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Stereodivergent Strategy for Neurofuran Synthesis via Palladium-Catalyzed Asymmetric Allylic Cyclization: Total Synthesis of 7-*epi*-ST-Δ^8-10-Neurofuran

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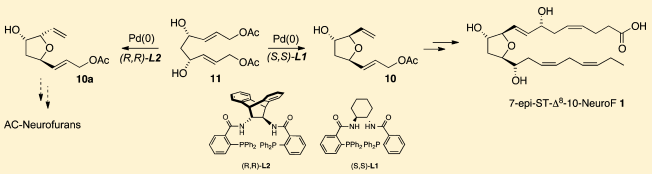
Supporting Information

ABSTRACT: Neurofurans are formed in vivo in the human brain as a consequence of an increased oxidative stress, and they could be valuable biomarkers of the neuronal oxidative stress. In this paper, an enantioselective stereodivergent approach to two key neurofuran precursors, belonging to the AC and ST classes, has been developed starting from a single achiral precursor, the *meso*-diol **11**. The absolute configuration of the THF cores was secured by a Pd-catalyzed asymmetric allylic alkylation using (*S*,*S*)-**L1** and (*R*,*R*)-**L2** ligands, respectively.



INTRODUCTION

Neurofurans (nFs) are formed in vivo in the human brain as a consequence of an increased oxidative stress; in particular, they are produced by peroxidation of esterified docosahexaenoic acid (DHA) in neuron membranes (Figure 1).[1]

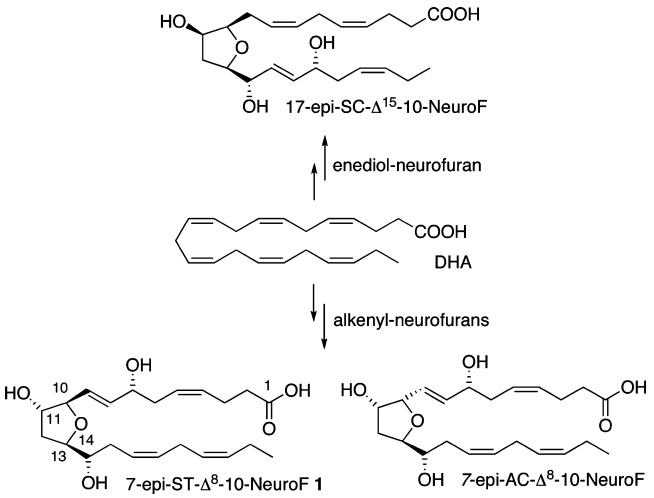


Figure 1. Representative examples of neurofuran families.

Along with neuroprostanes, isofurans, and isoprostanes, neurofurans have been suggested to be possible biomarkers of oxidative stress, which is considered the principal causative agent of neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's diseases.[2] In fact, nFs were found in significantly greater concentration in the brain tissue extracts of Tg 2576 transgenic mice, a widely used model for Alzheimer's disease, over their control littermates;[1a] however, they could not be detected in urine samples, therefore imposing a severe limitation to the potential use of nFs as valuable neuronal oxidative stress biomarkers. This discrepancy has been ascribed to the retention of nFs in brain tissues enriched with DHA or to their rapid metabolism to produce still unidentified compounds. Investigation of the nF metabolism in the brain remains, therefore, elusive.[1a]

This important goal can be pursued by using a suitably labeled nF, which requires an unprecedented asymmetric total synthesis. In this paper, we describe, for the first time, a general synthetic strategy to nFs that, in principle, enables the preparation of any of the possible 256 diastereomers and regioisomers within the large family of alkenyl-nFs.[1a,2] The total synthesis of 7-*epi*-ST-Δ^8-10-NeuroF **1** (Figure 2) was developed as a representative example of this general strategy.[2d]

The first example of a synthesis of the THF core of related products arising from the oxidative metabolism of arachidonic acid, isofurans, was reported by Taber and co-workers.[2d]

In their approaches, two different asymmetric trasformations, a Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation, have been used. However, neither the epoxidation nor the dihydroxylation proceeds with perfect enantiocontrol, and a distereomeric mixture of key tetrahydrofuran building blocks was obtained. Moreover, the key hydroxylic group on C-11 was epimeric to the natural product, and a carbinol inversion by a Mistunobo reaction was then required.

By contrast, in the present approach, only one enantioselective reaction, i.e., the Trost AAA, has been used with very high enantomeric excess (vide infra), and the C-11 hydroxylic group was installed with the correct configuration.

In this effort, we focused our attention on the establishment of the absolute configuration of the three tetrahydrofuran core stereocenters, the stereoselective building of the four double bonds and the introduction of the two hydroxyl groups on the

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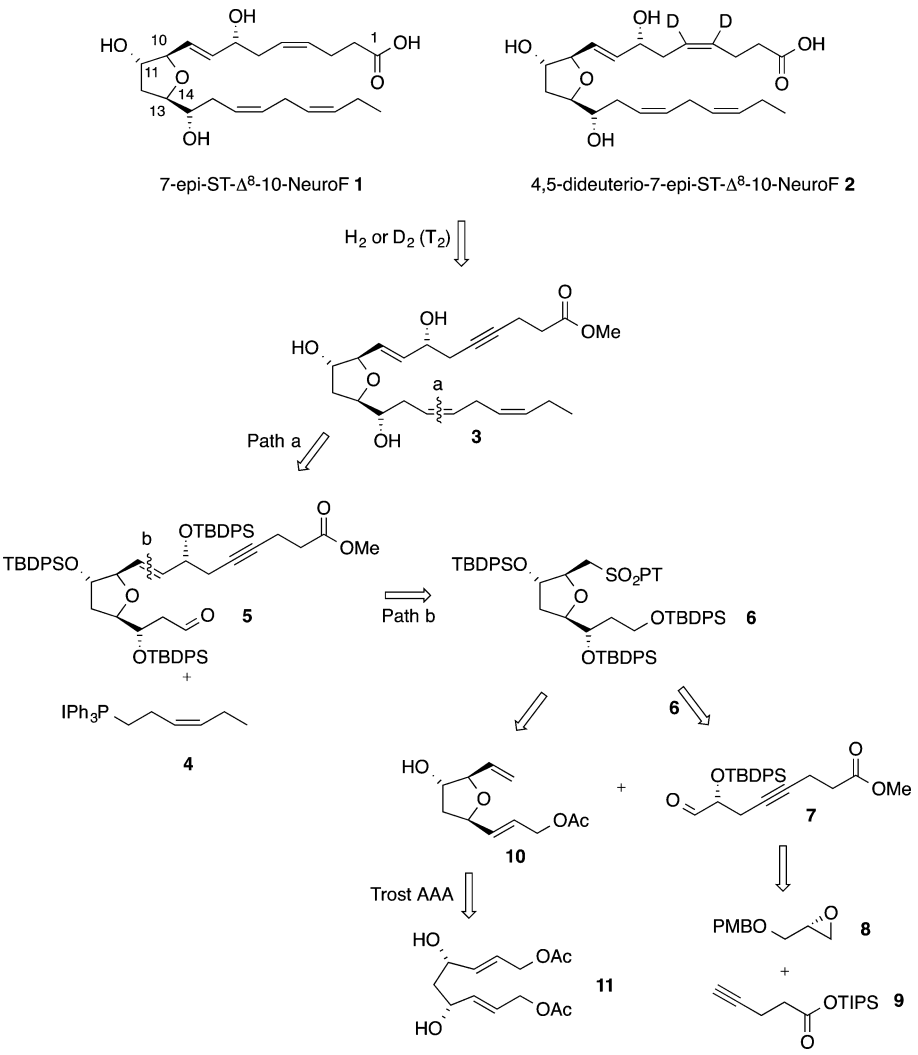


Figure 2. Retrosynthetic analysis of 7-*epi*-ST-Δ^8-10-neurofuran **1** and 4,5-dideuterio-7-*epi*-ST-Δ^8-10-neurofuran **2**. AAA = asymmetric allylic alkylation.

α and ω chains. Equally crucial was the introduction of a radioisotope labeling in the last step of the synthetic sequence, for which the Lindlar hydrogenation of a triple bond was deemed ideally suited. In the event, this labeling strategy has been validated by synthesizing 4,5-dideuterio-7-*epi*-ST-Δ^8-10-NeuroF **2** (Figure 2).

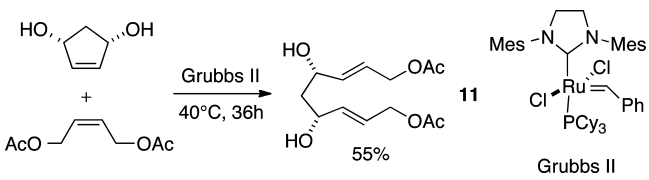
RESULTS AND DISCUSSION

Retrosynthetic Approach. According to our synthetic plan, both targets **1** and **2** appeared accessible from the key alkyne **3** (Figure 2). Retrosynthetically, this intermediate was envisaged to arise via sequential stereocontrolled installation of the lower and upper side chains, respectively. An *E*-stereoselective Wittig olefination of aldehyde **5** (path a) will be involved in the insallation of the lower side chain, while a Julia–Kocienski *Z*-alkene disconnection (path b) to sulfone **6** and alkyne aldehyde **7** will provide the upper side chian. The upper side chain precursor **7** seemed to be readily available through a regio- and stereocontrolled nucleophilic oxirane ring-opening of PMB-protected (*R*)-glycidol **8** by 4-pentynoic acid TIPS ester **9**. Finally, stereocontrolled synthesis of the heterocyclic core **6**, featuring four of the five stereocenters of the targets, could be traced back to an interesting desymmetrization of meso diol **11**, based on an intramolecular Pd-catalyzed Trost asymmetric allylic alkylation to give tetrahydrofuran **10**, followed by a straighforward manipulation of the resulting functional groups.

Synthesis of the Tetrahydrofuran Core 10. Diol **11** was prepared as a single (*E*,*E*)-stereoisomer (^{13}C NMR) in 55% isolated yield, in a single step, via ring-opening cross-metathesis of *cis*-cyclopent-4-ene-1,3-diol with (*Z*)-1,4-diacetoxybut-2-ene, both commercially available, using Grubbs II catalyst (Scheme 1).[3]

Although compound **10** was reported in the literature as the undesired product of Pd-catalyzed cyclization of diol **11** to a key synthetic precursor of halichondrin F-ring, we were unable

Scheme 1. Synthesis of (*R*,*S*)-Diol 10[a]



[a]Mes: 2,4,6-trimethylphenyl.

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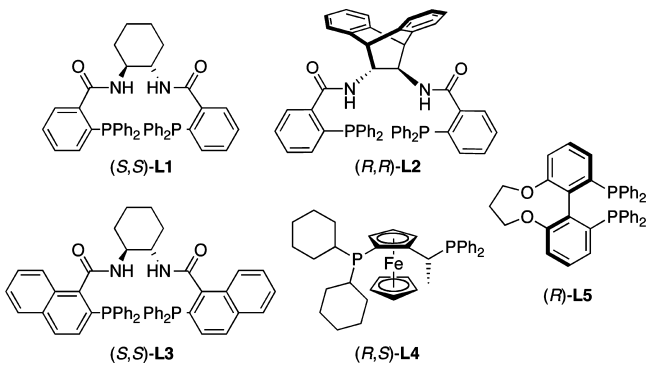
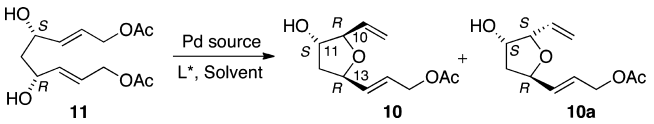


Figure 3. List of chiral ligands used in the Trost asymmetric cycloheterification.

Table 1. Asymmetric Allylic Palladium-Mediated Cyclization of *meso*-Diacetate 11[a]



entry	ligand	solvent	dr[b]	**10** ee (%)[c]	**10a** ee (%)[c]	yield (%)
1	(*S*,*S*)-**L1**	THF	61:39	94	11	61[d]
2	(*S*,*S*)-**L1**	CH_2Cl_2	80:20	96	3	86
3	(*R*,*R*)-**L2**	CH_2Cl_2	34:66	93	88	70
4	(*S*,*S*)-**L3**	CH_2Cl_2	37:63	89	28	82
5	(*R*,*S*)-**L4**	CH_2Cl_2	11:89	5	40[e]	17
6	(*R*)-**L5**	CH_2Cl_2	9:91	87	8[e]	10
7	(*R*,*R*)-**L2**	CH_2Cl_2	17:83	95	92	65[f]

[a]Unless otherwise noted, reactions were carried out at rt with $Pd_2(dba)_3{\cdot}CHCl_3$ adduct (3 mol %), chiral ligand L* (8 mol %), **11** (0.2 mmol), Cs_2CO_3 (1.05 equiv), solvent (2 mL, 0.1 M). [b]dr **10**:**10a** was determined by HPLC. [c]Enantiomeric excess was determined by chiral HPLC on Chiralpak AS-H and AS-3 columns. [d]Cs_2CO_3 was not used; $Pd_2(dba)_3{\cdot}CHCl_3$ (8 mol %) and ligand (*S*,*S*)-**L1** (31 mol %) were employed. [e]The corresponding *ent*-**10a** (10*R*,11*R*,13*S*) stereoisomer was obtained. [f]Reaction was carried out at −20 °C.

to reproduce the original data under the described experimental conditions.[4] In fact, cyclization of **11** could be only promoted by using 8 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ as the Pd source and 31 mol % of cyclohexyldiamine-derived ligand (*S*,*S*)-**L1** in THF at rt (Figure 3).

Under these conditions, mixture of two tetrahydrofurans ST-like **10**, 94% ee, and AC-like **10a**, 11% ee, in 61% isolated yield and 61:39 dr (HPLC) was obtained (Table 1, entry 1). This result was, indeed, rather unexpected since the significant formation of **10a** was not reported in the original work.[4] Catalyst loading could be reduced to 8 mol % of ligand and 3 mol % of Pd-precatalyst by adding Cs_2CO_3 and using DCM as a solvent.[5] Under these modified conditions (Table 1, entry 2), ST-tetrahydrofuran **10** was obtained in 80:20 dr (HPLC) and 96% ee, accompanied by the AC-diastereomer **10a**, 10% ee, in an overall yield of 85%.

The two compounds **10** and **10a** could not be separated by preparative column chromatography; therefore, we attempted to increase the diastereoselectivity of the cyclization step by changing ligands and temperature (Table 1).

Although no significant dr improvement was obtained, some results deserve an additional comment. In particular, we observed an unanticipated inversion in the diastereomeric products distribution in favor of **10a**, simply using the anthracenyldiamine-derived ligand (*R*,*R*)-**L2** instead of (*S*,*S*)-**L1**. In fact, the dr of **10a**:**10** was 66:34 for the reaction carried out at rt, the two diastereomers being obtained in 88% and 93% ee, respectively (Table 1, entry 3). Furthermore, lowering the reaction temperature to −20 °C resulted in an increase of the dr to 83:17 with a concomitant improvement of the enantiomeric excess of both **10a** and **10** to 92 and 95%, respectively (Table 1, entry 7).

Absolute configurations of 10*R*,11*S*,13*R* for **10** and 10*S*,11*S*,13*R* for **10a** were established by studies of the corresponding Mosher esters and n.O.e NMR spectra.[6] The Mosher method for enantioenriched **10** and **10a**, has been applied on the products of entry 2 and entry 7 (Table 1), while NOE studies were carried out on chromatographically separated *O*-TBDPS **12** and **12a** ethers.

Thus, the simple use of (*R*,*R*)-**L2** ligand enabled a straightforward entry to the AC neurofuran class in good yield and high enantiomeric excess, starting from the readily available meso diol **11**. This result stands in sharp contrast with the method previously developed by Burke and co-workers to build an enantioenriched *trans*-2,5-disubstituted THF-ring like **10a**. Actually, in that approach, an enantioenriched chiral diol,[7] prepared in 9.5% overall yield from prop-2-ynol and 4-chlorobut-2-ynol, had to be submitted to two enantioselective transformations, namely an asymmetric Sharpless epoxidation and a Pd-mediated Trost AAA, to establish the absolute stereochemistry.[4]

According to the asymmetric induction model proposed by Trost for the Pd-catalyzed AAA,[8] we can speculate that the stereoisomer **10** would be produced by the preferential coordination of the (*S*,*S*)-**L1**-Pd complex on the *Si* face of the allylic acetate moiety in **10** near the (*S*)-OH group.

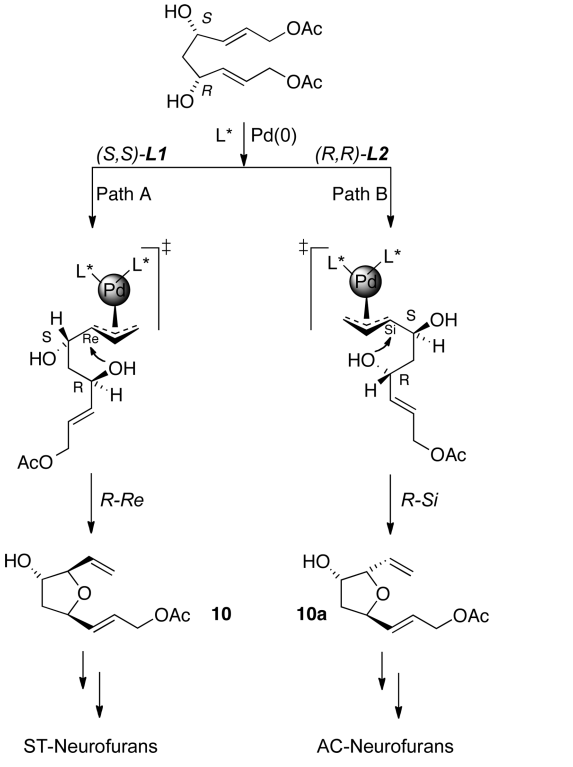


Figure 4. Stereochemical picture of asymmetric allylic Pd-mediated cyclization of *meso*-diacetate **11**.

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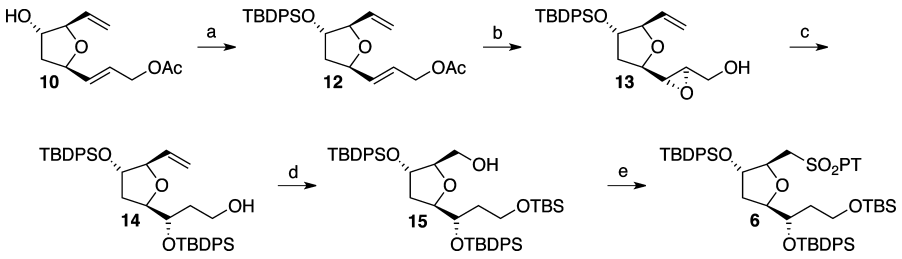
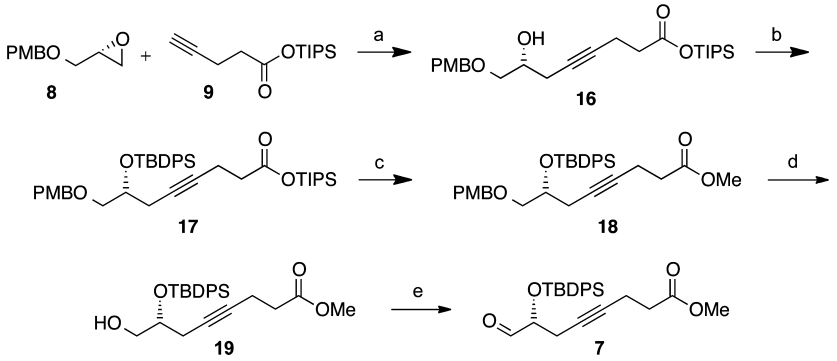
Scheme 2. Synthesis of Sulfone 6[a]



[a]Key: (a) TBDPSCl, Im, CH_2Cl_2, rt, 6 h, 74%, (ii) chromatographic separation; (b) (i) K_2CO_3, MeOH, rt, 20h, 94%, (ii) $Ti(iOPr)_4$, (−)-DET, *t*-BuOOH, CH_2Cl_2, −20 °C, 18 h, 89%; (c) Red-Al, THF, −30 to 0 °C, 6 h, 72%; (d) (i) TBSCl, Im, CH_2Cl_2, rt, 1 h, then TBDPSCl, Im, rt, 91%, (ii) O_3, CH_2Cl_2/MeOH (2:1), −78 °C, 1 h, then DMS, −78 °C to rt, 12 h, 89%, (iii) $NaBH_4$, MeOH, 0 °C, 1 h, 91%; (e) (i) PTSH, DEAD, Ph_3P, toluene, rt, 3 h, 85%, (ii) H_2O_2, $(NH_4)_2MoO_4$, *i*-PrOH, rt, 95%, (iii) TBSCl, Im, CH_2Cl_2, rt, 95%. PTSH = 1-phenyl-1*H*-tetrazole-5-thiol, Red-Al = sodium bis(2-methoxyethoxy)aluminum dihydride.

Scheme 3[a]



[a]Key: (a) BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 2 h, 71%; (b) TBDPSCl, Im, CH_2Cl_2, rt, 2 h, 97%; (c) K_2CO_3, THF/H_2O (1:1), rt, 16 h, followed by CH_3I, K_2CO_3, acetone, rt, 20 h, 79% over two steps; (d) DDQ, CH_2Cl_2/H_2O (3:1), rt, 1.45 h, 88%; (e) DMP, CH_2Cl_2, rt, 2 h, 75%.

Furan ring closure would thus result from intramolecular *anti* attack of the (*R*)-OH group on the *Re* face of the allylic Pd-complex, affording the prevalent (10*R*,11*S*,13*R*)-stereochemistry observed for **10** (Figure 4, path A). On the other hand, we assumed that the (*R*,*R*)-**L2**−Pd complex delivered the corresponding *trans*-diatereoisomer **10a** as preferentially the (10*S*,11*S*,13*R*)-enantiomer by nucleophilic addition of the (*R*)-OH onto the *Si* face of the (η^3-allyl)palladium complex intermediate (Figure 4, path B). Interestingly, using the enatiomers of ligands **L1** and **L2**, namely (*R*,*R*)-**L1** and (*S*,*S*)-**L2**, the corresponding enantiomers of **10** and **10a** were obtained with the same enantio- and diastereomeric excesses.

Synthesis of the Neurofurans 1 and 2. With a robust enantioselective cycloetherification protocol in hand, the synthesis of our two targets, nF **1** and the D_2-analogue **2**, proceeded in a straightforward manner from diacetate **11** through the preparation of the functionalized core **6** (Scheme 2) and the α side-chain reaction partner **7** (Scheme 3).

After silylation of the diastereomeric mixture of alcohol **10** and **10a**, silica gel chromatographic separation afforded diastereochemically pure *O*-TBDPS ether **12**. At this stage, the stereocenter at C-14 was introduced with the desired configuration by means of the asymmetric Sharpless epoxidation procedure,[9] followed by regioselective opening of the oxirane ring in **13** upon exposure to Red-Al at −30 °C. Diol **14** was thus obtained as a single stereoisomer (^{1}H NMR and ^{13}C NMR) in 60% overall yield from **10** (Scheme 2).[10]

Subsequently, diol **14** was fully protected as TBS ether and then the double bond was subjected to reductive ozonation to primary alcohol **15**. The key sulfone **6** was obtained by Mitsunobu thioetherification[11] (1-phenyl-1*H*-tetrazole-5-thiol, Ph_3P, DEAD), followed by Mo(VI)-mediated H_2O_2 oxidation.[12]

The α-side chain precursor **7** was obtained via nucleophilic addition of 4-pentynoic acid TIPS ester **9** to enantiopure PMB-protected (*R*)-glycidol **8** under Yamaguchi conditions (BuLi, −78 °C, followed by $BF_3{\cdot}Et_2O$ and epoxide **8**), as depicted in Scheme 3.

The corresponding PMB ether **16** was obtained as a single regioisomer in 71% isolated yield (^{1}H NMR and ^{13}C NMR).[13,14] Routine protective groups manipulation followed by Dess−Martin periodinane oxidation of alcohol **19** delivered the desired aldehyde **7** $[\alpha]^{20}_D$ = −25.7 (*c* = 1.63, CH_2Cl_2) in 75% isolated yield.[15]

For the completion of nF **1** and **2** synthesis, the upper and lower side chains were sequentially installed on sulfone **6** with the right *E* and *Z* stereochemistry, respectively, by means of a Julia−Kocienski and a Wittig reaction, respectively (Scheme 4).

In detail, condensation of lithiated sulfone **6** with aldehyde **7**, under the original conditions described by Kocienski, smoothly afforded the desired olefin **20** as a single (8*E*)-stereoisomer (^{13}C NMR) in 60% isolated yield.[16] Subsequently, selective TBS ether deprotection,[17] followed by Dess−Martin periodinane oxidation, delivered unstable aldehyde **5**, which was immediately exposed to a toluene solution of the ylide generated from phosphonium salt **4**[18] to afford the expected olefin **22** as a single (16*Z*)-stereoisomer (^{13}C NMR) in 63% isolated yield from **20**. Compound **22** was then elaborated into

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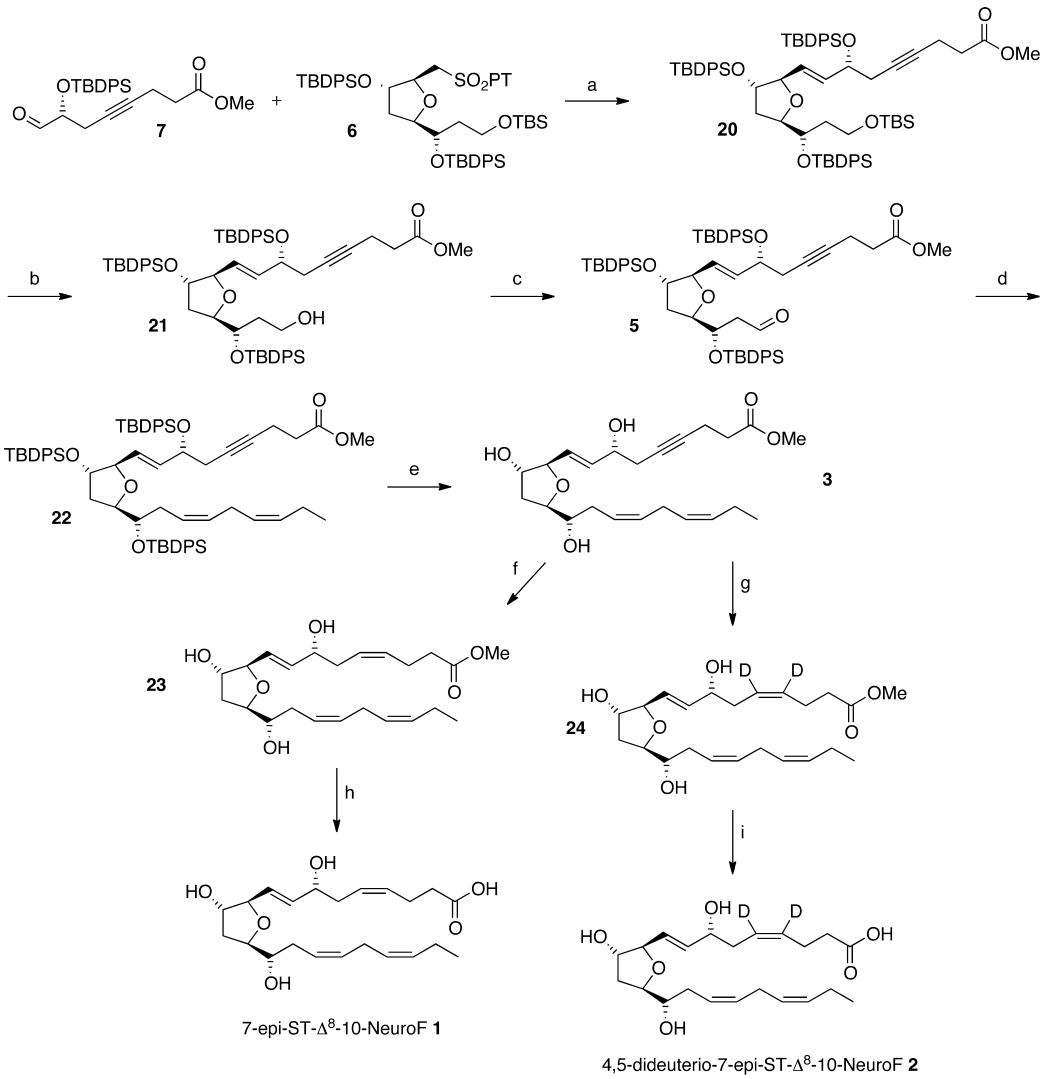
Scheme 4. Final Steps of Neurofuran Synthesis[a]



[a]Key: **6**, KHMDS, DME, −65 °C, 45 min, then **7**, −65 °C to rt, 1 h, 60%; (b) PPTS, CH_2Cl_2/MeOH (1:1), rt, 6 h, 86%; (c) DMP, CH_2Cl_2, rt, 0.75 h, 100%; (d) **4**, KHMDS, toluene, −95 °C to rt, 3.5 h, 74% over two steps; (e) TBAF, THF, rt, 2 days, followed by CH_2N_2, AcOEt, 0 °C, 0.25h, 55% over two steps; (f) Lindlar cat., H_2 (1 atm), quinoline, hexane/AcOEt (1:1), rt, 0.5 h, 80%; (g) Lindlar cat., D_2 (1 atm), quinoline, AcOEt/hexane (1:1), rt, 1 h, 73%; (h) H_2O, CAL-B, MTBE, rt, 18 h, 78%; (i) H_2O, CAL-B, MTBE, rt, 18 h, 81%. CAL-B = *Candida antarctica* lipase B.

key triene-yne triol **3** in 55% isolated yield by using routine protective groups manipulation. Finally, chemo- and stereoselective Lindlar hydrogenation[19] of the triple bond in **3**, afforded stereochemically pure *Z*-olefin **23** (^{13}C NMR) which was ezymatically hydrolyzed under "buffer-free" conditions,[20] delivering the 7-*epi*-ST-Δ^8-10-NeuroF **1** in 62% isolated yield, over two steps.

The corresponding 4,5-dideuterio-7-*epi*-ST-Δ^8-10-NeuroF **2** could be achieved in 59% isolated yield over two steps by using D_2 instead of H_2 in the Lindlar-mediated reduction.

CONCLUSION

In summary, we have developed a versatile strategy that has the potential to give access, in an enantioselective fashion, to different neurofurans via the highly convergent combination of the common meso building-block **10** with an aldehyde, e.g., **6**, and a phosphonium salt, e.g., **4**, both readily available.

Notably, the key Trost Pd-catalyzed cyclization protocol could be employed to efficiently construct the THF core ring of both the AC and ST series of neurofurans, by simply switching from an **L1**- to and **L2**-type chiral ligand. This streamlined approach will soon be utilized for the preparation of tritium-labeled neurofurans, to be employed for in vivo metabolism studies of this class of recently described DHA peroxidation products.[21] Moreover, a detailed study of the crucial AAA cycloetherification reaction is in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedures. All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF (Na/benzophenone), CH_2Cl_2, hexane, (CaH_2), toluene (Na/K). All other reagents were used as supplied. All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar in flame-dried glassware. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Routine monitoring of reactions was performed using silica gel 60 (0.25 mm), aluminum-supported TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to a 0.5% solution of vanillin in H_2SO_4/EtOH, followed by

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charring. Flash column chromatography (FCC) was performed on silica gel (40−63 μm). Yields are reported for isolated compounds with >96% purity established by NMR unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δC 77.00; residual $CHCl_3$ in $CDCl_3$: δH 7.26; CD_2Cl_2: δC 53.8; residual CH_2Cl_2 in CD_2Cl_2: δH 5.32 ppm). COSY, DEPT, NOESY spectra were recorded using a standard pulse program library. The number of H-atoms attached to each C-atom (s = 0H, d = 1H, t = 2H, q = 3H) was determined by DEPT experiments. Optical rotations were recorded on a digital polarimeter at 589 nm, concentration (c) in g/100 mL. Mass spectrometry was performed by Q-TOF using electrospray ionization (ESI) mode, [M + H$^+$]. (*S*,*S*)-**L1**, (*R*,*R*)-**L2**, (*S*,*S*)-**L3**, (*R*,*S*)-**L4**, and (*R*)-**L5** are commercially available.

(2*E*,7*E*)-4,6-Dihydroxynona-2,7-diene-1,9-diyl Diacetate (11). (*Z*)-1,4-Diacetoxy-2-butene (11868 mg, 69 mmol) was added to a dry bottom flask under Ar atmosphere. *cis*-4-Cyclopentene-1,3-diol (600 mg, 6 mmol) was then added, and the suspension was stirred at rt. After 10 min, Grubbs catalyst generation II (600 mg, 0.706 mmol) was added, and the reaction was stirred at 40 °C for 16 h. The reaction was monitored by TLC (hexane/EtOAc 3/7) and quenched by addition of CH_2Cl_2 (10 mL) and bubbling O_2 through reaction for 10 min. The CH_2Cl_2 was removed under vacuum, and the residue was purified by flash chromatography, eluting with hexane/EtOAc 4/6 to 3/7 to afford the pure product **11** as a pale yellow oil (898 mg, yield = 55%). FTIR (neat): 3432, 3006, 2942, 2882, 1739, 1436, 1382, 1366, 1242, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.86−5.72 (m, 4H), 4.54 (d, J = 4.1 Hz, 4H), 4.46−4.36 (m, 2H), 2.55−2.40 (bs, 2H), 2.05 (s, 6H), 1.70 (t, J = 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 136.4 (d), 124.6 (d), 72.0 (d), 64.1 (t), 43.0 (t), 20.9 (q). HRMS: calcd for $C_{13}H_{20}O_6$ 272.1260, found 272.1264

Trost Asymmetric Allylic Cyclization: Synthesis of (*E*)-3-((2*R*,4*S*,5*R*)-4-Hydroxy-5-vinyltetrahydrofuran-2-yl)allyl Acetate (10). Tetraol diacetate **11** (1.35 g, 4.96 mmol) was dissolved in dry CH_2Cl_2 (25 mL) under Ar, and solid Cs_2CO_3 was added in one portion. In a second two-necked round-bottom flask (*S*,*S*)-**L1** (284 mg, 0.411 mmol) was dissolved in dry CH_2Cl_2 (25 mL), and $Pd_2(dba)_3$ $CHCl_3$ adduct was added at once (156 mg, 0.151 mmol). After 20 min, the solution color changed form purple to orange, indicating the chiral Pd complex formation. Subsequently, this solution was cannulated to the substrate−Cs_2CO_3 suspension, and the mixture was stirred until complete conversion. The reaction was then filtered and concentrated under vacuum. The oily residue was purified by column chromatography on silica gel (hexane/Et_2O 4/6) to afford products **10** and **10a** (905 mg, 86% combined yield): **10** (HPLC: Chiralpak AS-H, heptane/*i*-PrOH 80:20, 1 mL/min, DAD detection, major peak at 12.2 min, minor peak at 6.6 min, 96% ee); **10a** (same conditions for **10**: major peak at 8.8 min, minor peak at 18.3 min, 3% ee); dr was calculated by the sum of the area peaks: 80:20, **10**:**10a**. $[\alpha]^{20}_D$ = +27.8 (c = 1.00, CH_2Cl_2). Data for analytical sample of **10** obtained after silyl ether separation (vide infra). TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 6/4). $[\alpha]^{21}_D$ = +38.57 (c = 0.7, CH_2Cl_2). FTIR (neat): 3427, 2957, 2922, 2872, 1737, 1643, 1369, 1230, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.93−5.77 (m, 3H), 5.37 (dt, J = 17.1, 1.5 Hz, 1H), 5.19 (dt, J = 10.5, 1.5 Hz, 1H), 4.70−4.63 (m, 1H), 4.58 (dd, J = 5.0, 0.9 Hz, 2H), 4.27 (ddt, J = 6.0, 2.9, 1.4 Hz, 1H), 4.20 (dt, J = 5.5, 2.7 Hz, 1H), 2.11−1.99 (m, 5H), 1.94−1.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.8 (s), 136.7 (d), 134.3 (d), 126.1 (d), 116.6 (t), 87.6 (d), 78.1 (d), 76.7 (d), 64.1 (t), 40.4 (t), 20.9 (q). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.27; H, 7.49.

Trost Asymmetric Allylic Cyclization: Synthesis of (*E*)-3-((2*R*,4*S*,5*S*)-4-Hydroxy-5-vinyltetrahydrofuran-2-yl)allyl Acetate (10a). Under the same procedure, at −20 °C, (*R*,*R*)-**L2** afforded products **10** and **10a** (65% yield): **7** (HPLC: Chiralpak AS-H, hexane/*i*-PrOH 80:20, 1 mL/min, DAD detection, major peak at 10.7 min, minor peak at 6.4 min, 95% ee); **10a** (same conditions for **10**: major peak at 14.8 min, minor peak at 8.1 min, 92% ee); dr was calculated by the sum of the area peaks: 17:83, **10**:**10a**. Data for analytical sample of **10** obtained after silyl ether separation (vide infra). TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 6/4). $[\alpha]^{21}_D$ = +30.46 (c = 1.30, CH_2Cl_2). FTIR (neat): 3427, 2957, 2922, 2872, 1737, 1643, 1369, 1230, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.98−5.80 (m, 3H), 5.51 (dt, J = 17.3, 1.7 Hz, 1H), 5.40 (dt, J = 10.6, 1.6 Hz, 1H), 4.78 (dt, J = 10.0, 5.2 Hz, 1H), 4.59 (d, J = 5.1 Hz, 2H), 4.57−4.51 (m, 1H), 4.36 (m, 1H), 2.28 (ddd, J = 13.2, 6.1, 1.2 Hz, 1H), 2.11−2.05 (s, 3H), 1.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 134.8 (d), 133.4 (d), 125.3 (d), 118.7 (t), 83.4 (d), 77.7 (d), 73.6 (d), 64.1 (t), 41.6 (t), 20.9 (q). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.26; H, 7.52.

Synthesis of (*E*)-3-((2*R*,4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyl)-oxy)-5-vinyltetrahydrofuran-2-yl)allyl acetate (12). To a magnetically stirred solution of **10** and **10a** (1.95 g, 9.19 mmol) in dry CH_2Cl_2 (90 mL) under Ar were added at rt imidazole (1.56 g, 22.9 mmol) and TBDPSCl (2.9 mL, 11.2 mmol). The reaction was completed after 6 h and was quenched with H_2O (90 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column (hexane/EtOAc 98/2, 95/5 and 9/1 as eluent) to afford the product (3.05 g of **12**, yield =74% and 370 mg of **12a**, yield = 8.9%). TLC (SiO_2): R_f = 0.2 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = +27.9 (c = 1.17, CH_2Cl_2). FTIR (neat): 2932, 2858, 1741, 1428, 1232 1113, 1078, 1026, 740, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80−7.60 (m, 4H), 7.50−7.30 (m, 6H), 5.95−5.70 (m, 2H), 5.55−5.40 (m, 1H), 5.20−5.05 (dt, J = 17.1, 1.7 Hz, 1H), 5.05−4.95 (dt, J = 10.4, 1.4 Hz, 1H), 4.80−4.70 (m, 1H), 4.60.4−50 (d, J = 5.7 Hz, 2H), 4.35−4.20 (m, 1H), 4.20−4.10 (m, 1H), 2.08 (s, 3H), 2.00−1.90 (ddd, J = 12.8, 5.2, 1.7 Hz, 1H), 1.70−1.55 (m, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 136.8 (d), 135.8 (d), 135.7 (d), 134.5 (d), 133.6 (s), 133.6 (s), 129.8 (d), 127.7 (d), 126.0 (d), 115.8 (t), 87.9 (d), 78.6 (d), 78.2 (d), 64.2 (t), 40.8 (t), 26.9 (q), 20.9 (q), 19.1 (s). HRMS: calcd for $C_{27}H_{34}O_4Si$ 450.2226, found 450.2231

Synthesis of ((2*R*,3*R*)-3-((2*R*,4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)oxiran-2-yl)methanol (13). *Acetate Hydrolysis.* To a magnetically stirred solution of **12** (3.02 g, 6.70 mmol) in MeOH (67 mL) was added K_2CO_3 (51 mg, 0.369 mmol) at rt. After 20 h, the reaction was completed and was filtered and concentrated under vacuum. The residue was purified by chromatography on a silica gel column (hexane/EtOAc 8/2 as eluent) to afford the corresponding primary alcohol as a light yellow oil (2.57 g, yield = 94%). TLC (SiO_2): R_f = 0.24 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = +32.8 (c = 1.05, CH_2Cl_2). FTIR (neat): 3400, 3072, 2932, 2858, 1472, 1428, 1363, 1113, 740, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70−7.60 (m, 4H), 7.50−7.35 (m, 6H), 6.00−5.90 (dtd, J = 16.3, 5.3, 0.9 Hz, 1H), 5.80−5.65 (ddt, J = 15.4, 7.1, 1.4 Hz, 1H), 5.60−5.40 (m, 1H), 5.20−5.05 (dt, J = 17.1, 1.6 Hz, 1H), 5.05−4.95 (dt, J = 10.4, 1.4 Hz, 1H), 4.85−4.70 (m, 1H), 4.35−4.30 (m, 1H), 4.20−4.10 (m, 3H), 2.00−1.90 (ddd, J = 12.8, 5.2, 1.7 Hz, 1H), 1.65−1.55 (m, 1H), 1.55−1.45 (m, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.9 (d), 135.8 (d), 135.7 (d), 134.5 (d), 133.7 (s), 133.6 (s), 131.5 (d), 131.5 (d), 129.8 (d), 127.7 (d), 115.7 (t), 87.8 (d), 78.8 (d), 78.3 (d), 62.9 (t), 40.8 (t), 26.9 (q), 19.1 (s). HRMS: calcd for $C_{25}H_{32}O_3Si$ 408.2121, found 408.2127.

Sharpless Asymmetric Epoxidation. To a dry round-bottom flask under Ar were added activated molecular sieves type 4 Å (200 mg), dry CH_2Cl_2 (16 mL), D-(−)-DET (110 μL, 0.643 mmol), and *t*-BuOOH (3.2 mL, 5.5 M in decane, 17.6 mmol), and the solution was stirred for 20 min at rt. The suspension was cooled to −20 °C, and Ti(O-*i*-Pr)$_4$ (135 μL, 0.461 mmol) was added. The solution was stirred at −20 °C for 20 min in order to obtain the chiral complex. In a second round-bottom flask under Ar were added at rt the primary alcohol (1.82 g, 4.45 mmol), dry CH_2Cl_2 (16 mL) and activated molecular sieves type 4 Å (200 mg). The suspension was stirred at rt for 20 min and then cooled to −20 °C. The solution of allylic alcohol **21**[21] was added dropwise to the solution of the chiral complex at −20 °C, and when the reaction was complete it was quenched at −20 °C

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with a solution of 10% (+)-tartaric acid (30 mL). The temperature was allowed to reach rt, and H_2O (30 mL) was added to the reaction in order to dissolve the molecular sieves. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography on a silica gel column using hexane/EtOAc 8/2 as eluent to afford the pure product **13** as a colorless to pale yellow oil (1.69 g, yield = 89%). TLC (SiO_2): R_f = 0.24 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = +38.9 (c = 1.03, CH_2Cl_2). FTIR (neat): 3436, 3071, 2932, 2858, 1472, 1428, 1112, 1078, 997, 931, 823, 739, 703, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.60 (m, 4H), 7.55−7.35 (m, 6H), 5.60−5.40 (m, 1H), 5.20−5.05 (dt, J = 17.1, 1.4 Hz, 1H), 5.05−4.95 (dt, J = 10.4, 1.4 Hz, 1H), 4.40−4.25 (m, 2H), 4.24−4.10 (m, 1H), 4.00−3.85 (m, 1H), 3.75−3.55 (m, 1H), 3.15−3.00 (m, 2H), 2.10−2.00 (t, J = 6.4 Hz, 1H), 2.00−1.90 (ddd, J = 12.7, 5.7, 2.2 Hz, 1H), 1.80−1.65 (m, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.4 (d), 135.8 (d), 135.7 (d), 133.5 (s), 133.5 (s), 129.8 (d), 127.7 (d), 116.2 (t), 87.8 (d), 78.0 (d), 77.8 (d), 61.2 (t), 56.8 (d), 56.2 (d), 36.4 (t), 26.9 (q), 19.0 (s). HRMS: calcd for $C_{25}H_{32}O_4Si$ 424.2017, found 424.2013.

Synthesis of (*S*)-1-((2*R*,4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyl)-oxy)-5-vinyltetrahydrofuran-2-yl)propane-1,3-diol (14). To a magnetically stirred solution of **13** (1.69 g, 3.98 mmol) in dry THF (40 mL) under Ar at −30 °C was added Red-Al (3.0 mL, 9.84 mmol), and the temperature after 1 h was allowed to reach 0 °C. When the reaction was complete, it was quenched with saturated aq potassium sodium tartrate (40 mL), H_2O (80 mL), and Et_2O (40 mL). The mixture was stirred at rt until two layers were observed. The layers were separated, and the aq layer was extracted with CH_2Cl_2 (3 × 80 mL). The comined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column using hexane/EtOAc 1/1 as eluent to afford the product **14** as a yellowish oil (1.22 g, yield = 72%). TLC (SiO_2): R_f = 0.22 (hexane/EtOAc 1/1). $[\alpha]^{21}_D$ = +19.8 (c = 0.84, CH_2Cl_2). FTIR (neat): 3392, 3071, 2931, 2858, 1472, 1428, 1363, 1112, 1058, 998, 930, 823, 740, 702, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.60 (m, 4H), 7.50−7.35 (m, 6H), 5.55−5.40 (m, 1H), 5.10−4.95 (m, 2H), 4.35−4.20 (m, 2H), 4.20−4.10 (m, 1H), 4.10−3.95 (dt, J = 9.46, 3.59 Hz, 1H), 3.90−3.80 (t, J = 5.73 Hz, 2H), 2.60−2.30 (bs, 2H), 1.95−1.75 (m, 2H), 1.75−1.55 (m, 2H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.5 (d), 135.8 (d), 135.7 (d), 133.6 (s), 133.6 (s), 129.8 (d), 127.7 (d), 116.5 (t), 87.9 (d), 81.6 (d), 78.1 (d), 72.0 (d), 61.7 (t), 34.5 (t), 34.3 (t), 26.9 (q), 19.1 (s). HRMS: calcd for $C_{25}H_{34}O_4Si$ 426.2226, found 426.2231.

Synthesis of ((2*R*,3*S*,5*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-((*S*)-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)tetrahydrofuran-2-yl)methanol (15). *Diol **14** Protection.* To a magnetically stirred solution of **14** (1.22 g, 2.86 mmol) in dry CH_2Cl_2 (28 mL) under Ar were added at rt imidazole (238 mg, 3.50 mmol) and TBSCl (467 mg, 3.10 mmol). When the primary alcohol was protected, imidazole (982 mg, 14.4 mmol) and TBDPSCl (900 mL, 3.46 mmol) were added to the reaction in order to complete the protection. The reaction was stirred at rt and was quenched with H_2O (50 mL). The layers were separated, and the aq layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column using hexane/Et_2O 97/3 as eluent to afford the bis-silyl ether product as a slight yellow oil (2.03 g, yield = 91%). TLC (SiO_2): R_f = 0.22 (hexane/Et_2O 97/3). $[\alpha]^{21}_D$ = −3.7 (c = 0.98, CH_2Cl_2). FTIR (neat): 3071, 2930, 2857, 1472, 1428, 1258, 1111, 1006, 937, 834, 776, 739, 701, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.55 (m, 8H), 7.50−7.25 (m, 12H), 5.50−5.35 (m, 1H), 5.15−5.00 (d, J = 17.2 Hz, 1H), 5.00−4.85 (d, J = 10.4 Hz, 1H), 4.25−4.10 (m, 2H), 4.05−3.95 (m, 1H), 3.95−3.85 (m, 1H), 3.60−3.40 (m, 2H), 1.80−1.55 (m, 4H), 1.1 (s, 9H), 1.0 (s, 9H), 0.8 (s, 9H), −0.1 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.7 (d), 136.0 (d), 135.9 (d), 135.8 (d), 134.2 (s), 133.9 (s), 133.6 (s), 129.7 (d), 129.5 (d), 129.4 (d), 127.6 (d), 127.4 (d), 127.4 (d), 116.3 (t), 87.5 (d), 81.3 (d), 77.6 (d), 72.3 (d), 59.8 (t), 37.5 (t), 36.2 (t), 27.0 (q), 26.9 (q), 25.9 (q), 19.5 (s), 19.1 (s), 18.2 (s), −5.4 (q), −5.4 (q). HRMS: calcd for $C_{47}H_{66}O_4Si_3$ 778.4269, found 778.4262.

Ozonolysis. To a magnetically stirred solution of bis-silyl ether (130 mg, 0.167 mmol) in CH_2Cl_2/MeOH 2/1 (15 mL) at −78 °C was added a mixture of O_3/O_2 until the color of the solution became cyan (45 min). When the starting material disappeared O_2 was added at −78 °C until the solution became colorless. N_2 was then added in order to move the residue away from O_2. At −78 °C. a solution of Pyridine (15 mg) in DMS (160 mL, 2.71 mmol) was added, and the reaction was allowed to reach rt and was stirred for 1 h. The reaction was concentrated under vacuum and to the residue were added Et_2O (15 mL) and H_2O (15 mL). The layers were separated, and the aq layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 95/5 as eluent to afford the pure aldehyde product as a yellowish oil (116 mg, yield = 89%). TLC (SiO_2): R_f = 0.2 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = −7.7 (c = 1.13, CH_2Cl_2). FTIR (neat): 2930, 2857, 1735, 1472, 1428, 1256, 1111, 835, 777, 740, 701, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.20 (d, J = 1.6 Hz, 1H), 7.75−7.55 (m, 8H), 7.50−7.25 (m, 12H), 4.45−4.30 (m, 2H), 4.20−4.15 (m, 1H), 4.10−3.95 (m, 1H), 3.65−3.45 (m, 2H), 1.85−1.60 (m, 3H), 1.55−1.45 (m, 1H), 1.1 (s, 9H), 1.0 (s, 9H), 0.8 (s, 9H), −0.04 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 200.9 (d), 136.0 (d), 135.9 (d), 135.8 (d), 135.7 (d), 133.9 (s), 133.4 (s), 132.9 (s), 129.9 (d), 129.9 (d), 129.6 (d), 129.6 (d), 127.8 (d), 127.7 (d), 127.5 (d), 127.5 (d), 91.0 (d), 82.8 (d), 75.1 (d), 71.8 (d), 59.6 (t), 37.3 (t), 36.9 (t), 27.0 (q), 26.8 (q), 25.9 (q), 19.5 (s), 19.1 (s), 18.2 (s), −5.4 (q). HRMS: calcd for $C_{46}H_{64}O_5Si_3$ 780.4062, found 780.4068

*Synthesis of **15**.* To a magnetically stirred solution of aldehyde (204 mg, 0.261 mmol) in MeOH (5 mL) was added $NaBH_4$ (20 mg, 0.522 mmol) at 0 °C, and the reaction was stirred at 0 °C. After 1 h, the reaction was completed and was quenched at 0 °C with acetone (1 mL) and then was allowed to reach rt. The reaction was concentrated under vacuum, and to the residue were added saturated aq NH_4Cl (10 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column (hexane/EtOAc 9/1 as eluent) to afford the desired product **15** (166 mg, yield = 91%). TLC (SiO_2): R_f = 0.25 (hexane/EtOAc 9/1). $[\alpha]^{21}_D$ = +9.0 (c = 1.21, CH_2Cl_2). FTIR (neat): 2931, 1560, 1474, 1427, 1113 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80−7.55 (m, 8H), 7.55−7.30 (m, 12H), 4.33−4.22 (m, 1H), 4.20−4.10 (m, 1H), 4.10−4.00 (m, 1H), 3.90−3.80 (m, 1H), 3.65−3.40 (m, 2H), 3.38−3.25 (m, 1H), 3.05−2.92 (m, 1H), 1.90−1.55 (m, 5H), 1.08 (s, 9H), 1.04 (s, 9H), 0.85 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 135.9 (d), 135.8 (d), 135.7 (d), 134.1 (s), 133.9 (s), 133.7 (s), 129.8 (d), 129.7 (d), 129.6 (d), 127.7 (d), 127.5 (d), 87.3 (d), 81.5 (d), 74.5 (d), 71.9 (d), 63.1 (t), 59.8 (t), 37.5 (t), 36.8 (t), 27.0 (q), 26.9 (q), 25.9 (q), 19.4 (s), 19.0 (s), 18.2 (s), −5.4 (q). HRMS: calcd for $C_{46}H_{66}O_5Si_3$ 782.4218, found 782.4222.

Synthesis of 5-((((2*S*,3*S*,5*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-5-((*S*)-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)tetrahydrofuran-2-yl)methyl)thio)-1-phenyl-1*H*-tetrazole (6). *Mitsunobu Reaction.* To a magnetically stirred solution of **15** (154 mg, 0.196 mmol) in dry toluene (2 mL) under Ar at rt were added PPh_3 (67 mg, 0.255 mmol), PTSH (38.5 mg, 0.216 mmol), and DEAD (120 mL, 0.262 mmol). The reaction was completed after 3 h and was concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 95/5 as eluent to afford the sulfide product as white foam (158 mg, yield = 85%). TLC (SiO_2): R_f = 0.2 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = −1.9 (c = 1.58, CH_2Cl_2). FTIR (neat): 2930, 2857, 1500, 1472, 1428, 1251, 1111, 834, 776, 740, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.70−7.20 (m, 25H), 4.30−4.20 (m, 1H), 4.20−

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4.05 (m, 2H), 4.05−3.95 (m, 1H), 3.60−3.40 (m, 2H), 3.39−3.34 (dd, J = 12.9, 4.3 Hz, 1H), 2.93−2.86 (dd, J = 12.9, 8.2 Hz, 1H), 1.90−1.75 (m, 2H), 1.75−1.40 (m, 2H), 1.09 (s, 9H), 1.02 (s, 9H), 0.84 (s, 9H), −0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.1 (s), 136.0 (d), 135.9 (d), 135.8 (d), 135.7 (d), 134.0 (s), 133.9 (s), 133.2 (s), 129.9 (d), 129.8 (d), 129.8 (d), 129.7 (d), 129.5 (d), 129.4 (d), 127.8 (d), 127.7 (d), 127.4 (d), 127.3 (d), 123.7 (d), 84.1 (d), 81.8 (d), 76.5 (d), 71.6 (d), 59.6 (t), 37.4 (t), 35.9 (t), 27.0 (q), 26.9 (q), 25.9 (q), 19.4 (s), 19.0 (s), 18.2 (s), −5.4 (q). HRMS: calcd for $C_{53}H_{70}N_4O_4SSi_3$ 942.4426, found 942.4433

Sulfone Oxidation. To a magnetically stirred solution of sulfide (158 mg, 0.167 mmol) in *i*PrOH (3 mL) were added at rt $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (120 mg, 0.097 mmol) and H_2O_2 35 wt % (800 μL, 9.1 mmol). The reaction was monitored by TLC (hexane/EtOAc 8/2), and every day $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.2 equiv) and H_2O_2 (15 equiv) were added until complete conversion was reached. The reaction was added dropwise to a stirred saturated aq Na_2SO_3 (5 mL) at 0 °C. The organic layer was concentrated under vacuum. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum.

The residue was dissolved in dry CH_2Cl_2 (2 mL) under Ar and at rt imidazole (55.8 mg, 0.820 mmol) and TBSCl (45 mg, 0.299 mmol) were added. The reaction was stirred at rt for 2 h and was quenched with H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined combined organic layers over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 95/5 as eluent to afford the product **6** as a yellowish oil (155 mg, yield = 95%). TLC (SiO_2): R_f = 0.2 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = +16.8 (c = 1.55, CH_2Cl_2). FTIR (neat): 2931, 2858, 1498, 1474, 1428, 1356, 1256, 1112, 835, 763, 740, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.25 (m, 25H), 4.20−4.05 (m, 2H), 4.00−3.90 (m, 1H), 3.85−3.75 (m, 1H), 3.58−3.38 (m, 2H), 3.22−3.00 (m, 2H), 1.87−1.70 (m, 2H), 1.52−1.35 (m, 2H), 1.07 (s, 9H), 1.00 (s, 9H), 0.84 (s, 9H), −0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 153.7 (s), 136.0 (d), 135.9 (d), 135.7 (d), 135.7 (d), 134.0 (s), 133.6 (s), 133.0 (s), 131.2 (d), 130.2 (d), 130.0 (d), 129.6 (d), 129.6 (d), 129.4 (d), 128.0 (d), 127.8 (d), 127.5 (d), 127.5 (d), 125.6 (d), 82.1 (d), 79.2 (d), 76.2 (d), 71.7 (d), 59.4 (t), 58.4 (t), 36.8 (t), 35.4 (t), 27.0 (q), 26.8 (q), 25.9 (q), 19.4 (s), 18.9 (s), 18.2 (s), −5.4 (q). HRMS: calcd for $C_{53}H_{70}N_4O_6SSi_3$ 974.4324, found 974.4319.

Synthesis of (*R*)-Triisopropylsilyl 7-hydroxy-8-((4-methoxybenzyl)oxy)oct-4-ynoate (16). To a magnetically stirred solution of **9** (2.75 g, 10.8 mmol) in dry THF (40 mL) under Ar at −78 °C was added dropwise *n*-BuLi (6.75 mL, 10.8 mmol). After 1 h, $BF_3{\cdot}Et_2O$ (1.35 mL, 10.7 mmol) was added, and after 10 min, **8** (1.05 g, 5.41 mmol) in dry THF (5 + 5 mL) was added. The reaction was monitored by TLC (hexane/EtOAc 8/2) and was quenched after 2 h at −78 °C with saturated aq NH_4Cl (60 mL) and CH_2Cl_2 (70 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 70 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromathography (hexane/EtOAc 9/1 as eluent) to afford the pure product **25** as a pale yellow oil (1.72 g, yield =71%). TLC (SiO_2): R_f = 0.24 (hexane/EtOAc 9/1). $[\alpha]^{21}_D$ = −6.5 (c = 0.71, CH_2Cl_2). FTIR (neat): 3430, 2946, 2868, 1718, 1613, 1514, 1466, 1369, 1248, 1174, 1105, 1037, 883, 820, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32−7.25 (m, 2H), 6.95−6.85 (dd, J = 6.6, 2.1 Hz, 2H), 4.55−4.45 (s, 2H), 3.95−3.85 (m, 1H), 3.83 (s, 3H), 3.63−3.53 (dd, J = 9.5, 4.0 Hz, 1H), 3.50−3.42 (dd, J = 9.5, 6.7 Hz, 1H), 2.60−2.52 (m, 2H), 2.52−2.43 (m, 2H), 2.42−2.35 (m, 2H), 2.35−2.20 (bs, 1H), 1.40−1.20 (m, 3H), 1.15−1.05 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.0 (s), 159.3 (s), 130.0 (s), 129.4 (d), 113.8 (d), 81.0 (s), 77.2 (s), 73.0 (t), 72.7 (t), 69.0 (d), 55.3 (q), 35.4 (t), 23.8 (t), 17.7 (q), 15.1 (t), 11.9 (d). HRMS: calcd for $C_{25}H_{40}O_5Si$ 448.2645, found 448.2650

Synthesis of (*R*)-Triisopropylsilyl 7-((*tert*-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)oct-4-ynoate (17). To a magnetically stirred solution of **16** (1.65 g 3.68 mmol) in dry CH_2Cl_2 (30 mL) under Ar were added imidazole (756 mg, 11.1 mmol) and TBDPSCl (1.0 mL, 3.85 mmol). The reaction was completed after 2 h and was quenched with H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried on $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column (hexane/EtOAc 95/5) to afford the product **17** as a slightly yellow oil (2.45 g, yield = 97%). TLC (SiO_2): R_f = 0.26 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = +0.47 (c = 0.85, CH_2Cl_2). FTIR (neat): 2946, 2867, 1719, 1514, 1465, 1428, 1368, 1301, 1248, 1174, 1112, 1038, 884, 822, 740, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.65 (dd, J = 7.8, 1.4 Hz, 4H), 7.50−7.30 (m, 6H), 7.20−7.10 (d, J = 8.7 Hz, 2H), 6.90−6.80 (d, J = 8.6 Hz, 2H), 4.40−4.30 (d, J = 3.5 Hz, 2H), 4.00−3.90 (m, 1H), 3.82 (s, 3H), 3.53−3.40 (m, 2H), 2.50−2.25 (m, 6H), 1.40−1.20 (m, 3H), 1.15−1.05 (m, 27H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.1 (s), 159.0 (s), 136.0 (d), 135.9 (d), 134.1 (s), 133.9 (s), 130.5 (s), 129.6 (d), 129.5 (d), 129.1 (d), 127.5 (d), 113.6 (d), 80.1 (s), 72.8 (t), 72.8 (t), 71.0 (d), 55.3 (q), 35.4 (t), 26.9 (q), 24.5 (t), 19.3 (s), 17.7 (q), 15.1 (t), 11.9 (d). HRMS: calcd for $C_{41}H_{58}O_5Si_2$ 686.3823, found 686.3799.

Synthesis of (*R*)-Methyl 7-((*tert*-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)oct-4-ynoate (18). To a magnetically stirred solution of **17** (2.45 g, 3.57 mmol) in THF (10 mL) at rt were added H_2O (10 mL) and K_2CO_3 (1.51 g, 10.9 mmol). After 16 h of stirring at rt, the reaction was quenched with saturated aq $NaHSO_4$ (20 mL), H_2O (20 mL), and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in acetone (20 mL), and under stirring at rt K_2CO_3 (750 mg, 5.43 mmol) and MeI (2.3 mL, 36.6 mmol) were added. After 20 h of stirring at rt the reaction was filtered, and the residue was washed with Et_2O (20 mL). The filterate was concentrated under vacuum, and the residue was recovered with Et_2O (30 mL) and H_2O (30 mL). The aqueous layer separated was extracted with Et_2O (3 × 40 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 95/5 as eluent) to afford the product **18** as a limpid yellowish oil (1.53 g, yield =79%). TLC (SiO_2): R_f = 0.30 (hexane/EtOAc 95/5). $[\alpha]^{21}_D$ = +2.0 (c = 3.6, CH_2Cl_2). FTIR (neat): 3448, 2933, 1735, 1654, 1618, 1560, 1509, 1458, 1174, 823 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75−7.65 (m, 4H), 7.50−7.30 (m, 6H), 7.20−7.10 (d, J = 8.6 Hz, 2H), 6.90−6.80 (d, J = 8.6 Hz, 2H), 4.42−4.27 (m, 2H), 4.02−3.90 (m, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.53−3.40 (m, 2H), 2.50−2.25 (m, 6H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.5 (s), 159.0 (s), 135.9 (d), 135.9 (d), 134.0 (s), 133.9 (s), 130.5 (s), 129.6 (d), 129.5 (d), 129.2 (d), 127.5 (d), 113.6 (d), 79.8 (s), 77.5 (s), 72.8 (t), 72.7 (t), 70.9 (d), 55.2 (q), 51.7 (q), 33.6 (t), 26.9 (q), 24.5 (t), 19.3 (s), 14.7 (t). HRMS: calcd for $C_{33}H_{40}O_5Si$ 544.2645, found 544.2648

Synthesis of (*R*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-8-hydroxyoct-4-ynoate (19). To a magnetically stirred solution of **18** (1.53 g, 2.81 mmol) in CH_2Cl_2 (20 mL) at rt were added H_2O (7 mL) and DDQ (783 mg, 3.45 mmol). The reaction was completed after 1 h 45 min and was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc 9/1 to 8/2 as eluent) to afford the product **19** as a colorless oil (1.05 g, yield = 88%). TLC (SiO_2): R_f = 0.25 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = −24.8 (c = 1.24, CH_2Cl_2). FTIR (neat): 3467, 2932, 2858, 1740, 1473, 1428, 1364, 1167, 1112, 1047, 938, 822, 741, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80−7.60 (m, 4H), 7.55−7.30 (m, 6H), 4.00−3.80 (m, 1H), 3.68 (s, 3H), 3.65−3.57 (d, J = 4.2 Hz, 2H), 2.50−2.35 (m, 5H), 2.35−2.20 (m, 1H), 1.95−1.65 (bs, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.5 (s), 135.8 (d), 135.7 (d), 133.5 (s), 129.9 (d), 129.9 (d), 127.8 (d), 127.7 (d), 80.3 (s), 77.2 (s), 72.4 (d), 65.5

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(t), 51.7 (q), 33.5 (t), 26.9 (q), 23.8 (t), 19.3 (s), 14.7 (t). HRMS: calcd for $C_{25}H_{32}O_4Si$ 424.2070, found 424.2066.

Synthesis of (*R*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-8-oxooct-4-ynoate (7). To a magnetically stirred solution of alcohol **19** (250 mg, 0.586 mmol) in dry CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (DMP) (281 mg, 0.663 mmol). The reaction was completed after 2 h and was quenched with H_2O (10 mL), MTBE (70 mL), saturated aq $NaHCO_3$ (35 mL), and saturated aq $Na_2S_2O_3$ (35 mL). The layers were separated, and the aqueous layer was extracted with MTBE/hexane 9/1. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered on silica gel (hexane/EtOAc 9/1 as eluent) to afford the product **7** as colorless oil (185 mg, yield = 75%) that was submitted to the next step without further purification.

Sunthesis of (*R*,*E*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-9-((2*R*,3*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((*S*)-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-tetrahydrofuran-2-yl)non-8-en-4-ynoate (20). Sulfone **6** (171 mg, 0.175 mmol) was dissolved in dry DME (3 mL) under Ar. The solution was cooled to −65 °C and KHMDS (390 mL, solution 0.5 M in toluene, 0.195 mmol) added dropwise. After 40 min, a solution of **7** (101 mg, 0.239 mmol) in dry DME (1.5 mL) under Ar was added dropwise to the reaction. The reaction mixture was stirred at −65 °C for 1 h and then allowed to reach rt. The reaction was quenched with saturated aq NH_4Cl (5 mL), H_2O (5 mL), and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 98/2 to afford the pure product **20** (123 mg, yield = 60%). TLC (SiO_2): R_f = 0.2 (hexane/EtOAc 98/2). $[\alpha]^{21}_D$ = −26.5 (*c* = 1.39, CH_2Cl_2). FTIR (neat): 2931, 2858, 1743, 1473, 1428, 1362, 1256, 1112, 938, 823, 776, 740, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.76–7.20 (m, 30H), 5.65 (t, *J* = 10.2 Hz, 1H), 4.99 (t, *J* = 10.4 Hz, 1H), 4.57 (dt, *J* = 8.8, 4.6 Hz, 1H), 4.04–3.96 (m, 2H), 3.91–3.82 (m, 2H), 3.68 (s, 3H), 3.53–3.39 (m, 2H), 2.47–2.34 (m, 4H), 2.18–1.96 (m, 2H), 1.68–1.45 (m, 4H), 1.08 (s, 9H), 0.99 (s, 9H), 0.97 (s, 9H), 0.83 (s, 9H), −0.06 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.6 (s), 136.0 (d), 135.9 (d), 135.8 (d), 135.6 (d), 134.3 (d), 134.0 (s), 133.8 (s), 133.7 (s), 129.7 (d), 129.6 (d), 129.5 (d), 129.4 (d), 129.4 (d), 128.8 (d), 127.7 (d), 127.6 (d), 127.4 (d), 127.3 (d), 81.4 (d), 80.8 (d), 79.8 (s), 78.0 (d), 77.6 (s), 72.1 (d), 67.4 (d), 59.8 (t), 51.7 (q), 37.5 (t), 36.1 (t), 33.6 (t), 28.8 (t), 27.0 (q), 27.0 (q), 26.9 (q), 25.9 (q), 19.4 (s), 19.3 (s), 19.0 (s), 18.2 (s), 14.8 (t), −5.4 (q), −5.4 (q). HRMS: calcd for $C_{71}H_{94}O_7Si_4$ 1170.6077, found 1170.6075

Synthesis of (*R*,*E*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-9-((2*R*,3*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxypropyl)tetrahydrofuran-2-yl)non-8-en-4-ynoate (21). Compound **20** (120 mg, 0.102 mmol) was solved in CH_2Cl_2/MeOH 1/1 (4 mL) and at rt was added PPTS (33 mg, 0.123 mmol). The reaction was stirred for 6h and was quenched with $NaHCO_3$ (21 mg, 0.250 mmol), filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 9/1 as eluent to afford the primary alcohol **21** as a slight yellow oil (92.4 mg, yield =86%). TLC (SiO_2): R_f = 0.25 (hexane/EtOAc 9/1). $[\alpha]^{21}_D$ = −35.0 (*c* = 1.07, CH_2Cl_2). FTIR (neat): 2932, 1742, 1474, 1428, 1363, 1112, 937, 823, 740, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.24 (m, 30H), 5.59 (t, *J* = 10.3 Hz, 1H), 4.91 (t, *J* = 10.2 Hz, 1H), 4.51 (m, 1H), 4.13–4.01 (m, 2H), 3.79–3.75 (m, 1H), 3.68–3.45 (m, 6H), 2.47–2.34 (m, 4H), 2.21–1.96 (m, 3H), 1.75–1.61 (m, 3H), 1.36–1.26 (m, 1H), 1.06 (s, 9H), 1.01 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.5 (s), 135.9 (d), 135.7 (d), 135.6 (d), 134.3 (d), 134.2 (d), 133.8 (s), 133.7 (s), 133.6 (s), 133.5 (s), 133.2 (s), 129.7 (d), 129.6 (d), 129.5 (d), 128.3 (d), 127.6 (d), 127.5 (d), 82.3 (d), 80.9 (d), 79.9 (s), 78.0 (d), 74.6 (d), 67.3 (d), 59.1 (t), 51.7 (q), 38.4 (t), 37.6 (t), 33.6 (t), 28.7 (t), 27.0 (q), 26.9 (q), 26.9 (q), 19.3 (s), 19.3 (s), 19.0 (s), 14.7 (t). HRMS: calcd for $C_{65}H_{80}O_7Si_3$ 1056.5830, found 1056.5829

Synthesis of (*R*,*E*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-9-((2*R*,3*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-oxopropyl)tetrahydrofuran-2-yl)non-8-en-4-ynoate (5). Primary alcohol **21** (87.0 mg, 0.0823 mmol) was dissolved in dry CH_2Cl_2 (1 mL) under Ar, and Dess–Martin periodinane (41.7 mg, 0.0983 mmol) was added at rt. The reaction was stirred at rt for 45 min and was quenched with saturated aq $Na_2S_2O_3$ (3 mL), saturated aq $NaHCO_3$ (3 mL), and H_2O (3 mL). The suspension was diluted with MTBE (6 mL), and the layers were separated.

The aqueous layer was extracted with MTBE/hexane 9:1 (3 × 6 mL), and the organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/EtOAc 9/1 as eluent to afford the product **5** as a pale yellow oil (87.0 mg, yield = quantitative). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.60–9.55 (t, *J* = 2.3 Hz, 1H), 7.79–7.24 (m, 30H), 5.63 (t, *J* = 10.2 Hz, 1H), 4.91 (t, *J* = 10.3 Hz, 1H), 4.53 (m, 1H), 4.19–3.97 (m, 3H), 3.83–3.76 (m, 1H), 3.73–3.68 (s, 3H), 2.48–2.33 (m, 6H), 2.18–1.98 (m, 2H), 1.69–1.61 (m, 1H), 1.35–1.21 (m, 1H), 1.07 (s, 9H), 1.02 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 201.0, 172.5, 135.9, 135.7, 135.6, 134.5, 133.6, 133.2, 133.2, 129.9, 129.7, 129.7, 129.6, 129.5, 128.1, 127.7, 127.6, 127.5, 127.5, 82.0, 80.7, 79.9, 77.9, 77.4, 71.7, 67.3, 53.4, 51.6, 47.9, 37.9, 33.6, 28.7, 26.9, 26.8, 19.3, 19.2, 18.9, 14.7. ESI: 1078 ($M + Na^+$).

Synthesis of (*R*,*E*)-Methyl 7-((*tert*-Butyldiphenylsilyl)oxy)-9-((2*R*,3*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((*S*,3*Z*,6*Z*)-1-((*tert*-butyldiphenylsilyl)oxy)nona-3,6-dien-1-yl)tetrahydrofuran-2-yl)non-8-en-4-ynoate (22). Phosphonium salt **4**[22] (156.6 mg, 0.332 mmol) was dissolved in dry PhMe (1.7 mL) under Ar, and KHMDS (650 μL, 0.325 mmol) was added dropwise at 0 °C. The suspension was stirred for 45 min at 0 °C, and then the stirring was stopped in order to separate the liquid layer from the solid residue. The red liquid layer was transferred to another dry round-bottom flask under Ar and was cooled to −95 °C. In another dry two-neck round-bottom flask the compound **5** (87.0 mg, 0.0821 mmol) was dissolved in dry PhMe (1.5 mL) under Ar, and the solution was cooled to −78 °C. The solution of the aldehyde was added to the solution of the ylide dropwise, and the solution was allowed to reach rt. The reaction was monitored by TLC (hexane/EtOAc 8/2), and when it was complete, the reaction was stirred at rt for 15 min and was quenched with saturated aq NH_4Cl (5 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane, hexane/Et_2O 98/2, hexane/Et_2O 95/5 as eluent to afford the product **22** (68.5 mg, yield = 74%). TLC (SiO_2): R_f = 0.25 (hexane/Et_2O 95/5). $[\alpha]^{21}_D$ = −11.4 (*c* = 1.37, CH_2Cl_2). FTIR (neat): 2932, 1743, 1654, 1560, 1474, 1428, 1112, 823, 739, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78–7.24 (m, 30H), 5.68 (t, *J* = 10.1 Hz, 1H), 5.42–5.06 (m, 5H), 4.59 (m, 1H), 4.08–4.00 (m, 2H), 3.94–3.83 (m, 2H), 3.73–3.71 (s, 3H), 2.52–2.36 (m, 6H), 2.20–1.90 (m, 6H), 1.85–1.50 (m, 2H), 1.09 (s, 9H), 1.15–0.90 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.6 (s), 136.1 (d), 136.0 (d), 135.9 (d), 135.8 (d), 135.6 (d), 134.4 (d), 133.8 (s), 133.7 (s), 133.6 (s), 133.5 (s), 133.2 (s), 131.9 (d), 130.0 (d), 129.7 (d), 129.6 (d), 129.5 (d), 129.4 (d), 128.8 (d), 127.5 (d), 127.4 (d), 127.4 (d), 127.0 (d), 124.9 (d), 81.3 (d), 79.8 (d), 78.1 (d), 77.5 (s), 73.8 (d), 67.4 (d), 51.6 (q), 35.3 (t), 33.6 (t), 32.3 (t), 28.7 (t), 27.0 (q), 26.9 (q), 26.9 (q), 25.5 (t), 20.5 (t), 19.3 (s), 19.0 (s), 14.7 (t), 14.3 (d). HRMS: calcd for $C_{71}H_{88}O_6Si_3$ 1120.5889, found 1120.5891.

Synthesis of (*R*,*E*)-Methyl 7-Hydroxy-9-((2*R*,3*S*,5*R*)-3-hydroxy-5-((*S*,3*Z*,6*Z*)-1-hydroxynona-3,6-dien-1-yl)tetrahydrofuran-2-yl)non-8-en-4-ynoate (3). To a magnetically stirred solution of silyl ether **22** (68.5 mg, 0.0611 mmol) in dry THF (1 mL) at rt, under Ar, was added TBAF (550 μL, 0.55 mmol). The reaction was stirred at rt and was monitored by TLC (silica gel RP-18, MeOH/H_2O 7/3). When the reaction was complete, AcOH was added (33 μL, 0.58 mmol), and the solvent was removed under vacuum. The residue was dissolved in EtOAc (2 mL), and CH_2N_2 in

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Et_2O was added at 0 °C until the solution became yellow. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel using hexane/EtOAc 4/6 as eluent to afford the pure product **3** (14 mg, yield =55%). TLC (SiO_2): R_f = 0.23 (hexane/EtOAc 4/6). $[\alpha]^{21}_D$ = +41.7 (c = 0.41, MeOH). FTIR (neat): 3402, 2921, 1734, 1438, 1169, 1038 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.75−5.20 (m, 6H), 4.75−4.55 (m, 2H), 4.30−4.05 (m, 2H), 3.95−3.80 (m, 1H), 3.72 (s, 3H), 2.90−2.70 (m, 3H), 2.60−2.35 (m, 6H), 2.30−2.15 (m, 3H), 2.15−1.95 (m, 2H), 1.95−1.50 (m, 3H), 1.15−0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.9 (s), 134.2 (d), 132.2 (d), 131.1 (d), 130.9 (d), 126.7 (d), 124.9 (d), 82.5 (d), 81.2 (d), 81.0 (s), 77.2 (s), 77.1 (d), 71.0 (d), 66.7 (d), 51.9 (q), 33.5 (t), 33.2 (t), 30.8 (t), 27.5 (t), 25.6 (t), 20.6 (t), 14.7 (t), 14.2 (q). HRMS: calcd for $C_{23}H_{34}O_6$ 406.2355, found 406.2345.

Synthesis of (*R*,4*Z*,8*E*)-Methyl 7-Hydroxy-9-((2*R*,3*S*,5*R*)-3-hydroxy-5-((*S*,3*Z*,6*Z*)-1-hydroxynona-3,6-dien-1-yl)tetrahydrofuran-2-yl)nona-4,8-dienoate (23). To a magnetically stirred solution of **3** (9.5 mg, 0.023 mmol) in hexane/EtOAc 1:1 (2 mL), were added quinoline (2 μL) and Lindlar catalyst (palladium on calcium carbonate poisoned with lead, 1 mg). The suspension was stirred at rt under H_2 atmosphere. The reaction was monitored by TLC (silica gel RP-18, MeOH/H_2O 6/4) and after 30 min was completed. The suspension was filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel RP-18, MeOH/H_2O 6:4 to 7:3 as eluent) to afford the product **23** (7.5 mg, yield = 80%). TLC (silica gel RP-18): R_f = 0.23 (MeOH/H_2O 6/4). $[\alpha]^{21}_D$ = +26.9 (c = 0.27, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.64−5.29 (m, 8H), 4.65−4.56 (m, 2H), 4.21−4.12 (m, 2H), 3.89−3.86 (m, 1H), 3.72−3.68 (m, 3H), 2.82 (t, J = 6.9 Hz, 2H), 2.45−2.03 (m, 13H), 1.84 (ddd, J = 13.0, 6.4, 3.2 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.2 (s), 135.2 (d), 132.2 (d), 131.2 (d), 130.7 (d), 129.9 (d), 126.7 (d), 126.4 (d), 124.9 (d), 82.6 (d), 81.1 (d), 77.2 (d), 71.1 (d), 68.1 (d), 51.8 (q), 35.2 (t), 33.7 (t), 33.5 (t), 30.9 (t), 25.7 (t), 22.8 (t), 20.6 (t), 14.2 (q). ESI-MS m/z 409.3 [$(M + H)^+$, 30], 431.6 [$(M + Na)^+$, 100], 447.4 [$(M + K)^+$, 18]. HRMS: calcd for $C_{23}H_{36}O_6$ 408.2512, found 408.2515.

Synthesis of 7-*epi*-ST-Δ^8-10-NeuroF 1. To a magnetically stirred solution of methyl ester **23** (5.2 mg, 0.013 mmol) in HPLC-grade MTBE (1 mL) was added HPLC-grade H_2O (11 μL, 0.65 mmol). To the resulting stirred solution was added solid supported CAL-B (5.2 mg), and the suspension was stirred at rt for 24 h. The enzime was filtered off over a sintered glass funnel and the solid was carefully washed with MeCN-MTBE and the solution was concentrated under vacuum. The residue was purified by column chromatography using silica gel RP-18 (MeOH/H_2O 6/4 as eluent) to afford the product **1** (4.0 mg, yield = 78%). TLC (silica gel RP-18): R_f = 0.30 (MeOH/H_2O 6/4). $[\alpha]^{21}_D$ = +25.5 (c = 0.22, MeOH). ^1H NMR (300 MHz, CD_3OD): δ (ppm) = 5.57−5.30 (m, 8H), 4.58−4.50 (m, 2H), 4.10−4.01 (m, 2H), 3.66−3.60 (m, 1H), 2.83 (t, J = 5.8 Hz, 2H), 2.41−2.04 (m, 11H), 1.88 (ddd, J = 12.9, 6.4, 3.3 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) = 136.3 (d), 133.1 (d), 132.0 (d), 131.4 (d), 131.3 (d), 128.5 (d), 127.2 (d), 127.1 (d), 83.8 (d), 82.8 (d), 78.3 (d), 74.3 (d), 68.7 (d), 37.0 (t), 36.8 (t), 36.7 (t), 33.1 (t), 26.9 (t), 25.1 (t), 21.8 (t), 15.0 (q). ESI-MS m/z 393.3 [$(M - H)^-$, 100], 788.0 [$(2M - H)^-$, 82]. HRMS: calcd for $C_{22}H_{34}O_6$ 394.2355, found 394.2358.

Synthesis of (*R*,4*Z*,8*E*)-Methyl 7-Hydroxy-9-((2*R*,3*S*,5*R*)-3-hydroxy-5-((*S*,3*Z*,6*Z*)-1-hydroxynona-3,6-dien-1-yl)tetrahydrofuran-2-yl)-4,5-dideuterionona-4,8-dienoate (24). To a magnetically stirred solution of **3** (8 mg, 0.020 mmol) in hexane/AcOEt 1/1 (2 mL), were added quinoline (2 μL) and Lindlar catalyst (palladium on calcium carbonate poisoned with lead, 1 mg). The suspension was stirred at rt under D_2 atmosphere. The reaction was monitored by TLC (silica gel RP-18, MeOH/H_2O 6/4) and after 30′ was completed. The suspension was filtered and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel RP-18, MeOH/H_2O 6/4 to 7/3 as eluent) to afford the product **24** (6 mg, yield =73%). TLC (Silica gel RP-18): R_f = 0.23 (MeOH/H_2O 6/4). $[\alpha]^{21}_D$ = +26.4 (c = 0.27, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.68−5.29 (m, 6H), 4.65−4.54 (m, 2H), 4.23−4.11 (m, 2H), 3.90−3.85 (m, 1H), 3.69−3.66 (s, 3H), 2.84−2.74 (m, 2H), 2.48−2.00 (m, 13H) 1.86 (dt, J = 6.6, 3.3 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.2 (s), 135.2 (d), 132.2 (d), 131.2 (d), 130.0 (d), 126.7 (d), 124.9 (d), 82.7 (d), 81.1 (d), 77.2 (d), 71.1 (d), 68.1 (d), 51.8 (q), 35.1 (t), 33.7 (t), 33.5 (t), 30.9 (t), 25.7 (t), 22.7 (t), 20.6 (t), 14.2 (q). ESI-MS m/z 433.33 [$(M + Na)^+$, 100].

Synthesis of 4,5-Dideuterio-7-*epi*-ST-Δ^8-10-NeuroF 2. To a magnetically stirred solution of ester **24** (4 mg, 0.010 mmol) in HPLC-grade MTBE (800 μL) was added HPLC-grade H_2O (9 μL, 0.5 mmol). To the resulting stirred solution was added solid-supported CAL-B (6 mg), and the suspension was stirred at rt for 24 h. The enzyme was filtered off over a sintered glass funnel, the solid was carefully washed with MeCN−MTBE, and the solution was concentrated under vacuum. The residue was purified by column chromatography using silica gel RP-18 (MeOH/H_2O 6:4 as eluent) to afford the product **2** (3.2 mg, yield = 81%). TLC (silica gel RP-18): R_f = 0.30 (MeOH/H_2O 6/4). $[\alpha]^{21}_D$ = +25.45 (c = 0.22, MeOH). ^1H NMR (300 MHz, CD_3OD): δ (ppm) = 5.54−5.34 (m, 6H), 4.57−4.50 (m, 2H), 4.05−4.02 (m, 2H), 3.63 (m, 1H), 2.83−2.80 (m, 2H), 2.35−2.05 (m, 11H), 1.88 (ddd, J = 12.9, 6.4, 3.4 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) = 177.7 (s), 136.3 (d), 133.1 (d), 131.5 (d), 131.3 (d), 128.5 (d), 127.1 (d), 83.8 (d), 82.8 (d), 78.3 (d), 74.3 (d), 68.6 (d), 36.6 (t), 35.4 (t), 33.1 (t), 31.1 (t), 26.9 (t), 24.3 (t), 21.8 (t), 14.9 (q). ESI-MS m/z 791.70 [$(2M - H)^-$, 100]; 419.19 [$(M + Na)^+$, 100]. HRMS: calcd for $C_{23}H_{34}D_2O_6$ 396.2481, found 396.2478.

Synthesis of Mosher Esters. *Separation of Tetrahydrofuran **10b** via Silyl Ether **12a**.* To a magnetically stirred solution of **10** and **10a** (73 mg, 0.343 mmol, from entry 7, Table 1) in dry CH_2Cl_2 (4 mL) under Ar were added at rt imidazole (59 mg, 0.860 mmol) and TBDPSCl (110 μL, 0.411 mmol). The reaction was completed after 6 h and was quenched with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 98/2, 95/5 and 9/1 as eluent) to afford the desired product **12a** (90 mg, yield = 59%). TLC (SiO_2): R_f = 0.23 (hexane/EtOAc 9/1). $[\alpha]^{21}_D$ = +14.25 (c = 0.4, CH_2Cl_2). FTIR (neat): 2932, 2858, 1741, 1428, 1232 1113, 1078, 1026, 740, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.71−7.64 (m, 4H), 7.48−7.35 (m, 6H), 6.12 (ddd, J = 17.4, 10.2, 7.3 Hz, 1H), 5.83−5.67 (m, 2H), 5.35−5.24 (m, 2H), 4.78−4.73 (m, 1H), 4.53 (d, J = 5.1 Hz, 2H), 4.48 (m, 1H), 4.32 (dd, J = 7.3, 3.8 Hz, 1H), 2.04 (s, 3H), 1.92 (ddd, J = 13.0, 6.0, 2.0 Hz, 1H), 1.64−1.55 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 135.9 (d), 135.8 (d), 135.2 (d), 135.0 (d), 134.0 (s), 133.3 (s), 129.8 (d), 127.7 (d), 127.6 (d), 125.3 (d), 117.8 (t), 84.5 (d), 75.8 (d), 64.2 (t), 41.8 (t), 26.9 (3q), 20.9 (q), 19.3 (s). HRMS: calcd for $C_{27}H_{34}O_4Si$ 450.2226, found 450.2231.

Synthesis of Pure 10a. To a magnetically stirred solution of **12a** (60 mg, 0.133 mmol) in dry THF (2 mL) under Ar was added TBAF (270 μL, 0.266 mmol) at 0 °C. The reaction was stirred at rt until complete conversion. The reaction was quenched with saturated aq NH_4Cl (2 mL) and was diluted with Et_2O (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 6/4 as eluent) to afford the product **10a** (26 mg, yield = 92%). TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 6/4).

*Synthesis of Mosher Ester of **10a** with (S)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl Chloride.* General method: To a magnetically stirred solution of **10a** (8 mg, 0.038 mmol) in dry CH_2Cl_2 (1 mL) under Ar were added at 0 °C pyridine (12 μL, 0.152 mmol) and (*S*)-(+)-MTPA-Cl (14 μL, 0.076 mmol). The reaction was allowed to reach rt and was quenched after 4 h with saturated aq $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 ×

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5 mL), and the combined organic layers were washed with saturated aq $CuSO_4$, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 8/2 as eluent) to afford the Mosher ester (11 mg, yield = 68%). TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = +34.16 (c = 0.57, CH_2Cl_2). FTIR (neat): 2951, 1748, 1498, 1452, 1369, 1241, 1170, 1124, 1082, 1028, 990, 896, 766, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.60−7.51 (m, 2H), 7.49−7.38 (m, 3H), 5.92−5.76 (m, 2H), 5.70−5.58 (m, 2H), 5.33 (dt, J = 17.0, 1.4 Hz, 1H), 5.13 (dt, J = 10.3, 1.4 Hz, 1H), 4.71−4.52 (m, 4H), 3.60−3.52 (s, 3H), 2.33 (ddd, J = 14.0, 6.1, 1.4 Hz, 1H), 2.19−2.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 165.7 (s), 133.6 (d), 132.2 (d), 131.8 (s), 129.7 (d), 128.4 (d), 127.4 (d), 126.3 (d), 125.1 (s), 121.3 (s) 118.9 (t), 82.3 (d), 78.3 (d), 77.6 (d), 63.9 (t), 55.4 (q), 39.4 (t), 20.9 (q). HRMS: calcd for $C_{21}H_{23}F_3O_6$ 428.1447, found 428.1449.

Synthesis of Mosher Ester of ***10a*** *with (R)-(−)-α-Methoxy-α-trifluoromethylphenylacetyl Chloride.* The Mosher ester was prepared following the general method using (*R*)-(−)-MTPA-Cl as acyl chloride. TLC (SiO_2): R_f = 0.23 (hexane/EtOAc 9/1). $[\alpha]^{21}_D$ = −7.27 (c = 0.22, CH_2Cl_2). FTIR (neat): 2951, 1748, 1498, 1452, 1369, 1241, 1170, 1124, 1082, 1028, 990, 896, 766, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.57−7.51 (m, 2H), 7.47−7.38 (m, 3H), 5.88−5.73 (m, 3H), 5.60 (t, J = 3.8 Hz, 1H), 5.38 (dt, J = 17.2, 1.4 Hz, 1H), 5.24 (dt, J = 10.4, 1.3 Hz, 1H), 4.64−4.50 (m, 4H), 3.56−3.53 (s, 3H), 2.25 (ddd, J = 14.0, 5.9, 1.3 Hz, 1H), 2.11−2.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.6 (s), 165.9 (s), 133.5 (d), 132.7 (d), 131.8 (s), 129.7 (d), 128.4 (d), 127.4 (d), 126.3 (d), 125.2 (s), 118.8 (t), 82.1 (d), 78.8 (d), 77.2 (d), 63.9 (t), 55.5 (q), 39.5 (t), 29.7 (s), 20.9 (q). HRMS: calcd for $C_{21}H_{23}F_3O_6$ 428.1447, found 428.1448.

Synthesis of Pure 10. Pure alcohol **10** was synthetized from the starting material **12** (entry 2, Table 1) following the same procedure described for the synthesis of the compound **10a** from **12a**. TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 6/4).

Synthesis of the Mosher Ester of ***10*** *with (S)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl Chloride.* The Mosher ester was prepared from the starting material **10** following the general method using (*S*)-(+)-MTPA-Cl as acyl chloride. TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = +61.0 (c = 0.4, CH_2Cl_2). FTIR (neat): 2951, 1748, 1498, 1452, 1369, 1241, 1170, 1124, 1082, 1028, 990, 896, 766, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.56−7.50 (m, 2H), 7.50−7.40 (m, 3H), 5.99−5.77 (m, 3H), 5.40 (dt, J = 17.1, 1.5 Hz, 1H), 5.32−5.22 (m, 2H), 4.59 (d, J = 5.0 Hz, 2H), 4.58−4.49 (m, 1H), 4.39 (dq, J = 5.4, 1.9 Hz, 1H), 3.59−3.52 (s, 3H), 2.30−1.87 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.6 (s), 166.1 (s), 135.3 (d), 132.9 (d), 131.8 (s), 129.8 (d), 128.5 (d), 127.3 (d), 127.1 (d), 125.1 (s), 121.3 (s), 117.1 (t), 84.4 (d), 80.9 (d), 78.5 (d), 63.9 (t), 55.4 (q), 37.4 (t), 20.9 (q). HRMS: calcd for $C_{21}H_{23}F_3O_6$ 428.1447, found 428.1443.

Synthesis of Mosher Ester of ***10*** *with (R)-(-)-α-Methoxy-α-trifluoromethylphenylacetyl Chloride.* Prepared from the starting material **10** following the general method using (*R*)-(−)-MTPA-Cl as acyl chloride. TLC (SiO_2): R_f = 0.28 (hexane/EtOAc 8/2). $[\alpha]^{21}_D$ = −19.59 (c = 0.49, CH_2Cl_2). FTIR (neat): 2951, 1748, 1498, 1452, 1369, 1241, 1170, 1124, 1082, 1028, 990, 896, 766, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.56−7.50 (m, 2H), 7.48−7.42 (m, 3H), 5.99−5.77 (m, 3H), 5.44 (dt, J = 17.1, 1.5 Hz, 1H), 5.29−5.23 (m, 2H), 4.59 (d, J = 4.7 Hz, 2H), 4.54−4.46 (m, 2H), 3.59−3.55 (s, 3H), 2.14−1.93 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7 (s), 166.1 (s), 135.4 (d), 133.0 (d), 131.9 (s), 129.8 (d), 128.5 (d), 127.5 (d), 127.2 (d), 127.1 (d), 125.1 (s), 121.3 (s), 117.3 (t), 84.2 (d), 80.9 (d), 78.6 (d), 63.9 (t), 55.5 (q), 37.2 (t), 20.9 (q). HRMS: calcd for $C_{21}H_{23}F_3O_6$ 428.1447, found 428.1450.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Nomenclature system for neurofurans; copies of ^1H, ^{13}C, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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