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A Flexible Enantioselective Synthesis of the Isofurans

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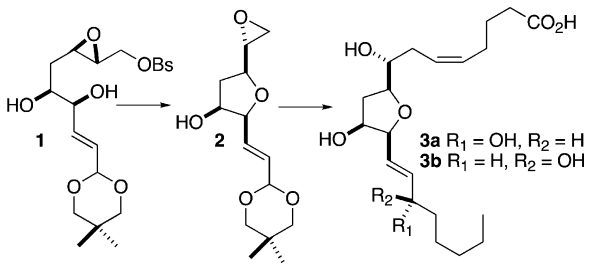
Recently, the isolation of a new class of human arachidonic acid tetrahydrofuran oxidation products, the isofurans (IsoF's), was reported. These new compounds are available from natural sources only in microgram quantities as mixtures. The enantioselective preparation of a versatile epoxide intermediate and its conversion to the enantiomerically pure isofurans SC-Δ^{13}-9-IsoF and 15-epi-SC-Δ^{13}-9-IsoF are described. This synthesis will make these metabolites available for physiological evaluation.

Introduction

Recently, the isolation of a new class of human arachidonic acid oxidation products, the isofurans (IsoF's), was reported.[1,2] These new compounds (Scheme 1) are produced in vivo by a free radical mechanism, independent of the cyclooxygenase enzymes. Because these compounds are tetrahydrofuran derivatives that are related biosynthetically to the isoprostanes, they were termed isofurans (IsoF's). Interestingly, with increased oxidative stress, the production of the isoprostanes falls, and free radical conversion of arachidonic acid switches to the isofurans.

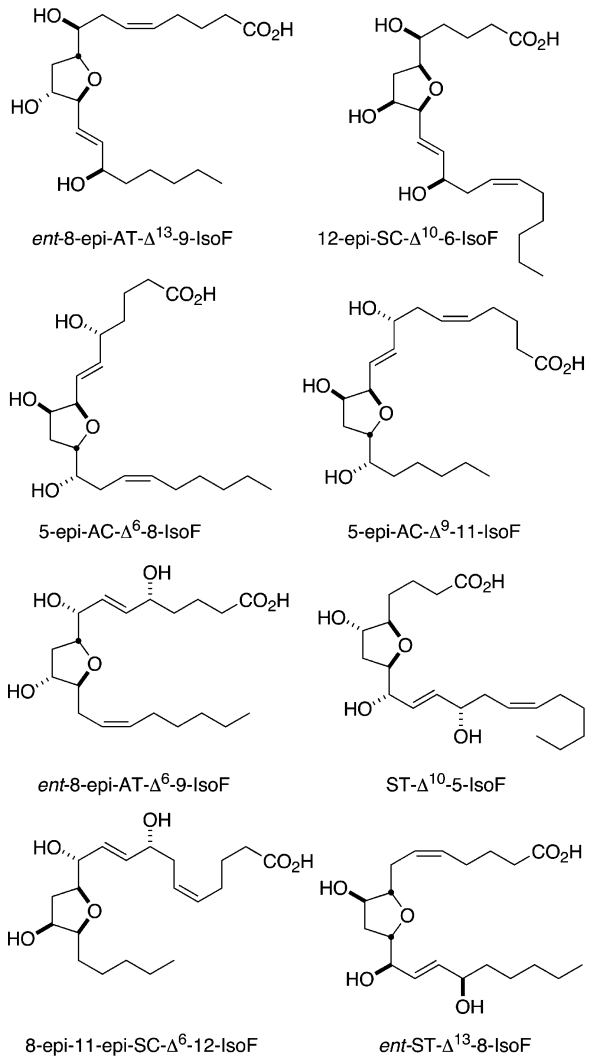
Even though they are nonenzymatic oxidation products, the isoprostanes have been found to have significant physiological activity. It is therefore important to also investigate the physiological role of the isofurans. To this end, we have developed a general synthetic strategy that will allow the preparation of each of the enantiomerically pure diastereomers of the several regioiosomers of the isofurans. We have illustrated this approach with the synthesis of the two isofurans that are closest in structure to the enzymatically produced prostaglandins, SC-Δ^{13}-9-IsoF (**3a)** and 15-epi-SC-Δ^{13}-9-IsoF **(3b**).



Results and Discussion

Synthetic Approach. Our interest was to develop a flexible route to the isofurans, such that each of the enantiomerically pure diastereomers could be prepared using a divergent strategy, branching from advanced intermediates. One such advanced intermediate would be the substituted tetrahydrofuran compound **2**.

SCHEME 1



We envisioned that the tetrahydrofuran **2** could be prepared by cascade cyclization[3] of the diol epoxide **1**. Although there are four different modes of epoxide opening available to the diol **1**, it seemed likely that exo cyclization would dominate over endo cyclization and that five-membered ring formation would be faster than four-mem-

(1) Fessell, J. P., Porter, N. A.; Moore, K. P.; Sheller, J. R.; Roberts, L. J., II. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 16713.

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bered ring formation. Ring closure of the intermediate alkoxide would then lead to the epoxide **2**.[3] We expect to observe this same selectivity for five-membered ring formation with the other three syn-diol diastereomers of **1**.

Eight different regioisomers of the IsoF's have been observed,[1] each of which can exist as 16 racemic diastereomers. Thus, there are 256 enantiomerically pure IsoF's,[4] representative examples of which are illustrated in Scheme 1. The relative and absolute configuration of **2** can be easily varied by the use of the opposite enantiomers of catalysts in the Sharpless asymmetric epoxidation and dihydroxylation reactions. We therefore expect that the synthetic approach outlined here will allow the preparation of each of the enantiomerically pure diastereomers of the several regioisomers of the isofurans.[5]

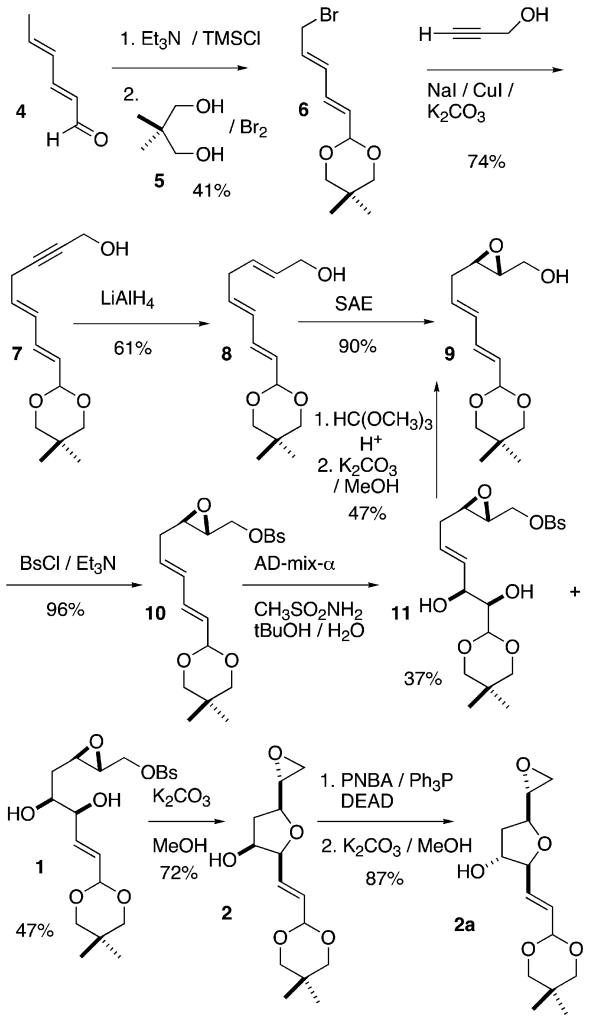
Preparation of the Triene Alcohol 8. We projected that the diol **1** could be prepared (Scheme 2) from the triene **8**, which in turn would be available from the bromodiene **6** by homologation with propargyl alcohol. While the dimethyl acetal corresponding to **6** was known, we thought that the acetal derived from 2,2-dimethylpropane-1,3-diol **5** would be more stable. This turned out to be a good choice, as the epoxide **2** derived from **5** was nicely crystalline.

Following the literature precedent, our synthesis (Scheme 2) started with the conversion of (*E,E*)-sorbaldehyde **4** to its silyl enol ether.[6] Bromination of the crude enol ether followed by quenching with 2,2-dimethylpropane-1,3-diol **5** afforded the bromoacetal **6**.[7] This allylic bromide was coupled with propargyl alcohol to give the acetylenic alcohol **7**.[8] Reduction of the alkyne **7** using Red-Al,[9] Na/NH_3,[10] or Li/1,3-diaminopropane[11] gave rearrangement to the allene. Reduction of the alkyne **7** using $LiAlH_4$ in THF[12] led to partial decomposition of the acetal. The allylic alcohol **8** was isolated, but only in poor yield. The best results for the reduction of **7** to **8** were obtained when powdered $LiAlH_4$ was employed and the reaction was carried out in dry diethyl ether.

Preparation and Crystallization of 2. The allylic alcohol **8** was carried on to the epoxy alcohol **9** by the Sharpless asymmetric epoxidation.[13] The derived benzenesulfonate **10** was subjected to the Sharpless asymmetric dihydroxylation using AD-mix-α.[14] We had thought that the desired target alkene would be the more electron-rich of the two, and so would react preferentially. This turned out to be true, but only marginally so. The dihydroxylation afforded a 1.3:1 mixture of the easily separable regioisomeric diols **1** and **11**. Fortunately, the undesired regioisomer **11** was readily recycled to **9** (43% overall) by thermal fragmentation[15] of the derived cyclic ortho ester.[16]

With the diol **1** in hand, we were ready to attempt the key cyclization. We tried the reaction both with potassium carbonate in methanol[17] and with potassium *tert*-butoxide in THF.[18] The reaction in methanol was cleaner, even though it was necessary to operate at 0 °C, as higher

SCHEME 2



(2) An IsoF-type compound has been reported as a product from enzymatic oxidation of arachidonic acid: (a) Pace-Asciak, C. *Biochemistry* **1971**, *10*, 3664. (b) Bild, G. S.; Bhat, S. G.; Ramadoss, C. S.; Axelrod, B.; Sweeley, C. C. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 486. Neither the relative nor the absolute configuration of this product was assigned.

(3) (a) A similar cascade cyclization was developed in our group several years ago: 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.

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

(5) For the only synthetic efforts reported to date toward IsoF type structures, see: (a) Just, G.; Oh, H. *Can. J. Chem.* **1981**, *59*, 2729. (b) Just, G.; Luthe, C.; Oh, H. *Tetrahedron Lett.* **1980**, *21*, 1001. Following our nomenclature, these would be 8-epi-ST-Δ^{13}-9-IsoF and 8-epi-15-epi-ST-Δ^{13}-9-IsoF.

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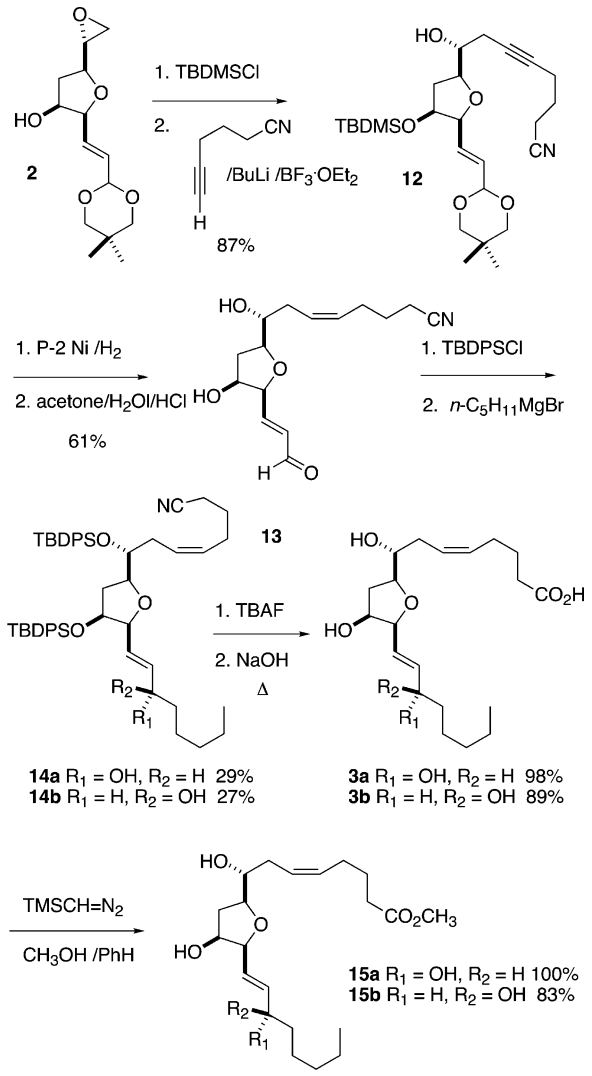
(18) Ho, D. K.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M. *J. Org. Chem.* **1987**, *52*, 342.

SCHEME 3



temperatures (even room temperature) and longer reaction times resulted in epoxide ring opening of **2** by methanol.

Neither the Sharpless asymmetric epoxidation nor the dihydroxylation proceeds with perfect enantiocontrol. We therefore expected that **2** would be contaminated with minor amounts of other diasteromers. As it turned out, the epoxide **2** was easily separated from trace contaminants by recrystallization. X-ray analysis confirmed both the relative and the absolute configuration of this central intermediate.

Inversion of the Secondary Alcohol. The epimeric alcohol **2a** will be the precursor to the ST series of the isofurans (Scheme 1). The inversion to prepare **2a** was a delicate transformation, as **2** was prone to further cyclization by intramolecular addition of the secondary alcohol to the epoxide. Nevertheless, the secondary alcohol of **2** participated efficiently in Mitsunobu inversion[19] to give, after methanolysis, the inverted alcohol **2a**.

Construction of the Upper Side Chain. Because of the propensity of the secondary alcohol of **2** to cyclize by intramolecular addition to the epoxide, it was necessary to first protect it (Scheme 3) before proceeding with the construction of the two side chains. It seemed sensible to extend the upper side chain first, since the epoxide of **2** was already primed for S_N2 opening.

For the upper side chain, Lewis-acid assisted opening of the epoxide **2** with the lithium anion derived from the commercially available nitrile required some optimization. Using BF_3·OEt_2 as the Lewis acid, the reaction temperature proved to be critical. An extended reaction time at low temperature was required to give efficient conversion to the alkyne **12**.[20] Partial hydrogenation using P-2 Ni catalyst followed by hydrolysis then afforded the *cis*-alkene **13**.[8,21]

Construction of the Lower Side Chain. The next step in the synthesis was the addition of a pentyl unit to complete the isofuran skeleton. While it would have been possible to control the allylic alcohol stereocenter by enantioselective addition, we in fact wanted to prepare both diastereomers of the isofurans. Direct addition of pentylmagnesium bromide to **13** indeed gave the triol as the expected 1:1 mixture of diastereomers. These alcohols, however, ran together on TLC with each of the solvent systems that we tried.

The solution to this problem turned out to be to first re-silylate the secondary alcohols of **13**. We found that the ring OH silylated much more readily than did the side-chain OH. In practice, it was most convenient to carry the diol **13** on to the bis-silylated intermediate. The addition of pentylmagnesium bromide then gave a 1:1 ratio of the *separable* alcohols **14a** and **14b**.

Assignment of the C-15 Absolute Configuration. The choice of silyl protecting group was dictated by the need for a UV chromophore, so we could develop the analytical HPLC separation of **14a** and **14b**. The mixture of **14a** and **14b** was then oxidized to the C-15 ketone, and the enone so prepared was reduced with (S)-DIP-Cl,[19,20] which was expected to give predominantly **14a**. This allowed us to assign the absolute configuration at C-15 of the two alcohol diastereomers.

Synthesis of the Isofurans. The final step in our synthesis was the hydrolysis, separately, of the nitriles **14a** and **14b**. When nitrile **14a** was heated in 15% NaOH and EtOH at 105 °C,[8,21] the desired carboxylic acid **3a** was isolated in low yield. However, when the hydrolysis was carried out on the deprotected compound, which was obtained by exposure of **14a** to TBAF, the desired carboxylic acid **3a** was isolated in excellent yield. For better characterization, the isofuran **3a** was converted to its methyl ester **15a** by treatment with trimethylsilyldiazomethane.[22] In a similar fashion, nitrile **14b** was converted into isofuran **3b** and its methyl ester **15b**.

The synthetic isofurans **3a** and **3b** were congruent (TLC, HPLC−MS) with the natural substances. The ^{1}H NMR data for the methyl esters **15a** and **15b** were very similar to those reported[5] for the methyl esters of 8-epi-ST-Δ^{13}-9-IsoF and 8-epi-15-epi-ST-Δ^{13}-9-IsoF.

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

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(22) (a) Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424. (b) Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett.* **2003**, *5*, 93.

Conclusion

We have established what we expect will be a general route to the isofurans. The key step is the cascade cyclization of the diol **1** to the epoxide **2**. This approach will make each of these natural products, previously known only in microgram quantities as mixtures, available in sufficient quantity to assess their individual physiological activity.

Experimental Section

Bromoketal 6. To (2*E*,4*E*)-2,4-hexadienal (9.19 g, 95.7 mmol) were added, sequentially, pentane (135 mL), TMSCl (16.0 mL, 126 mmol), and triethylamine (17.0 mL). A solution of NaI (19.8 g, 126 mmol) in acetonitrile (135 mL) was added dropwise. The mixture was stirred vigorously for 24 h and then maintained at reflux for 12 h. The reaction mixture was then partitioned between pentane and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was bulb-to-bulb distilled to give 1-(trimethylsilyloxy)hexa-1,3,5-triene as a colorless oil (10.2 g, 56.8 mmol), bp (pot) = 80−85 °C (10 mmHg). It was used immediately in the next reaction without further purification.

To a solution of 1-(trimethylsilyloxy)hexa-1,3,5-triene (10.2 g, 56.8 mmol) in DMF (90 mL) was added dropwise a solution of Br_2 (9.10 g, 56.9 mmol) in DMF (20 mL) at −55 °C. After the addition, the reaction mixture was stirred at −55 to −30 °C for 1.5 h. The mixture was cooled to −55 °C, and a solution of 2,2-dimethyl-1,3-propanediol (29.7 g, 286 mmol) in DMF (90 mL) was added dropwise over 30 min. The mixture was stirred at −55 °C overnight and allowed to warm to room temperature. The mixture was partitioned between diethyl ether and, sequentially, water, saturated aqueous $NaHCO_3$, and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give bromoketal **6** as a colorless oil (10.4 g, 39.8 mmol, 41% yield for two steps): TLC R_f (MTBE/petroleum ether = 1:9) = 0.40; ^{1}H NMR δ 0.75 (s, 3H), 1.22 (s, 3H), 3.51 (d, J = 10.6 Hz, 2H), 3.66 (d, J = 10.6 Hz, 2H), 4.01 (d, J = 7.9 Hz, 2H), 4.92 (d, J = 4.5 Hz, 1H), 5.76 (dd, J = 15.4, 7.9 Hz, 1H), 5.95 (dt, J = 14.9, 7.9 Hz, 1H), 6.28 (dd, J = 10.8, 14.9 Hz, 1H), 6.41 (dd, J = 10.8, 15.4 Hz, 1H); ^{13}C NMR δ u 77.5, 32.8, 30.2; d 133.7, 131.9, 131.1, 131.0, 100.2, 23.2, 22.1; IR (cm^{-1}) 1716, 1682, 1640; CI MS *m*/*z* (rel intensity) 261.1 (12, M + H), 181.1 (100), 115 (24), 95 (37); HRMS calcd for $C_{11}H_{18}O_2Br$ (M + H) 261.0490, obsd 261.0487.

Propargyl Alcohol 7. To a solution of bromoketal **6** (30.4 g, 116 mmol) in acetone (435 mL) was added propargyl alcohol (8.13 g, 145 mmol), anhydrous K_2CO_3 (32.2 g, 233 mmol), NaI (36.4 g, 242 mmol), CuI (24.9 g, 131 mmol), and heptane (24 mL). The mixture was stirred at rt for 45 h and then filtered. The solid was rinsed with MTBE (200 mL). The filtrate was concentrated, and the residue was chromatographed to give propargyl alcohol **7** as a colorless oil (20.3 g, 85.8 mmol, 74% yield): TLC R_f (MTBE/petroleum ether = 3:7) = 0.21; ^{1}H NMR δ 0.74 (s, 3H), 1.21 (s, 3H), 3.05 (m, 2H), 3.50 (d, J = 11.0 Hz, 2H), 3.65 (d, J = 11.0 Hz, 2H), 4.28 (m, 2H), 4.90 (d, J = 4.8 Hz, 1H), 5.65−5.76 (m, 2H), 6.23−6.30 (m, 1H), 6.40 (dd, J = 10.6, 15.4 Hz, 1H); ^{13}C NMR δ u 83.0, 80.7, 77.4, 51.5, 30.4, 22.2; d 132.8, 130.7, 130.0, 128.5, 100.7, 23.1, 22.1; IR (cm^{-1}) 3426, 2227, 1471; CI MS *m*/*z* (rel intensity) 237.1 (16, M + H), 115 (100); HRMS calcd for $C_{14}H_{21}O_3$ (M + H) 237.1491, obsd 237.1491.

Alkene 8. To a solution of propargyl acohol **7** (12.63 g, 53.4 mmol) in anhydrous diethyl ether (177 mL) was added carefully powdered $LiAlH_4$ (3.45 g, 90.9 mmol) over 15 min at 0 °C. After the addition, the suspension was stirred at rt for 6 h. The reaction mixture was cooled in an ice bath, and 3.5 mL of cold water was added dropwise over 5 min. After 30 min of vigorous stirring, 3.5 mL of aqueous NaOH (15% w/v) was added, and the mixture was stirred for an additional 30 min. Then 10.5 mL of water was added, and the mixture was stirred for another 30 min. The solid was filtered and rinsed with diethyl ether. The combined filtrate was concentrated, and the resulting residue was chromatographed to give alkene **8** as a colorless oil (7.80 g, 32.7 mmol, 61% yield): TLC R_f (MTBE/petroleum ether = 4:6) = 0.27; ^{1}H NMR δ 0.72 (s, 3H), 1.21 (s, 3H), 2.84 (t, J = 5.6 Hz, 2H), 3.50 (d, J = 10.6 Hz, 2H), 3.65 (d, J = 10.6 Hz, 2H), 4.10 (d, J = 3.9 Hz, 2H), 4.89 (d, J = 4.8 Hz, 1H), 5.60−5.80 (m, 4H), 6.03−6.09 (m, 1H), 6.39 (dd, J = 10.5, 15.6 Hz, 1H); ^{13}C NMR δ u 77.5, 63.8, 35.3, 30.4; d 134.4, 133.6, 130.5, 130.4, 127.5, 100.8, 23.2, 22.1; IR (cm^{-1}) 3416, 1470, 1091; CI MS *m*/*z* (rel intensity) 239.2 (30, M + H), 167.1 (47), 128.1(100), 115.0 (42); HRMS calcd for $C_{14}H_{23}O_3$ (M + H) 239.1647, obsd 239.1643.

Epoxide 9. To dry CH_2Cl_2 (20 mL) were added diethyl D-tartrate (1.17 g, 5.65 mmol) and titanium(IV) isopropoxide (1.60 g, 5.62 mmol) at −30 to −20 °C. The mixture was stirred for 30 min. A solution of alkene **8** (1.23 g, 5.18 mmol) in CH_2Cl_2 (29 mL) was added, and the mixture was stirred at −30 to −20 °C for 20 min. *tert*-Butyl hydroperoxide (3.4 mL, 4.0 M in CH_2Cl_2, 13.6 mmol) was then added dropwise over 10 min. The resulting mixture was stirred at −30 to −20 °C for 14.5 h. Aqueous L-(+) tartaric acid (10% w/w, 10.5 mL) was added. The mixture was stirred at −20 °C for 30 min, allowed to warm to rt, and stirred for 1 h. Aqueous NaOH (1 N, 28.5 mL) was added at 0 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was then partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **9** as a colorless oil (1.19 g, 4.69 mmol, 90% yield): TLC R_f (MTBE/petroleum ether = 1:1) = 0.19; ^{1}H NMR δ 0.74 (s, 3H), 1.21 (s, 3H), 1.72 (dd, J = 7.2, 5.6 Hz, 1H), 2.41 (m, 2H), 2.94 (dt, J = 4.2, 2.4 Hz, 1H), 3.04 (td, J = 5.3, 2.3 Hz, 1H), 3.51 (d, J = 10.8 Hz, 2H), 3.60−3.67 (m, 3H), 3.91 (ddd, J = 12.7, 4.5, 2.6 Hz, 1H), 4.90 (d, J = 4.8 Hz, 1H), 5.66 (dd, J = 15.6, 4.8 Hz, 1H), 5.75 (dt, J = 15.2, 7.2 Hz, 1H), 6.15 (dd, J = 10.6, 14.8 Hz, 1H), 6.39 (dd, J = 10.5, 15.6 Hz, 1H); ^{13}C NMR δ u 77.5, 61.6, 34.6, 30.4; d 133.3, 132.2, 130.5, 128.3, 100.7, 58.0, 54.9, 23.2, 22.1; IR (cm^{-1}) 3434, 1392, 1091; HRMS calcd for $C_{14}H_{23}O_4$ (M + H) 255.1596, obsd 255.1600; $[\alpha]_D$ = +21 (*c* 0.553, CH_2Cl_2).

Benzenesulfonate 10. To a solution of epoxide **9** (7.07 g, 27.8 mmol) in CH_2Cl_2 (160 mL) was added DMAP (0.456 g, 3.73 mmol). The solution was cooled to 0 °C, and Et_3N (9.82 g, 97.0 mmol) was added, followed by benzenesulfonyl chloride (12.2 g, 68.9 mmol) dropwise over 15 min. The mixture was allowed to warm to rt and stirred for 3.5 h. The reaction mixture was then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give benzenesulfonate **10** as a colorless oil (10.5 g, 26.6 mmol, 96% yield): TLC R_f (MTBE/petroleum ether = 1:1) = 0.39; ^{1}H NMR δ 0.74 (s, 3H), 1.21 (s, 3H), 2.87 (td, J = 2.1, 5.3 Hz, 1H), 2.96−2.99(m, 1H), 3.50 (d, J = 11.1 Hz, 2H), 3.65 (d, J = 11.1 Hz, 2H), 4.01 (dd, J = 5.8, 11.4 Hz, 1H), 4.22 (dd, J = 3.7, 11.4 Hz, 1H), 4.89 (d, J = 4.4 Hz, 1H), 5.62−5.69 (m, 2H), 6.11 (dd, J = 10.4, 14.9 Hz, 1H), 6.36 (dd, J = 10.4, 15.5 Hz, 1H), 7.55−7.60 (m, 2H), 7.65−7.70 (m, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR δ u 77.5, 70.2, 34.3, 30.4; d 134.2, 133.1, 132.6, 129.6, 129.5, 128.6, 128.1, 100.6, 55.7, 54.1, 23.2, 22.1; IR (cm^{-1}) 1716, 1682, 1640; HRMS calcd for $C_{20}H_{26}O_6NaS$ (M + Na) 417.1348, obsd 417.1343; $[\alpha]_D$ = +23 (*c* 0.435, CH_2Cl_2).

Diols 1 and 11. To benzenesulfonate **10** (7.92 g, 20.1 mmol), *t*-BuOH (100 mL), and H_2O (100 mL) cooled to 0 °C was added AD-mix-α (29.3 g). After 10 min, methanesulfonamide (1.93 g, 20.3 mmol) was added. The resulting mixture was stirred at 0 °C for 42 h. Solid $NaHSO_3$ (30.1 g, 289 mmol) was carefully added to the reaction mixture. It was stirred at rt for 1 h. The reaction mixture was then partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give diol **1** as a colorless oil (4.05 g, 9.45 mmol, 47% yield). Diol **11** was isolated as a side product (3.15 g, 7.35 mmol, 37% yield).

For diol **1**: TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.28; ^{1}H NMR δ 0.74 (s, 3H), 1.19 (s, 3H), 1.63−1.70 (m, 1H), 1.82 (dt, J = 14.6, 4.2 Hz, 1H), 2.81 (br, 1H), 3.01−3.07 (m, 3H), 3.49 (d, J = 10.9 Hz, 1H), 3.62−3.67 (m, 3H), 3.96−4.01 (m, 2H), 4.22 (dd, J = 3.4, 11.4 Hz, 1H), 4.87 (d, J = 4.3 Hz, 1H), 5.83 (dd, J = 4.3, 15.9 Hz, 1H), 5.92 (dd, J = 5.6, 15.8 Hz, 1H), 7.55−7.59 (m, 2H), 7.66−7.70 (m, 1H), 7.91−7.93 (m, 2H); ^{13}C NMR δ u 135.8, 77.4, 70.4, 34.5, 30.3; d 134.2, 133.6, 129.9, 129.5, 128.1, 100.2, 74.4, 72.0, 54.4, 54.3, 23.1, 22.0; IR (cm^{-1}) 3416, 1362, 1107; HRMS calcd for $C_{20}H_{28}O_8NaS$ (M + Na) 451.1403, obsd 451.1413; $[\alpha]_D$ = +16 (*c* 0.935, CH_2Cl_2).

For diol **11**: TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.49; ^{1}H NMR δ 0.75 (s, 3H), 1.19 (s, 3H), 2.32−2.36 (m, 2H), 2.66 (d, J = 6.1 Hz, 1H), 2.88−2.91 (m, 2H), 3.00−3.03 (m, 1H), 3.46−3.51 (m, 3H), 3.67 (d, J = 11.2 Hz, 2H), 4.00 (dd, J = 5.9, 11.4 Hz, 1H), 4.24 (dd, J = 3.7, 11.4 Hz, 1H), 4.41 (br, 1H), 4.58 (d, J = 3.8 Hz, 1H), 5.64−5.77 (m, 2H), 7.55−7.60 (m, 2H), 7.66−7.70 (m, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR δ u 135.8, 77.3, 70.3, 34.0, 30.7; d 134.2, 132.6, 129.5, 128.1, 126.3, 101.5, 73.9, 70.9, 55.7, 54.1, 23.1, 21.8; IR (cm^{-1}) 3472, 1449, 1188; HRMS calcd for $C_{20}H_{28}O_8NaS$ (M + Na) 451.1403, obsd 451.1413; $[\alpha]_D$ = +15 (*c* 0.375, CH_2Cl_2).

Diol 11 to Alcohol 7. A mixture of diol **11** (123 mg, 0.287 mmol), pyridinium *p*-toluenesulfonate (9.2 mg, 0.037 mmol), and trimethyl orthoformate (328 mg, 3.09 mmol) in THF (3 mL) was stirred at rt for 18 h. The solvent was evaporated, and the residue was chromatographed to give the orthoformate as a colorless oil (90.6 mg, 0.193 mmol, 67%): TLC R_f (MTBE/petroleum ether = 4:6) = 0.21. This was a mixture of diastereomers.

A mixture of the orthoformate (21.1 mg, 0.0448 mmol), $NaHCO_3$ (127 mg 1.51 mmol), and acetic anhydride (2 mL) was stirred at reflux for 1.8 h. The volatiles were evaporated, and the residue was partitioned between CH_2Cl_2 and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the diene acetate as a colorless oil (11.9 mg, 0.0402 mmol, 89% yield): TLC R_f (MTBE/petroleum ether = 1:1) = 0.61; ^{1}H NMR δ 0.75 (s, 3H), 1.21 (s, 3H), 2.09 (s, 3H), 2.41 (t, J = 6.2 Hz, 2H), 2.94 (td, J = 5.2, 2.0 Hz, 1H), 2.99 (m, 1H), 3.51 (d, J = 11.2 Hz, 2H), 3.66 (d, J = 11.2 Hz, 2H), 3.93 (dd, J = 12.2, 6.2 Hz, 1H), 4.36 (dd, J = 12.2, 3.0 Hz, 1H), 4.90 (d, J = 4.8 Hz, 1H), 5.66 (dd, J = 15.6, 4.8 Hz, 1H), 5.73 (dt, J = 15.2, 7.2 Hz, 1H), 6.15 (dd, J = 10.6, 15.2 Hz, 1H), 6.39 (dd, J = 10.6, 15.6 Hz, 1H); ^{13}C NMR δ u 171.0, 77.5, 64.6, 34.5, 30.4; d 133.2, 132.4, 130.1, 128.4, 100.7, 55.5, 54.8, 23.2, 22.1.

To a solution of diene acetate (9.6 mg, 0.032 mmol) in methanol (1 mL) was added finely powdered K_2CO_3 (35.5 mg, 0.257 mmol). The mixture was stirred at rt for 30 min. The volatiles were removed, and the residue was partitioned between CH_2Cl_2 and, sequentially, cold 5% aqueous HCl and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alcohol **7** as a colorless oil (6.0 mg, 0.024 mmol, 73% yield).

Epoxide 2. To a solution of diol **1** (1.61 g, 3.77 mmol) in CH_3OH (18 mL) was added finely powdered K_2CO_3 (1.06 g, 7.68 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **2** as a colorless solid (0.731 g, 2.70 mmol, 72% yield): mp 94−95 °C; TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.46; ^{1}H NMR δ 0.74 (s, 3H), 1.21 (s, 3H), 1.82 (ddd, J = 1.2, 3.6, 14.0 Hz, 1H), 2.28 (ddd, J = 5.2, 9.2, 14.0 Hz, 1H), 2.65 (dd, J = 3.0, 4.6 Hz, 1H), 2.68 (d, J = 6.8 Hz, 1H), 2.86 (t, J = 4.4 Hz), 3.26 (td, J = 4.0, 2.8 Hz, 1H), 3.49 (d, J = 11.2 Hz, 2H), 3.65 (d, J = 11.2 Hz, 2H), 4.16 (dt, J = 9.2, 3.6 Hz, 1H), 4.20−4.22 (m, 1H), 4.29 (ddd, J = 0.8, 3.2, 6.0 Hz, 1H), 4.92 (d, J = 4.4 Hz, 1H), 5.93 (ddd, J = 1.2, 4.8, 16.0 Hz, 1H), 6.08 (ddd, J = 1.2, 6.0, 16.0 Hz, 1H); ^{13}C NMR δ u 77.4, 46.0, 35.9, 30.3; d 130.9, 130.0, 100.4, 83.9, 77.9, 73.1, 53.8, 23.2, 22.1; IR (cm^{-1}) 3416, 1362, 1107; HRMS calcd for $C_{14}H_{22}O_5$ 270.1467, obsd 270.1472; $[\alpha]_D$ = +29 (*c* 0.593, CH_2Cl_2).

Epoxide 2a. To a solution of epoxide **2** (49.5 mg, 0.183 mmol), triphenylphosphine (254 mg, 0.967 mmol), and 4-nitrobenzoic acid (147 mg, 0.878 mmol) in THF (3.5 mL) at 0 °C was added diisopropyl azodicarboxylate (298 mg, 1.47 mmol) over 5 min. The mixture was stirred at rt for 11 h. The volatiles were removed, and the residue was chromatographed to give the *p*-nitrobenzoate as a colorless oil (70.7 mg, 0.169 mmol, 92% yield): TLC R_f (MTBE/petroleum ether = 4:6) = 0.32; ^{1}H NMR δ 0.75 (s, 3H), 1.22 (s, 3H), 3.51 (d, J = 10.6 Hz, 2H), 2.18−2.21 (m, 2H), 2.66 (dd, J = 2.6, 4.9 Hz, 1H), 2.88 (dd, J = 4.2, 4.7 Hz, 1H), 3.17−3.20 (m, 1H), 3.51 (d, J = 11.1 Hz, 2H), 3.65 (d, J = 11.1 Hz, 2H), 4.12−4.19 (m, 1H), 4.64−4.65 (m, 1H), 4.92 (d, J = 4.2 Hz, 1H), 5.34−5.36 (m, 1H), 5.97 (ddd, J = 1.4, 4.2, 15.7 Hz, 1H), 6.07 (ddd, J = 0.8, 4.9, 15.7 Hz, 1H), 8.19 (d, J = 9.0 Hz, 2H), 8.30 (d, J = 9.04 Hz, 1H); ^{13}C NMR δ u 164.2, 150.9, 135.2, 77.5, 45.8, 33.5, 30.4; d 131.6, 131.0, 129.4, 123.8, 100.1, 83.8, 80.3, 79.6, 52.7, 23.2, 22.1; IR (cm^{-1}) 1724, 1529, 1274.

To a solution of *p*-nitrobenzoate (11.8 mg, 0.0281 mmol) in CH_3OH (0.5 mL) was added finely powdered K_2CO_3 (250 mg, 1.81 mmol). The mixture was stirred at rt for 30 min. The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **2a** as a colorless oil (7.2 mg, 0.027 mmol, 95% yield): TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.38; ^{1}H NMR δ 0.74 (s, 3H), 1.21 (s, 3H), 1.92−2.04 (m, 2H), 2.61 (dd, J = 2.4, 4.8 Hz, 1H), 2.82 (t, J = 4.4 Hz, 1H), 3.08−3.11 (m, 1H), 3.49 (d, J = 10.8 Hz, 2H), 3.65 (d, J = 10.8 Hz, 2H), 4.10−4.15 (m, 1H), 4.21−4.24 (m, 1H), 4.29 (dd, J = 3.2, 5.4 Hz, 1H), 4.88 (d, J = 4.0 Hz, 1H), 5.86 (dd, J = 4.0, 16.0 Hz, 1H), 5.93 (dd, J = 5.6, 16.0 Hz, 1H); ^{13}C NMR δ u 77.4, 45.7, 35.8, 30.5; d 132.8, 129.0, 100.2, 86.3, 78.6, 76.3, 53.1, 23.2, 22.1; IR (cm^{-1}) 3435, 1393, 1095; HRMS calcd for $C_{14}H_{22}O_5$ 270.1467, obsd 270.1463; $[\alpha]_D$ = −35 (*c* 0.520, CH_2Cl_2).

Alkyne 12. To a solution of alcohol **2** (0.103 g, 0.381 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C were added TBDMSCl (0.126 g, 0.837 mmol) and imidazole (0.0625 g, 0.918 mmol). The mixture was stirred at rt overnight (12 h). The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the silyl ether as a colorless oil (0.141 g, 0.367 mmol, 97% yield): TLC R_f (MTBE/PE = 1:1) = 0.55; ^{1}H NMR δ 0.06 (s, 3H), 0.07 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9 H), 1.18 (s, 3H), 2.05 (ddd, J = 13.4, 3.4, 1.8 Hz, 1H), 2.31 (m, 1H), 2.68 (dd, J = 5.1, 2.6 Hz, 1H), 2.80−2.82 (m, 1H), 3.13−3.17 (m, 1H), 3.48 (d, J = 11.0 Hz, 2H), 3.63 (d, J = 11.0 Hz, 2H), 3.70−3.75 (m, 1H), 4.23−4.25 (m, 1H), 4.28−4.30 (m, 1H), 4.87 (d, J = 3.7 Hz, 1H), 5.78 (dd, J = 4.1, 15.8 Hz, 1H), 6.05 (ddd, J = 0.9, 7.4, 15.8 Hz, 1H); ^{13}C NMR δ u 77.4, 77.3, 47.3, 39.4, 30.4, 18.3; d 131.2, 130.2, 100.2, 84.2, 79.3, 74.6, 54.2, 26.0, 23.2, 22.1, −4.6, −4.8; IR (cm^{-1}) 1392, 1138, 1060; HRMS calcd for $C_{20}H_{36}O_5NaSi$ (M + Na) 407.2230, obsd 407.2243; $[\alpha]_D$ = +32 (*c* 0.523, CH_2Cl_2).

To a stirred solution of 5-hexynenitrile (0.301 g, 3.23 mmol) in THF (2.5 mL) was added dropwise *n*-BuLi (1.1 mL, 2.5 M in hexanes, 2.75 mmol) at −75 °C. The solution was stirred at −75 to −70 °C for 1 h. A solution of the silyl ether (0.228 g, 0.593 mmol) in THF (2.5 mL) was added, followed by the addition of $BF_3{\cdot}Et_2O$ (0.281 g, 1.98 mmol). After the addition, the mixture was stirred at −78 to −75 °C for 50 min. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL). The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alkyne **12** as a colorless oil (0.254 g, 0.532 mmol, 90% yield): TLC R_f (MTBE/PE = 1:1) = 0.25; ^{1}H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 1.19 (s, 3H), 1.80−1.87 (m, 2H), 2.02 (ddd, J = 13.7, 4.0, 1.2 Hz, 1H), 2.17−2.36 (m, 4H), 2.41−2.50 (m, 3H), 3.05 (d, J = 2.7 Hz, 1H), 3.48 (d,

J = 11.1 Hz, 2H), 3.63 (d, J = 11.1 Hz, 2H), 3.92 (m, 1H), 4.15 (dd, J = 2.8, 7.3 Hz, 1H), 4.22 (dd, J = 3.4, 11.4 Hz, 1H), 4.87 (dd, J = 4.0, 0.7 Hz, 1H), 5.79 (ddd, J = 15.9, 4.0, 0.7 Hz, 1H), 6.02 (ddd, J = 15.9, 7.3, 1.1 Hz, 1H); ^{13}C NMR δ u 119.5, 79.6, 78.4, 77.4, 77.3, 35.4, 30.4, 24.9, 24.2, 18.4, 18.1, 16.3; d 130.6, 130.4, 100.1, 83.6, 80.3, 74.5, 71.3, 25.9, 23.1, 22.1, −4.7, −4.8; IR (cm^{-1}) 3470, 2248, 1058; HRMS calcd for $C_{26}H_{43}NO_5NaSi$ (M + Na) 500.2808, obsd 500.2786; $[\alpha]_D$ = +17 (*c* 0.438, CH_2Cl_2).

Aldehyde 13. To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (16.5 mg, 0.0663 mmol) in ethanol (0.6 mL) was added $NaBH_4$ solution in ethanol (1 N, 65 μL, 0.065 mmol). The black mixture was evacuated and backfilled with H_2 three times. Ethylenediamine (4.5 μL, 0.0673 mmol) was added, followed by alkyne **12** (57.0 mg, 0.119 mmol) in ethanol (0.6 mL). The flask was evacuated and backfilled with H_2. The reaction mixture was stirred at rt under H_2 for 1.5 h. The black suspension was diluted with MTBE (5 mL), and the mixture was filtered through a short column packed with flash silica gel (7.0 g). The column was eluted with MTBE (50 mL). The solvent was removed to give the alkene as a colorless oil (52.0 mg, 0.11 mmol, 91% yield): TLC R_f (MTBE/PE = 1:1) = 0.30; ^{1}H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 1.18 (s, 3H), 1.70−1.77 (m, 2H), 2.02 (ddd, J = 13.6, 4.3, 1.2 Hz, 1H), 2.12−2.25 (m, 5H), 2.41−2.50 (m, 3H), 2.39 (t, J = 7.1 Hz, 2H), 2.96 (d, J = 1.6 Hz, 1H), 3.48 (d, J = 11.1 Hz, 2H), 3.63 (d, J = 11.1 Hz, 2H), 3.85−3.88 (m, 1H), 4.04−4.07 (m, 1H), 4.11 (dd, J = 2.8, 11.3 Hz, 1H), 4.24−4.26 (m, 1H), 4.87 (dd, J = 4.0, 0.6 Hz, 1H), 5.42−5.46 (m, 1H), 5.54−5.58 (m, 1H), 5.79 (ddd, J = 16.0, 4.1, 0.6 Hz, 1H), 6.03 (ddd, J = 15.9, 7.3, 1.0 Hz, 1H); ^{13}C NMR δ u 120.0, 77.4, 77.3, 35.1, 32.1, 30.4, 26.3, 25.4, 18.4, 16.6; d 130.6, 130.5, 129.4, 128.1, 100.1, 83.4, 81.0, 74.6, 72.1, 25.9, 23.1, 22.1, −4.7, −4.8; IR (cm^{-1}) 3479, 2247, 1059; HRMS calcd for $C_{26}H_{45}NO_5NaSi$ (M + Na) 502.2965, obsd 502.2966; $[\alpha]_D$ = +17 (*c* 0.519, CH_2Cl_2).

To a solution of the alkene (28.2 mg, 0.0588 mmol) in acetone (1.0 mL) was added dropwise aqueous HCl (1 N, 1.0 mL, 1.0 mmol) over 1 min. The mixture was stirred at rt for 2 h. The solvent was evaporated, and the residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give aldehyde **13** as a colorless oil (11.0 mg, 0.0394 mmol, 67% yield): TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.31; ^{1}H NMR δ 1.71−1.78 (m, 2H), 2.02 (dd, J = 14.2, 2.8 Hz, 1H), 2.16−2.26 (m, 4H), 2.31−2.39 (m, 3H), 3.75 (br, 1H), 3.91 (br, 1H), 4.20 (dt, J = 9.9, 2.4 Hz, 1H), 4.31 (m, 1H), 4.47−4.51 (m, 2H), 5.47−5.55 (m, 2H), 6.40 (ddd, J = 15.7, 8.1, 1.6 Hz, 1H), 6.93 (dd, J = 15.7, 4.6 Hz, 1H), 9.57 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ u 34.8, 32.1, 26.2, 25.1, 16.7; d 194.0, 152.8, 133.2, 130.7, 127.1, 83.1, 81.0, 72.9, 72.1; IR (cm^{-1}) 3397, 2247, 1688; HRMS calcd for $C_{15}H_{22}NO_4$ (M + H) 280.1549, obsd 280.1544; $[\alpha]_D$ = +15 (*c* 0.415, CH_2Cl_2).

Alcohols 14a and 14b. To a solution of aldehyde **13** (20.7 mg, 0.0741 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C were added TBDPSCl (209.5 mg, 0.762 mmol) and imidazole (24.2 mg, 0.355 mmol). The mixture was stirred at rt for 20 h. The reaction mixture was then partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the TBDPS-protected aldehyde as a colorless oil (45.5 mg, 0.0602 mmol, 81% yield): TLC R_f (MTBE/PE = 15:85) = 0.29; ^{1}H NMR δ 1.01 (s, 9H), 1.05 (s, 9H), 1.53−1.60 (m, 2H), 1.75−1.83 (m, 1H), 1.89−1.94 (m, 2H), 2.03−2.12 (m, 2H), 2.15 (t, J = 7.4 Hz, 2H), 2.29−2.36 (m, 1H), 3.69 (dt, J = 9.7 Hz, 6.0 Hz, 1H), 3.87−3.91 (m, 1H), 4.22−4.25 (m, 1H), 4.48−4.52 (q, J = 6.6 Hz, 1H), 5.25−5.28 (m, 1H), 5.43−5.49 (m, 1H), 6.09 (ddd, J = 15.7 Hz, 8.0 Hz, 1.4 Hz, 1H), 6.56 (dd, J = 15.7 Hz, 5.3 Hz, 1H), 7.34−7.40 (m, 8H), 7.41−7.47 (m, 4H), 7.54−7.59 (m, 4H), 7.65−7.73 (m, 4H), 9.36 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ u 134.2, 133.7, 133.4, 133.4, 119.9, 37.8, 32.2, 26.3, 25.4, 19.7, 19.3, 16.6; d 193.6, 154.5, 136.2, 136.2, 136.1, 136.0, 135.9, 132.8, 130.3, 130.2, 130.0, 130.0, 129.3, 128.1, 127.9, 127.8, 127.8, 127.1, 80.8, 79.7, 74.9, 74.7, 27.2, 27.1; IR (cm^{-1}) 2247, 1694, 1112; HRMS calcd for $C_{47}H_{57}NO_4NaSi_2$ (M + Na) 778.3724, obsd 778.3688; $[\alpha]_D$ = −46 (*c* 0.434, CH_2Cl_2).

To a stirred solution of the TBDPS-protected aldehyde (74.0 mg, 0.0979 mmol) in THF (0.5 mL) at 0 °C was added pentylmagnesium bromide in THF (1.25 M, 150 μL, 0.188 mmol). The mixture was stirred at 0 °C for 30 min. The reaction mixture was partitioned between saturated aqueous NH_4Cl and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was analyzed by HPLC. Column: Partisil 10; detector: UV 254 nm; flow rate: 1 mL/min; mobile phase: hexanes/ethyl acetate 85:15; retention times: 19.1 min for **14a**, 21.6 min for **14b**; ratio: **14a**/**14b** = 1:1.1. The residue was chromatographed to give alcohol **14a** as a colorless oil (29.5 mg, 0.0356 mmol, 36% yield). This was followed by alcohol **14b** (26.9 mg, 0.0325 mmol, 33% yield) as a colorless oil.

For alcohol **14a**: TLC R_f (Et_2O/CH_2Cl_2/petroleum ether = 1:3:6) = 0.44; ^{1}H NMR δ 0.88 (t, J = 6.8 Hz, 3H), 1.03 (s, 9H), 1.06 (s, 9H), 1.21−1.43 (m, 8H), 1.51−1.58 (m, 2H), 1.82−1.89 (m, 3H), 2.00−2.09 (m, 2H), 2.13 (t, J = 7.4 Hz, 2H), 2.23−2.30 (m, 1H), 3.58−3.63 (m, 1H), 3.87−3.99 (m, 3H), 4.41−4.46 (m, 1H), 5.18−5.25 (m, 1H), 5.37−5.44 (m, 1H), 5.57 (dd, J = 15.6, 6.4 Hz, 1H), 5.70 (dd, J = 15.6, 7.1 Hz, 1H), 7.33−7.37 (m, 8H), 7.41−7.45 (m, 4H), 7.58−7.62 (m, 4H), 7.67−7.73 (m, 4H); ^{13}C NMR δ u 134.5, 134.1, 133.9, 120.0, 38.1, 36.9, 32.3, 32.0, 26.3, 25.4, 25.3, 22.8, 19.7, 19.4, 16.5; d 136.7, 136.4, 136.2, 136.1, 136.0, 130.0, 129.9, 129.0, 128.0, 127.8, 127.8, 127.7, 127.7, 127.4, 82.7, 79.3, 75.0, 74.7, 72.6, 27.3, 27.1, 14.3; IR (cm^{-1}) 3483, 2248, 1112; HRMS calcd for $C_{52}H_{69}NO_4NaSi_2$ (M + Na) 850.4663, obsd 850.4677; $[\alpha]_D$ = −19 (*c* 0.670, CH_2Cl_2).

For alcohol **14b**: TLC R_f (Et_2O/CH_2Cl_2/petroleum ether = 1:3:6) = 0.35; ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 1.02 (s, 9H), 1.05 (s, 9H), 1.21−1.43 (m, 9H), 1.47−1.56 (m, 2H), 1.76−1.81 (m, 1H), 1.83−1.90 (m, 2H), 1.95−2.11 (m, 2H), 2.13 (t, J = 7.3 Hz, 2H), 2.20−2.27 (m, 1H), 3.58−3.63 (m, 1H), 3.86−3.90 (m, 1H), 3.94−4.00 (m, 2H), 4.39−4.44 (m, 1H), 5.18−5.25 (m, 1H), 5.37−5.44 (m, 1H), 5.60−5.73 (m, 2H), 7.33−7.37 (m, 8H), 7.40−7.45 (m, 4H), 7.58−7.62 (m, 4H), 7.66−7.72 (m, 4H); ^{13}C NMR δ u 134.4, 134.0, 133.9, 133.8, 120.0, 38.1, 37.0, 32.3, 32.0, 26.3, 25.3, 25.3, 22.8, 19.7, 19.4, 16.6; d 136.9, 136.3, 136.2, 136.1, 136.0, 130.0, 129.9, 129.9, 129.8, 129.0, 128.1, 127.8, 127.8, 127.7, 127.7, 127.4, 82.8, 79.3, 74.8, 72.6, 27.3, 27.1, 14.3; IR (cm^{-1}) 3492, 2248, 1112; HRMS calcd for $C_{52}H_{69}NO_4NaSi_2$ (M + Na) 850.4663, obsd 850.4641; $[\alpha]_D$ = −20 (*c* 0.730, CH_2Cl_2).

Oxidation and Chiral Reduction of 14a and 14b. To a stirred mixture of **14a** and **14b** (11.1 mg, 0.0134 mmol) in CH_2Cl_2 was added Dess−Martin periodinane (18.9 mg, 0.0446 mmol). The reaction mixture was stirred for 20 min and was then concentrated. The residue was chromatographed to give the enone as an oil (10.3 mg, 0.0125 mmol, 93%): TLC R_f (MTBE/petroleum ether = 1:2.7) = 0.59; ^{1}H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.01 (s, 9H), 1.06 (s, 9H), 1.17−1.68 (m, 8H), 1.74−1.82 (m, 1H), 1.86−1.92 (m, 2H), 1.99−2.10 (m, 2H), 2.14 (t, J = 7.4 Hz, 2H), 2.27−2.35 (m, 1H), 2.42 (t, J = 7.5 Hz, 2H), 3.65 (dt, J = 9.8, 5.9 Hz, 1H), 3.88−3.92 (m, 1H), 4.14 (td, J = 6.1, 1.2 Hz, 1H), 4.51 (q, J = 6.5 Hz, 1H), 5.21−5.27 (m, 1H), 5.40−5.46 (m, 1H), 6.09 (dd, J = 16.1, 1.3 Hz, 1H), 6.70 (dd, J = 16.1, 5.8 Hz, 1H), 7.33−7.38 (m, 8H), 7.41−7.46 (m, 4H), 7.56−7.62 (m, 4H), 7.66−7.72 (m, 4H); ^{13}C NMR δ u 200.6, 134.3, 133.8, 133.6, 133.4, 119.9, 39.8, 37.9, 32.3, 31.7, 26.3, 25.4, 23.9, 22.7, 19.7, 19.3, 16.5; d 143.0, 136.3, 136.2, 136.0, 135.9, 131.3, 130.1, 130.1, 129.9, 129.2, 127.9, 127.8, 127.8, 127.1, 81.4, 79.7, 75.0, 74.6, 27.3, 27.1, 14.2; IR (cm^{-1}) 2246, 1678, 1428; $[\alpha]_D$ = −32 (*c* 0.595, CH_2Cl_2).

To a solution of (−)-DIP-Cl (46 mg, 0.14 mmol) in THF (0.4 mL) was added a solution of the enone (11 mg, 0.014 mmol) in THF (0.5 mL) at −78 °C. The reaction mixture was stirred at rt for 8 h. The mixture was concentrated, and the residue

was partitioned between CH_2Cl_2 and, sequentially, 15% aqueous NaOH and saturated aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was analyzed by HPLC, as above: ratio: **14a**/**14b** = 3.8:1.

Isofuran 3a. To a stirred solution of alcohol **14a** (12.3 mg, 0.0149 mmol) in THF (0.5 mL) was added tetrabutylammonium fluoride (0.1 mL, 1 M in THF, 0.1 mmol). After 15 min of stirring, the mixture was partitioned between water and CH_2Cl_2. The combined organic extracts were concentrated. To the residue were added aqueous NaOH (15%, 0.5 mL) and ethanol (0.2 mL). The mixture was sealed in a vial and heated at 105 °C for 11 h. The mixture was cooled in an ice bath and acidified with NaH_2PO_4 buffer (0.5 M, 2 mL) and acetic acid (2 mL). The mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give isofuran **3a** as a colorless oil (5.4 mg, 0.0146 mmol, 98% yield): TLC R_f (Et_2O/0.5 M aqueous NaH_2PO_4/HOAc = 90:9:1, ether layer) = 0.25; ^{1}H NMR δ 0.81−0.90 (m, 3H), 1.25−1.72 (m, 14H), 2.12−2.37 (m, 4H), 3.88 (m, 1H), 4.11 (m, 4H), 5.02 (br, 3H), 5.47 (m, 2H), 5.82 (m, 2H); IR (cm^{-1}) 3382, 1711, 1048; HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 393.2253, obsd 393.2239; $[\alpha]_D$ = +28 (*c* 0.325, CH_2Cl_2).

Methyl Ester 15a. To a solution of isofuran **3a** (6.8 mg, 0.018 mmol) in CH_3OH/benzene (1:4, 0.5 mL) was added trimethylsilyl diazomethane (2.0 M in hexanes, 30 μL, 0.060 mmol). The mixture was stirred at rt for 1 h. The sovent was removed, and the residue was chromatographed to give methyl ester **15a** as a colorless oil (7.1 mg, 0.018 mmol, 100% yield): TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.39; ^{1}H NMR δ 0.86−0.90 (m, 3H), 1.25−1.32 (m, 3H), 1.48−1.60 (m, 2H), 1.65−1.77 (m, 3H), 2.02−2.29 (m, 7H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.47 (br, 1H), 3.31 (br, 1H), 3.67 (s, 3H), 3.85−3.90 (m, 1H), 4.05−4.20 (m, 4H), 5.41−5.54 (m, 2H), 5.80−5.89 (m, 2H); ^{13}C NMR δ u 174.3, 37.1, 34.5, 33.6, 32.1, 32.0, 29.9, 26.9, 25.3, 24.9, 22.8; d 137.9, 132.1, 126.1, 126.0, 84.2, 80.5, 73.1, 72.3, 72.2, 51.8, 14.2; IR (cm^{-1}) 3390, 1738, 1049; HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 407.2410, obsd 407.2415; $[\alpha]_D$ = +30 (*c* 0.285, CH_2Cl_2).

Isofuran 3b. The reaction was performed with the alcohol **14b** (8.3 mg, 0.014 mmol) in the same manner as described for the preparation of isofuran **3a** to give isofuran **3b** (4.7 mg, 0.013 mmol, 89% yield) as a colorless oil: TLC R_f (Et_2O/0.5 M aqueous NaH_2PO_4/HOAc = 90:9:1, ether layer) = 0.25; ^{1}H NMR δ 0.81−0.89 (m, 3H), 1.25−1.72 (m, 14H), 2.13−2.37 (m, 3H), 3.88 (m, 1H), 4.08−4.21 (m, 4H), 5.02 (br, 3H), 5.47 (br, 2H), 5.75−5.86 (m, 2H); IR (cm^{-1}) 3390, 1713, 1047; HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 393.2253, obsd 393.2235; $[\alpha]_D$ = +14 (*c* 0.425, CH_2Cl_2).

Methyl Ester 15b. The reaction was performed with the isofuran **3b** (8.5 mg, 0.023 mmol) in the same manner as described for the preparation of isofuran **15a** to give methy ester of isofuran **15b** (7.3 mg, 0.019 mmol, 83% yield) as a colorless oil: TLC R_f (acetone/CH_2Cl_2 = 2:8) = 0.38; ^{1}H NMR δ 0.83−0.89 (m, 3H), 1.25−1.32 (m, 3H), 1.35−1.60 (m, 3H), 1.67−1.74 (m, 2H), 1.99−2.16 (m, 7H), 2.21−2.29 (m, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 3.67 (s, 3H), 3.86−3.91 (m, 1H), 4.04 (q, *J* = 6.8 Hz, 1H), 4.11−4.21 (m, 3H), 4.50 (br, 2H), 5.44−5.51 (m, 2H), 5.72 (dd, *J* = 15.5 Hz, 5.3 Hz, 1H), 5.84 (dd, *J* = 15.5 Hz, 7.3 Hz, 1H); ^{13}C NMR δ u 174.3, 36.7, 34.2, 33.6, 32.4, 31.9, 29.9, 26.9, 25.5, 24.9, 22.8; d 136.5, 131.3, 126.7, 126.4, 83.2, 80.4, 73.1, 72.3, 71.9, 51.8, 14.3; IR (cm^{-1}) 3360, 1738, 1048; HRMS calcd for $C_{20}H_{34}O_6Na$ (M + Na) 407.2410, obsd 407.2394; $[\alpha]_D$ = +24 (*c* 0.365, CH_2Cl_2).

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Supporting Information Available: Experimental procedures and spectra for all new compounds and X-ray data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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