Synthesis of 15-Deoxy-12-hydroxy-10-(trifluoromethyl)-Δ^7-PGA$_1$ Methyl Ester

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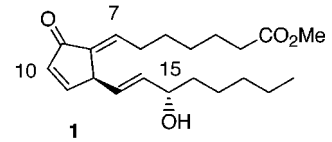
Cross-conjugated alkylidene prostaglandins have been shown to be potent cytostatic agents that exert their action through a unique and unusual mechanism. Compounds in this class also inhibit viral replication and have a role in osteogenesis and adipogenesis; consequently, they are of considerable current interest as pharmaceutical lead compounds. The purpose of our research was to define an efficent protocol for the assembly of the C-10 trifluoromethyl prostanoid mentioned in the title. This compound was predicted to show strong antitumor activity on the basis of the known structure−activity relationships within this series. A novel strategy for assembling the carbon skeleton of Δ^7-unsaturated prostanoids bearing oxygen functionality at C-12 through an ionic electrocyclic process has been described. Key steps of the synthesis are the preparation of dieneone **14b** through an electrocyclic ring-opening reaction and the ionic electrocyclization of **26a**, which creates the functionalized carbon skeleton. The target compound was found to be cytotoxic in vitro against two human tumor cell lines in the low μM range, confirming our prediction.

Certain alkylidenecyclopentenone prostaglandins (PGs) have been the focus of much research because of their involvement with cell-cycle regulation.[1] These PGs cause G1 cell arrest,[2] inhibit viral replication,[3] and show potent antitumor effects.[4] They also have a role in adipogenesis[5] and osteogenesis.[6] Δ^7-PGA$_1$ methyl ester (**1**) is currently being evaluated for the treatment of chemotherapeutically resistant ovarian cancer.[1] The range of activities that have been reported for the cross-conjugated PGs suggests a number of opportunities for therapeutic intervention and is one of the reasons for the sustained interest in this class of compounds. An efficient synthesis of these PGs can be accomplished by means of Noyori's three-component method[7ab] or according to Ciufolini's recent approach.[7c] Extensive work to define the mechanism of action and the structure−activity relationships (SAR) has been reported.[8] The mechanism of action is thought to involve reversible, carrier-mediated transport across the cellular and nuclear membranes, followed by covalent attachment to nuclear proteins.[1,9] Neither the absolute configuration nor the presence of the C-15 hydroxyl group influences the antitumor activity.[8] Limited SAR have also been defined for some of the halogenated marine prostaglandins. Punaglandin 4 (**2**) is representative of this class of marine natural products,[10] and it has been shown to be roughly 10-fold more potent than **1** in the L1210 mouse leukemia assay.[8] This strongly suggests that the presence of the C-12 hydroxyl group and substitution at C-10 by the electron-withdrawing chlorine strongly potentiates the antitumor activity within this series.



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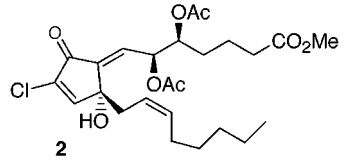

2

The three-component synthesis is not readily adaptable for the preparation of C-10 substituted PGs nor for the preparation of PGs that incorporate a hydroxyl at C-12, whereas the cationic cyclopentannelation reaction appears to be ideally suited to the task. The reaction forms a cross-conjugated cyclopentenone from an acyclic precursor, and functionality can be introduced at all the ring

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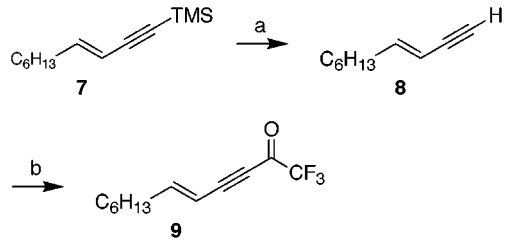
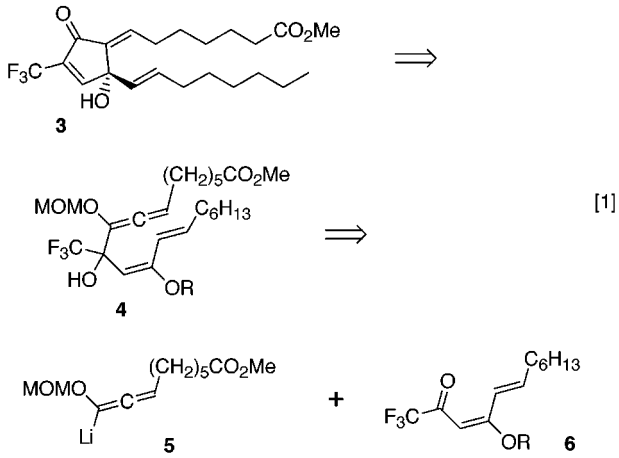
Scheme 1[a]



[a] Key: (a) K_2CO_3, MeOH, rt; 85%; (b) *n*-BuLi, CF_3CO_2Et; 78%.

carbons.[11] We chose as our target compound the α-trifluoromethyl PG **3**. This is a compound that combines all structural elements that are required for high antitumor activity, and it cannot be prepared through the three-component synthesis. Furthermore, the synthesis of **3** was expected to be challenging enough to define new limits for the applicability of the cyclopentannelation reaction.

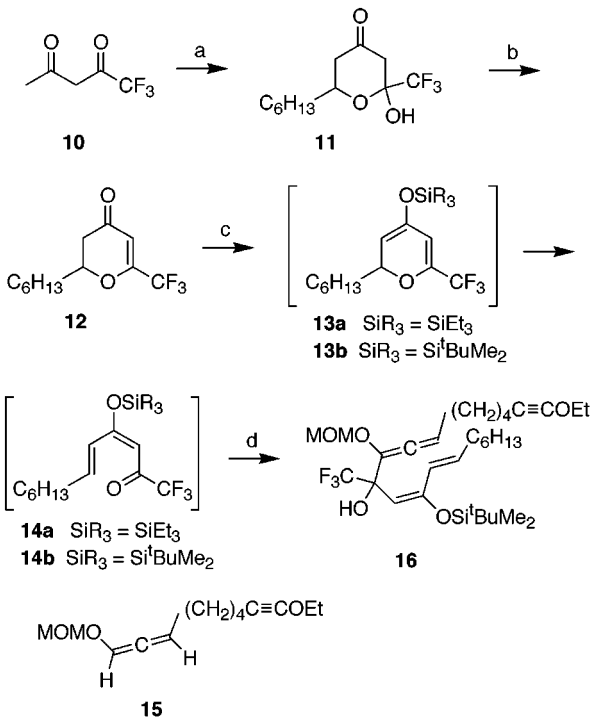


[1]

The retrosynthesis of **3** is outlined in eq 1. The direct precursor of **3** is tertiary alcohol **4**, which is accessible from the addition of a synthetic equivalent of lithioallene **5** (MOM = methoxymethyl) to β-alkoxy trifluoromethyl enone **6**. Neither of the two retrosynthetic steps is straightforward. Acid-catalyzed ionization of the tertiary alcohol in **4** must take place to generate a heptatrienyl cation, which is then required to undergo 4π electrocyclization to give **3**.[12] One can imagine many alternative reaction pathways for this cation. The preparation of allene **5** and ketone **6** also poses a significant challenge, due in part to the requirements for protection of the ester group in **5** and restrictions on the R group in **6** (vide infra).

The synthesis of **6** was attempted first (Scheme 1). Enyne **7**[13] was converted in two steps to trifluoromethyl enynone **9** in high yield. Michael addition of methanol to **9** provided only low yields of **6** (ca. 13%, R = methyl), along with the product of bis-addition of methanol to C4 and to C6 of **9**. This byproduct formed even when substoichiometric methanol was used. Since all attempts to optimize the synthesis of **6** according to Scheme 1

Scheme 2[a]



[a] Key: (a) LDA, THF, −78 °C; heptanal; 74%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; 95%; (c) **13a**: Et_3N, Et_3SiOTf, Et_2O, −78 °C, 1 h; 0 °C, 0.5 h; rt, 4 h; **13b**: Et_3N, *t*-$BuMe_2SiOTf$, Et_2O, −78 °C, 1 h; 0 °C, 0.5 h; rt, 4 h; (d) from **13b**: **15** + *n*-BuLi, THF, −78 °C; 55%.

failed, a brief alternative procedure was developed (Scheme 2). The starting material for the successful synthesis was 1,1,1-trifluoro-2,4-pentanedione **10**, which was converted to the corresponding dienolate and trapped at C5 with heptanal to produce hydroxypyrone **11** as the sole product in 74% yield. Dehydration of **11** took place in high yield upon exposure to boron trifluoride etherate.[14] Treatment of **12** with triethylsilyl triflate, or TBDMS triflate, and triethylamine in ether at −78 °C, followed by slow warming to 0 °C, led to enol ethers **13a** and **13b**, respectively. Formation of the enol ether was evidenced by the observation of a separate reaction phase consisting of the triethylammonium salt. Controlled slow warming of the solution to room temperature over 4 h resulted in electrocyclic ring opening to trifluoromethyl dienone **14a** or **14b**.[15] It appears that *E* to *Z* isomerization of the enol ether double bond in **14**, catalyzed by the triethylammonium hydrotriflate, took place on standing. The isomerization was evidently followed by migration of the trialkylsilyl group to the oxygen atom of the trifluoromethyl ketone because nucleophilic addition in the next step took place at C4, rather than at C2, as was required for the synthesis. To avoid this difficulty, it was necessary to trap **14** *in situ*. Deprotonation of allene **15**[13] with 1 equiv of *n*-butyllithium at −78 °C generated a solution of the lithio allenyl anion to which **14b** was transferred by cannula. This led to **16** in 55% yield based on **12**. The triethylammonium hydrotriflate that is present in the solution of **14b** was largely excluded from the reaction

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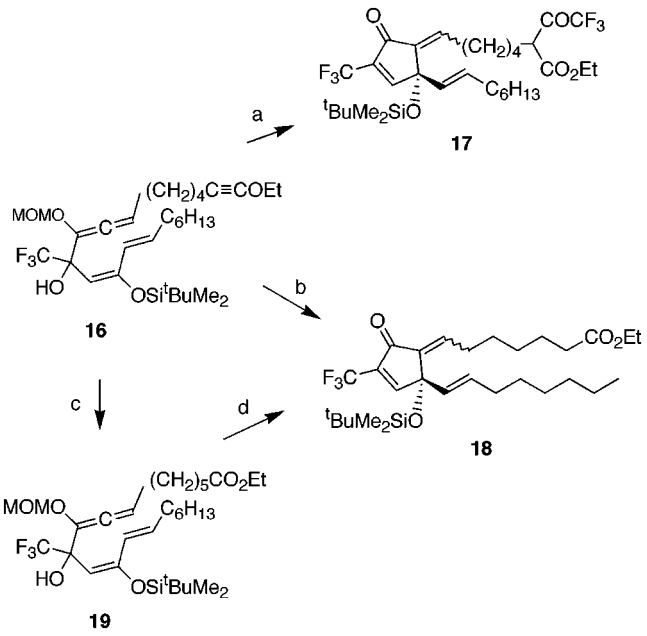
Scheme 3[a]



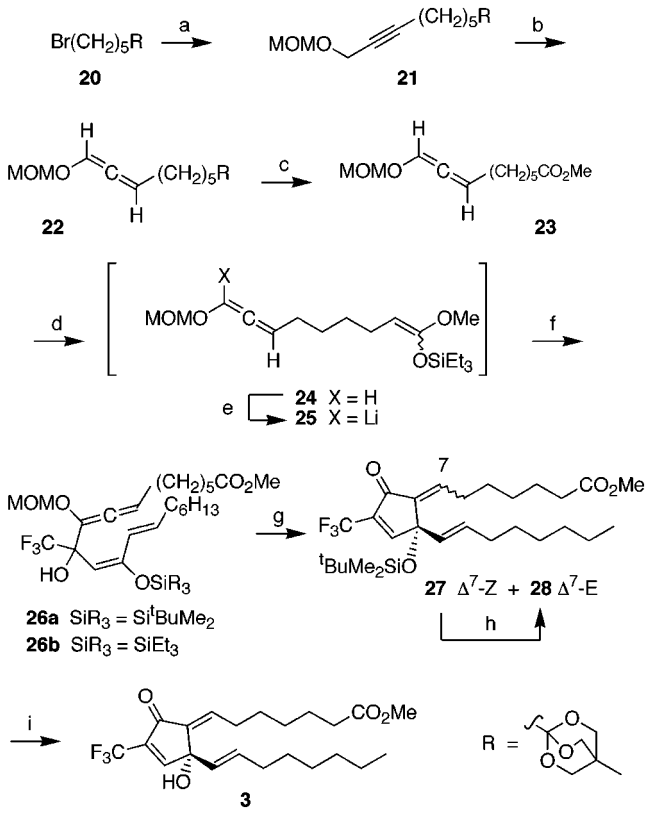
[a] Key: (a) 2,6-lutidine, TFAA, CH_2Cl_2, −78 to 0 °C; 67%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 5 min; 10%; (c) AcOH/THF/H_2O (6:3:1), 0 °C, 0.5 h; 50%; (d) 2,6-lutidine, TFAA, CH_2Cl_2, −78 to 0 °C; 76%.

mixture by performing the transfer at −78 °C. At this temperature, the ammonium salt solidifies into a glass in the bottom of the flask and is not transferred through the cannula. This makes it possible to avoid the use of a large excess of **15**.

The cyclization of trifluoromethyl carbinol **16** was expected to place demands on our experimental acumen, since the two acid-labile enol ether functions must remain intact during the ionization and cyclization processes. Premature loss of a proton from the heptatrienyl cation would also preclude cyclization. Indeed, treatment of **16** with an excess of TFAA and 2,6-lutidine, the optimal conditions for these cyclization reactions,[11] led to **17** in 67% yield as a mixture of Δ^7 *E* and *Z* isomers (Scheme 3). Electrophilic attack on the acetylenic ether was faster than the cyclization, since the trifluoroacetylation could not be suppressed by using only 1 equiv of TFAA. The lability of **17** to aqueous base discouraged us from exploring methods to cleave the trifluoroacetyl group. Our attempts to cyclize **16** by exposure to Lewis acids were also not encouraging. For example, **16** was converted to **18** in only 10% yield upon exposure to boron trifluoride etherate. This result was typical. Since the acetylenic ether was incompatible with the optimal conditions for the cyclization, **16** was first hydrolyzed to ester **19**. This was a delicate process. Exposure of **16** to acetic acid in aqueous THF at 0 °C for 30 min provided **19** in 50% yield, along with ca. 40% of unreacted **16**. The balance (ca. 10%) of the material was derived from protiodesilylation of **16**. Cyclization of **19** with TFAA and 2,6-lutidine, as for the reaction leading to **17**, provided **18** in 40% overall yield from **16** as a mixture of Δ^7 *E* and *Z* isomers. Although this approach provided the cyclic product, the difficult selective hydrolysis step that gave **19** would be difficult to reproduce on a large scale. We suspected that the overall process could be improved by devising a better synthesis of **19** or its equivalent.

Scheme 4 outlines the successful synthesis of **3**. Ortho

Scheme 4[a]



[a] Key: (a) methoxymethylpropargyl ether, *n*-BuLi, THF, 0 °C; **20**, DMSO, rt; 83%; (b) *n*-BuLi, TMEDA, −78 °C; 70% **22** + 30% **21**; (c) $KHSO_4$, DME, H_2O, 0 °C, 5 min; MeOH, K_2CO_3; 83%; (d) LDA, Et_3SiCl, THF, −78 °C to room temperature; (e) *sec*-BuLi, THF, −78 °C; (f) **14b**; 55% **26a** from **23**; (g) 2,6-lutidine, TFAA, −78 °C to −40 °C; 42% **27** + 16% **28**; (h) PhH, sunshine, 5 h; 68% **28** +21% **27**; (i) TREAT·HF, Et_3N, MeCN, 60 °C, 2 d; 76%.

ester **20**[16] was prepared from 6-bromohexanoyl chloride and was treated with the lithio anion derived from methoxymethyl propargyl ether to produce **21** in 83% yield. Isomerization of the propargyl ether function to the allenyl ether took place with *n*-butyllithium in the presence of TMEDA. This provided a 70/30 mixture of allene **22** and acetylene **21** in quantitative yield. Chromatographic separation of **22** allowed recovered **21** to be recycled. Selective hydrolysis of the ortho ester function[16] in **22** with potassium bisulfate in aqueous dimethoxyethane, followed by methanolic potassium carbonate, gave methyl ester **23** in 83% yield. The greater acidity of the ester α-hydrogens compared to the allene hydrogen was exploited in the next step. Exposure of **23** to LDA and triethylchlorosilane converted the ester group to the corresponding mixed ketene acetal **24**.[17] The crude material was converted to lithio anion **25** by treatment with *sec*-butyllithium at −78 °C. Addition of **14b** to the anion solution furnished tertiary alcohol **26a** in 55% yield based on **23**. Hydrolysis of the ketene acetal took place on workup. The process is remarkable in that five operations take place with no isolation of intermediates: two steps to convert **12** to **14b**, two steps to convert **23** to **25**, and the addition step. This efficient preparation of **26a** made the accumulation of material for the final

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steps of the synthesis much easier. Cyclization of **26a** to a 2.6/1 mixture of **27** and **28** was accomplished in 58% yield as was done for **19**. The major byproduct of this reaction was the β-trifluoromethyl enone, which is derived from the hydrolysis of the β-hydroxy TBDMS enol ether. We were unable to suppress this process, which may be caused by traces of water in the reaction. The undesired hydrolysis was the dominant reaction pathway when we attempted to cyclize **26b**. This forced us to use the more robust TBDMS protecting group. Geometrical isomers **27** and **28** were separated by flash column chromatography, and a degassed benzene solution of the *Z* isomer **27** was exposed to sunlight for 5 h.[18] Solvent evaporation followed by chromatography furnished *E* isomer **28** in 68% yield, along with 21% of recovered **27**. It is not clear whether this represents a true equilibrium mixture. The photoisomerization was interrupted after 5 h because of the appearance of byproducts.

Removal of the TBDMS protecting group from **28** in the final step was accomplished in acetonitrile at 60 °C for 2 d with excess triethylamine trishydrofluoride (TREAT·HF) containing 10% (v/v) added triethylamine.[19] The yield of **3** was 76% following purification by reversed-phase column chromatography. The final product was quite labile and underwent decomposition upon exposure to weak aqueous acid or base or to chromatography on silica gel. The lability of **3** precluded the use of more conventional conditions for the desilylation.

The cytotoxicity of the final product was evaluated against the KB (IC_{50} 10 μM) and LoVo (IC_{50} 1.6 μM) tumor cell lines. The IC_{50} of **3** against LoVo compares favorably with that of 10-chloro-15-deoxy-Δ^7-PGA_1 ethyl ester (IC_{50} 57 μM), whereas the IC_{50} against KB is comparable (IC_{50} 7 μM).[13] This provides a good indication that the combination of structural features in **3** all contribute to the observed activity. In conclusion, a convergent synthesis of 10-(trifluoromethyl)-12-hydroxy-Δ^7-PGA_1 methyl ester **3** has been described. The synthesis is noteworthy for its brevity (eight steps from **20**), the number of steps that are performed without isolation of intermediates, the use of electrocyclic processes for both key steps, and the use of a ketene acetal to protect the ester function *in situ*. The electrocyclic process that leads from **26** to **27** and **28** is unusual and suggests a tolerance for functionality that may be general. Brief, efficient syntheses of the highly functionalized marine PGs (cf. **2**) based on this approach can also be imagined.

Experimental Section

TLC was performed on EM reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Normal-phase flash column chromatography was performed on Brinkmann silica gel (0.040−0.063 mm). Reversed-phase column chromatography was performed on YMC-GEL BS-5001 silica. THF and ethyl ether were distilled from sodium−benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide and hexane from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. Elemental analyses were performed by Desert Analytics, Inc., Tucson, AZ.

6-*n*-Hexyl-2-hydroxy-2-(trifluoromethyl)tetrahydropyran-4-one (11). 1,1,1-Trifluoro-2,4-pentanedione (1.4 mL, 11.30 mmol) was added slowly to a freshly prepared solution of LDA (22.40 mmol) at −78 °C. The mixture was stirred for 2 h, and 1.5 mL (10.74 mmol) of heptanal was rapidly added. After 45 min, the mixture was quenched with 1 N aqueous HCl and partitioned between ether and water. The organic extracts were washed with water and brine and were dried over $MgSO_4$. Flash column chromatography furnished 2.14 g (74% yield) of pure **11**: R_f = 0.47 (20% EtOAc in hexane); mp 60−62 °C; IR (neat) 3400 br, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (m,1H), 2.82 (br, 1H), 2.66 (s, 2H), 2.44 (dd, J = 15.3, 2.7 Hz, 1H), 2.33 (dd, J = 15.3, 9.3 Hz, 1H), 1.70 (m, 2H), 1.39−1.21 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 122.3 (q, $^1J_{C-F}$ = 283.5 Hz), 96.3 (q, $^2J_{C-F}$ = 33.3 Hz), 71.1, 46.5, 44.1, 35.7, 31.9, 29.3, 25.0, 22.6, 14.3; mass spectrum *m/z* 268 (M^+, 2), 250 (1); exact mass calcd for $C_{12}H_{19}F_3O_3$ 268.1287, found 268.1300.

6-*n*-Hexyl-2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-4-one (12). A solution of 622 mg (2.32 mmol) of **11** in 10 mL of CH_2Cl_2 was treated with 0.9 mL (3 equiv) of $BF_3{\cdot}Et_2O$ at 0 °C. The mixture was allowed to warm to room temperature, was stirred overnight, and was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was partitioned between ether and water. The organic extracts were washed with water and brine and were dried over $MgSO_4$. Flash column chromatography furnished 547 mg (95% yield) of pure **12** as an oil: R_f = 0.38 (5% EtOAc in hexane); IR (neat) 1690, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 4.55 (m, 1H), 2.56 (d, J = 7.5 Hz, 2H), 1.82 (m, 2H), 1.48−1.30 (m, 8H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 159.5 (q, $^2J_{C-F}$ = 36.7 Hz), 119.1 (q, $^1J_{C-F}$ = 277.1 Hz), 104.9, 81.9, 41.6, 34.2, 31.8, 29.1, 24.8, 22.8, 14.2; mass spectrum *m/z* 250 (M^+, 10), 139 (100), 112 (50); exact mass calcd for $C_{12}H_{17}F_3O_2$ 250.1181, found 250.1194. Anal. Calcd for $C_{12}H_{17}F_3O_2$: C, 57.59; H 6.85. Found: C, 57.24; H, 6.92.

1-(5-Bromoamyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (20). A solution of 6.60 g (30 mmol) of 6-bromohexanoyl chloride in 20 mL of CH_2Cl_2 was treated with 2.7 mL (33 mmol) of pyridine and 3.44 g (33 mmol) of 3-methyl-3-oxetanemethanol at 0 °C. The mixture was stirred at 0 °C for 5 h and then quenched with 5% aqueous KH_2PO_4. Extraction with CH_2Cl_2, washing with brine, and drying (Na_2SO_4) furnished the crude product after solvent evaporation. Flash column chromatography gave 6.46 g (77% yield) of the 6-bromohexanoate ester as an oil. This material was dissolved in 25 mL of CH_2Cl_2, chilled to −15 °C, and treated with 0.5 mL (0.25 equiv) of $BF_3{\cdot}Et_2O$. The mixture was stirred at −15 °C for 1 h and at 0 °C for 1 h and was then quenched with 6 mL of Et_3N and diluted with ether. Filtration, solvent evaporation, and flash column chromatography furnished 5.62 g of ortho ester **20** as an oil (87% yield): R_f = 0.48 (10% EtOAc in hexane); IR (neat) 1460, 1395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 6H), 3.38 (t, J = 6.9 Hz, 2H), 1.84 (quint, J = 6.9 Hz, 2H), 1.69−1.63 (m, 2H), 1.50−1.35 (m, 4H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 72.5 (3C), 36.4, 33.8, 32.7, 30.1, 28.0, 22.3, 14.5.

1-[8-(Methoxymethoxy)oct-6-ynyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (21). A solution of 3.00 g (30.00 mmol) of methoxymethylpropargyl ether in 20 mL of THF was treated at −78 °C with 25.76 mmol of *n*-butyllithium (14 mL of a 1.84 M solution in hexane). The solution was warmed to 0 °C and was stirred for 15 min. Bromoortho ester **20** (5.62 g, 20.14 mmol) in 20 mL of THF was added to the solution of the anion followed by 20 mL of DMSO. The reaction was warmed to room temperature and was quenched with water after 4 h. The aqueous layers were thoroughly extracted with ether, and the combined organic phase was washed with half-saturated brine and dried (Na_2SO_4). Solvent evaporation followed by flash column chromatography provided 5.00 g (83% yield) of **21** as an oil: R_f = 0.35 (10% EtOAc in hexane); IR (neat) 2220 (w), 1460, 1390, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.19 (t, J = 2.1 Hz, 2H), 3.89 (s, 6H), 3.37 (s, 3H), 2.20 (tt, J = 7.3, 2.1 Hz, 2H), 1.64−1.48 (m, 8H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.8, 94.4, 86.7,

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75.3, 72.4, 55.3, 54.5, 36.4, 30.1, 28.5, 28.3, 22.5, 18.5, 14.4; mass spectrum *m*/*z* 298 (M^+, 0.5), 267 (2); exact mass calcd for $C_{16}H_{26}O_5$ 298.1781, found 298.1761. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.22; H, 9.04.

1-[8-(Methoxymethoxy)oct-6,7-dienyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (22). Into 5.1 mL (33.79 mmol) of TMEDA at 0 °C was added 18.3 mL of a 1.84 M solution of *n*-butyllithium in hexanes (33.67 mmol). The complex was stirred at room temperature for 15 min and was then transferred to a solution of 5.0 g (16.77 mmol) of acetylene **21** in 100 mL of THF at −78 °C. The mixture was stirred for 2 h. A mixture of crushed ice (15 g) with 15 mL of methanol and 1.0 g of K_2CO_3 was poured into the reaction. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water and brine and dried (Na_2SO_4). Flash column chromatography provided allene **22** (3.5 g, 70% yield, oil) and recovered acetylene **21** (1.5 g, 30% yield). **22**: R_f = 0.40 (10% EtOAc in hexane); IR (neat) 1960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (dt, J = 5.9, 2.2 Hz, 1H), 5.79 (dt, J = 6.3, 5.9 Hz, 1H), 4.77 (s, 2H), 3.88 (s, 6H), 3.40 (s, 3H), 2.06 (apparent dq, J = 6.3, 2.2 Hz, 2H), 1.63 (m, 2H), 1.43−1.30 (m, 6H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 117.7, 108.7, 106.1, 94.6, 72.3, 55.8, 36.5, 30.6, 30.0, 28.8, 28.1, 22.8, 14.4; mass spectrum *m*/*z* 298 (M^+, 0.3), 253 (3); exact mass calcd for $C_{16}H_{26}O_5$ 298.1781, found 298.1791.

Methyl 9-(Methoxymethoxy)nona-7,8-dienoate (23). A solution of allene ortho ester **22** (1.70 g, 5.70 mmol) in 25 mL of 1,2-dimethoxyethane was treated with 5% aqueous $KHSO_4$ at 0 °C for 5 min. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ether. The ether extracts were washed with water and brine and were dried (Na_2SO_4). Solvent evaporation gave a crude ester, which was dissolved in 30 mL of methanol in the presence of 50 mg (0.36 mmol) of K_2CO_3. The reaction was stirred at room temperature overnight. A volume of water was added, and the mixture was extracted with ether. The organic extracts were washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent produced 1.08 g (83% yield) of pure methyl ester **23** as an oil: R_f = 0.38 (5% EtOAc in hexane); IR (neat) 1960, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (dt, J = 5.9, 2.2 Hz, 1H), 5.81 (dt, J = 6.3, 5.9 Hz, 1H), 4.78 (s, 2H), 3.66 (s, 3H), 3.41 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 2.08 (apparent dq, J = 6.3, 2.2 Hz, 2H), 1.66−1.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 173.3, 117.6, 105.5, 94.3, 56.0, 51.3, 32.6, 30.5, 29.1, 28.8, 24.6.

Methyl 9-(Methoxymethoxy)-10-hydroxy-10-(trifluoromethyl)-12-(*tert*-butyldimethylsiloxy)eicocosa-7,8,11-(*E*),13(*E*)-tetraenoate (26a). Pyrone **12** (500 mg, 2.00 mmol) in 6 mL of ether was treated at −78 °C with 1.40 mL (5 equiv) of triethylamine and 0.55 mL (1.2 equiv) of TBDMS triflate. The mixture was stirred for 1 h at −78 °C, for 1 h at 0 °C, and for 4 h at room temperature. The reaction mixture was then cooled to −78 °C for 10 min. In a separate flask, allene ester **23** (340 mg, 1.49 mmol) in 3 mL of THF at −78 °C was slowly treated first with 1.1 equiv of a freshly prepared solution of LDA and then with 0.27 mL (1.57 mmol) of chlorotriethylsilane. The reaction mixture was gradually warmed to room temperature during 3 h and then chilled to −78 °C and quenched with saturated aqueous $NaHCO_3$ and diluted with pentane. The organic layer was washed with water and brine and dried (Na_2SO_4). Solvent evaporation produced the crude ketene acetal, which was immediately dissolved in 4 mL of ether, cooled to −78 °C, and treated with 1.9 mL of a 0.79 M solution of *sec*-butyllithium in heptane (1.50 mmol). After 10 min, the solution of trifluoromethyl ketone was transferred by cannula to the solution of the allenyl anion with good stirring. After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic extracts were washed with water and brine and dried (Na_2SO_4). Flash column chromatography produced 477 mg (55% yield based on **23**) of tertiary alcohol **26a** as a mixture of diastereoisomers. (Note: the allene is stereogenic.) **26a** as a labile oil: R_f = 0.27 (5% EtOAc in hexane); IR (neat) 3460, 1970, 1750, 1660, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, J = 15.9 Hz, 1H), 6.12 (dt, J = 15.9, 7.1 Hz, 1H), 6.04 (t, J = 7.3 Hz, 1H), 4.85 (br, 3H), 3.66 (s, 3H), 3.41 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 2.11 (m, 4H), 1.63−1.27 (m, 14H), 0.95 (s, 9H), 0.87 (t, J = 6.8 Hz, 3H), 0.15 (s, 6H). Because of the instability of this material, we were unable to obtain a mass spectrum.

12-(*tert*-Butyldimethylsiloxy)-15-deoxy-10-(trifluoromethyl)-Δ^7-PGA ((*Z*)-27 and (*E*)-28). A solution of 200 mg (0.34 mmol) of tertiary trifluoromethyl alcohol **26a** in 20 mL of dichloromethane at −78 °C was treated with 0.24 mL (6 equiv) of 2,6-lutidine and 0.24 mL (5 equiv) of TFAA. The reaction was stirred at −78 °C for 1 h, warmed gradually to −40 °C during 3 h, and then cooled to −78 °C and quenched by pouring onto 5% aqueous KH_2PO_4. The aqueous phase was extracted with ether, and the combined organic extracts were washed with water followed by brine and were dried (Na_2SO_4). Flash column chromatography afforded 76 mg (42% yield) of (*Z*)-**27** and 29 mg (16% yield) of (*E*)-**28**. (*Z*)-**27**: oil; R_f = 0.46 (10% EtOAc in hexane); IR (neat) 1750, 1720, 1660, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.24 (t, J = 7.3 Hz, 1H), 5.87 (dt, J = 15.4, 7.3 Hz, 1H), 5.31 (d, J = 15.4 Hz, 1H), 3.66 (s, 3H), 2.77 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 2.04 (q, J = 7.3 Hz, 2H), 1.66−1.27 (m, 14H), 0.89 (s, 9H), 0.88 (t, J = 6.8 Hz, 3H), −0.01(s, 3H), −0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 174.0, 159.0 (q, $^3J_{C-F}$ = 3.4 Hz), 145.6, 139.4, 135.6 (q, $^2J_{C-F}$ = 33.0 Hz), 131.7, 130.4, 120.6 (q, $^1J_{C-F}$ = 271.2 Hz), 78.0, 51.4, 33.9, 32.0, 31.6, 29.0, 28.9, 28.7, 28.4, 27.3, 25.6, 24.7, 22.6, 18.1, 14.0, −2.4, −2.6; mass spectrum *m*/*z* 530 (M^+, 3); exact mass calcd for $C_{28}SiH_{45}F_3O_4$ 530.3040, found 530.3068. Anal. Calcd for $C_{28}H_{45}F_3SiO_4$: C, 63.37; H, 8.55. Found: C, 63.34; H, 8.55. (*E*)-**28**: oil; R_f = 0.41 (10% EtOAc in hexane); IR (neat) 1740, 1730, 1660, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.71 (t, J = 7.1 Hz, 1H), 5.92 (dt, J = 15.4, 7.1 Hz, 1H), 5.35 (d, J = 15.4 Hz, 1H), 3.67 (s, 3H), 2.40 (m, 1H), 2.30 (m, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.05 (q, J = 7.1 Hz, 2H), 1.66−1.25 (m, 14H), 0.89 (s, 9H), 0.88 (t, J = 6.8 Hz, 3H), 0.02 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4, 173.9, 160.8 (q, $^3J_{C-F}$ = 3.3 Hz), 141.2, 139.3, 134.3 (q, $^2J_{C-F}$ = 33.5 Hz), 132.5, 129.4, 120.6 (q, $^1J_{C-F}$ = 271.5 Hz), 78.0, 51.5, 33.9, 32.0, 31.6, 29.0, 28.9, 28.8, 28.3, 27.8, 25.7, 24.7, 22.6, 18.2, 14.0, −2.1, −3.0; mass spectrum *m*/*z* 530 (M^+, 2); exact mass calcd for $C_{28}SiH_{45}F_3O_4$ 530.3040, found 530.3031. Anal. Calcd for $C_{28}H_{45}F_3SiO_4$: C, 63.37; H, 8.55. Found: C, 63.32; H, 8.64.

Isomerization of (*Z*)-27 to (*E*)-28. A solution of 28 mg (0.053 mmol) of (*Z*)-**27** in 5 mL of degassed benzene was exposed to sunlight under an argon atmosphere for 5 h at room temperature. Solvent evaporation followed by flash column chromatography gave 19 mg (68% yield) of (*E*)-**28** along with 6 mg (21% yield) of recovered (*Z*)-**27**.

15-Deoxy-12-hydroxy-10-(trifluoromethyl)-Δ^7-PGA_1 Methyl Ester (3). A solution of 15 mg (0.028 mmol) of (*E*)-**28** in 5 mL of acetonitrile was treated with 0.5 mL of triethylamine trishydrofluoride (TREAT-HF) followed by 50 μL of triethylamine. The reaction mixture was stirred at 60 °C for 2 d and was subsequently cooled in an ice−water bath and treated with 5% aqueous KH_2PO_4 solution. The aqueous phase was extracted with ether, and the combined organic extracts were washed with water and brine. Drying, solvent evaporation, and purification by reversed-phase column chromatography (C-18, acetonitrile/water, v/v 3/2) produced 9 mg (76% yield) of **3** as a colorless oil:[20] **3**: R_f = 0.36 (20% EtOAc in hexane); IR (neat) 1740, 1710, 1660, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 6.73 (t, J = 7.3 Hz, 1H), 5.86 (dt, J = 15.4, 7.3 Hz, 1H), 5.52 (d, J = 15.4 Hz, 1H), 3.64 (s, 3H), 2.58 (m, 1H), 2.30 (m, 1H), 2.30 (t, J = 7.1 Hz, 2H), 2.07 (q, J = 7.3 Hz, 2H), 1.61−1.27 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 174.6, 160.7 (q, $^3J_{C-F}$ = 3.1 Hz), 141.5, 139.3, 134.2 (q, $^2J_{C-F}$ = 34.0 Hz), 133.6, 127.7, 120.6 (q, $^1J_{C-F}$ = 272.0 Hz), 76.5, 51.6, 33.7, 32.2, 31.6, 28.9, 28.8, 28.4, 27.7, 27.6, 23.9, 22.6, 14.0; ^{19}F NMR (472 MHz, $CDCl_3$) δ 65.5; mass spectrum *m*/*z* 417 (M^+ + 1, 24), 416 (M^+,

(20) This material is extremely sensitive even to weak aqueous acids or bases. Solvent evaporation was done using a silanized glass flask.

100), 398 (23); exact mass calcd for $C_{22}H_{31}O_4F_3$ 416.2175, found 416.2383. Anal. Calcd for $C_{22}H_{31}F_3O_4$: C, 63.34; H, 7.50. Found: C, 63.07; H, 7.40.

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Supporting Information Available: Experimental details and spectra for compounds **12**, **21**−**23**, **26a**, **27**, **28**, and **3** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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