Diels−Alder Approach to Isoprostanes. Total Synthesis of $iPF_{2\alpha}$-V

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Abstract: Isoprostanes (iPs) are a group of natural products formed in vivo by a free-radical oxygenation of arachidonic acid. They are isomeric with prostaglandins; whereas enzymatically produced prostaglandins, such as $PGF_{2\alpha}$ have the two side chains in the *trans* stereochemistry, the side chains of the isoprostanes are mostly in the *cis* configuration. A novel synthesis of iPs is described and illustrated with the synthesis of $iPF_{2\alpha}$-V, **8**. The synthetic material allowed us to identify this iP in human urine. Because of this *cis* relationship between the two side chains in the structures of iPs, we selected a synthetic design based on the Diels−Alder rection which will guarantee that the two side chains, which will be derived from the diene part, will be *cis* to each other. By substituting the OH of the hydroxycyclopentenone **14** with a bulky TBDPS group, we controlled the face selectivity of the approaching diene **17a** from the less hindered top face of the five-membered ring. We would obtain eventually the two OH groups of the isoprostanes α to the plane of the ring and the two isoprostane side chains *cis* to each other and *anti* to the OH groups.

Introduction

Isoprostanes (iPs), a newly discovered class of natural products are isomeric with prostaglandins and are produced in vivo by a nonenzymatic free-radical peroxidation process on polyunsaturated fatty acids and esters.[1] Arachidonic acid (AA), a major polyunsaturated fatty acid, is the substrate for several enzymatic systems such as the cyclooxygenases, which produce prostaglandins, and the lipoxygenases, which make leukotrienes and HPETEs. It has been proposed that AA, which is mostly esterified to phospholipid membranes and lipoproteins, can also form four groups of isoprostanes, III, IV, V, and VI, by a free-radical oxygenation process[1−6] (Scheme 1).

We have proposed two mechanisms for the formation of iPs[7] based in part on some original reports.[8−12] Scheme 1 also shows the *syn-anti-syn* structures **6**−**9**. These are the isoprostanes we selected to focus on synthetically, and group V in particular. These are also the representatives on which we have based our newly proposed nomenclature for isoprostanes.[13] The broader issue we are facing in this field is to know which classes of iPs are produced in vivo and in what proportions and what is the biological impact of the individual iPs. For example, we already know by using mass spectrometric determinations, that iPs appear to be formed in much higher amounts than their isomers, the prostaglandins,[1] and that $iPF_{2\alpha}$-III[2] is a potent vasoconstrictor,[14,15] aggregates platelets, and may possibly express its biological activity via a receptor.[16] We have also shown that 8,12-*iso*-$iPF_{2\alpha}$-III possesses biological activity similar to that of $PGF_{2\alpha}$.[17] In addition, since AA is mainly esterified to phospholipids, which are the main constituents of cell membranes, the formation of polyhydroxylated derivatives such as the iPs in the midst of phospholipids is bound to disturb the hydrophobicity of the tight cell membrane, leading to cell leakage and death. Another important application resulting from our discovery of group VI iPs in urine is the possibility of quantitating them and using them as a noninvasive index of oxygen stress in diseases.[18,19] For example, we have been able to show that increased levels of $iPF_{2\alpha}$-VI are formed as a result of the oxidation of low-density lipoprotein or LDL. The use

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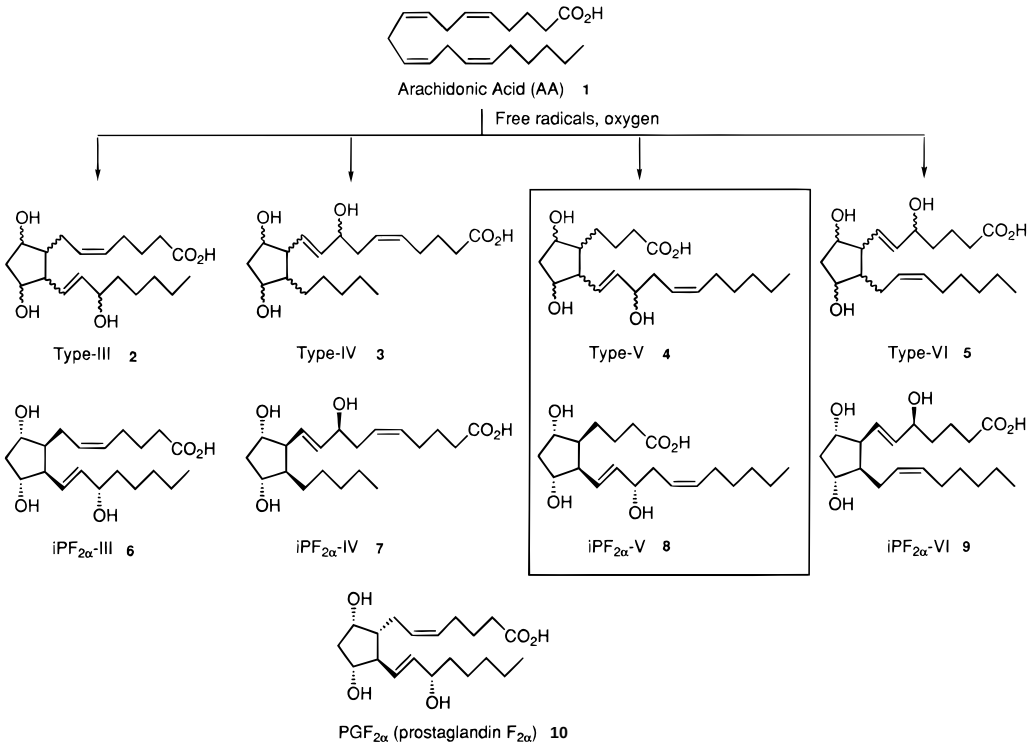
Scheme 1



of vitamin E, a free-radical inhibitor, has reduced the free-radical oxidation as judged by the lowering of $iPF_{2\alpha}$-VI to normal levels.[18] Oxidation of LDL is thought to be the initial step leading to plaque deposition and atherosclerosis.

The availability of synthetic isoprostanes at this early juncture is the rate-determining factor for progress in the field. We have reported on a general method for the synthesis of iPs which we applied to groups III, IV, and VI, the main feature of which is a radical cyclization step to form the five-membered ring and at the same time orient the two side chains in the desired *cis* configurations.[2−5,20−22] Other independent syntheses of some of group III iPs have appeared recently.[23−25]

We are reporting here on a novel and general method for the synthesis of iPs based on the Diels−Alder reaction and its use in the first total synthesis of a group V isoprostane, namely $iPF_{2\alpha}$-V, **8**. We are also reporting, using the synthetic standard, on the first identification of a Group V iP in human urine.

Retrosynthesis

One of the important differences between the structures of prostaglandins, e.g., $PGF_{2\alpha}$, **10**, and those of the isoprostanes is the *cis* relationship of the side chains in the latter, as compared to the *trans* side chains in the enzymatically produced compounds. This difference changes the complexion of the chemistry one is contemplating when dealing with the isoprostanes. The predominance of the *cis* structural arrangement in five-membered ring molecules formed by a radical cyclization has been documented.[2,8,26−28] Whereas it is possible and, in fact, expected that some *trans*-isoprostanes will be formed, we anticipate these to be minor components.[7]

Because of this *cis* relationship between the two side chains in the structures of iPs, we selected a synthetic design based on the Diels−Alder reaction[29,30] (Scheme 2) which will guarantee that the two side chains, which will be derived from the diene part, will be *cis* to each other. Furthermore, we thought that by controlling the face selectivity by having the diene approaching from the less hindered face, we would obtain eventually the two OH groups of the isoprostanes α to the plane of the five-membered ring and the two isoprostane side chains *cis* to each other and *anti* to the OH groups or β with respect to the plane of the ring. To achieve this purpose we substituted the hydroxy group with a TBDPSi group. We were encouraged in that route by some past results in which we had been able to control the face-selectivity in an inverse electron demand Diels−Alder reaction. We were particularly impressed by the exclusive control of the stereochemistry by a substituent α to the double bond of the dienophile, resulting in an approach of the diene from the opposite face of this substituent.[31−33]

An important structural feature of the isoprostanes, which we took into account from the outset, is the position of the double bonds on the two side chains. As can be seen from the

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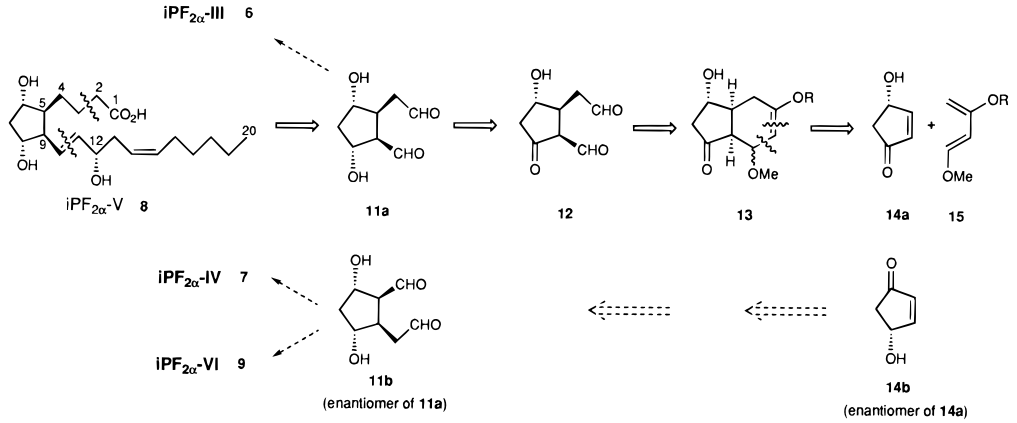
Scheme 2



four groups of iPs derived from AA (Scheme 1), we have three structural variations of the side chains. All are accessible by the strategy proposed here, and the four groups of *syn-anti-syn* isoprostanes can be prepared from intermediates such as **11a** and its enantiomer, **11b**.

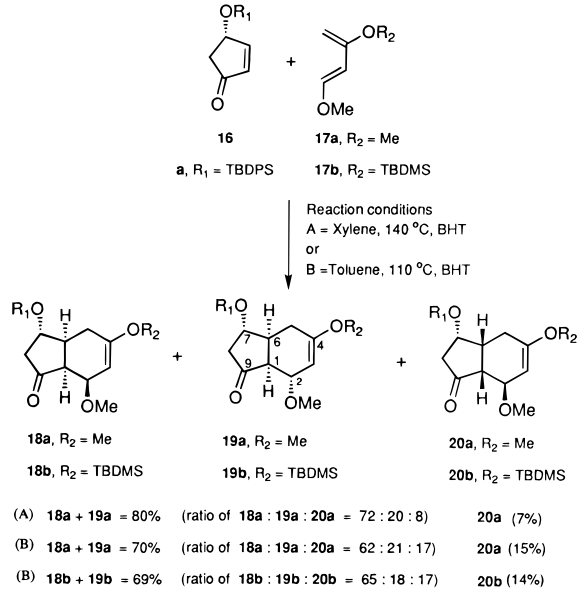
The selection of the electron-rich Danishefsky dienes[34] was made in order to ensure exclusive regioselectivity in the Diels−Alder reaction and that at some point later in the synthesis we could excise by oxidative cleavage the unnecessary carbon to afford a two-carbon substituent for the elaboration of the top side chain and one carbon for the elaboration of the bottom side chain.

Another issue we considered before the start of the synthesis was the stereocontrolled reduction of the five-membered ring carbonyl on the Diels−Alder adducts. Here again, we were counting on the shielding of the α face by the bulky TBDPSi group to force the hydride attack from the top or β face in order to afford the desired α-hydroxy derivative. A hydride reduction not unlike the one we were considering has been described.[35] However, as can be seen later, the hydride reduction did not proceed as anticipated. In summary, our plan was to use the asymmetric center in **14**, which would correspond to carbon 6 in the final isoprostane, to control the stereocenters at 5 and 9 by the Diels−Alder reaction and the asymmetric center at 8 by a stereocontrolled reduction. The fifth asymmetric center at carbon 12 can be introduced by a stereoselective reduction of an α,β-unsaturated carbonyl.

Results and Discussion

The reaction between the dienophile **16a**, prepared in high enantiomeric excess (≥99%),[36] and the diene **17a**[37] was carried out in xylene as described in Scheme 3. Three products, **18a**, **19a**, and **20a**, were obtained in 87% yield and in a ratio of 72, 20, and 8, respectively, or in a 92:8 ratio of products resulting from attack of the diene from the less hindered side to the product resulting from an attack from the more hindered side. The reaction has also been carried out in a similar fashion in toluene at 110 °C. The reaction times are longer (∼18 h), and the yields somewhat lower. More importantly from our perspective is the fact that there was significantly less attack from the hindered face, **18a** and **19a** were obtained in 80% isolated yield instead of 70% in toluene, and **20a** was obtained

Scheme 3



in 7% yield instead of ∼14−15% in toluene. 2,6-Di-*tert*-butyl-4-methyl phenol (BHT) was added in all of the experiments to prevent or slow the polymerization of the dienes.

The major product was the anticipated one and is probably formed by an *endo−anti* attack of the less hindered face (Scheme 4). The minor *syn-anti-syn* product **19a** is possibly formed by an *exo−anti* attack from the less hindered face. This is also a useful product for our purposes since we intended to cleave this ring in any event. The other way this product could have been formed is by an *endo−anti* attack from the less hindered face by the *cis* methoxy isomer of the diene **17a** if it were present in our original diene. We could not, however, find NMR evidence for that. The third product of the reaction is most likely the result of an *exo−syn* attack from the more hindered face.

The identity of the products was established by NMR, COSY, NOE, and MS studies and by chemical transformations. The three products clearly show by NOE, decoupling studies and by coupling constant analysis, the *cis* relationship of the ring junction protons, indicating to us that those are primary Diels−Alder products (see Experimental Section). The zero coupling constant observed for C2−H and C1−H for the α product **19a** is an indication that the dihedral angle between the two hydrogens is about 90°. This situation fits only the α structure **19a** and is confirmed by model studies. Equally, the coupling constant between the same two hydrogens in the major β product

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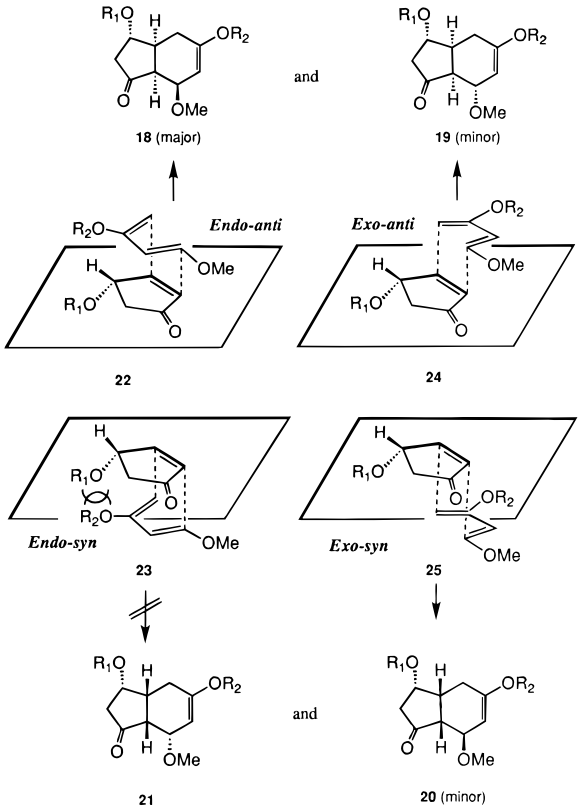
Scheme 4

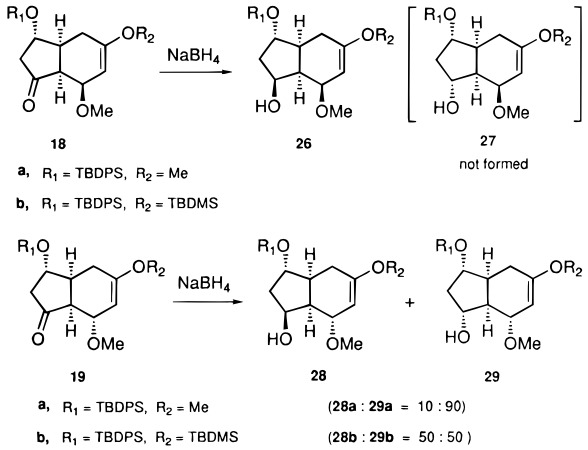


18a is 5.7 (benzene), indicating a dihedral angle of 40−60°. Examination of molecular models shows that the dihedral angles between these two hydrogens can vary from −50° to a maximum of 40° by changing the conformation of the molecule. This set of data fits only the β structure **18a**. It is interesting to note that MM_2 calculations for the minimum energy conformation for **19a** show a dihedral angle of 88° for the α compound and 45° for the β compound **18a**, which fits quite well with our experimental observations and model studies. NOE studies in two different solvent systems also confirm the identity of **18a**, **18b**, and **19a** and **19b**. The fact that **18a** and **19a** are methoxy epimers was also established unambiguously by rearranging the allylic methoxy of the two products to a single compound, the dimethyl ketal **30a**, (Scheme 6). Furthermore, aldehyde **37** (Scheme 9) has been transformed to bicyclic lactone **45** and compared to an authentic sample.[2] This transformation is discussed later in this section. This establishes the stereochemical assignment of structures **18** and **19**. The structural assignment of **20** was based on NMR evidence, NOE, MS, and the fact that there is a zero coupling constant between hydrogens at C2 and C1, indicating a dihedral angle of approximately 90°. This arrangement fits only structure **20**.

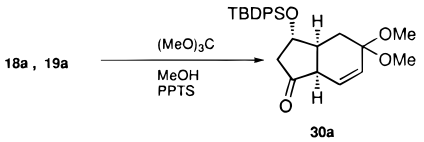
We have also performed the Diels−Alder reaction with **17b** R_2 = TBDMS without appreciable differences in results (Scheme 3). The bicyclic Diels−Alder products **18**, **19**, and **20** are not stable in all cases and do not store well. The two dimethoxy epimers **18a** and **19a** overlap on TLC and have been purified by careful repeated chromatography for characterization purposes. Usually the mixture is used as such for the next step as is described later. The TBDMS products **18b** and **19b** are slightly more stable and somewhat easier to separate. However, for reasons which will become apparent later, these intermediates have not been selected to complete the total synthesis of **8**.

The next step in the planned synthesis was the reduction of the carbonyl group in **18a** and **18b**, and as mentioned, we were

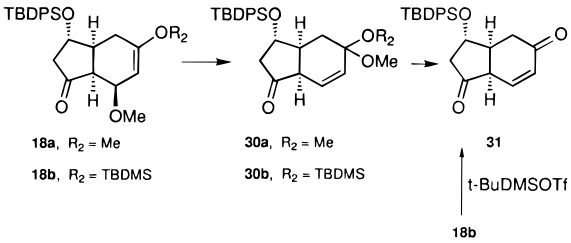
Scheme 5



Scheme 6



Scheme 7

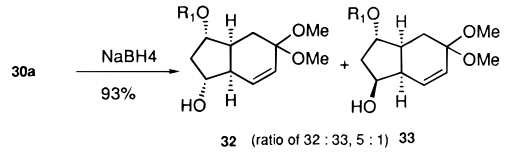


expecting a hydride attack from the β face, which we anticipated to be the less crowded face, to yield the desired α-hydroxy group. We were counting on the shielding of the α face by the bulky TBDPS group to force the reduction from the top. Instead, the reduction of **18a** proceeded entirely the opposite way, and **26a** was obtained exclusively (Scheme 5). Under the same conditions, the epimeric α product **19a** afforded a 10:90 mixture of **28a** and **29a**, respectively, favoring hydride attack from the top face.

It was becoming obvious that the β-methoxy group in the major product **18a** was interfering seriously with an approach from the top. At this point, we turned to a plan we had considered in our original design, that is, to remove the methoxy group from that position. Equally, when we planned the Diels−Alder reaction, we were not sure of the extent of the formation of the α-methoxy isomer **19a**, if any, and to take advantage of the two products for further synthetic manipulations, we considered transforming **18a** and **19a** by an allylic rearrangement to a common gem dimethoxy derivative **30a** (Scheme 6). Alternatively, a related transformation to yield α,β-unsaturated ketones was described in the literature,[38] and we thought we could take advantage of it. As it turned out (Scheme 7), both reactions worked very well, in fact, quantitatively. The transformation of **18a** and **19a** to the gem dimethoxy derivative **30a** was effected as described in Scheme 6 in 98% yield. The formation of the α,β-unsatured ketone **31** (Scheme 7) using *t*-BuDMSOTf[38] was accomplished in quantitative yield. The hydrolysis product **31** obtained from the gem dimethoxy derivative **30a** and the one obtained by the *t*-BuDMSOTf

(38) *Aldrichimica Acta* **1986**, *19*, 42.

Scheme 8



procedure in Scheme 7 are identical. We also attempted the allylic rearrangement on the TBDMS derivative **18b** with limited success. A mixture of **30b** and **30a** was obtained in low yield. We elected to proceed with **18a** and **19a** instead of **18b** and **19b** for the completion of the total synthesis. The enone **31** presented, at this point, no particular advantage since the carbonyl in the 6-membered ring in **30a** was already protected. The reduction of **30a** with $NaBH_4$ at −78 °C afforded in 93% yield a 5:1 mixture of **32**:**33** in favor of the desired β-hydride attack (Scheme 8). Similar distribution of products is obtained with $LiBH_4$ and $LiAlH_4$. The major product is easily separated by silica gel chromatography to afford **32**. Because of the quantitative formation of the gem dimethoxy **30a** from **18a** and **19a**, we found it convenient to carry out the reduction in the same pot by simply cooling the reaction mixture to −78 °C and then adding the $NaBH_4$.

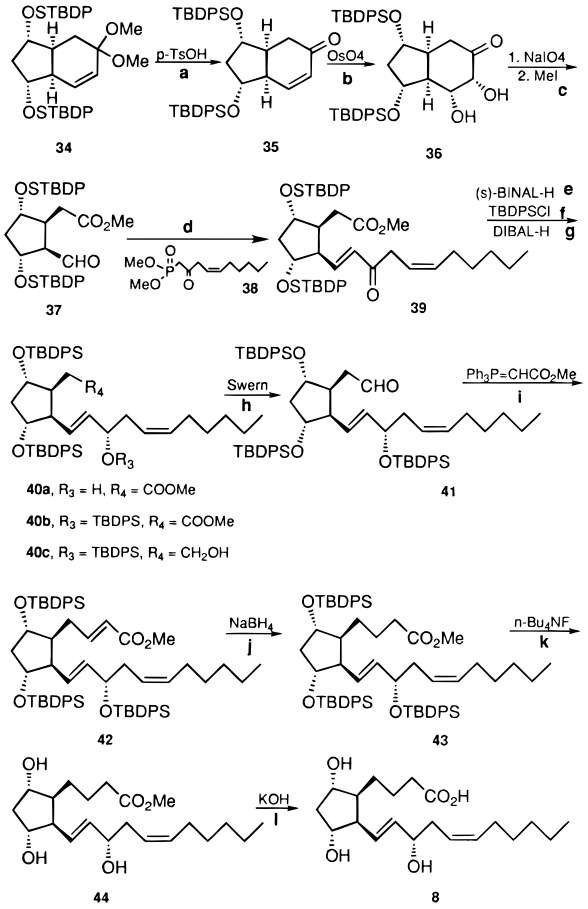
The TBDPS derivative **34** was prepared in 85% yield (Scheme 9). The dimethyl acetal group in **34** was hydrolyzed under mild conditions using *p*-TsOH to give enone **35** in 93% yield. The osmium tetraoxide oxidation of **35** proceeded well from the sterically less hindered convex face of the molecule to yield the *cis* diol **36** in 95% yield. The stereochemistry of the *cis* diol **36** was confirmed by NOE experiments (see Experimental Section). It is also interesting to note that all of the hydrogens except the ring junction ones in this molecule are pointing inward from the concave face of the molecule and NOEs between remote protons can be seen. The cleavage of the diol **36** with sodium periodate followed by treatment of the crude product with methyl iodide and diisopropylamine afforded methyl ester aldehyde **37** in 73% yield. Introduction of the lower side chain was performed by carrying out the Wittig reaction with phosphonate **38** at −78−0 °C for 12 h to give **39** in 72% yield. The enantioselective reduction of the C12 *keto* function in **39** proceeded smoothly with (*S*)-BINAL-H with >95% ee[2−5,39] and afforded the 12-S derivative **40a** in 85% yield. The hydroxyl group in **40a** was protected as the TBDPS derivative **40b** in 90% yield and the ester function was converted to alcohol **40c** by the reduction of **40b** with DIBAL-H in 92% yield.

The introduction of the upper side chain was performed by first preparing the aldehyde **41** by Swern oxidation of **40c** in 95% yield, and the two-carbon extension was performed by carrying out the Wittig reaction to yield **42** in 90% yield. The selective reduction of the α,β-unsaturated double bond in **42** was performed in 85% yield using sodium borohydride in THF. Finally, after desilylation of **43** using tetrabutylammonium fluoride, the basic hydrolysis of **44** yielded the desired iPF$_{2\alpha}$-V **8** in 91% yield.

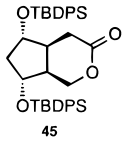
As mentioned previously, **37** was converted to the bicyclic six-membered ring lactone **45** and compared with an authentic sample we prepared previously by a different methodology.[2] The lactone **45** was prepared as follows. Aldehyde ester **37** was reduced with L-selectride. On acidification and solvent evaporation, lactone **45** was obtained.

The Diels−Alder reaction described above worked as intended and afforded high face selectivity, with the diene

Scheme 9[a]



[a] Reaction conditions: (a) Acetone, 3 h, 93%; (b) *t*-BuOH/CH_3CN (3:1), 1 h, 95%; (c) (1) MeOH/H_2O (3:1), 20 h, (2) diisopropyl amine, rt 24 h, 72%; (d) $NaN(SiMe_3)_2$, THF, −78 °C to 0 °C, 12 h, 72%; (e) THF, −100 °C for 3 h then −78 °C for 2 h, 85%; (f) Imd., DMF, 2 h, 90%; (g) CH_2Cl_2, 0 °C, 18 h, 92%; (h) 2 equiv $(COCl)_2$, 3 equiv DMSO, CH_2Cl_2, −78 °C, 15 min, then alcohol, −78 °C, 30 min, 6 equiv Et_3N, −78 °C, 95%; (i) THF, 18 h, 90%; (j) THF, reflux, 18 h, 85%; (k) THF, 18 h, 83%; (l) dioxane/H_2O (3:1), 0 °C, 10 min, 5% aqueous KH_2PO_4 (pH = 4.2), 92%.



approaching the dienophile from the less hindered top face by an *endo* approach and, to a lesser extent, by an *exo* approach. Recently some elegant mechanistic work described the opposite face selectivity in a Lewis acid-catalyzed Diels−Alder reaction, with the diene approaching from the more hindered face. The ratio of the hindered/nonhindered approach was 96:4[35,40] (Scheme 10). The reason for the unusual face selectivity was explained in terms of orbital interaction between the diene and dienophile.[35,41]

We were intrigued by the contrasting results we obtained as compared to those in Scheme 10B and decided to have a closer look at the differences between the two reactions. (1) Our dienophile carried a TBDPS group (Scheme 3) versus the TBDMS in Scheme 10B. (2) A dimethoxy and a silyloxymethoxy diene are used in our reaction versus the unsub-

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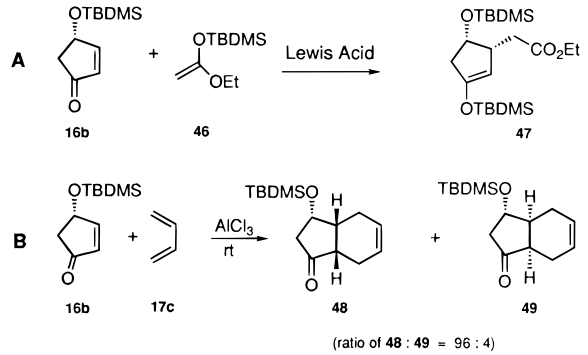
Scheme 10[a]



[a] A: reference 40. B: reference 35.

stituted butadiene **17c** (Scheme 10B). (3) Our Diels−Alder reaction was done thermally, with no Lewis acid present.

We carried out the Diels−Alder reaction with dienophile **16b** and butadiene **17c**, under $AlCl_3$ conditions (Scheme 11, entry 1). We then tried, under the same conditions, the reaction between the bulkier TBDPS derivative **16a** and butadiene **17c** (entry 2). In this case, the bulkier TBDPS derivative is causing more of the butadiene to approach from the less hindered face.

We then performed the same reaction using our conditions (without $AlCl_3$), entries 3 and 4, resulting in a preponderance of the unhindered approach.

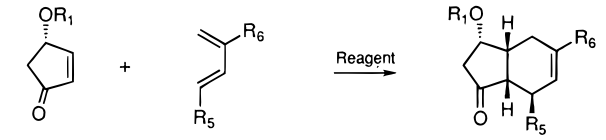
Entries 6 and 7 are the results reported in Scheme 3. Entry 5 was performed to find out if changing R_1 and keeping the substituted diene had any influence on the outcome of the Diels−Alder reaction. As can be seen, entries 5, 6, and 7 produce identical results and ratios of *syn* to *anti* products. This probably means that the 3-substituent on the diene has a controlling effect, and we do not observe any difference between the TBDMS and TBDPS on the dienophile. Looking back at Scheme 4 shows that R_1 and R_2 on an *endo*−*syn* approach from the more hindered side, **23**, will experience the maximum steric interference. This is probably why we did not obtain **21** in entries 5, 6, 7, and 8. Finally, entry 8 shows that temperature alone can influence the ratio of *syn* to *anti*, and it is the lowest we have experienced. From the synthetic perspective, this was the best reaction, and we are now using these conditions routinely for the synthetic applications.

The results shown in Scheme 11 indicate that an *endo*−*syn* approach (approach **23**, Scheme 4) of the substituted dienes from the less hindered face of a five-membered ring dienophile is not favored. We have been unable to obtain a reaction of **16a** with dimethoxy butadiene **17a** using $AlCl_3$ as catalyst due to polymerization of the diene.

In conclusion, the thermal reaction (entries 3−8) is influenced by the bulk of the substituent on the five-membered ring, by the substituent (R_6) on the diene (Scheme 4, approach **23**), and by the temperature, all of which contribute synergistically and afford a high face selectivity from the less hindered face 92:8.

We have used the synthetic $iPF_{2\alpha}$-V to identify by LC/MS its existence in urine (elution and coelution retention times, 11.83 min). A linear solvent gradient was used. Solvent A was water; solvent B was acetonitrile/methanol, 95:5, both with 0.005% acetic acid, pH adjusted to 5.7 with ammonium hydroxide, flow rate 200 μL/min. Quantitative information is not as yet available since we have not yet prepared the deuterated standard. This is the first proof for the existence of group V in vivo. The discovery of $IPF_{2\alpha}$-III[1] and the proposal of four groups of iPs derived from AA by a free-radical mechanism in vivo have previously been reported.[1,2,6] Before the present report, using our synthetic standards, we had identified groups III, IV, and VI in human urine. The discovery in urine of $IPF_{2\alpha}$-V, a group V iP, reported here, completes one of our initial objectives which was to discover the individual iPs and confirm, using synthetic standards, the existence of four

Scheme 11



16a, R_1 = TBDPS
16b, R_1 = TBDMS

17a, R_5 = R_6 = OMe
17b, R_5 = OMe, R_6 = OTBDMS
17c, R_5 = R_6 = H

Syn
R_1 = TBDMS, R_5 = R_6 = H **(48)**
R_1 = TBDPS, R_5 = R_6 = H **(50)**
R_1 = TBDPS, R_5 = R_6 = OMe **(20a)**
R_1 = TBDPS, R_5 = OMe, R_6 = OTBDMS **(20b)**
R_1 = TBDMS, R_5 = R_6 = OMe **(51)**

Anti
R_1 = TBDMS, R_5 = R_6 = H **(49)**
R_1 = TBDPS, R_5 = R_6 = H **(52)**
R_1 = TBDPS, R_6 = OMe, R_5 = β-OMe **(18a)**
R_1 = TBDPS, R_6 = OMe, R_5 = α-OMe **(19a)**
R_1 = TBDPS, R_6 = OTBDMS, R_5 = β-OMe **(18b)**
R_1 = TBDPS, R_6 = OTBDMS, R_5 = α-OMe **(19b)**
R_1 = TBDMS, R_6 = OMe, R_5 = β-OMe **(53)**
R_1 = TBDMS, R_6 = OMe, R_5 = α-OMe **(54)**

Entry	R_1	R_5	R_6	Reagent	Temp.	ratio Syn product (No.) : Anti product (No.)
1	TBDMS	H	H	$AlCl_3$	rt	**(48)** 95 : 5 **(49)**
2	TBDPS	H	H	$AlCl_3$	rt	**(50)** 80 : 20 **(52)**
3	TBDMS	H	H	-	110 °C	**(48)** 50 : 50 **(49)**
4	TBDPS	H	H	-	110 °C	**(50)** 33 : 67 **(52)**
5	TBDMS	OMe	OMe	-	110 °C	**(51)** 17 : 83 **(53 + 54)**
6	TBDPS	OMe	OMe	-	110 °C	**(20a)** 17 : 83 **(18a + 19a)**
7	TBDPS	OMe	TBDMS	-	110 °C	**(20b)** 17 : 83 **(18b + 19b)**
8	TBDPS	OMe	OMe	-	140 °C	**(20a)** 8 : 92 **(18a + 19a)**

groups of iPs formed in vivo by the free-radical peroxidation of arachidonic acid.

Experimental Section

Reagents and Methods. Unless stated otherwise, all reagents and chemicals were obtained from commercial sources and used without further purification.

^{1}H NMR and ^{13}C NMR spectra were recorded on a 360 MHz spectrometer with tetramethylsilane as an internal standard, and *J* values are given in Hz.

All reactions were carried out under an inert (nitrogen or argon) atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials.

The NOEs were performed in either d_6-acetone or d_6-benzene, and the results of several compounds are shown under the appropriate headings in the Experimental Section.

4(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]cyclopent-2-en-1-one (16a). A mixture of (−)4(*S*)-hydroxy-cyclopentenone (**14a**)[36] (0.70 g, 7.14 mmol), triethylamine (6 mL, 42.80 mmol), and *tert*-butyldiphenyl chlorosilane (2.35 g, 8.85 mmol) in dry methylene chloride (12 mL) containing a catalytic amount of DMAP was stirred at 0 °C for 10 min and then at room-temperature overnight (20 h). Water (50 mL) was added, and the product was extracted with ether (2 × 50 mL). The combined organic phase was washed with water (50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, elution with 3:7 hexanes/methylene chloride) to give 1.4 g (60%) of 4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]cyclopentenone **16a**. ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.41 (m, 6 H), 7.33 (dd, J = 5.7, 2.2 Hz, 1 H), 6.10 (dd, J = 5.7, 0.9 Hz, 1 H), 4.93 (m, 1 H), 2.49 (dd, J = 18.2, 5.9 Hz, 1 H), 2.32 (dd, J = 18.2, 2.2 Hz, 1 H), 1.06 (s, 9 H). ^{13}C NMR (($CDCl_3$) δ 206.23, 163.60, 135.74, 135.70 (2 C), 134.55, 133.11, 130.15 (2 C), 127.98 (2 C), 71.88, 44.82, 26.88 (2 C), 19.13.

Diels−Alder Reaction of 4-*tert*-Butyldiphenylsilyloxycyclopentenone (16a) with 1,3-Dimethoxy-1,3-butadiene (17a). Procedure a: A solution of 4-*tert*-butyldiphenylsilyloxycyclopentenone (**16a**, 0.100 g, 0.294 mmol) and 1,3-dimethoxy-1,3-butadiene (**17a**, 0.100 g, 0.877 mmol) in xylene (0.5 mL) containing 2,6-di-*tert*-butyl-4-methyl phenol (BHT, 5 mg) was heated at 140 °C in a sealed tube for 10 h. Evaporation of the solvent and chromatography of the residue (silica gel, elution with 8:2 hexanes/ether) gave a mixture of **18a** and **19a** 0.110 g (80%) and 0.010 g (7%) of **20a**.

Spectral data for 18a and 19a: ^{1}H NMR (C_6D_6) δ 7.75 (m, 4H), 7.22 (m, 6 H), 4.65 (m, 1 H), 4.51 (d, J = 5.8 Hz, 1 H), 4.01 (t, J = 5.6 Hz, 1 H), 3.10 (s, 3 H), 2.87 (s, 3 H), 2.53 (dd, J = 17.9, 7.1 Hz, 1 H), 2.48 (d, J = 15.5 Hz, 1 H), 2.20 (dd, J = 17.9, 7.5 Hz, 1 H), 1.19 (s, 9 H). ^{13}C NMR (C_6D_6) δ 211.94, 159.51, 135.86 (2 C), 135.84 (2 C), 134.0, 133.80, 129.67 (2 C), 127.70 (4 C), 91.35, 75.58, 73.68, 53.47, 51.09, 48.36, 42.56, 27.31, 26.88 (3 C), 19.07.

The mixture of **18a** and **19a** is usually used as such in the next step. To isolate **18a** and **19a** in the pure form, the mixture was separated by flash column chromatography (silica gel, elution with benzene).

Spectral data for (1*S*,2*S*,6*S*,7*S*)-2,4-dimethoxy-7-[(*tert*-butyldiphenylsilyl)oxy]bicyclo[4.3.0.]non-3-en-9-one (18a): ^{1}H NMR (d_6-acetone) δ 7.70 (m, 4H), 7.46 (m, 6 H), 4.94 (d, J = 5.8 Hz, 1 H), 4.47 (m, 1 H), 3.98 (t, J = 5.6 Hz, 1 H), 3.50 (s, 3 H), 2.97 (s, 3 H), 2.61 (m, 1 H), 2.47 (m, 1 H), 2.29 (m, 2 H), 2.05−2.2 (m, 2 H), 1.08 (s, 9 H). ^{13}C NMR (C_6D_6) δ 211.94, 159.51, 135.86 (2 C), 135.84 (2 C) 134.0, 133.80, 129.67 (2 C), 127.70 (4 C), 91.35, 75.58, 73.68, 53.47, 51.09, 48.36, 42.56, 27.31, 26.88 (3 C), 19.07.

Spectral data for (1*S*,2*R*,6*S*,7*S*)-2,4-dimethoxy-7-[(*tert*-butyldiphenylsilyl)oxy]bicyclo[4.3.0.]non-3-en-9-one (19a): ^{1}H NMR (C_6D_6) (d_6-acetone) δ 7.71 (m, 4H), 7.48 (m, 6 H), 4.81(d, J = 4.5 Hz, 1 H), 4.33 (d, J = 5.3 Hz, 1 H), 4.17 (d, J = 4.7 Hz, 1 H), 3.50 (s, 3 H), 3.27 (s, 3 H), 3.03 (d, J = 7.7 Hz, 1 H), 2.67 (m, 1 H), 2.42 (dd, J = 19.2, 5.3 Hz, 1 H), 2.27 (d, J = 19.2 Hz, 1 H), 1.94 (dd, J = 17.6, 8.0 Hz, 1 H), 1.08 (s, 9 H).

Spectral data for (1*R*,2*S*,6*R*,7*S*)-2,4-dimethoxy-7-[(*tert*-butyldiphenylsilyl)oxy]bicyclo[4.3.0.]non-3-en-9-one (20a): ^{1}H NMR (C_6D_6) δ 7.70 (m, 4 H), 7.24 (m, 6 H), 4.83 (d, J = 4.0, 1 H), 4.57 (d, J = 4.7, 1 H), 4.26 (ddd, J = 8.4, 8.3, 6.0 Hz, 1 H), 3.22 (s, 3 H), 3.19 (s, 3 H), 2.83 (m, 1 H), 2.54 (dd, J = 18.2, 7.8 Hz, 1 H), 2.37 (dd, J = 18.2, 10.1, 1 H), 2.20 (d, J = 7.0 Hz, 1 H), 2.12 (t, J = 8.4 Hz, 2 H), 1.11 (s, 9 H). ^{13}C NMR (C_6D_6) δ 209.98, 157.56, 135.63 (2 C), 135.56 (2 C), 133.74, 133.50, 129.90, 129.86, 127.83 (4 C), 92.97, 71.67, 70.48, 54.93, 53.54, 53.49, 43.05, 36.67, 26.65, 24.12, 18.97.

Procedure b. A solution of 4-*tert*-butyldiphenylsilyloxycyclopentenone **16a** (0.164 g, 0.488 mmol) and 1,3-dimethoxy-1,3-butadiene **17a** (0.222 g, 1.95 mmol) in toluene (0.5 mL) containing 2,6-di-*tert*-butyl-4-methyl phenol (BHT, 5 mg) was heated at 110 °C in a sealed tube for 18 h. Evaporation of the solvent and chromatography of the residue (silica gel, elution with 8:2 hexanes/ether) gave a mixture of **18a** and **19a** 0.154 g (70%) and 0.033 g (15%) of **20a**. The spectral data were identical to those described above.

(1*S*,6*S*,7*S*,9*R*)-4,4-Dimethoxy-7-[(*tert*-butyldiphenylsilyl)oxy]bicyclo-[4.3.0.]non-3-en-9-ol (32). A solution of the *cis*-adducts **18a** and **19a** (0.154 g, 0.342 mmol) and methyl orthoformate (0.360 mL, 3.42 mmol) in dry methanol (4 mL) containing a catalytic amount of pyridinium *p*-toluenesulfonate (PPTs) was stirred at room temperature for 2 h. The reaction mixture was cooled to −78 °C and treated with excess sodium borohydride with stirring maintained at −78 °C for 3 h. The solvent was removed under reduced pressure, and the organic material was extracted with ether (2 × 150 mL), washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, elution with 5:5 hexanes/ether) gave 0.130 g (77%) of **32** and 0.024 g (14%) of **33**. The two steps have been performed individually in yields of 98% for the gem dimethoxy derivative **30a** and 93% for the sodium borohydride step.

Spectral data for 32: ^{1}H NMR (C_6D_6) δ 7.81 (m, 4 H), 7.26 (m, 6 H), 5.82 (m, 2 H), 4.20 (m, 1 H), 3.89 (m, 1 H), 3.08 (s, 3 H), 3.0 (s, 3 H), 2.93 (m, 1 H), 2.77 (m, 1 H), 2.54 (d, J = 9.1 Hz, 1 H), 1.86 (m, 2 H), 1.61 (dd, J = 12.8, 5.8 Hz, 1 H), 1.19 (s, 9 H), 1.04 (dd, J = 12.6, 10.3 Hz, 1 H). ^{13}C NMR (C_6D_6) δ 136.65, 136.56, 134.62, 134.57, 132.13, 130.40, 130.38, 129.26, 128.42, 128.41, 97.83, 80.42, 78.71, 48.76, 48.75, 48.13, 44.48, 43.42, 33.61, 27.52, 19.53. HEIMS calcd for $C_{22}H_{23}O_3Si$ 363.1417 (M − *t*-Bu − $CH_3OH)^+$, found 363.1423.

Spectral data for 33: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.56 (t, J = 11.6 Hz, 1 H), 1.88 (dd, J = 13.2, 5.0 Hz, 1 H), 2.0 (dt, J = 13.7, 5.1 Hz, 1 H), 2.16 (ddd, J = 12.0, 6.4, 2.7 Hz, 1 H), 2.72 (m, 2 H), 3.12 (s, 3 H), 3.20 (s, 3 H), 4.09 (m, 1 H), 4.49 (m, 1 H), 5.56 (dd, J = 10.3, 3.2 Hz, 1 H), 6.09 (d, J = 10.3 Hz, 1 H), 7.32 (m, 6 H), 7.87 (m, 4 H).

(1*S*,6*S*,7*S*,9*R*)-4,4-Dimethoxy-7,9-bis-[(*tert*-butyldiphenylsilyl)oxy]-bicyclo[4.3.0.]non-2-en (34). To a mixture of alcohol **33** (0.130 g, 0.285 mmol) and imidazole (0.077 g, 1.14 mmol) in DMF (7 mL) was added *tert*-butyldiphenylchlorosilane (0.312 g, 0.57 mmol) in DMF (7 mL), and the solution was stirred at room temperature for 2 h. Triethylamine (0.5 mL) was added at 0 °C prior to the addition of water (100 mL). The reaction mixture was extracted with ether (2 × 100 mL), washed with water (2 × 50 mL) and brine (50 mL), and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, elution with 9:1 hexanes/ether) to afford 0.153 g of **34** (85%). ^{1}H NMR (C_6D_6) δ 7.80 (m, 8 H), 7.26 (m, 12 H), 5.79 (dd, J = 10.5, 3.4 Hz, 1 H), 5.73 (d, J = 10.5, 1 H), 4.00 (m, 2 H), 3.08 (s, 3 H), 3.04 (m, 1 H), 2.96 (s, 3 H), 2.74 (m, 1 H), 2.02 (m, 2 H), 1.59 (dd, J = 12.6, 5.1 Hz, 1 H), 1.24 (s, 18 H), 0.94 (t, J = 12.0 Hz, 1 H). ^{13}C NMR (C_6D_6) δ 136.14(4C), 136.10(4C), 134.69, 134.45, 134.43, 134.31, 131.34, 129.83, 129.76, 129.67, 129.63, 128.44, 127.78 (8 C), 97.49, 78.31, 77.61, 48.19, 47.50, 47.43, 45.01, 43.78, 33.23, 27.09 (6 C), 19.25, 19.19; HEIMS calcd for $C_{38}H_{41}O_3Si_2$ 601.2595 (M − *t*-Bu −$CH_3OH)^+$, found 601.2573.

(1*S*,6*S*,7*S*,9*R*)-7,9-Bis-[(*tert*-butyldiphenylsilyl)oxy]bicyclo[4.3.0.]-non-2-en-4-one (35). A solution of the dimethyl ketal **34** (0.153 g, 0.242 mmol) in dry acetone (18 mL) was stirred at room temperature for 40 min in the presence of a catalytic amount of *p*-TsOH. The solvent was evaporated, and the product was purified by flash chromatography (silica gel, elution with 8:2 hexanes/ether) to yield 0.130 g (92%) of **34**. ^{1}H NMR (C_6D_6) δ 7.76 (m, 8 H), 7.28 (m, 12 H), 5.75 (d, J = 10.4 Hz, 1 H), 5.65 (d, J = 10.4 Hz, 1 H), 3.87 (m, 2 H), 2.74 (m, 2 H), 2.26 (dd, J = 16.8, 5.0 Hz, 1H), 2.07 (dd, J =

16.6, 5.2 Hz, 1 H), 1.92 (m, 2 H), 1.23 (s, 18 H). ^{13}C NMR(C_6D_6) δ 196.40, 147.97, 136.60, 136.52, 136.49, 134.89, 134.60, 134.50, 134.20, 130.56, 130.54, 130.47, 130.36, 129.84, 128.55, 128.47, 128.40, 78.05, 76.93, 47.98, 46.22, 45.54, 37.99, 27.56, 27.50, 19.72, 19.62. HEIMS calcd for $C_{37}H_{39}O_3Si_2$ 587.24387 (M − *t*-Bu)$^+$, found 587.2410.

(1*S*,2*R*,3*R*,6*S*,7*S*,9*R*)-2,3-Dihydroxy-7,9-bis-[(*tert*-butyldiphenylsilyl)-oxy]bicyclo[4.3.0.]non-4-one (36). A mixture of **35** (0.130 g, 0.222 mmol) and trimethylamine oxide dihydrate (0.5 g) in *t*-BuOH/CH_3CN/H_2O (21 mL:11 mL:5 mL) was treated with a catalytic amount of osmium tetraoxide and stirred at room temperature for 1 h. Most of the organic solvent was evaporated, and the reaction mixture was extracted with ether (2 × 100 mL). The combined ether extracts were washed with water (40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography of the residue (silica gel, elution with 5:5 hexanes/ether) afforded 0.140 g (95%) of **36**. ^{1}H NMR (C_6D_6) δ 7.80 (m, 8 H), 7.32 (m, 12 H), 4.45 (br s, 1 H), 4.13 (m, 1 H),), 3.81 (br s, 1 H), 3.61 (m, 1 H), 3.43 (br s, 1 H), 3.32 (m, 1 H), 2.85 (br s, 1 H), 2.80 (m, 1 H), 2.06 (m, 2 H), 1.81 (dd, J = 14.3, 6.4 Hz, 1 H), 1.23 (s, 9 H), 1.19 (s, 9 H). ^{13}C NMR(C_6D_6) δ 208.11, 136.06 (2 C), 135.94 (2 C), 135.86 (2 C), 135.79 (2 C), 134.18, 134.14, 133.70, 133.67, 130.10, 129.86, 129.84, 129.70, 127.83 (8 C), 77.10, 74.25, 73.70, 72.96, 51.32, 46.28, 44.12, 38.82, 26.95 (2 C), 26.83 (2 C), 19.05, 18.94; HEIMS calcd for $C_{37}H_{41}O_5Si_2$ 621.2493 (M − C_4H_9)$^+$, found 621.2489 and calcd for $C_{37}H_{39}O_4Si_2$ 603.2387 (M − *t*-Bu − H_2O)$^+$, found 603.2407.

Methyl 2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-(carboxaldehyde)-1β-cyclopentane}-acetate (37). The diol **36** (0.140 g, 0.20 mmol) in a mixture of methanol/water (42 mL:14 mL) was treated with sodium periodate (0.526 g, 2.46 mmol) at 0 °C and was stirred at room temperature for 20 h. After evaporation of the solvent, the organic material was extracted with ether (2 × 100 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue dissolved in acetonitrile/ether (3 mL:3 mL) was treated with excess diisopropylethylamine (1.5 mL, 8.2 mmol) and methyl iodide (0.5 mL, 7.1 mmol) and stirred for 24 h. Water (50 mL) was added and extracted with ether (100 mL). The ether extract was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, elution with 8:2 hexanes/ether) to afford 0.100 g (72%) of **37**. ^{1}H NMR (C_6D_6) δ 9.31 (S, 1 H), 7.74 (m, 8 H), 7.24 (m, 12 H), 4.49 (q, J = 6.0 Hz, 1 H), 4.0 (q, J = 6.2, 1 H), 3.54 (m, 1 H), 3.25 (s, 3 H), 3.09 (m, 1 H), 2.29 (dd, J = 16.0, 5.7 Hz, 1 H), 2.22 (dd, J = 16.0, 9.6 Hz, 1 H), 1.89 (t, J = 6.2 Hz, 2 H), 1.20 (s, 9 H), 1.19 (s, 9 H). ^{13}C NMR (C_6D_6) δ 201.83, 172.77, 136.58 (4 C), 136.53 (4 C), 134.77, 134.48, 134.32, 134.09, 130.53, 130.48, 130.38 (2 C), 128.45 (8 C), 77.31, 72.32, 61.65, 51.49, 45.99, 44.10, 33.01, 27.57 (3 C), 27.50 (3 C), 19.75, 19.64. HEIMS calcd for $C_{37}H_{41}O_5Si_2$ 621.24933 (M − *t*-Bu)$^+$, found 621.24929.

Methyl 2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-[(E,Z)-1,5-undecadien-3-one]-1β-cyclopentane}acetate (39). To a stirred solution of the phosphonate **38** (0.078 g, 0.29 mmol) in dry THF was added sodium hexamethyldisilazide (0.267 mL, 0.267 mmol) at −78 °C. The solution was stirred at this temperature for 30 min, and aldehyde **37** (0.1 g, 0.15 mmol) in dry THF (2 mL) was added at −78 °C. The reaction mixture was warmed to 0 °C and stirred at 0 °C for 12 h. The reaction was quenched with $KHSO_4$ (5% in water, 5 mL) and extracted with ether (3 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (benzene) to afford **39** (103 mg, 72%) as a colorless oil. ^{1}HNMR (C_6D_6) δ 7.72 (m, 8 H), 7.20 (m, 12 H), 6.39 (dd, J = 15.6, 10.2 Hz, 1 H), 5.94 (d, J = 15.6 Hz,1 H), 5.70 (m, 1 H), 5.54 (m, 1 H), 3.94 (m, 2 H), 3.28 (m, 1 H), 3.24 (s, 3 H) 3.09 (m, 1 H), 3.02 (d, J = 7.1 Hz, 2 H), 2.05 (dd, J = 16.25, 6.06, 1 H), 1.90 (m, 5 H), 1.23 (m, 5 H), 1.18 (s, 18 H), 1.11 (m, 1 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR (C_6D_6) δ 195.89, 172.50, 144.00, 136.70, 136.64 (2 C), 136.58 (2 C), 134.96, 134.73, 134.55, 134.43, 133.62, 132.27, 130.45, 130.36, 130.35, 128.91, 128.25, 122.24, 77.43, 77.04, 53.46, 51.40, 48.09, 44.32, 40.60, 33.68, 32.12, 29.74, 28.22, 27.58 (3 C), 27.54 (3 C), 23.26, 19.75, 19.65, 14.58. NH_3-DCIMS calcd for $C_{51}H_{66}O_5Si_2$ 815.23, found 832 (M + $NH_4$$^+$).

Methyl 2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-[(3*S*)-(*E*,*Z*)-1,5-undecadien-3-ol]-1β-cyclopentane}acetate (40a). The BINAL reagent was prepared by treating a solution of LAH (0.48 mL of 1 M solution in THF, 0.48 mmol) in a flame-dried flask under nitrogen with absolute alcohol (0.48 mL of 1 M solution in THF, 0.48 mmol) and then subsequently with bis(*S*)-naphthol (0.137 g, 0.48 mmol) in dry THF (2 mL) at room temperature. The resulting milky solution was stirred at room temperature for 20 min before **39** (0.065 g, 0.080 mmol) in THF was injected at −100 °C dropwise. After an additional 1 h stirring at −100 °C, the reaction mixture was maintained at −78 °C for 4 h. The reaction mixture was quenched with methanol followed by $KHSO_4$ (5% in water, 5 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with water (10 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography of the residue on silica (5:1 hexanes/ether) gave **40a** (55 mg, 85%) as a colorless oil. ^{1}HNMR (C_6D_6) δ 7.74 (m, 8 H), 7.25 (m, 12 H), 5.52 (m, 1 H), 5.43 (m, 1 H), 5.36 (dd, J = 6.2, 15.3 Hz, 1H), 5.01 (dd, J = 15.3, 9.4 Hz, 1 H), 3.94 (m, 2 H), 3.82 (m, 1H), 3.30 (s, 3 H), 3.17 (m, 2 H), 2.31−2.12 (m, 3 H), 2.28 (dd, J = 16.01, 5.1 Hz, 1H), 2.02 (q, J = 7.2 Hz, 2H), 1.93 (t, J = 6 Hz, 2 H), 1.29 (m, 8 H), 1.12 (s, 9 H), 1.19 (s, 9 H), 0.88 (t, J = 6.19 Hz, 3 H). ^{13}C NMR (C_6D_6) δ 172.87, 136.97, 136.78, 136.69, 136.66, 136.63, 135.16, 135.12, 134.86, 135.12, 133.16, 130.36, 130.28, 130.22, 128.73, 128.64, 128.27, 128.25, 77.72, 77.63, 72.48, 53.36, 51.30, 47.57, 44.40 (2 C), 36.11, 33.97, 32.66, 30.24, 28.10, 27.61 (6 C), 23.27, 19.76, 19.34, 14.68. NH_3-DCIMS calcd for $C_{51}H_{68}O_5Si_2$ 817.25, found 834 (M + $NH_4$$^+$).

Methyl 2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-{[(3*S*)-(*tert*-butyldiphenylsilyl)oxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}-acetate (40b). To a solution of imidazole (0.018 g, 0.27 mmol) and *tert*-butyldiphenylsilyl chloride (0.029 g, 0.11 mmol) in anhydrous DMF (5 mL) was added **40a** (0.044 g, 0.054 mmol) in DMF (2 mL), and the solution was stirred at room temperature for 2 h. Water (20 mL) was added, and the product was extracted into ether (2 × 50 mL). The combined organic extracts were washed with water (25 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the product by flash chromatography on silica (with 9:1 hexanes/ether) gave **40b** (49 mg, 90%) as a viscous liquid. ^{1}H NMR (C_6D_6) δ 7.0−7.6 (m, 30 H), 5.52 (m, 1 H), 5.13 (dd, J = 15.2, 6.5 Hz, 1H), 5.0 (m, 1 H), 4.59 (dd, J = 15.2, 6.5 Hz, 1 H), 3.86 (q, J = 6.3, 1 H), 3.66 (m, 2 H), 3.5 (s, 3 H), 2.83 (m, 1 H), 2.70 (m, 1 H), 2.17 (dd, J = 16.2, 4.9 Hz, 1 H), 2.11 (m, 1 H), 1.95 (m, 1 H), 1.82 (dd, J = 16.2, 10.4 Hz, 1 H), 1.67 (q, J = 6.8 Hz, 2 H), 1.59 (m, 2 H), 1.15 (m, 6 H), 1.03 (s, 9 H), 1.00 (s, 9 H), 0.91 (s, 9 H), 0.81 (t, J = 7 Hz, 3 H); ^{13}C NMR δ (C_6D_6) δ 173.79, 136.54 (3 C), 136.47 (3 C), 136.43 (3 C), 136.41 (3 C), 136.15, 135.14, 134.97, 134.74, 134.72, 134.63, 132.34, 130.20, 130.14, 130.12, 130.09, 130.04, 130.02, 128.20 (3 C), 128.19 (3 C), 128.12 (4 C), 128.01 (3 C), 127.92 (2 C), 127.76, 125.36, 53.34, 51.84, 46.66, 43.84, 36.45, 35.61, 33.72, 32.07, 29.82, 27.83, 27.60 (9 C), 23.17, 19.81 (2 C), 19.79, 14.20.

2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-{[(3*S*)-*tert*-butyldiphenylsilyl)oxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}ethan-1-ol (40c). A solution of **40b** (0.049 g, 0.046 mmol) in toluene (3 mL) was treated with DIBAL-H (0.140 mL of 1 M solution in toluene, 0.14 mmol) at −78 °C and stirred at the same temperature for 4 h. The reaction mixture was quenched with 5% $KHSO_4$ (10 mL) and extracted with ether (3 × 20 mL). The organic layers were washed with water (10 mL) and sodium bicarbonate (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography of the residue (elution with 9:1 hexanes/ether) afforded **40c** (44 mg, 92%) as an oil. ^{1}HNMR (C_6D_6) δ 7.74 (m, 12 H), 7.16 (m, 18 H), 5.37 (m, 3 H), 4.90 (dd, J = 15.3, 9.6 Hz, 1 H), 4.12 (m, 1 H), 4.02 (m, 1 H), 3.96 (m, 1 H), 3.41 (m, 2 H), 2.79 (m, 2 H), 2.37 (m, 2 H), 2.27 (m, 1 H), 1.82 (m, 4 H), 1.51-(hx, J = 6.7 Hz, 1 H), 1.37 (m, 6 H), 1.25 (s, 9 H), 1.23 (s,9 H), 1.15 (s, 9 H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (C_6D_6) δ 136.59 (2 C), 136.52 (2 C), 136.48 (2 C), 136.41 (4 C), 136.39 (2 C), 135.60, 135.43, 135.16, 135.06, 134.90, 134.74, 134.70, 130.38, 130.28, 130.24, 130.17, 130.11, 130.07, 130.01 128.44, 128.35 (2 C), 128.21 (2 C), 128.20 (2 C), 128.12 (2 C), 128.02 (2 C), 127.90 (2 C), 125.40 78.946, 78.11, 74.38, 62.45, 54.01, 46.86, 43.84, 36.54, 32.61, 32.07, 29.82, 27.89 (3 C), 27.63 (3 C), 27.58 (3 C), 27.19, 23.17, 19.84 (2 C), 19.74, 14.67.

2-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-{[(3*S*)-*tert*-butyldiphenylsilyl)oxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}ethan-1-

al (41). To a stirred solution of oxalyl chloride (0.172 mL of 1 M solution in CH_2Cl_2, 0.172 mmol) was added dimethyl sulfoxide (0.019 g, 0.243 mmol) dropwise at −78 °C. After the reaction mixture stirred for 20 min at −78 °C, the alcohol **40c** (0.044 mg, 0.043 mmol) was added followed by the addition of triethylamine (0.052 g, 0.51 mmol). The reaction mixture was warmed to 0 °C and stirred at this temperature for 4 h. Water (20 mL) was added, and the mixture was extracted with ether (3 × 25 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on silica (elution with 9:1 hexanes/ether) to afford product **41** (42 mg, 95%) as a viscous oil. ^{1}HNMR (C_6D_6) δ 9.41 (s, 1 H), 7.29 (m, 30 H), 5.22 (m, 1H), 5.07 (dd, J = 15.4, 6.4 Hz, 1 H), 5.02 (m, 1 H), 4.54 (dd, J = 15.1, 10 Hz, 1 H), 3.8 (m, 1 H), 3.66 (m, 2 H), 2.81 (m, 1 H), 2.61 (m, 1 H), 2.04 (m, 3 H), 1.85 (dd, J = 17.2, 9.2 Hz, 1 H), 1.67 (m, 2 H), 1.54 (m, 2 H), 1.16 (m, 6 H), 1.03 (s, 9 H), 0.99 (s, 9 H), 0.90 (s, 9 H), 0.81 (t, J = 7.2 Hz, 3 H). NH_3-DCIMS calcd for $C_{66}H_{84}O_4Si_3$ 1025.63, found 1043 (M + NH_4^+).

Methyl 4-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-{[(3*S*)-*tert*-butyldiphenylsilyl)oxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}but-2-ene-1-oate (42). A solution of aldehyde **41** (0.042 g, 0.041 mmol) and carbomethoxymethelene triphenyphosphorane (0.031 g, 0.092 mmol) in THF (2 mL) was refluxed for 2 days. Evaporation of the solvent and chromatography of residue on silica (20:1 hexanes/ether) afforded **42** (40 mg, 90%) as a viscous oil. ^{1}HNMR (C_6D_6) δ 7.79 (m, 8 H), 7.72 (dd, J = 2 Hz, 2 H), 7.63 (d, J = 6.6 Hz, 2H), 7.25 (m, 12 H), 7.09 (m, 7 H), 5.85 (d, J = 15.6 Hz, 1 H), 5.40 (m, 2 H), 5.32 (dd, J = 6.4, 15.2 Hz, 1 H), 4.85 (dd, J = 15.2, 6.4 Hz, 1 H), 4.13 (m, 1 H), 3.9 (m, 2 H), 3.4 (s, 3H), 2.86 (m, 1 H), 2.56 (m, 1 H), 2.31 (m, 2 H), 2.04 (m, 1 H), 1.88 (m, 5 H), 1.29 (m, 6 H), 1.14 (s, 9 H), 0.87 (t, J = 7 Hz, 3 H). ^{13}C NMR (C_6D_6) δ 166.72, 148.45, 136.74 (3 C), 136.66 (3 C), 136.33 (3 C), 136.59 (3 C), 136.28, 135.25, 135.13, 135.05, 134.97, 134.88, 134.85, 132.47, 131.11 (2 C), 130.40, 130.38, 130.32 (2 C), 130.27 (2 C), 128.49 (6 C), 128.25 (6 C),125.58, 122.59, 78.45, 78.40, 74.56, 53.85, 51.18, 49.99, 44.12, 36.75, 32.19, 32.09, 29.99, 28.11, 27.65 (9 C), 19.89, 19.81, 19.75, 14.64. NH_3-DCIMS calcd for $C_{69}H_{88}O_5Si_3$ 1081.69, found 1098 (M + NH_4^+).

Methyl 4-{3α,5α-Bis-[(*tert*-butyldiphenylsilyl)oxy]-2β-{[(3*S*)-*tert*-butyldiphenylsilyl)oxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}-butanoate (43). Sodium borohydride (0.1 g, 2.7 mmol) was added in one portion to a solution of **42** (40 mg, 0.37 mmol) in dry THF (2 mL) and refluxed for 2 days. The reaction mixture was concentrated, diluted with water, and extracted with ether (2 × 20 mL). Drying of the organic extracts (Na_2SO_4) and concentration gave an oil which was purified by flash chromatography (elution with 20:1 hexanes/ether) to obtain **43** (35 mg, 85%) as a viscous oil. ^{1}HNMR (C_6D_6) δ 7.82 (m, 8 H), 7.73 (d, J = 5.6 Hz, 2 H), 7.65 (d, J = 6.7 Hz, 2H), 7.26 (m, 18 H), 5.38 (m, 2 H), 5.33 (dd, J = 15.2, 6.8 Hz, 1 H), 4.83 (dd, J = 15.2, 9.9 Hz, 1 H), 4.11 (m, 1 H), 3.98 (m, 2 H), 3.37 (s, 3 H), 2.81 (m, 1 H), 2.66 (m, 1 H), 2.26 (m, 1 H), 2.39 (m, 1 H), 2.14 (t, J = 7.6 Hz, 2 H), 1.87 (m, 4 H), 1.58 (m, 2 H), 1.38 (m, 2 H), 1.26 (s, 9 H), 1.24 (s, 9 H), 1.26 (m, 8 H), 1.15 (s, 9 H), 0.89 (t, J = 7 Hz, 3 H). ^{13}C NMR (C_6D_6) δ 173.47, 136.79, 136.75 (2 C), 136.63 (8 C), 135.78, 135.52, 135.31, 135.18, 135.15, 135.11, 134.89, 132.32, 130.34, 130.28, 130.27, 130.23, 130.22 (2 C), 128.76 (3 C), 128.45 (3 C), 128.49 (3 C), 128.23 (3 C), 125.70, 79.02, 78.70, 74.80, 53.92, 51.24, 50.26, 44.34, 36.87, 34.71, 32.18, 36.83, 34.71, 32.17, 29.99, 28.86, 28.09, 27.70 (3 C), 27.69 (3 C), 27.65 (3 C), 24.15, 23.30, 19.90, 19.86, 19.80, 14.63. NH_3-DCIMS calcd for $C_{69}H_{90}O_5Si_3$ 1083.71, found 1101 (M + NH_4^+).

Methyl 4-{3α,5α-Dihydroxy-2β-[(3*S*)-hydroxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane} butanoate (44). A solution of **43** (18 mg, 0.0166 mmol) in THF (2 mL) was treated with tetra-*n*-butylammonium fluoride (1 mL of 1 M solution in THF, 1.0 mmol), and the mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 1:9 hexanes/ethyl acetate) to give **44** (5 mg, 83%) as an oil. ^{1}H NMR ($CDCl_3$) δ 5.63 (dd, J = 15.4, 6.2 Hz, 1 H), 5.56 (m, 1 H), 5.43 (dd, J = 15.3, 9.7 Hz, 1 H), 5.37 (m, 1 H), 4.13 (q, J = 6.2 Hz, 1 H), 4.0 (m, 2 H), 3.67 (s, 3 H), 2.76 (m, 1 H), 2.42 (m, 1 H), 2.35 (m, 1 H), 2.32 (t, J = 7.3 Hz, 2 H), 2.28 (m, 1 H), 2.05 (q, J = 7.1 Hz, 2 H), 1.79 (bs, 1 H), 1.67(m, 3 H), 1.30 (m, 9 H), 0.89 (t, J = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 174.43, 135.63, 133.75, 125.01, 124.56, 77.67, 77.15, 72.57, 54.33, 52.14, 50.76, 43.30, 35.99, 34.62, 32.12, 29.89, 29.55, 28.06, 24.05, 23.15, 14.62. NH_3-DCIMS calcd for $C_{21}H_{36}O_5$ 368.50, found 386 (M + NH_4^+).

4-{3α,5α-Dihydroxy-2β-[(3*S*)-hydroxy]-(*E*,*Z*)-1,5-undecadien]-1β-cyclopentane}butanoic acid (8). Potassium hydroxide (0.5 mL of 1 M in water, 0.5 mmol) was added to a solution of **44** (5 mg, 0.0135 mmol) in dioxane/water (3:2, 1 mL) at 0 °C, and the mixture was stirred at this temperature for 1 h. The reaction mixture was acidified with KH_2PO_4 (5% in water, 20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 20:1 ethyl acetate/methanol) to give **8** (4.5 mg, 92%) as an oil. ^{1}H NMR (CD_3COCD_3) δ 5.54 (dd, J = 15.3, 6.2 Hz, 1 H), 5.42 (m, 3 H), 4.03 (q, J = 6.4 Hz, 1 H), 3.90 (m, 1 H), 3.8 (m, 1 H), 2.63 (td, J = 8.22, 3.36 Hz, 1 H), 2.38 (m, 1 H), 2.04 (m, 4 H), 2.26 (t, J = 7.4 Hz, 2 H), 2.26 (m, 2 H), 2.04 (m, 4 H), 1.64 (m, 2 H), 1.53 (m, 1 H), 1.38 (m, 8 H), 0.88 (t, J = 6.88 Hz, 3 H). ^{13}C NMR (CD_3COCD_3) δ 175.83, 136.95, 132.59, 130.39, 127.43, 77.21, 76.91, 73.42, 54.88, 50.81, 44.72, 37.07, 35.17, 32.85, 30.55, 29.70, 28.65, 24.96, 23.81, 14.92. Electrospray MS m/z 353.2 (M − H)$^+$. HRMS (CI − CH_4) m/z calcd for $C_{20}H_{31}O_3$ [(M + 1) − $2H_2O$]$^+$ 319.2274, found 319.2286.

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Supporting Information Available: Forty-five pages of Supporting data and information (45 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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