Total Synthesis of Iso[7]-Levuglandin D_2

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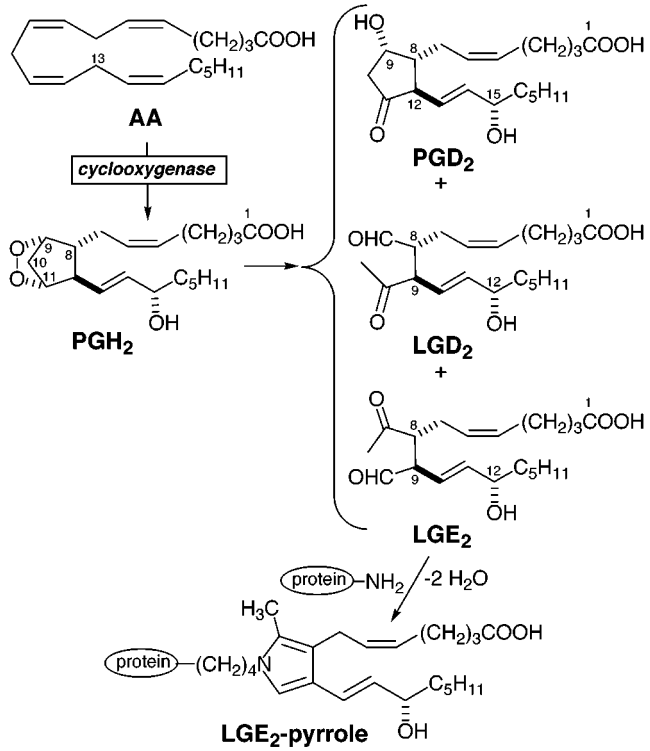
Iso[7]-levuglandin D_2 (iso[7]-LGD_2, 9-acetyl-8-formyl-5-hydroxy-6(*E*),11(*Z*)-heptadecadienoic acid) is a structural isomer of levuglandin D_2 (9-acetyl-8-formyl-12-hydroxy-5(*Z*),10(*E*)-heptadecadienoic acid) that we postulate to be generated during nonenzymatic free radical-induced oxidation of arachidonic acid. To facilitate detection and identification in biological samples, a total synthesis of iso[7]-LGD_2 was devised. The functionality in iso[7]-LGD_2 is diverse and chemically sensitive, and an acid-catalyzed lactonization of the allylically activated δ-hydroxy acid array present in the synthetic target was encountered that occurs readily in aqueous solution. Nevertheless, conjugate addition of a multifunctional vinyl cyanocuprate to achieve the final carbon−carbon bond-forming step, followed by a sequence of functional and protecting group manipulations, reproducibly delivered a readily separable 3:7 mixture of iso[7]-LGD_2 lactone and the free acid.

Introduction

Levuglandins (LGs) D_2 and E_2 are highly oxidized lipids that are cogenerated[1] with prostaglandins (PGs),[2] e.g., PGD_2 (Scheme 1), by rearrangements of the endoperoxide, PGH_2, that occur readily under the conditions of its cyclooxygenase-promoted biosynthesis from arachidonic acid (AA). LGE_2 binds covalently with proteins,[3] forming protein-bound pyrrole derivatives (LGE_2-pyrrole).[4] Using polyclonal antibodies raised against a protein adduct of LGE_2, we previously detected immunoreactive LGE_2-protein modifications in human blood.[5]

Our recent observation that LGE_2-protein adduct immunoreactivity is generated during free radical-induced oxidation of low-density lipoprotein (LDL)[6] indicated a nonenzymatic route to LGs. This probably involves an endoperoxide intermediate, i.e., the 2-lysophosphatidylcholine (PC) ester 8-epi-PGH_2-PC, as in nonenzymatic formation of prostaglandin isomers from AA-PC in LDL (Scheme 2).[7] Rearrangement of 8-epi-PGH_2-PC would produce 8-epi-LGE_2-PC. Because the stereocenter at C8 is lost upon Paal−Knoor condensation[8] with lysyl ϵ-amino groups, reaction of 8-epi-LGE_2−PC with LDL protein, in conjunction with hydrolytic release of lysophosphatidylcholine, would generate the same LGE_2-pyrrole as that produced by the cyclooxygenase pathway (Scheme 1). However, because hydrogen atom abstraction can occur nonregioselectively at any doubly allylic methylene, we also expect the free radical pathway to generate six structurally isomeric levulinaldehyde derivatives with nonprostanoid side chains, isoLGs. For example, hydrogen atom abstraction from the 10- or 7-positions of AA-PC followed by cyclization of an intermediate 8- or 9-peroxy radical could lead to iso[4]-LGE_2 and iso[7]-LGD_2, respectively (Scheme 2), where the number in brackets signifies the length of the carboxylic side chain appended to a levulinaldehyde core. To provide a practical source of supply for biological testing and authentic samples for mass spectral identification of derivatives

Scheme 1



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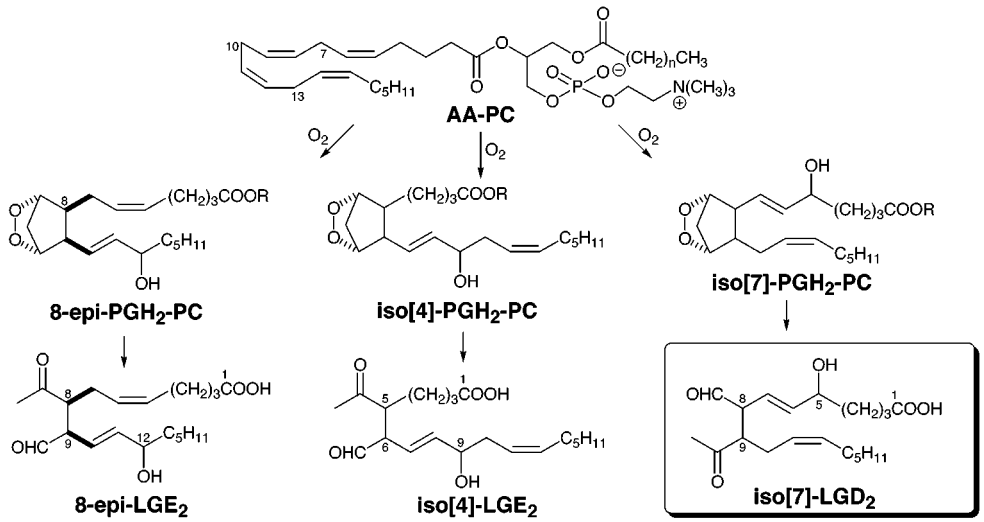
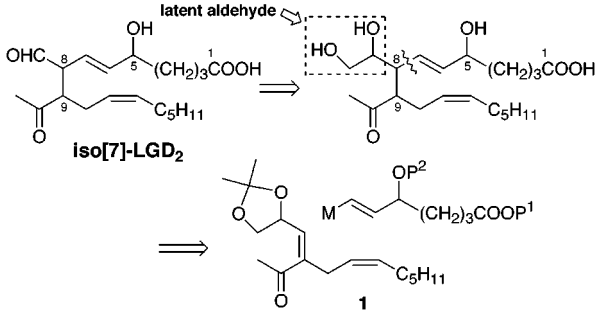
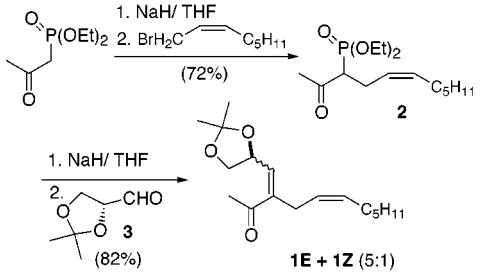
Scheme 2



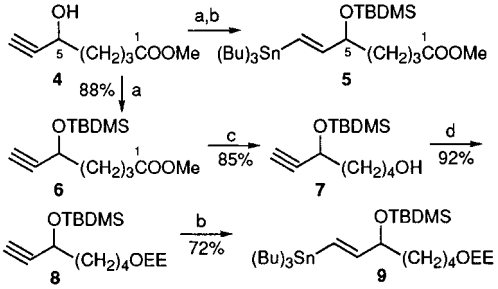
Scheme 3



Scheme 4



Scheme 5



(a) TBDMS-Cl, imidazole, DMF, 15 h, rt; (b) Bu_3SnH, AIBN, 130 °C, 2 h; (c) LAH, Et_2O, 0 °C, 2h; (d) ethyl vinyl ether, PPTS, CH_2Cl_2, 1 h, rt.

produced from naturally occurring iso-LGs, we now report a synthesis of iso[7]-LGD_2.

Results and Discussion

A convergent synthetic strategy (Scheme 3) similar to that used previously for the total syntheses of LGE_2 and iso[4]-LGE_2 was adopted.[9,10] Thus, a vicinal diol is exploited as a latent aldehyde, and 1,4-addition of a vinyl nucleophile to a γ-alkoxy enone is used as the key carbon−carbon bond-forming step. Because two (C8 and C9) of the three stereocenters in iso[7]-LGD_2 will be destroyed upon condensation with ϵ-amino groups in lysyl residues of proteins to generate pyrroles and also because free radical oxidation is expected to generate iso[*n*]-LGs as stereoisomeric mixtures, no effort was made to achieve stereocontrol. The primary synthetic challenges were to devise an appropriately masked derivative of the requisite multifunctional vinyl nucleophile and to generate the sensitive functional array of the final product without, inter alia, dehydration or rearrangement of the vinylogous aldol moiety. Furthermore, in contrast with LGE_2 and iso[4]-LGE_2, which have carboxyl and hydroxyl functionality well separated, the proximity of these functional groups in iso[7]-LGD_2 was cause for concern. In fact, lactonization of the neighboring carboxyl and allylic hydroxyl groups nearly derailed the synthetic plan (vide infra).

Michael Acceptor and Vinyl Nucleophile Synthons. The Michael acceptor **1** for the iso[7]-LGD_2 carbon skeleton was assembled by alkylation of diethylphosphonoacetone with 1-bromo-*cis*-2-octene, followed by Horner−Emmons condensation with isopropylidene-D-glyceraldehyde (**3**)[11] (Scheme 4). Multifunctional vinylstananes were assembled from methyl 5-hydroxy-6-heptynoate (**4**) (Scheme 5). Direct hydrostannylation provided **5**. However, attempts to generate a vinyl cuprate by the reaction of **5** with $Li_2Me_2Cu(CN)$ indicated loss of the carbomethoxyl. Therefore, an indirect synthesis was required which carried the desired carboxyl functionality in a less reactive, latent form. Thus, reduction of the carbomethoxyl in silyl ether **6** followed by masking the resulting alcohol **7** as an α-ethoxyethyl (EE) ether in **8** and hydrostannylation delivered vinylstanane **9**.

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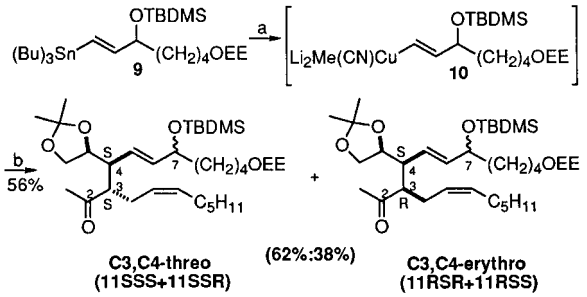
Scheme 6

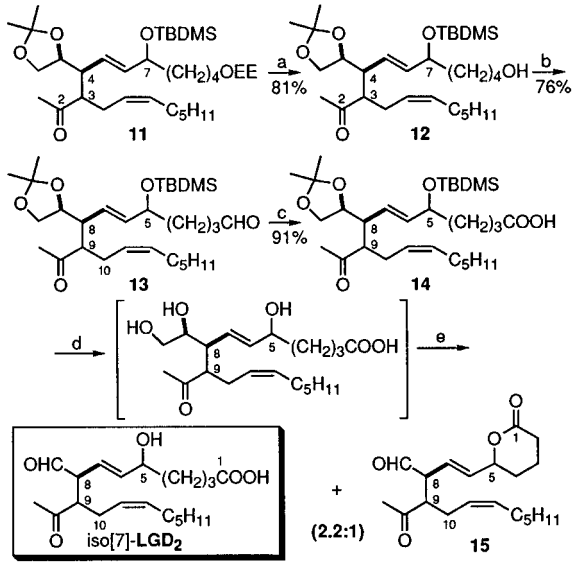


(a) CuCN, MeLi, THF, then **9**, rt, 1.5 h; (b) **1**, THF, −78 °C, 10 min, then −30 °C, 10 min.

Construction of the Iso[7]-LGD$_2$ Skeleton. The higher order cyanocuprate **10** was prepared by transmetalation of vinylstannane **9** with $Li_2Me_2Cu(CN)$.[12] Addition of a mixture of isomeric enones **1E** and **1Z** (5:1) to the higher order vinylcyanocuprate **10** provided a mixture of diastereomeric conjugate addition products **11**. The diastereomeric products were separated by flash column chromatography to provide C3,C4-threo (**11SSS** + **11SSR**)[13] and C3,C4-erthyro (**11RSR** + **19RSS**)[13] isomers in the ratio of 62:38 (Scheme 6). The overall yield of conjugate addition products was 65% based on the enone reacted. The stereochemical assignments are based on the similarity in the C3 proton resonance chemical shifts to those of the similar C5 and C8 protons in the corresponding conjugate addition products reported previously for analogous iso[4]-LGE$_2$ and LGE$_2$ precursors. This resonance comes at δ 2.94−3.10 for the erythro diastereomers and δ 2.60−2.84 for the threo diastereomers.[9,10]

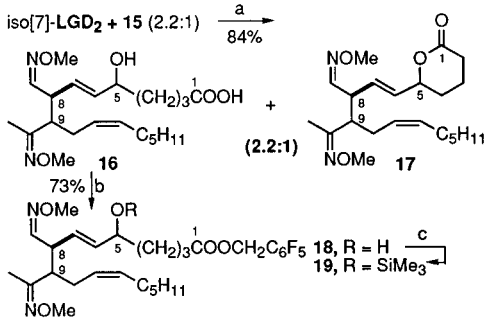
Final Adjustments of Functionality. The carboxyl group was regenerated by a mild three-step sequence (Scheme 7). Selective deprotection of the requisite primary hydroxyl in **11** was achieved by PPTS-catalyzed transacetalization. The primary alcohol in **12** was then converted by Swern oxidation to an aldehyde **13**, which was then oxidized further to provide the carboxylic acid **14**. Intermediate **14** is a stable precursor, suitable for long-term storage, which can be converted in a one-pot procedure into iso[7]-LGD$_2$. Thus, treatment with warm aqueous acetic acid removes the acetonide and silyl ether protecting groups. Subsequent addition of sodium periodate to the reaction mixture cleaves the vicinal diol to deliver the aldehyde group. However, this sequence also produces the lactone **15**. Because variations of the reaction times failed to change the ratio of iso[7]-LGD$_2$ to its lactone, it appears that an equilibrium mixture of lactone and free acid is generated, probably at the vicinal diol stage, by reversible acid-catalyzed nucleophilic substitution at the reactive allylic position. It is noteworthy that similarly acidic environments occur in vivo, e.g., inside the lysosomes that process oxidatively modified LDL, where lactonization of iso[7]-LGD$_2$ or its protein-bound derivatives might be promoted. Therefore, such lactones may be useful indicators of acidic processing in vivo. Fortunately, the isoLG lactone and free acid are readily separable by extraction of iso[7]-LGD$_2$ into aqueous bicarbonate solution, from which it is readily recovered after acidification with KH_2PO_4.

Scheme 7



(a) PPTS, *i*-PrOH−Et_2O (1:1), rt, 4 h; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N; (c) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH−H_2O (5:1), rt, 3 h; (d) AcOH−H_2O (2:1), 40 °C, 4 h; (e) $NaIO_4$, acetone−H_2O (30%), rt, 1.75 h.

Scheme 8



(a) $MeONH_3Cl$, py, rt, 24 h; (b) $C_6F_5CH_2Br$, *i*-Pr_2NH, MeCN, rt, 6 h; (c) BTMSTFA, DMF, 15 min, 37 °C.

Iso[7]-LGD$_2$ Methoxime Derivatives. Because iso[7]-LGD$_2$ is a chemically sensitive vinylogous β-hydroxy aldehyde, it is not expected to survive gas chromatography. However, in analogy with PGD$_2$ and other LG isomers, it was expected to be converted into a stable methoxime derivative upon treatment with methoxylamine hydrochloride in pyridine.[14] Furthermore, methoxime derivatives of PGs having sensitive β-ketol functionality are suitable for GC analysis, and pentafluorobenzyl (PFB) esters of methoxime trimethylsilyl (TMS) ethers of these PGs have been exploited for GC−MS analysis.[15]

Reaction of a mixture of iso[7]-LGD$_2$ and the lactone **15** with methoxylamine hydrochloride in pyridine proceeds cleanly to give the bismethoximes **16** and **17**, that are stable and readily separable by flash chromatography (Scheme 8). The pentafluorobenzyl ester **18** was prepared by treatment of **16** with pentafluorobenzyl bromide and diisopropylamine. For mass spectral analysis, the hydroxyl group in **18** was silylated by treatment with *N*,*N*′-bis(trimethylsilyl)trifluoroacetamide to provide **19**.

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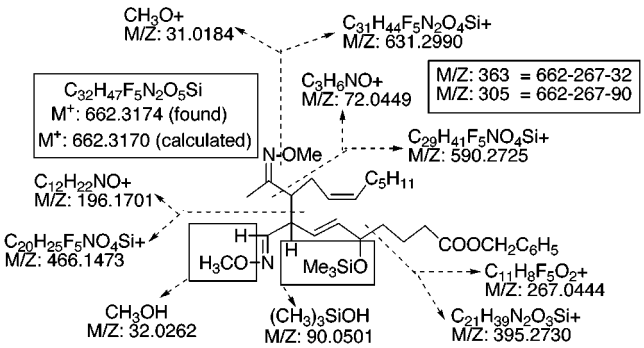
Chart 1. Characteristic Ions from Iso[7]-LGD$_2$ Derivative 19



Mass Spectral Characterization of Iso[7]-LGD$_2$. Characteristic mass spectral fragments of iso[7]-LGD$_2$ derivative **19** are summarized in Chart 1. The fragmentation pattern is reminiscent of those of the corresponding iso[4]-LGE$_2$ and LGE$_2$ derivatives. Thus, all of the LGs and isoLGs show intense $C_3H_6NO^+$ ion peaks at *m/z* 72 which correspond to the methoxime derivative of an acylium ion (*m/z* 43), as well as parent ions at *m/z* 662 and ions at *m/z* 590, corresponding to loss of the methoxime of an acyl group.

Especially characteristic of the iso[7]-LGD$_2$ derivative **19** are ions at *m/z* 466 and 196 corresponding to fragmentation of the molecule between the acetyl- and formyl-substituted tertiary carbons. In contrast, the corresponding derivatives of iso[4]-LGE$_2$ and LGE$_2$ show similar fragmentations resulting in ions at *m/z* 310 and 352 and *m/z* 270 and 392, respectively. Another characteristic fragmentation of LG and isoLG bismethoxime pentafluorobenzyl ester trimethylsilyl ether derivatives occurs between the silyloxy substituted allylic carbon and a neighboring methylene group. For the iso[7]-LGD$_2$ derivative **19**, this fragmentation gives ions at *m/z* 395 and 267. Similar fragmentations of the corresponding iso[4]-LGE$_2$ and LGE$_2$ derivatives give ions at *m/z* 551 and 111 or 591 and 71, respectively. GC−MS experiments using the iso[7]-LGD$_2$ derivative **19** as an authentic standard to detect and confirm the production of iso[7]-LGD$_2$ during in vitro free radical oxidation of arachidonic acid are planned.

Using isoLGs now available by total syntheses, we recently developed immunoassays for selectively detecting iso[7]- and iso[4]-LGE$_2$-protein adducts in vitro and in vivo. These studies will be reported elsewhere.

Experimental Procedures

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and are reported as described previously.[9] High-resolution mass spectra, solvent purification, and chromatography were performed as usual.[9] All reactions conducted in an inert atmosphere were in argon unless otherwise specified. (*Z*)-1-Bromo-2-octene[16] and isopropylidene-D-glyceraldehyde (**3**)[11] were prepared by literature procedures.

(*Z*)-3-Diethylphosphono-2-oxo-5-undecene (2). To a magnetically stirred suspension of NaH (232 mg, 95% pure, 9.18 mmol) in anhydrous THF (5 mL) at 0 °C was added dropwise a solution of diethyl phosphonoacetone[9,10] (1.91 g, 9.98 mmol) in THF (5 mL) during 30 min. The reaction mixture was allowed to stir for 30 min at that temperature and 4 h at room temperature until all the NaH was dissolved to form a clear yellow solution. Then the solution was cooled to −10 °C, and (*Z*)-1-bromo-2-octene (1.5 g, 7.85 mmol) was added dropwise. The cooling bath was removed, and the reaction mixture was stirred for 20 h at room temperature. The resulting solution was concentrated under reduced pressure, and the residue obtained was treated with 10% HCl (10 mL) and extracted with diethyl ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). After removal of solvent under reduced pressure, the residue was flash chromatographed over silica gel (40% ethyl acetate in hexanes) to afford the alkenyl phosphonate **2** (1.72 g, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.44−5.35 (m, 1H), 5.22−5.14 (m, 1H), 4.16−4.04 (4H), 3.13 (ddd, J = 23.1, 10.8, 3.9 Hz, 1H), 2.76−2.65 (m, 1H), 2.53−2.41 (m, 1H), 2.26 (s, 3H), 2.05−2.00 (m, 2H), 1.35−1.09 (12H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.37, 132.83, 125.58 and 125.37 (d, J = 63.3 Hz, C7 split by ^{31}P), 62.50, 54.52, 52.88, 31.49, 29.16, 27.20, 24.40, 22.53, 16.40, 16.33, 14.07, 14.03; HRMS (20 ev) M^+ calcd for $C_{15}H_{29}O_4P$ 304.1803, found 304.1803.

5(*Z*)-3-[(3,3-Dimethyl-2,4-dioxolanyl)methylene]-undec-5-en-2-ones (1E and 1Z). A magnetically stirred suspension of NaH (101 mg, 95% pure, 3.95 mmol) in anhydrous THF (5 mL) was cooled to −5 °C. A solution of β-ketophosphonate **2** (1 g, 3.29 mmol) in THF (5 mL) was added dropwise during 20 min. Stirring was continued for 4 h at this temperature. Then a solution of freshly prepared isopropylidene-D-glyceraldehyde (**3**) (610 mg, 3.95 mmol) in THF (3 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, and the stirring was continued for an additional 12 h. Then the solvent was removed by rotary evaporation. Water (20 mL) was added to the brown residue, and the mixture was extracted with diethyl ether. The combined organic extracts were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the light yellow residue was subjected to flash chromatography over silica gel (10% ethyl acetate in hexanes) to furnish **1Z** (R_f = 0.47, 125 mg, 14%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (d, J = 7.9 Hz, 1H), 5.57−5.49 (m, 1H), 5.33−5.25 (m, 1H), 4.87 (q, J = 7.1 Hz, 1H), 4.28 (dd, J = 14.9, 6.8 Hz, 1H), 3.54 (dd, J = 14.9, 6.8 Hz, 1H), 3.02 (d, J = 7.1 Hz, 2H), 2.23 (s, 3H), 2.05−1.97 (m, 2H), 1.41 (s, 3H), 1.33 (s, 3H), 1.46−1.20 (6H), 0.86 (t, J = 6.9 Hz, 3H); HRMS (20 ev) M^+ calcd for $C_{17}H_{28}O_3$ 280.2038, found 280.2045 and **1E** (R_f = 0.42, 630 mg, 68%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.48 (d, J = 7.9 Hz, 1H), 5.37−5.29 (m, 1H), 5.11−5.03 (m, 1H), 4.88 (q, J = 7.3 Hz, 1H), 4.13 (t, J = 7.9 Hz, 1H), 3.59 (t, J = 7.9 Hz, 1H), 3.11−2.95 (m, 2H), 2.29 (s, 3H), 2.10−2.03 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.43−1.21 (6H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.63, 142.97, 129.73, 131.17, 126.41, 110.01, 72.86, 69.00, 31.58, 29.15, 29.01, 27.37, 26.68, 25.84, 24.29, 22.58, 14.06; HRMS (20 ev) M^+ calcd for $C_{17}H_{28}O_3$ 280.2038, found 280.2045. The mixture of **1E** and **1Z** isomers (5:1) was used without separation for the next reaction.

Methyl 5-(1,1,2,2-Tetramethyl-1-silapropoxy)hept-6-ynoate (6). A solution of methyl 5-hydroxy-6-heptynoate (**4**)[17] (2.22 g, 14.23 mmol), *tert*-butyldimethylsilyl chloride (3.22 g, 21.35 mmol), and imidazole (2.9 g, 42.69 mmol) in dry DMF (45 mL) was stirred at room temperature under N_2 for 15 h. The reaction mixture was then poured into a mixture of hexanes (25 mL) and saturated aqueous $NaHCO_3$ (45 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an oily residue. The residue was purified by column chromatography over silica gel (1% ethyl acetate in hexanes) to furnish **6** (4.42 g, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35−4.34 (dt, J = 6.3, 2.1 Hz, 1H), 3.65 (s, 3H), 2.37−2.31 (3H), 1.78−1.67 (4H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.70, 85.07, 72.36, 62.31, 51.41, 37.70, 33.57, 25.72, 20.56, 18.14, −4.61, −5.14; HRMS (20 ev) M^+ − H calcd for $C_{14}H_{25}O_3Si$ 269.1573, found 269.1568.

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5-(1,1,2,2-Tetramethyl-1-silapropoxy)hept-6-yn-1-ol (7). A solution of the ester **6** (2.25 g, 9.25 mmol) in anhydrous diethyl ether (4 mL) was added dropwise to an ice-cold suspension of lithium aluminum hydride (370 mg, 95% pure, 9.25 mmol) in diethyl ether (16 mL) under N_2. After 2 h of stirring at 0 °C, the reaction was quenched by addition of ethyl acetate (1 mL). The lithium salts were precipitated by sequential addition of water (400 μL), NaOH (400 μL, 6 N), and water (1.2 mL). The white salts were removed by filtration, and the resulting solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oily residue that was purified by flash chromatography over silica gel (25% ethyl acetate in hexanes) to furnish the alcohol **7** (1.91 g, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35−4.29 (dt, J = 6.3, 2.1 Hz, 1H), 3.64−3.59 (t, J = 6.3 Hz, 2H), 2.8−2.6 (bs, 1H) 2.35−2.34 (d, J = 2.1 Hz, 1H), 1.71−1.44 (6H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s,3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 85.43, 72.21, 62.67, 62.37, 38.21, 32.22, 25.95, 25.75, 21.32, 18.17, −4.59, −5.08; HRMS (20 ev) M^+ − H calcd for $C_{13}H_{25}O_2Si$ 241.1624, found 241.1624.

1-(1-Ethoxyethoxy)-5-(1,1,2,2-tetramethyl-1-silapropoxy)-hept-6-yne (8). Ethyl vinyl ether (1.11 g, 15.47 mmol) was added to an ice-cold solution of the alcohol **7** (1.9 g, 7.85 mmol) and PPTS (65 mg, 0.26 mmol) in CH_2Cl_2 (24 mL) under Ar. The solution was stirred for 1 h at room temperature and then poured into a 1:1 mixture of hexanes and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford pure **8** (2.3 g, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4 0.72−4.61 (apparent q, J = 5.1 Hz, 1H), 4.32−4.28 (dt, J = 6.3, 2.1 Hz, 1H), 3.62−3.38 (4 H), 2.35−2.34 (d, J = 1.8 Hz, 1H), 1.69−1.46 (6H), 1.29−1.27 (d, J = 5.4 Hz, 3H), 1.20−1.16 (t, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 99.38, 85.42, 72.06, 64.77, 62.56, 60.46, 38.27, 29.43, 25.70, 21.87, 19.73, 18.11, 15.26, −4.62, −5.16; HRMS (20 ev) M^+ − H calcd for $C_{17}H_{33}O_3Si$ 313.2198, found 313.2196.

8,8-Dibutyl-1-(1-ethoxyethoxy)-5-(1,1,2,2-tetramethyl-1-silapropoxy)-8-stannadodec-6-ene (9). A mixture of Bu_3-SnH (2.99 g, 10.29 mmol), alkyne **8** (2.25 g, 7.16 mmol), and AIBN (14 mg) was heated on an oil bath at 130 °C for 2 h under an inert atmosphere and then cooled to room temperature. The residue was purified by flash chromatography over silica gel (2% ethyl acetate in hexanes) to afford **9** (3.1 g, 72%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.03−5.90 (m, 2H), 4.67−4.65 (apparent q, J = 5.4 Hz, 1H), 4.01−3.99 (apparent q, J = 5.4 Hz, 1H), 3.65−3.36 (4H), 1.58−1.16 (36H), 0.94−0.77 (12H), 0.02 (s, 3H), 0.003 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.87, 126.51, 99.47, 76.73, 65.20, 65.10, 60.54, 60.48, 37.88, 29.89, 29.13, 27.25, 25.93, 22.15, 19.83, 15.32, 13.72, 9.43, −4.27, −4.79; HRMS (20 ev) M^+ − C_4H_9 calcd for $C_{25}H_{53}O_3SiSn$ 547.2780, found 547.2786.

11-(1-Ethoxyethoxy)-4-(3,3-dimethyl-2,4-dioxolanyl)-7-(1,1,2,2-tetramethyl-1-silapropoxy)-3-oct-2(*Z*)-enylundec-5(*E*)-en-2-one (11). Copper cyanide (46 mg, 0.51 mmol, flame-dried under Ar) in anhydrous THF (1 mL) was treated with MeLi (770 μL, 1.4 M, 1.08 mmol) at 0 °C. The cooling bath was removed and vinyl stannane **9** (378 mg, 0.51 mmol) in THF (0.5 mL) was added dropwise with an airtight syringe. After 1.5 h of stirring at room temperature, the reaction mixture was cooled to −78 °C with a dry ice−acetone bath. Then, the enone **1** (100 mg, 0.36 mmol) in THF (0.5 mL) was added dropwise. After 10 min of stirring at −78 °C and 10 min of stirring at −30 °C, the reaction mixture was quenched with a solution of saturated aqueous NH_4Cl and NH_4OH (9:1, v/v, 10 mL). The resulting mixture was extracted with diethyl ether. The combined organic extracts were successively washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was flash chromatographed over silica gel (12% ethyl acetate in hexanes) to afford the threo isomers **11SSS** and **11SSR** (R_f = 0.28, 86 mg) and erythro isomers **11RSR** and **11RSS** (R_f = 0.34, 54 mg). The ratio of threo and erythro isomers was 1.6:1. The overall yield was 65%. **Erythro isomers (11RSR** and **11RSS):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.49−5.22 (4H), 4.67 (q, J = 5.4 Hz, 1H), 4.05−3.88 (3H), 3.67−3.35 (5H), 3.08−3.01 (m, 1H), 2.33−2.23 (m, 2H), 2.18 (s, 3H), 2.17−1.94 (3H), 1.63−1.17 (24H), 0.93−0.83 (12H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.04, 138.47, 132.24, 126.40, 125.41, 109.37, 99.52, 76.19, 73.02, 69.12, 65.23, 65.10, 60.63, 60.54, 52.29, 49.88, 38.41, 32.35, 31.58, 29.91, 29.29, 28.21, 27.38, 26.99, 25.87, 25.63, 22.61, 22.03, 19.88, 18.23, 15.36, 14.10, −4.6, −4.81; HRMS (20 ev) M^+ calcd for $C_{34}H_{64}O_6Si$ 596.4472, found 596.4461. **Threo isomers (11SSS** and **11SSR):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.54−5.13 (4H), 4.62 (q, J = 5.5 Hz, 1H), 4.03−3.84 (3H), 3.61−3.29 (5H), 2.69−2.64 (m,1H), 2.51−2.47 (m, 1H), 2.28−1.81 (7H, including two singlets at 2.08 and 2.07), 1.54−1.12 (24H), 0.85−0.75 (12H), 0.00- −0.04 (6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.69, 138.30, 132.05, 131.98, 126.38, 126.25, 125.62, 125.53, 125.33, 109.56, 99.51, 72.66, 72.61, 68.81, 68.70, 65.14, 65.03, 60.54, 54.75, 54.55, 49.64, 38.23, 31.56, 30.93, 30.77, 29.86, 29.28, 27.45, 27.32, 27.17, 26.92, 26.77, 26.43, 26.32, 25.82, 25.62, 22.58, 22.03, 21.86, 19.85, 18.18, 15.33, 14.07, −4.43, −4.81; HRMS (20 ev) M^+ calcd for $C_{34}H_{64}O_6Si$ 596.4472, found 596.4470. The mixture of isomers without purification was used for the next reaction.

4-(3,3-Dimethyl-2,4-dioxolanyl)-11-hydroxy-7-(1,1,2,2-tetramethyl-1-silapropoxy)-3-oct-2(*Z*)-enylundec-5(*E*)-en-2-one (12). A mixture of the α-ethoxyethyl ether **11** (93 mg, 0.16 mmol) and PPTS (10 mg, 0.04 mmol) in 2-propanol−diethyl ether (1:1, v/v, 2 mL) was stirred for 4 h at room temperature under Ar. Then the volatiles were removed under reduced pressure. Saturated aqueous $NaHCO_3$ (2 mL) was added to the residue. The resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and filtered. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (25% ethyl acetate in hexanes) to furnish the threo isomers **12SSS** and **12SSR** (R_f = 0.23, 41 mg, 43%) and the erythro isomers **12RSR** and **12RSS** (R_f = 0.27, 26 mg, 38%). The overall yield was 81% and the ratio of threo and erythro isomers was 1.6:1. **Erythro isomers (12RSR** and **12RSS)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.49−5.20 (4H), 4.04 (q, J = 5.6 Hz, 1H), 4.07−3.87 (m, 2H), 3.63−3.50 (3H), 3.07−3.00 (m, 1H), 2.33−2.24 (m, 2H), 2.16 (s, 3H), 2.15−1.93 (3H), 1.58−1.17 (19H, including two singlets at 1.39 and 1.31), 1.06−0.81 (12H), 0.007 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.27, 138.33, 132.30, 126.31, 125.55, 109.41, 76.24, 73.09, 69.11, 62.87, 52.41, 49.81, 38.15, 32.72, 32.34, 31.57, 29.28, 28.23, 27.38, 26.98, 25.86, 25.62, 22.60, 21.36, 18.23, 14.09, 1.04, −4.40, −4.79; HRMS (20 ev) M^+ calcd for $C_{30}H_{56}O_5Si$ 524.3897, found 524.3884. **Threo isomers (12SSS** and **12SSR):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55−5.11 (4H), 4.08−3.83 (3H), 3.63−3.46 (3H), 2.81−2.68 (m, 1H), 2.53−2.43 (m, 1H), 2.38−2.27 (m, 1H), 2.14 and 2.12 (two apparent singlets, 3H), 2.16−1.86 (3H), 1.54−1.18 (19H), 0.81−0.79 (12H), −0.01- −0.06 (6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.54, 214.20, 138.57, 138.36, 138.19, 132.55, 132.37, 126.11, 125.78, 125.57, 125.11, 109.89, 76.14, 72.82, 72.75, 72.25, 68.82, 68.73. 68.65, 62.95, 55.10, 54.85, 53.18, 49.75, 49.47, 37.80, 32.16, 31.52, 30.79, 30.66, 29.23, 28.03, 27.31, 27.15, 26.98, 26.79, 26.42, 26.29, 26.07, 25.98, 25.80, 25.47, 22.55, 21.13, 21.05, 20.98, 20.83, 20.58, 18.17, 14.05, −4.44, −4.85; HRMS (20 ev) M^+ calcd for $C_{30}H_{56}O_5Si$ 524.3897, found 524.3897. The mixture of threo and erythro isomers without purification was used for the next reaction.

9-Acetyl-8-(3,3-dimethyl-2,4-dioxolanyl)-5-(1,1,2,2-tetramethyl-1-silapropoxy)-heptadeca-6(*E*),11(*Z*)-dienal (13). To a magnetically stirred solution of oxalyl chloride (97 mg, 0.76 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C under Ar was added dropwise a solution of DMSO (120 mg, 1.53 mmol) in CH_2Cl_2 (1 mL). After 10 min, a solution of the alcohol **12** (200 mg, 0.38 mmol) in CH_2Cl_2 (4 mL) was added dropwise to the reaction mixture, and stirring was continued for 1 h at that temperature. Et_3N (311 mg, 3.07 mmol) was added dropwise to the reaction mixture, which was then stirred for 30 min at −78 °C and 30 min at room temperature and then quenched with water (5 mL). The resulting mixture was extracted with diethyl ether. The ether layer was washed with brine, dried

($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (10% ethyl acetate in hexanes) to afford the threo isomers **13SSS** and **13SSR** (R_f = 0.42, 95 mg, 47%) and the erythro isomers **13RSR** and **13RSS** (R_f = 0.47, 59 mg, 29%). The overall yield was 76%, and the ratio of threo and erythro isomers was 1.6:1. **Erythro isomers (13RSR** and **13RSS)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1H), 5.53−5.15 (4H), 4.10−4.04 (m, 1H), 3.95−3.86 (m, 2H), 3.55−3.49 (m, 1H), 3.06−3.00 (m, 1H), 2.42−2.22 (4H), 2.16 (s, 3H), 2.09−1.91 (3H), 1.68−1.20 (16H), 0.91−0.77 (12H), 0.07−0.005 (6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.07, 202.31, 137.90, 132.29, 126.30, 125.93, 109.41, 76.15, 72.78, 72.66, 69.10, 52.20, 49.86, 43.77, 37.78, 32.43, 31.58, 29.27, 28.28, 27.38, 26.99, 25.85, 25.61, 22.60, 18.19, 17.82, 14.09, −4.38, −4.84; HRMS (20 ev) M^+ calcd for $C_{30}H_{54}O_5Si$ 522.3740, found 522.3746. **Threo isomers (13SSS** and **13SSR)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (d, J = 3 Hz, 1H), 5.74−5.15 (4H), 4.09−4.01 (m, 1H), 3.99−3.79 (m, 2H), 3.58−3.44 (m, 1H), 2.99−2.20 (4H), 2.19−1.84 (7H), 1.76−1.62 (16H), 0.90−0.71 (12H), −0.01 to −0.10 (6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.86, 210.51, 202.16, 137.87, 137.74, 132.50, 132.00, 126.36, 126.22, 125.74, 125.56, 109.57, 109.34, 76.05, 75.82, 72.52, 72.15, 68.86, 68.64, 54.59, 54.09, 52.50, 49.74, 49.51, 43.72, 37.76, 37.59, 32.46, 32.31, 31.55, 31.34, 30.88, 30.72, 29.26, 29.06, 28.29, 27.31, 27.16, 26.91, 26.47, 26.35, 26.13, 25.80, 25.59, 22.57, 18.15, 17.61, 14.06, −4.34, −4.87; HRMS (20 ev) M^+ calcd for $C_{30}H_{54}O_5Si$ 522.3740, found 522.3742. The mixture of threo and erythro isomers without purification was used for the next reaction.

9-Acetyl-8-(3,3-dimethyl-2,4-dioxolanyl)-5-(1,1,2,2-tetramethyl-1-silapropoxy)-heptadeca-6(*E*),11(*Z*)-dienoic Acid (14). To a magnetically stirred solution of the aldehyde **13** (125 mg, 0.24 mmol) in *tert*-butyl alcohol−water (5:1, v/v, 4 mL) was added successively NaH_2PO_4 (40 mg, 0.30 mmol), 2-methyl-2-butene (110 μL, 1.4 mmol), and $NaClO_2$ (65 mg, 0.70 mmol).[18] The mixture was stirred for 3 h at room temperature. Volatiles were removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (50% ethyl acetate in hexanes) to furnish the acid **14** (R_f = 0.25, 116 mg, 91%) as a mixture of threo and erythro isomers in a ratio of 2.8:1. The ratio was determined from the integral area for the C9 hydrogen resonance for the erythro isomer at δ 2.98 and for the threo isomer at δ 2.74. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73−5.18 (4H), 4.10−4.05 (m, 1H), 4.03−3.83 (m, 2H), 3.61−3.48 (m, 1H), 3.03−1.90 (11H), 1.60−1.13 (16H), 0.99−0.74 (12H), 0.04−0.01 (6H); HRMS (20 ev) $M^+ - CH_3$ calcd for $C_{29}H_{51}O_6Si$ 523.3338, found 523.3454. The unseparated mixture of erythro and threo diastereomeric acids **14** was used for the next step.

Iso[7]-LGD$_2$ (9-Acetyl-8-formyl-5-hydroxy-6(*E*),11(*Z*)-heptadecadienoic Acid) and 3-Acetyl-2-(2-(3-oxo(2-oxanyl))vinyl)undec-5(*Z*)-enal (15). A magnetically stirred solution of the acid **14** (20 mg, 0.036 mmol) in acetic acid−water (1 mL, 2:1, v/v) was warmed to 40 °C. After 4 h of stirring, TLC analysis showed that the resulting solution contained completely deprotected triol acid, R_f = 0.15 (20% 2-propanol/1.5% acetic acid in hexanes, v/v/v). This solution was then added to a solution of $NaIO_4$ (12 mg, 0.056 mmol) in acetone−water (5 mL, 3:7, v/v). After 1.75 h of stirring at room temperature, the reaction was quenched by addition of ethylene glycol (15 mg, 0.24 mmol). After an additional 15 min of stirring, the reaction mixture was extracted with diethyl ether. The ether layer was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), dried ($MgSO_4$), and filtered. To the filtrate was added *n*-heptane (50 mL), the solvent volume was reduced to 10 mL under reduced pressure at 20 °C, and another portion of *n*-heptane (25 mL) and diethyl ether (10 mL) was added. The solvents were removed completely under reduced pressure, and the *tert*-butyldimethylsilanol byproduct was removed by vacuum transfer into a trap cooled to −78 °C at 0.01 mmHg for 30 min to afford the lactone **15** (4.1 mg, 30% material balance). The purity of the product was determined by the ratio of the integrated area of the aldehydic proton resonance (two singlets at δ 9.51 and 9.39, 1H) to the proton attached to the oxygenated carbon of the lactone ring (δ 4.85−4.75, m, 1H). The integrated area of the aldehydic resonance was 57% of the expected value relative to that of the proton at C5 of the lactone ring. Characteristic resonances of the lactone **15** and their assignments include δ 9.51 and 9.39 (2s, 1H, CHO), 5.81−5.14 (4H, olefinic protons), 4.85−4.75 (m, 1H, CH−O−), 3.57−3.47 (m, 1H, CH), 3.03−2.95 (m, 1H, CH), 2.24 and 2.22 (2s, 3H, $COCH_3$). The chemically sensitive lactone **15** was further characterized as a stable bismethoxime (vide infra).

The aqueous bicarbonate extract was carefully acidified with 5% aqueous KH_2PO_4 (50 mL) and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and filtered. To the filtrate was added *n*-heptane (60 mL), the solvent volume was reduced to 10 mL under reduced pressure at 20 °C, and another portion of *n*-heptane (25 mL) and ethyl acetate (10 mL) was added. The solvents were removed completely under reduced pressure to afford iso[7]-LGD$_2$ (9.6 mg, 70% material balance). The purity of the product was determined by the ratio of the integrated area of the aldehydic proton resonance (two doublets at δ 9.50 and 9.38, J = 4.5 and 6 Hz, respectively, 1H) to the proton at C5 (δ 4.19−4.05, m, 1H). The integrated area of the aldehydic resonance was 49% of the expected value relative to that of the proton at C5. Characteristic resonances of iso[7]-LGD$_2$ and their assignments include δ 9.50 and 9.38 (2d, J = 4.5 and 6 Hz, respectively, 1H, CHO), 5.80−5.16 (4H, olefinic protons), 4.19−4.05 (m, 1H, CH−O-), 3.51 (t, J = 9.6 Hz, 1H,CH), 3.01−2.94 (m, 1H, CH), 2.22 (s, 3H, $COCH_3$).

8-(2-Aza-2-methoxyvinyl)-9-(2-aza-1-methyl-2-methoxyvinyl)-5-hydroxyheptadeca-6,11-dienoic Acid (16) and Lactone 17. A solution of a mixture of iso[7]-LGD$_2$ and the lactone **15** (20 mg) and methoxylamine hydrochloride (60 mg, 0.71 mmol) in andydrous pyridine (1 mL) was stirred for 24 h under N_2. TLC analysis showed the presence of two new spots (R_f = 0.14 and 0.50 using 60% ethyl acetate in hexanes). Pyridine was evaporated under a stream of nitrogen, and then water (2 mL) was added to the solid residue. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The oily residue was flash chromatographed over silica gel (60% ethyl acetate in hexanes) to afford the lactone **17** (R_f = 0.50, 6 mg, 25%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, J = 5.8 Hz, 1H), 5.69−5.58 (m, 2H), 5.40−5.34 (m,1H), 5.23−5.15 (m, 1H), 4.81−4.77 (m, 1H), 3.80, 3.79, 3.77, and 3.76 (4 s, 6H), 3.08 (q, J = 8.2 Hz, 1H), 2.60−2.06 (3H), 1.96−1.81 (2H), 1.73−1.42 (7H including two singlets at δ 1.69 and 1.67), 1.36−1.17 (8H), 0.94−0.84 (3H); HRMS (20 ev) M^+ calcd for $C_{22}H_{36}N_2O_4$ 392.2675, found 392.2669 and the acid **16** (R_f = 0.14, 14 mg, 59%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, J = 5.8 Hz, 1H), 5.69−5.50 (2H), 5.47−5.34 (m, 1H), 5.23−5.15 (m, 1H), 4.11−4.02 (m, 1H), 3.80, 3.79, and 3.76 (3 s, 6H), 3.09−3.01 (m,1H), 2.55−2.05 (3H), 1.95−1.81 (2H), 1.77−1.40 (7H including two singlets at δ 1.69 and 1.67), 1.37−1.11 (8H), 0.85 (t, J = 6.5 Hz, 3H); HRMS (20 ev) M^+ calcd for $C_{22}H_{38}N_2O_5$ 410.2780, found 410.2766.

(2,3,4,5,6-Pentafluorophenyl)methyl 8-(2-Aza-2-methoxyvinyl)-9-(2-aza-1-methyl-2-methoxyvinyl)-5-hydroxyheptadeca-6(*E*),11(*Z*)-dienoate (18). To a solution of the acid **16** (6 mg, 0.015 mmol) and diisopropylamine (10 mg, 0.09 mmol) in acetonitrile (500 μL) was added a solution of pentafluorobenzyl bromide (15 mg, 0.07 mmol) in acetonitrile (100 μL). The reaction mixture was stirred for 6 h at room temperature. TLC analysis in 25% ethyl acetate in hexanes revealed disappearance of the starting material and appearance of two new spots. The solvent was removed in vacuo, and the residue was purified by HPLC using 30% ethyl acetate in hexanes as eluent at a flow rate of 2 mL/min. The major isomer (3.7 mg, 45%) had a retention time of 8.0 min, and the minor isomer (2.3 mg, 28%) had a retention time of 10.0 min. **Major isomer:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, J = 8.6 Hz, 1H), 5.61−5.55 (2H), 5.42−5.34 (m, 1H), 5.24−5.14 (3H, including a singlet at δ 5.17), 4.10−4.06 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.09−3.01 (m, 1H), 2.46−1.90 (8H), 1.77−1.44 (7H, including a singlet at δ 1.69), 1.35−1.19 (6H), 0.85 (t, J = 6.6

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Table 1. HRMS of Iso[7]-LGD$_2$ Derivative 19

formula	ion	*m*/*z* (calcd)	*m*/*z* (found)	rel intensity
$C_{32}H_{47}F_5N_2O_5Si^+$	M^+	662.3174	662.3170	8.84
$C_{31}H_{44}F_5N_2O_4Si^+$	$M^+ - 31$	631.2990	631.2980	9.56
$C_{27}H_{36}F_5N_2O_5Si^+$	$M^+ - 71$	591.2313	591.2960	0.44
$C_{29}H_{41}F_5N_2O_4Si^+$	$M^+ - 72$	590.2725	590.2728	0.69
$C_{20}H_{25}F_5NO_4Si^+$	$M^+ - 196$	466.1473	466.2151	2.03
$C_{21}H_{39}N_2O_3Si^+$	$M^+ - 267$	395.2730	395.2439	3.32
$C_{18}H_{19}F_5NO_3^+$	$M^+ - 270$	392.1285	392.2624	16.01
$C_{11}H_8F_5O_2^+$	$M^+ - 395$	267.0444	267.1750	3.62
$C_{12}H_{22}NO^+$	$M^+ - 466$	196.1701	196.1675	100
$C_3H_6NO^+$	$M^+ - 590$	72.0449	72.0862	2.25
$C_5H_{11}^+$	$M^+ - 591$	71.0861	71.0845	12.40

Hz, 3H); HRMS (20 ev) M^+ calcd for $C_{29}H_{39}F_5N_2O_5$ 590.2779, found 590.2765. **Minor isomer:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 8.6 Hz, 1H), 5.61−5.57 (2H), 5.49−5.36 (m, 1H), 5.22−5.18 (3H, including a singlet at δ 5.17), 4.11−4.06 (m, 1H), 3.80, 3.79, 3.77 and 3.76 (4 s, 6H), 3.05−3.01 (m, 1H), 2.42−1.90 (8H), 1.79−1.43 (7H, including two singlets at δ 1.69 and 1.67), 1.35−1.18 (6H), 0.85 (t, J = 6.6 Hz, 3H); HRMS (20 ev) M^+ calcd for $C_{29}H_{39}F_5N_2O_5$ 590.2783, found 590.2776. Iso-[7]-LGD$_2$ was further characterized as the TMS ether **19** of **18**.

(2,3,4,5,6-Pentafluorophenyl)methyl 8-(2-Aza-2-methoxyvinyl)-9-(2-aza-1-methyl-2-methoxyvinyl)-5-(1,1-dimethyl-1-silaethoxy)heptadeca-6(*E*),11(*Z*)-dienoate (19). A solution of **18** (1 mg) in DMF (70 μL) was stirred with bis-(trimethylsilyl)trifluoroacetamide (200 μL) at 37 °C for 15 min. The volatiles were removed with a stream of dry nitrogen. The HRMS (20 ev) showed the characteristic ions that were assigned above in Chart 1 and are summarized by calculated and observed exact masses in Table 1.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds (32 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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