*RS*,26*S*) based on NMR analyses and the specific rotation values of the synthetic compounds. The absolute configuration of the natural virgineone was presumed to be (2*S*,7*S*,26*S*) based on NMR analyses of the synthetic virgineone aglycone.

Significant attention has been paid to naturally occurring tetramic acid derivatives due to their unique biological activities, and there are many reports on the synthetic studies of such tetramic acids.[1] The natural tetramic acid derivatives are known to be biosynthesized from an amino acid assembled by a polyketide chain, so the structural variety exhibited is therefore derived from both the amino acid moiety and the polyketide chain. Some tetramic acids possess a cyclized side chain, and others possess a glycosylated side chain. Although the structure and the stereochemistry of many tetramic acid natural products have been elucidated, there exist some tetramic acids whose structures have not previously been fully elucidated, such as vancoresmycin,[2] lydicamycin,[3] and pyrroindomycins.[4]

A tyrosine-derived tetramic acid, virgineone (**1**), was isolated from saprotrophic *Lachnum virgineum* by Singh and co-workers in 2009.[5] Although the structure of **1** was elucidated on the basis of UV, NMR, and HRESIFTMS analyses as shown in Figure 1, the relative and absolute configuration of the natural product was not assigned, except for the β-D-mannoside portion of the molecule. From a structural view point, **1** is similar to epicoccamides (**3** and **4**, Fig. 1) isolated from a jellyfish-derived fungus *Epicoccum purpurascens* and the *Epicoccum* sp. associated with a tree fungus.[6] The absolute configuration of epicoccamides has also previously remained undetermined.

Virgineone was discovered by the *Candida albicans* fitness test (CaFT) and shown to exhibit broad-spectrum antifungal activity against a number of key pathogenic fungal strains such as *C. albicans*, *Aspergillus fumigatus*, and *Trichophyton mentagrophytes*.[5] It is noteworthy that virgineone was reported to show different CaFT profiling from radicicol, cyclosporine A, FK506, and rapamycin, which indicates that the target or mechanism of action (MOA) of virgineone is different from other well-known natural antibiotics. We were interested in synthesizing virgineone to conduct detailed biological studies, including the MOA analysis of virgineone. However, a clarification of the absolute configuration of the natural virgineone was needed prior to performing the biological studies.

Before starting the synthetic studies we found a slightly curious difference in the reported ^{1}H NMR spectra of virgineone recorded in DMSO-d_6 and CD_3OD.[5] A doublet corresponding to the C28 methyl group was observed at 0.80 ppm in DMSO-d_6, while two pairs of doublets were observed at 0.91–0.98 ppm in CD_3OD. These results suggested the following two possibilities: (1) the tautomerism of virgineone caused this difference seen in the different solvent[7] or (2) virgineone is a stereoisomeric mixture at C2 and/or C7 and the corresponding diastereomers were indistinguishable when DMSO-d_6 was used in the NMR analysis. To clarify this, we focused on virgineone aglycone (**2**), derived from the natural virgineone because structural analysis of **2** would be easier than that of **1**. Data, including the NMR spectra and specific rotation value of **2** were also reported.[5] Thus, we selected **2** as the first synthetic target to determine the absolute configuration of the natural product. This Letter describes the first total synthesis of **2** and a left-hand segment of **1** and the determination of the stereochemistry of natural virgineone.

We assumed that it would be possible to determine the absolute configuration of the C26 stereogenic center by a simple comparison of the NMR spectra of the two diastereomers originating

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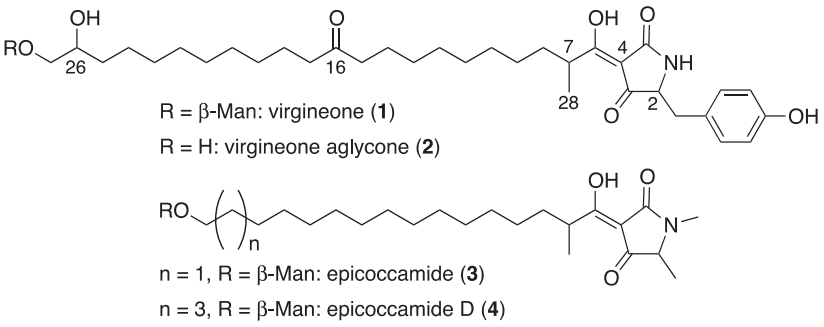
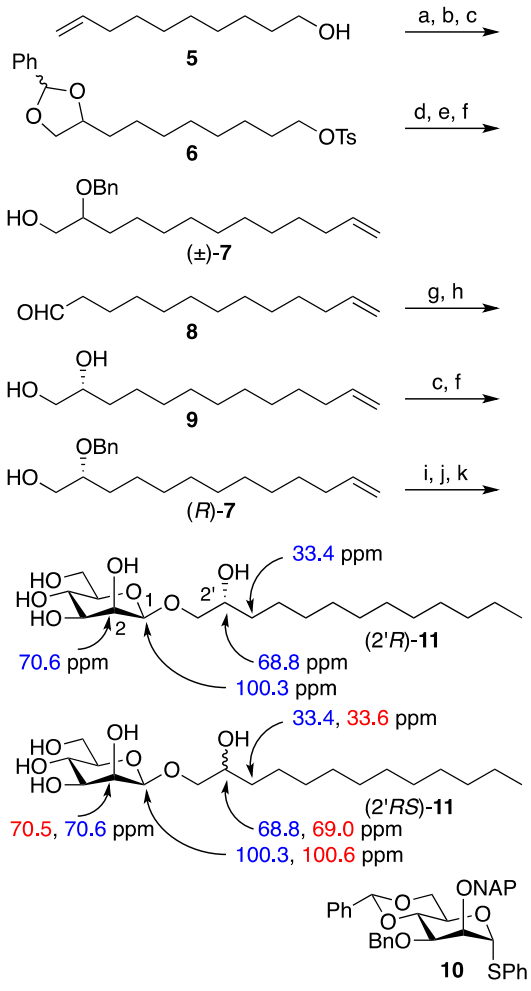


Figure 1. Structures of virgineone and related tetramic acids.

from the terminal β-mannoside and the C26 secondary hydroxy group. We first synthesized the left-hand segment of **1** (Scheme 1). The racemic glycosyl acceptor **7** was synthesized from the commercially available **5**. Alcohol **5** was tosylated, and a dihydroxylation of the double bond of the obtained tosylate was followed by a protection of the resulting two hydroxy groups as a benzylidene acetal to afford **6**. Tosylate **6** was converted into the corresponding iodide, and the resulting iodide was alkylated by allyl cuprate, followed by the reductive opening of the benzylidene acetal with DIBAL to give (±)-**7**. Optically active **7** was derived from aldehyde **8**[8] via asymmetric α-aminoxylation[9] employing L-proline as an organocatalyst. The enantiomeric ratio (er) of (*R*)-**7** was determined to be 99:1 by the HPLC analysis.[10] The obtained (*R*)-**7** was glycosylated with **10**[11] under Crich's conditions[12] to afford the corresponding β-mannnoside selectively. The yield of the β-mannnoside was relatively low (ca. 30%) due to the formation of unknown by-products presumably derived from an unwanted side reaction at the terminal double bond. Fortunately, the side reaction was suppressed by conducting the glycosylation in the presence of 1-hexene as a scavenger to afford the β-mannnoside in 60–70% yield. Although the minor α-isomer was completely eliminated after the removal of the 2-naphthylmethyl (NAP) group by DDQ, the precise α/β selectivity of the glycosylation step could not be determined because of the difficulty of the separation of the α-isomer from other unknown compounds. Hydrogenolysis of the two benzyl groups and a benzylidene acetal concomitant hydrogenation of the terminal double bond gave (2′*R*)-**11**. The diastereomeric mixture (2′*RS*)-**11** was also synthesized from (±)-**7**.

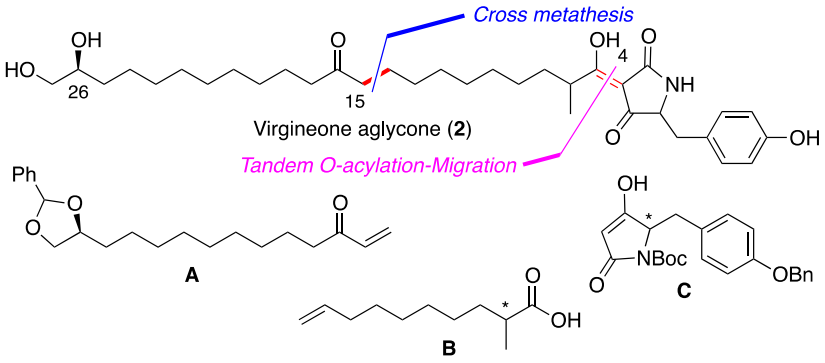


Scheme 1. Synthesis of the left-hand segment of virgineone. The ^{13}C NMR chemical shifts indicated in red are identical with those of the reported data. Reagents, conditions and yields: (a) TsCl, py., 0 °C; (b) OsO_4, NMO, *t*-BuOH, H_2O, 0 °C to rt, 95% in two steps; (c) $PhCH(OMe)_2$, CSA, MeCN, 0 °C to rt, 93% for **6**, 72% from **9**; (d) NaI, acetone, 70 °C; (e) allylmagnesium bromide, CuI, THF, 0 °C to rt, 62% in two steps; (f) DIBAL, toluene, −20 °C, 83% for (±)-**7**, 96% for (*R*)-**7**; (g) PhNO, L-proline, CH_2Cl_2, then $NaBH_4$, EtOH, 0 °C, 57%; (h) $CuSO_4{\cdot}5H_2O$, MeOH, 54%; (i) **10**, BSP, TTBP, Tf_2O, 1-hexene, MS3A, CH_2Cl_2, −65 °C, 64%; (j) DDQ, CH_2Cl_2, H_2O, 0 °C to rt, 56%; (k) H_2, Pd/C, *t*-BuOH, MeOH, 70%.

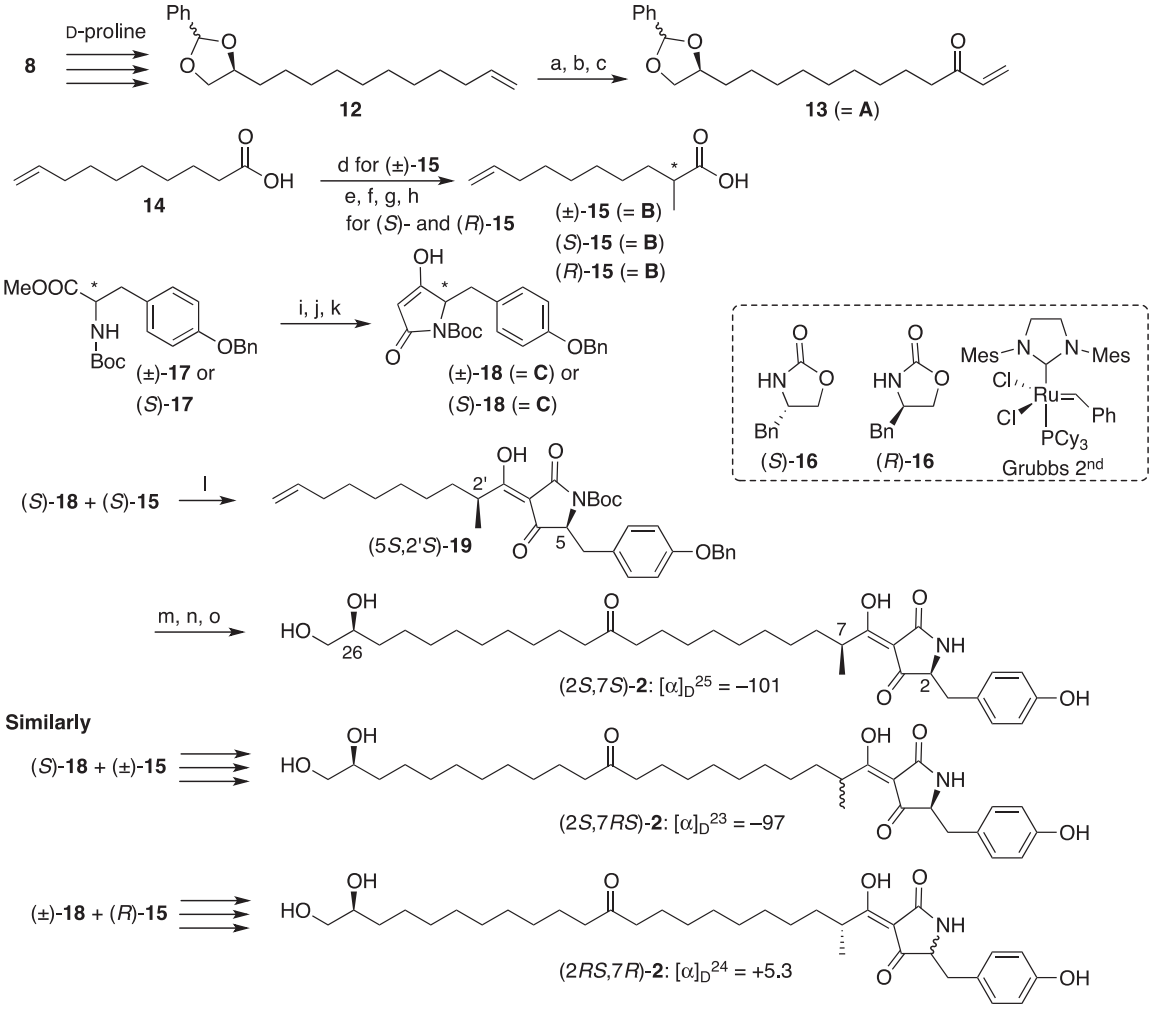
Although a significant difference was not observed between the ^1H NMR spectra of (2′*R*)- and (2′*RS*)-**11**, small differences were observed in their ^{13}C NMR spectra. The spectrum of (2′*RS*)-**11** was in good accordance with the left-hand part of virgineone except for the additional four peaks of 33.4, 68.8, 70.6, and 100.3 ppm (indicated in blue in Scheme 1) assigned to be C3′, C2′, C1, and C2, respectively.[13] The peaks were also observed in the spectrum of (2′*R*)-**11**. Because the additional peaks in the spectrum of (2′*RS*)-**11** (indicated in blue) must be originated from (2′*R*)-**11**, the absolute configuration of the natural virgineone C26 was determined to be *S*.

Next, we planned to synthesize the virgineone aglycone (**2**) with a 26*S* stereochemistry to determine the remaining stereochemistries of C2 and C7. Our retrosynthetic analysis of **2** is shown in Scheme 2. Considering the synthesis of various virgineone derivatives for future structure–activity relationship studies, we employed a segment coupling strategy. The appropriate segments **A**, **B**, and **C** would be assembled employing olefin cross-metathesis[14] and the tandem *O*-acylation–migration.[15]

Segment **A** was prepared from **12** derived from **8** in the similar manner as shown in Scheme 1 via oxidative cleavage of the terminal double bond, addition of vinyl Grignard reagent, and Dess–Martin oxidation of the resulting hydroxy group to give **13** (= **A**) (Scheme 3). Because virgineone aglycone might be a diastereomeric mixture as described above, we prepared racemic and optically active segments **B** and **C** to compare the synthetic stereoisomers of **2**. Racemic **15** (= **B**) was synthesized from commercially available **14** by a simple alkylation, and the optically active (*S*)- and (*R*)-**15** were synthesized via an Evans



Scheme 2. Retrosynthetic analysis of virgineone aglycone.



Scheme 3. Synthesis of virgineone aglycone. Reagents, conditions, and yields: (a) (1) OsO_4, NMO, acetone, H_2O, 0 °C to rt, (2) $NaIO_4$, ether, H_2O, 0 °C to rt, quant.; (b) vinylmagnesium bromide, THF, −78 °C, 98%; (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 97%; (d) LDA, MeI, DMPU, THF, −15 °C to rt, 60%; (e) PivCl, Et_3N, LiCl, −20 °C; (f) (*S*)-**16** for (*S*)-isomer or (*R*)-**16** for (*R*)-isomer, *n*-BuLi, THF, −78 °C; then mixed anhydride, 97% for (*S*)-isomer and 94% for (*R*)-isomer; (g) NaHMDS, MeI, THF, −78 °C, 76% for (*S*)-isomer and 96% for (*R*)-isomer; (h) LiOH, H_2O_2, THF, H_2O, 0 °C, 94% for (*S*)-isomer and 74% for (*R*)-isomer; (i) 1 N NaOH aq, MeOH, 0 °C; (j) Meldrum's acid, DCC, DMAP, CH_2Cl_2; (k) AcOEt, reflux, 40% in three steps; (l) DCC, DMAP, CH_2Cl_2, 76%; (m) **13**, Grubbs 2nd catalyst, CH_2Cl_2, reflux; (n) TFA, CH_2Cl_2, 37% in two steps; (o) H_2, $Pd(OH)_2$/C, TFA, *t*-BuOH, 61%.

diastereoselective alkylation[16] (dr = 98:2) from **14**. The racemic and optically active **18** (= **C**) was synthesized from (±)- or (*S*)-**17** via acylation of Meldrum's acid and the subsequent thermal Lacey–Dieckmann cyclization.[17]

With the segments **A**, **B**, and **C** in hand, the couplings of the segments were investigated (Scheme 3). Our preliminary studies revealed that the tandem *O*-acylation–migration reaction was difficult when employing a carboxylic acid with a long carbon chain. Thus, we first tried to couple the segments **B** and **C** instead of the segments **A** and **B**. Namely, (*S*)-**18** was successfully O-acylated with (*S*)-**15** in the presence of DCC and a stoichiometric amount of DMAP, then the DMAP mediated *O*- to *C*-migration

reaction proceeded smoothly in one pot to give **19**.[7a] Recently, Yoda and co-workers reported employing a stepwise *O*-acylation–acyl rearrangement strategy in their syntheses of naturally occurring tetramic acids.[18] They used $CaCl_2$ or NaI as an additive to accelerate the rearrangement reaction without an epimerization at C2′ of the 3-acyltetramic acids. Because the amide nitrogen of our substrate **18** was protected by a Boc group, epimerization at C5 and/or C2′ was suppressed to less than 5% as determined by the ^{1}H NMR analysis of **19**. Next, the olefin cross-metathesis reaction of **19** with **13** catalyzed by the Grubbs second-generation catalyst[19] gave the coupling product in a moderate yield. After removal of the Boc and the benzylidene acetal groups by TFA, hydrogenolysis of the benzyl group and concomitant hydrogenation of the double bond furnished the desired virgineone aglycone (2*S*,7*S*)-**2**. The stereoisomeric mixtures of virgineone aglycones (2*S*,7*RS*)-**2** and (2*RS*,7*R*)-**2** were also synthesized in a similar fashion.

The ^{1}H NMR spectra of (2*S*,7*RS*)-**2** and (2*RS*,7*R*)-**2** were in good accordance with that of the reported virgineone aglycone, while ^{1}H NMR spectrum of (2*S*,7*S*)-**2** was a partial match.[20] Namely, two pairs of doublets were observed at 0.91–0.98 ppm in the ^{1}H NMR spectra of (2*S*,7*RS*)-**2** and (2*RS*,7*R*)-**2**, while only one doublet was observed at 0.95 ppm in the ^{1}H NMR spectrum of (2*S*,7*S*)-**2**. These results clearly suggested that the virgineone aglycone is a diastereomeric mixture. Because the ratio of the diastereomers is estimated to be approximately 1:1 as judged by the reported NMR spectra, virgineone aglycone would possess C2 and/or C7 in the completely epimerized form. Next, optical rotation values of the synthetic isomers were compared to determine the stereochemistry of C2 and C7. As shown in Scheme 3, (2*S*,7*S*)-**2** and (2*S*,7*RS*)-**2** exhibited relatively similar $[\alpha]_D$ values as the reported virgineone aglycone [$[\alpha]_D^{23}$ −60, (*c* 0.3, MeOH)],[5] while (2*RS*,7*R*)-**2** exhibited an opposite sign and a rather low $[\alpha]_D$ value. This clearly shows that the methyl group at C7 does not have a significant effect on the $[\alpha]_D$ values and that the stereochemistry of C2 has a great influence on the $[\alpha]_D$ values. Considering the results of the NMR analyses and the $[\alpha]_D$ values of the synthetic isomers of **2**, the absolute configuration of the reported virgineone aglycone is concluded to be 2*S*,7*RS*,26*S*.

Interestingly, careful comparison of the ^{1}H and ^{13}C NMR spectra of the synthetic and the reported virgineone aglycone with those of the natural virgineone revealed that the natural virgineone would not be a diastereomeric mixture. Namely, the additional peaks observed in the spectra of synthetic (2*S*,7*RS*)-**2** and (2*RS*,7*R*)-**2** and reported aglycone have not been recorded in the reported ^{13}C NMR spectra of natural virgineone. These results suggest that C7 of aglycone could have epimerized during the course of the hydrolysis of the mannoside portion of the natural virgineone.

In summary, we achieved the first total synthesis of virgineone aglycone with an *O*-acylation–acyl migration and an olefin cross-metathesis as key steps. We also synthesized the left-hand segment of virgineone via β-selective mannosylation. The absolute configuration of the C26 of virgineone was determined to be *S* on the basis of a simple comparison of the ^{13}C NMR spectra of the synthesized left-hand segment to that of the natural product. The stereochemistry of the C2 and C7 stereogenic centers of reported virgineone aglycon were assigned as 2*S*,7*RS* on the basis of the comparison of the NMR spectra and $[\alpha]_D$ values of the synthesized stereoisomers of virgineone aglycone. Since the ^{1}H NMR chemical shift of C28-methyl group of the synthetic (2*S*,7*S*)-**2** is similar to that of natural virgineone, it is reasonable to assume that the absolute configuration of C7 of the natural virgineon would be *S*. Further studies including the total synthesis of virgineone and the confirmation of C7 stereochemistry of the natural product are currently underway.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of **2**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.006.

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11. Compound **10** was prepared from a known compound by protection of its 3-OH group as benzyl ether. Preparation of the compound: see Boltje, T. J.; Li, C.; Boons, G.-J. *Org. Lett.* **2010**, *12*, 4636–4639.
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13. *Physical properties of the synthetic* ***11***: (2′*R*)-**11**: ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.26–1.48 (m, 20H), 3.20 (ddd, *J* = 2.5, 6.0, 9.5 Hz, 1H), 3.44 (dd, *J* = 3.4, 9.4 Hz, 1H), 3.52–3.59 (m, 2H), 3.68–3.77 (m, 3H), 3.86 (dd, *J* = 2.5, 9.6 Hz, 1H), 3.88 (d, *J* = 3.2 Hz, 1H), 4.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.0, 22.1, 25.1, 28.7, 29.02, 29.04, 29.06, 29.10, 29.2, 31.3, 33.4, 61.4, 67.1, 68.8, 70.6, 73.4, 73.6, 77.5, 100.3; HR-MS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{38}O_7Na$, 401.2515; found 401.2505; (2′*RS*)-**11**: ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.26–1.48 (m, 20H), 3.20 (ddd, *J* = 2.5, 6.0, 9.5 Hz, 1H), 3.41–3.45 (m, 1.5H), 3.52–3.58 (m, 1.5H), 3.67–3.76 (m, 2.5H), 3.85–3.90 (m, 2.5H), 4.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.0, 22.1, 25.1, 28.7, 29.02, 29.05, 29.07, 29.10, 29.2, 31.3, 33.4, 33.6, 61.4, 67.1, 68.8, 69.0, 70.5, 70.6, 73.4, 73.6, 77.5, 100.3, 100.6; HR-MS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{38}O_7Na$, 401.2515; found 401.2505.
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20. *Physical properties of the synthetic* ***2***: (2*S*,7*S*)-**2**: $[\alpha]_D^{25}$ −101 (*c* 0.16, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (d, *J* = 6.4 Hz, 3H), 1.15–1.22 (m, 26H), 1.35–1.50 (m, 4H), 2.36 (m, 4H), 2.61 (br s, 1H), 2.82 (dd, *J* = 4.1, 13.7 Hz, 1H), 3.21 (m, 2H), 3.34 (m, 1H), 3.50 (m, 1H), 3.90 (m, 1H), 6.58 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.6, 23.4, 25.3, 27.1, 28.8–29.4(×7), 33.2, 33.6, 36.9, 37.0, 42.0, 61.2, 66.2, 71.3, 100.4, 114.9, 130.6, 155.8, 175.8, 194.6, 210.8; HR-MS-ESI (*m*/*z*): $[M+Na]^+$ calcd for

$C_{34}H_{53}O_7NNa$, 610.3720; found 610.3710; (2*S*,7*RS*)-**2**: $[\alpha]_D^{23}$ −97 (c = 0.32, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (d, J = 6.4 Hz, 1.5H), 0.96 (d, J = 6.4 Hz, 1.5H), 1.15–1.22 (m, 26H), 1.35–1.50 (m, 4H), 2.36 (m, 4H), 2.72 (m, 1H), 2.80 (m, 1H), 3.21 (m, 2H), 3.34 (m, 1H), 3.50 (m, 1H), 3.90 (m, 1H), 6.56, 6.57 (2 × d, J = 8.2 Hz, 2H), 6.89, 6.91 (2 × d, J = 8.2 Hz, 2H), 9.11 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 17.0, 17.4, 23.4, 25.4, 26.8, 27.0, 28.8–29.5(×7), 33.0, 33.4, 33.6, 36.3, 36.5, 42.0, 61.7, 66.2, 71.3, 100.6, 114.89, 114.92, 126.6, 130.7, 156.0, 175.5, 194.8, 210.8; HR-MS-ESI (m/z): $[M+Na]^+$ calcd for $C_{34}H_{53}O_7NNa$, 610.3720; found 610.3717; (2*RS*,7*R*)-**2**: $[\alpha]_D^{24}$ +5.3 (*c* 0.28, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (d, J = 6.4 Hz, 1.5H), 0.97 (d, J = 6.4 Hz, 1.5H), 1.15–1.22 (m, 26H), 1.35–1.50 (m, 4H), 2.37 (m, 4H), 2.73 (m, 1H), 2.82 (m, 1H), 3.24 (m, 2H), 3.35 (m, 1H), 3.51 (m, 1H), 3.90 (m, 1H), 6.58, 6.59 (2 × d, J = 8.2 Hz, 2H), 6.90, 6.91 (2 × d, J = 8.2 Hz, 2H), 9.14 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 16.9, 17.2, 23.3, 25.2, 26.6, 26.8, 28.8–29.5(×7), 32.8, 33.4, 34.3, 36.2, 36.6, 41.8, 65.4, 66.0, 71.2, 100.5, 114.69, 114.74, 126.5, 130.8, 155.8, 175.4, 194.6, 210.7; HR-MS-ESI (m/z): $[M+Na]^+$ calcd for $C_{34}H_{53}O_7NNa$, 610.3720; found 610.3705. Although the NMR spectra of (2*S*,7*RS*)-**2** and (2*RS*,7*R*)-**2** were in good accord with those of the reported spectra,[5] we could not observe a signal (C3, δ = 191.7 ppm)[5] in the ^{13}C NMR spectra of our synthetic **2**.