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Farnesyl Chain Modification of Squalene Synthase Inhibitor Benzylfarnesylamine: Conversion to the Terminal Bis(trifluoromethyl) Derivative

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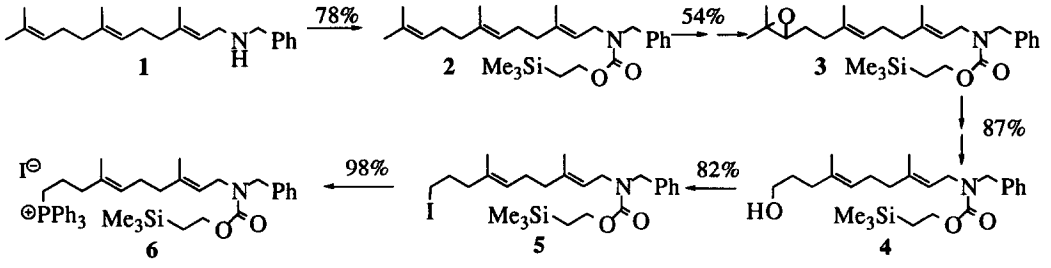
Abstract: Potent squalene synthase inhibitor **1** was converted to the bis(trifluoromethyl) analog **14** in 11% overall yield for 9 steps. The amine nitrogen of **1** was protected with the 2-(trimethylsilyl)ethoxycarbonyl (TEOC) protecting group. The 10,11 olefin was selectively epoxidized, cleaved and converted to the phosphonium salt **6**. The ylid from **6** underwent a Wittig condensation with hexafluoroacetone to give the TEOC containing olefin **8**. Tetrabutylammonium fluoride or HF could not remove the TEOC group without isomerizing the 10,11 olefin of the farnesyl chain to the E-9,10 olefin. The bis(trifluoromethyl) olefin of **8** is very sensitive to either acidic or basic conditions. However, it was found that BF_3•Et_2O could remove the TEOC group without the undesired isomerization to give **14**.

Squalene synthase catalyzes the first dedicated step in the biosynthesis of cholesterol and as such has been an attractive target for the development of new antihypercholesterolemic agents.[1] Compound **1** is a potent inhibitor of squalene synthase in vitro.[2] In a study to develop structure activity relationships for the farnesyl chain of this compound, we set out to prepare the bis(trifluoromethyl) analog **14**. Previous preparations of trifluoromethyl-containing farnesyl chain analogs have involved the synthesis of each olefin in the chain in a stepwise manner.[3] Since **1** already contains the desired *E*-2,3 and *E*-6,7 olefins, it would be efficient to use **1** to prepare a synthon for making variations in the 10,11 olefin portion of the farnesyl chain.



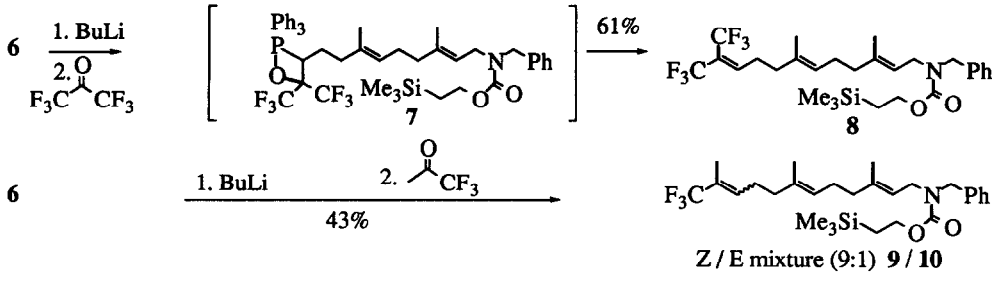
Scheme 1.

Oxidative cleavage of the 10,11 olefin of a suitably protected form of **1** could easily lead to a phosphonium salt **6**. Since there is precedent for Wittig condensations of non-stabilized ylids with fluorinated ketones, we prepared **14** by this approach.[4] In light of the importance of farnesyl chain containing molecules in

the biochemistry of many organisms, and the importance of fluorine as a hydrogen bioisostere in medicinal chemistry, we felt it important to present the experimental details of this particular farnesyl chain transformation.

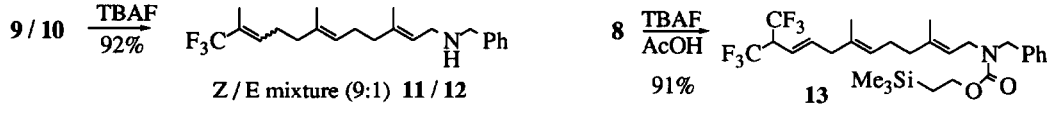
We chose to protect the amine nitrogen of **1** with the TEOC group.[5] Early experiments in our lab had shown that the *t*-butoxycarbonyl (BOC) group could not be removed without causing olefin isomerization in the farnesyl chain. The trifluoroacetyl-protected amine could be deprotected under strongly alkaline conditions in some farnesyl chain analogs, but we anticipated that these conditions would be too harsh for the desired terminal bis(trifluoromethyl)-containing olefin. In contrast to these protecting groups, the TEOC group could be removed easily with *n*-Bu_4NF in THF.

Compound **2** was converted to **3** in 54% yield using conditions described by van Tamelen.[6] Oxidative cleavage of **3** with H_5IO_6,[7] followed by $NaBH_4$ reduction, and iodination of the resulting alcohol[8] gave **5** (six steps from **1** ---30% yield). Attempts to convert **5** into **6** by heating with PPh_3 in toluene led to products that could not be characterized or purified by crystallization. However, using sulfolane[9] as a solvent, **6** was obtained in 98% yield.



Scheme 2.

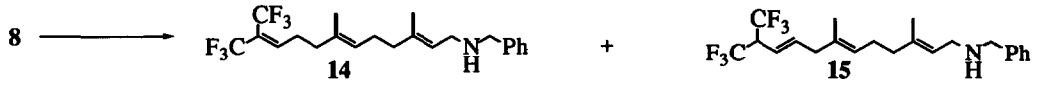
Treatment of **6** with *n*-butyllithium in THF at -78 °C gave an orange solution. Bubbling hexafluoroacetone into the solution caused the color to disappear almost immediately. TLC showed that **6** was consumed and two new less-polar materials resulted. Upon quenching the reaction at -78 °C, diluting and stirring for 2 hours at rt, the lower of the two new TLC spots disappeared; after work-up, **8** was obtained in 61% yield. In contrast to literature reports of similar reactions, the decomposition of presumed oxaphosphetane **7** to **8** does not require excessive heating.[10] Wittig condensation of **6** with trifluoroacetone gave immediately a mixture of **9** and **10** (9:1 ratio, 42% yield) without the appearance of a TLC detectable intermediate.



Scheme 3.

The mixture of **9/10** could be deprotected with *n*-Bu_4NF to give a mixture of **11/12** in 92% yield. However, treating **8** under these same conditions resulted in the disappearance of the starting material and the appearance of several unidentified products which did not include the desired amine **14**. Using *n*-Bu_4NF with AcOH[11] led to **13**, the compound resulting from isomerization of the 10,11 olefin to the E-9,10 olefin, in 85%

yield. Using HF (4 h in CH_3CN), we obtained **14** as the major product with some of the *E*-9,10 olefin compound **15** in varying amounts, with a 10/1 mixture of **14/15** being the best. These results are not surprising in view of a report by Wakselman[12] showing the susceptibility of β,β-bis(trifluoromethyl)acrylic esters to conjugate addition by fluoride ions and other nucleophiles directed by the bis(trifluoromethyl) functionality instead of the ester group. On closer examination, the 10,11 olefin was found to be sensitive to isomerization induced by SiO_2 or $CDCl_3$. We found that $BF_3{\cdot}Et_2O$ removed the TEOC group faster (40 min vs. 4 h) than HF and with chromatography on base-treated silica gel, gave a > 40 to 1 ratio of **14/15**.[13] Although the use of $BF_3{\cdot}Et_2O$ has been reported for the removal of silicon-based protecting groups,[14] it has not been reported in the removal of the TEOC group. We are currently studying the scope of the $BF_3{\cdot}Et_2O$ removal of TEOC protecting groups in the presence of other sensitive functionality.



A. HF/CH_3CN, 4 h → 10:1 ratio in 84% yield
B. $BF{\cdot}Et_2O/CH_2Cl_2$, 40 min → >40:1 ratio in 60% yield

Scheme 4.

In summary, farnesyl chain-containing amine **1** was converted into the terminal bis(trifluoromethyl) derivative **14** in 9 steps (11 % yield). The main advantage of this method is the ability to use and preserve the E-2,3 and E-6,7 olefin of the original farnesyl chain. Even though the bis(trifluoromethyl) olefin of **14** was sensitive to the conditions that normally remove the TEOC protecting group, $BF_3{\cdot}Et_2O$ was mild enough to prevent this complication.

ACKNOWLEDGMENT

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EXPERIMENTAL

Analytical TLC was performed on precoated SiO_2 254F plates (0.25-mm thickness) and visualized with a solution of 10% phosphomolybdic acid in EtOH. Flash chromatography was carried out with silica gel 60 (230-400 mesh). For ^{31}P-NMR, phosphoric acid was used as an external standard and for ^{19}F-NMR, hexafluorobenzene was used as an external standard.

(*E,E*)-*N*-phenylmethyl-*N*-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-*O*-(2-trimethylsilyl)ethyl carbamic acid (2) A solution of 2-(trimethylsilyl)ethyl *p*-nitrophenyl carbonate (2.3 g, 8.04 mmol) in 55 mL of 1,2-dichloroethane (DCE) was added to a solution of **1** (2.5 g, 8.04 mmol)[2a] and DMAP (982 mg, 8.04 mmol) in 25 mL of DCE and stirred for 16 h at rt. The reaction mixture was diluted with Et_2O (200 mL) and washed with 2

N HCl (1 X 100 mL), then sat'd aq $NaHCO_3$ (1 X 100 mL), then sat'd aq NH_4Cl (1 X 100 mL) and then brine (1 X 100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated, and the residue was purified by flash chromatography (40% CH_2Cl_2-hexane) to give **2** (2.85 g, 78%) as a clear oil. R_f 0.83 (20% EtOAc-hexane). IR (neat): ν = 2955, 2918, 2856, 1699 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40-7.05 (m, 5H), 5.24-5.00 (m, 3H), 4.43 (s, 2H), 4.25-4.16 (m, 2H), 3.91 (br s, 2H), 2.14-1.87 (m, 8H), 1.67 (s, 3H), 1.60 (s, 6H), 1.56 (s, 3H), 1.02 (t, 2H, J=8Hz), 0.06 (s, 9H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138.1, 135.3, 131.3, 128.4, 127.9, 127.4, 127.1, 124.3, 123.9, 120.0, 63.6, 49.2, 43.5, 39.7, 39.6, 26.8, 26.3, 25.7, 17.9, 17.7, 16.1, 16.0, -1.5 ppm. CI-MS (NH_3) *m/z* (%) = 473 ($M+NH_4^+$, 27), 456 (MH^+, 100), 428 (MH^+-CH_2=CH_2, 84) amu. Anal calcd for $C_{28}H_{45}NO_2Si$: C, 73.79; H, 9.95; N, 3.07. Found: C, 74.03; H, 10.01; N, 3.03.

(*E,E*)-*N*-[9-(3,3-dimethyl-2-oxiranyl)-3,7-dimethyl-2,6-nonadienyl]-*N*-phenylmethyl-*O*-(2-trimethylsilyl)ethyl carbamic acid (3) Compound **2** (9.45 g, 20.8 mmol) was dissolved in 200 mL of THF and cooled in an ice-water bath. H_2O was added until the cooled solution remained cloudy (~100 mL) and then just enough THF was added to make the solution clear again. The ice bath was removed and *N*-bromosuccinimide (4.07 g, 22.9 mmol) was added in one portion to the stirred solution. After 2 h at rt the reaction was diluted with H_2O (300 mL) and extracted with Et_2O (3 X 200 mL). The combined organic layers were washed with brine (1 X 200 mL), dried (Na_2SO_4), and concentrated to give the crude bromohydrin (12.28 g, R_f 0.45 (20% EtOAc-hexane)) as an oil. This crude product was dissolved in MeOH (100 mL). K_2CO_3 (9.24 g, 66.9 mmol) was added to this solution and the reaction was stirred for 16 h at rt. The reaction was poured into H_2O (400 mL) and extracted with Et_2O (3 X 200 mL). The combined organic layers were washed with brine (1 X 300 mL), dried (Na_2SO_4), concentrated, and the residue purified by flash chromatography (10% EtOAc-hexane) to give **3** (5.28 g, 54%) as a clear oil. R_f 0.70 (20% EtOAc-hexane). IR (neat): ν = 2954, 2922, 2858, 1697, 1669 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38-7.15 (m, 5H), 5.15 (t, 2H, J=6 Hz), 4.46 (s, 2H), 4.30-4.20 (m, 2H), 3.81 (br s, 2H), 2.71 (t, 1H, J=6.75 Hz), 2.24-1.93 (m, 6H), 1.73-1.51 (m, 2H), 1.61 (s, 3H), 1.51 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.04 (t, 2H, J=7.5 Hz), 0.05 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) 138.1, 134.4, 128.4, 127.9, 127.4, 127.2, 124.5, 120.1, 64.2, 63.7, 58.3, 48.8, 43.5, 39.5, 36.4, 27.5, 26.4, 24.9, 18.8, 17.9, 16.2, 16.0, -1.5 ppm. CI-MS (NH_3) *m/z* (%) = 489 ($M+NH_4^+$, 36), 472 (MH^+, 100),461 ($M+NH_4^+$-CH_2=CH_2, 7), 444 (MH^+-CH_2=CH_2, 92) amu. Anal calcd for $C_{28}H_{45}NO_3Si$: C, 71.29; H, 9.61; N, 2.97. Found: C, 71.12; H, 9.76; N, 2.90.

(*E,E*)-*N*-(10-hydroxy-3,7-dimethyl-2,6-decadienyl)-*N*-phenylmethyl-*O*-(2-trimethylsilyl)ethyl carbamic acid (4) A solution of H_5IO_6 (713 mg, 3.13 mmol) was added to a stirred solution of **3** (1.1 g, 2.34 mmol) in 50 mL of THF. After 5 min, 60 mL sat'd aq $NaHCO_3$ was poured into the reaction mixture which was then extracted with EtOAc (2 X 200 mL). The combined organic layers were washed with sat'd aq $NaHCO_3$ (1 X 150 mL), brine (1 X 150 mL), dried (Na_2SO_4), and concentrated to give the crude aldehyde (1.3 g, R_f 0.73 (20% EtOAc-hexane)) as an oil. This crude product was dissolved in MeOH (150 mL) and cooled in an ice bath. $NaBH_4$ (115 mg, 3.03 mmol) was added to this solution and the reaction was stirred for 15 min at 0 °C. The reaction was concentrated and the residue purified by flash chromatography (20% EtOAc-hexane) to give **4** (876 mg, 87%) as a clear oil. R_f 0.18 (20% EtOAc-hexane). IR (neat): ν = 3457, 2950, 1697 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36-7.08 (m, 5H), 5.18-5.02 (m, 2H), 4.39 (s, 2H), 4.26-4.15 (m, 2H), 3.77 (br s, 2H), 3.57 (q, 2H, J=5.7 Hz), 2.13-1.88 (m, 6H), 1.68-1.40 (m, 2H), 1.57 (s, 3H), 1.50 (s, 3H), 0.94 (t, 2H, J=7.5

Hz), 0.03 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 138.8, 138.1, 135.0, 128.4, 127.4, 127.2, 124.4, 124.1, 121.1, 120.3, 63.7, 62.6, 49.3, 43.4, 39.5, 35.9, 30.7, 26.1, 17.9, 16.1, 15.9, -1.51 ppm. CIMS (NH_3) *m/z* (%) = 449 ($M+NH_4^+$, 4), 432 (MH^+, 100), 404 ($MH^+-CH_2=CH_2$, 23) amu.

(*E,E*)-*N*-(10-iodo-3,7-dimethyl-2,6-decadienyl)-*N*-phenylmethyl-*O*-(2-trimethylsilyl)ethyl carbamic acid (5) I_2 (2.45 g, 9.65 mmol) was added in one portion to an ice bath-cooled solution of **4** (3.2 g, 7.42 mmol), PPh_3 (2.34 g, 8.91 mmol) and imidazole (710 mg, 10.39 mmol) in Et_2O-CH_3CN (3:1) (120 mL). After stirring for 1 h while maintaining ice bath cooling, the reaction was poured into H_2O (300 mL) and extracted with Et_2O (3 X 200 mL). The combined organic layers were washed with sat'd aq $Na_2S_2O_3$ (1 X 150 mL) and H_2O (1 X 150 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (10% EtOAc-hexane) to give **5** (3.27 g, 82%) as a clear oil, R_f 0.82 (20% EtOAc-hexane). IR (neat): ν = 3106, 2951, 2914, 2852, 1697, 1669 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34-7.12 (m, 5H), 5.20-5.03 (m, 2H), 4.38 (s, 2H), 4.25-4.14 (m, 2H), 3.75 (br s, 2H), 3.10 (t, 2H, J=7 Hz), 2.12-1.78 (m, 8H), 1.55 (s, 3H), 1.50 (s, 3H), 0.96 (t, 2H, J=7.5 Hz), 0.0 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 138.1, 133.5, 128.4, 127.1, 125.4, 63.3, 50.0, 43.5, 40.0, 39.5, 31.5, 26.3, 17.9, 16.1, 15.8, 6.6, -1.5 ppm. CI-MS (NH_3) *m/z* (%) = 559 ($M+NH_4^+$, 43), 542 (MH^+, 55), 531 ($M+NH_4^+-CH_2=CH_2$, 14), 514 ($MH^+-CH_2=CH_2$, 100) amu. Anal calcd for $C_{25}H_{41}NO_3Si$: C, 55.44; H, 7.44; N, 2.59. Found: C, 55.46; H, 7.46; N, 2.48.

(*E,E*)-[4,8-dimethyl-10-(phenylmethyl)[(2-trimethylsilyl)ethoxycarbonyl]amino-4,8-decadienyl]triphenylphosphonium iodide (6) **5** (292.6 mg, 0.54 mmol) and PPh_3 (155.8 mg, 0.594 mmol) were dissolved in sulfolane (0.27 mL, 2 M) and heated in an 90 °C oil bath for 3.5 h. The mixture was diluted with $CHCl_3$ (0.94 mL) and added dropwise to a flask containing stirred Et_2O (50 mL) causing the product to oil out of solution. Iodide salt **6** (426 mg, 98%) was collected as a viscous oil by decanting off the Et_2O and removing traces of solvent in vacuo at <1 torr for 16 h. This material was used to form the ylid for the Wittig condensation reactions. An analytical sample was obtained by preparative TLC (20 x 20 cm, 1000 μm, SiO_2, 10% MeOH-CH_2Cl_2), R_f 0.40 (10% MeOH-CH_2Cl_2). IR (neat): ν = 3433, 3054, 2948, 1690 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88-7.55 (m, 5H), 7.33-7.13 (m, 5H), 5.16-4.97 (m, 2H), 4.36 (s, 2H), 4.24-4.11 (m, 2H), 3.73 (br s, 2H), 3.72-3.52 (m, 2H), 2.28 (t, 2H, J=7 Hz), 2.08-1.88 (m, 4H), 1.78-1.64 (m, 2H), 1.30 (s, 3H), 1.24 (s, 3H), 0.98 (t, 2H, J=7.5 Hz), 0.04 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 138.1, 135.13, 135.09, 133.8, 133.7, 132.9, 130.6, 130.5, 128.5, 127.2, 126.6, 119.9, 118.9, 117.7, 63.7, 44.78 (d, J=724 Hz), 44.0, 39.4, 26.6, 22.7, 22.0, 20.6, 17.9, 16.3, 15.8, -1.4 ppm. ^{31}P-NMR (121 MHz, $CDCl_3$): δ 25.8 ppm. Anal calcd for $C_{43}H_{55}NO_2SiPI$: C, 64.25; H, 6.90; N, 1.74. Found: C, 64.16; H, 6.87; N, 1.71.

(*E,E*)-*N*-(12,12,12-trifluoro-3,7-dimethyl-11-trifluoromethyl-2,6,10-dodecatrienyl)-*N*-phenylmethyl-*O*-(2-trimethylsilyl)ethyl carbamic acid (8) *n*-BuLi (430 μL of 1.6 M in hexane, 0.68 mmol) was added via syringe to a solution of **6** (500 mg, 0.623 mmol) in THF (5 mL) stirred in a dry ice/acetone bath under argon. The resulting red-orange solution was allowed to stir for 10 min, and then hexafluoroacetone was bubbled into the solution via a syringe needle until the color dimmed to pale yellow (~10 sec). This mixture was allowed to stir 15 min. At this point, TLC revealed consumption of **6** and appearance of two new spots at R_f 0.47 and 0.72 (SiO_2, 20% EtOAc/hexane). The reaction was removed from the cooling bath and treated with sat'd aq NH_4Cl, then diluted with H_2O (10 mL) and Et_2O (20 mL) and allowed to stir at rt (2 h). At this point TLC showed

disappearance of the Rf 0.47 spot and only the Rf 0.72 spot (**8**) remained. The mixture was extracted with Et_2O (2 X 100 mL), washed with brine (1 X 100 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (10% EtOAc-hexane) to give **8** (215 mg, 61%) as a clear oil, Rf 0.72 (20% EtOAc-hexane). IR (neat): ν = 3030, 2955, 2920, 2859, 1698, 1674 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36-7.15 (m, 5H), 6.71 (t, 1H, J=7.5 Hz), 5.15 (t, 2H, J=7 Hz), 4.42 (s, 2H), 4.24-4.15 (m, 2H), 3.82 (br s, 2H), 2.62-2.44 (m, 2H), 2.16 (t, 2H, J=7.5 Hz), 2.14-1.90 (m, 4H), 1.62 (s, 3H), 1.53 (s, 3H), 1.0 (t, 2H, J=7.5 Hz), 0.04 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 147.0, 138.1, 132.7, 128.4, 127.5, 127.2, 126.2, 120.2, 63.7, 49.12, 43.5, 39.3, 37.9, 26.4, 26.3, 17.9, 16.2, 15.7, -1.5 ppm. ^{19}F-NMR (282 MHz, $CDCl_3$):[15] δ -58.76, -64.54 ppm. Anal calcd for $C_{28}H_{39}NO_2SiF_6$: C, 59.24; H, 6.92; N, 2.47. Found: C, 59.51; H, 7.01; N, 2.32.

(*E,E,Z/E*)-*N*-(12,12,12-trifluoro-3,7,11-trimethyl-2,6,10-dodecatrienyl)-*N*-phenylmethyl-*O*-(2-trimethylsilyl)ethyl carbamic acid (mixture of 9 and 10) *n*-BuLi (400 μL of 1.6 M in hexane, 0.64 mmol) was added via syringe to a solution of **6** (500 mg, 0.623 mmol) in THF (3 mL) stirred in an ice bath under argon. The resulting red-orange solution was allowed to stir for 10 min, and then trifluoroacetone (170 μL, 1.87 mmol) was added via syringe. The resulting light yellow mixture was allowed to stir 15 min. The reaction was poured into H_2O (50 mL) and extracted with Et_2O (3 X 75 mL). The combined organic materials were washed with brine, dried (Na_2SO_4), concentrated, and the residue purified by flash chromatography (10% EtOAc-hexane) to give 135 mg of a clear oil (43%) as a 9 to 1 mixture of **9** and **10** (as determined by ^{1}H-NMR integration). Rf 0.67 (20% EtOAc-hexane). IR (neat): ν = 2952, 2929, 2857, 1697, 1454, 1419, 12,47, 1239, 1158, 1116 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (*Z*-isomer) 7.36-7.15 (m, 5H), 5.56 (t, 1H, J=8 Hz), 5.26-5.07 (m, 2H), 4.45 (s, 2H), 4.30-4.20 (m, 2H), 3.83 (br s, 2H), 2.43-1.92 (m, 8H), 1.87 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.02 (t, 2H, J=7.5 Hz), 0.07 (s, 9H) ppm; δ (*E*-isomer)-all peaks overlap except triplet at 6.07 replaces triplet at 5.56. ^{19}F-NMR (282 MHz, $CDCl_3$): δ (*Z*-isomer) -61.83 ppm; δ (*E*-isomer) -69.60 ppm. Anal calcd for $C_{28}H_{42}NO_2SiF_3$: C, 65.98; H, 8.31; N, 2.75. Found: C, 66.13; H, 8.19; N, 2.51.

(*E,E,Z/E*)-*N*-(12,12,12-trifluoro-3,7,11-trimethyl-2,6,10-dodecatrienyl)-benzenemethanamine (mixture of 11 and 12) *n*-Bu_4NF (250 μL of a 1 M solution in THF, 0.25 mmol) was added to a solution of the mixture of **9** and **10** (25 mg, 0.049 mmol) in THF (1 mL). After 16 h, the reaction mixture was concentrated and the residue purified by flash chromatography (3% MeOH-CH_2Cl_2) to yield a mixture of **11** and **12** (16.5 mg, 92%) as a clear oil in a ratio of 9 to 1. Rf 0.39 (10% MeOH-CH_2Cl_2). IR (neat): ν = 3424, 2980, 2927, 1454, 1386, 1116, 1083 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (*Z*-isomer) 7.40-7.20 (m, 5H), 5.65 (t, 1H, J=7 Hz), 5.33 (t, 1H, J=7 Hz), 5.13 (t, 1H, J=7 Hz), 3.81 (s, 2H), 3.28 (d, 2H, J=7 Hz), 2.51 (br s, 1H), 2.20-1.94 (m, 8H), 1.85 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H) ppm; δ (*E*-isomer) all peaks overlap except a triplet at 6.02 which replaces a triplet at 5.65. ^{19}F-NMR (282 MHz, $CDCl_3$): δ (*Z*-isomer) -61.85 ppm; δ (*E*-isomer) -69.60 ppm. CI-MS (NH_3) *m/z* (%) = 366 (MH^+, 100) amu. Anal calcd for $C_{22}H_{30}NF_3$: C, 72.30; H, 8.27; N, 3.83. Found: C, 71.46; H, 8.30; N, 3.76.

(*E,E,E*)-*N*-(12,12,12-trifluoro-3,7-dimethyl-11-trifluoromethyl-2,6,9-dodecatrienyl)-*N*-phenylmethyl--*O*-(2-trimethylsilyl)ethyl carbamic acid (13) A solution of *n*-Bu_4NF (280 μL of a 1 M solution in THF, 0.28 mmol) and AcOH (360 μL, 0.36 mmol) in THF (1 mL) was added to a solution of **8** in THF (1 mL). After 16 h at rt the reaction mixture was concentrated and the residue was purified by flash chromatography (5%

EtOAc-hexane) to yield **13** (32.6 mg, 91%) as a clear oil, Rf 0.73 (20% EtOAc-hexane). IR (neat): ν = 2953, 2918, 2857, 1697, 1674, 1419, 1401, 1240, 1157 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38-7.12 (m, 5H), 5.87 (dt, 1H, J=15, 7.5 Hz), 5.40 (dd, 1H, J=15, 9 Hz), 5.12 (t, 2H, 7 Hz), 4.42 (s, 2H), 4.28-4.15 (m, 2H), 3.82 (br s, 2H), 3.5 (m, 1H), 2.76 (d, 2H, J=7.5 Hz), 2.20-1.95 (m, 4H), 1.58 (s, 3H), 1.54 (s, 3H), 1.02 (t, 2H, J=7.5 Hz), 0.07 (s, 9H) ppm. ^{19}F-NMR (282 MHz, $CDCl_3$):[16] δ -61.57 ppm.

***(E,E)*-*N*-(12,12,12-trifluoro-3,7-dimethyl-11-trifluoromethyl-2,6,10-dodecatrienyl)-benzenemethanamine (14) via HF/CH_3CN** A solution of HF (890 μL, 1 M in CH_3CN, 0.89 mmol) was added to a solution of **8** (100 mg, 0.18 mmol) in CH_3CN (5 mL). After 4 h at rt the reaction was concentrated and the residue was purified by flash chromatography (3% MeOH-CH_2Cl_2) to yield **14** (62 mg, 84%) as a clear oil. ^{1}H-NMR showed that this material contained ~9% of the undesired *E*-9,10 olefin isomer **15**. Rf 0.40 (10% MeOH-CH_2Cl_2). IR (neat): ν = 2922, 2856, 1673, 1228, 1212, 1155 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (**14**) 7.37-7.15 (m, 5H), 6.68 (t, 1H, J=7.5 Hz), 5.30 (t, 1H, J=7.5 Hz), 5.15 (t, 1H, J=6.5 Hz), 3.79 (s, 2H), 3.27 (d, 2H, 7.5 Hz), 2.6-2.24 (m, 3H), 2.22-1.92 (m, 6H), 1.62 (s, 6H) ppm, plus peaks indicating the presence of **15**[17] (~9% relative to **14**) and a very small amount of an unidentified impurity.[18] ^{19}F-NMR (282 MHz, $CDCl_3$):[19] δ (**14**) -58.78, -64.60 and (**15**) -67.59 ppm. Anal calcd for $C_{22}H_{27}NF_6$: C, 63.00; H, 6.49; N, 3.34. Found: C, 62.73; H, 6.45; N, 3.28.

14 via BF_3•Et_2O/CH_2Cl_2 BF_3•Et_2O (22 μL, 0.18 mmol) was added to a solution of **8** (20 mg, 0.036 mmol) in CH_2Cl_2 (1 mL). After 40 min at rt the reaction mixture was poured into sat'd $NaHCO_3$ (aq), extracted with Et_2O (3 X 25 mL), washed with H_2O, dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (3% MeOH-CH_2Cl_2, silica gel prewashed with 3 column volumes of 0.5% isopropylamine-CH_2Cl_2) to yield **14** (9 mg, 60%) as a clear oil. ^{19}F-NMR showed that this material contained <2.5% of the undesired *E*-9,10 olefin isomer **15**. Rf 0.40 (10% MeOH-CH_2Cl_2). IR (neat): ν = 2925, 2853, 1673, 1228, 1212, 1155 cm^{-1}. ^{1}H-NMR (300 MHz, C_6D_6): δ 7.60-7.0 (m, 5H), 6.35 (t, 1H, J=7 Hz), 5.49 (t, 1H, J=7 Hz), 5.14-5.0 (m, 1H), 3.76 (s, 2H), 3.34 (d, 2H, 7.5 Hz), 3.25 (s, 1H), 2.20-1.85 (m, 6H), 1.75-1.65 (m, 2H), 1.57 (s, 3H), 1.37 (t, 3H) ppm. ^{19}F-NMR (282 MHz, C_6D_6):[20] δ -58.78, -64.60 ppm. Anal calcd for $C_{22}H_{27}NF_6$: C, 63.00; H, 6.49; N, 3.34. Found: C, 63.15; H, 6.48; N, 2.76.

REFERENCES AND NOTES

1. For leading references see (a) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Nallin Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 80. (b) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705. (c) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Marretta, J.; Ciosek, C. P., Jr. *J. Med. Chem.* **1991**, *34*, 1914. (d) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 3734. (e) Steiger, A.; Pyun, H. J.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 3444.

2. (a) Prashad, M.; Kathawala, F. G.; Scallen, T. *J. Med. Chem.* **1993**, *36*, 1501. (b) Bertolino, A.; Altman, L. J.; Vasak, J.; Rilling, H. C. *Biochim. Biophys. Acta* **1978**, *530*, 17.
3. (a) Camps, F.; Sanchez, F.; Messeguer, A. *Synthesis* **1988**, 823. (b) Camps, F.; Canela, R.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1978**, *34*, 2179.
4. Herz, J. E.; Montalvo, S. C. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1233.
5. (a) Carpino, L. A.; Tsao, J.-H.;Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358. (b) Rosowsky, A.; Wright, J. E. *J. Org. Chem.* **1983**, *48*, 1539.
6. van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295.
7. Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599.
8. (a) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, 4883. (b) Millar, J. G.; Underhill, E. W. *J. Org. Chem.* **1986**, *51*, 4726.
9. Secrist, J. A., III; Wu, S. *J. Org. Chem.* **1979**, *44*, 1434.
10. (a) Ref. 4 mentions that 6 h of reflux in THF is required to get olefin from a similar Wittig reaction. (b) Example of a stable phosphetane: Schmidpeter, A.; von Criegern, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 55. (c) First characterized example of a stable, cyclic ylid-ketone adduct: Birum, G. H.; Matthews, C. N. *J. Org. Chem.* **1967**, *32*, 3554.
11. AcOH added to buffer any basicity of *n*-Bu_4NF.
12. Martin, V.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1992**, *57*, 5530.
13. NMR spectra of this compound were determined in C_6D_6 to eliminate isomerization caused by adventitious DCl in $CDCl_3$.
14. Kelly, D. R.; Roberts, S. M. *Synth. Commun.* **1979**, *9*, 295.
15. Two small but distinguishable peaks are detected in the ^{19}F-NMR spectrum (δ -58.60, -67.43 ppm). GC-MS (25 m capillary SiO_2 column (OV 1701)) indicates two small impurities having the same molecular weight as compound **8**, 3.7% and 4.5%. Since our original source of the farnesyl chain comes from (*E,E*)-farnesyl bromide (95%) (Aldrich), it is possible that these impurities are olefin isomers. These impurities are carried through the synthesis and their congeners found in **13**, **14** and **15**, as well.
16. A slight impurity can be distinguished (δ -67.41 ppm), possibly an olefin isomer.
17. The side peaks that could be distinguished matched the ^1H-NMR of a pure sample of **15** prepared by a variation of the chemistry described in this paper. Farnesyl-*t*-butyldimethylsilyl ether was treated to the same conditions in Scheme I, followed by conditions used to make **8**, and gave (*E,E*)-12,12,12-trifluoro-3,7-dimethyl-11-trifluoromethyl-2,6,10-dodecatrienyl-*t*-butyldimethylsilyl ether. Removal of the silyl protecting group with *n*-Bu_4NF/AcOH, gave (*E,E,E*)-12,12,12-trifluoro-3,7-dimethyl-11-trifluoromethyl-2,6,9-dodecatrienol, which was treated with PBr_3 followed by benzylamine to give **15** (10 steps, 4% yield). IR (neat): ν = 2920, 2856, 1359, 1254, 1147, 1094 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$): δ 7.45-7.10 (m, 5H), 5.90 (dt, 1H, J=7.5, 15 Hz), 5.35 (dd, 1H, J=10, 15 Hz), 5.32 (t, 1H, J=7.5 Hz), 5.12 (t, 1H, J=7.5 Hz), 3.82 (s, 2H), 3.47 (d heptet, 1H, J=9, 9 Hz), 3.27 (d, 2H, 7.5 Hz), 2.73 (d, 2H, J=7.5 Hz), 2.62 (br s, 1H), 2.18-1.96 (m, 4H), 1.60 (s, 3H), 1.53 (s, 3H) ppm. ^{19}F-NMR (282 MHz, $CDCl_3$): δ -67.59 ppm. Anal calcd for $C_{22}H_{27}NF_6 \cdot 0.5H_2O$: C, 61.67; H, 6.59; N, 3.27. Found: C, 61.56; H, 6.46; N, 3.18.
18. Small peaks near the δ 6.68 (t) ppm of **14.**
19. Small peaks at δ -58.60, -65.60, -67.40 ppm of unknown origin.
20. Small peaks at δ -67.20, 67.37 ppm of unknown origin.

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