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A stereoselective method for the construction of the C8′–O–C6″ ether of nigricanoside-A: synthesis of simple models for the C20 lipid chain/galactosyl glycerol segment

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ABSTRACT

A method for the stereoselective construction of the C8′–O–C6″ ether of nigricanoside-A, an antimitotic natural product from the green alga *Avrainvillea nigricans*, has been developed based on chirality-transferring Ireland–Claisen rearrangement. The method was successfully applied to the synthesis of simple models for the C20 lipid chain/galactosyl glycerol segment of the natural product.

Nigricanoside-A (**1**) (Fig. 1), isolated as a strong antimitotic agent [IC_{50} of nigricanoside-A dimethyl ester (**2**): 3 nM against human breast cancer MCF-7 cells] from the green alga *Avrainvillea nigricans* by Andersen,[1] is a unique oxylipin derivative including two oxygenated fatty acids and a galactosyl glycerol moiety that are connected to each other by ether bonds.[2] Although the planar structure and the partial relative stereochemistry of **1** have been elucidated by intensive NMR analysis of the dimethyl ester (**2**) of **1**, full assignment of the relative and absolute stereochemistries of **1** has yet to be completed. The unique structure and the strong bioactivity of **1** have prompted us to attempt its total synthesis and full stereochemical assignment. At the beginning of the project, we developed an effective method for the stereoselective construction of the C8′–O–C6″ ether bond of **1** connecting the galactose moiety to the C20 fatty acid chain based on chirality transferring Ireland–Claisen rearrangement.[3] Here, the details of the development and application of the method to the synthesis of simple models [(**8′*S*,2‴*R***)-**3** and (**8′*R*,2‴*R***)-**3**] for the C20 lipid chain/galactosyl glycerol segment of **1** are described.

Model compounds (**8′*S*,2‴*R***)-**3** and (**8′*R*,2‴*R***)-**3**, excluding the C16 fatty acid chain and the oxygen functionalities at C11′ and C12′, were designed for the following purpose: (i) a simple demonstration of the stereoselective construction of the C8′–O–C6″ ether

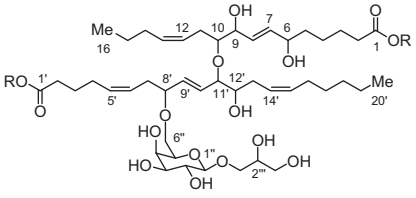

Figure 1.

of **1**, (ii) comparison of the NMR spectra with **2** to predict the configuration at C8′ of **1**, and (iii) investigation of the structure–activity relationship in antimitotic/cytotoxic assays of **1**. The (2‴*R*)-configuration of the models was designed according to the proposed (*R*)-configuration at C2‴ of the glycerol of **1**, which was based on the assumption that nigricanosides were oxidative metabolites of monogalactosyl diacyl glycerols (MGDGs), known as chloroplast membrane lipids, having a common 3-galactosyl-

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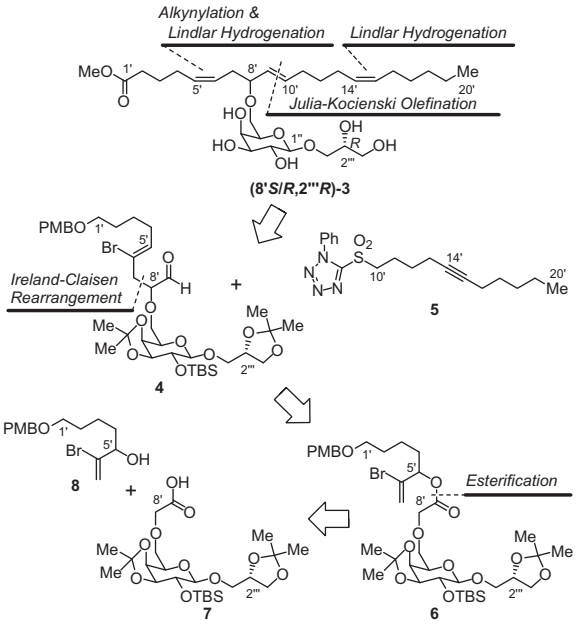
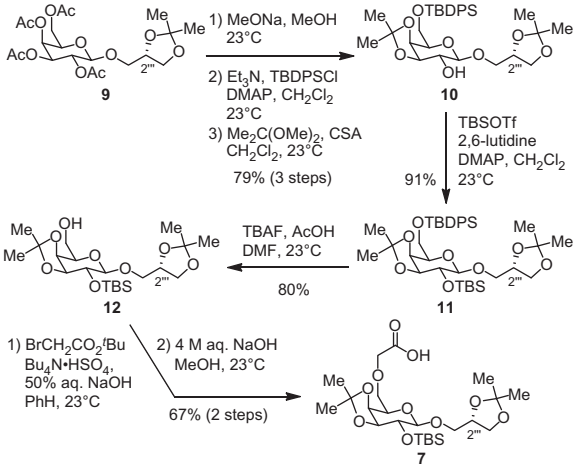


Scheme 1. Synthetic plan for model **3**.

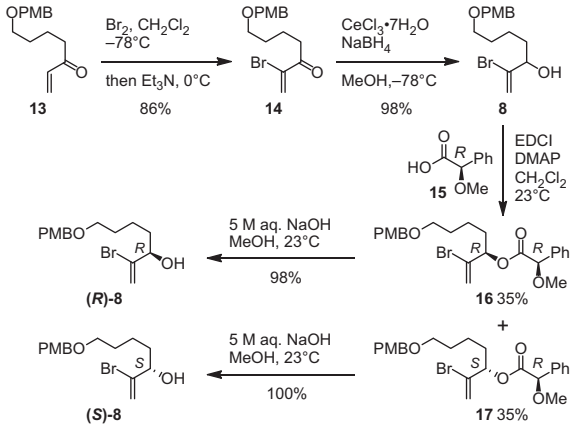
sn-glycerol structure.[4] In this preliminary report, we disclose the synthesis and NMR analysis of the models.[5]

The synthetic plan for the model compounds (**3**) is outlined in Scheme 1. The *Z*-olefin groups at C5′ and C14′ of **3** were scheduled to be formed by Lindlar hydrogenation of the corresponding alkyne groups at the final stage of the synthesis after aldehyde **4** and sulfone **5** were connected by Julia–Kocienski olefination[6] to form the *E*-olefin at C9′. The *Z*-bromoalkene at C5′ of **4** would be converted into an alkyne group under mild basic conditions after the olefination step. For the construction of the C8′ stereocenter and the *Z*-bromoalkene of **4**, the Ireland–Claisen rearrangement of ester **6** was employed. The rearrangement was expected to exhibit perfect chirality transfer from C5′ of **6** to C8′ of **4**. Therefore, bromoalkenol **8**, which would be condensed with glycolic acid derivative **7** to form **6**, must be obtained in enantiomerically pure form. Thus, both enantiomers (***S***)-**8** and (***R***)-**8** would be prepared by chiral resolution.

The synthesis of glycolic acid **7** from the known 3-galactosyl-*sn*-glycerol derivative **9**[7] is shown in Scheme 2. The acetate groups of



Scheme 2. Synthesis of carboxylic acid **7**.



Scheme 3. Synthesis of chiral alcohols (***R***)-**8** and (***S***)-**8**.

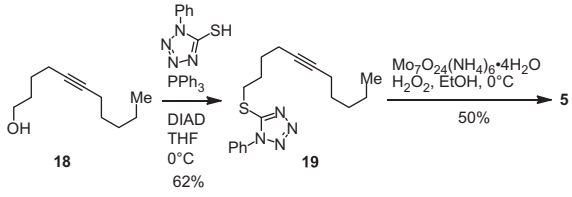
9 were removed by methanolysis, and the resulting tetraol was subjected to stepwise protection with TBDPSCl and 2,2-dimethoxypropane to give alcohol **10** (79% over three steps). The protection of **10** as a TBS ether (91%) followed by the selective removal of the TBDPS group[8] produced alcohol **12** (80%), which was successfully converted into **7** through etherification with *tert*-butyl bromoacetate followed by basic hydrolysis (67% over two steps).

The preparation of chiral allylic alcohols (***R***)-**8** and (***S***)-**8** started from the known enone **13**[9] (Scheme 3). Bromination of **13** followed by elimination of HBr with Et_3N produced α-bromo enone **14** (86%), which was reduced under Luche conditions to give racemic alcohol **8** (98%).[10] After the condensation of **8** with (*R*)-(−)-α-methoxyphenylacetic acid (**15**), the resulting diastereomeric esters **16** and **17** were separated by preparative HPLC (**16**: 35%; **17**: 35%).[11] The hydrolysis of esters **16** and **17** afforded homochiral alcohols (***R***)-**8** (98%) and (***S***)-**8** (100%),[12] respectively. The absolute configurations of the alcohols were determined by application of the modified Mosher's method on alcohol (***S***)-**8**.[13]

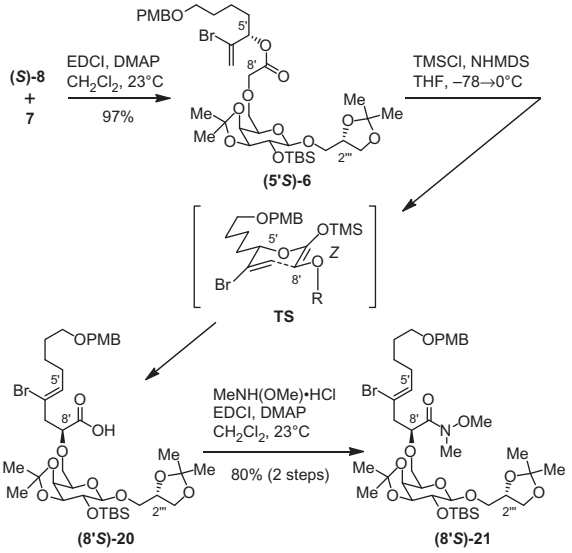
Sulfone **5** was prepared from undec-5-yn-1-ol (**18**)[14] via a process including Mitsunobu reaction[15] with 1-phenyl-1*H*-tetrazole-5-thiol (62%) and oxidation with H_2O_2 in the presence of ammonium molybdate hydrate[16] (50%) (Scheme 4).

The stereoselective construction of the C8′ stereocenter by Ireland–Claisen rearrangement is shown in Scheme 5. First, glycolic acid **7** was esterified with alcohol (***S***)-**8** to afford ester (**5′*S***)-**6** (97%). The treatment of (**5′*S***)-**6** with NHMDS in the presence of TMSCl in THF at −78 °C produced a ketene silyl acetal intermediate, which was then warmed to 0 °C to give rearranged product (**8′*S***)-**20** as a single diastereomer. Carboxylic acid (**8′*S***)-**20** was condensed with *N*,*O*-dimethylhydroxylamine to furnish *N*-methoxy-*N*-methylamide (**8′*S***)-**21** in good yield (80% over two steps).

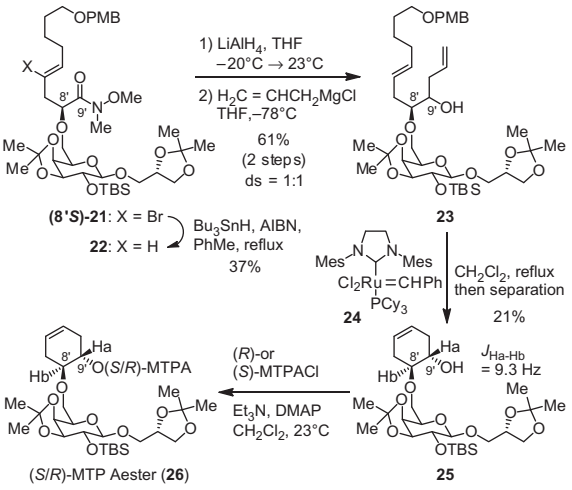
The absolute stereochemistry at C8′ of (**8′*S***)-**21** was determined as shown in Scheme 6. First, the bromoalkene of (**8′*S***)-**21** was reduced with Bu_3SnH to alkene **22** (37%). After the reduction of **22** with $LiAlH_4$,[17] the resulting aldehyde was reacted with allyl magnesium chloride to give **23** as a 1:1 mixture of diastereomers



Scheme 4. Preparation of sulfone **5**.



Scheme 5. The Ireland–Claisen rearrangement of ester (**5′*S***)-**6**.

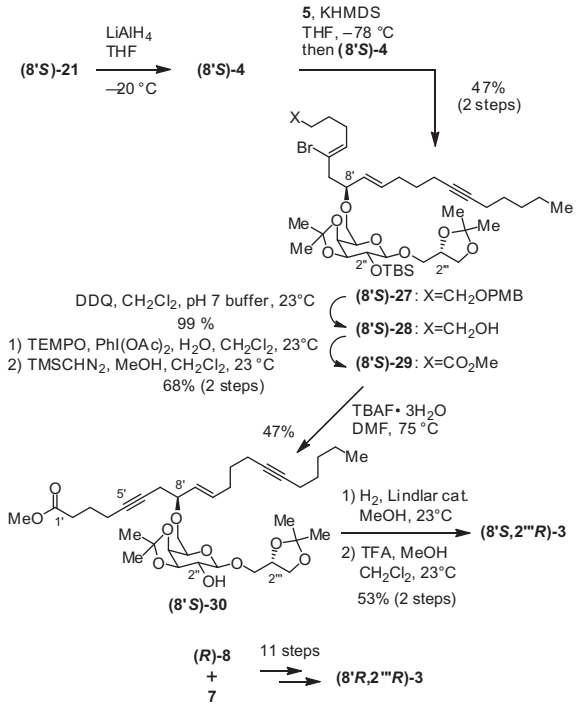


Scheme 6. Determination of the stereochemistry at C8′ of (**8′*S***)-**21**.

at C9′ (61%). Diene **23** was then cyclized by ring-closing olefin metathesis with Grubbs' first generation catalyst (**24**),[18] and *trans*-disubstituted cyclohexene **25**, of which the *trans*-relationship between Ha and Hb was confirmed by the large *J* value (9.3 Hz) between these protons, was obtained in 21% yield after separation from the corresponding *cis*-isomer. Alcohol **25** was converted into (*S*)- and (*R*)-MTPA esters (**26**). Application of modified Mosher's analysis[13] to these MTPA esters established the (*S*)-configuration at C9′, which thus determined the (8′*S*)-configuration in conjunction with the *trans*-relationship between Ha and Hb.

The established (8′*S*)-configuration of **26** also explained the stereoselectivity of the Ireland–Claisen rearrangement of (**5′*S***)-**6** producing (**8′*S***)-**20**. The initial formation of the ketene silyl acetal would be highly *Z*-selective, and the *Z*-ketene silyl acetal would be rearranged via a stable chair form transition state (**TS** in Scheme 5), which would effectively promote the chirality transfer from C5′ to C8′ and produce (**8′*S***)-**20** exclusively.

The completion of the synthesis of model compound (**8′*S***)-**3** is illustrated in Scheme 7. Weinreb amide (**8′*S***)-**21** was reduced with $LiAlH_4$ to give aldehyde (**8′*S***)-**4**, which was subjected to Julia–Kocienski olefination with sulfone **5** using KHMDS to produce *E*-alkene (**8′*S***)-**27** (47% over two steps). The PMB group of (**8′*S***)-**27** was



Scheme 7. Completion of the synthesis of (**8′*S*,2‴*R***)-**3** and (**8′*R*,2‴*R***)-**3**.

removed with DDQ (99%), and the resulting alcohol (**8′*S***)-**28** was converted into methyl ester (**8′*S***)-**29** through TEMPO oxidation in the presence of water[19] followed by treatment with trimethylsilyldiazomethane (68% over two steps).[20] The bromoalkene group of (**8′*S***)-**29** was transformed into an acetylene group [(**8′*S***)-**30**, 47%] by treatment with TBAF·$3H_2O$ in DMF at 75 °C, which also removed the TBS ether at C2″, according to Mori's procedure.[21] Lindlar hydrogenation of (**8′*S***)-**30** followed by acidic methanolysis of the acetonides produced (**8′*S*,2‴*R***)-**3**[22] (53% over two steps). Thus, model compound (**8′*S*,2‴*R***)-**3** was stereoselectively synthesized from 3-galactosyl-*sn*-glycerol derivative **9** via a route including chirality transferring Ireland–Claisen rearrangement as a key step. This route was also successfully applied to the synthesis of (**8′*R*,2‴*R***)-**3**[23] from (**R**)-**8** and **7**.[24]

With both model compounds (**8′*S*,2‴*R***)-**3** and (**8′*R*,2‴*R***)-**3** in hand, we compared the ^{1}H NMR data of the model compounds in C_6D_6/DMSO-d_6 (25:2) with the reported data of **2**. The deviation of the chemical shifts of the models from those of **2** is shown in Fig. 2. While there are large differences in the chemical shifts in the H9′–H16′ region between each model and **2** due to the absence of the C16 fatty acid chain and the oxygen functionalities at C11′

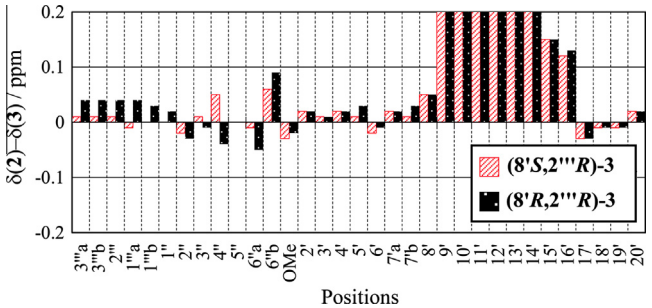


Figure 2. Deviation of ^{1}H NMR chemical shifts of **3** from the reported values of **2**. ^{1}H NMR spectra of **3** were measured in 25:2 C_6D_6/DMSO-d_6 according to the literature.[1]

and C12′ in the model compounds, the chemical shift deviations in other regions of both models are small (within ±0.1 ppm). The similarity of the ^{1}H NMR spectrum of (**8′*S*,2‴*R***)-**3** with that of **2** is suggested from the fact that the average of the absolute values of the chemical shift deviations of (**8′*S*,2‴*R***)-**3** from **2** (for all protons, except H9′–H16′ and hydroxy protons, of the model) is smaller (0.018 ppm) than that of (**8′*R*,2‴*R***)-**3** (0.028 ppm). However, the *S*-configuration at C8′ of **2** cannot be asserted with confidence at this stage due to the presence of significant chemical shift deviations of H4″ and H6″b of (**8′*S*,2‴*R***)-**3**, as well as the observation that the ^{13}C NMR data of both models significantly deviated from those of **2** (data not shown). Further studies with alternative model compounds are required for the determination of the stereochemistry at C8′ of **2**.[5]

In conclusion, a method for the stereoselective construction of the C8′–O–C6″ ether of nigricanoside-A (**1**), an antimitotic natural product from the green alga *Avrainvillea nigricans*, has been developed based on chirality-transferring Ireland–Claisen rearrangement. The method was successfully applied to the synthesis of simple models [(**8′*S*,2‴*R***)-**3** and (**8′*R*,2‴*R***)-**3**] for the C20 lipid chain/galactosyl glycerol segment of **1**. Studies on the bioactivity of the model compounds as well as the development of methodologies toward the total synthesis of **1** are in progress.

Acknowledgments

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References and notes

1. Williams, D. E.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. For other synthetic studies on nigricanosides, see: (a) Kurashina, Y.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 605; See, also: (b) Espindola, A. P. D. M.; Crouch, R.; DeBergh, J. R.; Ready, J. M.; MacMillan, J. B. *J. Am. Chem. Soc.* **2009**, *131*, 15994; (c) Tortosa, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3950.
3. (a) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868; A review: b McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; p 117.
4. For a review: Maréchal, É.; Block, M. A.; Dorne, A.-J.; Douce, R.; Joyard, J. *Physiol. Plant.* **1997**, *100*, 65.
5. Models (**8′*S*,2‴*S***)-**3** and (**8′*R*,2‴*S***)-**3** are also in preparation using the same synthetic method reported in this Letter for the comparison of NMR data with **1** to determine the configurations at C8′ and C2‴ of **1**. The details will be published in due course as a full paper along with the results of bioassays of the four models.
6. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
7. Sias, B.; Ferrato, F.; Grandval, P.; Lafont, D.; Boullanger, P.; De Caro, A.; Leboeuf, B.; Veger, R.; Carrière, F. *Biochemistry* **2004**, *43*, 10138.
8. Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.
9. Jung, S. H.; Kim, S. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 13.
10. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
11. The separation of **16** (polar) from **17** (less polar) was performed by HPLC using a pre-packed column (YMC-Pack SIL-06-5 μm, 500 × 20 mm ID) supplied by YMC Co., Ltd with hexane–ethyl acetate eluent (20 mL/min).
12. *Spectral and physical data of (**R**)-**8**:* a colorless oil; $[\alpha]_D^{24}$ − 11.2 (*c* 0.14, $CHCl_3$); IR (neat) *ν* 3414, 3034, 3000, 2939, 2862, 1612, 1586, 1513, 1463, 1442, 1363, 1303, 1248, 1173, 1092, 1036, 899, 820, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.30–1.53 (2H, m, –C*H*$_2$–), 1.53–1.79 (4H, m, –C*H*$_2$– ×2), 1.97 (1H, d, *J* = 6.0 Hz, O*H*), 3.45 (2H, t, *J* = 6.4 Hz, –OC*H*$_2$–), 3.80 (3H, s, –OC*H*$_3$), 4.08 (1H, q, *J* = 6.0 Hz, –C*H*(OH)–), 4.42 (2H, s, –OC*H*$_2$–Ar), 5.55 (1H, br d, *J* = 1.8 Hz, =CH–), 5.86 (1H, br s, =CH–), 6.88 (2H, d, *J* = 8.5 Hz, PMB), 7.26 (2H, d, *J* = 8.5 Hz, PMB); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 21.9 (CH_2), 29.2 (CH_2), 34.8 (CH_2), 55.2 (CH_3), 69.7 (CH_2), 72.4 (CH_2), 75.7 (CH_2), 113.7 (CH ×2), 116.7 (CH_2), 129.2 (CH ×2), 130.5 (C), 137.5 (C), 159.0 (C); EI-HRMS *m*/*z* calcd for $C_{15}H_{21}BrO_3$ ([M$^+$]) 328.0674, found 328.0696. Spectral and physical data of (**S**)-**8**: a colorless oil; $[\alpha]_D^{23}$ + 11.1 (*c* 0.14, $CHCl_3$); IR, ^{1}H NMR and ^{13}CNMR spectra are identical with those of (**R**)-**8**; EI-HRMS *m*/*z* calcd for $C_{15}H_{21}BrO_3$ ([M$^+$]) 328.0674, found 328.0674.
13. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
14. Evans, R. W.; Sprecher, H. *Chem. Phys. Lipids* **1985**, *38*, 327.
15. Mitsunobu, O. *Synthesis* **1981**, *13*, 1.
16. Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.
17. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
18. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
19. Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *J. Org. Chem.* **2009**, *74*, 9524.
20. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1457.
21. Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.
22. *Spectral and physical data of (**8′*S*,2‴*R***)-**3**:* a pale yellow oil; $[\alpha]_D^{23}$ − 2.2 (*c* 0.10, $CHCl_3$); IR (neat) *ν* 3406, 2925, 2855, 1731 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6/DMSO-d_6 [25:2], C_6HD_5 as 7.15 ppm) *δ* 0.86 (3H, t, *J* = 7.0 Hz, H20′), 1.30 (2H, m, H18′), 1.30 (2H, m, H19′), 1.32 (2H, m, H17′), 1.39 (2H, m, H12′), 1.61 (2H, m, H3′), 1.97 (2H, m, H11′), 1.99 (2H, m, H4′), 2.03 (2H, m, H13′), 2.03 (2H, m, H16′), 2.14 (2H, t, *J* = 7.6 Hz, H2′), 2.30 (1H, m, H7′a), 2.47 (1H, m, H7′b), 3.40 (3H, s, OMe), 3.65 (1H, m, H5″), 3.68 (1H, m, H3″), 3.73 (1H, m, H6″a), 3.75 (1H, m, H8′), 3.87 (2H, m, H3‴), 3.95 (1H, m, H6″b), 3.95 (1H, m, H1‴a), 3.97 (1H, m, H2″), 3.98 (1H, m, H4″), 4.08 (1H, m, H2‴), 4.14 (1H, m, H1‴b), 4.41 (1H, d, *J* = 7.6 Hz, H1″), 5.40 (1H, m, H5′), 5.40 (1H, m, H9′), 5.40 (1H, m, H14′), 5.40 (1H, m, H15′), 5.57 (1H, m, H10′), 5.61 (1H, m, H6′) [Chemical shifts are shown as exact values derived from ^{1}D, COSY, HSQC, and HMBC measurements.]; ^{13}C NMR (100 MHz, C_6D_6/DMSO-d_6 [25:2], C_6D_6 as 128.0 ppm) *δ* 14.25 (CH_3, C20′), 22.87 (CH_2, C19′), 25.05 (CH_2, C3′), 26.99 (CH_2, C4′), 27.08 (CH_2, C13′), 27.51 (CH_2, C16′), 29.62 (CH_2, C12′), 29.69 (CH_2, C17′), 31.75 (CH_2, C18′), 32.09 (CH_2, C11′), 33.39 (CH_2, C2′), 34.26 (CH_2, C7′), 51.05 (CH_3, OMe), 64.06 (CH_2, C3‴), 68.14 (CH_2, C6″), 69.62 (CH, C4″), 71.64 (CH, C2‴), 71.98 (CH, C2″), 72.39 (CH_2, C1‴), 74.51 (CH, C3″), 74.78 (CH, C5″), 81.38 (CH, C8′), 105.05 (CH, C1″), 127.19 (CH, C6′), 129.77 (CH, C14′), 130.30 (CH, C5′), 130.40 (CH, C15′), 131.33 (CH, C9′), 133.57 (CH, C10′), 173.46 (C, C1′); FD-HRMS calcd for $C_{30}H_{52}O_{10}Na$ [M+Na$^+$]: 595.3458, found: 595.3463.
23. *Spectral and physical data of (**8′*R*,2‴*R***)-**3**:* a pale yellow oil; $[\alpha]_D^{24}$ + 2.8 (*c* 0.10, $CHCl_3$); IR (neat) *ν* 3387, 2926, 2861, 1737 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6/DMSO-d_6 [25:2], C_6HD_5 as 7.15 ppm) *δ* 0.86 (3H, t, *J* = 7.0 Hz, H20′), 1.30 (2H, m, H18′), 1.30 (2H, m, H19′), 1.32 (2H, m, H17′), 1.38 (2H, m, H12′), 1.61 (2H, m, H3′), 1.96 (2H, m, H11′), 1.99 (2H, m, H4′), 2.02 (2H, m, H13′), 2.02 (2H, m, H16′), 2.14 (2H, *J* = 7.6 Hz, H2′), 2.30 (1H, m, H7′a), 2.45 (1H, m, H7′b), 3.39 (3H, s, OMe), 3.65 (1H, m, H5″), 3.70 (1H, m, H3″), 3.75 (1H, m, H8′), 3.77 (1H, m, H6″a), 3.84 (2H, m, H3‴), 3.90 (1H, m, H1‴a), 3.92 (1H, m, H6″b), 3.98 (1H, m, H2″), 4.05 (1H, m, H2‴), 4.07 (1H, m, H4″), 4.11 (1H, m, H1‴b), 4.39 (1H, d, *J* = 7.7 Hz, H1″), 5.38 (1H, m, H5′), 5.39 (1H, m, H9′), 5.40 (1H, m, H14′), 5.40 (1H, m, H15′), 5.57 (1H, m, H10′), 5.60 (1H, m, H6′) [Chemical shifts are shown as exact values derived from ^{1}D, COSY, HSQC, and HMBC measurements.]; ^{13}C NMR (100 MHz, C_6D_6/DMSO-d_6 [25:2], C_6D_6 as 128.0 ppm) *δ* 14.25 (CH_3, C20′), 22.87 (CH_2, C19′), 25.05 (CH_2, C3′), 26.99 (CH_2, C4′), 27.06 (CH_2, C13′), 27.51 (CH_2, C16′), 29.54 (CH_2, C12′), 29.68 (CH_2, C17′), 31.75 (CH_2, C18′), 32.06 (CH_2, C11′), 33.39 (CH_2, C2′), 34.23 (CH_2, C7′), 51.04 (CH_3, OMe), 64.05 (CH_2, C3‴), 67.67 (CH_2, C6″), 69.38 (CH, C4″), 71.61 (CH, C2‴), 71.99 (CH, C2″), 72.41 (CH_2, C1‴), 74.32 (CH, C5″), 74.54 (CH, C3″), 81.26 (CH, C8′), 105.13 (CH, C1″), 127.19 (CH, C6′), 129.74 (CH, C14′), 130.29 (CH, C5′), 130.41 (CH, C15′), 131.30 (CH, C9′), 133.68 (CH, C10′), 173.43 (C, C1′); FD-HRMS calcd for $C_{30}H_{52}O_{10}Na$ [M+Na$^+$]: 595.3458, found: 595.3473.
24. The Ireland–Claisen rearrangement of ester (**5′*R***)-**6** gave stereoselectively (**8′*R***)-**21** as an almost single isomer in 67% yield after amidation.