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Versatile Synthesis of the C3−C14 Domain of 7-Deoxyokadaic Acid

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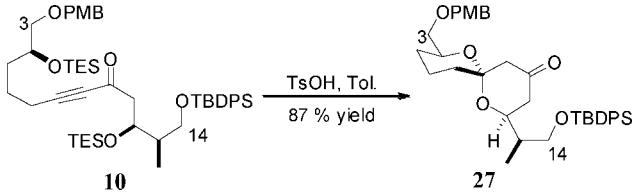
Received August 05, 2008

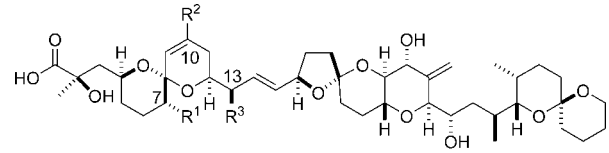


10 **27**

Described is a flexible synthesis of the C3−C14 domain of 7-deoxyokadaic acid that is amenable to facile structural diversification. Treatment of ynone **10** under acidic conditions led to net bis-conjugate addition of the latent diol to give the thermodynamically favored spiroketal **27**, a versatile intermediate, en route to 7-deoxyokadaic acid and analogs.

Okadaic acid (**1**, Figure 1) is the archetypal seriene/threonine protein phosphatase inhibitor.[1] The natural product 7-deoxyokadaic acid (**2**) maintains similar protein serine/threonine phosphatase inhibitory activity,[2] whereas omission of the C7 hydroxyl group substantially simplifies synthetic access.[3] Hence, 7-deoxyokadaic acid has become the primary template for our research into the development of selective phosphatase inhibitors.

The primary amino acid sequences of the okadaic acid receptors protein phosphatases 1 and 2A (PP1 and PP2A, respectively) are ca. 50% conserved.[4] Subtle yet significant structural differences in and about the active sites of PP1 and PP2A may contribute to differential sensitivities toward 7-deoxyokadaic acid, with K_i = 150 and 30 nM for PP1 and PP2A, respectively.[2,5,6] Differential levels of binding affinities to PP1 versus PP2A have also been reported for most members of the okadaic acid class of inhibitors.[7] The continued development of an empirical understanding of the essential structural differences between the binding of inhibitors to PP1 versus PP2A is expected to facilitate the identification of novel small molecules with enhanced levels of specificity.



1 R^1 = OH, R^2 = Me, R^3 = Me
2 R^1 = H, R^2 = Me, R^3 = Me
3 R^1 = H, R^2 = Me, R^3 = H
4 R^1 = H, R^2 = H, R^3 = Me
5 R^1 = H, R^2 = H, R^3 = H

FIGURE 1. Okadaic acid and some targeted analogues.

The availability of X-ray crystallographic data for cocrystals of okadaic acid and both PP1 and PP2A now provide a wealth of information toward this goal.[8,9] Within the similar topologies of the PP1/PP2A active sites, where the C1−C14 portion of okadaic acid docks, there are several likely binding interactions involving the C10 and C13 methyl substituents of okadaic acid. For the C10 methyl group, contacts may occur with Cys273 (3.72 Å), Glu275 (3.29 Å), and Phe275 (3.74 Å) of PP1 and with Cys266 (3.97 Å), Arg268 (3.70 Å), and Cys269 (3.84 Å) when bound to PP2A.[9] The C13 methyl substituent has potential interactions with Val250 (3.95 Å), Tyr 255 (4.53 Å), and Phe276 (3.72 Å) of PP1 and with Leu243 (3.47 Å) and Tyr265 (4.32 Å) of PP2A.[9] These crystallographic correlations have prompted the development of a versatile new synthetic entry to the C3−C14 domain of okadaic acid that may vary in functionalization at C10, C13 (e.g., **3**−**5**), and other sites.

The original retrosynthesis of 7-deoxyokadaic acid began with a disconnection between C14 and C15 leading to the C1−C14 aldehyde **6** and the C15−C38 β-ketophosphonate **7** (Scheme 1).[3] Compound **6** could, in turn, be prepared from the lithium enolate of Seebach's lactate (**8**)[10] and the C3−C14 aldehyde **9**.[3] At this juncture, we planned to assemble the spiroketal from ynone **10** via a double intramolecular hetero-Michael addition (DIHMA) process.[11] We anticipated that under thermodynamic

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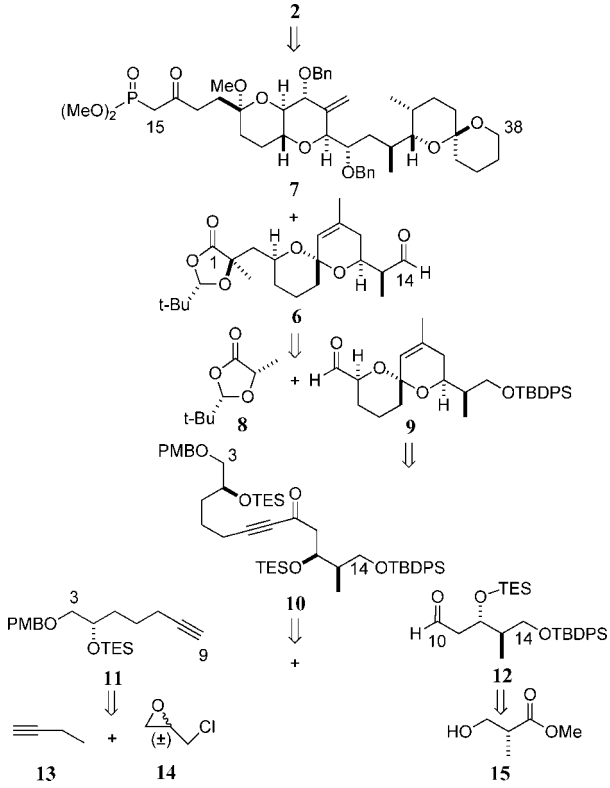
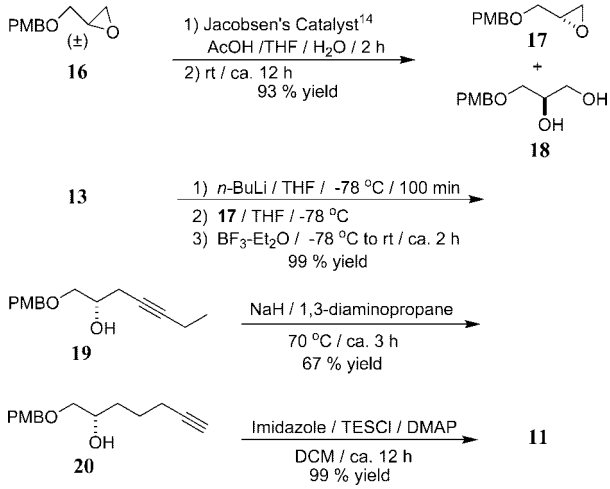
10.1021/jo8017457 CCC: $40.75
Published on Web 12/15/2008

SCHEME 1. Retrosynthesis of 7-Deoxyokadaic Acid



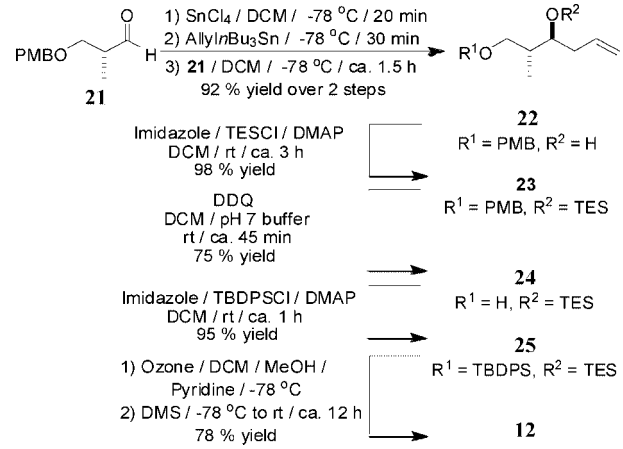
SCHEME 2. Synthesis of the C3−C9 Fragment



control the resident configurations at C4 and C12 would favor the formation of the natural product's C8 stereogenic center.

Intermediate **10** was prepared from the C3−C9 fragment alkyne **11** and C10−C14 aldehyde **12**, both of which were obtained from commercially available compounds 1-butyne (**13**), epichlorohydrin (**14**), and methyl-(*R*)-3-hydroxy-2-methylpropionate (**15**). The synthesis of the C3−C9 alkyne **11** began with protected glycidol ether **16** (Scheme 2), which was prepared as previously described and identified via ^{1}H NMR spectroscopic comparison.[12,13] Hydrolytic kinetic resolution (HKR)[14] of **16**

SCHEME 3. Synthesis of the C10−C14 Fragment



provided enantiomerically enriched **17**,[13] which was converted into the internal alkyne **19** via reaction with in situ formed 1-lithio-1-butyne.[15] At the stage of **19** it was found that the HKR process had given an approximate 6.4:1 ratio of (*R*)-**17** to (*S*)-**17**, based on chiral column analysis against a racemic standard.[16]

Compound **19** was isomerized to the terminal alkyne **20** under Brown's strongly basic conditions.[17] Attempts to accomplish this conversion in the presence of silyl protecting groups were unsuccessful. The secondary alcohol **20** was converted into the TES ether **11**, completing the synthesis of the C3−C9 fragment in ca. 61% overall yield over four steps from (±)-**16**.

The synthesis of the C10−C14 fragment began with the known aldehyde **21**[18] (Scheme 3), which was identified via ^{1}H NMR spectroscopic comparison. The C12 stereogenic center was installed via allylation[19] of **21** to give the terminal alkene **22** in a 15:1 diastereomeric ratio based upon ^{1}H NMR spectroscopy. Subsequent protection of the secondary alcohol **22** with TESCl gave **23**. Cleavage of the PMB ether of **23**, followed by TBDPS ether formation, yielded **25**. These protecting group manipulations became necessary for two reasons. First, in the synthesis of **11**, the PMB protecting group aided the alkyne migration process. Second, the presence of the PMB protecting group facilitated the tin-mediated chelation controlled allylation reaction leading to **12**, and the subsequent conversion to the TBDPS protecting group was preferred for terminal differentiation post convergence with **11**. Ozonolysis of **25** gave aldehyde **12**, completing the synthesis of the C10−C14 fragment in an overall yield of ca. 50% over five steps from **21**.

Completion of the synthesis of the C3−C14 domain began with the coupling of the lithium acetylide derived from **11** with **12** to afford the propargylic alcohols **26** (Scheme 4) as a diastereomeric mixture (epimeric at both C4 and C10). Oxida-

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(16) HP Series 1100, Chiralcel OD, column no. OD00CE-AJ015, 1.0 μL injection, 0.5 mL/min, 95:5 hexane/iPrOH, UV detection $\lambda = 280$ nm.

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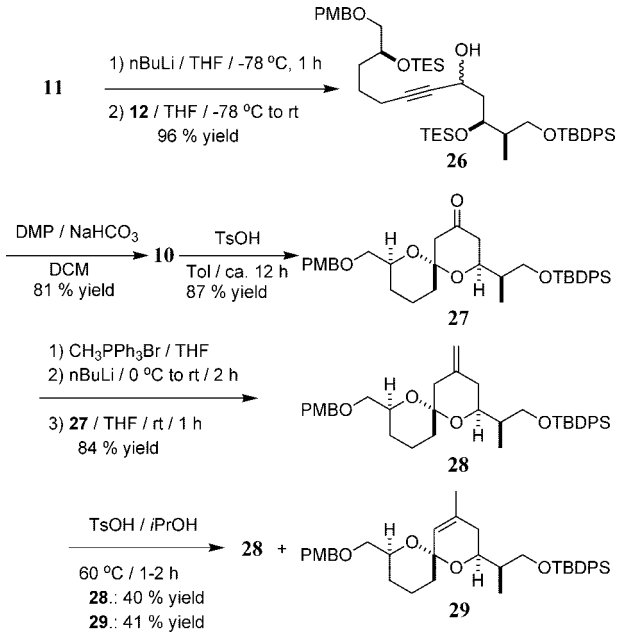
SCHEME 4. Synthesis of the C3−C14 Domain



tion of alcohols **26** gave ynones (4*R/S*)-**10**. At this stage, the minor (4*R*)-diastereomer resulting from the HKR of (±)-**16** was chromatographically separated from (4*S*)-**10**. Subsequent implementation of the DIHMA process using the (4*S*)-diastereomer of **10** provided spiroketal **27**. For this, prolonged exposure to acid was intended to assist equilibration to capture the benefit of mutual anomeric stablization in **27**. To complete the synthesis of the 7-deoxyokadaic acid intermediate **29**, ketone **27** was subjected to Wittig olefination to yield the exo methylene compound **28**. Subsequent isomerization to the internal alkene **29** was accomplished under acidic conditions (Scheme 4). Remarkably, none of the alternative endocyclic alkene isomer was detected to accompany **29**. This regioselective alkene migration may reflect an enhanced acidity of the α-ketal methylene protons and/or alkene conjugation with a transient oxocarbenium intermediate. In any event, it places the alkene α to the C8 spiroketal center as is observed among okadaic acid and its congeners.

The synthesis of the C3−C14 domain was thus completed in an overall yield of ca. 23% over 10 steps from **21**. The assignment of relative configuration at the spiroketal center of **29** was made via conversion into a C3,C14-diol, a known compound obtained from an intermediate used in the total synthesis of **2**.[20] Comparison of the ^{1}H NMR spectral data indicated identical relative stereochemistry at C4, C8, C12, and C13, as well as the location of the alkene at C9 between **29** and the natural product 7-deoxyokadaic acid.

The advantages of this new route to the functionalized C3−C14 spiroketal domain of **2** are its efficiency and its applicability to readily access several analogs with only minor changes to the overall synthetic route. For instance, 13-desmethyl-7-deoxyokadaic acid analog **3** has been obtained by a simple change of starting material **21** to 1,3-propanediol with essentially the same reaction sequence to assemble a C10−C14 intermediate. Similarly, employing the identical synthetic route to spiroketal **27**, the versatile C10 ketone could provide access to various derivatives. This has been successfully employed in the synthesis of the 10-desmethyl-7-deoxyokadaic acid analog **4**. A combination of such tactics has led to 7-deoxyokadaic acid analog **5**. Potentially synergystic efforts are also underway to probe the effects of structural variations about the terminal C30−C38 spiroketal of okadaic acid analogs.[21]

Incorporation of C3−C14 structural variants into full length okadaic acid analogs will allow comparative phosphatase binding assays to be performed. This should contribute to an enhanced understanding of the essential roles of the structural moieties within the active site-occupying domain of okadaic acid, as suggested by X-ray crystallography.

Experimental Section

Yneone 10. To a magnetically stirred, room temperature solution of **26** (6.294 g, 7.43 mmol) in methylene chloride (74 mL) was added $NaHCO_3$ (9.36 g, 111.4 mmol) and Dess−Martin periodinane (6.3 g, 14.9 mmol). After TLC indicated no remaining **26**, saturated aqueous $NaHCO_3$ (50 mL) was added dropwise. The separated aqueous phase was extracted with methylene chloride (3 × 25 mL), and the combined organic phase was washed with H_2O (50 mL) and then brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 20:1, v/v) to give **10** as an oil (5.06 g, 5.98 mmol, 81%): $[\alpha]^{25}_D$ +0.5 (*c* 3.1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.69−7.64 (m, 4H), 7.46−7.35 (m, 6H), 7.25 (d, J = 9 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 4.62−4.59 (m, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.50 (d, J = 7 Hz, 2H), 3.36 (dd, J = 5.5, 9.5 Hz, 1H), 3.32 (dd, J = 5.5, 9.5 Hz, 1H), 2.66 (dd, J = 9, 15.5 Hz, 1H), 2.58 (dd, J = 5.5, 15.5 Hz, 1H), 2.33 (t, J = 7 Hz, 2H), 2.04−1.96 (m, 1H), 1.72−1.48 (m, 5H), 1.07 (s, 9H), 0.96−0.88 (m, 18H), 0.83 (d, J = 7 Hz, 3H), 0.63−0.55 (m, 12H); ^{13}C NMR (125 MHz) δ 187.0, 159.4, 135.8, 133.8, 130.6, 129.8, 129.5, 127.9, 113.9, 94.1, 81.7, 81.0, 74.4, 73.2, 71.1, 69.7, 66.0, 55.5, 49.3, 34.2, 31.8, 27.0, 23.8, 22.9, 19.4, 14.3, 11.7, 7.1, 5.2; IR (neat) 3080−3000, 3000−2850, 2212, 1741, 1676, 1612, 1588, 1513, 1462, 1247, 1120−1060 cm^{-1}; HRMS calcd for $C_{49}H_{76}Si_3O_6Na$ (M + Na) 867.4847, found 867.4881; R_f = 0.30 (hexanes: ethyl acetate, 8:1, v/v).

Pyranone 27. To a magnetically stirred, room temperature solution of ynone **10** (710 mg, 845 μmol) in toluene (8.4 mL) was added *p*-toluenesulfonic acid monohydrate (192 mg, 1.00 mmol). The mixture was stirred 1 d before saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was diluted with diethyl ether (10 mL) and the aqueous phase was separated. The organic phase was washed with H_2O (10 mL), then brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes: ethyl acetate, 4:1, v/v) to give **27** as a colorless oil (451 mg, 731 μmol, 87%): $[\alpha]_D^{24}$ −36 (*c* 3.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.65 (d, J = 8 Hz, 4H), 7.44−7.35 (m, 6H), 7.18 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.39 (d, J = 2.5 Hz, 2H), 3.92−3.90 (m, 1H), 3.81 (s, 3H), 3.69 (t, J = 4.5 Hz, 1H), 3.70 (dd, J = 5.5, 10 Hz, 1H), 3.65−3.60 (m, 1H), 3.28 (d, J = 5 Hz, 2H), 2.42 (t, J = 13 Hz, 2H), 2.34 (d, J = 14 Hz, 1H), 2.25 (dd, J = 11.5, 14.5 Hz, 1H), 1.95−1.85 (m, 1H), 1.75−1.65 (m, 2H), 1.46−1.41 (m, 2H), 1.29−1.20 (m, 2H), 1.05 (s, 9H), 0.97 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 206.6, 159.2, 135.8, 133.8, 130.8, 129.8, 129.2, 127.8, 113.8, 99.2, 73.0, 72.8, 70.0, 69.7, 65.2, 55.4, 52.0, 44.4, 41.2, 34.7, 27.1, 26.7, 19.4, 18.7, 13.3; IR (neat) 3070, 3048, 3000−2850, 1726, 1612, 1588, 1513, 1464, 1428, 1248, 1110−1000, 823, 741, 705 cm^{-1}; HRMS calcd for $C_{37}H_{48}SiO_6Na$ (M + Na) 639.3112, found 639.3106; R_f = 0.35 (hexanes/ethyl acetate, 4:1, v/v).

Exocyclic Alkene 28. To a magnetically stirred, 0 °C solution of methyltriphenylphosphonium bromide (72 mg, 202 μmol) in THF

(20) Dounay, A. B. Thesis, University of Minnesota, 2001, pp 24−25; ^{1}H NMR spectra, ABD-II-233 and ABD-II-238.

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(2 mL) was added *n*-BuLi (73 μL of a 2.5 M solution in hexanes, 182 μmol). After 5 min, the mixture was allowed to warm to room temperature and stirred for 2 h before a solution of **27** (25 mg, 40.5 μmol) in THF(1 mL) was added. The mixture was stirred 1 h before saturated aqueous NH_4Cl (4 mL) was added. The separated aqueous phase was extracted with ethyl acetate (3 × 1 mL), and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1, v/v) to give **28** as a colorless oil (21 mg, 34 μmol, 84%): $[\alpha]^{24}_D$ −30 (*c* 3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.69 (d, J = 6.5 Hz, 4H), 7.45−7.36 (m, 6H), 7.23 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 4.81 (s, 1H), 4.78 (s, 1H), 4.50 (d, J = 7 Hz, 1H), 4.44 (d, J = 7 Hz, 1H), 3.88 (dd, J = 4.5, 9.5 Hz, 1H), 3.82 (s, 3H), 3.64 (dd, J = 7, 10 Hz, 1H), 3.63−3.60 (m, 1H), 3.58−3.54 (m, 1H), 3.34 (t, J = 4.5 Hz, 2H), 2.32−2.28 (m, 2H), 2.13 (d, J = 13 Hz, 1H), 1.97, (t, J = 13 Hz, 1H), 1.85−1.82 (m, 1H), 1.72−1.68 (m, 1H), 1.68−1.62 (m, 1H), 1.55−1.51 (m, 1H), 1.46−1.41 (m, 2H), 1.30−1.23 (m, 1H), 1.09 (s, 9H), 1.02 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 159.1, 142.4, 135.9, 134.1, 131.2, 129.7, 129.2, 127.7, 113.8, 110.2, 97.1, 73.0, 72.9, 70.8, 69.6, 65.8, 55.4, 44.8, 41.4, 37.4, 35.2, 27.2, 27.1, 19.5, 18.8, 13.6; IR (neat) 3072, 3000−2850, 1656, 1614, 1588, 1513, 1463, 1429, 1247, 1120−1000, 910, 823, 770 cm^{-1}; HRMS calcd for $C_{38}H_{50}SiO_5Na$ (M + Na) 637.3320, found 637.3326; R_f = 0.34 (hexanes/ethyl acetate, 8:1, v/v).

Endocyclic Alkene 29. To a magnetically stirred, room temperature solution of **28** (88.4 mg, 144 μmol) in isopropyl alcohol (1.44 mL) was added *p*-toluenesulfonic acid monohydrate (8.2 mg, 43 μmol). The mixture was heated to 60 °C and allowed to stir for ca. 1 h before saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was allowed to cool to room temperature and then diluted with diethyl ether (2 mL). The aqueous layer was removed, and the organic phase was washed with H_2O (2 mL) and then brine (2 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate. 50:1, then 35:1, then 20:1 v/v) to give **29** (36 mg, 58.5 μmol, ca. 41%) and **28** (35.2 mg, 57.2 μmol, ca. 40%), both as colorless oils. Data for **29**: $[\alpha]^{24}_D$ −36 (*c* 2.8, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.69−7.67 (m, 4H), 7.42−7.34 (m, 6H), 7.17 (d, J = 8 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 5.34 (s, 1H), 4.37 (d, J = 7 Hz, 1H), 4.33 (d, J = 7 Hz, 1H), 4.00 (dd, J = 4.5, 10 Hz, 1H), 3.81 (s, 3H), 3.77−3.73 (m, 1H), 3.72−3.68 (m, 1H), 3.55 (dd, J = 7.5, 9.5 Hz, 1H), 3.32 (dd, J = 4.5, 20 Hz, 1H), 3.25 (dd, J = 5, 20 Hz, 1H), 1.94−1.89 (m, 2H), 1.81 (dd, J = 3, 17 Hz, 2H), 1.70 (s, 3H), 1.58−1.52 (m, 2H), 1.51−1.41 (m, 2H), 1.30−1.26 (m, 1H), 1.08 (s, 9H), 1.03 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 159.2, 136.1, 135.9, 134.2, 130.9, 129.7, 129.6, 127.7, 124.9, 113.8, 94.9, 73.4, 72.8, 69.2, 68.6, 66.4, 55.4, 41.1, 35.1, 33.2, 27.5, 27.1, 23.2, 19.5, 18.7, 13.6; IR (neat) 3069, 3049, 3000−2850, 1740, 1613, 1587, 1513, 1463, 1428, 1247, 1110−990, 823, 704 cm^{-1}; HRMS calcd for $C_{38}H_{50}SiO_5Na$ (M + Na) 637.3325, found 637.3286; R_f = 0.31 (hexanes/ethyl acetate, 8:1, v/v).

Acknowledgment. This publication was made possible by grant number ES10615 from the National Institute of Environmental Health Sciences (NIEHS), NIH, and generous unrestricted funding from The Ohio State University. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH. We thank Dr. A. B. Dounay (Pfizer) for the acquisition of spectral correlation data.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H NMR and ^{13}C NMR spectra for previously unreported compounds, HPLC trace for compound **19**, and comparative ^{1}H NMR spectra.[20] This material is available free of charge via the Internet at http://pubs.acs.org.

JO8017457