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Asymmetric Synthesis of 14-A_{4t}-Neuroprostane: Hunting for a Suitable Biomarker for Neurodegenerative Diseases

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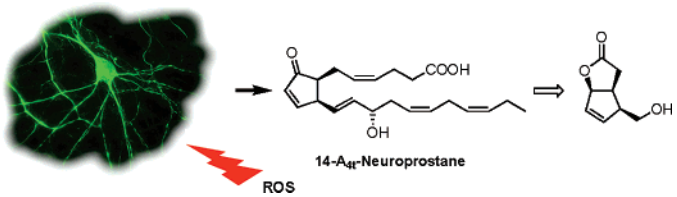

Oxidative stress has long been associated with aging and age-related pathologies, such as neurodegenerative diseases. One of the direct effects of oxidative stress in vivo is the formation of prostaglandin-like compounds, named isoprostanes, by the action of reactive oxygen species on membrane phospholipids. A particular subclass of isoprostanes, named neuroprostanes, is formed from docosahexaenoic acid (C22:6ω3, DHA) and is considered to be specific for neuronal oxidative stress. Since isoprostanes are considered as golden standards for oxidative stress, and due to the specificity of neuroprostanes for this condition in neurons and their relation with Alzheimer's and Parkinson's diseases, they are envisioned to be suitable biomarkers for these pathologies. Herein we describe the first total synthesis of 14-A_{4t}-NeuroP in an enantioselective and stereoselective fashion, by means of a new and rapid approach for the installation of the ω chain based on a chemoselective Julia−Kocienski olefination. Furthermore, the construction of the 4,5-*cis*-disubstituted cyclopentenone moiety characteristic of class A neuroprostanes is achieved in a stereospecific fashion, and suitable reaction conditions have been tuned to avoid epimerization of the labile stereogenic centers.

Introduction

Neurodegenerative diseases, such as Alzheimer, mild cognitive impairment, dementia with Lewy bodies, and Parkinson, affect millions of people, greatly reducing their quality of life and, in many cases, causing death. Diagnosis is currently achieved primarily by clinical criteria, supported by laboratory investigations and functional neuroimaging analysis; quite often, a definitive diagnosis is made only after postmortem examination. Tremendous efforts have, therefore, been made in recent years to identify the neuropathological, biochemical, and genetic biomarkers of the diseases to enhance early diagnosis and assessment of disease progression and treatment response. Since the lipid peroxidation induced by oxidative stress has been implicated in the pathogenesis of various central nervous system diseases, it has been proposed to use the radical mediated peroxidation products of DHA, named neuroprostanes (NeuroP's), as specific and practical biomarkers for the oxidative stress and neuronal damage, as well as for the effects of therapies.[1]

Indeed, DHA is highly enriched in neuronal membranes and the formation of the corresponding peroxidation products is relatively specific for neuronal oxidative injury.[1] Though different families of neuroprostanes are thus produced (Figure 1), in 2002 Morrow et al. demonstrated that the formation of cyclopentenone neuroprostanes (A_4-NeuroP's and J_4-NeuroP's) is a favored route of the DHA oxidation pathway and supported the notion that quantification of A_4-NeuroPs (or J_4-NeuroPs) may be a more sensitive indicator of DHA oxidation, and neural tissue oxidative stress, than other classes of NeuroPs.[2a] In addition, one expects that the highly electrophilic cyclopentenone moiety of A_4-NeuroPs (or J_4-NeuroPs) would endow these compounds with a wide variety of potent biological actions, as is very well documented by the structurally related cyclopentenone prostaglandins and isoprostanes of the A/J classes.[2b] NeuroP's are present in minute amounts in neuronal tissues; their preparation is therefore indispensable to provide sufficient

(1) Montine, T. J.; Morrow, J. D. *Am. J. Pathol.* **2005**, *166*, 1283.

(2) (a) Fam, S. S.; Murphey, L. J.; Terry, E. S.; Zackert, W. E.; Chen, Y.; Gao, L.; Pandali, S.; Milne, G. L.; Roberts, J. L.; Porter, N. A.; Montine, T. J.; Morrow, J. D. *J. Biol. Chem.* **2002**, *277*, 36076. (b) Musiek, E. S.; Breeding, R. S.; Milne, G. L.; Zanoni, G.; Morrow, J. D.; McLaughlin, B. D. *J. Neurochem.* **2006**, *97*, 1301.

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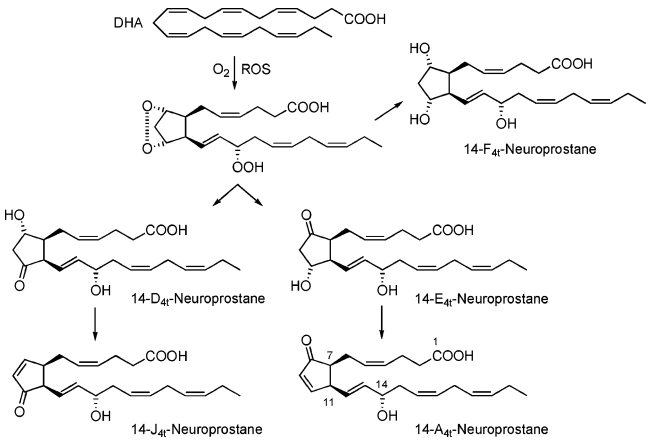


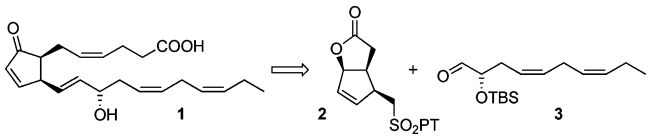
FIGURE 1. ROS: reactive oxygen species. DHA: docosahexaenoic acid.

quantities for their in vivo detection and quantification and to assess their biological profile. Motivated by these considerations and lack of previous synthesis of A_4-NeuroP's, even as racemate, we embarked ourselves in this synthetic adventure. Among the 32 possible stereomers formed by peroxidation of DHA,[2] we decided to prepare 14-A_{4t}-NeuroP (**1**) in an enantioselective fashion in order to set the strategy for the preparation of the remaining A_4-NeuroP's (Figure 1).

Results and Discussion

The convergent synthesis of **1** commenced with the installation of the ω side chain through a Julia−Kocienski condensation between phenyltetrazolyl sulfone **2** and chiral dienal **3** (Chart 1).

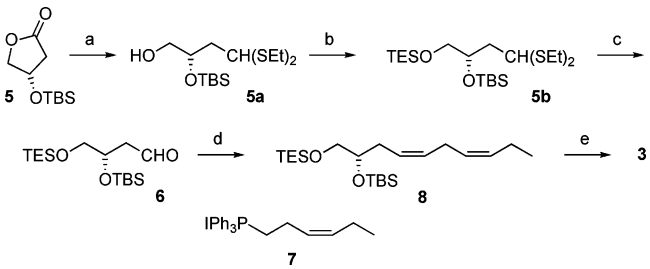
CHART 1



Aldehyde **3** was prepared from commercially available highly enantioenriched (*S*)-β-hydroxybutyrolactone (ee 99%), which was protected to known *O*-TBS ether **5**[4] (Scheme 1). Subsequently, lactone **5** was elaborated to free aldehyde **6** by simple manipulation of functional groups involving (1) DIBAL-H reduction to lactol, (2) $ZnCl_2$-promoted dithioacetal formation (EtSH, $ZnCl_2$), (3) primary hydroxyl group protection to *O*-TES derivative, and finally (4) NBS dithioacetal deprotection to unmask the free carbonyl group (NBS, H_2O) (Scheme 1) of aldehyde **6**, obtained in a gratifying 80% overall yield.

Compound **6** was subsequently (5) condensed with the ylide formed from phosphonium salt **7** under salt-free conditions.[5] In the event, to salt **7**[6] suspended in dry PhMe was added KHMDS (0.5 M in PhMe) at rt, and the surnatant clear red solution was added to aldehyde **6** in PhMe at −95 °C. Under these conditions, the expected skipped diene **8**, $[\alpha]^{20}_D$ +0.25 (*c* 0.9, DCM), was obtained as a single (*Z*,*Z*)-stereomer (^{13}C NMR) in 92% yield on a multigram scale. One-pot chemoselective TES−ether deprotection during Swern oxidation of the free primary alcohol delivered aldehyde **3** (ee 99%, estimated by enantioselective GC, $[\alpha]^{20}_D$ −5.9, *c* 0.25, DCM), in 93% isolated yield.[7]

SCHEME 1[a]



[a] Reaction conditions: (a) (i) DIBAl-H, DCM, −78 °C, 98%; (ii) EtSH, $ZnCl_2$, DCM, 93%; (b) TESCl, Im, DMAP, DCM, 90%; (c) NBS, 2,6-lutidine, MeCN/H_2O/MeCOMe (8:2:1), 97%; (d) KHMDS, **7**, PhMe, rt, followed by aldehyde **6**, PhMe, −95 °C, 92%; (e) DMSO, $(COCl)_2$, NEt_3, DCM, 93%.

Sulfone **2** was easily prepared in two steps from key hydroxylactone **4**, which is easily available in enantiopure form by enantioselective HPLC separation of the racemic mixture (see the Supporting Information).[3] Thus, Mitsunobu thioetherification of compound **4** with 1-phenyl-1*H*-tetrazole-5-thiol (PT-SH) in the presence of Ph_3P and DEAD, followed by chemoselective thioether oxidation (H_2O_2, $(NH_4)_2MoO_4$, MeOH), delivered the expected sulfone **2**, $[\alpha]^{20}_D$ −71.7 (*c* 0.4, DCM), in 86% overall yield (Scheme 2).

The subsequent crucial Julia−Kocienski condensation between **2** and **3** was accomplished according to the original conditions described by Kocienski for achieving *E*-olefins with high stereoselectivity.[8] We anticipated that, in spite of the comparable thermodynamic acidity of lactone and sulfone α-hydrogens,[9a] kinetic factors would have governed chemoselective α-deprotonation of the sulfone moiety.[9b,c]

A fine-tuning of the reaction conditions, e.g., in the choice of the solvent, reaction time, and base/aldehyde equivalents ratio, was, however, necessary to perform the synthesis of tetraene **9** in useful yields. Under optimal conditions, sulfone **2** immediately developed a yellow anion upon exposure to KHMDS (1.12 equiv) in DME (0.06 M) at −78 °C (45 min), and smoothly reacted with aldehyde **3** (1.16 equiv, −78 °C), affording, after 5 h at 0 °C, the expected tetraene **9** in 60% isolated yield. ^{13}C NMR spectroscopy revealed compound **9** to be constituted by the single (12*E*)-olefin and (14*S*)-stereomer, proving the excellent stereoselectivity of the Julia−Kocienski reaction and the conservation of the C-14 carbinol strereochemical integrity.

This procedure, avoiding the lengthy manipulation of the lactone group before and after the Julia−Kocienski olefination, did represent a great improvement in comparison to our previous approach to A/J-isoprostanes.[10] With the key tetraene **9** in hand

(3) For racemic synthesis of lactone **4**: Zanoni, G.; Porta, A.; Meriggi, A.; Franzini, M.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 6064. For enzymatic resolution of **4**: Zanoni, G.; Agnelli, F.; Meriggi, A.; Vidari, G. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1779 .

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(5) Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 2776 and references cited therein.

(6) Kojioama, K.; Koyama, K.; Amemiya, S. *Tetrahedron* **1985**, *41*, 4449.

(7) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J.; Lee, T. H. *Tetrahedron* **2001**, *57*, 25.

(8) For a review see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

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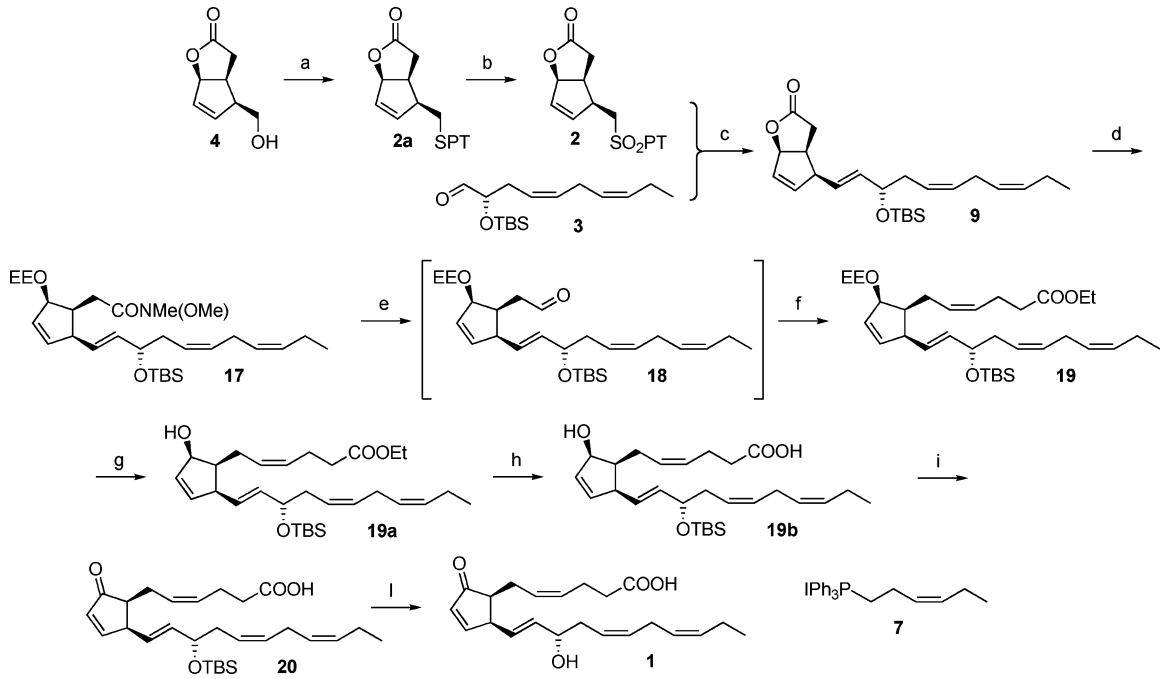
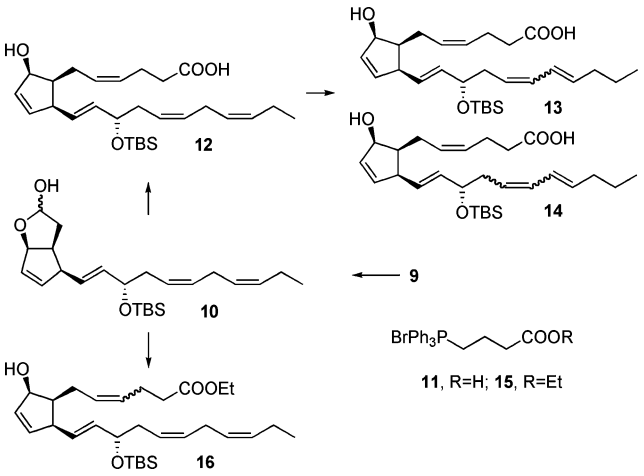
SCHEME 2[a]



[a] Reaction conditions: (a) PT-SH, Ph_3P, DEAD, PhMe, 96%; (b) H_2O_2, $(NH_4)_2MoO_4$, MeOH, 90%; (c) KHMDS, **2**, DME, −78 °C, 1 h, followed by aldehyde **3**, DME, −70 °C to rt, 60%; (d) (i) Me(MeO)NH·HCl, *n*BuLi, THF, −78 °C; (ii) PPTS, EVE, DCM, 64% overall yield; (e) DIBAl-H, THF, −78 °C; (f) KHMDS, **15**, PhMe, rt, followed by aldehyde **18**, −78 °C, 70%; (g) PPTS, EtOH/DCM (6:1), 74%; (h) $Ba(OH)_2{\cdot}8H_2O$, MeOH, 99%; (i) DMP, DCM, 85%; (l) 48% aq HF, MeCN, rt, 95%.

CHART 2



the synthesis was expected to proceed readily to the target neuroprostane **1**.

In the event, DIBAL-H reduction of **9** provided lactol **10**, which on Wittig condensation with free acid phosphonium salt **11** delivered the desired compound **12** contaminated by an inseparable byproduct lacking the characteristic NMR signal of bis-allylic H_2-18 (δ 2.8, m) and showing an UV-band at 256 nm, attributed to a diene chromophore (Chart 2).

We speculated that the skipped diene **12** underwent, via a still unclear mechanism, a formal hydrogen shift to a more stable conjugated diene such as **13** (or **14**). All attempts to eliminate this side reaction by changing the base and the solvent in the Wittig reaction were unsuccessful.

In contrast, the use of the ethyl ester phosphonium salt **15** prevented the formation of the conjugated diene, affording, however, the skipped diene **16** as an *Z/E* (9:1) mixture at C-4.[11] Eventually, the α side chain of **1** was installed via a newly developed protocol (Scheme 1). Thus, formation of 1-ethoxyethyl ether (EE) protected Weinreb amide **17** from lactone **9** (MeO(Me)NLi, followed by ethylvinyl ether (EVE) followed by DIBAL-H reduction), giving unstable free aldehyde **18**, which was immediately used in the next step without purification. Wittig olefination of **18** with phosphonium salt **15** afforded the expected *Z* olefin **19** as a single stereomer (^{13}C NMR) in 70% isolated yield form **17**. *O*-EE acetal deprotection, followed by ester hydrolysis and cyclopentenol Dess−Martin periodinane (DMP) oxidation, delivered enone **20** in 63% overall yield, without appreciable epimerization of the labile stereocenters C-7 and C-11. Finally, aq HF cleavage of the *O*-TBS ether smoothly gave 14-A_{4t}-NeuroP (**1**), $[\alpha]^{20}_D$ +163.3 (*c* 0.5, EtOAc). 2D-NOESY experiments confirmed the cis stereochemistry of the disubstituted cyclopentenone ring characteristic of neuroprostanes: an intense NOE cross-peak was observed between H-7 and H-11, while no interaction was detected between H-11 and H-6 (see the Supporting Information).

Conclusion

In conclusion, we have described the first enantioselective approach to the synthesis of cyclopentenone NeuroP's. Our strategy features a chemo- and stereoselective Julia−Kocienki olefination for the installation of the ω chain with a newly developed protocol for the construction of the α chain, leading to the target molecule **1** in good overall yields (15% from lactone **4**). Studies regarding the biological activity of 14-A_{4t}-NeuroP

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(11) Marianoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(**1**), in order to deeply understand the role of NeuroP's in neurodegenerative diseases, are in progress. This synthesis also paves the way for a detailed study of the metabolism of cyclopentenone NeuroP's, in order to create new noninvasive diagnostic tests for neuronal oxidative stress.

Experimental Section

Dithioacetal 5. $ZnCl_2$ (1 equiv, 0.64 mL, 1 M in Et_2O) and EtSH (11.2 equiv, 0.536 mL) were added to a stirred solution of lactol, obtained by DIBAL-H reduction of lactone **5** (0.14 g, 0.642 mmol) in CH_2Cl_2 (6.4 mL) under an Ar atmosphere at 0 °C. After 10 min a saturated solution of NH_4Cl (10 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/Et_2O (85:15) gave the resulting dithioacetal **5a** (0.194 g, 93%) as a colorless oil. $[\alpha]^{20}_D$ +9.45 (*c* 0.92, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ (tilde) 3440, 2929, 2857, 1472, 1257, 1113, 1046, 837, 777, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.10 (m, part X of an ABXCD system, 1H), 3.90 (dd, J = 8.5, 5.9 Hz, part Q of a XCDQ system, 1H), 3.64 (dd, J = 11.2, 4.1 Hz, part A of an ABX system, 1H), 3.51 (dd, J = 11.2, 3.9 Hz, part B of an ABX system, 1 H), 2.78−2.54 (m, 4H), 2.07 (ddd, J = 13.6, 7.7, 6.1 Hz, part C of a XCDQ system, 1 H), 1.95 (ddd, J = 13.6, 8.5, 4.8 Hz, part D of a XCDQ system, 1 H), 1.88−1.77 (br s, 1H, -OH), 1.28 (t, J = 7.4 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.4 d, 66.2 t, 47.4 d, 40.3 t, 25.8 q, 24.1 t, 23.6 t, 18.0 s, 14.4 q, 14.3 q, −4.4 q, −4.5 q. HRMS (EI, *m*/*z*) calcd for $C_{14}H_{32}O_2{}^{32}S_2Si$ 324.1613, found 324.1609.

Silyl Ether 5b. Imidazol (4 equiv, 110 mg), triethylsilyl chloride (1.2 equiv, 0.082 mL), and catalytic DMAP where added to a stirred solution of the free alcohol (0.132 g, 0.406 mmol) in dry CH_2Cl_2 (4 mL) under an Ar atmosphere. After 2 h H_2O (15 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL).

The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/Et_2O (98:2) gave the desired silyl ether **5b** (0.16 g, 90%) as a colorless oil. $[\alpha]^{20}_D$ −11.04 (*c* 0.11, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 2956, 2877, 1460, 1252, 1118, 1084, 1005, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08−3.98 (m, part X of an ABXCD system, 1H), 4.01 (dd, J = 10.3, 4.4 Hz, and part Q of a XCDQ system, 1 H), 3.60 (dd, J = 9.8, 5.2 Hz, part A of an ABX system, 1 H), 3.40 (dd, J = 9.8, 6.8 Hz, part B of an ABX system, 1 H), 2.77−2.53 (m, 4 H), 2.07 (ddd, J = 14.0, 10.3, 3.3 Hz, part C of a XCDQ system, 1 H), 1.85 (ddd, J = 14.0, 8.8, 4.3 Hz, part D of a XCDQ system, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.8 Hz, 9 H), 0.90 (s, 9 H), 0.61 (q, J = 7.8 Hz, 6 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.9 d, 67.2 t, 47.8 d, 41.2 t, 26.1 q, 24.5 t, 23.2 t, 18.2 s, 14.6 q, 14.5 q, 6.9 q, 4.5 t, −3.9 q, −4.5 q. HRMS (EI, *m*/*z*) calcd for $C_{20}H_{46}O_2{}^{32}S_2Si_2$ 438.2478, found 438.2473.

Aldehyde 6. NBS (8 equiv, 0.162 g) and 2,6-lutidine (16 equiv, 0.211 mL) were added to a stirred solution of the above dithioacetal (50 mg, 0.114 mmol) in $CH_3CN/H_2O/CH_3COCH_3$ 8:2:1 (2 mL) at 0 °C. After 5 min a saturated solution of $Na_2S_2O_3$ (10 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/Et_2O (96:4) gave compound **6** (37 mg, 97%) as a colorless oil. $[\alpha]^{20}_D$ −12.9 (*c* 1.64, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.83 (dd, J = 2.8, 2.2 Hz, part Q of CDQ system, 1 H), 4.23 (m, part X of an ABXCD system, 1H), 3.65 (dd, J = 9.8, 5.0 Hz, part A of an ABX system, 1 H), 3.46 (dd, J = 9.8, 7.0 Hz, part B of an ABX system, 1H), 2.67 (ddd, J = 15.8, 5.3, 2.2 Hz, part C of a XCDQ system, 1 H), 2.52 (ddd, J = 15.8, 6.4, 2.8 Hz, part D of a XCDQ system, 1 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.88 (s, 9 H), 0.61 (q, J = 7.9 Hz, 6 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.7 s, 69.2 d, 66.7 t, 48.9 t, 25.8 q, 18.1 s, 6.8 t, 4.3 t, −4.2 q, −4.8 q. HRMS (EI, *m*/*z*) calcd for $C_{16}H_{36}O_3Si_2$ 332.2203, found 332.2209.

Skipped Diene 8. KHMDS (4.2 equiv, 50.5 mL, 0.5 M in toluene) was added to a suspension of phosphonium iodide **7** (4.5 equiv, 12.77 g) in dry toluene (120 mL) under an Ar atmosphere, and the resulting red mixture was stirred for 45 min, then the agitation was stopped for 1 h. The salt-free solution of ylide (157 mL) was then added to a solution of aldheyde **6** (2 g, 6.01 mmol) in dry toluene (60 mL) under an Ar atmosphere at −94 °C. After 1 h a saturated solution of NH_4Cl (300 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (99:1) gave compound **8** (2.2 g, 92%) as a colorless oil. $[\alpha]^{20}_D$ +0.25 (*c* 0.9, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3012, 1957, 2929, 2858, 1471, 1255, 1116, 1005, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.53−5.27 (m, 4 H), 3.73 (m, part X of an ABXCD system,1 H), 3.52 (dd, part A of an ABX system, 1 H), 3.45 (dd, part B of an ABX system, 1 H), 2.80 (m, 2 H), 2.36 (dt, part C of a XCDQ system, 1 H), 2.21 (dt, part D of a XCDQ system, 1 H), 2.09 (qt, J = 7.4 Hz, 2 H), 1.02−0.94 (m, 12 H), 0.94 (s, 9 H), 0.62 (q, J = 7.8 Hz, 6 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.8 d, 129.8 d, 127.2 d, 126.0 d, 73.3 d, 66.7 t, 32.3 t, 25.9 q, 25.7 t, 20.4 t, 18.2 s, 14.2 q, 6.8 q, 4.3 t, −4.4 q, −4.7 q. HRMS (EI, *m*/*z*) calcd for $C_{22}H_{46}O_2Si_2$ 398.3036, found 398.3038.

Aldehyde 3. Oxalyl chloride (4.4 equiv, 0.305 mL, 2 M in CH_2Cl_2) was added to a stirred solution of DMSO (8.8 equiv, 0.087 mL) in CH_2Cl_2 (0.55 mL) under an Ar atmosphere at −70 °C. After 15 min a solution of compound **8** (50 mg, 0.139 mmol) in CH_2Cl_2 (0.55 mL) was added. After 20 min the temperature was raised to −40 °C for 20 min, then Et_3N (15 equiv, 0.291 mL) was added at −70 °C. The reaction was allowed to warm for 1 h, then a saturated solution of NH_4Cl (5 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/Et_2O (99:1) gave compound **3** (27.4 mg, 70%) and recovered compound **8** (11.5 mg, 23%) as colorless oils. $[\alpha]^{20}_D$ −5.88 (*c* 0.25, CH_2Cl_2); ee 99%, column: Megadex, DMePeBETACDX, 25 m, film thickness 025 μm, i.d. 0.25 mm; carrier: He, 1.5 mL/min; oven temperature gradient 100 °C (1 min)→2 °C/min→110 °C (15 min)→2 °C/min→130 °C (1 min)→5 °C/min→180 °C (15 min); injector temperature 220 °C; detector temperature 250 °C. IR (liquid film) $\tilde{\nu}$ 3010, 1958, 1930, 2875, 2871, 1738, 1417, 1254, 1114, 838, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.63 (d, J = 1.5 Hz, 1H), 5.58−5.23 (m, 4 H), 4.02 (dt, J = 6.3, 1.5 Hz, 1 H), 2.8 (bt, 2 H), 2.44 (t, J = 6.3 Hz, 2 H), 2.08 (qt, J = 7.4 Hz, 2 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.94 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9 s, 132.3 d, 131.2 d, 126.7 d, 132.6 d, 77.6 d, 31.0 t, 25.8 q, 25.7 t, 20.4 t, 18.3 s, 14.3 q, −4.6 q, −4.8 q. HRMS (EI, *m*/*z*) calcd for $C_{16}H_{30}O_2Si$ 282.2015, found 282.2010.

Phenyltetrazoyl Thioether 2a. Bu_3P (1.3 equiv, 2.87 g) and PTSH (1.2 equiv, 1.65 g) were added to a stirred solution of compound **4** (1.3 g, 8.44 mmol) in dry toluene (56 mL). The resulting mixture was cooled to 0 °C and DEAD (1.3 equiv, 5 mL, 40% in toluene) was added dropwise. The temperature was allowed to raise to rt. After 3 h the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash

chromatography on silica gel. Elution with CH_2Cl_2/EtOAc (95:5) gave pure thioether **2a** (2.69 g, 96%). $[\alpha]^{20}_D$ −57.00 (*c* 0.5, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3058, 2961, 1774, 1597, 1500, 1413, 1388, 1267, 1174, 1029, 763, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.6 (m, 5 H), 6.1 (m, 1 H), 6.0 (m, 1 H), 5.5 (m, 1 H), 3.6−3.3 (m, 4 H), 2.7−2.3 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0 s, 153.4 s, 137.3 d, 133.5 d, 130.5 d, 130.4 d, 130.0 d, 123.9 d, 88.3 d, 45.7 d, 39.6 d, 34.0 t, 29.3 t. HRMS (EI, *m*/*z*) calcd for $C_{15}H_{14}N_4O_2{}^{32}S$ 314.0837, found 314.0841.

Phenyltetrazoyl Solfone 2. $(NH_4)_2MoO_4$ (0.403 g) and H_2O_2 30% (9.5 mL) were added to a stirred solution of the above sulfide (2.69 g, 8.31 mmol) in MeOH (100 mL). After 18 h an excess of solid $Na_2S_2O_4$ was added and the resulting mixture was filtered and concentrated under reduced pressure. CH_2Cl_2 (20 mL) and a saturated solution of NH_4Cl (20 mL) were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (70:30) gave compound **2** (2.25 g, 78%) as a white foam. $[\alpha]^{20}_D$ −71.7 (*c* 0.4, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3063, 1769, 1480, 1344, 1160, 1034, 766, 736; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.7 (m, 5 H), 6.1 (s, 2 H), 5.5 (m, 1 H), 4.1−3.8 (m, part AB of an ABX system, 2 H), 3.7 (m, part X of an ABX system, 1 H), 3.5 (m, part Y of a CDY system, 1 H), 2.7 (m, part C of a CDY system, 1 H), 2.3 (m, part D of a CDY system, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3 s, 153.4 s, 135.2 d, 132.9 s, 131.8 d, 131.5 d, 130.0 d, 125.0 d, 87.7 d, 56.5 t, 40.4 d, 40.2 d, 30.0 t. HRMS (EI, *m*/*z*) calcd for $C_{15}H_{14}N_4O_4{}^{32}S$ 346.0736, found 346.0735.

Skipped Diene 9. KHMDS (1.15 equiv, 0.342 mL, 15% in toluene) was added to a stirred solution of compound **2** (68 mg, 0.196 mmol) in dry DME (2.2 mL) under an Ar atmosphere at −78 °C. After 50 min a solution of aldehyde **3** (1.2 equiv, 66.7 mg) in dry DME (1 mL) was added and the reaction was allowed to warm for 4 h, then a saturated solution of NH_4Cl (5 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (93:7) gave compound **9** (43 mg, 60%) as a colorless oil. $[\alpha]^{20}_D$ +26.37 (c 0.89, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3012, 2958, 2857, 1779, 1474, 1360, 1254, 1166, 1076, 1028, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.02−5.92 (m, 2 H), 5.62−5.27 (m, 7 H), 4.17 (m, 1 H), 3.55 (br t, 1 H), 3.24 (br qt, 1 H), 2.78 (m, 2 H), 2.47 (d, J = 8.5, 2 H), 2.34−2.23 (m, 2 H), 2.08 (qt, J = 7.4 Hz, 2 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.9 s, 139.3 d, 136.9 d, 132.1 d, 130.3 d, 129.3 d, 127.6 d, 127.0 d, 125.3 d, 88.7 d, 72. 8 d, 50.0 d, 40.2 d, 36.4 t, 30.6 t, 25.8 q, 25.7 t, 20.6 t, 18.3 s, 14.3 q, −4.3 q, −4.6 q. HRMS (EI, *m*/*z*) calcd for $C_{24}H_{38}O_3Si$ 402.2590, found 402.2597.

Weinreb Amide 17. n-BuLi (12 equiv, 2.72 mL, 2.5 M in hexane) was added to a stirred suspension of HNMeOMe·HCl (6 equiv, 0.332 g) in dry THF (5.4 mL) under an Ar atmosphere at −78 °C. After 5 min the temperature was raised to 0 °C for 20 min, then the solution was cooled to −78 °C and a solution of lactone **9** (0.228 g, 0.567 mmol) in dry THF (5.9 mL) was added. After 1 h a saturated solution of NH_4Cl (30 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was partially purified by flash chromatography on silica gel. Elution with hexane/EtOAc (70:30) gave a crude product (0.243 g) that was directly subjected to the next step because of its high tendency to reyield the lactone.

The crude was dissolved in CH_2Cl_2/EVE 1:1 (5 mL) and PPTS (cat.) was added. The resulting mixture was stirred for 2 h, then excess solid $NaHCO_3$ was added, followed by a saturated solution of $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel.

Elution with CH_2Cl_2/EtOAc (98:2) gave the desired acetal (0.194 g, 64%, 1:1 mixture of anomers) and recovered lactone **9** (23.5 mg, 10%) as colorless oils. IR (liquid film) $\tilde{\nu}$ 2931, 1671, 1387, 1253, 1124, 1005, 963, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.02 and 6.00 (m, 1 H), 5.96 and 5.90 (m, 1 H), 5.51−5.26 (m, 6 H), 4.74 and 4.66 (q, J = 5.2 Hz, 1 H), 4.58 and 4.50 (dd, J = 5.9, 2.2 and 6.3, 2.4 Hz, 1 H), 4.10 (br q, 1 H), 3.68 and 3.67 (s, 3 H), 3.67−3.34 (m, 2 H), 3.20 (m, 1 H), 3.17 (s, 3 H), 2.79 (m, 4 H), 2.42−2.16 (m, 3 H), 2.08 (q, J = 7.4 Hz, 2 H), 1.29−1.14 (m, 6 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1 s, 139.2 and 138.1 d, 134.5 d, 132.1 and 131.8 d, 131.3 d, 130.9 d, 129.6 d, 127.0 d, 125.0 d, 100.8 and 98.2 d, 82.1 and 78.0 d, 73.0 d, 60.9 q, 60.6 and 59.6 t, 50.3 and 50.1 d, 40.8 and 40.6 d, 36.4 t, 32.0 q, 28.6 and 28.3 t, 25.8 q, 25.6 t, 20.8 and 20.2 q, 20.4 t, 18.1 s, 15.2 q, 14.2 q, −4.4 q, −4.9 q. HRMS (EI, *m*/*z*) calcd for $C_{30}H_{53}NO_5Si$ 535.3693, found 535.3697.

EE-Ester 19. DIBAl-H (1.2 equiv, 0.337 mL, 1 M in hexane) was added under an Ar atmosphere to a stirred solution of amide **17** (0.150, 0.281 mmol) in dry THF (2.8 mL) at −78 °C. After 50 min a saturated solution of Rochelle's salt (20 mL) was added and the resulting mixture was stirred until a clean separation of the two layers was obtained (3 h). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was partially purified by filtration on silica gel. Elution with hexane/EtOAc (95:5) gave a crude product (0.170 g) that was directly subjected to the next step due to its tendency to lose acetal protection. KHMDS (4.5 equiv, 2.35 mL, 0.5 M in toluene) was added under an Ar atmosphere to a stirred suspension of 3-carboxypropyl-triphenyl phosphonium bromide (4.5 equiv, 0.538 g) in dry toluene (5.4 mL). After 45 min the magnetic agitation was stopped for 1 h. The salt-free orange solution of the resulting ylide (5.8 mL) was added under Ar to a stirred solution of crude aldehyde in dry toluene (3.2 mL) at −78 °C. After 1 h a saturated solution of NH_4Cl (20 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (95:5) gave compound **19** (0.124 g, 82%, 1:1 mixture of anomers) as a colorless oil. IR (liquid film) $\tilde{\nu}$ 2931, 1739, 1463, 1372, 1253, 1160, 1124, 836, 776 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 6.09−6-00 (m, 1 H), 5.98 and 5.93 (m, 1 H), 5.58−5.29 (m, 8 H), 4.77 and 4.71 (q, J = 5.3 Hz, 1 H), 4.48 and 4.32 (dd, J = 5.7, 2.2, and 2.4 Hz, 1 H), 4.15 (m, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.71−3.40 (m, 2 H), 2.82 (br t, 2 H), 2.42−1.97 (m, 11 H), 1.29−1.15 (m, 9 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 200.6 s, 173.1 s, 139.9 and 138.9 d, 134.4 d, 131.8 d, 131.4 d, 131.3 and 131.2 d, 131.0 d, 129.6 d, 129.5 and 127.8 d, 127.2 d, 125.8 d, 100.4 and 97.5 d, 81.5 and 77.1 d, 73.3 d, 60.2 t, 58.9 t, 50.6 d, 46.8 d, 36.5 t, 34.3 t, 25.9 q, 25.7 t, 24.0 t, 23.0 t, 20.5 t, 20.5 and 20.1 q, 18.2 s, 15.3 q, 14.2 q, 14.2 q, −4.3 q, −4.8 q. HRMS (EI, *m*/*z*) calcd for $C_{34}H_{58}O_5Si$ 574.4054, found 574.4055.

Cyclopentenol 19a. PPTS (cat.) was added to a stirred solution of acetal **19** (0.124 g, 0.215 mmol) in EtOH/CH_2Cl_2 6:1 (7 mL) and the resulting mixture was stirred for 9 h. An excess of solid $NaHCO_3$ was added and the resulting mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (90:10) gave the desired alcohol **19a** (79.4 mg, 74%) as a

colorless oil. $[\alpha]^{20}_D$ +55.11 (*c* 0.22, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3502, 2931, 1713, 1472, 1358, 1360, 1254, 1077, 986, 840, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.06 (m, 1 H), 6.00 (m, 1 H), 5.59−5.27 (m, 8 H), 4.51 (br s, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.12 (m, 1 H), 3.16 (m, 1 H), 2.79 (br t, 2 H), 2.59−2.45 (m, 1 H), 2.44−1.98 (m, 10 H), 1.66 (br s, 1 H, −OH), 1.27 (t, J = 7.2 Hz, 3 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 s, 139.0 d, 134.5 d, 133.1 d, 132.0 d, 131.9 d, 130.0 d, 129.7 d, 128.5 d, 127.1 d, 125.7 d, 75.8 d, 73.1 d, 60.3 t, 49.9 d, 46.8 d, 36.3 t, 33.9 t, 25.8 q, 25.7 t, 24.1 t, 22.7 t, 20.5 t, 18.1 s, 14.1 q, 14.1 q, −4.5 q, −4.8 q. HRMS (EI, *m*/*z*) calcd for $C_{30}H_{50}O_4Si$ 502.3478, found 502.3480.

Cyclopentenol Acid 19b. $Ba(OH)_2 \cdot 8H_2O$ (4 equiv, 0198 g) was added to a stirred solution of the above ester (79.4 g, 0.158 mmol) in MeOH (3.15 mL). After 18 h AcOH (8 equiv, 0.075 mL) was added and the resulting mixture was concentrated under reduced pressure. EtOAc (10 mL) and brine (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (70:30) gave the free carboxylic acid **19b** (74.8 mg, 99%) as a colorless oil. $[\alpha]^{20}_D$ +88.15 (*c* 0.27, CH_2Cl_2); IR (liquid film) $\tilde{\nu}$ 3310−2590 (OH and COOH), 2930, 2857, 1712, 1462, 1252, 1065, 838, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.08−5.98 (m, 2 H), 5.60−5.25 (m, 8 H), 4.52 (dd, J = 5.5, 2.4 Hz, 1 H), 4.13 (m, 1 H), 3.16 (m, 1 H), 2.79 (t, J = 6.3 Hz, 2 H), 2.61−1.97 (m, 11 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2 s, 139.5 d, 134.8 d, 133.0 d, 132.0 d, 132.0 d, 130.3 d, 129.9 d, 128.5 d, 127.2 d, 125.7 d, 76.0 d, 73.3 d, 50.1 d, 47.0 d, 36.5 t, 33.5 t, 26.0 q, 25.8 t, 24.2 t, 22.7 t, 20.7 t, 18.3 s, 14.4 q, −4−3 q, −4.6 q. HRMS (EI, *m*/*z*) calcd for $C_{28}H_{46}O_4Si$ 474.3165, found 474.3167.

Cyclopentenone 20. DMP (1.2 equiv, 40.2 mg) was added to a stirred solution of the above free acid (35.6 mg, 0.08 mmol) in dry CH_2Cl_2 (1.6 mL). After 55 min Et_2O (6 mL) was added and the resulting mixture was filtered over a short pad of silica gel, which was thoroughly washed with hexane/Et_2O (1:1, 70 mL). The resulting mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (80:20) gave compound **20** (32.7 mg, 92%) as a colorless oil. $[\alpha]^{20}_D$ +144.1 (*c* 0.195, EtOAc); IR (liquid film) $\tilde{\nu}$ 3210−2600 (CO*OH*), 2931, 2856, 1714, 1585, 1461, 1252, 1080, 972, 836, 775 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 7.59 (dd, J = 5.7, 2.8 Hz, 1 H), 6.17 (dd, J = 5.7, 1.7 Hz, 1 H), 5.62−5.26 (m, 8 H), 4.23 (m, 1 H), 3.75 (m, 1 H), 2.79 (t, J = 5.9 Hz, 2 H), 2.54−2.20 (m, 9 H), 2.08 (qt, J = 7.4 Hz, 2 H), 0.97 (t, J = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (CD_3CN, 75 MHz) δ 209.9 s, 173.5 s, 165.3 d, 136.8 d, 132.1 d, 131.6 d, 129.7 d, 128.7 d, 128.7 d, 127.3 d, 127.1 d, 125.5 d, 72.6 d, 49.4 d, 47.1 d, 35.9 t, 33.0 t, 25.4 t, 25.2 q, 24.3 t, 22.6 t, 20.2 t, 17.7 s, 13. 6 q, −5.2 q, −5.5 q. HRMS (EI, *m*/*z*) calcd for $C_{28}H_{44}O_4Si$ 472.3009, found 472.3012.

Neuroprostane 1. Aqueous HF (48%, 0.063 mL) was added to a stirred solution of silyl ether **20** (20.2 mg, 0.0427 mmol) in CH_3CN in a PE test tube. After 4 h a phosphate buffer (pH 6.8, 5 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (50:50) gave pure 14-A_{4t}-NeuroP (**1**) (15.2 mg, 99%) as a colorless oil. $[\alpha]^{20}_D$ +163.3 (c 0.15, EtOAc); IR (liquid film) $\tilde{\nu}$ 4313, 2928, 1705, 1581, 1240, 968 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 7.59 (dd, J = 5.7, 2.8 Hz, 1 H), 6.18 (dd, J = 5.7 Hz, 1.7, 1 H), 5.61−5.27 (m, 8 H), 4.08 (m, 1 H), 3.71 (m, 1 H), 2.78 (t, J = 6.3 Hz, 2 H), 2.47 (m, 1 H), 2.35 (m, 1 H), 2.30−2.19 (m, 6 H), 2.15−2.03 (m, 3 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (CD_3CN, 75 MHz) δ 209.9 s, 173.7 s, 165.5 d, 136.6 d, 132.1 d, 131.7 d, 129.9 d, 128.9 d, 128.8 d, 127.5 d, 127.0 d, 125.5 d, 71.2 d, 49.5 d, 47.0 d, 35.0 t, 33.1 t, 25.3 t, 24.3 t, 22.7 t, 20.2 t, 13.6 q. HRMS (EI, *m*/*z*) calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2146.

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Supporting Information Available: A nomenclature system for neuroprostanes, copies of ^1H, ^{13}C, and 2D NMR spectra, and chiral CG and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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