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A Divergent Synthesis of the Δ^{13}-9-Isofurans

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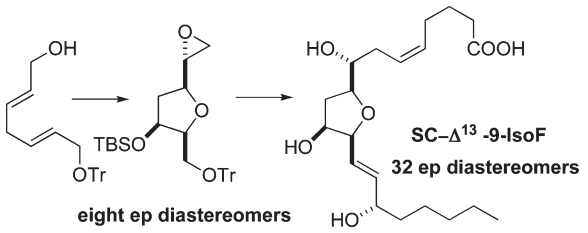


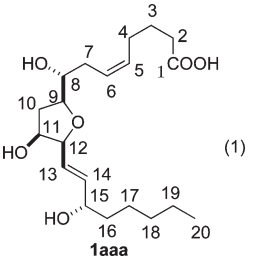
A stereodivergent total synthesis of the Δ^{13}-9-isofurans has been developed. The four core substituted tetrahydrofurans were prepared by the Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation followed by cascade cyclization. The relative configuration at C-8 was inverted by oxidation followed by immediate L-Selectride reduction. The relative configuration of the C-15 diastereomers was assigned by (*S*)-Binol/LAH/EtOH reduction of the corresponding enone. This synthesis of the Δ^{13}-9-isofurans will provide sufficient material for further investigation of their biological activity.

Introduction

The isofurans (Figure 1), represented by SC-Δ^{13}-9-IsoF **1aaa**, are produced by human metabolism of arachidonic acid.[1,2] Previously,[3] we prepared the two diastereomeric isofurans that we judged were the closest in structure to the enzymatically produced human hormone $PGF_{2\alpha}$. One of the diastereomers was found to have significant bioactivity. On repreparation, however, no bioactivity was observed. Suspecting that the initially observed bioactivity might have been due to a minor contaminating diastereomer, we have developed a general strategy for the preparation of each of the 32 of the enantiomerically pure (ep) diastereomers of the Δ^{13}-9-isofurans. As the previous route to the isofurans had suffered from poor regioselectivity in the dihydroxylation step, we have devised an improved and much more robust route to the isofurans.

Results and Discussion

Our interest was to develop a stereodivergent route to the Δ^{13}-9-isofurans, such that each of the enantiomerically pure (ep) diastereomers could be prepared by branching from advanced intermediates. The eight substituted tetrahydrofurans **2a**−**h** (Scheme 1) would each lead to four of the final 32 diastereomers. The four intermediates **2a**−**d** were to be prepared from the previously unknown monotrityl ether **3** by Sharpless asymmetric epoxidation (SAE)[4] followed by Sharpless asymmetric dihydroxylation (SAD).[3,5] We planned to prepare the tetrahydrofurans **2e**−**h** from the



(1)

FIGURE 1. There are 32 ep diastereoisomers of SC−Δ^{13}-9-IsoF.

(1) (a) Fessell, J. P.; Porter, N. A.; Moore, K. P.; Sheller, J. R.; Roberts, L. J. II. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 16713. (b) For a recent review, see: John, U.; Galano, J.-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894.

(2) For a detailed account of isofuran nomenclature, see: Taber, D. F.; Morrow, J. D.; Roberts, L. J. *Prostaglandins Other Lipid Mediators* **2004**, *73*, 47.

(3) (a) Taber, D. F.; Pan, Y.; Zhao, X. *J. Org. Chem.* **2004**, *69*, 7234. (b) Taber, D. F.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 926.

(4) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(5) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

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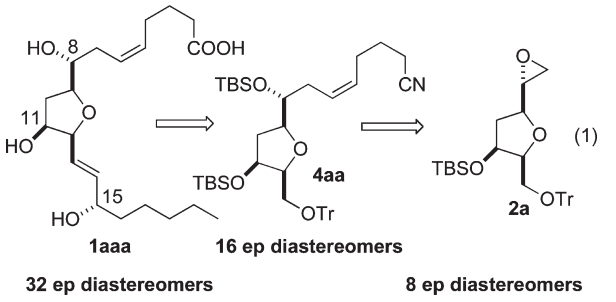
intermediates **2a**−**d** by Mitsunobu esterification[3,6] followed by hydrolysis.

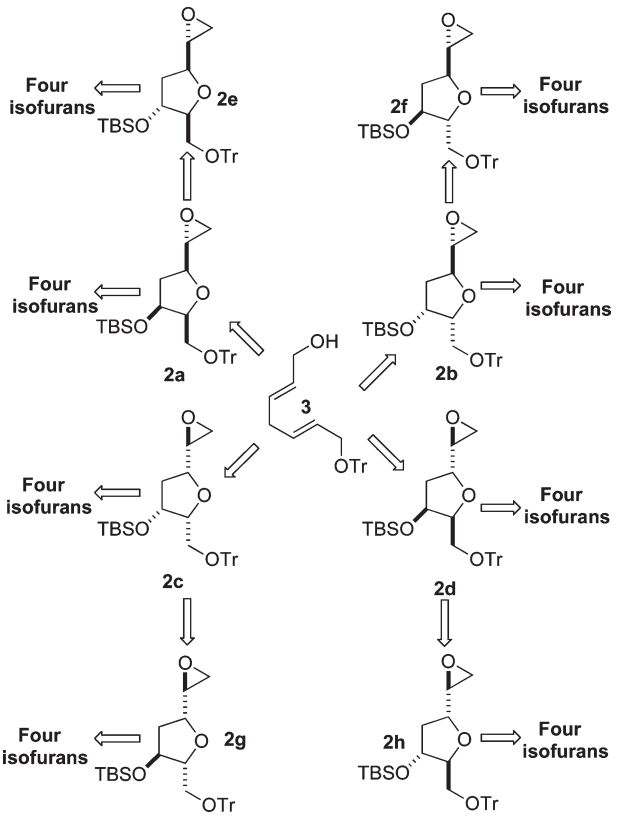
For this approach to the isofurans to be successful, there were three central issues to be addressed (eq 1): (1) Would the asymmetric dihydroxylation of the epoxy sulfonate derived from **3** show matched vs unmatched diastereoselectivity? (2) Could the stereocenters at C-8 and C-11 be inverted without elimination? (3) Could the anticipated C-15 allylic alcohol diastereomers be separated?



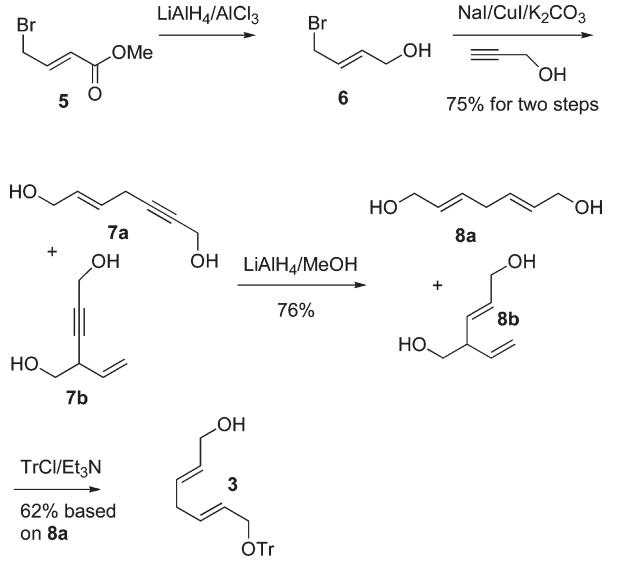
Preparation of the Monotrityl Ether 3. We prepared **3** (Scheme 2) from methyl 4-bromocrotonate **5**. Reduction by $LiAlH_4/AlCl_3$[7] afforded the allylic alcohol **6**. This alcohol were coupled[8] with propargyl alcohol to give a mixture (2:1) of the linear product **7a** and the branched product **7b** that were not easily separable. The mixture was submitted to $LiAlH_4$ reduction to give the diols **8a** and **8b**. After protection with TrCl, the monoether **3** was readily purified.

Preparation of the Four Core Tetrahydrofurans. The monoether **3** was first carried on (Scheme 3, Table 1) to the epoxy alcohol **9a** by Sharpless asymmetric epoxidation with the adjunct D-diethyl tartrate (D-DET) (Scheme 3). The derived benzenesulfonate **10a** was subjected to the Sharpless asymmetric dihydroxylation with AD-mix followed by direct treatment with K_2CO_3 in MeOH[3,9] to give the cyclized product. Using D-DET in the Sharpless asymmetric epoxidation, when AD-mix α was employed (entry 1), it gave a 3:1 mixture of diastereomers that were not readily separable by silica gel chromatography. We were pleased to observe that the two diastereomers were readily separable after silylation of the secondary hydroxyl group, leading to **2a** and **2b**. The structure of **2a** was confirmed by X-ray analysis of the crystalline free alcohol (**11a**, Scheme 4). Alternatively, when AD-mix β was used (entry 2), primarily (>9:1) the single diastereomer **2b** was found. Similarly, using L-DET in the Sharpless asymmetric epoxidation and AD-mix α in the dihydroxylation (entry 4) delivered primarily (>9:1) the diastereomer **2d**, whereas L-DET followed by AD-mix β (entry 3) gave a 2:1 mixture of diastereomers of **2c** and **2d**. Note that the major diastereomers prepared this way showed >99% ee (chiral HPLC), while the minor

SCHEME 1



SCHEME 2



diastereomers (entry 1, entry 3) were about 67% ee and 53% ee, respectively (chiral HPLC). Only the high ee diastereomers were carried on in the synthesis.

Inversion of the C-11 Stereochemistry. To achieve stereodivergence, it was necessary to invert the alcohols at C-11 (isofuran numbering, Scheme 4). Deprotection of the silyl group of **2a** with TBAF gave the free alcohol **11a**. The secondary alcohol at C-11 participated efficiently in Mitsunobu esterification[6] to give, after methanolysis, the inverted

(6) (a) Mitsunobu, O. *Synthesis* **1981**, 1 and references cited therein . (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett*. **1991**, *32*, 3017.

(7) (a) Jorgenson, M. J. *Tetrahedron Lett*. **1962**, 559. (b) Brown, H. C.; Hess, H. M. *J. Org. Chem*. **1969**, *34*, 2206.

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(9) (a) For the development of this strategy, see: Taber, D. F.; Bhamidipati, R. S.; Thomas, M. L. *J. Org. Chem*. **1994**, *59*, 3442. (b) For a related acid-catalyzed cyclization, see: Sivakumar, M.; Borhan, B. *Tetrahedron Lett*. **2003**, *44*, 5547. (c) For a recent application, see: Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett*. **2008**, *10*, 4179.

SCHEME 3

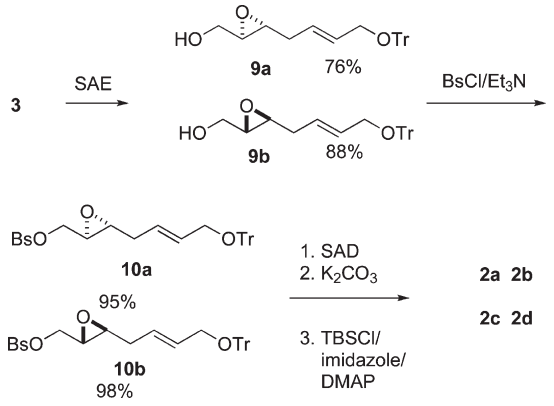
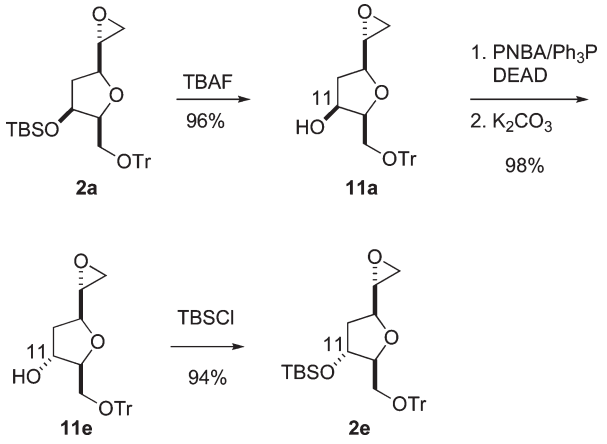


TABLE 1. Tetrahydrofurans by Sequential SAE and SAD

entry	SAE	SAD	products	ratio	yield[a] (%)
1	D-DET	AD-mix α	**2a/2b**	3:1	66
2	D-DET	AD-mix β	**2b**	>9:1	57
3	L-DET	AD-mix β	**2c/2d**	2.2:1	54
4	L-DET	AD-mix α	**2d**	>9:1	62

[a]Combined yield of the two diastereomers.

SCHEME 4

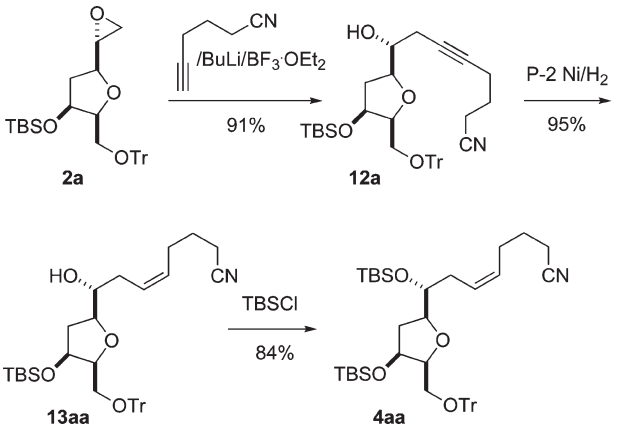


alcohol **11e**. Protection of **11e** with TBS gave the tetrahydrofuran diastereomer **2e**. Similarly, **2b**−**d** were converted to **2f**−**h**.

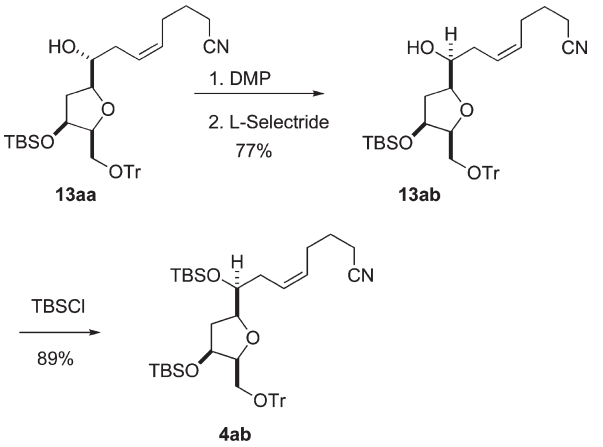
Construction of the Upper Side Chain. Lewis acid $BF_3 \cdot OEt_2$-assisted[10] opening (Scheme 5) of the epoxide **2a** with the lithium anion derived from the commercially available 4-pentynenitrile at low temperature gave efficient conversion to the alkyne **12a**. Partial hydrogenation using P-2 Ni catalyst[11] afforded the *cis*-alkene **13aa**. Protection of **13aa** with TBS resulted in the trityl ether **4aa**.

Inversion of the C-8 Stereochemistry. When Mitsunobu inversion was attempted with alcohol **13aa** (Scheme 6), predominantly dehydration was observed. Fortunately, oxidation[12] followed by immediate L-Selectride reduction of the alcohol **13aa** gave predominantly the inverted

SCHEME 5



SCHEME 6



alcohol **13ab**. Protection of **13ab** with TBS gave the diastereomer **4ab**.

Construction of the Lower Side Chain. The next step in the synthesis was the removal of the trityl group from **4aa** (Scheme 7). Formic acid[13] worked well with **4aa** but destroyed **4ab**. Deprotection of **4aa** with 3 equiv of Et_2AlCl at −50 °C[14] gave the desired alcohol **14aa** accompanied by some unidentified impurities. Fortunately, deprotection of **4aa** and related compounds with 5 equiv of Et_2AlCl at −78 °C for 10 min gave clean conversion to the primary alcohol. Dess−Martin oxidation[12] of the alcohol **14aa** afforded the aldehyde. Horner−Emmons condensation of the aldehyde with commercial dimethyl 2-oxoheptylphosphonate **15** gave the enone **16aa**. Luche reduction[15] of the enone gave the allylic alcohols **17aaa** and **17aab** in a ratio of about 1:1. We were pleased to observe that these two diastereomers were readily separable by silica gel chromatography.

Assignment of the C-15 Absolute Configuration. The enone **16aa** (Scheme 7) was also reduced with $LiAlH_4$/(*S*)-Binol/EtOH at −100 °C, that was expected[16] to give predominantly **17aaa**.

(10) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067.
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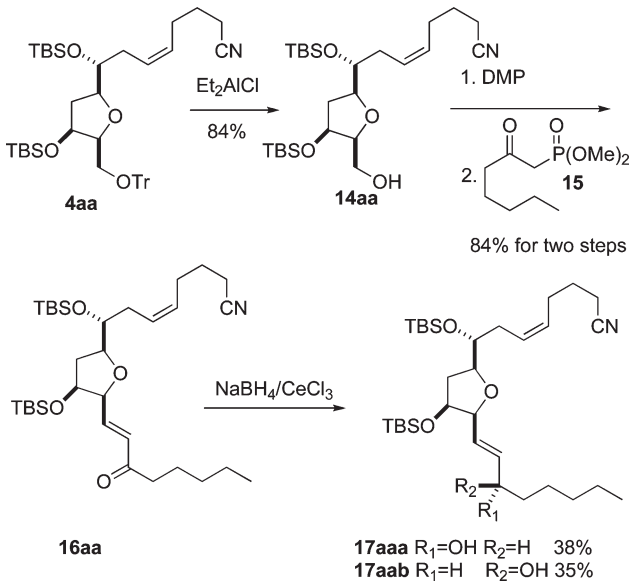
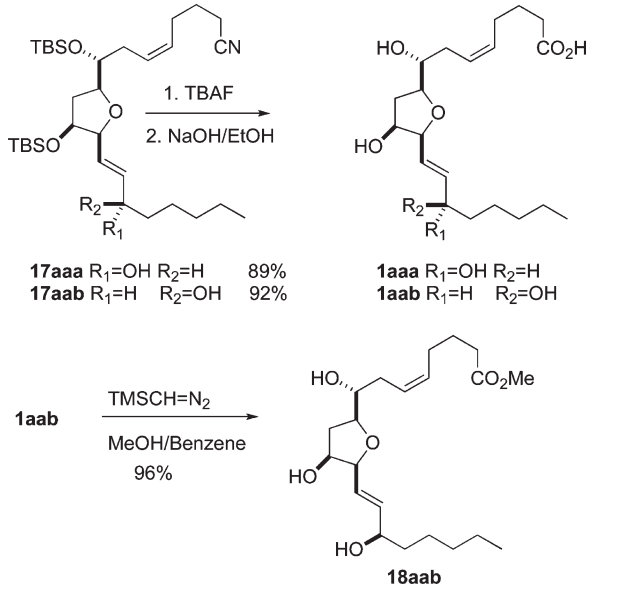
(14) Koster, H.; Sinha, N. D. *Tetrahedron Lett.* **1982**, *23*, 2641.
(15) Germal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(16) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

SCHEME 7



SCHEME 8



The major diastereomer from the reduction was contaminated with the (*S*)-Binol. However, this material was found to be congruent with the upper TLC spot from the Luche reduction by ^{13}C NMR (δ 72.4 vs 72.4, lower spot δ 72.6). This allowed us to assign the absolute configurations at C-15 of the two diastereomeric alcohols **17aaa** (*S*) and **17aab** (*R*).

Synthesis of the Isofurans. Desilylation of **17aaa** with TBAF gave the free alcohol (Scheme 8). The nitrile group was hydrolyzed[17] with 15% aqueous NaOH in EtOH at 85 °C, and the desired carboxylic acid **1aaa** was isolated in excellent yield. Isofuran **1aab** was prepared in the same way. The ^{13}C NMR of the two free acids appeared to be complicated, so the **1aab** was converted to its methyl ester **18aab**. Both **1aaa** and **1aab** and the methyl ester **18aab** were found to be congruent (^{1}H, ^{13}C NMR, $[\alpha]_D$) to the substances that we had previously[3a] prepared.

Using this approach, we have prepared all 32 of the enantiomerically pure diastereomers of Δ^{13}-9-IsoF. The full experimental details for the preparation of a representative six more of those diastereomers are included in the Supporting Information, along with physical characteristics and spectroscopic data for each of the other 31 enantiomerically pure diastereomers of the Δ^{13}-9-isofurans.

Conclusion

We have developed a general route to the enantiomerically pure diastereomers of Δ^{13}-9-IsoF. The four key intermediates **2a**−**d** were obtained by Sharpless asymmetric epoxidation and Sharpless dihydroxylation, followed by cascade cyclization. Mitsunobu inversion of each of these four key intermediates (**2a**,**b**) gave the other four diastereomers (**2e**−**h**). This approach has made each of the 32 ep diastereomers of Δ^{13}-9-IsoF, previously known only in microgram quantities as mixtures, available in sufficient quantity to assess the individual physiological activity of each. We believe that the robust synthetic approach outlined here will allow ready access both to the other regioisomeric isofurans and to the neurofurans.[18,19]

Experimental Section

((2*R*,3*R*)-3-((*E*)-4-trityloxybut-2-enyl)oxiran-2-yl)methanol (9a). To a stirred solution of diethyl D-tartrate (680 mg, 3.3 mmol) in CH_2Cl_2 (150 mL) was added Ti(O^iPr)$_4$ (924 mg, 3.3 mmol) at − 30 to − 20 °C. The reaction mixture was stirred for 30 min at this temperature, and then a solution of **3** (1.11 g, 3.0 mmol) in CH_2Cl_2 (18 mL) was added over a period of 15 min. After an additional 30 min at − 30 to −20 °C, ^{t}BuOOH (4.7 M in CH_2Cl_2, 1.7 mL, 8.0 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred for 3 h at − 30 to −20 °C. Aqueous L-(+) tartaric acid (10%, 6 mL) was added, and then the reaction mixture was stirred at −20 °C for 25 min, allowed to warm to rt, and stirred for 40 min. Aqueous NaOH (1 N, 18 mL) was added at 0 °C, and the resulting reaction mixture was stirred for 1.5 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the epoxide **9a** as a colorless oil (879 mg, 76% yield from monotrityl ether **3**): TLC R_f (MTBE/petroleum ether = 3/7) = 0.28; $[\alpha]_D$ +13.8 (c 1.0, CH_2Cl_2); ^{1}H NMR δ 7.44−7.46 (m, 6 H), 7.20−7.30 (m, 9 H), 5.67−5.75 (m, 2 H), 3.87−3.91 (m, 1 H), 3.58−3.63 (m, 3 H), 3.02−3.05 (m, 1 H), 2.93−2.95 (m, 1 H), 2.34−2.37 (m, 2 H), 2.03 (t, 1 H, J = 6.0 Hz); ^{13}C NMR δ u[20] 144.2, 86.9, 64.6, 61.6, 34.4, d 130.1, 128.7, 127.9, 127.0, 126.0, 58.1, 55.0; IR (film) 3415, 2862, 1447, 1049, 751 cm^{-1}; HRMS calcd for $C_{26}H_{26}O_3Na$ 409.1774, found 409.1775.

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(19) (a) Durand, T; Guy, A.; Vidal, J-P; Viala, J.; Rossi, J.-C. *Tetrahedron Lett.* **2000**, *41*, 3859. (b) Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424. (c) Quan, L. G.; Cha, J. K. *Chem. Phys. Lipids* **2004**, *128*, 3. (d) Kim, S.; Lawson, J. A.; Pratico, D.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **2002**, *43*, 2801. (e) Durand, T.; Guy, A.; Herry, O..; et al. *Chem. Phys. Lipids* **2004**, *128*, 14. (f) Rokach, J.; Kim, S.; Bellone, S..; et al. *Chem. Phys. Lipids* **2004**, *128*, 35.

(20) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u".

((2*R*,3*R*)-3-((*E*)-4-Trityloxybut-2-enyl)oxiran-2-yl)methyl Benzenesulfonate (10a). To a stirring solution of **9a** (879 mg, 2.28 mmol) in CH_2Cl_2 (20 mL) were added DMAP (20 mg, cat) and Et_3N (806 mg, 7.98 mmol) at 0 °C. Then a solution of benzensulfonyl chloride (1.01 g, 5.70 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was stirred for 30 min at 0 °C and then partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the desired epoxide **10a** (1.14 g, 95% yield from epoxide **9a**): TLC R_f (MTBE/petroleum ether = 2/8) = 0.28; $[\alpha]_D$ +14.7 (*c* 1.6, CH_2Cl_2); ^{1}H NMR δ 7.90−7.93 (m, 2 H), 7.62−7.64 (m, 1 H), 7.52−7.58 (m, 2 H), 7.42−7.45 (m, 6 H), 7.21−7.32 (m, 9 H), 5.66−5.68 (m, 2 H), 4.24 (dd, 1 H, *J* = 11.2 and 3.6 Hz), 4.01 (dd, 1 H, *J* = 11.2 and 6.0 Hz), 3.57 (d, 2 H, *J* = 3.6 Hz), 2.92−2.99 (m, 1 H), 2.87−2.88 (m, 1H), 2.32−2.33 (m, 2 H); ^{13}C NMR δ u 144.1, 135.8, 86.9, 70.1, 64.5, 34.0, d 134.0, 130.5, 129.3, 128.6, 127.9, 127.8, 127.0, 125.2, 55.7, 54.0; IR (film) 3058, 1447, 1185, 863,753 cm^{-1}; HRMS calcd for $C_{32}H_{30}O_5SNa$ 549.1731, found 549.1713.

(2*S*,3*S*,5*S*)-Tetrahydro-5-((*S*)-oxiran-2-yl)-2-(trityloxymethyl)furan-3-yloxy)-*tert*-butyldimethylsilane (2a). To a stirred solution of **10a** (770 mg, 1.46 mmol) in a mixed ^{t}BuOH and H_2O solution (v/v 1:1, 3 mL) was added AD-mix-α (2.13 g). After 10 min at room temperature, methanesulfonamide (141 mg, 1.48 mmol) was added. The reaction mixture was stirred for 60 h. $NaHSO_3$ (2.18 g, 21.0 mmol) was added, and the mixture was stirred for 60 min. The reaction mixture was partitioned between EtOAc and water. The organic extract was dried (Na_2SO_4) and concentrated to afford the diol crude (871 mg).

To a stirred solution of the crude diol (499 mg) in MeOH (7.5 mL) at 0 °C was added powdered K_2CO_3 (307 mg, 2.23 mmol). After an additional 2.5 h at 0 °C, the reaction mixture was partitioned between EtOAc and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the mixture of alcohol **11a** and **11b** (244 mg, two steps, 72% yield from **10a**).

To a stirred solution of the mixture of alcohols (360 mg, 0.90 mmol) in CH_2Cl_2 (7 mL) were added TBSCl (405 mg, 2.69 mmol), imidazole (350 mg, 5.15 mmol), and DMAP (6 mg, cat) at room temperature. After an additional 40 min, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford **2b** (110 mg, 24% yield from mixture of **11a** and **11b**, 17% yield for three steps from **10a**): TLC R_f (MTBE/petroleum ether = 1/9) = 0.46; $[\alpha]_D$ −23.8 (*c* 1.0, CH_2Cl_2). Further elution gave **2a** as a colorless oil (316 mg, 68% yield from the mixture of **11a** and **11b**, 49% yield for three steps from **10a**): TLC R_f (MTBE/petroleum ether = 1/9) = 0.31; $[\alpha]_D$ +42.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.46−7.49 (m, 6 H), 7.19−7.29 (m, 9 H), 4.29−4.31 (m, 1 H), 4.05−4.09 (m, 1 H), 3.79−3.83 (m, 1 H), 3.43 (dd, 1 H, *J* = 6.8 and 10.0 Hz), 3.13 (dd, 1 H, *J* = 4.0 and 10.0 Hz), 3.04−3.10 (m, 1 H), 2.78 (dd, 1 H, *J* = 4.0 and 5.2 Hz), 2.70 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 2.23−2.30 (m, 1 H), 1.95 (ddd, 1H, *J* = 2.0 Hz, 3.6 and 14.6 Hz), 0.70 (s, 9 H), −0.03 (s, 3 H), −0.18 (s, 3 H); ^{13}C NMR δ u 144.1, 86.9, 64.2, 46.9, 38.9, 17.8, d 128.8, 127.7, 126.9, 83.2, 78.6, 72.5, 54.0, 25.7, −4.8, −5.4; IR (film) 2930, 2857, 1254, 1074, 835 cm^{-1}; HRMS calcd for $C_{32}H_{40}O_4SiNa$ 539.2594, found 539.2572.

(2*S*,3*S*,5*S*)-2-((Trityloxy)methyl)-tetrahydro-5-((*S*)-oxiran-2-yl)furan-3-ol (11a). To a stirred solution of **2a** (1.57 g, 3.3 mmol) in THF (20 mL) at room temperature was added a Bu_4NF solution in THF (1M, 6.6 mL, 6.6 mmol) at 0 °C. After an additional 5 h, the mixture was partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford **11a** as a solid (1.15 g, 96% yield from **2a**). A 50 mg portion was crystallized from 1.0 mL of 1:5 CH_2Cl_2/hexanes: mp = 142 °C; TLC R_f (MTBE/petroleum ether = 3/7) = 0.33; $[\alpha]_D$ +13.3 (*c* 0.60, CH_2Cl_2); ^{1}H NMR δ 7.44−7.48 (m, 6 H), 7.19−7.30 (m, 9 H), 4.32 (d, 1 H, *J* = 5.2 Hz), 4.06−4.08 (m, 1 H), 3.94 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 3.45 (dd, 1 H, *J* = 5.6 and 9.6 Hz), 3.38 (dd, 1 H, *J* = 5.6 and 9.6 Hz), 3.17−3.20 (m, 1 H), 2.77−2.82 (m, 2 H), 2.60 (dd, 1 H, *J* = 2.8 and 4.8 Hz), 2.18−2.26 (m, 1 H), 1.75−1.79 (m, 1 H); ^{13}C NMR δ u 143.8, 87.1, 62.8, 45.7, 36.0, d 128.8, 128.0, 127.2, 82.3, 77.8, 72.1, 53.7; IR (film) 3458, 1265, 1072, 756 cm^{-1}; HRMS calcd for $C_{26}H_{26}O_4Na$ 425.1729, found 425.1733.

Alkyne 12a. To a stirred solution of 5-hexynenitrile (1.07 g, 11.44 mmol) in THF (10 mL) was added dropwise *n*-BuLi (2.28 M in hexane, 4.1 mL, 9.36 mmol) at −78 °C over a period of 5 min. After an additional 40 min at −78 °C, a solution of **2a** (1.00 g, 1.94 mmol) in THF (15 mL) was added, followed by the addition of a solution of $BF_3 \cdot OEt_2$ (986 mg, 6.95 mmol) in THF (3 mL) over a period of 3 min. The reaction mixture was stirred for 40 min at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford **12a** (1.08 g, 91% yield from **2a**): TLC R_f (MTBE/petroleum ether = 3/7) = 0.30; $[\alpha]_D$ +27.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.45−7.48 (m, 6 H), 7.20−7.30 (m, 9 H), 4.26−4.27 (m, 1 H), 4.19−4.21 (m, 1 H), 3.97−4.01 (m, 1 H), 3.87−3.93 (m, 1 H), 3.42 (dd, 1 H, *J* = 6.8 and 10.0 Hz), 3.12 (dd, 1 H, *J* = 4.0 and 10.0 Hz), 2.73 (d, 1 H, *J* = 2.8 Hz), 2.43−2.49 (m, 3 H), 2.33−2.37 (m, 3 H), 2.12−2.17 (m, 1 H), 1.93 (ddd, 1H, *J* = 0.8 Hz, 4.4 and 14.6 Hz), 1.81−1.88 (m, 2 H), 0.71 (bs, 9H), −0.03 (s, 3 H), −0.19 (s, 3 H); ^{13}C NMR δ u 144.1, 119.3, 86.9, 79.5, 78.3, 64.0, 35.1, 24.8, 24.0, 18.0, 17.9, 16.2, d 128.8, 127.8, 127.0, 82.6, 80.0, 72.6, 71.1, 25.7, −4.9, −5.4; IR (film) 3454, 2932, 2048, 1256, 1072, 705 cm^{-1}; HRMS calcd for $C_{38}H_{47}NO_4SiNa$ 632.3172, found 632.3177.

Alkene 13aa. To a stirred solution of $Ni(OAc)_4 \cdot 4H_2O$ (259 mg, 1.04 mmol) in EtOH (8 mL) was added a $NaBH_4$ solution in EtOH (1 M, 1.0 mL, 1.0 mmol). The black mixture was evacuated and backfilled with H_2 three times. Ethylenediamine (70 uL, 0.95 mmol) was added, followed by alkyne **12aa** (317 mg, 0.52 mmol) in EtOH (5 mL). The reaction mixture was stirred for 2.5 h at rt under H_2. The reaction mixture was diluted in MTBE and filtered through a pad of silical gel. The filtrate was concentrated, and the residue was chromatographed to afford the desired alkene **13aa** as a colorless oil (301 mg, 95% yield from the alkyne **12aa**): TLC R_f (MTBE/petroleum ether = 3/7) = 0.37; $[\alpha]_D$ +24.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.64−7.66 (m, 6 H), 7.38−7.48 (m, 9 H), 5.75−5.81 (m, 1 H), 5.61−5.65 (m, 1 H), 4.43−4.46 (m, 1 H), 4.22−4.26 (m, 1 H), 4.12−4.14 (m, 1 H), 4.04−4.08 (m, 1 H), 3.61 (dd, 1 H, *J* = 6.4 Hz and 10,0 Hz), 3.32 (dd, 1 H, *J* = 4.0 and 10.0 Hz), 2.83 (s, 1 H), 2.50 (t, 2 H, *J* = 7.2 Hz), 2.29−2.41 (m, 1 H), 2.11−2.15 (m, 1 H), 1.89−1.93 (m, 2 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.00(s, 3 H); ^{13}C NMR δ u 144.1, 119.7, 86.9, 63.9, 34.7, 31.8, 26.1, 25.3, 17.9, 16.5, d 130.0, 128.8, 127.9, 127.8, 127.0, 82.4, 80.6, 72.6, 71.8, 25.7, −4.9, −5.5; IR (film) 3440, 2933, 2245, 2048. 1448, 1072, 774, 704 cm^{-1}; HRMS calcd for $C_{38}H_{49}NO_4SiNa$ 634.3329, found 634.3329.

Alkene 4aa. To a stirred solution of **13aa** (348.3 mg, 0.57 mmol) in CH_2Cl_2 (8 mL) were added TBSCl (430 mg, 2.85 mmol), imidazole (371 mg, 5.70 mmol), and DMAP (5 mg, cat.) at room temperature. After an additional 17 h, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford **4aa** (349 mg, 84% yield from **13aa**): TLC R_f (MTBE/petroleum ether = 1/9) = 0.50; $[\alpha]_D$ +14.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.70−7.72 (m, 6 H), 7.43−7.53 (m, 9 H), 5.87−5.91 (m, 1 H), 5.65−5.68 (m, 1 H), 4.45−4.48 (m, 1 H), 4.13−4.17 (m, 1 H), 4.03−4.06 (m, 1 H), 3.89−3.94 (m, 1 H), 3.57−3.60 (m, 1 H), 3.29 (dd, 1 H, *J* = 2.4 and 10.0 Hz), 2.78−2.85 (m, 1 H), 2.42−2.50 (m, 6 H), 1.92−1.97 (m, 3 H), 1.10

(s, 9 H), 0.92 (s, 9 H), 0.31 (s, 3 H), 0.27 (s, 3 H), 0.14 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR δ u 144.3, 119.9, 86.6, 64.7, 38.8, 32.3, 26.4, 25.5, 18.1, 17.9, 16.4, d 128.9, 128.9, 127.7, 126.9, 82.5, 79.6, 74.4, 73.0, 25.9, 25.8, −4.0, −4.3, −4.8, −5.4; IR (film) 3432, 2932, 2264, 1253, 1078, 834 cm^{-1}; HRMS calcd for $C_{44}H_{63}NO_4Si_2Na$ 748.4193, found 748.4192.

Alcohol 14aa. To a stirred solution of **4aa** (20 mg, 0.0275 mmol) in CH_2Cl_2 (4 mL) was added diethyl aluminum chloride (1 N in hexane, 0.15 mL, 0.15 mmol) at − 78 °C. After an additional 10 min, the reaction mixture was quenched with water and filtered through a pad of silica gel, washing with methanol. The filtrate was concentrated, and the residue was chromatographed to give the desired alcohol **14aa** (11.2 mg, 84% yield from the ether **4aa**): TLC R_f (MTBE/petroleum ether = 3/7) = 0.32; $[\alpha]_D$ −5.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 5.58−5.61 (m, 1 H), 5.38−5.41 (m, 1 H), 4.50 (dd, 1 H, *J* = 6.0 and 13.2 Hz), 3.79−3.83 (m, 2 H), 3.72−3.75 (m, 2 H), 3.63−3.68 (m, 1 H), 2.32−2.40 (m, 4 H), 2.17−2.25 (m, 4 H), 1.78−1.83 (m, 1 H), 1.70−1.76 (m, 2 H), 0.88 (s, 18 H), 0.07 (s, 12 H); ^{13}C NMR δ u 119.7, 62.7, 38.1, 32.5, 26.5, 25.3, 18.1, 18.0, 16.5, d 128.8, 127.7, 81.1, 79.4, 73.8(2), 25.9, 25.8, −4.2, −4.4, −4.6, −5.2; IR (film) 2932, 2256, 1254, 1079, 835 cm^{-1}; HRMS calcd for $C_{25}H_{49}NO_4Si_2Na$ 506.3098, found 506.3097.

Enone 16aa. To a stirred solution of **14aa** (64 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added Dess−Martin periodinane (111 mg, 0.26 mmol). After an additional 40 min at rt, the reaction mixture was directly poured on the silica gel and chromatographed to afford the crude aldehyde (53 mg).

To a stirred suspension of NaH (26 mg, 0.66 mmol) in THF (5 mL) was added dimethyl 2-oxoheptylphosphonate **15** (244 mg, 1.10 mmol) at 0 °C. After an additional 1 h at 0 °C, a solution of the crude aldehyde (53 mg) in THF (1 mL) was added. After an additional 40 min at 0 °C, the mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford **16aa** (64 mg, 84% yield from **14aa**): TLC R_f (MTBE/petroleum ether = 3/7) = 0.73; $[\alpha]_D$ +5.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 6.79 (dd, 1 H, *J* = 4.2 and 16.0 Hz), 6.26 (dd, 1 H, *J* = 1.6 and 16.0 Hz), 5.59−5.64 (m, 1 H), 5.39−5.45 (m, 1 H), 4.42−4.46 (m, 1 H), 4.28 (dt, 1 H, *J* = 1.6 and 5.6 Hz), 3.86 (q, 1 H, *J* = 5.2 Hz), 3.74 (q, 1 H, *J* = 7.2 Hz), 2.54−2.58 (m, 2 H), 2.43−2.50 (m, 1 H), 2.19−2.35 (m, 6 H), 1.82−1.89 (m, 1 H), 1.70−1.77 (m, 2 H), 1.59−1.66 (m, 2 H), 1.25−1.37 (m, 4 H), 0.86−0.90 (m, 21 H), 0.09 (s, 6 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR δ u 200.5, 119.7, 39.9, 38.3, 32.4, 31.5, 26.3, 25.3, 23.8, 22.5, 18.1, 18.0, 16.5, d 142.7, 130.8, 128.9, 127.6, 82.3, 80.1, 74.3, 73.8, 25.9, 25.8, 13.9, −4.1, −4.3, −4.7, −5.0; IR (film) 3442, 2929, 2250, 1641, 833, 775 cm^{-1}; HRMS calcd for $C_{32}H_{59}NO_4Si_2Na$ 600.3880, found 600.3876.

Alcohols 17aaa and 17aab. To a stirred solution of **16aa** (118 mg, 0.20 mmol) in MeOH (6 mL) was added $CeCl_3 \cdot 7H_2O$ (74 mg, 0.20 mmol). After 5 min, $NaBH_4$ (12 mg) was added. The mixture was stirred for an additional 30 min at rt, and then the reaction mixture was filtered through a pad of silica gel, washing with MTBE, the filtrate was concentrated, and the residue was chromatographed to give the desired alcohol **17aaa** (45 mg, 38% yield from the enone **16aa**): TLC R_f (Et_2O/CH_2Cl_2/petroleum ether = 1/3/6) = 0.23; $[\alpha]_D$ +4.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 5.75−5.82 (m, 2 H), 5.58−5.62 (m, 1 H), 5.36−5.43 (m, 1 H), 4.28−4.31 (m, 1 H), 4.06−4.15 (m, 2 H), 3.84 (q, 1 H, *J* = 4.8 Hz), 3.66 (q, 1 H, *J* = 7.2 Hz), 2.65 (d, 1 H, *J* = 9.6 Hz), 2.39−2.47 (m, 1 H), 2.30−2.34 (m, 2 H), 2.17−2.27 (m, 4 H), 1.83−1.87 (m, 1 H), 1.68−1.76 (m, 2 H), 1.50−1.56 (m, 4 H), 1.26−1.43 (m, 4 H), 0.87−0.90 (m, 21 H), 0.03−0.08 (m, 12 H); ^{13}C NMR δ u: 119.8, 38.3, 37.1, 32.3, 31.8, 26.4, 25.3, 25.2, 22.6, 18.2, 18.1, 16.5 d: 136.3, 128.7, 127.9, 127.6, 83.5, 79.7, 74.3, 74.0, 72.4, 25.9 (3), 25.9 (3), 14.1, −4.1, −4.3, −4.6, −4.9; IR (film) 2931, 2250, 1464, 1252, 1073, 834 cm^{-1}; HRMS calcd for $C_{32}H_{61}NO_4Si_2Na$ 602.4033, found 602.4025. Further elution gave **17aab** (41 mg, 35% yield from the enone **16aa**): TLC R_f (Et_2O/CH_2Cl_2/petroleum ether = 1/3/6) = 0.33; $[\alpha]_D$ +6.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 5.68−5.81 (m, 2 H), 5.58−5.64 (m, 1 H), 5.37−5.42 (m, 1 H), 4.25−4.29 (m, 1 H), 4.03−4.13 (m, 2 H), 3.82−3.86 (m, 1 H), 3.64−3.70 (m, 1 H), 2.65 (d, 1 H, *J* = 9.6 Hz), 2.42−2.48 (m,1 H), 2.31−2.35 (m, 2 H), 2.18−2.25 (m, 4 H), 1.81−1.86 (m, 1 H), 1.60−1.75 (m, 4 H), 1.49−1.55 (m, 2 H), 1.37−1.44 (m, 1 H), 1.26−1.36 (m, 3 H), 0.88−0.90 (m, 21 H), 0.01−0.09 (m, 12 H); ^{13}C NMR δ u 119.9, 38.6, 37.1, 32.2, 31.8, 26.4, 25.3, 25.2, 22.6, 18.2, 18.1, 16.5, d 136.8, 128.7, 128.0, 127.8, 83.9, 79.7, 74.1, 74.0, 72.6, 25.90 (3), 25.87 (3), 14.1, −4.1, −4.3, −4.6, −4.9; IR (film) 3449, 2932, 2250, 1254, 1074, 835 cm^{-1}; HRMS calcd for $C_{32}H_{61}NO_4Si_2Na$ 602.4037, found 602.4023.

Isofuran 1aaa. To a stirred solution of **17aaa** (45 mg, 0.078 mmol) in THF (0.8 mL) was added a 1 M solution of Bu_4NF (1.0 M in THF, 1.0 mL). After an additional 1.5 h at rt, the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic extract was concentrated to afford the crude triol. The crude triol was dissolved in EtOH (1.0 mL), and then 15% aqueous NaOH (2.0 mL) was added. After an additional 16 h at 85 °C, the reaction mixture was cooled to rt and acidified with NaH_2PO_4 (0.5 M, 3 mL) and AcOH (3 mL). The mixture was partitioned beween CH_2Cl_2 and water. The organic extract was concentrated, and the residue was chromatographed to give **1aaa** (26 mg, 89% yield from **17aaa**): TLC R_f (Et_2O/0.5 M aqueous NaH_2PO_4/HOAc = 90/9/1) = 0.35; $[\alpha]_D$ +25.0 (*c* 0.5, CH_2Cl_2), $[\alpha]_D$ +35.4 (*c* 0.58, CH_3OH); ^{1}H NMR δ 5.98 (s, 3 H), 5.81−5.82 (m, 2 H), 5.44−5.49 (m, 2 H), 4.08−4.16 (m,4 H), 3.86−3.87 (m, 1 H), 2.35 (s, 1 H), 2.02−2.27 (m, 7 H), 1.70 (s, 2 H), 1.22−1.53 (m, 9 H), 0.86−0.91 (m, 3 H); ^{13}C NMR δ u 36.7, 34.1, 31.8, 26.4, 25.2, 24.4, 22.6, d 137.5, 131.6, 126.0, 125.9, 84.0, 80.4, 73.1, 72.0, 71.8, 30.3, 14.1; the carbonyl carbon was not observed; IR (film) 3334, 2925, 1708, 1018 cm^{-1}; HRMS calcd for $C_{20}H_{34}O_6Na$ 393.2253, found 393.2246.

Isofuran 1aab. The reaction was performed with the alcohol **17aab** (36 mg, 0.062 mmol) in the same manner as described for the preparation of isofuran **1aaa** to give isofuran **1aab** (24 mg, 92% yield from **17aab**): TLC R_f (Et_2O/0.5 M aqueous NaH_2PO_4/HOAc = 90/9/1) = 0.38; $[\alpha]_D$ +15.6 (*c* 0.48, CH_2Cl_2), $[\alpha]_D$ +23.1 (c 0.50, CH_3OH); ^{1}H NMR δ 5.71−5.88 (m, 3 H), 5.43−5.48 (m, 3 H), 4.05−4.20 (m, 4 H), 3.89 (s, 1 H), 2.36 (s, 2 H), 2.04−2.27 (m, 6 H), 1.70−1.73 (m, 2 H), 1.43−1.57 (m, 3 H), 1.25−1.36 (m, 7 H), 0.86−0.89 (m, 3 H); ^{13}C NMR δ u 178.1, 36.5, 34.2, 32.0, 31.8, 26.4, 25.2, 24.4, 22.6, d 136.5, 131.3, 126.2, 126.2, 83.1, 80.3, 72.7, 72.3, 71.8, 30.3, 14.1; the carbonyl carbon was not initially observed, but when **1aab** was prepared by saponification of the ester **18aab**, the carbonyl was evident; IR (film) 3447, 3034, 2926, 1708, 1240, 1018 cm^{-1}; HRMS calcd for $C_{20}H_{34}O_6Na$ 393.2253, found 393.2246.

Ester 18aab. To a stirred solution of isofuran **1aab** (8 mg, 0.021 mmol) in MeOH/benzene (1:4, 0.5 mL) was added trimethylsilyl diazomethane (2.0 M in Et_2O, 50 uL). The mixture was stirred at room temperature for 20 min. The mixture was concentrated, and the residue was chromatographed to afford the ester **18aab** (8 mg, 96% yield from the isofuran **1aab**): TLC R_f (acetone/CH_2Cl_2 = 4/1) = 0.38; $[\alpha]_D$ +23.8 (*c* 0.38, CH_2Cl_2), $[\alpha]_D$ +23.1 (*c* 0.55, CH_3OH); ^{1}H NMR δ 5.81−5.87 (m, 1 H), 5.73 (dd, *J* = 15.6 and 5.2 Hz, 1 H), 5.44−5.51 (m, 2 H), 4.88 (s, 1 H), 4.79 (s, 1 H), 4.18−4.20 (m, 1 H), 4.11−4.16 (m, 2 H), 4.02−4.08 (m, 1 H), 3.85−3.90 (m, 1 H), 3.70−3.85 (m, 1 H), 3.67 (s, 3 H), 2.32 (t, 2 H, *J* = 7.2 Hz), 2.03−2.29 (m, 5 H), 1.66−1.74 (m, 3 H), 1.41−1.60 (m, 2 H), 1.21−1.38 (m, 6 H), 0.87 (t, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ u 174.0, 36.5, 34.0, 33.4, 32.2, 31.7, 26.7, 25.3, 24.7, 22.6, d 136.4, 131.2, 126.5, 126.2, 83.1, 80.2, 72.8, 72.2, 71.8, 51.5, 14.1; HRMS calcd for $C_{21}H_{36}O_6Na$ 407.2404, found 407.2410.

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Supporting Information Available: General experimental procedures, experimental procedures and spectra for all new compounds, and details of the X-ray structural analysis of **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.