JOC Article
pubs.acs.org/joc

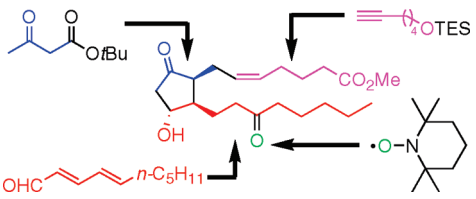
# Toward the Elucidation of the Metabolism of 15-$E_2$-Isoprostane: The Total Synthesis of the Methyl Ester of a Potential Central Metabolite

Ullrich Jahn*,† and Emanuela Dinca‡

†*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo namesti 2, 16610 Prague 6, Czech Republic, and* ‡*Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany*

*jahn@uochb.cas.cz*

*Received April 6, 2010*




An 11-step total synthesis of the methyl ester of a potential metabolite of the autoxidatively formed natural product 15-$E_2$-IsoP, whose metabolism is not known, is reported. Several vinylogous Mukaiyama aldol additions were tested for the assembly of the acyclic C7−C20 precursor. A new oxidative dianion cyclization served to access the cyclopentane core. The full carbon skeleton was synthesized by an acetylide alkylation. The overall yield of the metabolite amounts to 1.4% for the most efficient route. The results demonstrate convincingly that $E_2$-IsoP metabolites are highly epimerization-sensitive and that they may thus also contribute to $PGE_2$-action and metabolism.

## Introduction

The interest in autoxidatively formed oxygenated lipid-derived natural products has grown considerably in recent years. Among them, the isoprostanes (IsoP) are the most prominent members,[1] since they display a wide range of biological activities, which are related to the most incidental human diseases, such as atherosclerosis, inflammation, and neurological disorders like Alzheimer's syndrome.[2] Due to their autoxidative formation from polyunsaturated fatty acids like arachidonic acid (C20:4 $\omega$-6, AA) or eicosapentaenoic acid (C20:5 $\omega$-3, EPA) they form as regio- and stereoisomeric mixtures in vivo. The by far most thoroughly investigated class of IsoPs are the $F_2$-IsoP, namely 15-$F_{2t}$-IsoP (**V**), which is the diastereomer of prostaglandin $F_{2\alpha}$ (**I**) ($PGF_{2\alpha}$) (Scheme 1). $F_2$-IsoP (**V**) are today the gold standard for monitoring oxidative stress in vivo.

The metabolism of PG such as $PGF_{2\alpha}$ (**I**) or $PGE_2$ (**II**) was studied in detail and consists of initial enzymatic oxidation of the 15-alcohol to the ketone and reduction of the 13,14-double bond.[3] The in vivo stability of metabolite **IV** was determined to be very low. The more stable major urinary metabolite of $PGE_2$ was synthesized very recently, but this compound represents a later stage of $PGE_2$ metabolism.[4] The metabolic fate of **V** was also fairly well investigated and proved to follow contrasting pathways in humans and rodents, respectively.[2] Initial degradation of the α-chain to **VI** was found to be the dominant pathway in man, while metabolism in rabbits paralleled that of **I** and **II**[3] giving 13,14-dihydro-15-oxo derivative **VII**. Moreover, it was discovered that $F_2$-IsoP metabolites in contrast to those of $PGF_{2\alpha}$ display biological activities themselves.[2] Another important IsoP is the to $PGE_2$ (**II**) diastereomeric 15-$E_2$-IsoP (**1**).[5] It forms when the reducing capacity of tissues is already impaired. It is also a potent vasoconstrictor, induces the aggregation of platelets, and is the precursor to the potent

(1) Isolation: (a) Morrow, J. D.; Hill, K. E.; Burk, R. F.; Nammour, T. M.; Badr, K. F.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9383–9387. (b) Morrow, J. D.; Awad, J. A.; Boss, H. J.; Blair, I. A.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 10721–10725.

(2) Recent reviews: (a) Jahn, U.; Galano, J. M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894–5955. (b) Forum issue:*Antioxid. Redox Signal.* **2005**, *7*, 153−275. (c) *Chem. Phys. Lip.* **2004**, *128*, Issue 1−2.

(3) Reviews: (a) Marks, F.; Fürstenberger, G. *Prostaglandins, Leukotrienes, and Other Eicosanoids*; Wiley-VCH: Weinheim, 1999. (b) *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*; Willis, A. L., Ed.; CRC Press: Boca Raton, 1987; Vol. 1 + 2.

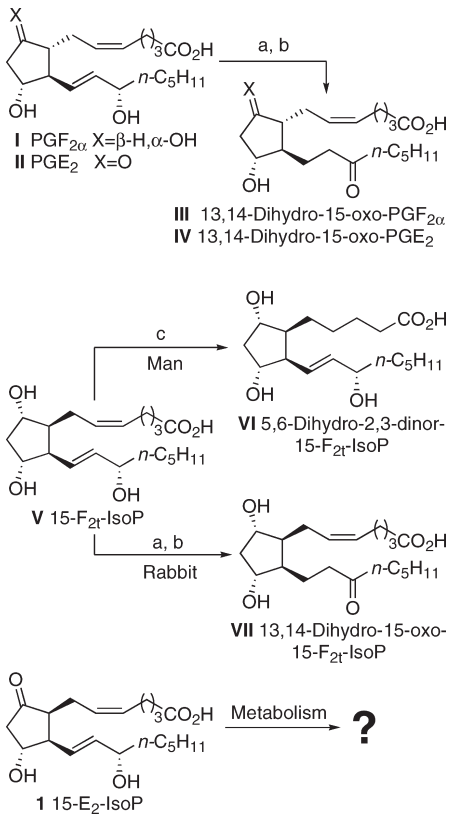
(4) Taber, D. F.; Gu, P. M. *Tetrahedron* **2009**, *65*, 5904–5907.

(5) For two very recent total syntheses of 15-$E_2$-IsoP (**1**) and 15-$D_2$-IsoP, see: (a) Pinot, E.; Guy, A.; Fournial, A.; Balas, L.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2008**, *73*, 3063–3069. (b) Brinkmann, Y.; Oger, C.; Guy, A.; Durand, T.; Galano, J.-M. *J. Org. Chem.* **2010**, *75*, 2411–2414.



Published on Web 06/09/2010 DOI: 10.1021/jo1006569

**SCHEME 1. Initial Metabolic Steps of $PGF_{2\alpha}$, 15-$F_{2t}$-IsoP, and $PGE_2$**




[a]15-PGDH. [b]$\Delta^{13}$-Reductase. [c]$\beta$-Oxidation.

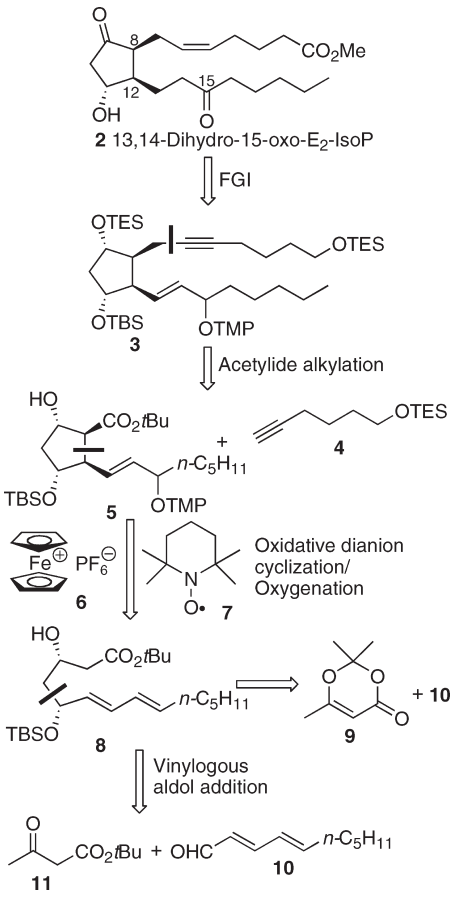
electrophilic A-type IsoP.[2] In contrast to $F_2$-IsoP, nothing is known about the degradation of 15-$E_2$-IsoP in humans and the biological actions of their metabolites.

Thus, there is a great need for making reference compounds and potential metabolites available that may help unraveling the metabolic pathways of potent **1** and the possible biological activities of these metabolites in humans. We reasoned that access to 13,14-dihydro-15-oxo-15-$E_2$-IsoP (**2**) and to racemic 13,14-dihydro-15-oxo-$PGE_2$ (**IV**), which are similar to **III** or **VII**, would be a good starting point to investigate the metabolism of **1** in more detail. We have recently developed one of the shortest total syntheses of 15-$F_{2t}$-IsoP (**V**)[6a] and report here the first synthesis of both compounds 13,14-dihydro-15-oxo-15-$E_2$-IsoP (**2**) and racemic 13,14-dihydro-15-oxo-$PGE_2$ (**IV**).

## Results and Discussion

The strategy for the synthesis of 13,14-dihydro-15-oxo-15-$E_2$-IsoP (**2**) is outlined in Scheme 2. Since **2** as well as other late synthetic intermediates should be very sensitive to epimerization in the 8- and/or 12-position, its retrosynthesis calls for the adjustment of the correct oxidation states of the functionality late in the synthesis after formation of the fully assembled skeleton **3**. This compound can be accessed by alkylation of the lithium acetylide of **4** with the triflate derived from ester **5**. The cyclopentane with the appended

**SCHEME 2. Retrosynthesis of 2**




functionalized $\omega$-chain **5** will be synthesized by an oxidative cyclization of the dianion of **8** triggered by ferrocenium hexafluorophosphate (**6**) and concomitant oxygenation by TEMPO (**7**).[6b] Dihydroxy ester **8** should be prepared by several vinylogous aldol additions of 2,2,6-trimethyldioxin-4-one (**9**) or *tert*-butyl acetoacetate (**11**) to (*E*,*E*)-decadienal (**10**).

The synthesis of **2** commenced with studies on the vinylogous aldol addition of different acetoacetate equivalents to decadienal **10** (Scheme 3). Initially, vinylogous aldol additions starting from 2,2,6-trimethyl-1,3-dioxin-4-one (**9**) and decadienal **10** were explored.[6b,7] Using LDA for deprotonation and addition of **10** led to a mixture of the desired kinetic vinylogous aldol addition product **12** and thermodynamic Michael addition product **13**. The **12/13** ratio was improved somewhat by shortening the reaction time to 25 min. Hydroxy dioxinone **12** was obtained as the exclusive product by lowering the reaction temperature to −90 °C and keeping the reaction time as short as possible, but the 63% yield was nonetheless not satisfactory.

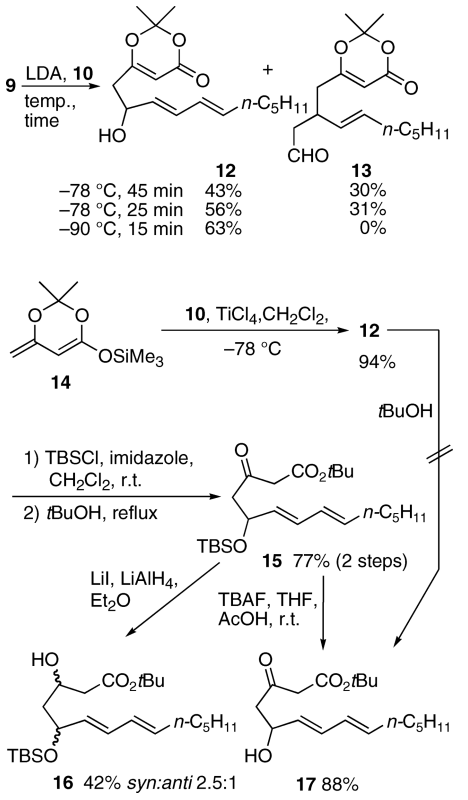
Better results were obtained by applying a titanium-promoted vinylogous Mukaiyama aldol addition of the silyl ketene acetal **14**[8] derived from **9**. Desired **12** was isolated in a

(6) (a) Jahn, U.; Dinca, E. *Chem.—Eur. J.* **2009**, *15*, 58–62. For model studies, see: (b) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2002**, 718–735.

(7) More recent examples: (a) Peuchmaur, M.; Saidani, N.; Botte, C.; Marechal, E.; Vial, H.; Wong, Y. S. *J. Med. Chem.* **2008**, *51*, 4870–4873. (b) Shimamura, H.; Sunazuka, T.; Izuhara, T.; Hirose, T.; Shiomi, K.; Omura, S. *Org. Lett.* **2007**, *9*, 65–67. (c) Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem.—Eur. J.* **2006**, *12*, 2488–2503. (d) Katritzky, A. R.; Wang, Z. Q.; Wang, M. Y.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854–4856. (e) Gu, Y. H.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385–4388.

(8) Prepared according to: Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283.

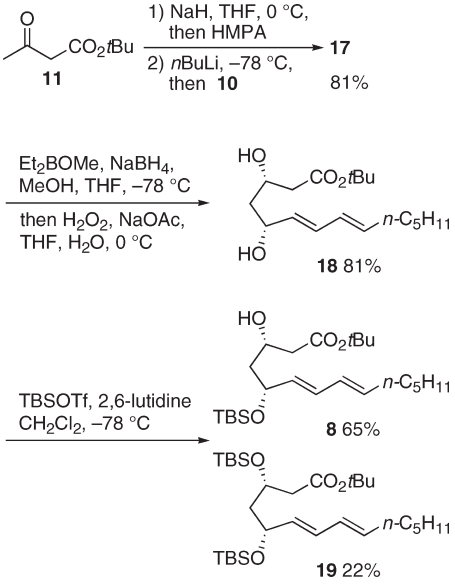
**SCHEME 3. Synthesis of the C7−C20 Precursor 17 from Dioxinone 9**




much improved 94% yield.[9] Needless to say, this reaction can be performed asymmetrically in the presence of chiral Lewis acids if desired.[10] Despite many attempts, hydroxy dioxinone **12** could not be transformed directly to 5-hydroxy-3-oxo ester **17** due to its propensity to dehydration to highly unsaturated esters under the required reflux conditions. This reactivity problem was circumvented by silylation of the alcohol function. Subsequent thermal transesterification of the cyclic acetonide furnished the silylated $\beta$-keto ester **15** in 77% yield over the two steps. Attempted stereoselective direct reduction of **15** using lithium aluminum hydride in the presence of lithium iodide[11] furnished the silylated hydroxy ester **16** only in moderate yield as a 2.5:1 mixture of inseparable *syn*- and *anti*-diastereomers. Therefore, the hydroxy group was deprotected using TBAF buffered with acetic acid providing desired keto ester **17** in 88% yield. It is worth noting that desilylation using TBAF alone or the pyridine−HF complex gave much lower yields due to the competing formation of dehydrated products.

Overall, the route using **9** turned out to be too long to provide sufficient amounts of **17**. Thus, *tert*-butyl acetoacetate (**11**) was tested as an alternative precursor (Scheme 4). Its deprotonation by NaH/*n*-BuLi generated the corresponding diene diolate, which added cleanly to **10**, provided that the

**SCHEME 4. Synthesis of the Cyclization Precursor 8 from *tert*-Butyl Acetoacetate (11)**



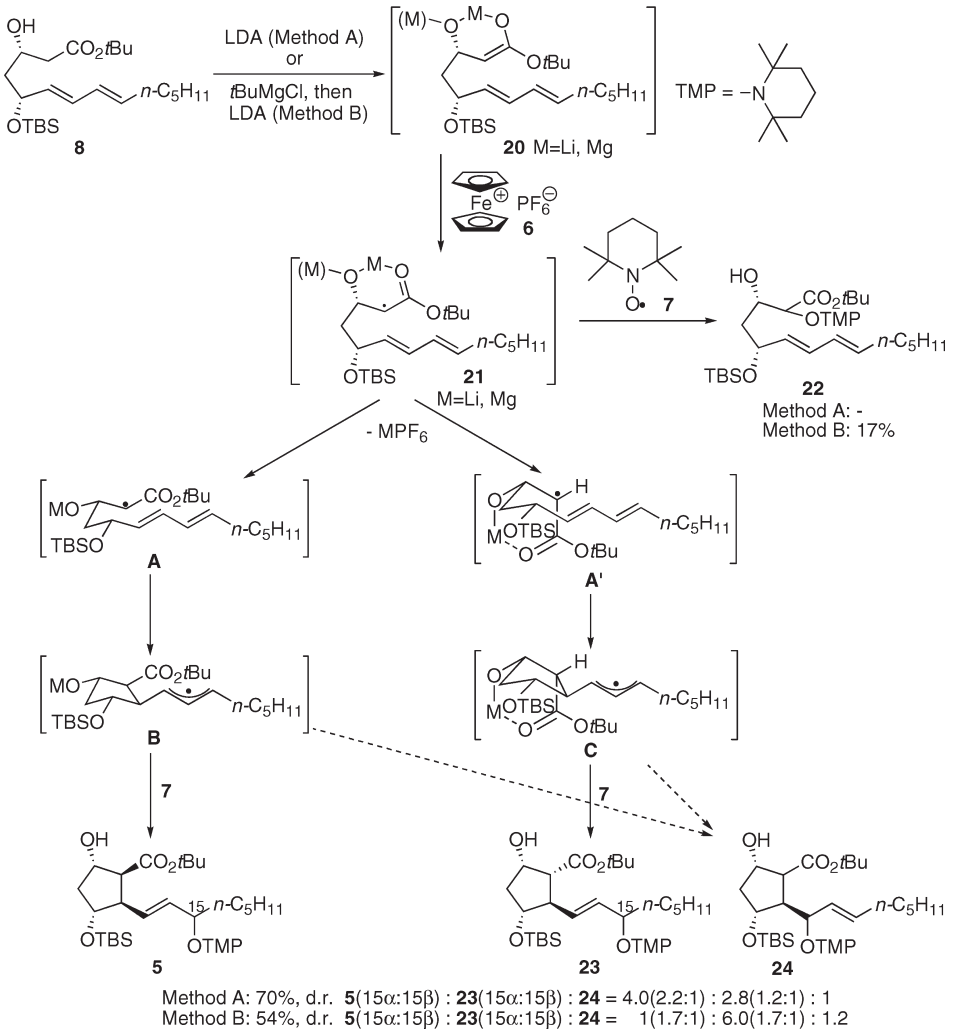

reaction temperature was low and HMPA was present as an additive.[12] Keto ester **17** was isolated in a gratifying 81% yield as a 18:1 mixture of keto and (*Z*)-enol tautomers (only keto tautomer shown). Its *syn*-selective reduction mediated by $Et_2BOMe/NaBH_4$ provided 81% of the corresponding diol **18** with complete *syn*-selectivity.[13] The following monoprotection proceeded with reasonable selectivity. In addition to 65% of desired **8**, 22% of the bis(TBS ether) **19** was also isolated. It is very important to keep the temperature low during addition of TBSOTf, especially on larger scale. The selectivity of silylation is moderate,[14] but the result is in line with results obtained by Roush et al., who also observed recently similar regioselectivities using TBSCl as the reagent.[15]

The key step for the assembly of the cyclopentane core consisted of the oxidative dianion cyclization of **20**, which was performed in two ways (Scheme 5). The first consisted of dideprotonation of ester **8** by 2.5 equiv of LDA leading to the dilithium dianion **20** (method A). The oxidative cyclization was initiated by addition of a mixture of ferrocenium hexafluorophosphate (**6**) and TEMPO (**7**). The resulting radical anion **21** underwent the desired 5-*exo* cyclization and subsequent trapping by **7** in 70% isolated yield as a partly separable mixture of diastereomers **5** and **23**. Moreover, the regioisomeric product **24** of TEMPO trapping at the 13-position was isolated in small amounts. However, acyclic ester **22** resulting from premature coupling of radical **21** with **7** was not detected.

Coupling of the allylic radical **A** with **7** proceeded with good regio- and even some diastereoselectivity. The relative

(9) Prepared in analogy to: Bach, T.; Kirsch, S. *Synlett* **2001**, 1974–1976.
(10) Review: Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682–4698.
(11) Precedent: (a) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783–8788. (b) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419–5422.
(12) Kondo, K.; Umemoto, T.; Yako, K.; Tunemoto, D. *Tetrahedron Lett.* **1978**, 3927–3930.
(13) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233–2238. (b) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
(14) For similarly selective silylations of diols with TBDMSOTf in other applications, see: (a) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161–4167. (b) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *Chem. Commun.* **2002**, 742–743. (c) Esumi, T.; Okamoto, N.; Hatakeyama, S. *Chem. Commun.* **2002**, 3042–3043. (d) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *J. Am. Chem. Soc.* **2003**, *125*, 8238–8243. (e) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733–736.
(15) Hicks, J. D.; Huh, C. W.; Legg, A. D.; Roush, W. R. *Org. Lett.* **2007**, *9*, 5621–5624.

**SCHEME 5. Oxidative Dianion Cyclization of Ester 8**




IsoP configuration of the major diastereomer **5** was established on the basis of NOE experiments. The configuration at the exocyclic stereocenter was assigned by comparison to model compounds.[6b]

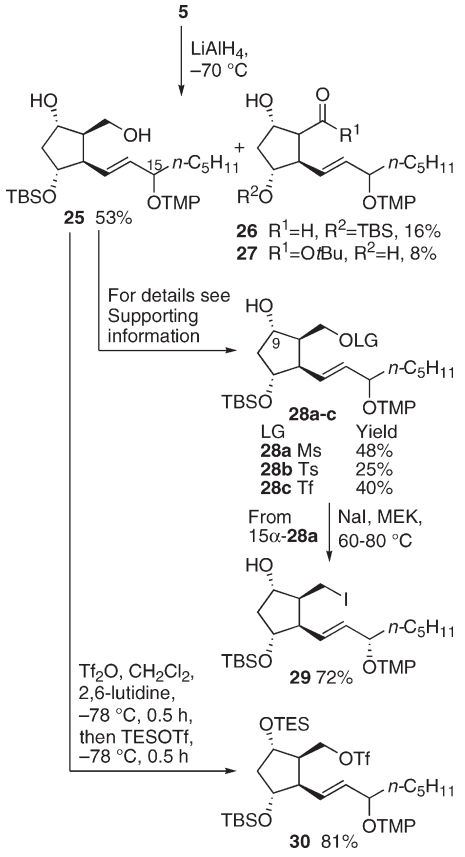
When the corresponding magnesium dianion of **20** was generated by alcohol deprotonation with *tert*-butylmagnesium chloride and subsequent ester deprotonation with LDA (method B), oxidative cyclization and coupling with **7** gave a reversed diastereoselectivity of **5**/**23** = 1:6. The cyclization proceeded somewhat slower, since in this case also 17% of acyclic coupling product **22** was formed. The relative ring configuration of the major PG isomer was assigned on the basis of an NOESY experiment.

The reaction course can be rationalized by assuming an equilibrium between chelated and nonchelated radical anion **21** (only chelated form shown). For the lithium cation, the open form seems to be favored and cyclization occurs preferentially via open transition state **A** and predominant coupling of **B** with **7** from the front side giving **5** as the major diastereomer. In contrast, the chelated form should be more stable for the corresponding magnesium radical anion **21**, and the cyclization proceeds thus via transition state **A′**. Oxygenation of allylic radical **C** by coupling with **7** provides **23** with good diastereoselectivity. Thus, in principle, both PG- and IsoP-stereoisomers could be synthesized by this approach. Here we concentrated, however, on the synthetic access to the so far unknown potential 15-$E_2$-IsoP metabolite **2**. The diastereomers of **5** at the 15-position are separable and some further experiments were performed with pure isomers (vide infra). However, since the stereocenter in 15-position of **5** will be destroyed anyway in the course of the synthesis, the diastereomeric mixture of **5** was used for the completion of the total synthesis.

The *tert*-butyl ester unit in **5** was reduced to alcohol **25** with an excess of lithium aluminum hydride (Scheme 6). The reduction was very slow and afforded **25** in only 53% yield. Additionally, 16% of aldehyde **26** and 8% of desilylated dihydroxy ester **27** were isolated. Selective conversion of the primary alcohol unit of **25** into a leaving group proved to be challenging.

Attempted monomesylation or -tosylation gave the desired products **28a** and **28b** only in low yields. Substantial amounts of regioisomeric 9-monosulfonates and of disulfonylation products were also isolated (not shown; for details, see the Supporting Information). The O-triflation proceeded in contrast very selectively; only monotriflate **28c** was detected with good mass recovery in the crude reaction mixture. The product was, however, not very stable and decomposed partly

**SCHEME 6. Conversion of Ester 5 to Activated Alkylation Precursors 28−30**




during purification by column chromatography. Therefore, the isolated yield of 40% was rather low. The monomesylate **28a** resulting from mesylation of 15α-**25** was transformed in good yield to iodide **29** by a Finkelstein exchange reaction using sodium iodide in methyl ethyl ketone.

Reasoning that the free hydroxy group interferes with the stability and isolation of triflate **28c**, we performed an in situ protection of the secondary alcohol function as a triethylsilyl ether. This one-pot O-triflation of the primary alcohol unit in **25** and TES protection of the secondary gratifyingly gave the somewhat more stable triflate **30** in very good yield.[16]

The assembly of the full carbon skeleton **3** of the IsoP metabolite was the next task. Initial attempts to apply hydroxy sulfonates **28a−c** or iodide **29** in the alkylation reaction met no success using the lithium acetylide of **4** generated by butyllithium in THF/HMPA solution. However, when protected triflate **30** was used in the alkylation with the lithium acetylide of **4**, the C20-compound **3** was obtained in 72% yield. Surprisingly, also 25% of TES alkyne **31** was isolated, which must arise from competitive attack of the anion of **4** on the TES ether functionalities of **4** or **30**. Desired **3** was not separable from **4** and **31** by chromatography and therefore used as a mixture in the next step.

Both TES ether functions were cleaved and oxidized under Swern reaction conditions,[17] and the resulting crude keto aldehyde was subjected immediately to further oxidation to the carboxylic acid[18] and subsequent esterification with trimethylsilyldiazomethane. Keto ester **32** was obtained in a good 72% yield from **3**. Deprotection of the remaining TBS ether by pyridine−HF provided **33**. Epimerization at the acidic 8-position was observed to a small extent during deprotection, resulting in a 9:1 mixture of **33** and **34** having the PG configuration. The mixture of compounds **33** and **34** was subjected to oxidative deprotection of the alkoxyamine with *m*-CPBA.[19] Despite keeping the temperature low and the reaction time very short, extensive epimerization of the 8-position occurred giving an inseparable 2.25:1 mixture of **35** and **36** in 75% isolated yield. Moreover, a minor third isomer was detected in the reaction mixture, which was assigned structure **37**. This compound results probably from epimerization at the 12-position. The epimerization sensitivity of oxo-PG and oxo-IsoP is well-known and can apparently not be avoided.[20]

Finally, Lindlar hydrogenation of **35**, **36**, and **37** provided a partly separable 1.5:1 diastereomeric mixture of 13,14-dihydro-15-oxo-15-$E_2$-IsoP (**2**) and of the corresponding $PGE_2$-metabolite *rac*-**IV** by concomitant reduction of the alkyne and the enone functions (Scheme 7). Some further epimerization of the acidic 8-position was observed also under the slightly basic Lindlar hydrogenation conditions. The structure of **2** was assigned on the basis of its NMR data. The configuration of PGE derivative *rac*-**IV** was proven by comparison of its NMR data with those of authentic 13,14-dihydro-15-oxo-$PGE_2$ methyl ester (see the Supporting Information).[21]

The assignment of the relative configurations of all compounds and especially the distinction of IsoP and PG isomers by NMR spectroscopy deserves comment. In all cyclic compounds described in this manuscript and before,[6a] the chemical shifts of the ring protons in 8-position of IsoP and PG isomers differ significantly, no matter whether they belong to the F- or E-ring substitution pattern. Generally, this proton is downfield-shifted in IsoP isomers by 0.5−1.1 ppm with respect to the corresponding PG isomers (For a detailed list of significant chemical shifts, see Table 3 of the Supporting Information). The shift difference is at the larger end for the $E_2$-IsoP/$PGE_2$ substitution pattern. Considering only $F_{2t}$-IsoP/$PGF_2$ derivatives, for example, **5**, **23**, **25**, **28−30**, the proton shifts in the 10-position are very significant for the assignment of the diastereomers. While the $F_2$-IsoP isomers always display two well-separated signals at 1.5−1.8 and 2.1−2.5 ppm, respectively, both H10 protons in $PGF_2$ isomers absorb very close to each other at 1.6−1.9 ppm. This distinction is, however, not valid for $E_2$-IsoP/$PGE_2$ isomers **32−36**, **2**, and *rac*-**IV**. The shifts of all other protons do not display clear trends.

(16) For a similar procedure that was developed in parallel, see: Clark, J. S.; Conroy, J.; Blake, A. J. *Org. Lett.* **2007**, *9*, 2091–2094.

(17) Review: (a) Muzart, J. *Synthesis* **1993**, 11. For precedent for the direct oxidation of silyl ethers to aldehydes in IsoP chemistry, see: (b) Jacobo, S. H.; Chang, C.-T.; Lee, G.-J.; Lawson, J. A.; Powell, W. S.; Pratico, D.; FitzGerald, G. A.; Rokach, J. *J. Org. Chem.* **2006**, *71*, 1370–1379. (c) Roland, A.; Durand, T.; Rondot, B.; Vidal, J.-P.; Rossi, J.-C. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1149–1154.

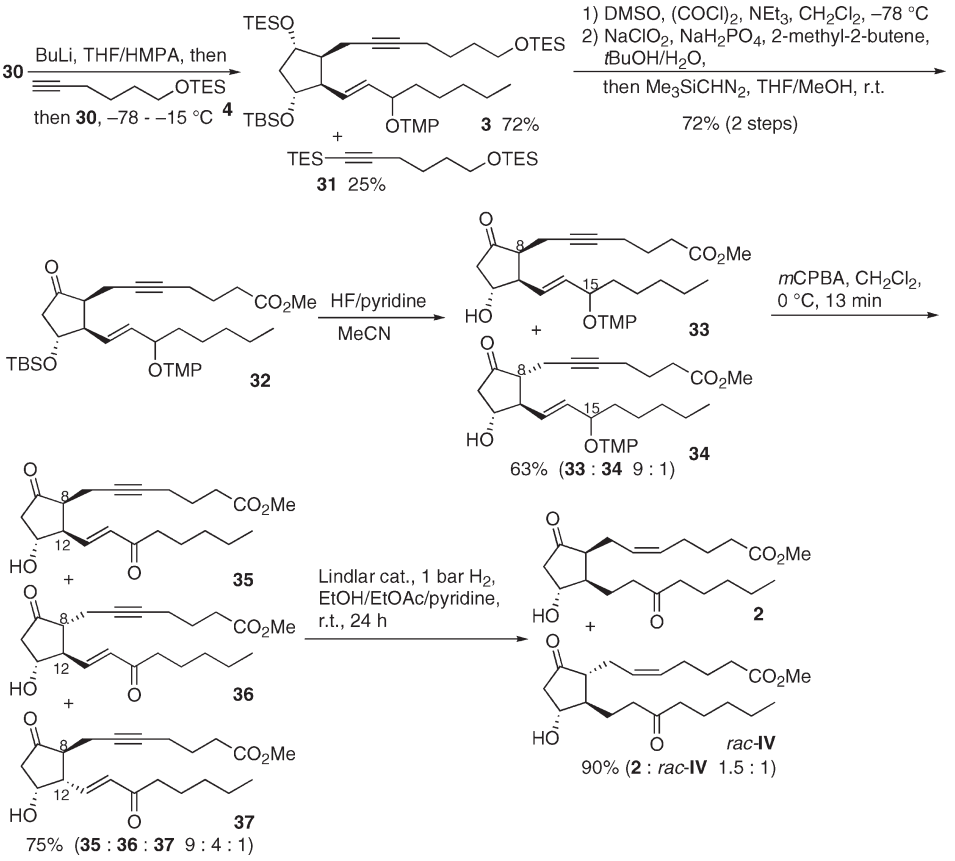
(18) Recent reviews: (a) Krapcho, A. P. *Org. Prep. Proced. Int.* **2006**, *38*, 177–216. (b) Lin, S.; Yan, L.; Liu, P. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2006; Vol. 20a, pp 93−135.

(19) Inokuchi, T.; Kawafuchi, H. *Tetrahedron* **2004**, *60*, 11969–11975.

(20) Gao, L.; Zackert, W. E.; Hasford, J. J.; Danekis, M. E.; Milne, G. L.; Remmert, C.; Reese, J.; Yin, H.; Tai, H.-H.; Dey, S. K.; Porter, N. A.; Morrow, J. D. *J. Biol. Chem.* **2003**, *278*, 28479–28489. and references cited therein.

(21) The acid is commercially available from Cayman Chemical, Ann Arbor, MI (catalogue no. 14650).

**SCHEME 7. Completion of the Total Synthesis of 2 and of *rac*-IV**




The $^{13}C$ NMR chemical shifts of the ring carbon atoms are not distinct enough to allow unambiguous conclusions concerning the configration at the ring. The difference of the chemical shifts $\Delta(\delta C14-\delta C13)$ of the vinyl carbon atoms is, however, significantly distinct in $E_2$- and $F_{2t}$-IsoP versus $PGE_2$ and $PGF_2$ isomers. The difference amounts to 6.5−14 ppm in IsoP isomers, while it is with 0−2.5 ppm much smaller for the PG isomers. Exceptions in the difference range are **25** ($\Delta\delta_{IsoP}$ 4.9/2.8 ppm, $\Delta\delta_{PG}$ 1.8 ppm) and **34** ($\Delta\delta_{IsoP}$ 9.2/10.1 ppm, $\Delta\delta_{PG}$ 6.2 ppm), but the relationship holds well overall, since in IsoP isomers show always the significantly larger differences.

## Conclusion

We developed an 11-step synthesis of the potential 15-$E_2$-IsoP metabolite **2** and of *rac*-13,14-dihydro-15-oxo-$PGE_2$ (*rac*-**IV**) in 1.4% overall yield, which features vinylogous aldol additions to synthesize the fully functionalized C7−C20 precursor. An oxidative radical anion cyclization/oxygenation reaction served to prepare the central cyclopentane core of the metabolite. This cyclization can be conducted in a diastereodivergent manner to access IsoP and PG skeletons. The alkylation of an alkynyllithium served to assemble the full C20 core. These methodologies were not used in PG and IsoP chemistry before. The synthesis proves the sensitivity of potential 15-$E_2$-IsoP metabolites toward epimerization and supports the assumption that autoxidatively formed 15-$E_2$-IsoP contributes to $PGE_2$ action and metabolism. The access enables the in vivo study of 15-$E_2$-IsoP metabolism and thus deeper insight into the roles of isoprostanes in oxidative stress. Research along these lines is underway.

## Experimental Section

**(*E*,*E*)-6-(2-Hydroxyundeca-3,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (12) via Vinylogous Aldol Addition under Basic Conditions (General Procedure).** To a solution of 0.42 mL of *i*-$Pr_2NH$ (3 mmol) in 8 mL of dry THF was added 1.87 mL (3 mmol) of *n*-BuLi (1.6 M in *n*-hexane) at −78 °C under a nitrogen atmosphere. After the mixture was stirred for 20 min, a solution of 0.40 mL (3 mmol) of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**9**) in 1 mL of dry THF was added. After this solution was stirred for 30 min at −78 °C, 0.35 mL (2 mmol) of (2*E*,4*E*)-deca-2,4-dienal (**10**) dissolved in 1 mL of dry THF was added at the given temperature (see Scheme 3). The reaction was stirred until complete by TLC. The reaction mixture was quenched with a few drops of saturated $NH_4Cl$ solution, warmed to rt, and diluted with diethyl ether. The layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined etheral layers were washed with water, dried over $Na_2SO_4$, and concentrated in vacuum. The product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to 1:1). The Michael adduct **13** eluted first, followed by product **12**. For yields, see Scheme 3.

**(*E*,*E*)-6-(2-Hydroxyundeca-3,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (12) via Vinylogous Mukaiyama Aldol Addition.** 2,2-Dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-dioxine (**14**) (1.8 g, 8.5 mmol) in 20 mL of dry $CH_2Cl_2$ was added dropwise to a solution of 1.05 mL (5.1 mmol) (2*E*,4*E*)-2,4-decadienal (**10**) (85% purity) and 0.59 mL (5.4 mmol) of $TiCl_4$ in 40 mL of dry $CH_2Cl_2$ at −78 °C. The homogeneous red solution changed to a dark color. The consumption was monitored by TLC (hexane/ethyl

acetate 3.5:1 ($R_f$ (**10**) = 0.59, $R_f$ (**9**) = 0.22)). After 35 min, another 0.17 mL (0.8 mmol) of **10** was added, and stirring was continued at −78 °C for 1.5 h. The reaction mixture was quenched with 20 mL of a satd $NaHCO_3$ solution and warmed to rt. The aqueous layer was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The crude oily product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to 2:1). Some **9** eluted first with hexane/ethyl acetate 5:1 followed by 1.64 g (94% based on **10**) of **12** as a pale yellow oil that crystallizes slowly: $R_f$(hexane/ethyl acetate 2:1) = 0.34; mp 47−49 °C; IR (film) 3443, 3023, 2997, 2959, 2922, 2853, 1693, 1629, 1392, 1379, 1336, 1279, 1254, 1201, 1097, 1044, 1016, 990, 906, 876, 840, 811, 618 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.85 (t, $J$ = 6.9 Hz, 3H), 1.19−1.30 (m, 4H), 1.35 (quint, $J$ = 7.2 Hz, 2H), 1.64 (s, 3H), 1.65 (s, 3H), 2.04 (q, $J$ = 7.1 Hz, 2H), 2.29 (br s, 1H), 2.42 (AB part of ABX system, $J$ = 14.4, 7.6, 5.5 Hz, 2H), 4.39 (dt, $J$ = 6.8, 6.4 Hz, 1H), 5.28 (s, 1H), 5.52 (dd, $J$ = 15.2, 6.8 Hz, 1H), 5.70 (dt, $J$ = 15.1, 6.9 Hz, 1H), 5.96 (dd, $J$ = 15.1, 10.4 Hz, 1H), 6.19 (dd, $J$ = 15.2, 10.4 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 14.0 (q), 22.4 (t), 24.9 (q), 25.3 (q), 28.7 (t), 31.3 (t), 32.5 (t), 41.5 (t), 69.6 (d), 95.2 (d), 106.7 (s), 128.8 (d), 130.9 (d), 132.3 (d), 137.0 (d), 161.2 (s), 168.5 (s); MS (EI) $m/z$ 294 (2) [$M^+$], 276 ( < 1), 236 (52), 218 (12), 208 (9), 192 (20), 190 (14), 179 (9), 165 (16), 153 (29), 150 (12), 137 (17), 126 (39), 121 (11), 111 (16), 98 (25), 95 (30), 84 (100), 79 (37), 69 (28), 67 (46), 59 (16), 55 (23), 44 (8); HRMS calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1822. Anal. Calcd for $C_{17}H_{26}O_4$ (294.39): C, 69.36; H, 8.90. Found: C, 69.68; H, 9.10.

**(*E* and *Z*)-6-(2-(2-Oxoethyl)-3-nonenyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (13):** $R_f$(hexane/ethyl acetate 2:1) = 0.46; IR (film) 3100, 2997, 2957, 2926, 2856, 2722, 1721, 1632, 1389, 1375, 1270, 1251, 1202, 1012, 971, 901, 837, 803 $cm^{-1}$; MS (EI) $m/z$ 294 ( < 1) [$M^+$], 236 (30), 218 (9), 207 (35), 193 (25), 175 (8), 161 (16), 152 (21), 137 (49), 124 (61), 112 (30), 98 (59), 95 (34), 91 (27), 84 (92), 79 (50), 69 (100), 67 (61), 55 (55), 44 (21), 43 (89); MS (ESI) $m/z$ = 317 [M + $Na^+$]; HRMS calcd for $C_{17}H_{26}O_4$ + $Na^+$ 317.1723, found 317.1722. (*E*)-**13**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.80 (t, $J$ = 7.0 Hz, 3H), 1.13−1.28 (m, 6H), 1.59 (s, 3H), 1.61 (s, 3H), 1.90 (m, 2H), 2.17 (A part of ABM system, $J$ = 14.3, 8.8 Hz, 1H), 2.29 (B part of ABM system, $J$ = 14.2, 5.6 Hz, 1H), 2.42 (dd, $J$ = 6.9, 1.9 Hz, 2H), 2.89 (m, 1H), 5.15 (s, 1H), 5.18 (ddt, $J$ = 15.3, 8.3, 1.4 Hz, 1H), 5.45 (ddt, $J$ = 14.7, 6.8, 1.1 Hz, 1H), 9.64 (t, $J$ = 1.9 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 13.9 (q), 22.3 (t), 24.9 (q), 25.3 (q), 28.8 (t), 31.2 (t), 32.2 (t), 34.4 (d), 39.0 (t), 48.3 (t), 94.7 (d), 106.5 (s), 129.9 (d), 133.2 (d), 160.8 (s), 169.2 (s), 200.8 (d). (*Z*)-**13** (detectable resonances): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.18 (m, 1H), 5.45 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 24.86 (q), 25.2 (q), 27.6 (t), 29.1 (t), 31.5 (t), 39.2 (t), 48.7 (t), 94.7 (d), 106.3 (s), 129.6 (d), 132.6 (d), 161.7 (s), 200.6 (d).

**(*E*,*E*)-6-[(2-*tert*-Butyldimethylsilyloxy)undeca-3,5-dienyl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one.** To a yellow solution of 1.0 g (3.40 mmol) of dioxinone **12**, 580 mg (8.50 mmol, 2.5 equiv) of imidazole, and 41 mg (0.34 mmol) of DMAP in 10 mL of dry $CH_2Cl_2$ was added 615 mg (4.10 mmol, 1.2 equiv) of TBSCl at rt. A precipitate formed immediately. The mixture was stirred at rt for 4.5 h when it was finished by TLC (hexane/ethyl acetate 20:1 and 5:1). The reaction mixture was quenched with 2 mL of water and extracted with diethyl ether, and the combined etheral layers were washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to give 1.60 g of a pale yellow oil, which was purified by flash chromatography (hexane/ethyl acetate 20:1, gradient to 5:1) to give 1.10 g (80%) of the silyl ether as a colorless oil: $R_f$(hexane/ethyl acetate 10:1) = 0.68; IR (film) 3000, 2957, 2928, 2856, 1732, 1636, 1465, 1375, 1272, 1251, 1203, 1067, 1011, 989, 899, 832, 807, 774 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ −0.07 (s, 3H), −0.05 (s, 3H), 0.78 (s, 9H), 0.82 (m, 3H), 1.16−1.25 (m, 4H), 1.29 (tt, $J$ = 14.3, 7.2 Hz, 2H), 1.56 (s, 3H), 1.58 (s, 3H), 1.97 (dt, $J$ = 7.2, 7.3 Hz, 2H), 2.30 (AB part of ABM system, $J$ = 14.0, 7.0, 5.4 Hz, 2H), 4.31 (dt, $J$ = 6.6, 6.2 Hz, 1H), 5.16 (s, 1H), 5.39 (dd, $J$ = 15.1, 6.9 Hz, 1H), 5.59 (dt, $J$ = 14.6, 7.2 Hz, 1H), 5.88 (dd, $J$ = 15.0, 10.5 Hz, 1H), 6.02 (dd, $J$ = 15.0, 10.5 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ −4.3 (q), 14.0 (q), 18.0 (s), 22.4 (t), 24.6 (q), 25.6 (q), 25.7 (q), 28.8 (t), 31.4 (t), 32.6 (t), 43.1 (t), 70.5 (d), 95.3 (d), 106.3 (s), 128.9 (d), 131.1 (d), 131.9 (d), 136.0 (d), 161.1 (s), 168.5 (s); MS (EI) $m/z$ 408 ( < 1) [$M^+$], 350 (4), 293 (87), 267 (53), 251 (8), 225 (4), 195 (5), 169 (7), 147 (7), 143 (12), 141 (45), 115 (7), 99 (33), 79 (20), 73 (100), 69 (15), 59 (10), 43 (37). Anal. Calcd for $C_{23}H_{40}O_4Si$ (408.65): C, 67.60; H, 9.87. Found: C, 67.69; H, 10.03.

**(6*E*,8*E*)-*tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-3-oxotetradeca-6,8-dienoate (15).** The TBS-protected dioxinone (1.0 g, 2.45 mmol) was refluxed in 25 mL of dry *tert*-butyl alcohol under an argon atmosphere at 150 °C bath temperature for 32 h until the reaction was complete by TLC (hexanes/ethyl acetate 10:1). The colorless solution was evaporated. The remaining oil was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give 1.0 g (96%) of the silylated *tert*-butyl ester and 50 mg of recovered dioxinone: $R_f$(hexanes/EtOAc 10:1) = 0.52; IR (film) 2956, 2928, 2857, 1745, 1717, 1648, 1476, 1409, 1367, 1318, 1250, 1144, 1070, 988, 942, 832, 807, 776 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.00 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.86 (t, $J$ = 6.6 Hz, 3H), 1.23−1.29 (m, 4H), 1.36 (quint, $J$ = 7.1 Hz, 2H), 1.43 (s, 9H), 2.03 (q, $J$ = 7.1 Hz, 2H), 2.55 (A part of ABX system, $J$ = 15.1, 4.9 Hz, 1H), 2.75 (B part of ABX system, $J$ = 15.1, 7.7 Hz, 1H), 3.34 (s, 2H), 4.60 (dt, $J$ = 5.0, 6.9 Hz, 1H), 5.48 (dd, $J$ = 15.2, 6.7 Hz, 1H), 5.65 (dt, $J$ = 15.1, 6.9 Hz, 1H), 5.94 (dd, $J$ = 15.1, 10.4 Hz, 1H), 6.11 (dd, $J$ = 15.2, 10.4 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −5.0 (q), −4.4 (q), 14.0 (q), 18.1 (s), 22.5 (t), 25.8 (q), 28.0 (q), 28.8 (t), 31.4 (t), 32.6 (t), 51.2 (t), 52.1 (t), 70.1 (d), 81.7 (s), 129.2 (d), 130.5 (d), 132.4 (d), 135.6 (d), 166.2 (s), 201.5 (s); MS (EI) $m/z$ 424 ( < 1) [$M^+$], 368 (6), 311 (17), 293 (12), 267 (30), 215 (8), 187 (7), 177 (8), 159 (100), 153 (27), 143 (12), 135 (8), 115 (13), 91 (9), 75 (82), 73 (30), 57 (25), 43 (7), 41 (22); HRMS calcd for $C_{24}H_{44}O_4Si$ 424.3009, found 424.2988. Anal. Calcd for $C_{24}H_{44}O_4Si$ (424.69): C, 67.87; H, 10.44. Found: C, 67.66; H, 10.48. Enol form (detectable resonances): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ −0.02 (s, 3H), −0.01 (s, 3H), 1.44 (s, 9H), 2.25 (m, 2H), 4.46 (m, 1H), 4.88 (s, 1H), 5.48 (m, 1H), 5.65 (m, 1H), 5.94 (m, 1H), 6.11 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −5.3 (q), −4.5 (q), 18.2 (s), 25.8 (q), 28.3 (q), 44.7 (t), 70.3 (d), 80.5 (s), 93.0 (d), 129.4 (d), 130.1 (d), 133.0 (d), 135.1 (d), 172.5 (s), 174.2 (s).

**(6*E*,8*E*)-*tert*-Butyl 5-Hydroxy-3-oxo-6,8-tetradecadienoate (17) from 15.** To a solution of 600 mg (1.41 mmol) of **15** in 10 mL of dry THF was added consecutively 0.086 mL (1.5 mmol) of glacial AcOH and 3 mL (3.00 mmol) of a 1 M TBAF solution in THF at 0 °C. The mixture was warmed to rt and stirred for 4 h when finished by TLC (hexanes/ethyl acetate 2:1). The reaction mixture was diluted with diethyl ether, 0.25 mL of water was added, and the mixture was filtered through a pad of silica gel. The solvent was evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 5:1, gradient to 2:1) to give 385 mg (88%) of **17** as a colorless oil.

**(6*E*,8*E*)-*tert*-Butyl 5-Hydroxy-3-oxo-6,8-tetradecadienoate (17) from 10 and 11.** *tert*-Butyl acetoacetate **11** (2.4 g, 15.1 mmol) dissolved in 3 mL of dry THF was added dropwise via syringe to a suspension of 660 mg of NaH (16.5 mmol, 60% in mineral oil) in 50 mL of dry THF at 0 °C under nitrogen. To the resulting clear pale yellow homogeneous solution, which resulted after the gas evolution ceased, was added 3.12 mL (18 mmol) of dry HMPA at −65 °C followed by addition of 9.84 mL of *n*-BuLi (15.75 mmol, 1.6 M in hexanes) with good stirring over 10 min. The reaction mixture was stirred at −65 °C for 20 min, whereupon it turned white inhomogeneous. Decadienal **10** (2.4 g, 15 mmol, 95% purity) was added via syringe at −78 °C over 5−10 min with vigorous stirring. The orange, inhomogeneous reaction mixture

was stirred at −78 °C for 20 min and then allowed to warm to −45 °C over 1 h, during which time it became homogeneous. Stirring was continued at this temperature for 3 h until the reaction was complete by TLC (hexane/ethyl acetate 5:1). The mixture was quenched with 20 mL of a 0.1 M HCl solution at −40 °C, diluted with 20 mL of diethyl ether, and allowed to warm to rt. The layers were separated, and the aqueous was extracted three times with 20 mL of diethyl ether. The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over $Na_2SO_4$, and concentrated in vacuum to give 6.0 g of the crude product as an orange oil. Purification by flash chromatography (hexane/ethyl acetate, gradient 20:1 to 2:1) recovered 0.18 g of acetoacetate, followed by elution of 2.22 g of impure and 2.20 g of pure **17** as a mixture of keto and enol tautomers in a of 19:1 ratio ($^1$H NMR). A second purification of impure **17** gave another 1.59 g of pure material as a mixture of keto and enol tautomers in a ratio of 16:1 ($^1$H NMR). Yield 3.79 g (81%). The somewhat labile product should be stored in a freezer or used immediately: $R_f$ (hexane/ethyl acetate 5:1) = 0.25; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.28 (m, 4H), 1.38 (m, 2H), 1.46 (s, 9H), 2.06 (q, $J$ = 7.2 Hz, 2H), 2.75 (m, 2H), 3.22 (br s, 1H), 3.39 (s, 2H), 4.62 (q, $J$ = 6.1 Hz, 1H), 5.56 (dd, $J$ = 15.2, 6.4 Hz, 1H), 5.69 (dt, $J$ = 15.1, 7.0 Hz, 1H), 6.00 (dd, $J$ = 15.2, 10.3 Hz, 1H), 6.22 (dd, $J$ = 15.1, 10.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 13.7 (q), 22.2 (t), 27.6 (q), 28.6 (t), 31.1 (t), 32.3 (t), 49.5 (t), 51.0 (t), 67.9 (d), 81.7 (s), 129.1 (d), 130.8 (d), 131.1 (d), 135.5 (d), 166.0 (s), 202.6 (s); MS (ESI) $m/z$ 333 (100); HRMS calcd for $C_{18}H_{30}O_4 + Na^+$ 333.2042, found 333.2036.

***syn*-(6*E*,8*E*)-*tert*-Butyl 3,5-Dihydroxy-6,8-tetradecadienoate (18).**[22] To a solution of **17** (3.53 g, 11.4 mmol) in 100 mL of dry THF/MeOH (4:1) was added 17.1 mL (17.1 mmol) of diethyl(methoxy)borane (1.0 M solution in THF) via syringe at −78 °C over 5 min. The solution was stirred at −78 to −65 °C for 1 h. With good stirring, 650 mg (17.1 mmol, 1.5 equiv) of $NaBH_4$ was added in portions at −95 °C. A strong gas evolution was observed that lasted about 0.5 h. The reaction mixture was stirred at −78 °C for 3 h when it was complete by TLC. The reaction was quenched at −78 °C with 10 mL of AcOH, diluted with 50 mL of diethyl ether, and allowed to warm to rt during 15 min. Saturated $NaHCO_3$ solution (100 mL) was added slowly, and the mixture was stirred for 5 min. The aqueous layer was extracted three times with 30 mL of diethyl ether. The combined organic layers were washed five times with 30 mL of saturated $NaHCO_3$ solution and twice with 50 mL of brine, dried over $Na_2SO_4$, concentrated, and dried in vacuum to give a crude mixture of the cyclic boronate ($R_f$ (hexane/ethyl acetate 2:1) = 0.82) as the main product and small amounts of the diol.

The crude mixture was dissolved in 40 mL of THF/$H_2O$ (3:1), and 1.9 g (23 mmol, 2 equiv) of NaOAc was added. The resulting mixture was stirred for 5 min. It was immersed in an ice bath, and 12 mL (1.05 mL/mmol) of a 30% solution of $H_2O_2$ was added slowly with stirring. The mixture was stirred at 0 °C for 0.5 h when it was judged complete by TLC. At 0 °C, 40 mL of a saturated $Na_2SO_3$ solution was added slowly, followed by 40 mL of diethyl ether. Stirring was continued at rt for 10 min. The layers were separated, and the aqueous layer was extracted three times with 25 mL of diethyl ether. The combined organic layers were washed once with water and brine, dried over $Na_2SO_4$, and concentrated to give the crude product. The almost pure diol was purified by flash chromatography (hexane/ethyl acetate 5:1 and 2:1): yield 2.9 g (81%) as a colorless oil; $R_f$ (hexane/ethyl acetate 2:1) = 0.40; IR (film) 3393, 2957, 2928, 2858, 1726, 1368, 1301, 1255, 1149, 1067, 988, 844 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.23−1.33 (m, 4H), 1.39 (m, 2H), 1.46 (s, 9H), 1.60 (ddd, $J$ = 14.2, 3.5, 3.1 Hz, 1H), 1.70 (ddd, $J$ = 14.2, 9.7, 9.3 Hz, 1H), 2.06 (q, $J$ = 7.0 Hz, 2H), 2.40 (m, 2H), 4.21 (m, 1H), 4.42 (m, 1H), 5.56 (dd, $J$ = 15.2, 6.7 Hz, 1H), 5.70 (dt, $J$ = 15.1, 7.3 Hz, 1H), 6.00 (dd, $J$ = 15.1, 10.4 Hz, 1H), 6.21 (dd, $J$ = 15.2, 10.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 14.3 (q), 22.8 (t), 28.4 (q), 29.2 (t), 31.7 (t), 32.9 (t), 42.9 (t), 43.1 (t), 68.7 (d), 72.6 (d), 81.7 (s), 129.6 (d), 131.1 (d), 132.9 (d), 136.0 (d), 172.3 (s); MS (EI) $m/z$ 312 (0.5) [M$^+$], 276 (8), 256 (18), 238 (10), 220 (21), 179 (12), 167 (18), 151 (14), 131 (14), 128 (17), 113 (26), 105 (18), 91 (36), 79 (55), 67 (25), 57 (100). Despite many attempts, neither a satisfactory combustion analysis nor HRMS was obtained. The compound is, however, pure by NMR (see the Supporting Information).

**(3*S**,5*R**,6*E*,8*E*)-*tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-3-hydroxytetradeca-6,8-dienoate (8).** 2,6-Lutidine (2.9 mL, 24.9 mmol) was added to a solution of 2.59 g (8.3 mmol) of dihydroxy ester **18** in 78 mL of dry $CH_2Cl_2$. The mixture was cooled to −78 °C, and 2.3 mL (10 mmol) of TBSOTf was added dropwise via syringe. The reaction mixture was stirred at −78 °C for 3.5 h and monitored by TLC (for details, see the Supporting Information). The reaction was quenched with 60 mL of saturated $KHSO_4$ solution, diluted with ethyl acetate (100 mL), and allowed to warm to rt with stirring. The layers were separated. The aqueous layer was extracted twice with diethyl ether and twice with ethyl acetate. The combined organic layers were washed subsequently with water, saturated $NaHCO_3$ solution, and twice with brine. The mixture was dried over $Na_2SO_4$, evaporated, and dried in vacuum to give the crude product, which was purified by flash chromatography (hexane/ethyl acetate 10:1, gradient to 2:1) to give 0.99 g (22%) of disilyl diether **19** and 2.3 g (65%) of **8** as colorless oils: $R_f$ (hexane/ethyl acetate 5:1) = 0.55; IR (film) 3516, 2956, 2929, 2857, 1728, 1467, 1367, 1253, 1151, 1070, 988, 834, 775, 669 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ −0.04 (s, 3H), 0.00 (s, 3H), 0.81 (m+s, 12H), 1.10−1.25 (m, 4H), 1.35 (m, 2H), 1.37 (s, 9H), 1.51 (ddd, $J$ = 13.9, 5.8, 3.4 Hz, 1H), 1.67 (ddd, $J$ = 13.9, 9.0, 7.5 Hz, 1H), 1.99 (q, $J$ = 7.0 Hz, 2H), 2.30 (AB part of ABX system, $J$ = 16.0, 7.0, 5.5 Hz, 2H), 3.40 (d, $J$ = 2.7 Hz, 1H), 4.01 (m, 1H), 4.30 (q, $J$ = 6.8 Hz, 1H), 5.41 (dd, $J$ = 15.1, 7.3 Hz, 1H), 5.59 (dt, $J$=14.4, 6.9 Hz, 1H), 5.90 (dd, $J$=14.9, 10.4 Hz, 1H), 6.02 (dd, $J$ = 15.0, 10.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.8 (q), −4.0 (q), 14.0 (q), 18.0 (s), 22.5 (t), 25.8 (q), 28.1 (q), 28.8 (t), 31.4 (t), 32.6 (t), 42.7 (t), 44.5 (t), 66.6 (d), 72.8 (d), 80.8 (s), 129.3 (d), 130.7 (d), 133.2 (d), 135.6 (d), 171.7 (s); MS (ESI) $m/z$ 876 (5), 875 (8), 449 (100). Anal. Calcd for $C_{24}H_{46}O_4Si$: C, 67.55; H, 10.87. Found: C, 67.77; H, 11.12.

**Oxidative Cyclizations of 8. Method A.** *i*-$Pr_2NH$ (0.62 mL, 4.4 mmol, 2.5 equiv) was added under nitrogen to a solution of 524 mg (12.3 mmol, 7 equiv) of flame-dried LiCl in 45 mL of dry THF, and the mixture was cooled to −78 °C. BuLi (2.75 mL, 4.4 mmol, 1.6 M in hexane, 2.5 equiv) was added. After the mixture was stirred for 0.5 h, **8** (750 mg, 1.76 mmol) dissolved in 5 mL of dry THF was added to the LDA solution at −78 °C. The mixture was warmed from −78 to −40 °C over 1 h and stirred for an additional 0.5 h at −40 °C. After the mixture was cooled to −78 °C, 1.8 mL (10.6 mmol, 6 equiv) of HMPA was added dropwise followed by addition of 55 mg (0.35 mmol, 0.2 equiv) of TEMPO (**7**) as a solid. The reaction mixture was stirred at −78 °C for 10 min. In the meantime, 220 mg (1.41 mmol, 0.8 equiv) of **7** and 583 mg (1.76 mmol, 1 equiv) of $FeCp_2PF_6$ (**6**) were mixed to homogeneity in a vial. This mixture of **6** and **7** was added in small portions with vigorous stirring over a period of 13 min. Each portion was added after consumption of the previous as monitored by the disappearance of the blue color. After the addition was complete, the mixture did not remain blue; therefore, a further 320 mg (0.97 mmol, 0.55 equiv) of **6** was added in three portions, and the blue inhomogeneous reaction mixture was stirred at −78 to −60 °C for 30 min. For setups smaller than 0.7 mmol of **8**, TEMPO **7** was added prior to **6** as in method B.

(22) Liberation of diol **18** from the boronate was performed in analogy to: Galobardes, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2002**, *43*, 6145–6148.

**Method B.** A 20% solution of *t*-BuMgCl in THF (0.61 mL, 0.97 mmol, 1.5 equiv) was added via syringe to a solution of 278 mg (0.65 mmol) of **8** in 5 mL of dry THF at −78 °C. The mixture was stirred at −78 °C for 40 min. A 2 M LDA solution in THF/*n*-heptane (0.71 mL, 1.43 mmol, 2.2 equiv) was added, and the mixture was stirred at −78 to −40 °C for 1.25 h. Dry THF (15 mL) and 0.68 mL (3.9 mmol, 6 equiv) of HMPA were added at −78 °C followed by 122 mg (0.78 mmol, 1.2 equiv) of TEMPO (**7**) as a solid, and the reaction mixture was stirred for 10 min. $FeCp_2PF_6$ (**6**) (380 mg) was added in small portions with vigorous stirring at −78 °C during 5−10 min until the reaction mixture remained blue and inhomogeneous. Each portion was added after consumption of the previous as monitored by the disappearance of the blue color. A further 210 mg of **6** was added subsequently (total 590 mg (1.8 mmol, 2.7 equiv)). After the addition was complete, the reaction mixture was stirred at −78 to −65 °C for 20 min.

**Workup and Isolation.** The reaction mixture was quenched with seven drops of water, diluted with diethyl ether, and allowed to warm to rt. It was filtered through a pad of silica, which was washed with diethyl ether (200 mL). Most of the solvent was evaporated, and the remaining material was preadsorbed on silica gel and purified by flash chromatography (hexane/ethyl acetate, gradient 50:1, 20:1, 10:1, 5:1 and 2:1). Ferrocene eluted first at a polarity 50:1 hexane/ethyl acetate. Starting from a polarity of 20:1, products eluted in the following order: (**22** +) **24**, **8** + **24**, traces of two unknown cyclic products (not always detected), and finally a diastereomeric mixture of **23** and **5**. The purity of this mixture was determined by combustion analysis. Subsequently, diastereomeric **23** and **5** were separated by further flash chromatography and their structure and diastereomeric composition determined by NMR spectroscopy. For yields and ratios, see Scheme 5: IR (film) 3515, 2954, 2930, 2858, 1734, 1466, 1366, 1252, 1153, 1129, 1070, 1003, 975, 901, 836, 776, 714, 668 $cm^{-1}$; MS (ESI) *m*/*z* 1185 (19), 604 (82), 464 (11), 448 (100), 158 (12). Anal. Calcd for $C_{33}H_{63}NO_5Si$: C, 68.11; H, 10.91; N, 2.41. Found: C, 67.93; H, 11.01; N, 2.36.

**(1*S**,2*R**,3*R**,5*S**)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate (15α-5):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (m, 3H), 0.89 (s, 9H), 0.99−1.15 (m, 12H), 1.18−1.34 (m, 7H), 1.35−1.52 (m, 6H), 1.42 (s, 9H), 1.62 (m, 1H), 1.68 (ddd, $J$ = 14.3, 3.2, 1.6 Hz, 1H), 2.36 (ddd, $J$ = 14.3, 7.7, 5.0 Hz, 1H), 2.50 (d, $J$ = 7.2 Hz, 1H), 2.97 (br t, $J$ = 8.4 Hz, 1H), 3.10 (dd, $J$ = 7.8, 5.2 Hz, 1H), 3.99 (dt, $J$ = 7.3, 6.7 Hz, 1H), 4.15 (m, 1H), 4.50 (m, 1H), 5.18 (dd, $J$ = 15.4, 9.0 Hz, 1H), 5.53 (ddd, $J$ = 15.4, 8.6, 0.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.8 (q), −4.6 (q), 14.1 (q), 17.3 (t), 18.0 (s), 20.3 (q), 22.6 (t), 25.1 (t), 25.8 (q), 28.2 (q), 32.1 (t), 34.0 (q), 34.9 (t), 35.3 (q), 40.3 (t), 42.4 (t), 53.8 (d), 57.1 (d), 59.0 (s), 60.1 (s), 74.1 (d), 78.3 (d), 80.6 (s), 84.4 (d), 128.1 (d), 136.1 (d), 172.4 (s).

**(1*S**,2*R**,3*R**,5*S**)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*R**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate (15β-5):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.05 (s, 6H), 0.87 (m, 3H), 0.88 (s, 9H), 0.98−1.14 (m, 12H), 1.19−1.32 (m, 7H), 1.37−1.51 (m, 6H), 1.46 (s, 9H), 1.66 (m, 2H), 2.34 (m, 1H), 2.52 (m, 1H), 2.96 (m, 1H), 3.06 (dd, $J$ = 8.4, 4.4 Hz, 1H), 3.99 (m, 1H), 4.10 (dt, $J$ = 5.4, 2.7 Hz, 1H), 4.44 (m, 1H), 5.27 (dd, $J$ = 15.6, 8.3 Hz, 1H), 5.52 (dd, $J$ = 15.5, 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.8 (q), 14.0 (q), 17.1 (t), 17.9 (s), 20.2 (q), 20.4 (q), 22.6 (t), 25.1 (t), 25.8 (q), 28.2 (q), 32.0 (t), 34.0 (q), 34.3 (t), 35.3 (q), 40.0 (t), 42.6 (t), 53.1 (d), 56.9 (d), 59.0 (s), 60.1 (s), 74.2 (d), 78.5 (d), 80.7 (s), 84.3 (d), 127.9 (d), 135.9 (d), 172.5 (s).

**(1*R**,2*R**,3*R**,5*S**)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate (15α-23):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ −0.02 (s, 3H), 0.00 (s, 3H), 0.79 (m, 3H), 0.80 (s, 9H), 0.94−1.10 (m, 12H), 1.12−1.20 (m, 7H), 1.31−1.53 (m, 6H), 1.38 (s, 9H), 1.59 (m, 1H), 1.78 (br d, $J$ = 13.8 Hz, 1H), 1.85 (dt, $J$ = 13.9, 4.7 Hz, 1H), 2.52 (dd, $J$ = 8.4, 5.3 Hz, 1H), 3.09 (dt, $J$ = 8.1, 5.5 Hz, 1H), 3.17 (d, $J$ = 9.7 Hz, 1H), 3.88 (dt, $J$ = 8.4, 4.6 Hz, 1H), 3.94 (m, 1H), 4.32 (m, 1H), 5.23 (dd, $J$ = 15.4, 8.0 Hz, 1H), 5.36 (dd, $J$ = 15.6, 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.9 (q), −4.7 (q), 14.0 (q), 17.2 (t), 17.8 (s), 20.2 (q), 20.4 (q), 22.6 (t), 25.1 (t), 25.7 (q), 28.1 (q), 31.9 (t), 34.0 (q), 34.5 (t), 35.6 (q), 40.2 (t), 43.1 (t), 51.6 (d), 57.2 (d), 58.8 (s), 60.0 (s), 75.3 (d), 79.6 (d), 80.5 (s), 85.0 (d), 131.6 (d), 133.8 (d), 170.9 (s).

**(1*R**,2*R**,3*R**,5*S**)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2-[(*R**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentanecarboxylate (15β-23):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.00 (s, 3H), 0.02 (s, 3H), 0.80 (m, 3H), 0.81 (s, 9H), 0.91−1.09 (m, 12H), 1.11−1.25 (m, 7H), 1.30−1.54 (m, 6H), 1.38 (s, 9H), 1.59 (m, 1H), 1.79 (br d, $J$ = 13.8 Hz, 1H), 1.87 (dt, $J$ = 13.8, 4.9 Hz, 1H), 2.47 (dd, $J$ = 8.6, 5.3 Hz, 1H), 3.10 (m, 1H), 3.18 (d, $J$ = 9.6 Hz, 1H), 3.93 (dt, $J$ = 8.3, 4.6 Hz, 1H), 4.02 (m, 1H), 4.33 (m, 1H), 5.26 (dd, $J$ = 15.5, 7.8 Hz, 1H), 5.39 (dd, $J$ = 15.4, 8.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.9 (q), −4.6 (q), 14.0 (q), 17.3 (t), 17.9 (s), 20.2 (q), 20.4 (q), 22.6 (t), 25.1 (t), 25.7 (q), 28.1 (q), 31.8 (t), 34.0 (q), 34.4 (t), 35.3 (q), 40.2 (t), 43.1 (t), 51.4 (d), 57.4 (d), 59.0 (s), 60.0 (s), 75.1 (d), 79.1 (d), 80.6 (s), 84.9 (d), 131.4 (d), 133.6 (d), 170.9 (s).

**4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-[(*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]cyclopentan-1-ols (15α- and 15β-25).** To a suspension of 55 mg (1.44 mmol, 3 equiv) of $LiAlH_4$ in 5 mL of THF was added slowly 280 mg (0.48 mmol) of **5** (15α/β 5.5:1), dissolved in 2 mL of THF, at −70 °C with constant stirring. The solution was allowed to warm to 0 °C over 1.5 h and stirred at 0 °C for 30 min. The reaction mixture was quenched carefully with 10 drops of water at 0 °C, diluted with diethyl ether, and stirred for 20 min at rt. The reaction mixture was filtered through a pad of silica gel, which was washed thoroughly with diethyl ether. After evaporation of the solvent, flash chromatography (hexane/ethyl acetate 10:1, gradient to 2:1) gave 40 mg (16%) of the unstable aldehydes **26**, 130 mg (53%) of an inseparable 4.5:1 15α/β mixture of pure diol **25**, and at last 20 mg (8%) of the TBS-deprotected cyclopentanecarboxylates **27** all as a colorless oils: $R_f$ (hexane/ethyl acetate 2:1) = 0.38; IR (film) 3381, 2928, 2857, 1465, 1376, 1360, 1254, 1182, 1130, 1098, 1061, 1025, 976, 836, 775, 715 $cm^{-1}$; MS (ESI) *m*/*z* 512 (100) [M + $H^+$], 158 (13); HRMS calcd for $C_{29}H_{58}NO_4Si$ + $H^+$ 512.4135, found 512.4130. 15α-**25**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.00 (s, 6H), 0.82 (m + s, 12H), 0.99 (br s, 3H), 1.00 (br s, 3H), 1.05 (br s, 3H), 1.08 (br s, 3H), 1.13−1.28 (m, 8H), 1.30−1.53 (m, 5H), 1.59 (m, 1H), 1.64 (dt, $J$ = 13.8, 4.3 Hz, 1H), 2.20 (br s, 2H), 2.25 (ddd, $J$ = 13.7, 7.1, 5.3 Hz, 1H), 2.36 (m, 1H), 2.75 (dt, $J$ = 8.4, 3.4 Hz, 1H), 3.61 (AB part of ABX system, $J$ = 11.4, 6.5, 6.0 Hz, 2H), 4.00 (dt, $J$ = 5.3, 8.2 Hz, 1H), 4.08 (m, 2H), 5.27 (dd, $J$ = 15.5, 8.4 Hz, 1H), 5.44 (ddd, $J$ = 15.5, 8.8, 0.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.7 (q), −4.6 (q), 14.0 (q), 17.3 (t), 17.9 (s), 20.5 (q), 22.6 (t), 25.2 (t), 25.8 (q), 31.9 (t), 34.1 (q), 34.6 (t), 35.0 (q), 40.1 (t), 43.3 (t), 52.2 (d), 52.6 (d), 59.2 (s), 62.9 (t), 75.5 (d), 76.7 (d), 84.8 (d), 129.8 (d), 134.7 (d). 15β-**25**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.00 (s, 6H), 0.83 (m+s, 12H), 1.01 (s, 3H), 1.04 (s, 3H), 1.09 (s, 3H), 1.10 (s, 3H), 1.14−1.63 (m, 14H), 1.68 (dt, $J$ = 13.8, 3.5 Hz, 1H), 2.16 (ddd, $J$ = 13.7, 6.9, 5.0 Hz, 1H), 2.44 (m, 2H), 2.76 (m, 1H), 3.08 (br s, 1H), 3.69 (A part of ABX system, $J$=11.9, 7.9 Hz, 1H), 3.76 (B part of ABX system, $J$ = 11.8, 4.6 Hz, 1H), 3.89 (m, 1H), 4.00 (m, 1H), 4.11 (m, 1H), 5.28 (dd, $J$ = 15.4, 10.7 Hz, 1H), 5.51 (dd, $J$ = 15.1, 9.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.9 (q), −4.8 (q), 14.0 (q), 17.2 (t), 18.0 (s), 20.6 (q), 20.7 (q), 22.6 (t), 25.2 (t), 25.8 (q), 31.9 (t), 34.2 (q), 34.5 (t), 39.1 (t), 39.6 (t), 43.0 (t), 53.4 (d), 53.6 (d), 59.4 (s), 60.9 (s), 61.4 (t), 74.3 (d), 78.3 (d), 84.0 (d), 132.5 (d), 135.3 (d).

**[(1*S**,2*S**,3*R**,4*R**)-4-(*tert*-Butyldimethylsilyloxy)-3-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-1-(triethylsilyloxy)cyclopent-2-yl]methyl Triflates (15α- and 15β-30).** To a solution of 270 mg (0.528 mmol) of diol **25**

(15$\beta$/$\alpha$ = 2.1:1) in 7 mL of dry $CH_2Cl_2$ was added 0.18 mL (1.58 mmol, 3 equiv) of dry 2,6-lutidine via syringe at −78 °C. After the solution was stirred for a short time, 0.091 mL (0.55 mmol, 1.05 equiv) of freshly opened triflic anhydride was added very slowly with good stirring, and the reaction mixture was stirred at −78 °C for ca. 30 min until complete by TLC. Then, 0.18 mL (0.79 mmol, 1.5 equiv) of triethylsilyl triflate was added at −78 °C, and the reaction mixture was stirred at this temperature for another 30 min. The consumption was monitored by TLC. The reaction mixture was quenched at −80 °C with 5 mL of water, diluted with 20 mL of diethyl ether, and warmed to rt in 10 min. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed twice with $NaHCO_3$ solution, twice with brine, and dried over $Na_2SO_4$. The solvent was evaporated in vacuo to give 400 mg of crude product. It was purified immediately on a short column (hexane/ethyl acetate 40:1, gradient to 20:1) to give 320 mg (81%) of **30** as an inseparable 2.1:1 mixture of 15$\beta$/$\alpha$-isomers as a colorless, unstable oil: $R_f$(hexane/ethyl acetate 10:1) = 0.57; IR (film) 2955, 2932, 2878, 1464, 1416, 1377, 1245, 1207, 1146, 1068, 1006, 975, 935, 834, 776, 728 $cm^{-1}$; MS (ESI) *m*/*z* 776 (16), 759 (48), 758 (100) [$M^+$], 690 (8), 668 (13), 625 (28), 624 (57), 608 (49), 557 (8), 536 (19), 535 (45), 494 (15), 476 (7), 379 (24), 322 (8), 158 (16); HRMS calcd for $C_{36}H_{70}F_3NO_6SSi_2 + H^+$ 758.4493, found 758.4495. 15$\beta$-**30**: $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ −0.003 (s, 3H), 0.000 (s, 3H), 0.51 (q, *J* = 7.9 Hz, 6H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 1.09−1.21 (m, 13H), 1.24−1.40 (m, 8H), 1.40−1.61 (m, 4H), 1.73 (m, 2H), 2.28 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.62 (dq, *J* = 8.1, 6.4 Hz, 1H), 2.82 (m, 1H), 3.89 (dt, *J* = 6.5, 5.2 Hz, 1H), 4.01 (dt, *J* = 7.3, 6.2 Hz, 1H), 4.17 (m, 1H), 4.51 (A part of ABX system, *J* = 10.1, 6.1 Hz, 1H), 4.60 (B part of ABX system, *J* = 9.9, 6.4 Hz, 1H), 5.17 (dd, *J* = 15.3, 9.5 Hz, 1H), 5.54 (dd, *J* = 15.3, 8.6 Hz, 1H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ −4.5 (q), −4.4 (q), 6.8 (t), 7.1 (q), 14.3 (q), 17.7 (t), 18.2 (s), 20.7 (q), 23.1 (t), 25.7 (t), 26.0 (q), 32.5 (t), 34.6 (q), 35.02 (t), 35.05 (q), 40.6 (t), 44.8 (t), 50.4 (d), 52.1 (d), 59.4 (s), 72.9 (d), 76.4 (d), 77.3 (t), 84.9 (d), 119.4 (q, $J_{C-F}$ = 320 Hz), 128.5 (d), 138.0 (d). 15$\alpha$-**30**: $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.02 (s, 3H), 0.04 (s, 3H), 0.52 (q, *J* = 7.9 Hz, 6H), 0.90 (t, *J* = 8.1 Hz, 9H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 9H), 1.09−1.21 (m, 13H), 1.24−1.40 (m, 8H), 1.40−1.61 (m, 4H), 1.73 (m, 2H), 2.17 (ddd, *J* = 6.4, 7.8, 14.1 Hz, 1H), 2.70 (quint, *J* = 7.1 Hz, 1H), 2.82 (m, 1H), 3.91 (m, 1H), 3.96 (ddd, *J* = 13.7, 7.1, 3.3 Hz, 1H), 4.17 (m, 1H), 4.44 (m, 2H), 5.08 (dd, *J* = 15.3, 9.4 Hz, 1H), 5.53 (dd, *J* = 15.1, 8.7 Hz, 1H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ −4.45 (q), −4.41 (q), 5.1 (t), 7.0 (q), 14.3 (q), 17.7 (t), 18.2 (s), 20.7 (q), 23.0 (t), 25.7 (t), 26.0 (q), 32.5 (t), 34.6 (q), 35.0 (t), 35.3 (q), 40.6 (t), 44.6 (t), 50.1 (d), 52.5 (d), 60.5 (s), 73.1 (d), 76.2 (d), 77.1 (t), 85.2 (d), 119.4 (q, $J_{C-F}$ = 320 Hz), 127.5 (d), 138.1 (d).

**(1*R**,2*R**,3*S**,4*S**)-1-(*tert*-Butyldimethylsilyloxy)-3-[7-(triethylsilyloxy)hept-2-yn-1-yl]-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-en-1-yl]-4-(triethylsilyloxy)cyclopentane (15$\alpha$- and 15$\beta$-3).** BuLi (0.21 mL, 0.336 mmol, 1.19 equiv based on **4**, 1.6 M in hexane) was added to a solution of 60 mg (0.283 mmol, 1.95 equiv based on **30**) of alkyne **4** in 4 mL of THF/HMPA 5:1 and stirred at −60 to −40 °C for 25 min. Triflate **30** (110 mg, 0.145 mmol, 15$\beta$/$\alpha$ = 2.1:1) dissolved in 1 mL of THF was added to the lithium acetylide at −78 °C. The vial and the syringe were rinsed with 1 mL of THF, and another 0.4 mL of HMPA was added to the reaction mixture. The reaction mixture was stirred for 3 h from −78 to 0 °C, until complete by TLC (hexane/ethyl acetate 20:1). The reaction was quenched with 10 mL of water and diluted with diethyl ether at 0 °C. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over $Na_2SO_4$. The solvent was evaporated in vacuo, and the crude product was purified by flash column chromatography using a short column (hexane/ethyl acetate 5:1). Compounds **3** (15$\beta$/$\alpha$ = 1.6:1), **4**, and **31** were isolated as an inseparable mixture of 140 mg weight. The yield of 15$\alpha$/$\beta$-**3** was calculated to be 72% from the $^1$H NMR spectrum and that of **31** to be 25%. The mixture was used without further separation in the next step: $R_f$ (hexane/ethyl acetate 20:1) = 0.4; MS (ESI) *m*/*z* 820 (100) [M + $H^+$], 706 (22), 688 (8), 608 (9), 494 (7), 158; HRMS calcd for $C_{47}H_{93}NO_4Si_3 + H^+$ 820.6491, found 820.6504. 15$\beta$-**3**: $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ −0.01 (s, 3H), 0.00 (s, 3H), 0.39−0.60 (m, 12H), 0.79−1.00 (m, 30H), 1.02−1.30 (m, 19H), 1.31−1.57 (m, 10H), 1.74 (m, 2H), 2.02 (m, 4H), 2.20−2.48 (m, 2H), 2.97 (m, 1H), 3.45 (t, *J* = 5.7 Hz, 2H), 4.07 (m, 1H), 4.17 (m, 2H), 5.49 (m, 2H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ −4.3 (q), −4.2 (q), 5.1 (t), 7.8 (q), 14.4 (q), 17.8 (t), 18.3 (s), 18.9 (t), 19.1 (t), 20.7 (q), 20.8 (q), 23.1 (t), 25.6 (t), 26.08 (t), 26.15 (q), 32.2 (t), 32.6 (t), 34.6 (q), 35.20 (t), 35.3 (q), 40.7 (t), 45.2 (t), 50.8 (d), 52.9 (d), 59.4 (s), 60.4 (s), 62.5 (t), 75.5 (d), 76.5 (d), 80.1 (s), 81.1 (s), 85.4 (d), 131.6 (d), 136.0 (d). 15$\alpha$-**3**: $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.01 (s, 3H), 0.04 (s, 3H), 0.39−0.60 (m, 12H), 0.79−1.00 (m, 30H), 1.02−1.30 (m, 19H), 1.31−1.57 (m, 10H), 1.74 (m, 2H), 2.02 (m, 2H), 2.20−2.48 (m, 4H), 2.97 (m, 1H), 3.43 (t, *J* = 6.4 Hz, 2H), 3.96 (m, 1H), 4.07 (m, 1H), 4.17 (m, 1H), 5.30 (dd, *J* = 15.3, 9.2 Hz, 1H), 5.58 (m, 1H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ −4.3 (q), −4.2 (q), 5.3 (t), 7.1 (q), 14.4 (q), 17.8 (t), 18.3 (s), 18.9 (t), 19.0 (t), 20.6 (q), 20.7 (q), 23.2 (t), 25.79 (t), 25.84 (t), 26.2 (q), 32.3 (t), 32.5 (t), 34.5 (q), 35.16 (t), 35.4 (q), 40.8 (t), 45.1 (t), 50.6 (d), 53.4 (d), 59.4 (s), 60.5 (s), 62.5 (t), 75.9 (d), 76.1 (d), 79.7 (s), 80.8 (s), 85.8 (d), 129.8 (d), 136.3 (d).

**Methyl 7-[(1*S**,2*R**,3*R**)-3-(*tert*-Butyldimethylsilyloxy)-5-oxo-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)-oct-1-enyl]cyclopent-1-yl]hept-5-ynoate (15$\alpha$- and 15$\beta$-32). 1. Tandem TES Deprotection/Swern-Type Oxidation.** A 2.0 M solution of oxalyl chloride in $CH_2Cl_2$ (0.43 mL, 0.86 mmol, 7 equiv) was added at −70 °C to a solution of 0.122 mL (1.72 mmol, 14 equiv) of DMSO in 2 mL of dry $CH_2Cl_2$ and stirred for 40 min at this temperature. The mixture of 15$\alpha$/$\beta$-**3** (0.042 mmol), **4** (0.047 mmol), and **31** (0.034 mmol) (60 mg, 1.25:1.4:1) dissolved in 3 mL of dry $CH_2Cl_2$ was added at −70 °C. The reaction mixture was stirred for 1 h 40 min at −70 to −40 °C. It was cooled to −75 °C, and 0.48 mL $Et_3N$ (3.44 mmol, 28 equiv) was added. The consumption was followed by TLC. The reaction was stirred at −40 to 0 °C for 2.5 h and quenched with 5 mL of water. The aqueous layer was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuum. The crude product was suspended in diethyl ether and separated from a white solid to give 100 mg of a pale yellow oil. The reaction was similarly repeated with further 30 mg of the same mixture of 15$\alpha$,$\beta$-**3**, **4**, and **31**. The combined crude products from both experiments (total 130 mg) were used immediately for the next step.

**2. Aldehyde to Acid Oxidation and Esterification to 32.** The crude mixture of aldehydes (130 mg) was dissolved in 4.2 mL of a 2:1 *t*-BuOH/$H_2O$ mixture. $NaH_2PO_4$ (104.4 mg, 0.87 mmol) dissolved in a small amount of water and 2-methyl-2-butene (0.184 mL, 1.74 mmol) were added to this solution. $NaClO_2$ (79 mg, 0.87 mmol) was added in one portion at 0 °C, and the reaction was stirred at rt for 2 h. The consumption of the aldehydes was followed by TLC. The reaction mixture was quenched with 4 mL of a 5% HCl solution. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuum. The mixture of crude acids (100 mg) was dissolved in 5.6 mL of a dry 8.5:1 THF/MeOH mixture. Trimethylsilyldiazomethane (0.725 mL, 1.45 mmol, 2.0 M in $Et_2O$) was added, and the reaction mixture was stirred at rt for 3 h. The formation of the methyl esters was followed by TLC. The solvent was evaporated to give 100 mg of crude esters. Flash chromatography (hexane/ethyl acetate 40:1, gradient to 2:1) gave first 20 mg of TES-alkyne methyl ester (with hexane/ethyl acetate 40−20:1), 5 mg of a mixture of 15$\beta$-**32** and a PG isomer (5.25:1, with hexane/ethyl acetate 10:1, for details see Supporting

Information), and 23 mg of **32** (15$\beta$/$\alpha$ = 1.4:1, with hexane/ethyl acetate 5:1): yield 28 mg (72%) from 15$\alpha$/$\beta$-**3** in an overall 15$\beta$/$\alpha$-ratio of 1.8:1 and a **32**:PG isomer ratio of 34:1; $R_f$(hexane/ethyl acetate 5:1) = 0.54; IR (film) 2953, 2931, 2858, 1745, 1466, 1437, 1375, 1361, 1255, 1133, 1077, 1006, 975, 909, 836, 778 $cm^{-1}$; MS (ESI) *m*/*z* 640 (100) [M + $Na^+$], 618 (16), 484 (52), 158 (26); HRMS calcd for $C_{36}H_{63}NO_5Si + Na^+$ 640.4373, found 640.4371. 15$\beta$-**32**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.02 (s, 3H), 0.07 (s, 3H), 0.92 (m, 12H), 1.14−1.52 (m, 12H), 1.21 (s, 3H), 1.23 (s, 3H), 1.26 (s, 3H), 1.27 (s, 3H), 1.57 (m, 1H), 1.68 (m, 2H), 1.84 (m, 1H), 2.02 (m, 2H), 2.20 (m, 1H), 2.25 (t, *J* = 7.4 Hz, 2H), 2.35 (dd, *J* = 18.7, 5.7 Hz, 1H), 2.41 (ddt, *J* = 16.7, 9.5, 2.4 Hz, 1H), 2.88 (ddt, *J* = 16.6, 3.8, 2.3 Hz, 1H), 2.95 (dt, *J* = 3.6, 8.9 Hz, 1H), 3.16 (br t, *J* = 8.6 Hz, 1H), 3.33 (s, 3H), 4.25 (m, 1H), 4.33 (dt, *J* = 2.7, 5.5 Hz, 1H), 5.30 (dd, *J* = 15.4, 9.3 Hz, 1H), 5.72 (dd, *J* = 15.4, 8.8 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ −4.75 (q), −4.71 (q), 14.27 (q), 16.0 (t), 17.69 (t), 18.23 (s), 18.4 (t), 20.6 (q), 20.73 (q), 23.07 (t), 24.50 (t), 25.7 (t), 25.96 (q), 32.3 (t), 32.82 (t), 34.5 (q), 34.9 (t), 35.3 (q), 40.4 (t), 40.6 (t), 46.1 (t), 50.8 (d), 50.99 (q), 52.1 (d), 59.4 (s), 60.5 (s), 73.1 (d), 79.6 (s), 80.3 (s), 85.2 (d), 128.6 (d), 137.5 (d), 172.9 (s), 213.6 (s). 15$\alpha$-**32**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.02 (s, 3H), 0.08 (s, 3H), 0.89 (m, 12H), 1.11−1.51 (m, 12H), 1.18 (s, 3H), 1.22 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.56 (m, 1H), 1.66 (m, 2H), 1.88 (m, 1H), 2.01 (m, 2H), 2.08 (m, 3H), 2.23 (t, *J* = 7.7 Hz, 2H), 2.82 (m, 1H), 2.98 (ddd, *J* = 3.9, 7.6, 11.3 Hz, 1H), 3.22 (m, 1H), 3.33 (s, 3H), 4.13 (dt, *J* = 4.6, 8.9 Hz, 1H), 4.25 (m, 1H), 4.96 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.75 (dd, *J* = 15.2, 9.0 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ −4.81 (q), −4.68 (q), 14.34 (q), 15.9 (t), 17.68 (t), 18.23 (s), 18.3 (t), 20.4 (q), 20.73 (q), 23.14 (t), 24.54 (t), 25.6 (t), 25.98 (q), 32.4 (t), 32.78 (t), 34.2 (q), 35.0 (t), 36.2 (q), 40.5 (t), 40.7 (t), 45.6 (t), 49.9 (d), 51.01 (q), 52.9 (d), 59.2 (s), 60.6 (s), 72.6 (d), 79.1 (s), 80.0 (s), 85.8 (d), 127.2 (d), 138.6 (d), 172.8 (s), 213.9 (s).

**Methyl 7-[(1*S**,2*R**,3*R**)-3-Hydroxy-5-oxo-2-[(*R**,*E* and *S**,*E*)-3-(2,2,6,6-tetramethylpiperidin-1-yloxy)oct-1-enyl]cyclopentyl]hept-5-ynoate (33).** HF (40%, 0.11 mL, 2.5 mmol, 9.2 equiv based on pyridine) was added to a solution of 0.022 mL of pyridine (0.272 mmol, 8.5 equiv based on 15$\alpha$/$\beta$-**32**) in 1.5 mL of $CH_3CN$ at 0 °C. A solution of 20 mg (0.032 mmol) of pure **32** (15$\beta$/$\alpha$ 1.4:1) dissolved in 1 mL of acetonitrile was added at 0 °C to this solution, and the flask was rinsed with 1 mL of acetonitrile. The reaction mixture was allowed to warm to room temperature and stirred until complete by TLC ($R_f$ (**32**, hexane/ethyl acetate 5:1) = 0.56; $R_f$ (**33**-major, hexane/ethyl acetate 2:1) = 0.48; $R_f$ (**33**-minor, hexane/ethyl acetate 2:1) = 0.57). After 19 h, the reaction was quenched with satd $NaHCO_3$ solution and diluted with $CH_2Cl_2$. The aqueous layer was extracted three times with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuum. The crude product (18.7 mg) was purified by flash chromatography (hexane/ethyl acetate 4:1, gradient to 2:1, and finally to ethyl acetate). Product 15$\alpha$/$\beta$-**33** eluted with hexane/ethyl acetate 2:1: yield 10.2 mg (63%) with an IsoP:PG ratio of > 9:1; IR (film) 3475, 2931, 2871, 1742, 1459, 1437, 1376, 1240, 1162, 1134, 975 $cm^{-1}$; MS(ESI) (110 V) *m*/*z* 1029 (20) [2M + $Na^+$], 526 (100) [M + $Na^+$], 370 (39); HRMS calcd for $C_{30}H_{49}NO_5 + Na^+$ 526.3508, found 526.3506. **33** (major isomer): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.73 (br s, 1H), 0.91 (m, 3H), 1.11−1.44 (m, 21H), 1.48−1.62 (m, 4H), 1.66 (m, 2H), 1.83 (m, 1H), 1.95−2.09 (m, 3H), 2.12−2.28 (m, 3H), 2.37 (m, 1H), 2.79 (m, 1H), 2.87 (m, 1H), 2.93 (m, 1H), 3.31 (s, 3H), 4.03 (m, 1H), 4.19 (m, 1H), 5.17 (dd, *J* = 15.4, 9.2 Hz, 1H), 5.65 (dd, *J* = 15.4, 8.8 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.31 (q), 15.9 (t), 17.7 (t), 18.5 (t), 20.6 (q), 20.7 (q), 23.09 (t), 24.48 (t), 25.7 (t), 32.3 (t), 32.85 (t), 34.5 (q), 35.0 (t), 35.2 (q), 40.5 (t), 40.6 (t), 45.1 (t), 50.7 (d), 51.06 (q), 51.4 (d), 59.4 (s), 60.6 (s), 71.9 (d), 79.7 (s), 80.22 (s), 85.2 (d), 128.3 (d), 137.5 (d), 173.1 (s), 213.6 (s). **33** (minor isomer): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.73 (br s, 1H), 0.91 (m, 3H), 1.11−1.44 (m, 21H), 1.48−1.62 (m, 4H), 1.66 (m, 2H), 1.83 (m, 1H), 1.95−2.09 (m, 3H), 2.12−2.28 (m, 4H), 2.70 (m, 1H), 2.79 (m, 1H), 2.93 (m, 1H), 3.33 (s, 3H), 4.09 (m, 1H), 4.19 (m, 1H), 5.13 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.69 (dd, *J* = 15.2, 8.9 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.35 (q), 16.1 (t), 17.6 (t), 18.3 (t), 20.5 (q), 20.7 (q), 23.13 (t), 24.49 (t), 25.6 (t), 32.4 (t), 32.81 (t), 34.2 (q), 35.1 (t), 35.7 (q), 40.4 (t), 40.5 (t), 45.0 (t), 49.9 (d), 51.07 (q), 52.1 (d), 59.3 (s), 60.4 (s), 71.6 (d), 79.1 (s), 80.21 (s), 85.6 (d), 127.8 (d), 137.9 (d), 173.0 (s), 213.9 (s). **34** (detectable resonances): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 1.63 (m, 1H), 2.13 (m, 1H), 2.45 (m, 1H), 2.85 (m, 1H), 3.28 (s, 3H), 3.59 (m, 1H), 4.25 (m, 1H), 5.24 (dd, *J* = 15.4, 8.3 Hz, 1H), 5.73 (dd, *J* = 15.4, 9.0 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 47.0 (t), 51.10 (q), 52.5 (d), 53.6 (d), 72.1 (d), 78.1 (s), 81.4 (s), 85.5 (d), 131.0 (d), 137.2 (d), 173.2 (s), 211.3 (s).

**Methyl 7-[(1*S**,2*R**,3*R**)-3-Hydroxy-5-oxo-2-[(*E*)-3-oxooct-1-enyl]cyclopentyl]hept-5-ynoate (35), (1*R**,2*R**,3*R**)-(36), and (1*S**,2*S**,3*R**)-(37).** *m*-CPBA (70%, 10 mg, 0.04 mmol, 2 equiv) was added to a solution of 10 mg of ketone 15$\alpha$,$\beta$-**33** and **34** (0.02 mmol, 9:1) in 3 mL of dry $CH_2Cl_2$ at 0 °C. The reaction was monitored by TLC. After 13 min, the reaction was quenched with 5 mL of concd $Na_2S_2O_3$ solution, diluted with ethyl acetate, and stirred for 10 min at rt. The aqueous layer was extracted three times with ethyl acetate and three times with diethyl ether. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuum. The crude product was purified on a short column with hexane/ethyl acetate 5:1 gradient to ethyl acetate. The product contaminated with *m*-chlorobenzoic acid (total 10 mg) eluted with hexane/ethyl acetate 1:1 and ethyl acetate. A second purification with hexane/ethyl acetate 2:1 and 1:1 gave 5.4 mg (75% yield) of an inseparable mixture of **35**, **36**, and **37** in a ratio of IsoP/PG/12-*epi*-IsoP = 9:4:1: IR (film) 3463 (br), 2954, 2931, 2870, 1740, 1669, 1628, 1436, 1373, 1341, 1319, 1226, 1161, 1079, 984 $cm^{-1}$; MS (ESI) *m*/*z* 747 (15), 385 (100) [M + $Na^+$]; HRMS calcd for $C_{21}H_{30}O_5 + Na^+$ 385.1991, found 385.1988. **35** (IsoP isomer): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.86 (m, 3H), 1.13−1.26 (m, 4H), 1.32 (m, 1H), 1.53−1.68 (m, 4H), 1.92−1.98 (m, 3H), 2.01−2.16 (m, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 2.48 (ddt, *J* = 17.0, 4.4, 2.3 Hz, 1H), 2.68 (dt, *J* = 4.1, 8.9 Hz, 1H), 2.84 (ddd, *J* = 11.5, 8.3, 3.2 Hz, 1H), 3.31 (s, 3H), 3.86 (dt, *J* = 5.9, 3.1 Hz, 1H), 6.18 (dd, *J* = 15.6, 0.6 Hz, 1H), 6.54 (dd, *J* = 15.6, 9.9 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.2 (q), 16.3 (t), 18.4 (t), 23.0 (t), 24.1 (t), 24.5 (t), 31.8 (t), 32.9 (t), 41.0 (t), 45.4 (t), 50.2 (d), 51.18 (q), 51.5 (d), 71.2 (d), 78.7 (s), 81.0 (s), 133.3 (d), 140.8 (d), 173.1 (s), 198.4 (s), 212.8 (s). **36** (PG isomer): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.86 (m, 3H), 0.96 (br s, 1H), 1.13−1.26 (m, 4H), 1.53−1.68 (m, 5H), 1.92−1.98 (m, 2H), 2.01−2.16 (m, 2H), 2.17 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 2.37 (dd, *J* = 18.3, 7.5 Hz, 1H), 2.58 (ddt, *J* = 17.0, 4.9, 2.4 Hz, 1H), 2.78 (dt, *J* = 11.8, 8.7 Hz, 1H), 3.28 (s, 3H), 3.48 (m, 1H), 6.24 (dd, *J* = 15.6, 0.7 Hz, 1H), 6.63 (dd, *J* = 15.6, 8.5 Hz, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.2 (q), 17.3 (t), 18.2 (t), 23.0 (t), 24.0 (t), 24.4 (t), 31.9 (t), 32.9 (t), 41.4 (t), 46.7 (t), 51.22 (q), 52.6 (d), 53.1 (d), 71.6 (d), 77.8 (s), 81.9 (s), 132.2 (d), 144.2 (d), 173.3 (s), 198.4 (s), 210.3 (s). **37** (12-*epi*-IsoP isomer, detectable resonances): $^1$H NMR (600 MHz, $C_6D_6$) 2.01−2.16 (m, 3H), 2.25 (m, 1H), 2.64 (ddt, *J* = 16.9, 4.5, 2.3 Hz, 1H), 2.73 (ddd, *J* = 12.0, 8.7, 3.7 Hz, 1H), 3.30 (s, 3H), 3.79 (t, *J* = 4.1 Hz, 1H), 6.91 (dd, *J* = 16.0, 8.5 Hz, 1H).

**13,14-Dihydro-15-oxo-15-$E_2$-IsoP Methyl Ester (2) and 13,14-Dihydro-15-oxo-PG$E_2$ Methyl Ester (*rac*-IV).** In a Schlenk flask, 5 mg of the Lindlar catalyst (~5% Pd on calcium carbonate, poisoned with lead, filling code 1308421 11607082) was evacuated and flushed with nitrogen three times. In a separate Schlenk flask, a 10:6:1 mixture of HPLC-grade ethyl acetate/HPLC-grade ethanol/distilled pyridine was deoxygenated by five freeze−pump−thaw cycles, and 2 mL of this solvent mixture was added to the catalyst. The suspension was subsequently evacuated and flushed three times with hydrogen and stirred under a positive pressure of

$H_2$ at rt for 50 min. Hydrogenation was started by addition of a carefully deoxygenated solution of 5 mg (0.014 mmol) of 15-oxo-5,6-dehydro-$E_2$-IsoP, 15-oxo-5,6-dehydro-$PGE_2$, and 12-*epi*-15-oxo-5,6-dehydro-$E_2$-IsoP **35/36/37** (9:4:1) in 1.7 mL of the same solvent mixture. The reaction mixture was stirred at rt for 24 h under a slightly positive pressure of hydrogen (two balloons of 26 cm diameter). The reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite, which was washed with ethyl acetate and diethyl ether. The crude product was purified by flash chromatography (hexane/ethyl acetate 5:1, gradient to ethyl acetate). Products **2** and *rac*-**IV** were obtained as a partly separable mixture with hexane/ethyl acetate 1:1 and ethyl acetate ($R_f$ (hexane/ethyl acetate 1:1) = 0.23, 0.30): yield 4.6 mg (90%) in a ratio of 1.5:1; IR (film) 3464 (br), 3007, 2953, 2931, 2869, 1738, 1715, 1438, 1372, 1243, 1163, 1079, 1016 $cm^{-1}$; MS (ESI) *m*/*z* 389 (100) [M + $Na^+$]; HRMS calcd for $C_{21}H_{34}O_5$ + $Na^+$ 389.2304, found 389.2302. **2**: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.87 (m, 3H), 1.06 (m, 1H), 1.12−1.18 (m, 2H), 1.21−1.30 (m, 2H), 1.30 (br s, 1H), 1.43−1.66 (m, 5H), 1.99 (t, $J$ = 7.4 Hz, 2H), 1.87−2.00 (m, 6H), 2.01−2.12 (m, 3H), 2.18 (m, 1H), 2.50 (m, 1H), 2.63 (m, 1H), 3.36 (s, 3H), 3.73 (dt, $J$ = 5.9, 2.7 Hz), 5.32 (m, 1H), 5.43 (m, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.2 (q), 21.1 (t), 22.9 (t), 23.1 (t), 23.7 (t), 24.97 (t), 26.9 (t), 31.7 (t), 33.30 (t), 40.4 (t), 42.6 (t), 44.9 (t), 46.7 (d), 50.6 (d), 51.02 (q), 70.5 (d), 128.4 (d), 130.4 (d), 173.6 (s), 208.4 (s), 215.0 (s). *rac*-**IV** methyl ester: $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ 0.87 (m, 3H), 1.12−1.18 (m, 2H), 1.21−1.30 (m, 2H), 1.43−1.66 (m, 7H), 1.68 (m, 1H), 1.88 (br s, 1H), 1.93 (dd, $J$ = 18.3, 7.2 Hz, 1H), 2.04 (t, $J$ = 7.4 Hz, 2H), 2.01−2.12 (m, 4H), 2.18 (dt, $J$ = 7.0, 3.1 Hz, 2H), 2.29 (ddd, $J$ = 18.1, 6.8, 1.1 Hz, 1H), 2.35 (m, 1H), 2.48 (m, 1H), 3.33 (s, 3H), 3.53 (q, $J$ = 6.9 Hz, 1H), 5.32 (m, 1H), 5.38 (m, 1H); $^{13}$C NMR (150 MHz, $C_6D_6$) $\delta$ 14.2 (q), 22.9 (t), 23.7 (t), 25.05 (t), 26.0 (t), 26.7 (t), 26.8 (t), 31.7 (t), 33.32 (t), 39.9 (t), 42.7 (t), 47.1 (t), 47.9 (d), 51.08 (q), 53.9 (d), 73.1 (d), 127.7 (d), 131.1 (d), 173.4 (s), 209.4 (s), 214.1 (s). The NMR data of *rac*-**IV** methyl ester are in agreement with those of the methyl ester synthesized from commercially available 13,14-dihydro-15-oxo-$PGE_2$; see the Supporting Information.

**Acknowledgment.** We gratefully acknowledge generous funding by Deutsche Forschungsgemeinschaft (Ja896/3-1) and a grant of the Czech Academy of Sciences (Z4 055 0506). E.D. thanks Friedrich-Ebert-Stiftung for a doctoral fellowship.

**Supporting Information Available:** Procedures, analytical and full spectral characterization of compounds **2**, **3**, **5**, **8**, **12**−**19**, **22**−**30**, **32**−**37**, and *rac*-**IV**. Copies of $^1$H and $^{13}$C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.