Synthesis of Functionalized Cannabinoids

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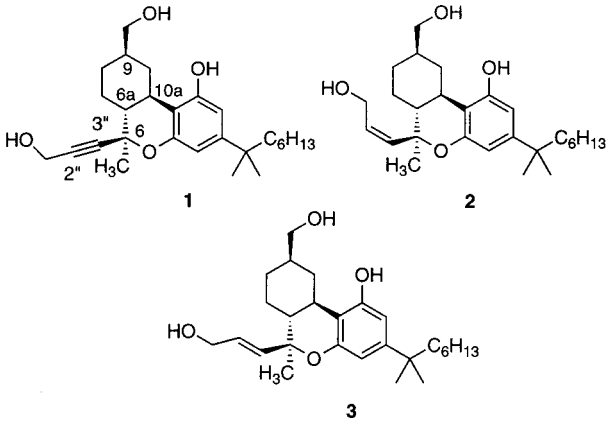
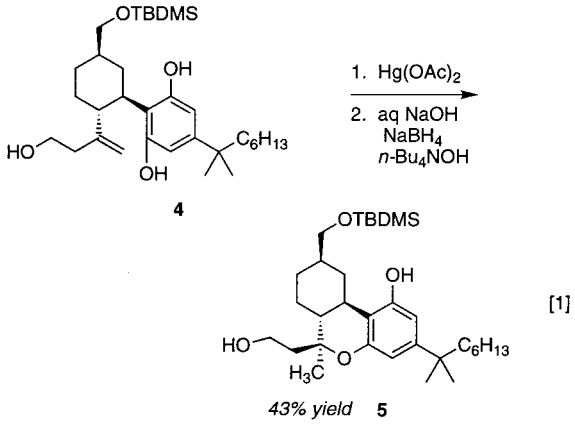
An effective synthesis of tricyclic, nonclassical cannabinoids has been developed on the basis of a cation−olefin cyclization that forms the two nonaromatic rings with the desired stereochemistry in a single step.

Introduction

Earlier efforts in our groups had revealed a correlation between the stereochemistry of the southern aliphatic hydroxyl (SAH) group, the chain length, and the affinity of the compounds for CB1 and CB2, the two known cannabinoid receptors, within a series of hybrid cannabinoids.[1] A systematic study, in which C6 stereochemistry and the chain length of the group appended to this carbon were varied, revealed that the C6β hydroxypropyl analogue had a high affinity for both CB1 and CB2 cannabinoid receptors. To further refine our understanding of the stereochemical preferences of the receptor for the hybrid cannabinoids, we sought to obtain additional information on the stereochemical preferences of the SAH group with respect to its ability to interact with the CB1 and CB2 binding sites. This information was obtained by introducing a triple or double bond at the C2″ position of the 6β-hydroxypropyl chain and led to a series of novel cannabinoid receptor probes (**1**−**3**). The challenge to the synthetic chemist that is posed by these structures is control of C6 stereochemistry. There is an insignificant difference in energy between the C6 diasteroisomers of **1**; consequently, stereochemical control cannot be exercised under reaction conditions that would lead to equilibration of this stereogenic carbon. A stereoselective approach to **1** is only possible through a kinetically controlled process.

An early solution to the problem posed by C6 stereochemistry is illustrated by eq 1. Intramolecular oxymercuration−demercuration of **4** led to **5** in 43% yield.[1,2] The probable origin for the preference for the axial acetoxymercuriomethyl group has been discussed.[3] Although the yield for the dihydrobenzopyran ring-forming step was modest in this instance, this approach was successfully applied to the synthesis of cannabinoid analogues.[1]





[1]

A related approach from our group is shown in eq 2, wherein the cyclization of **6** leads to formation of two rings and also determines the stereochemistry at carbon atoms 10a, 6a, and 6 in a single process.[4] The yield of product **7** was low, and we were unable to improve the reaction. The synthesis which is described herein evolved from a consideration of these earlier efforts.

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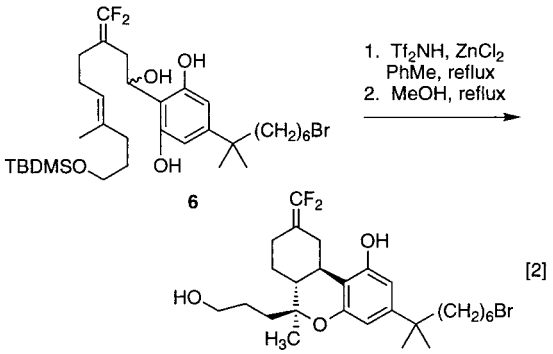


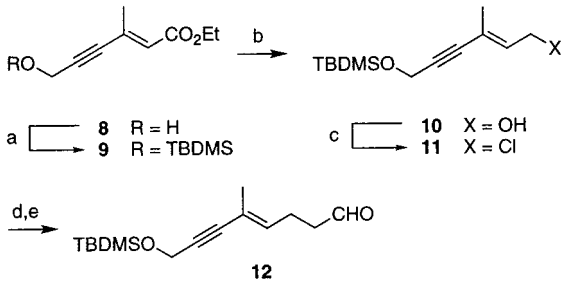
ca. 38% yield **7**

Discussion

Two mechanisms can be imagined which would rationalize the conversion of **6** to **7**. Either an intramolecular Diels−Alder cycloaddition of an *o*-quinone methide[5] or a cation−olefin cyclization initiated by ionization of the benzylic alcohol function.[6] The intramolecular Diels−Alder reaction would be expected to be concerted or synchronous, whereas the cation-olefin process would, in all likelihood, be stepwise. Cyclization of **6** may be nonconcerted, as evidenced by the isolation of a partially cyclized byproduct, and this is in part responsible for the poor yield of the reaction.[7] If the yield for such a cyclization could be improved, it would represent a very attractive method; preparation of intermediates such as **6** is generally much more convenient than the synthesis of compounds analogous to **4**. Since we had evidence that the cyclization of **6** was not concerted, we postulated that unsaturation at C2″−C3″ would lead to a more stable carbocationic intermediate, and that this in turn would result in an improved yield for the cyclization. Our hypothesis is supported by Johnson's approach to corticosteroids in which a strategically placed 2,2-dimethylvinyl group which stabilizes a key carbocation cyclization intermediate results in dramatically enhanced product yield, and shorter reaction time.[8] There is a risk to this approach. As the cations along the reaction pathway become more stable, the reaction is likely to become less stereoselective in a cyclization in which stereochemistry is kinetically controlled, as is the case at hand.[9] Notwithstanding, we decided to proceed by designing a stabilized intermediate for the key cyclization step.

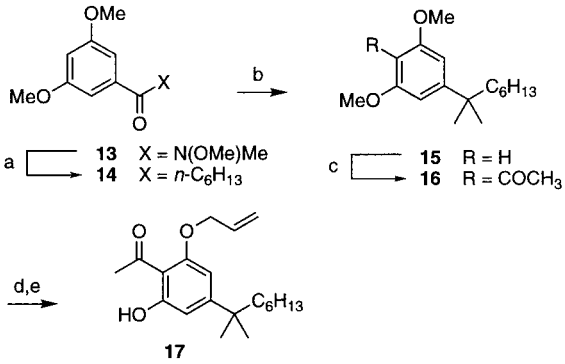
The retrosynthesis of **1** leads to an aliphatic fragment **12** (Scheme 1) and to an aromatic fragment **17** (Scheme 2). Trost's elegant method was used to control the geometry of the trisubstituted alkene in the aliphatic fragment.[10] Palladium acetate catalyzed coupling of propargyl alcohol with ethyl 2-butynoate led to enoate **8** as a single isomer in 75% yield. Protection of the primary hydroxyl group in **8** as the TBDMS ether (**9**)[11] was followed by ester carbonyl group reduction to give allylic alcohol **10**. Conversion of **10** to allylic chloride **11** took place in 70% yield with NCS and triphenylphosphine.[12] The allylic chloride was labile, and was immediately treated with the anion derived from acetaldehyde *tert*-butylimine and LDA.[13] Imine hydrolysis with acetic acid in aqueous THF gave aldehyde **12** in 77% overall yield from **11**.

Scheme 1[a]



[a] Key: (a) TBDMSCl, imidazole, DMAP cat., THF, rt, 1.5 h; 96%; (b) DIBALH, CH_2Cl_2, −78 °C, 1 h; 97%; (c) NCS, PPh_3, THF, rt, 2 h; 70%; (d) acetaldehyde *tert*-butylimine, LDA, THF, −78 to −45 °C, 1 h; (e) AcOH, THF/H_2O (4:1), 0 °C, 1 h; 77% from **11**.

Scheme 2[a]



[a] Key: (a) *n*-hexylmagnesium bromide, THF, 0 °C, 30 min; 90%; (b) $TiCl_4$, $AlMe_3$, CH_2Cl_2, −45 °C to rt, 18 h; 59%; (c) Ac_2O, $Yb(OTf)_3$, $MeNO_2$, rt, 12 h; 86%; (d) BBr_3, CH_2Cl_2, −78 °C to rt, 36 h; (e) allyl bromide, *n*-Bu_4NOH, CH_2Cl_2:H_2O (3:2), rt, 12 h; 81% from **16**.

Preparation of the aromatic fragment proceeds from Weinreb amide **13**.[4] Addition of excess hexylmagnesium bromide to **13** gave phenone **14** in 90% yield.[14] The *gem*-dimethyl group was introduced by exposing **14** to titanium tetrachloride and trimethylaluminum.[15] The yield for this process (59%) is somewhat lower than when dimethylzinc is used as the methyl source. The trimethylaluminum procedure was chosen for the sake of convenience. Ytterbium(III) triflate-catalyzed acylation of **15** with acetic anhydride gave phenone **16** in 86% yield.[16] High catalyst loads were necessary in order to obtain an

(5) For example, see Marino's synthesis of HHC: Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671−3672. Also see: Miyazaki, H.; Honda, K.; Asami, M.; Inoue, S. *J. Org. Chem.* **1999**, *64*, 9507−9511.

(6) The two mechanisms are related. Participation of the nonbonding electron pair of one of the phenolic oxygen atoms in the ionization of the benzylic alcohol would produce the protonated *o*-quinone methide.

(7) A reviewer has pointed out that the partially cyclized byproduct which is derived from **6** cannot be taken as evidence that the reaction which leads to **7** is nonconcerted. The partially cyclized byproduct may have been formed by a competing process.

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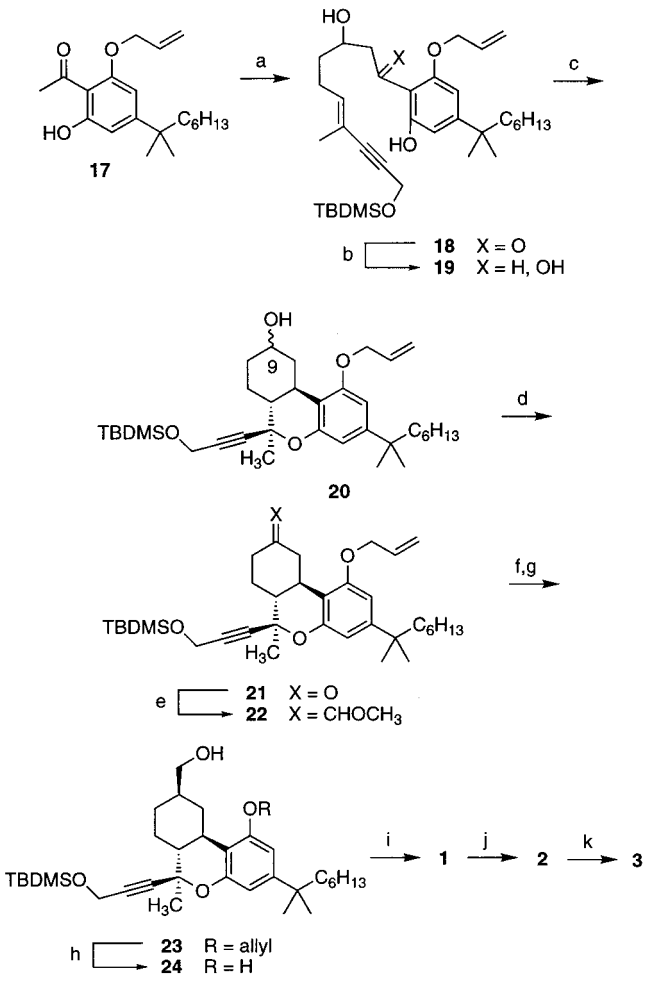
Scheme 3[a]



[a] Key: (a) (i) LDA, THF, −78 °C, 30 min,(ii) **12**, −78 °C, 30 min, (iii) AcOH; 68%; (b) $NaBH_4$, MeOH, rt, 5 min; 97%; (c) TFA, $CHCl_3$, 0.02 M, 0 °C, 3.5 h; 76%; (d) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, 2.5 h; 69%; (e) $Ph_3PCH_2OMe^+Cl^-$, Na *tert*-amylate, PhH, rt, 15 min; 88%; (f) wet Cl_3CCO_2H, CH_2Cl_2, rt, 45 min; (g) (i) K_2CO_3, MeOH, rt, 2 h, (ii) $NaBH_4$, rt, 15 min; 91% from **22**; (h) $NaBH_4$, 6 mol % $Pd(PPh_3)_4$, THF, rt, 23 h; 94%; (i) triethylamine trihydrofluoride, Et_3N, CH_2Cl_2, rt, 18 h; 96%; (j) 8 mol % Lindlar's catalyst, quinoline, 1 atm H_2, PhH, rt, 2 h; 91%; (k) PhSSPh, PhH, *hν*, rt, 22 h; 64%.

acceptable yield of **16**. Cleavage of the two phenolic methyl ether groups in **16** was accomplished by exposure to boron tribromide.[17] Allylation with allyl bromide and tetra-*n*-butylammonium hydroxide in dichloromethane/H_2O led to monoallyl ether **17** in 81% yield for the two steps from **16**.[1] It was essential for the success of the allylation that electrophile be added before the base. The reverse sequence led to complicated mixtures of products. This reactivity is typical and is a consequence of the sensitivity of the phenoxide intermediate to traces of oxygen.

The two large fragments were combined in an aldol reaction (Scheme 3) which produced **18**. It is critical that the aldol reaction be quenched at low temperature with acetic acid, otherwise the lithium alkoxide undergoes *retro*-aldol fragmentation during quench and workup. Reduction of the ketone carbonyl group of **18** with DIBALH led to recovery of **19** in low yield and with only modest (ca. 3:1) selectivity for the syn diol isomer.[18] The low stereoselectivity in this step is an indication of multiple, competing modes of bidentate complexation of **18** with the Lewis-acidic reagent. Reduction of **18** with sodium borohydride was not stereoselective, but produced **19** as a ca. 1:1 mixture of *syn* and *anti* diastereoisomers in 97% yield. Exposure of the diastereomeric mixture of alcohols **19** to trifluoroacetic acid in dry chloroform at 0 °C produced tricyclic alcohol **20** as a ca. 1:1 mixture of C9 diastereoisomers in 76% yield, following column chromatography. The diastereoisomers of **19** were separated by flash column chromatography, and were cyclized independently to give **20**, again as a ca. 1:1 mixture of C9 diastereoisomers in each case. Oxidation of the diastereoisomers of **20** with the Dess−Martin periodinane gave ketone **21**.[19] The relative stereochemistry of the three contiguous asymmetric carbon atoms in **21** was determined through a series of NOE experiments on **1** (vide infra).

The ease and the high yield for the cyclization of **19** is in sharp contrast with our experience with **6**. Although in the case of **6** it is conceivable that the difluoromethylene function exerted some deleterious influence on the cyclization, it appears to be more likely that the stabilization of the presumed carbocationic intermediate derived from **19** by the adjacent alkyne function was decisive in determining the success of the cyclization of **19**. Cyclization of **19** produces exclusively the desired stereochemistry at C10a, C6a and C6, but is stereorandom at C9. This suggests that under the conditions for the cyclization there is an insignificant difference in transition state energies, one with the hydroxyl group equatorial, the other axial. This is consistent with the experience of others in this area.[20]

Ketone **21** was exposed to (methoxymethyl)triphenylphosphorane to give enol ether **22** in 88% yield as a 2:1 mixture of geometrical isomers.[21] Selective hydrolysis of the enol ether function of **22**, followed by epimerization of the resulting aldehyde and reduction with sodium borohydride gave *β*-equatorial alcohol **23** in 91% overall yield from **22**. Palladium-catalyzed reductive cleavage of the phenolic allyl ether function[22] took place in 94% yield to produce phenol **24**. Silyl ether removal with triethylamine trihydrofluoride led to **1** in 96% yield.[23] Reductive cleavage of the allyl ether *after* removal of the silyl group resulted in sharply attenuated yields of **1** (ca. 40%), as a result of competing reduction of the alkyne function to produce **2**. The bulky silyl protecting group evidently suppressed reduction of the adjacent alkyne. Semihydrogenation of **1** in the presence of Lindlar's catalyst gave **2** in 91% yield; isomerization of an irradiated (tungsten filament lamp) solution of **2** in benzene in the presence of phenyl disulfide produced **3** in 64% yield.[24]

The stereochemistry of **1** was determined as follows (Figure 1). Irradiation of the C10a methine signal at 2.50 ppm resulted in strong NOE enhancements of the signals

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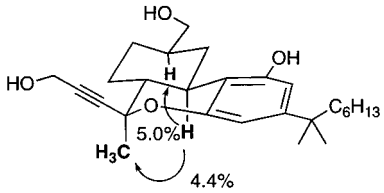

Figure 1. NOE enhancements which were used to assign the stereochemistry of compound **1**.

Table 1. K_i Values (nM) for Compounds 1-3 Competing with [^{3}H]CP-55,940 for CB1 (Brain) and CB2 (Spleen) Receptors[a]

compd	CB_1	CB_2
1	1.21 (1.13−1.31)	0.30 (0.20−0.42)
2	2.24 (1.90−2.59)	0.33 (0.26−0.41)
3	0.66 (0.53−0.81)	8.60 (6.87−10.80)

[a] The reported values are averages of at least three experiments; numbers in parentheses represent extreme values.

for the C6 methyl at 1.37 ppm, and for the C9 methine at 3.29 ppm. Since the ring junction stereochemistry must be trans, because of the large (J = 11.1 Hz) coupling constant between the protons at C10a and C6a, the stereochemistry of **1** is as shown.

The affinities of the racemates of **1**−**3** for the CB1 and CB2 cannabinoid receptors were obtained using procedures described elsewhere[1] and are summarized in Table 1.

All three compounds exhibit significantly high affinities for the CB1 and CB2 receptors with K_i values ranging from subnanomolar to single digit nanomolar. Thus, these classical/nonclassical hybrid analogues which encompass conformationally restricted southern aliphatic chains can be considered as a novel class of highly potent synthetic cannabinoids. Additionally, the three analogues exhibit a certain degree of selectivity for the CB1 or CB2 receptors. In this regard **3** is the most interesting, with a 13-fold selectivity for CB1 over CB2, a feature which places it among the most CB1-selective cannabinoids known to date.

Conclusion

A concise, high-yielding procedure for assembly of hybrid cannabinoids has been described. The synthesis provides racemic materials, however, semipreparative separation of the enantiomers of **1**, **2** and **3** can be readily accomplished on a Daicel Chiralcel-OD HPLC column. Consequently, this method offers much more rapid and convenient access to materials than our earlier route.[1] The synthesis of other analogues of this series will be carried out in the future according to the protocols described herein. Noteworthy features of the synthesis include the application of Trost's metallo-ene reaction for the stereospecific synthesis of aldehyde **12**, and the efficient cyclization of **19**, which preserves the stereochemical information present in the trisubstituted olefin. This methodology is potentially applicable to the stereospecific synthesis of other dihydrobenzopyrans.

Experimental Section

HPLC was performed using a 5 μm Phenomenex silica column (150 × 4.60 mm). Purity and homogeneity of all materials was determined chromatographically and from ^{1}H NMR and ^{13}C NMR, combustion analysis or HPLC. Tetahydrofuran and ether were purchased in anhydrous grade and stored over activated 4 Å molecular sieves. Diisopropylamine and pyridine were distilled from calcium hydride and stored over potassium hydroxide. Nitromethane and chloroform were distilled from calcium hydride and stored over activated 4 Å molecular sieves. Methylene chloride, acetic anhydride, and benzene were distilled from calcium hydride immediately before use. Methanol was distilled from $Mg(OMe)_2$ and stored over activated 4 Å molecular sieves. *N*-Chlorosuccinimide was recrystallized from benzene. Other reagents were used as received. All moisture-sensitive reactions were performed under a static nitrogen or argon atmosphere in oven-dried or flame-dried glassware. Combustion analyses were performed by Desert Analytics, Inc. Homogeneity and purity of all compounds was determined by HPLC.

Ethyl (2*E*)-6-Hydroxy-3-methylhex-2-en-4-ynoate 8. To a solution of palladium(II) acetate (153 mg, 0.68 mmol) and tris(2,6-dimethoxyphenyl)phosphine (298 mg, 0.67 mmol) in 21 mL of benzene at room temperature was added ethyl 2-butynoate (4.0 mL, 3.8 g, 34 mmol). After 15 min, a solution of propargyl alcohol (1.493 g, 26.63 mmol) in 4 mL of benzene was added. The reaction mixture was stirred at room temperature for 12 h and concentrated. Purification by flash column chromatography on silica gel (20% to 30% EtOAc in hexanes) gave ester **8** (3.353 g, 75% yield) as a colorless oil: R_f = 0.20 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (q, J = 1.5 Hz, 1H), 4.43 (d, J = 6.1 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 2.28 (d, J = 1.5 Hz, 3H), 1.72 (t, J = 6.2 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 137.1, 124.3, 91.9, 86.9, 60.1, 51.0, 19.6, 14.1; IR (neat) 3440, 3000, 1720, 1625 cm^{-1}; mass spectrum m/z 168 (M^+, 15), 150 (43), 139 (27), 123 (100), 122 (70); exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0837.

Ethyl (2*E*)-6-*tert*-Butyldimethylsilyloxy-3-methylhex-2-en-4-ynoate 9. To a solution of alcohol **8** (3.205 g, 19.06 mmol), imidazole (2.198 g, 32.29 mmol), and DMAP (spatula tip) in 50 mL of THF at room temperature was added a solution of *tert*-butyldimethylsilyl chloride (4.276 g, 28.37 mmol) in 6 mL of THF. The reaction mixture was stirred at room temperature for 1.5 h and then diluted with petroleum ether and water. The aqueous phase was extracted with petroleum ether (2×), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (1.25% to 2.5% EtOAc in hexanes) gave **9** (5.159 g, 96% yield) as a colorless oil: R_f = 0.26 (1.25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (q, J = 1.5 Hz, 1H), 4.46 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.28 (d, J = 1.5 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 137.3, 124.1, 92.4, 86.6, 60.0, 52.1, 25.8, 19.7, 18.3, 14.3, −5.0; IR (neat) 2965, 2940, 2870, 1720, 1620 cm^{-1}; mass spectrum m/z 225 (48), 197 (24), 195 (100), 75 (99); exact mass calcd for $C_{15}H_{26}O_3$-Si 282.1651, found 282.1669.

(2*E*)-6-*tert*-Butyldimethylsilyloxy-3-methylhex-2-en-4-yn-1-ol 10. To a solution of ester **9** (5.14 g, 18.2 mmol) in 100 mL of CH_2Cl_2 at −78 °C was added 7.10 mL of DIBALH (5.67 g, 39.8 mmol). After 1 h, the reaction mixture was quenched with an aqueous potassium sodium tartrate solution, warmed to room temperature, stirred for 2 h, and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (10% to 20% to 30% EtOAc in hexanes) gave alcohol **10** (4.223 g, 97% yield) as a colorless oil: R_f = 0.24 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (tq, J = 6.8, 1.5 Hz, 1H), 4.41 (s, 2H), 4.20 (d, J = 6.8 Hz, 2H), 1.80 (m, 3H), 1.76 (s br, 1H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 120.3, 86.9, 86.0, 59.0, 52.1, 25.9, 18.3, 17.4, −5.0; IR (neat) 3460, 2940, 2870, 1370 cm^{-1}; mass spectrum m/z 183 (48), 153 (100), 135 (49), 99 (62), 75 (100); exact mass calcd for $C_{13}H_{24}O_2Si$ 240.1546, found 240.1558.

(4*E*)-6-Chloro-1-*tert*-butyldimethylsilyloxy-4-methylhex-4-en-2-yne 11. To a solution of *N*-chlorosuccinimide (189 mg, 1.42 mmol) in 9 mL of THF at room temperature was added a solution of triphenylphosphine (372 mg, 1.42 mmol) in 5 mL of THF followed by a solution of alcohol **10** (310 mg, 1.29 mmol) in 5 mL of THF at room temperature. After 2 h, the reaction

mixture was diluted with ether/pentane (1:1) and water. The aqueous phase was extracted with ether/pentane (1:1) (3×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (1% EtOAc in hexanes) gave chloride **11** (235 mg, 70% yield) as a colorless oil: R_f = 0.49 (2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (tq, J = 8.1, 1.5 Hz, 1H), 4.43 (s, 2H), 4.10 (d, J = 8.1 Hz, 2H), 1.87 (m, 3H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.2, 123.4, 88.0, 86.3, 52.1, 39.5, 25.9, 18.3, 17.1, −5.0; IR (neat) 2945, 2870, 1465 cm^{-1}; mass spectrum m/z 171 (29), 137 (17), 135 (29), 95 (36), 91 (28); exact mass calcd for $C_{13}H_{23}{}^{35}ClOSi$ 258.1207, found 258.1266.

(2*E*)-8-*tert*-Butyldimethylsilyloxy-5-methyloct-4-en-6-ynal 12. To a solution of diisopropylamine (1.50 mL, 1.08 g, 10.7 mmol) in 30 mL of THF at −78 °C was added *n*-BuLi (4.50 mL, 2.37 M in hexanes, 10.7 mmol). After 20 min, a solution of acetaldehyde *tert*-butylimine (1.45 mL, 1.06 g, 10.6 mmol) in 5 mL of THF was added via cannula. The reaction mixture was warmed from −78 to −15 °C over 1 h and cooled to −78 °C, and a solution of chloride **11** (1.904 g, 7.36 mmol) in 15 mL of THF was added via cannula. The reaction mixture was warmed from −78 to −45 °C over 1 h, quenched with saturated $NaHCO_3$, warmed to room temperature, and diluted with water and petroleum ether. The aqueous phase was extracted with petroleum ether (3×) and the combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated to give the crude imine. The crude imine was dissolved in 20 mL of THF and 5 mL of water and cooled to 0 °C, and acetic acid (490 μL, 504 mg, 8.39 mmol) was added. After 1 h, the reaction mixture was diluted with water and petroleum ether. The aqueous phase was extracted with petroleum ether (3×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (1.25% to 2.5% to 5% EtOAc in hexanes) gave aldehyde **12** (1.504 g, 77% yield) as a colorless oil: R_f = 0.24 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 1.2 Hz, 1H), 5.76 (tq, J = 7.3, 1.5 Hz, 1H), 4.40 (s, 2H), 2.53 (tt, J = 7.2, 1.5 Hz, 2H), 2.39 (q, J = 7.2 Hz, 2H), 1.79 (s br, 3H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 135.0, 119.1, 87.2, 85.0, 52.2, 43.1, 25.9, 21.1, 18.4, 17.1, −5.0; IR (neat) 2945, 2870, 2725, 1735, 1470 cm^{-1}; mass spectrum m/z 165 (83), 115 (59), 105 (87), 101 (55), 91 (92), 77 (58), 75 (100); exact mass calcd for $C_{15}H_{26}O_2Si$ 266.1702, found 266.1707.

(3,5-Dimethoxyphenyl)-*N*-methoxy-*N*-methylcarboxamide 13. To a suspension of 3,5-dimethoxybenzoic acid (10.0 g, 54.9 mmol) in 31 mL of CH_2Cl_2 at room temperature was added DMF (several drops) followed by oxalyl chloride (16.0 mL, 23.3 g, 183 mmol). The reaction mixture was heated to reflux for 1 h, and the excess oxalyl chloride and solvent were removed by distillation at atmospheric pressure. The crude acid chloride was dissolved in 10 mL of CH_2Cl_2 and added via cannula to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (6.49 g, 66.5 mmol) and pyridine (10.0 mL, 9.78 g, 124 mmol) in 20 mL of CH_2Cl_2 at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h, and quenched with saturated KH_2PO_4. The organic phase was washed with water (2×) and brine (2×) and dried ($MgSO_4$). Concentration and purification by distillation under reduced pressure (1 mmHg) gave amide **13** (11.86 g, 96% yield) as a pale yellow oil: bp 148−150 °C (1 mmHg); R_f = 0.31 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 2.2 Hz, 2H), 6.46 (t, J = 2.2 Hz, 1H), 3.72 (s, 6H), 3.51 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 160.2, 135.8, 105.7, 102.5, 60.8, 55.2, 33.7; IR (neat) 2950, 1650, 1600, 1460 cm^{-1}; mass spectrum m/z 225 (M^+, 4), 195 (24), 166 (17), 165 (100); exact mass calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.1004.

1-(3,5-Dimethoxyphenyl)heptan-1-one 14. To magnesium metal (796 mg, 32.7 mmol) in 20 mL of THF at room temperature was added 1-bromohexane (3.50 mL, 4.12 g, 24.9 mmol) over 30 min. The solution of Grignard reagent was stirred for 1 h and added via cannula to a solution of amide **13** (2.295 g, 10.23 mmol) in 10 mL of THF at 0 °C. After 30 min, the reaction mixture was quenched with 1 M HCl and diluted with petroleum ether and water. The aqueous phase was extracted with petroleum ether (3×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (2.5% to 5% EtOAc in hexanes) gave phenone **14** (2.293 g, 90% yield) as a white solid: mp 27−28 °C; R_f = 0.28 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 2.5 Hz, 2H), 6.64 (t, J = 2.2 Hz, 1H), 3.83 (s, 6H), 2.91 (t, J = 7.4 Hz, 2H), 1.71 (quint, J = 7.3 Hz, 2H), 1.43−1.23 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 160.8, 139.0, 105.9, 105.0, 55.6, 38.8, 31.7, 29.1, 24.5, 22.6, 14.1; IR (neat) 2940, 1685, 1600, 1455, 1430 cm^{-1}; mass spectrum m/z 250 (M^+, 29), 180 (57), 166 (29), 165 (100); exact mass calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1551. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.0; H, 8.9. Found: C, 72.20; H, 9.04.

5-(1,1-Dimethylheptyl)-1,3-dimethoxybenzene 15. To a solution of $TiCl_4$ (4.89 mL, 8.46 g, 44.6 mmol) in 167 mL of CH_2Cl_2 at −30 °C was added trimethylaluminum (22.3 mL, 4 M solution in CH_2Cl_2, 89.2 mmol). The reaction mixture was stirred for 20 min, cooled to −45 °C, and a solution of ketone **14** (11.164 g, 44.6 mmol) in 56 mL of CH_2Cl_2 at −45 °C was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 18 h, quenched with water, and diluted with ether and 1 M HCl. The aqueous layer was extracted with ether (3×) and the combined organic layers were washed with 1 M HCl (1×) and brine (2×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (hexanes to 2.5% EtOAc in hexanes) gave **15** (6.991 g, 59% yield) as a colorless oil: R_f = 0.58 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J = 2.2 Hz, 2H), 6.31 (t, J = 2.2 Hz, 1H), 3.80 (s, 6H), 1.56 (m, 2H), 1.33−1.02 (m, 8H), 1.27 (s, 6H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 152.5, 104.6, 96.5, 55.2, 44.5, 38.0, 31.8, 30.1, 29.0, 24.7, 22.7, 14.1; IR (neat) 2940, 1600, 1460, 1425 cm^{-1}; mass spectrum m/z 264 (M^+, 15), 181 (12), 180 (100), 179 (52), 165 (23); exact mass calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2098. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.2; H, 10.7. Found: C, 77.49; H, 10.73.

1-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]ethan-1-one 16. To a suspension of ytterbium(III) trifluoromethanesulfonate (5.684 g, 9.16 mmol) in 5 mL of nitromethane at room temperature was added a solution of **15** (5.444 g, 20.59 mmol) in 35 mL of nitromethane. Acetic anhydride (4.0 mL, 4.3 g, 42 mmol) was added, and the reaction mixture was stirred at room temperature for 10 h, at which time additional ytterbium(III) trifluoromethanesulfonate (ca. 50 mg) and acetic anhydride (500 μL, 541 mg, 5.30 mmol) were added. After 2 h, the reaction mixture was diluted with ether, water, and saturated $NaHCO_3$. The aqueous phase was extracted with ether (4×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (1.25% to 2.5% to 5% EtOAc in hexanes) gave **16** (5.451 g, 86% yield) as a colorless oil: R_f = 0.18 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 2H), 3.79 (s, 6H), 2.46 (s, 3H), 1.56 (m, 2H), 1.32−1.02 (m, 8H), 1.27 (s, 6H), 0.83 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 156.4, 153.4, 117.9, 101.9, 55.7, 44.4, 38.4, 32.3, 31.7, 29.9, 28.9, 24.6, 22.6, 14.0; IR (neat) 2940, 1710, 1610, 1575, 1470, 1455, 1410 cm^{-1}; mass spectrum m/z 306 (M^+, 16), 291 (88), 222 (100), 221 (68), 207 (31), 206 (24), 179 (39); exact mass calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2212.

1-[4-(1,1-Dimethylheptyl)-2-hydroxy-6-prop-2-enyloxyphenyl]ethan-1-one 17. To a solution of phenone **16** (8.29 g, 27.1 mmol) in 51 mL of CH_2Cl_2 at −78 °C was added a solution of BBr_3 (132 mL, 1 M in CH_2Cl_2, 132 mmol) at −78 °C via cannula. The reaction mixture was warmed to room temperature, stirred for 36 h, quenched with saturated $NaHCO_3$, and diluted with ether. The aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$), and concentrated to give the crude resorcinol. The crude resorcinol was dissolved in 140 mL of CH_2Cl_2 and allyl bromide (2.34 mL, 3.27 g, 27.0 mmol), 90 mL of water, and tetrabutylammonium hydroxide (17.7 mL, 40 wt. % solution in water, 27.0 mmol) were added. The reaction mixture was stirred vigorously at room temperature for 12 h and diluted with ether and water.

The aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (hexanes to 1.5% EtOAc in hexanes) gave **17** (6.98 g, 81% yield) as a pale yellow oil: R_f = 0.24 (2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.29 (s, 1H), 6.54 (d, J = 1.5 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 6.09 (ddt, J = 17.1, 10.7, 5.6 Hz, 1H), 5.43 (dd, J = 17.3, 1.2 Hz, 1H), 5.33 (dd, J = 10.3, 1.0 Hz, 1H), 4.63 (d, J = 5.6 Hz, 2H), 2.67 (s, 3H), 1.55 (m, 2H), 1.29−0.97 (m, 8H), 1.24 (s, 6H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 164.3, 159.9, 159.3, 132.6, 118.5, 109.2, 108.5, 100.4, 69.6, 44.0, 38.6, 33.6, 31.7, 29.9, 28.5, 24.6, 22.6, 14.1; IR (neat) 2925, 2855, 1630, 1560, 1410 cm^{-1}; mass spectrum m/z 318 (M^+, 9), 205 (100), 180 (80), 179 (41), 165 (50); exact mass calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2211. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.54; H, 9.63.

(6*E*)-1-[4-(1,1-Dimethylheptyl)-2-hydroxy-6-prop-2-enyloxyphenyl]-3-hydroxy-10-*tert*-butyldimethylsilyloxy-7-methyldec-6-en-8-yn-1-one 18. To a solution of diisopropylamine (1.80 mL, 1.30 g, 12.8 mmol) in 24 mL of THF at −78 °C was added *n*-BuLi (5.45 mL, 2.37 M in hexanes, 12.9 mmol). After 20 min, a solution of ketone **17** (1.974 g, 6.20 mmol) in 8 mL of THF at −78 °C was added via cannula. After 30 min, a solution of aldehyde **12** (1.533 g, 5.75 mmol) in 8 mL of THF at −78 °C was added via cannula. After 30 min, the reaction mixture was quenched with acetic acid (1.40 mL, 1.47 g, 24.5 mmol), warmed to room temperature, and diluted with ether and water. The aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (2.5% to 5% to 10% EtOAc in hexanes) gave ketone **18** (2.278 g, 68% yield) as a pale yellow oil: R_f = 0.27 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.05 (s, 1H), 6.54 (d, J = 1.7 Hz, 1H), 6.32 (d, J = 1.5 Hz, 1H), 6.07 (ddt, J = 17.3, 10.5, 5.6 Hz, 1H), 5.84 (tm, J = 7.5 Hz, 7.5 Hz, 1H), 5.43 (dd, J = 17.1, 1.5 Hz, 1H), 5.35 (dd, J = 10.5, 1.0 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 4.41 (s, 2H), 4.16 (m, 1H), 3.29 (dd, J = 18.2, 2.4 Hz, 1H), 3.13 (s, 1H), 3.12 (dd, J = 18.3, 9.3 Hz, 1H), 2.30−2.16 (m, 2H), 1.79 (s br, 3H), 1.69−1.49 (m, 4H), 1.37−0.98 (m, 8H), 1.23 (s, 6H), 0.90 (s, 9H), 0.83 (t, J = 6.7 Hz, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.5, 165.6, 160.4, 159.6, 137.9, 132.8, 118.44, 118.41, 109.9, 109.5, 100.5, 88.4, 85.1, 69.6, 67.0, 52.5, 52.4, 44.3, 38.7, 36.3, 32.2, 30.5, 28.63, 28.60, 26.1, 25.1, 25.0, 23.2, 18.5, 17.3, 14.4, −4.8; IR (neat) 3560, 2915, 2860, 2220, 1630, 1600, 1410, 1370 cm^{-1}; mass spectrum m/z 165 (25), 105 (24), 101 (17); exact mass calcd for $C_{31}H_{47}O_5Si$ (M^+ − *t*-Bu) 527.3193, found 527.3203.

(6*E*)-1-[4-(1,1-Dimethylheptyl)-2-hydroxy-6-prop-2-enyloxyphenyl]-10-*tert*-butyldimethylsilyloxy-7-methyldec-6-en-8-yne-1,3-diol 19. To a solution of ketone **18** (2.128 g, 3.64 mmol) in 50 mL of MeOH at room temperature was added $NaBH_4$ (207 mg, 5.47 mmol) in one portion. After 5 min, the reaction mixture was quenched with acetic acid (1.5 mL) and diluted with ether and water. The aqueous phase was extracted with ether (4×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (5% to 10% to 20% to 30% EtOAc in hexanes) gave diol **19** (2.064 g, 97% yield) as a colorless oil as a 1:1 mixture of diastereomers: R_f = 0.20 and 0.16 (20% EtOAc in hexanes); IR (neat) 3320, 2925, 2855, 1620, 1580, 1415 cm^{-1}; mass spectrum m/z 151 (30), 192 (53), 191 (37), 177 (18), 165 (26); exact mass calcd for $C_{35}H_{56}O_4Si$ ($M^+ - H_2O$) 568.3948, found 568.3929. ***syn*-19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 6.49 (d, J = 1.7 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 6.02 (ddt, J = 17.3, 10.5, 5.1 Hz, 1H), 5.79 (t br, J = 7.1 Hz, 1H), 5.57 (ddd, J = 9.3, 3.7, 1.5 Hz, 1H), 5.37 (dm, J = 17.1 Hz, 1H), 5.27 (dm, J = 10.5 Hz, 1H), 4.53−4.46 (m, 3H), 4.42 (s, 2H), 3.94 (m, 1H), 2.40 (d, J = 3.7 Hz, 1H), 2.17 (q br, J = 7.6 Hz, 2H), 2.05−1.85 (m, 2H), 1.77 (s br, 3H), 1.60−1.49 (m, 2H), 1.26−0.99 (m, 10H), 1.22 (s, 6H), 0.91 (s, 9H), 0.84 (t, J = 6.8 Hz, 3H), 0.13 (s, 6H). ***anti*-19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 6.48 (d, J = 1.5 Hz, 1H), 6.33 (d, J = 1.5 Hz, 1H), 6.01 (ddt, J = 17.3, 10.7, 5.1 Hz, 1H), 5.83 (t br, J = 7.3 Hz, 1H), 5.72 (dt, J = 10.3, 2.1 Hz, 1H), 5.38 (dm, J = 17.1 Hz, 1H), 5.26 (dm, J = 10.5 Hz, 1H), 4.51−4.49 (m, 2H), 4.42 (s, 2H), 4.02 (m, 1H), 3.97 (d, J = 2.2 Hz, 1H), 2.25−2.16 (m, 3H), 1.96 (d, J = 4.9 Hz, 1H), 1.84−1.49 (m, 5H), 1.78 (s br, 3H), 1.26−1.00 (m, 8H), 1.22 (s, 6H), 0.92 (s, 9H), 0.84 (t, J = 6.8 Hz, 3H), 0.13 (s, 6H).

Tricyclic C9 Alcohol 20. To a solution of diol **19** (2.00 g, 3.41 mmol) in 175 mL of $CHCl_3$ at 0 °C was added TFA (290 μL, 429 mg, 3.76 mmol). After 3.5 h, the reaction mixture was quenched with saturated $NaHCO_3$ and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (2×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (5% to 10% to 20% EtOAc in hexanes) gave alcohol **20** (1.480 g, 76% yield) as a colorless oil as a 1:1 mixture of diastereomers: R_f = 0.29 and 0.21 (20% EtOAc in hexanes); IR (neat) 3360, 2925, 2855, 2340, 1610, 1565, 1410 cm^{-1}; mass spectrum m/z 568 (M^+, 6), 131 (8), 119 (10), 76 (9), 75 (100); exact mass calcd for $C_{35}H_{56}O_4Si$ 568.3948, found 568.3937. Anal. Calcd for $C_{35}H_{56}O_4Si$: C, 73.9; H, 9.9. Found: C, 73.92; H, 9.82. **20**, C9-β-hydroxyl: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, J = 1.5 Hz, 1H), 6.37 (d, J = 1.7 Hz, 1H), 6.07 (ddt, J = 17.1, 10.5, 5.1 Hz, 1H), 5.40 (dm, J = 17.3, 1H), 5.27 (dm, J = 10.5 Hz, 1H), 4.55−4.48 (m, 2H), 4.41 (s, 2H), 3.84 (m, 1H), 3.42 (d br, J = 12.0 Hz, 1H), 2.51 (td, J = 11.2, 2.7 Hz, 1H), 2.26−2.12 (m, 2H), 1.84 (td, J = 11.5, 2.0 Hz, 1H), 1.78 (d, J = 2.9 Hz, 1H), 1.63−0.76 (m, 13H), 1.34 (s br, 3H), 1.21 (s, 6H), 0.92 (s, 9H), 0.84 (t, J = 7.1 Hz, 3H), 0.13 (s, 6H). **20**, C9-α-hydroxyl: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, J = 1.7 Hz, 1H), 6.37 (d, J = 1.7 Hz, 1H), 6.07 (ddt, J = 17.3, 10.5, 5.1 Hz, 1H), 5.44 (dm, J = 17.1 Hz, 1H), 5.27 (dm, J = 10.7 Hz, 1H), 4.53−4.51 (m, 2H), 4.42 (s, 2H), 4.23 (s br, 1H), 3.25 (dm, J = 13.7 Hz, 1H), 2.98 (td, J = 11.2, 2.7 Hz, 1H), 1.99 (t br, J = 13.2 Hz, 2H), 1.84 (t br, J = 10.7 Hz, 1H), 1.66−0.79 (m, 14H), 1.39 (s br, 3H), 1.21 (s, 6H), 0.91 (s, 9H), 0.84 (t, J = 7.2 Hz, 3H), 0.13 (s, 6H).

Tricyclic C9 Ketone 21. To a solution of alcohol **20** (1.40 g, 2.46 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added Dess−Martin periodinane (1.375 g, 3.76 mmol). After 30 min, additional periodinane (155 mg, 0.37 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C, warmed to room temperature, and stirred for 30 min, and additional periodinane (180 mg, 0.42 mmol) was added. After 1 h, the reaction mixture was quenched with saturated $NaHCO_3$, and sodium thiosulfate pentahydrate (1.965 g, 7.92 mmol) was added. The two-phase mixture was stirred for 15 min and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (2.5% to 5% EtOAc in hexanes) gave ketone **21** (956 mg, 69% yield) as a colorless oil: R_f = 0.31 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (d, J = 1.7 Hz, 1H), 6.38 (d, J = 1.7 Hz, 1H), 6.05 (ddt, J = 17.3, 10.5, 5.1 Hz, 1H), 5.39 (dm, J = 17.3 Hz, 1H), 5.28 (dm, J = 10.5 Hz, 1H), 4.53 (dm, J = 5.4 Hz, 2H), 4.42 (s, 2H), 3.82 (ddd, J = 15.1, 3.7, 2.0 Hz, 1H), 2.87 (td, J = 12.0, 3.7 Hz, 1H), 2.66−2.38 (m, 3H), 2.28 (td, J = 11.7, 2.2 Hz, 1H), 2.11 (dd, J = 14.9, 12.9 Hz, 1H), 1.68−1.48 (m, 3H), 1.39 (s, 3H), 1.24−0.98 (m, 8H), 1.21 (s, 6H), 0.92 (s, 9H), 0.84 (t, J = 6.8 Hz, 3H), 0.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 156.9, 152.5, 150.7, 133.2, 117.5, 108.9, 108.6, 102.5, 85.6, 84.0, 74.2, 68.9, 51.7, 46.5, 45.7, 44.4, 40.8, 37.8, 33.8, 31.8, 30.0, 28.79, 28.76, 27.5, 25.8, 24.6, 22.7, 19.3, 18.3, 14.1, −5.0; IR (neat) 2930, 2860, 2340, 1710, 1610, 1565, 1415 cm^{-1}; mass spectrum m/z 566 (M^+, 9), 91 (8), 85 (8), 76 (9), 75 (100); exact mass calcd for $C_{35}H_{54}O_4Si$ 566.3791, found 566.3796. Anal. Calcd for $C_{35}H_{54}O_4Si$: C, 74.2; H, 9.6. Found: C, 74.13; H, 9.75.

Tricyclic Methyl Enol Ether 22. To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.073 g, 3.13 mmol) in 15 mL of benzene at room temperature was added sodium *tert*-amylate (6.20 mL, 0.55 M in benzene, 3.4 mmol). After 10 min, a solution of ketone **21** (356 mg, 0.63 mmol) in 15 mL of benzene was added via cannula at room temperature. After 15 min, the reaction mixture was diluted with water and the aqueous phase was extracted with ether (3×). The combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on

silica gel (1.25% EtOAc in hexanes) gave enol ether **22** (327 mg, 88% yield) as a colorless oil as a 2:1 mixture of isomers: $R_f = 0.33$ (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 2H), 6.38 (s br, 2H), 6.22−6.03 (m, 2H), 5.86 (s br, 2H), 5.55−5.44 (m, 2H), 5.32−5.26 (m, 2H), 4.54−4.52 (m, 4H), 4.42 (s, 4H), 4.28 (dd, J = 13.4, 2.4 Hz, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.48 (dd, J = 13.2, 2.9 Hz, 1H), 2.94 (d br, J = 13.9 Hz, 1H), 2.43 (td, J = 11.2, 2.9 Hz, 2H), 2.28−2.17 (m, 3H), 2.08 (td, J = 13.9, 5.1 Hz, 1H), 1.96 (tm, J = 11.2 Hz, 2H), 1.82 (td, J = 13.7, 4.6 Hz, 2H), 1.67 (t, J = 12.5 Hz, 2H), 1.53−1.48 (m, 4H), 1.42−0.97 (m, 17H), 1.34 (s, 6H), 1.21 (s, 12H), 0.92 (s, 18H), 0.84 (t, J = 6.7 Hz, 6H), 0.14 (s, 12H); IR (neat) 2920, 2850, 1680, 1610, 1565, 1410, 1365 cm^{-1}; mass spectrum m/z 594 (M^+, 7), 509 (9), 115 (9), 85 (12), 76 (11), 75 (100); exact mass calcd for $C_{37}H_{58}O_4Si$ 594.4104, found 594.4117.

Alcohol 23. To a solution of enol ether **22** (317 mg, 0.53 mmol) in 50 mL of CH_2Cl_2 at room temperature was added wet trichloroacetic acid (600 μL, 917 mg, 5.61 mmol). The reaction mixture was stirred at room temperature for 45 min, quenched with saturated $NaHCO_3$, and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated to give the crude aldehyde. The crude aldehyde was dissolved in 40 mL of MeOH and added via cannula to powdered K_2CO_3 (284 mg, 2.05 mmol). After 2 h at room temperature, $NaBH_4$ (48 mg, 1.3 mmol) was added in one portion. After 15 min, the reaction mixture was quenched with 2 M AcOH in water, partially concentrated, and diluted with ether and water. The aqueous phase was extracted with ether (3×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (5% to 10% to 20% EtOAc in hexanes) gave alcohol **23** (282 mg, 91% yield) as a colorless oil: $R_f = 0.30$ (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, J = 1.7 Hz, 1H), 6.37 (d, J = 1.7 Hz, 1H), 6.06 (ddt, J = 17.1, 10.8, 4.9 Hz, 1H), 5.41 (dm, J = 17.3 Hz, 1H), 5.26 (dm, J = 10.7 Hz, 1H), 4.51 (dm, J = 5.1 Hz, 2H), 4.41 (s, 2H), 3.55−3.43 (m, 2H), 3.23 (d br, J = 12.2 Hz, 1H), 2.51 (td, J = 11.0, 2.4 Hz, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.85−1.66 (m, 3H), 1.52−1.47 (m, 2H), 1.43−0.73 (m, 11H), 1.36 (s, 3H), 1.21 (s, 6H), 0.91 (s, 9H), 0.84 (t, J = 6.7 Hz, 3H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 152.7, 149.8, 133.6, 116.8, 110.5, 108.7, 102.5, 86.2, 83.5, 74.6, 68.8, 68.5, 51.8, 48.4, 44.5, 40.8, 37.7, 34.6, 33.3, 31.8, 30.0, 29.6, 28.8, 28.4, 25.8, 24.6, 22.7, 19.5, 18.3, 14.1, −5.0; IR (neat) 3450 (br), 2920, 2855, 1610, 1565, 1410, 1250 cm^{-1}; mass spectrum m/z 582 (M^+, 6), 131 (6), 119 (6), 77 (11), 76 (7), 75 (100); exact mass calcd for $C_{36}H_{58}O_4Si$ 582.4104, found 582.4066.

Diol 24. To a solution of alcohol **23** (194 mg, 0.33 mmol) in 13 mL of THF at room temperature was added tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and $NaBH_4$ (127 mg, 3.36 mmol). The reaction mixture was stirred at room temperature for 23 h, quenched with 2 M AcOH in water, and diluted with ether and water. The aqueous phase was extracted with ether (4×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (10% to 20% to 30% EtOAc in hexanes) gave phenol **24** (169 mg, 94% yield) as a white foam: mp 62−63 °C; R_f = 0.19 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s br, 1H), 6.43 (d, J = 1.5 Hz, 1H), 6.24 (d, J = 1.7 Hz, 1H), 4.40 (s, 2H), 3.61 (dd, J = 10.7, 5.4 Hz, 1H), 3.45 (dd, J = 10.5, 7.8 Hz, 1H), 3.38 (d br, J = 12.9 Hz, 1H), 2.71 (s br, 1H), 2.48 (td, J = 11.1, 2.2 Hz, 1H), 2.22 (dm, J = 10.5 Hz, 1H), 1.94−1.75 (m, 3H), 1.49−1.43 (m, 2H), 1.33 (s, 3H), 1.26−0.76 (m, 17H), 0.91 (s, 9H), 0.84 (t, J = 6.7 Hz, 3H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.1, 150.1, 108.9, 108.0, 106.0, 86.1, 83.5, 74.6, 68.3, 51.8, 48.2, 44.5, 40.6, 37.3, 34.3, 33.0, 31.8, 30.1, 29.4, 28.73, 28.66, 28.3, 25.8, 24.6, 22.7, 19.6, 18.3, 14.1, −5.0; IR (neat) 3350 (br), 2920, 2865, 1625, 1575, 1420 cm^{-1}; mass spectrum m/z 542 (M^+, 6), 323 (7), 143 (8), 85 (10), 75 (56); exact mass calcd for $C_{33}H_{54}O_4Si$ 542.3791, found 542.3787.

Alkyne 1. To a solution of phenol **24** (159 mg, 0.29 mmol) in 15 mL of CH_2Cl_2 at room temperature was added triethylamine trihydrofluoride (500 μL, 495 mg, 3.07 mmol) and triethylamine (50 μL, 36 mmol, 0.36 mmol). The reaction mixture was stirred at room temperature for 18 h and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (4×) and the combined organic extracts were washed with brine (1×) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (3% to 4% to 5% EtOH in CH_2Cl_2) gave alcohol **1** (120 mg, 96% yield) as a white foam: mp 87−88 °C; $R_f = 0.18$ (5% EtOH in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, J = 1.7 Hz, 1H), 6.24 (d, J = 1.7 Hz, 1H), 5.68 (s br, 1H), 4.37 (d, J = 4.6 Hz, 2H), 3.59−3.45 (m, 2H), 3.29 (d br, J = 12.5 Hz, 1H), 2.50 (td, J = 11.1, 2.7 Hz, 1H), 2.20 (m, 1H), 1.97−1.69 (m, 5H), 1.50−1.44 (m, 2H), 1.37 (s, 3H), 1.27−0.76 (m, 17H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.0, 150.3, 108.8, 108.1, 106.1, 87.3, 83.1, 74.7, 68.4, 51.2, 48.2, 44.5, 40.6, 37.4, 34.3, 33.0, 31.8, 30.1, 29.5, 28.7, 28.3, 24.6, 22.7, 19.7, 14.1; IR (neat) 3340 (br), 2935, 2860, 1625, 1575, 1420, 1330 cm^{-1}; mass spectrum m/z 428 (M^+, 67), 344 (43), 249 (33), 105 (30), 91 (50), 85 (32), 83 (33), 79 (40); exact mass calcd for $C_{27}H_{40}O_4$ 428.2927, found 428.2939.

(*Z*)-Alkene 2. To a solution of quinoline (31 mg, 0.24 mmol) in 5 mL of benzene at room temperature was added Lindlar catalyst (27 mg, 2.5% on $CaCO_3$, 6.3 μmol) and a solution of alkyne **1** (35 mg, 0.082 mmol) in 20 mL of benzene. The static nitrogen atmosphere was replaced by hydrogen from a double balloon and the reaction mixture was stirred at room temperature for 2 h, filtered through Celite, and concentrated. Purification by flash column chromatography on silica gel (2% to 3% EtOH in CH_2Cl_2) gave (*Z*)-alkene **2** (32 mg, 91% yield) as a white foam: mp 68−69 °C; $R_f = 0.26$ (6% EtOH in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (s br, 1H), 6.34 (d, J = 1.7 Hz, 1H), 6.27 (d, J = 1.7 Hz, 1H), 5.75 (dt, J = 12.0, 6.4 Hz, 1H), 5.60 (d br, J = 12.2 Hz, 1H), 4.51 (m, 1H), 4.33 (m, 1H), 3.58−3.43 (m, 2H), 3.33 (d br, J = 12.0 Hz, 1H), 2.51 (td, J = 10.7, 2.4 Hz, 1H), 2.54−2.39 (m, 2H), 1.96−1.75 (m, 4H), 1.69 (td, J = 11.0, 2.2 Hz, 1H), 1.50−1.45 (m, 2H), 1.28−0.73 (m, 19H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 153.4, 150.2, 135.2, 130.6, 109.4, 107.6, 106.0, 79.5, 68.4, 59.2, 49.0, 44.4, 40.5, 37.3, 34.9, 33.0, 31.8, 30.0, 29.6, 28.7, 28.6, 27.7, 24.6, 22.7, 19.1, 14.1; IR (neat) 3340 (br), 2940, 2875, 1630, 1580, 1420, 1335 cm^{-1}; mass spectrum m/z 430 (M^+, 16), 249 (49), 164 (30), 163 (33); exact mass calcd for $C_{27}H_{42}O_4$ 430.3083, found 430.3094.

(*E*)-Alkene 3. A solution of (*Z*)-alkene **2** (33 mg, 0.077 mmol) and diphenyl disulfide (4 mg, 0.02 mmol) in 12 mL of benzene was irradiated with a 50 W incandescent flood lamp at room temperature for 12 h, at which time additional diphenyl disulfide (3 mg, 0.01 mmol) was added. Irradiation was continued for 10 h, and the reaction mixture was concentrated. Purification by flash column chromatography on silica gel (30% to 50% EtOAc in hexanes) gave alcohol **3** (21 mg, 64% yield) as a white foam: mp 82−83 °C; R_f = 0.14 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s br, 1H), 6.38 (d, J = 1.7 Hz, 1H), 6.25 (d, J = 1.7 Hz, 1H), 6.00 (td, J = 15.6, 5.1 Hz, 1H), 5.85 (d br, J = 15.9 Hz, 1H), 4.30−4.19 (m, 2H), 3.58−3.43 (m, 2H), 3.34 (d br, J = 12.7 Hz, 1H), 2.58 (s br, 1H), 2.51 (td, J = 11.0, 2.0 Hz, 1H), 1.96−1.71 (m, 4H), 1.55−1.43 (m, 3H), 1.28−0.72 (m, 20H), 0.83 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 154.0, 150.0, 135.5, 129.6, 109.2, 107.7, 105.7, 77.9, 68.4, 63.3, 48.5, 44.5, 40.5, 37.3, 34.9, 33.2, 31.8, 30.1, 29.6, 28.73, 28.69, 27.5, 24.7, 22.7, 16.5, 14.1; IR (neat) 3440 (br), 2940, 2870, 1625, 1575, 1420, 1330 cm^{-1}; mass spectrum m/z 430 (M^+, 46), 399 (100), 249 (68), 163 (58); exact mass calcd for $C_{27}H_{42}O_4$ 430.3083, found 430.3068.

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Supporting Information Available: Copies of ^{1}H and ^{13}C spectra, IR spectra, mass spectra, and product characterization data for **1**−**3** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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