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A Potential Route to Neuroprostanes and Isoprostanes: Preparation of the Four Enantiomerically Pure Diastereomers of 13-F_{4t}-NeuroP

Douglass F. Taber,*,† P. Ganapati Reddy,† and Kyle O. Arneson‡

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, and Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

taberdf@udel.edu

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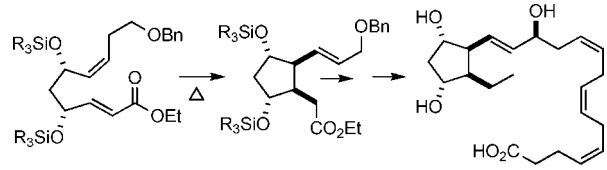
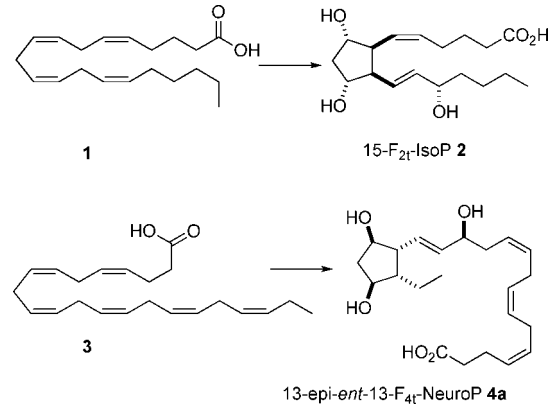


We report a potential synthetic route to the isoprostanes and the neuroprostanes that could allow ready access to each of the enantiomerically pure diastereomers of the several regioisomers of these important human metabolites. The key transformation in the synthesis is a highly diastereoselective thermal intramolecular ene reaction. A critical observation is that the four enantiomerically pure diastereomers of an intermediate acetylenic ester are easily separated from one another. Each of these four has been carried on to a different enantiomerically pure diastereomer of 13-F_{4t}-neuroprostane.

Introduction

Isoprostanes (Scheme 1) are produced in vivo by nonenzymatic free radical-mediated oxidation of arachidonic acid **1**. First identified in human plasma samples in microgram quantities as mixtures, the isoprostanes (e.g., **2**) were shown to have structures similar to the prostaglandins, but with *cis*-dialkyl stereochemistry on the cyclopentane rings.[1] The neuroprostanes were later identified.[2] They are structurally similar to the isoprostanes, but are derived from *cis*-4,7,10,13,16,19-docosahexaenoic acid (DHA, **3**). The isoprostanes, prepared by total synthesis,[3] have been shown to have a wide range of biological activities.[4] The neuroprostanes are only available from natural sources in microgram quantities as mixtures, so to explore the biological activity, it will be necessary to also prepare them by total synthesis.[5] Even though the in vivo nonenzymatic synthesis leads to racemic products, the individual enantiomers of each

SCHEME 1



† University of Delaware.
‡ Vanderbilt University School of Medicine.

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(3) For leading references to synthesis of the isoprostanes, see: (a) Taber, D. F.; Hoerner, R. S. *J. Org. Chem.* **1992**, *57*, 441. (b) Hwang, S. W.; Adiyaman, M.; Khanapure, S. P.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829. (c) Pudukulathan, Z.; Manna, S.; Hwang, S. W.; Khanapure, S. P.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *J. Am. Chem. Soc.* **1998**, *120*, 11953. (d) Taber, D. F.; Kanai, K. *Tetrahedron* **1998**, *54*, 11767. (e) Taber, D. F.; Kanai, K.; Pina, R. *J. Am. Chem. Soc.* **1999**, *121*, 7773. (f) Taber, D. F.; Jiang, Q. *J. Org. Chem.* **2001**, *66*, 1876. (g) Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998. (h) Taber, D. F.; Xu, M.; Hartnett, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 13121. (i) Durand, T.; Guy, A.; Vidal, J.-F.; Rossi, J.-C. *J. Org. Chem.* **2002**, *67*, 3615. (j) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2002**, *43*, 9249. (k) Durand, T.; Guy, A.; Henry, O.; Roland, A.; Bernad, S.; El Fngour, S.; Vidal, J.-F.; Rossi, J.-C. *Chem. Phys. Lipids* **2004**, *128*, 15. (l) Schmidt, A.; Boland, W. *J. Org. Chem.* **2007**, *72*, 1699.

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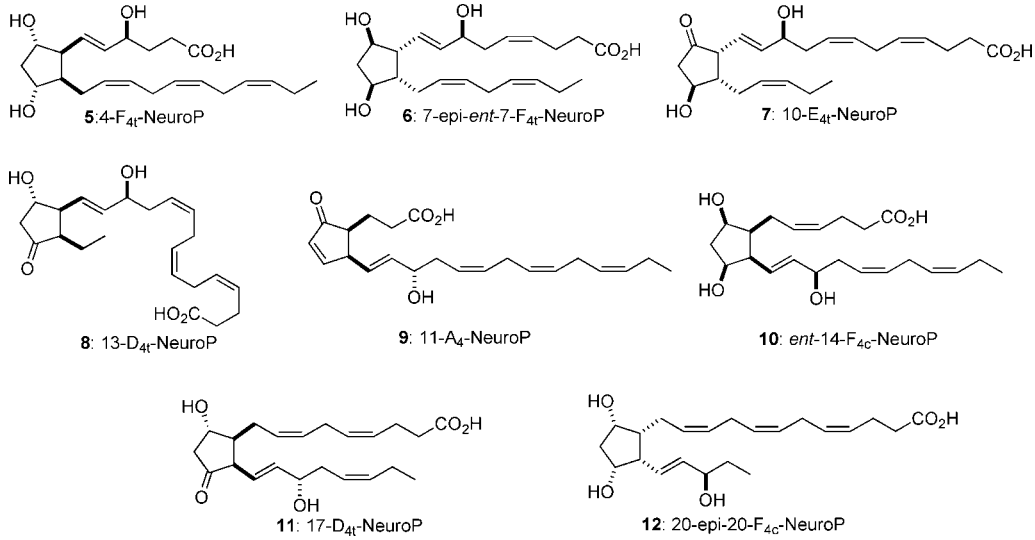


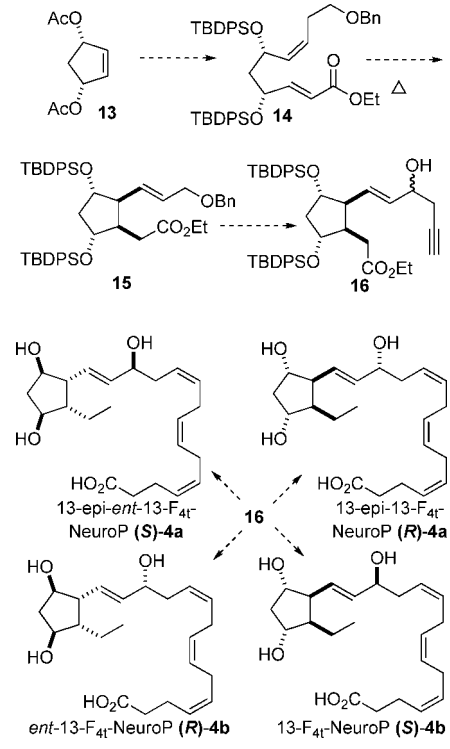
FIGURE 1. The eight families of the neuroprostanes.

of the neuroprostanes are expected[4] to interact differently with biological receptors. The only previous synthetic routes to neuroprostanes have each begun with enantiomerically pure starting materials.

While there are only four regioisomeric families of the isoprostanes,[1] there are eight regioisomeric families of the neuroprostanes (Figure 1).[2] It was therefore expedient to develop a unified synthetic approach that would allow the preparation of *any* of the neuroprostanes (or isoprostanes) from a single advanced intermediate. We report the development of such a stereodivergent synthetic route to the isoprostanes[3] and the neuroprostanes, culminating in the preparation of the four enantiomerically pure diastereomers of 13-F_{4t}-NeuroP **4a**.

Given the results of Sarkar,[6] it seemed likely that the thermal intramolecular ene reaction of **14** would proceed with high diastereocontrol to give **15**, having the requisite *cis*-dialkyl substitution on the cyclopentane ring. The key question was, could the racemic diastereomers of **16** be separated? If they could, then individual resolution of each of them would lead to the four enantiomerically pure diastereomers of **16**, each a precursor to one of the four enantiomerically pure neuroprostanes or isoprostanes (Scheme 2).

SCHEME 2



Results and Discussion

Preparation of the Ene Substrate 14 and the Ene Cyclization. The preparation (Scheme 3) of the ene substrate **14** started with the diacetate **13**, readily available by singlet oxygenation of cyclopentadiene.[7] Ozonolysis[8] followed by Wittig homologation of the intermediate aldehyde, deprotection, and silylation delivered the diene **18**. Monoepoxidation gave **19**, which was carried on by oxidative cleavage and homologation to **14**.

The Alder ene reaction of substrates such as **14** can be carried out either with Lewis acid catalysis[9] or thermally.[6,10] While the Lewis acid protocol can be carried out at lower temperatures, it is reported[6b–d,9] to lead to products having the alkyl substituents both cis and trans on the cyclopentane ring. In contrast, thermal ene cyclizations had been found[6] to give cleanly the cis product. We were pleased to observe (Scheme 3) that the thermal cyclization of **14** proceeded readily, delivering the

(4) For an overview of the physiological activity of the isoprostanes, see: (a) Cracowski, J.-L.; Durand, T. *Fundam. Clin. Pharmacol.* **2006**, *20*, 417. (b) Montine, T. J.; Quinn, J. F.; Kaye, J. A.; Morrow, J. D. *Oxid. Stress Dis.* **2006**, *22*, 147. (c) Montuschi, P.; Barnes, P.; Roberts, L. J., II. *Current Med. Chem.* **2007**, *14*, 703.

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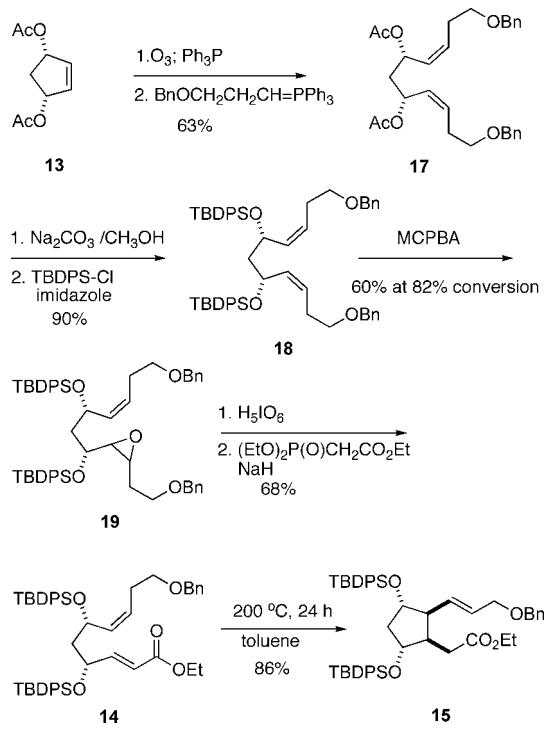
SCHEME 3

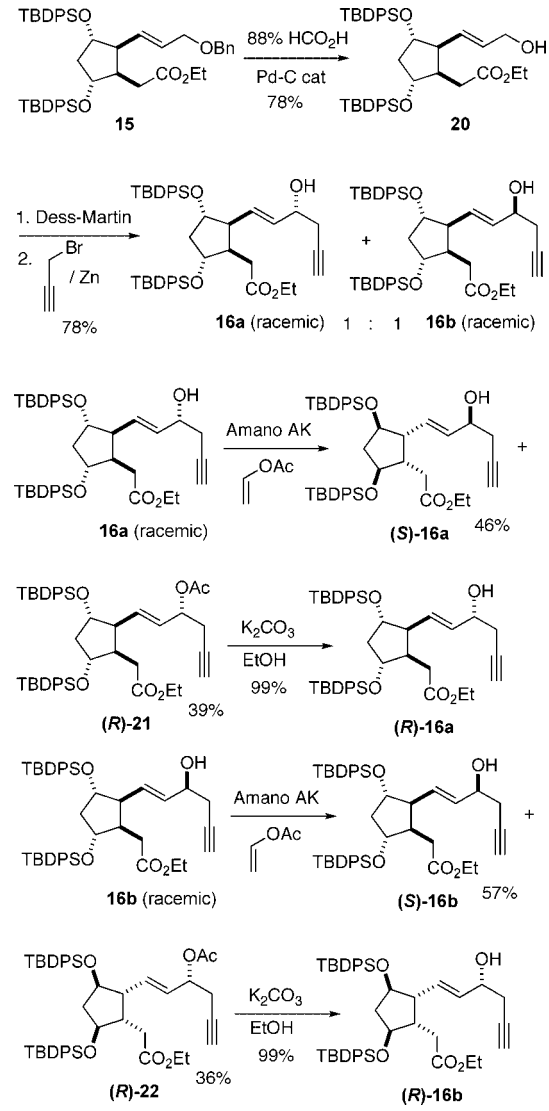


product **15** as a single diastereomer. The *cis*-dialkyl stereochemistry of the cyclopentane was suggested by the ^{13}C chemical shifts of the methines attached to alkyl side chains (^{13}C δ 52.5 and δ 46.3). This assignment was later confirmed by the X-ray structure of a 4-bromobenzoate derived from (*R*)-**16b**. For a detailed discussion of the use of ^{13}C to assign relative configuration of a 1,2-dialkyl cyclopentane, see ref 3h.

Preparation and Resolution of the Side Chain Allylic Alcohols. Selective debenzylation of **15** (Scheme 4) could be effected with palladium on carbon, using 88% aqueous formic acid as the reductant.[11] If the reaction was run too long, the allylic alcohol was hydrogenolyzed, leaving a propenyl side chain. Oxidation of **20** followed by addition of the propargyl zinc reagent[12] led to the expected 1:1 mixture of racemic **16a** and **16b**. The key observation was that **16a** and **16b** were readily separable by preparative column chromatography.

Separately, because they reacted at quite different rates, racemic **16a** and **16b** were subjected to *R*-selective[3f] acetylation with Amano lipase AK and vinyl acetate. Initially, each acetylation was run to about 40% conversion. The (*R*)-**21** and (*R*)-**22** so prepared were deacetylated to give respectively (*R*)-**16a** and (*R*)- **16b**, which were shown individually (chiral HPLC) to be >99% ee. The residual **16a** from the initial acetylation

SCHEME 4



was again subjected to *R*-selective acetylation with Amano lipase AK and vinyl acetate, and again, acetylation was run to about 40% conversion. The remaining (*S*)-**16a** was shown (chiral HPLC) to be >99% ee. The relative and absolute configurations of the products were assigned by comparison (optical rotation, TLC behavior) with the analogous isoprostane intermediates that had previously been described.[3d–g] These assignments were confirmed (Supporting Information) by an X-ray structure of the tris-4-bromobenzoate derived from (*R*)-**16b**.

The reaction of the lipase with racemic **16b** was very slow. Sufficient (*R*)**-22** could be prepared this way, but the residual (*S*)**-16b** had low ee (84%). The side chain hydroxyl of the enriched (*S*)**-16b** was therefore inverted (Scheme 5) by Mitsunobu esterification[13] with *p*-nitrobenzoic acid to give **23**. Hydrolysis followed by *R*-selective acetylation with Amano lipase AK delivered, after hydrolysis of the acetate so prepared, the alcohol (*R*)**-16a**. Mitsunobu inversion of the side chain hydroxyl and again hydrolysis led to (*S*)**-16b** in high ee (>99%).

Preparation of the Four Enantiomerically Pure Diastereomers of 13-F_{4t}-neuroprostane. The ester of (*S*)**-16a** was

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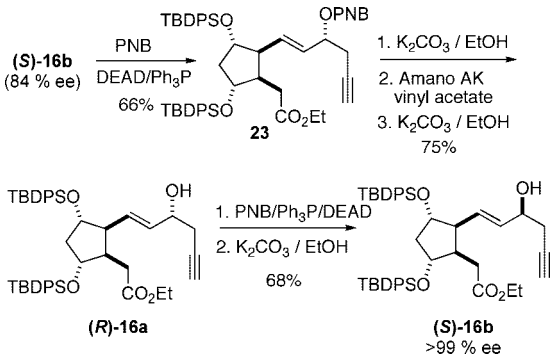
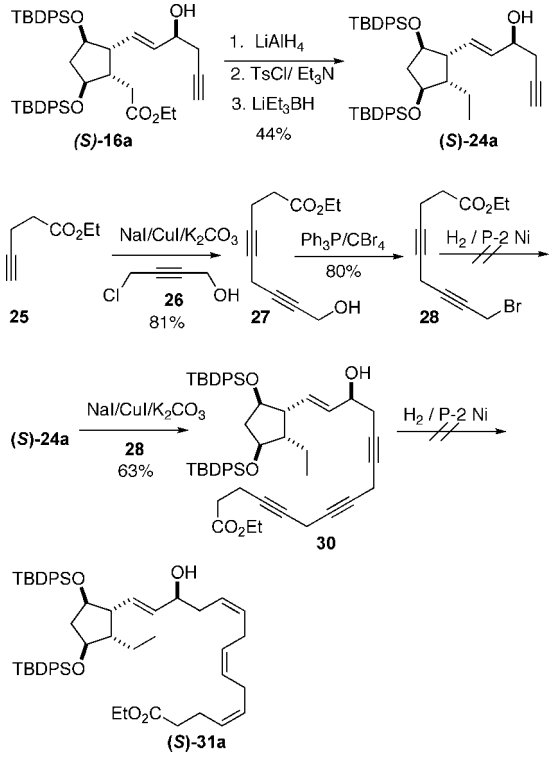
SCHEME 5

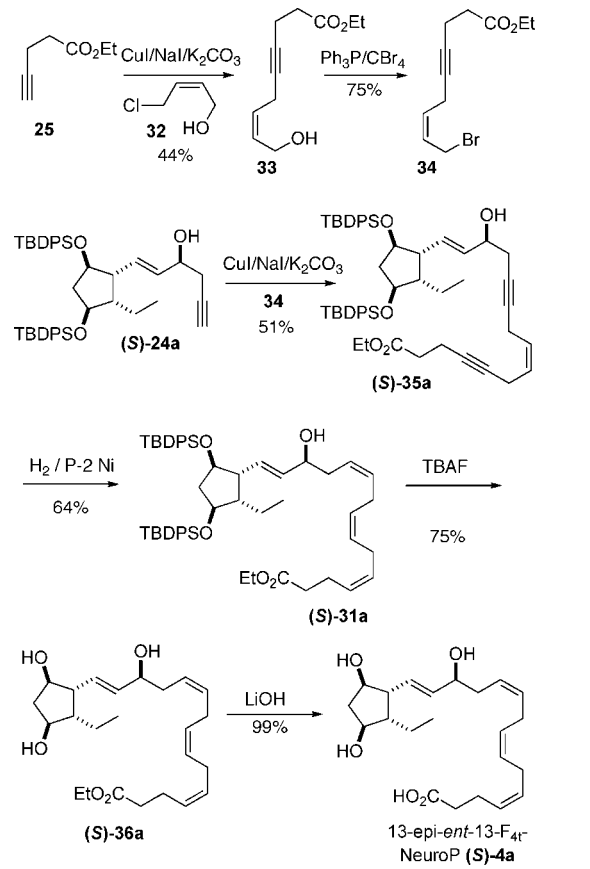


SCHEME 6



reduced (Scheme 6) to the alcohol, and the derived tosylate was further reduced to give (*S*)-**24a**. The alkylation of (*S*)-**24a** with *cis*-1,4-dichloro-2-butene (Scheme 6) using the protocol that we had reported[14] was successful, but in the process the residual allylic chloride was converted into the unstable and so unusable iodide. We next prepared the diyne **28** from **25** using the previously described[15] protocol. Despite an encouraging report,[15] partial hydrogenation[3a,16] of diynes **27** or **28** gave in our hands only mixtures of over-reduced products, accompanied by some dimer from **28**. Alternatively, coupling of the diyne **28** with (*S*)-**24a** did give the triyne **30**. Once again, however, the partial hydrogenaton of **30** was not successful, leading to a complex mixture of products.

SCHEME 7



In a modification of our previous report,[14] we prepared the cis allylic bromide **34** (Scheme 7). Coupling of ethyl 4-pentynoate **25** with *cis*-4-chloro-2-buten-1-ol **32**[17] gave **33**. Bromination of the alcohol **33** delivered the bromide **34**. Coupling of (*S*)-**24a** with the bromo ester **34** gave (*S*)-**35a** and the easily separated S_N2' byproduct (not shown in the scheme) in about a 3:1 ratio. To our delight, partial hydrogenation of (*S*)-**35a**, using P2−Ni,[3a,16] afforded the required tetraene (*S*)-**31a** with only traces of an over-reduced byproduct, which was also easily separated. Desilylation followed by saponification delivered 13-epi-*ent*-13-F_{4t}-NeuroP (*S*)-**4a**. By using this same procedure, the other three enantiomerically pure diastereomers (*R*)-**16a**, (*R*)-**16b**, and(*S*)-**16b** were carried on to the corresponding 13-F_{4t}-NeuroPs (*R*)-**4a**, (*R*)-**4b**, and (*S*)-**4b** (Scheme 2). The synthetic materials were shown to be congruent (GC retention time, fragmentation) with the previously reported[2] 13-F_{4t}-NeuroPs. The enantiomeric purity of our final products is assumed, based on the established enantiomeric purity of each of the four precursors.

Although we have so far only prepared the trans neuroprostanes using this approach, we have previously shown[3h] in the isoprostane series that Mitsunobu inversion followed by hydrolysis efficiently converted the trans to the cis series. Thus, *each* of the eight enantiomerically pure diastereomers of an isoprostane or a neuroprostane are accessible by using this approach.

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Conclusion

It is apparent that the thermal ene cyclization of **14** is indeed a powerful method for the construction of *cis*-2,3-dialkyl cyclopentanes. We feel that this route to the isoprostanes and the neuroprostanes is the most succinct and flexible yet described, and that it will therefore become the standard approach when the objective is to prepare each of the enantiomerically pure diastereomers of one of these natural products. The four enantiomerically pure diastereomers (*R*)**-16a**, (*S*)**-16a**, (*R*)**-16b**, and (*S*)**-16b** are universal precursors for the synthesis of any isoprostane or neuroprostane.[18] We chose the 13-F_{4t}-NeuroPs as our initial target because they bear the technically most challenging side chain of any of the neuroprostanes. Studies are underway of the physiological activity of the synthetic neuroprostanes we have prepared.

Experimental Section

Ene Product 15. A solution of **14** (1.3 g, 1.60 mmol) in toluene (26 mL) was taken up in a sealed tube and placed in a Parr pressure reactor. Toluene (30 mL) was added to the reactor to maintain equal pressure around the sealed tube, and the reactor was maintained at 200 °C for 24 h. The toluene was evaporated and the residue was chromatographed to give **15** (1.12 g, 86% yield) as a colorless syrup; TLC R_f 0.46 (10% MTBE/petroleum ether); IR (neat) 3070, 2930, 1743, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–7.56 (m, 8H), 7.37–7.25 (m, 17H), 5.36 (dt, J = 15.3, 5.8 Hz, 1H), 5.07 (dd, J = 15.3, 9.8 Hz, 1H), 4.36 (s, 2H), 4.03 (dq, J = 7.2, 3.2 Hz, 2H), 3.85–3.76 (m, 4H), 2.97–2.75 (m, 2H), 2.24 (dd, J = 16.0, 5.4 Hz, 1H), 1.99 (dd, J = 16.0, 9.8 Hz, 1H), 1.80 (quintet, J = 7.2 Hz, 1H), 1.66 (dt, J = 14.1, 4.8 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H), 1.07 (s, 9H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u:[19] 172.7, 138.4, 134.3, 134.2, 133.9, 71.6, 70.4, 60.2, 43.4, 33.6, 19.2, 19.1; d: 135.9, 135.84, 135.82, 130.8, 129.7, 129.6, 129.5, 129.4, 128.3, 127.7, 127.6, 127.53, 127.52, 127.5, 127.48, 76.6, 52.5, 46.3, 27.0, 26.9, 14.2; HRMS calcd for $C_{51}H_{62}NaO_5Si_2$ 833.4033 (M + Na), found 833.4023.

Allylic Alcohol 20. To a stirred solution of benzyl ether **15** (1.6 g, 1.97 mmol) in a mixture of 88% aqueous formic acid (6 mL) and methanol (50 mL) was added 10% Pd/C (160 mg). After 24 h at rt the catalyst was filtered off. The filtrate was concentrated and the residue was chromatographed to yield **20** (743 mg, 78% yield based on recovered starting material **15**) as a colorless syrup, accompanied by **15** (652 mg). For **20**: TLC R_f 0.25 (30% MTBE/petroleum ether); IR (neat) 3432, 3070, 2930, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–7.54 (m, 8H), 7.47–7.28 (m, 12H), 5.35 (dt, J = 15.2, 5.6 Hz, 1H), 5.01 (dd, J = 15.2, 10.0 Hz, 1H), 4.02 (dq, J = 6.8, 1.2 Hz, 2H), 3.85 (d, J = 5.6 Hz, 2H), 3.83–3.79 (m, 1H), 3.76 (q, J = 6.8 Hz, 1H), 2.89 (app dt, J = 9.2, 4.0 Hz, 1H), 2.83–2.76 (m, 1H), 2.20 (dd, J = 16.0, 5.2 Hz, 1H), 1.93 (dd, J = 16.0, 10.0 Hz, 1H), 1.85 (quint, J = 6.8 Hz, 1H), 1.69 (dt, J = 14.0, 5.6 Hz, 1H), 1.50 (br s, 1H), 1.18 (t, J = 6.8 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.8, 134.3, 134.2, 134.1, 133.9, 63.3, 60.3, 43.5, 33.9, 19.2, 19.1; d: 136.0, 135.9, 135.8, 132.2, 129.7, 129.67, 129.61, 129.57, 129.51, 127.64, 127.57, 127.5, 127.4, 76.7, 76.6, 52.3, 46.4, 27.0, 26.9, 14.2; HRMS calcd for $C_{44}H_{56}NaO_5Si_2$ 743.3564 (M + Na), found 743.3565.

Racemic Alcohols 16a and 16b. To a stirred solution of allylic alcohol **20** (1.1 g, 1.5 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (713 mg, 1.7 mmol) at rt. After being stirred for 1 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, 1 M aqueous NaOH, water, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to give the crude aldehyde (1.07 g, quantitative yield) as a colorless liquid; TLC R_f 0.66 (30% MTBE/petroleum ether); IR (neat) 2931, 2855, 1727, 1689 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.17 (d, J = 8.0 Hz, 1H), 7.65–7.52 (m, 8H), 7.46–7.28 (m, 12H), 6.11 (dd, J = 15.6, 10.0 Hz, 1H), 5.76 (dd, J = 15.6, 7.6 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.92 (dt, J = 6.8, 4.8 Hz, 1H), 3.81 (q, J = 6.4 Hz, 1H), 3.16 (dt, J = 8.4, 4.4 Hz, 1H), 2.90–2.83 (m, 1H), 2.19 (dd, J = 16.0, 5.6 Hz, 1H), 1.96–1.84 (m, 2H), 1.78 (dt, J = 14.0, 5.6 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.0, 134.0, 133.8, 133.7, 133.5, 60.5, 43.6, 33.5, 19.3, 19.1; d: 193.2, 155.4, 136.0, 135.9, 135.8, 134.7, 130.0, 129.9, 129.82, 129.8, 127.8, 127.73, 127.7, 76.4, 75.9, 52.8, 47.1, 27.1, 27.0, 14.2; HRMS calcd for $C_{44}H_{54}NaO_5Si_2$ 741.3407 (M + Na), found 741.3374.

To a stirred solution of crude aldehyde (1.07 g, 1.5 mmol) in 1:1 mixture of THF and DMF (20 mL) was added activated zinc dust (195 mg, 3.0 mmol) followed by propargyl bromide (357 mg, 3.0 mmol) at rt. After being stirred for 2 h the reaction mixture was partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on a TLC mesh silica gel to give alcohol **16a** (439 mg, 39% yield) and **16b** (442 mg, 39% yield) as colorless liquids. For **16a**: TLC R_f 0.42 (30% MTBE/petroleum ether); IR (neat) 3445, 3294, 1734, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–7.52 (m, 8H), 7.46–7.28 (m, 12H), 5.24 (dd, J = 15.2, 6.0 Hz, 1H), 5.06 (ddd, J = 15.2, 9.6, 0.8 Hz, 1H), 4.07–3.97 (m, 3H), 3.83 (app quintet, J = 7.2 Hz, 1H), 3.77 (q, J = 6.4 Hz, 1H), 2.88 (app dt, J = 10.0, 3.3 Hz, 1H), 2.83–2.78 (m, 1H), 2.27–2.19 (m, 3H), 1.95 (dd, J = 16.4, 10.0 Hz, 1H), 1.94 (t, J = 2.8 Hz, 1H), 1.85 (quintet, J = 7.2 Hz, 1H), 1.69 (dt, J = 14.0, 5.2 Hz, 1H), 1.60 (d, J = 4.4 Hz, 1H), 1.19 (t, J = 6.8 Hz, 3H), 1.06 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.7, 134.3, 134.1, 134.0, 133.9, 80.4, 70.7, 60.2, 43.5, 33.7, 27.2, 19.2, 19.1; d: 136.0, 135.9, 135.8, 133.6, 129.9, 129.7, 129.6, 129.58, 129.5, 127.6, 127.55, 127.52, 127.5, 76.6, 70.5, 52.3, 46.3, 27.0, 26.9, 14.2. HRMS calcd for $C_{47}H_{58}NaO_5Si_2$ 781.3720 (M + Na), found 781.3756.

Alcohol 16b. TLC R_f 0.40 (30% MTBE/petroleum ether); IR (neat) 3436, 3306, 2931, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64–7.59 (m, 8H), 7.54–7.29 (m, 12H), 5.24 (dd, J = 15.2, 6.4 Hz, 1H), 5.10 (dd, J = 15.2, 9.6 Hz, 1H), 4.08–3.99 (m, 3H), 3.82–3.78 (m, 1H), 3.75 (q, J = 6.8 Hz, 1H), 2.85–2.77 (m, 2H), 2.31–2.20 (m, 3H), 1.96 (dd, J = 16.0, 10.4 Hz, 1H), 1.93 (t, J = 1.6 Hz, 1H), 1.83 (quintet, J = 7.2 Hz, 1H), 1.68 (dt, J = 14.0, 5.6 Hz, 1H), 1.60 (d, J = 4.4 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.9, 134.3, 134.2, 134.0, 133.9, 80.4, 70.7, 60.3, 43.5, 33.8, 27.2, 19.2, 19.1; d: 135.93, 135.9, 135.82, 135.81, 133.8, 130.0, 129.7, 129.6, 129.56, 129.51, 127.6, 127.54, 127.5, 76.6, 76.5, 70.3, 52.2, 46.3, 27.0, 26.9, 14.2; HRMS calcd for $C_{47}H_{58}NaO_5Si_2$ 781.3720 (M + Na), found 781.3747.

Resolution of Racemic Alcohol 16a. To a stirred solution of racemic alcohol **16a** (1.04 g, 1.37 mmol) in vinyl acetate (28 mL) was added Amano lipase AK (5.18 g, 5 mass equiv). The reaction mixture was stirred at 55 °C (oil bath) for 20 h. The suspension was filtered with MTBE, and the filtrate was concentrated under reduced pressure. The residue was chromatographed to give acetate (*R*)-**21** (425 mg, 39% yield) and recovered alcohol **16a** (620 mg) as colorless syrups. The residual alcohol **16a** was again subjected to similar reaction conditions as given above to give (*S*)-**16a** (508 mg, 46% yield) accompanied by enriched (*R*)-**21** (98 mg, 9% yield)) as colorless syrups. For (*S*)-**16a**: $[\alpha]_D$ +17.0 (*c* 1.0, CH_2Cl_2). The ee of (*S*)-**16a** was determined to be >99% by HPLC (column: CHIRALCEL OD (Diacel Chemical Industry Ltd.); mobile phase: 0.5% 2-propanol in hexanes; flow: 1.0 mL/min; UV: 254 nm; retention times: 15.7 min for (*S*)-**16a** and 18.7 min for (*R*)-**16a**)). The other analytical data for (*S*)-**16a** were found to be identical with those of the racemic **16**.

(18) The intermediate ester **15** could also serve as a precursor for the synthesis of other cis dialkyl cyclopentanes, including jasmonic acid and tuberonic acid. For leading references to previous syntheses in these series, see: Nonaka, H.; Wang, Y.-G.; Kobayashi, Y. *Tetrahedron Lett.* **2007**, *48*, 1745.

(19) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u".

Acetate (*R*)-21. TLC R_f 0.72 (30% MTBE/petroleum ether); $[\alpha]_D$ −9.8 (*c* 1.0, CH_2Cl_2); IR (neat) 3290, 2931, 1736, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63–7.55 (m, 8H), 7.41–7.30 (m, 12H), 5.27 (dd, J = 15.2, 7.2 Hz, 1H), 5.18–5.12 (m, 2H), 4.06–3.97 (m, 2H), 3.82 (quintet, J = 3.6 Hz, 1H), 3.75 (q, J = 6.8 Hz, 1H), 2.95–2.89 (m, 1H), 2.84–2.79 (m, 1H), 2.41–2.30 (m, 2H), 2.20 (dd, J = 16.0, 5.6 Hz, 1H), 1.99 (dd, J = 16.0, 10.0 Hz, 1H), 1.98 (s, 3H), 1.87 (t, J = 3.0 Hz, 1H), 1.80 (quintet, J = 7.2 Hz, 1H), 1.66 (dt, J = 14.0, 5.0 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H), 1.05 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.6, 169.8, 134.3, 134.2, 133.9, 79.4, 70.5, 60.2, 43.4, 33.4, 24.6, 19.2, 19.1; d: 135.9, 135.8, 135.7, 132.1, 129.6, 129.57, 129.52, 129.5, 127.6, 127.53, 127.51, 127.5, 76.6, 76.4, 71.9, 52.5, 46.3, 27.0, 26.9, 21.1, 14.2; HRMS calcd for $C_{49}H_{60}NaO_6Si_2$ 823.3826 (M + Na), found 823.3848.

Alcohol (*R*)-16a. To a stirred solution of acetate (*R*)-**21** (425 mg, 0.531 mmol) in ethanol (10 mL) was added K_2CO_3 (366 mg, 2.66 mmol). After the mixture was stirred at rt for 24 h it was partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give (*R*)-**16a** (402 mg, quantitative yield) as a colorless syrup. $[\alpha]_D$ −17.3 (*c* 1.0, CH_2Cl_2). The ee of (*R*)-**16a** was determined to be >99% by HPLC as described above (retention times: 15.7 min for (*S*)-**16a** and 18.7 min for (*R*)-**16a**). The other analytical data for (*R*)-**16a** were found to be identical with those of the racemic **16a**.

Resolution of Racemic Alcohol 16b. To a stirred solution of racemic alcohol **16b** (800 mg, 1.06 mmol) in vinyl acetate (21.6 mL) was added Amano lipase AK (4.0 g, 5 mass equiv). The reaction mixture was stirred at 60 °C (oil bath) for 48 h. The suspension was filtered with MTBE, and the filtrate was concentrated under reduced pressure. The residue was chromatographed to give acetate (*R*)-**22** (303 mg, 36% yield) and recovered alcohol (*S*)-**16b** (458 mg, 57% yield) as colorless syrups. The ee of (*S*)-**16b** was determined to be 84% by HPLC (column: CHIRALCEL OD (Diacel Chemical Industry Ltd.); mobile phase: 0.5% 2-propanol in hexanes; flow: 1.0 mL/min; UV: 254 nm; retention times: 16.8 min for (*R*)-**16b** and 21.9 min for (*S*)-**16b**). The other analytical data for (*R*)-**16b** were found to be identical with those of the racemic **16b**.

Acetate (*R*)-22. TLC R_f 0.71 (30% MTBE/petroleum ether); $[\alpha]_D$ +28.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3292, 2931, 1737, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64–7.54 (m, 8H), 7.39–7.29 (m, 12H), 5.21–5.19 (m, 2H), 5.13–5.09 (m, 1H), 4.09–3.97 (m, 2H), 3.82 (q, J = 3.6 Hz, 1H), 3.78 (dd, J = 13.2, 7.2 Hz, 1H), 2.91–2.86 (m, 1H), 2.85–2.77 (m, 1H), 2.38–2.27 (m, 2H), 2.22 (dd, J = 16.0, 5.2 Hz, 1H), 2.00 (s, 3H), 1.98 (dd, J = 16.8, 9.6 Hz, 1H), 1.84 (t, J = 2.8 Hz, 1H), 1.80 (quintet, J = 7.2 Hz, 1H), 1.66 (dt, J = 14.0, 4.8 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.6, 169.0, 134.3, 134.2, 134.0, 133.9, 79.4, 70.5, 60.1, 43.4, 33.4, 24.5, 19.2, 19.1; d: 135.9, 135.88, 135.84, 135.8, 132.7, 129.6, 129.56, 129.5, 129.2, 127.6, 127.5, 127.4, 76.6, 76.5, 71.8, 52.3, 46.4, 21.1, 14.2; HRMS calcd for $C_{49}H_{60}NaO_6Si_2$ 823.3826 (M + Na), found 823.3808.

Alcohol (*R*)-16b. To a stirred solution of acetate (*R*)-**22** (304 mg, 0.38 mmol) in ethanol (7.5 mL) was added K_2CO_3 (262 mg, 1.9 mmol). After the mixture was stirred at rt for 12 h it was partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give (*R*)-**16b** (288 mg, quantitative yield) as a colorless syrup. $[\alpha]_D$ +19.0 (*c* 1.0, CH_2Cl_2). The ee of (*R*)-**16b** was determined to be >99% by HPLC (column: CHIRALCEL OD (Diacel Chemical Industry Ltd.); mobile phase: 0.5% 2-propanol in hexanes; flow: 1.0 mL/min; UV: 254 nm; retention times: 16.8 min for (*R*)-**16b** and 21.9 min for (*S*)-**16b**). The other analytical data for (*R*)-**16b** were found to be identical with those of the racemic **16**.

Alcohol (*S*)-16b (using double Mitsunobu inversion of alcohol (*S*)-16b with 84% ee). To a stirred solution of enriched (*S*)-**16b** (458 mg, 0.6 mmol) in toluene (6 mL) were added 4-nitrobenzoic acid (202 mg, 1.2 mmol) and PPh_3 (472 mg, 1.8 mmol). The reaction flask was then wrapped with aluminum foil, and then a 40% w/w solution of DEAD in toluene (783 mg, 1.8 mmol) was added. After 1 h at rt, the toluene was evaporated and the residue was chromatographed to give the 4-nitrobenzoate **23** (360 mg, 66% yield) as a white foamy solid; TLC R_f 0.69 (30% MTBE/petroleum ether); IR (neat) 3299, 2934, 1729, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H), 7.66–7.54 (m, 8H), 7.44–7.25 (m, 12H), 5.45–5.38 (m, 2H), 5.31 (ddd, J = 18.4, 9.2, 4.0 Hz, 1H), 4.15–4.00 (m, 2H), 3.85 (dt, J = 6.8, 4.0 Hz, 1H), 3.78 (q, J = 7.2, 1H), 2.96 (dt, J = 9.8, 3.6 Hz, 1H), 2.88–2.81 (m, 1H), 2.55 (dd, J = 5.6, 2.4 Hz, 2H), 2.25 (dd, J = 16.0, 5.6 Hz, 1H), 2.01 (dd, J = 16.0, 10.0 Hz, 1H), 1.94 (t, J = 2.6 Hz, 1H), 1.85 (quintet, J = 7.2 Hz, 1H), 1.69 (dt, J = 14.4, 5.2 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.08 (s, 9H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 172.5, 163.5, 150.6, 135.6, 134.2, 134.0, 133.9, 78.9, 71.0, 60.2, 43.4, 33.5, 24.7, 19.2, 19.1; d: 135.9, 135.83, 135.82, 135.8, 133.5, 130.8, 129.7, 129.6, 129.5, 129.46 128.8, 127.6, 127.55, 127.48, 127.5, 123.5, 76.5, 76.3, 73.7, 52.4, 46.4, 27.0, 26.9, 14.1; HRMS calcd for $C_{54}H_{61}NNaO_8Si_2$ 930.3833 (M + Na), found 930.3865.

To a stirred solution of 4-nitrobenzoate **23** (360 mg, 0.4 mmol) in ethanol (10 mL) was added K_2CO_3 (274 mg, 1.98 mmol). After the mixture was stirred at rt for 24 h, it was partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give enriched (*R*)-**16a** (297 mg, 99% yield) as a colorless syrup. Resolution of the above enriched (*R*)-**16a** with Amano lipase AK (1.49 g, 5 mass equiv) and vinyl acetate (8 mL) followed by hydrolysis of the acetate in the same manner as described for racemic **16a** afforded again (*R*)-**16a** (223 mg, 75% yield), $[\alpha]_D$ −17.5 (*c* 1.0, CH_2Cl_2). The ee of (*R*)-**16a** was determined to be >99% by HPLC (as described above).

Mitsunobu inversion of (*R*)-**16a** followed by hydrolysis in the same manner as described for enriched (*S*)-**16b** again gave (*S*)-**16b** (152 mg, 68% yield, 2 steps). $[\alpha]_D$ −18.2 (*c* 1.0, CH_2Cl_2). The ee of (*S*)-**16b** was determined to be >99% by HPLC (as described above). The other analytical data for (*S*)-**16b** were found to be identical with those of the racemic **16b**.

Alkyne (*S*)-24a. To a stirred solution of (*S*)-**16a** (508 mg, 0.67 mmol) in THF (3.4 mL) was added a 1 M solution of LAH in THF (0.7 mL, 0.70 mmol) at 0 °C. After being stirred for 2 h the reaction was quenched with saturated aqueous Na_2SO_4 (0.5 mL), the white solid was filtered with MTBE, and the filtrate was concentrated to give the diol (455 mg, 95% yield) as a colorless syrup; TLC R_f 0.15 (50% MTBE/petroleum ether); $[\alpha]_D$ +10.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3305, 2930, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–7.60 (m, 6H), 7.57–7.43 (m, 2H), 7.42–7.28 (m, 12H), 5.25 (dd, J = 15.2, 6.4 Hz, 1H), 5.15 (dd, J = 15.2, 9.4, 1H), 4.03 (quintet, J = 5.2 Hz, 1H), 3.90–3.82 (m, 2H), 3.41 (app q, J = 5.6 Hz, 2H), 2.76–2.71 (m, 1H), 2.30 (quintet, J = 7.2 Hz, 1H), 2.28 (dd, J = 6.0, 2.8 Hz, 2H), 1.95 (t, J = 2.8 Hz, 1H), 1.84 (quintet, J = 7.2 Hz, 1H), 1.69 (dt, J = 14.4, 4.4 Hz, 1H), 1.64 (d, J = 4.4 Hz, 1H), 1.38–1.32 (m, 3H), 1.07 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ u: 134.4, 134.3, 134.2, 134.1, 80.5, 70.7, 61.7, 43.5, 31.7, 27.4, 19.2, 19.1; d: 135.94, 135.91, 135.89, 135.85, 133.3, 130.6, 129.7, 129.6, 129.59, 129.5, 127.6, 127.56, 127.54, 127.52, 77.7, 77.2, 70.5, 53.0, 46.8, 27.0, 26.9; HRMS calcd for $C_{45}H_{56}NaO_4Si_2$ 739.3615 (M + Na), found 739.3609.

To a stirred solution of crude diol (455 mg, 0.64 mmol) in CH_2Cl_2 (1.8 mL) was added Et_3N (0.22 mL, 1.59 mmol) followed by TsCl (133 mg, 0.70 mmol) and a catalytic amount of DMAP (5 mg). After being stirred for 24 h the mixture was partitioned between water and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the monotosylate (310 mg, 56% yield) as a foamy solid; TLC R_f 0.65 (50% MTBE/petroleum ether); $[\alpha]_D$ +16.9 (*c* 1.0, CH_2Cl_2); IR (neat) 3293, 2930, 1427 cm^{-1}.

To a stirred solution of the monotosylate (310 mg, 0.36 mmol) in THF (2.0 mL) was added a 1 M solution of $LiEt_3BH$ in THF (3.56 mL, 3.56 mmol). After the mixture was stirred at rt for 3 h it was partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give (*S*)**-24a** (207 mg, 42% yield from (*S*)**-16a**) as a colorless syrup; TLC R_f 0.81 (30% MTBE/petroleum ether); $[\alpha]_D$ +10.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3307, 2930, 1427 3439 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66–7.63 (m, 6H), 7.60–7.57 (m, 2H), 7.41–7.31 (m, 12H), 5.27 (dd, J = 15.2, 6.4 Hz, 1H), 5.15 (dd, J = 15.2, 9.6 Hz, 1H), 4.03 (quintet, J = 6.0 Hz, 1H), 3.88–3.81 (m, 2H), 2.81–2.76 (m, 1H), 2.28–2.26 (m, 2H), 2.13 (quintet, J = 7.2 Hz, 1H), 1.95 (t, J = 2.8 Hz, 1H), 1.87 (quintet, J = 7.2 Hz, 1H), 1.67 (dt, J = 14.4, 4.0 Hz, 1H), 1.52 (d, J = 4.4 Hz, 1H), 1.17–0.99 (m, 2H), 1.07 (s, 9H), 1.06 (s, 9H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 134.6, 134.4, 134.33, 134.3, 80.5, 70.6, 43.7, 27.4, 21.1, 19.3, 19.2; d: 136.0, 135.94, 135.9, 132.7, 131.0, 129.6, 129.52, 129.5, 129.47, 127.5, 77.2, 77.1, 70.7, 52.6, 52.2, 27.1, 27.0, 12.5; HRMS calcd for $C_{45}H_{56}NaO_3Si_2$ 723.3666 (M + Na), found 723.3645.

Bromoester 34. To a stirred solution of ethyl-4-pentynoate (1.09 g, 7.94 mmol) in DMF (8 mL) were added K_2CO_3 (2.41 g, 17.5 mmol), NaI (2.63 g, 17.5 mmol), and CuI (1.58 g, 8.34 mmol). After the mixture was stirred for 30 min at rt, *cis*-4-chloro-2-buten-1-ol (1.27 g, 11.9 mmol) was added and the stirring was continued for an additional 24 h. The reaction mixture quenched with saturated aqueous NH_4Cl and then partitioned between water and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the alcohol **33** (680 mg, 44% yield) as a colorless liquid. TLC R_f 0.35 (30% MTBE/petroleum ether); IR (neat) 3414, 2982, 2924, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (dtt, J = 15.2, 5.6, 1.6 Hz, 1H), 5.68 (dtt, J = 15.2, 5.2, 1.6 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.13 (dq, J = 7.2, 1.2 Hz, 2H), 2.93 (dt, J = 5.2, 1.6 Hz, 2H), 2.55–2.46 (m, 4H), 1.99 (s, 1H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 172.2, 80.6, 77.6, 63.0, 60.6, 33.9, 21.6, 14.7; d: 130.5, 126.7, 14.2; HRMS calcd for $C_{11}H_{17}O_3$ 197.1178 (M + H^+), found 197.1178.

To a stirred solution of alcohol **33** (175 mg, 1.34 mmol) in CH_2Cl_2 (5 mL) was added PPh_3 (351 mg, 1.34 mmol). The mixture was cooled to 0 °C. CBr_4 (444 mg, 1.34 mmol) was then added portionwise over 5 min and the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated and the residue was chromatographed to give bromoester **34** (172 mg, 74% yield) as a colorless liquid. TLC R_f 0.81 (30% MTBE/petroleum ether); IR (neat) 2980.9, 1734.4 1170.3 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.96 (tqunitet, J = 7.6, 1.8 Hz, 1H), 5.74 (dtt, J = 15.2, 5.2, 1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.97 (ddd, J = 7.2, 1.6, 0.8 Hz, 2H), 2.96–2.94 (m, 2H), 2.52–2.51 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 172.1, 81.2, 76.8, 60.6, 33.9, 32.4, 21.6, 14.8; d: 130.4, 127.6, 14.3; HRMS calcd for $C_{11}H_{16}BrO_2$ (Br = 79) 259.0334 (M + H^+), found 259.0329.

Dienediyne (*S*)-35a. To a stirred solution of (*S*)**-24a** (172 mg, 0.25 mmol) in DMF (0.3 mL) were added K_2CO_3 (136 mg, 0.98 mmol), NaI (148 mg, 0.98 mmol), and CuI (98 mg, 0.52 mmol) at rt. After the mixture was stirred for 30 min bromoester **34** (127 mg, 0.49 mmol) was added. The reaction mixture was stirred for 48 h and then partitioned between MTBE and, sequentially, aqueous NH_4Cl and water. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford (*S*)**-35a** (110 mg, 51% yield) as a colorless oil. TLC R_f 0.20 (15% MTBE/petroleum ether); $[\alpha]_D$ +11.2 (*c* 1.0, CH_2Cl_2); IR (neat) 3501, 2931, 2858, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–7.63 (m, 6H), 7.62–7.58 (m, 2H), 7.43–7.29 (m, 12H), 5.67–5.57 (m, 2H), 5.26 (dd, J = 15.6, 6.2 Hz, 1H), 5.14 (dd, J = 15.6, 9.8 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.00 (quintet, J = 5.6 Hz, 1H), 3.88–3.83 (m, 2H), 2.94–2.83 (m, 4H), 2.82–2.75 (m, 1H), 2.52–2.47 (m, 4H), 2.33–2.21 (m, 2H), 2.14 (quintet, J = 7.2 Hz, 1H), 1.85 (quintet, J = 7.2 Hz, 1H), 1.67 (dt, J = 14.4, 4.0 Hz, 1H), 1.62 (d, J = 4.4 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.16–0.98 (m, 2H), 1.07 (s, 9H), 1.06 (s, 9H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 172.12, 134.7, 134.4, 134.35, 134.3, 80.4, 79.7, 78.1, 77.9, 60.6, 43.7, 34.0, 28.0, 21.7, 21.6, 21.1, 19.2, 19.1, 14.8; d: 135.94, 135.92, 135.9, 133.2, 130.5, 129.52, 129.50, 129.46, 129.44, 127.5, 126.2, 126.0, 77.3, 77.2, 71.0, 52.7, 52.2, 27.0, 26.9, 14.3, 12.5; HRMS calcd for $C_{56}H_{70}NaO_5Si_2$ 901.4659 (M + Na), found 901.4641.

Tetraene (*S*)-31a. To a stirred suspension of $Ni(OAc)_2 \cdot 4H_2O$ (312 mg, 1.25 mmol) in ethanol (1.0 mL) was added a 1 M solution of $NaBH_4$ in ethanol (2.5 mL, 2.5 mmol) under an H_2 atmosphere. After the black suspension was stirred for 5 min, ethylenediamine (83 mg, 1.38 mmol) was added followed by (*S*)**-35a** (110 mg, 0.125 mmol) in ethanol (0.5 mL). The reaction flask was evacuated and purged with H_2 three times and then H_2 gas was bubbled through the stirring solution for 5 min. The reaction mixture was stirred under H_2 atmosphere for 30 min, and then filtered through a pad of silica gel with MTBE. The filtrate was concentrated and the residue was chromatographed to give (*S*)**-31a** (85 mg, 77% yield) as a colorless oil. TLC R_f 0.35 (15% MTBE/petroleum ether); $[\alpha]_D$ +4.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3469, 2958, 2931, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–7.63 (m, 6H), 7.62–7.58 (m, 2H), 7.43–7.29 (m, 12H), 5.49–5.27 (m, 6H), 5.24 (dd, J = 15.2, 6.4, Hz, 1H), 5.09 (dd, J = 15.2, 9.8 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.90–3.81 (m, 3H), 2.80–2.74 (m, 3H), 2.72–2.69 (m, 2H), 2.38–2.31 (m, 4H), 2.23–2.07 (m, 3H), 1.86 (quintet, 7.2 Hz, 1H), 1.67 (dt, J = 14.4, 4.0 Hz, 1H), 1.27 (d, J = 3.6 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.18–1.09 (m, 1H), 1.08 (s, 9H), 1.06 (s, 9H), 1.03–0.98 (m, 1H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 173.2, 134.7, 134.5, 134.4, 134.3, 60.4, 43.8, 35.1, 34.3, 30.6, 30.3, 22.8, 21.1, 19.3, 19.2; d: 136.0, 135.9, 134.4, 130.6, 129.8, 129.54, 129.52, 129.49, 129.46, 129.0, 128.7, 128.67, 128.2, 128.0, 127.9, 127.7, 127.5, 127.2, 125.4, 77.4, 77.3, 72.3, 52.7, 52.2, 27.1, 27.0, 14.3, 12.5; HRMS calcd for $C_{56}H_{74}NaO_5Si_2$ 905.4972 (M + Na), found 905.4979.

Triol (*S*)-36a. A solution of tetraene (*S*)**-31a** (70 mg, 0.079 mmol) in THF (0.1 mL) was treated with a 1 M solution of TBAF in THF (0.79 mL, 0.79 mmol) and the mixture was stirred for 72 h. The reaction mixture was partitioned between EtOAc and water. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give (*S*)**-36a** (24 mg, 75% yield) as a colorless oil. TLC R_f 0.16 (EtOAc); $[\alpha]_D$ +3.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3344, 2958, 2927, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57 (dd, J = 15.2, 7.2 Hz, 1H), 5.52–5.35 (m, 7H), 4.12 (q, J = 7.2 Hz, 2H), 4.09 (q, J = 6.8 Hz, 1H), 3.99–3.93 (m, 2H), 2.79–2.71 (m, 5H), 2.6–3.4 (broad, 3H), 2.46–2.21 (m, 6H), 2.28–2.22 (m, 1H), 2.00–1.94 (m, 1H), 1.63 (dt, J = 14.4, 4.0 Hz, 1H), 1.39–1.21 (m, 2H), 1.23 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 173.3, 60.4, 42.5, 35.3, 34.3, 30.6, 30.3, 22.7, 21.9; d: 135.0, 130.7, 129.9, 129.0, 128.8, 128.6, 128.2, 125.3, 76.4, 76.3, 72.5, 53.5, 52.4, 14.2, 12.8; HRMS calcd for $C_{24}H_{38}NaO_5$ 429.2617 (M + Na), found 429.2625.

13-*epi*-*ent*-13-F_{4t}-NeuroP (*S*)-4a. To a stirred solution of (*S*)**-36a** (24 mg, 0.059 mmol) in THF (1.2 mL) was added a solution of $LiOH \cdot H_2O$ (49.5 mg, 1.18 mmol) in water (1.2 mL) at rt. After being stirred for 10 h the mixture was acidified to pH 2.0 and then partitioned between water and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed with a 75–100% EtOAc/PE gradient to give (*S*)**-4a** (22 mg, quantitative) as a colorless oil. TLC R_f 0.03 (EtOAc); $[\alpha]_D$ +18.8 (*c* 1.0, MeOH); IR (neat) 3333, 2928, 1710 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.57 (dd, J = 15.2, 6.4 Hz, 1H), 5.53–5.40 (m, 7H), 4.09 (q, J = 6.4 Hz, 1H), 3.94 (dt, J = 7.2, 3.8 Hz, 1H), 3.88 (q, J = 6.8 Hz, 1H), 2.85–2.74 (broad, 4H), 2.68 (app dt, J = 13.2, 3.6 Hz, 1H), 2.46–2.23 (m, 7H), 1.98 (quintet, J = 7.6 Hz, 1H), 1.57 (dt, J = 14.0, 4.8 Hz, 1H), 1.46–1.30 (m, 2H), 0.93 (t, J =

7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ u: 173.8, 43.7, 36.0, 33.9, 30.9, 30.5, 23.0, 22.1; d: 135.7, 129.5, 129.3, 129.2, 129.1, 129.0, 127.0, 76.0, 75.9, 72.4, 53.6, 52.0, 12.8; HRMS calcd for $C_{22}H_{34}NaO_5$ 401.2304 (M + Na), found 401.2318.

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Supporting Information Available: General experimental procedures, experimental procedures, and spectra for all new compounds, and details of the X-ray structure of the tris-4-bromobenzoate derived from (*R*)-**16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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