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Intramolecular Nitrile Oxide Cycloaddition Route to Carbocyclics: A Formal Total Synthesis of $PGF_{2\alpha}$

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A formal total synthesis of the prostaglandin $F_{2\alpha}$ is reported which is based on the reaction of a nitrile oxide, generated by the sodium hypochlorite oxidation of an oxime, with a tethered olefin. The present study reveals the importance of an existing ring structure to control both the kinetics and the stereochemical course of the cycloaddition process. The possibility of carrying out the present synthesis in a chiral-selective fashion through employment of a chiral epoxide is also discussed.

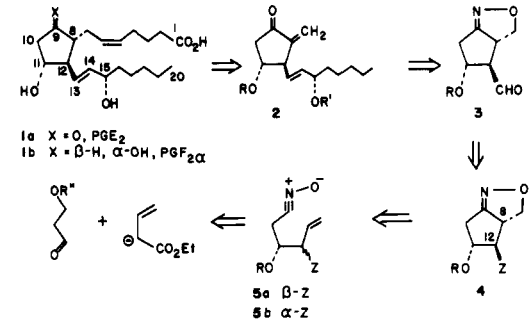
We have shown how one could use the intramolecular nitrile oxide cycloaddition (INOC) reaction to achieve rapid access to sarkomycin, one of the simplest biologically active cyclopentanoid natural products.[1] In this synthesis the isoxazoline ring derived from the cycloaddition of nitrile oxide to olefin was transformed to a β-hydroxy ketone by hydrogenation and thence to an enone by dehydration. We pointed out that one could possibly use the same chemistry to gain access to members of the prostaglandin family, for one needs only to build into the sarkomycin nucleus an additional oxygen substituent. In this paper we report an extension of our original work that does provide a straightforward and efficient entry into this important class of biological regulators.[2]

Results and Discussion

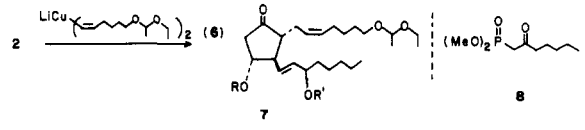
The synthetic strategy is diagrammed in Scheme I. While it was not our initial intention to achieve a chiral-selective assembly of a prostaglandin, the analysis shown below does lend itself to such a possibility as will be discussed later in the paper. The initial goals of our research thus became the synthesis of a threo/erythro mixture of the alkoxy esters **5a** and **5b** (Z = CO_2Et), an examination of the relative rates of intramolecular cyclization of **5**, and finally the conversion of the stereochemically correct [3 + 2] cycloaddition product to $PGF_{2\alpha}$.

Stork and co-workers have already accomplished a synthesis of $PGF_{2\alpha}$ from the methylenecyclopentanone **2** (R = Bzl, R′ = (benzyloxy)methyl) by addition of the cuprate **6** to provide **7**.[3] The primary alcohol of **2** was

Scheme I. An INOC-Based Retrosynthetic Analysis of the Prostanoids



deprotected and oxidized to acid, the ketone was reduced to alcohol, and the protecting groups were removed to provide $PGF_{2\alpha}$ in reasonable overall yield. Thus, the production of **2** via the INOC process would in itself constitute a formal total synthesis of the naturally occurring prostanoid $PGF_{2\alpha}$.



In our projected synthesis, the conversion of **3** to **2** would entail introduction of the lower side chain by a Wadsworth–Emmons process, reduction of C(15) ketone to alcohol, and the conversion of isoxazoline to a conjugated enone unit. Since condensation reactions with the anion of the commercially available phosphonate **8** and various cyclopentanecarboxaldehydes are well precedented in the prostaglandin field, the chain extension step should con-

(1) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023.
(2) For an overview of prostaglandin synthesis, see: Bindra, J. S. Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. Bindra, J. S. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4.
(3) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745 and 6260.

0022-3263/84/1949-2301$01.50/0

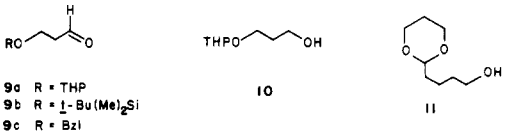
stitute no serious problem. Similarly both stereo- and nonstereoselective methods for the reduction of the C(15) keto group of this lower side chain are a matter of record.[2] While catalytic hydrogenation procedures using Raney nickel/aluminum chloride (or boron trichloride) have been used to transform isoxazolines to β-hydroxy ketones[4] which can in turn be converted to enones by a mesyl chloride/triethylamine dehydration procedure,[1] some question did exist as to whether the integrity of the C(13)–C(14) double bond of the Wadsworth–Emmons condensation product would be placed in jeopardy by such a protocol. If this hydrogenation reaction did indeed prove untenable, one could perhaps rely on a published chemical reduction method for the conversion of an isoxazoline to β-hydroxy ketone. Ti (III) has in fact proven to be useful in this regard.[5] Additionally, the use of molybdenum hexacarbonyl or iron pentacarbonyl in wet acetonitrile might be considered, since these reagents are known to cause the ring-opening of *isoxazoles*.[6,7]

Aldehyde **3** should arise through appropriate manipulations of the Z group of isoxazoline **4**, the product of the intramolecular nitrile oxide cycloaddition process. On the basis of stereochemical results observed in the sarkomycin synthesis, the cycloaddition reaction of **5a** was anticipated to provide exclusively the product possessing a trans relationship between the C(8) and C(12) substituents. Since the stereochemistry at the C(8) center of **4** will be removed in its conversion to **2**, stereocontrol in the cyclization process is actually immaterial to the present synthesis. *Of some more substantial note is the fact that in no prior synthesis of the prostaglandins from acycylic precursors has the five-membered ring ever been generated by forming a bond between C(8) and C(9).*[2] The above retrosynthetic analysis is thus quite unique from this standpoint alone.

Construction of a precursor to the nitrile oxide **5** required that we carry out an aldol reaction between the anion of ethyl crotonate and some protected derivative **9** of β-hydroxypropionaldehyde. The simplest route to **9** appeared to be monoprotection of 1,3-propanediol as its THP ether and subsequent oxidation. While treatment of 1,3-propanediol with DHP and *p*-TsOH in $CHCl_3$/THF provided a 1:1 mixture of mono- and diprotected derivatives after separation by distillation, it was discovered that alcohol **10** was contaminated with the isomeric alcohol **11**. The formation of similar products in the THP protection of related diols is, in fact, the subject of a recent paper.[8]

While the hydroboration/oxidation reaction of the THP derivative of allyl alcohol was also examined and found unsatisfactory,[9] pure **9a** was finally obtained in good yield from the inexpensive starting material, 3-hydroxypropionitrile. This nitrile was protected (TsOH, DHP) and then reduced with Dibal-H in ether.[10] The use of citric acid in the workup procedure is quite critical to obtaining good yields of **9a**. The silyl ether derivative **9b** was obtained from the same nitrile in an analogous fashion (*t*-Bu-$(Me)_2SiCl$, imidazole, DMF; then Dibal-H).

The benzyl-protected aldehyde **9c** was generated in a different manner. 1,3-Propanediol was converted to its



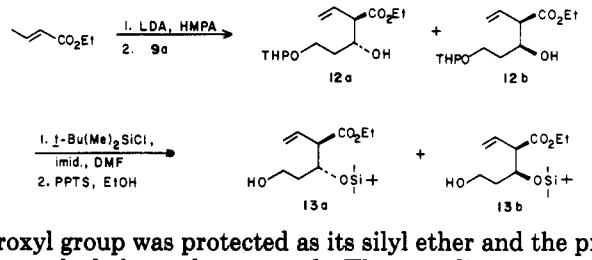
9a R = THP
9b R = *t*-Bu$(Me)_2$Si
9c R = Bzl

10 **11**

benzylidene acetal, and this acetal was reduced according to a well-precedented procedure using a mixed hydride system.[11] The resulting monobenzyl derivative of 1,3-propanediol was then simply oxidized with PCC/NaOAc to deliver **9c**.

With these three differently protected β-hydroxypropionaldehyde derivatives available, we were now ready to examine the aldol step utilizing the anion of ethyl crotonate generated according to Schlessinger's procedure (LDA, HMPA).[12] Although a plethora of diastereo- and enantioselective aldol reactions have been developed to date, we chose this nonselective route for its simplicity.

The anion of ethyl crotonate was thus reacted with **9a** to afford an inseparable mixture of **12a** and **12b** in 80–90% yield after column chromatography. The secondary hy-



droxyl group was protected as its silyl ether and the primary alcohol was deprotected. The new diastereomeric mixture of alcohols **13a** and **13b** could be separated by HPLC in an isolated ratio of 0.8:1, respectively. The assignment of structure to these materials rests on the magnitude of their H_3–H_4 coupling constants. The more polar, minor threo product **13a** displayed $J_{3,4}$ = 5.66 Hz, while the less polar, major erythro product **13b** displayed $J_{3,4}$ = 8.79 Hz. These coupling constants are in accord with established literature values.[13]

We were now ready to convert the free alcohol to a nitro group in preparation for the [3 + 2] cycloaddition reaction.[14] Treatment of a mixture of **13a** and **13b** with Ph_3P/CBr_4 in ether produced no recognizable products. Tosylation followed by a Finkelstein reaction (NaI, acetone) produced an oil in low yield (23%) whose ^1H NMR spectrum revealed the absence of the silyl ether group. Since the yield of **13** from **12** was not particularly good, we were prompted to protect the C(3) hydroxyl group of **12** as its more stable MEM ether instead.

The MEM ether derivative **14** was easily formed by stirring **12a/12b** with excess MEMCl and diisopropylethylamine in CH_2Cl_2 overnight. A new problem arose, however, when removal of the THP group was attempted.

(4) Wollenberg, R. H.; Goldstein, J. E. *Synthesis*, **1980**, 757. Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. Kozikowski, A. P.; Ghosh, A. K. *Ibid.* **1983**, *24*, 2623.

(5) Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta Chem. Scand., Ser. B* **1982**, *36*, 1. Grund, H., Jäger, V. *Liebigs Ann. Chem.* **1980**, 80.

(6) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877; *Chem. Lett.* **1983**, 51; *Tetrahedron Lett.* **1982**, *23*, 3925.

(7) Some preliminary experiments carried out in these laboratories indicate that isoxazolines can be cleaved by $Mo(CO)_6$ and $Fe(CO)_5$ to β-hydroxy ketones. The yields have not been optimized: Stein, P. D., unpublished results.

(8) The use of Me_2SO as solvent has been noted to suppress this rearrangement: Nouquier, R. *Tetrahedron Lett.* **1982**, *23*, 2951.

(9) Brown, H. C.; Cope, O. J. *J. Am. Chem. Soc.* **1964**, *86*, 1801.

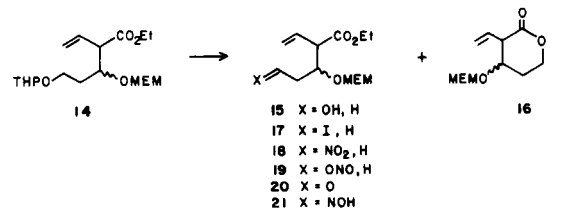
(10) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858. Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *Ibid.* **1970**, *35*, 186.

(11) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371.

(12) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433. For a related aldol reaction, see: Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163.

(13) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, England, 1969; pp 291–292.

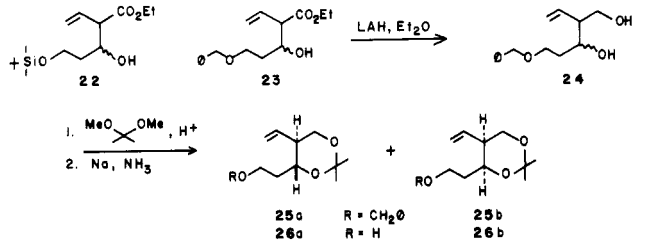
(14) (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Grundmann, C.; Grünager, P. "The Nitrile Oxides"; Springer-Verlag: Berlin, 1971.



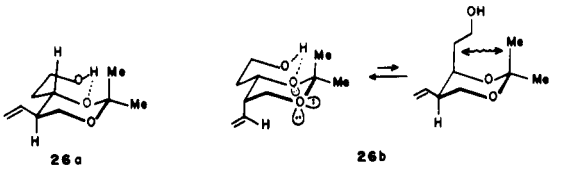
Deprotection of **14** using a number of well-established methods proved erratic in both yield and product.[15] While **15** could be isolated in low amounts, NMR evidence indicated that formation of the lactone **16** as well as other products was competitive. A tosylation/Finkelstein sequence served to convert **15** to its iodide, but this proved to be a very unstable intermediate. Moreover, this iodide proved unreactive toward displacement with silver nitrite,[16a,b] while its exposure to $NaNO_2$/DMF gave rise to 1:1 mixture of the nitro compound **18** and nitrite **19**.[16b,c]

Since each step in the conversion of **14** to **17** was problematic, we felt that some precursor to **5a** other than a nitro compound should be found. Nitrile oxides can, for example, be generated from oximes by oxidation (usually a metal hypohalite in an aqueous medium is employed) or from α-halo oximes by treatment with base (Et_3N or NaOMe).[14b] To pursue this course, we sought to oxidize the primary alcohol of **15** to aldehyde. PCC and PDC both produced fair yields of aldehyde **20**, which was condensed with hydroxylamine hydrochloride in pyridine to generate oxime **21**. When oxime **21** was treated with *n*-BuLi and NBS in ether or NBS/Et_3N in DMF,[17] only complex mixtures resulted.

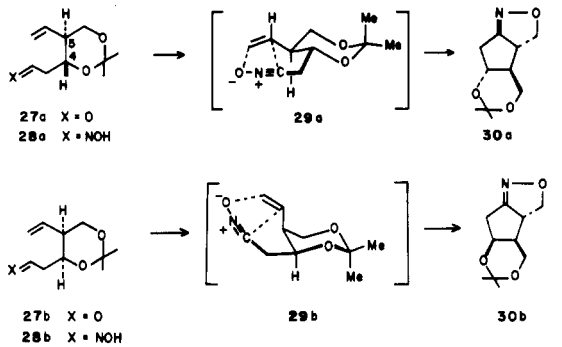
Since the attempted in situ generation of a halo oxime from **21** failed, we now needed to explore methods of direct oxidation instead. A more satisfactory route to **15** or an analogue of **15** which avoided the acid catalyzed removal of the THP group was, however, required first. Pursuant to this, ethyl crotonate was condensed with the silyl aldehyde **9b** to yield alcohol **22**. Reduction of the ester



might in turn provide a diol that could be protected as its acetonide. Unfortunately, both LAH and Dibal-H failed to satisfactorily reduce this ester. On the other hand, hydroxy ester **23**, obtained in 90% yield from ethyl crotonate and **9c**, was reduced in good yield (80–90%) by LAH in ether to the diol **24**. Reaction of **24** with 2,2-dimethoxypropane and Amberlyst-15 furnished the acetonide **25**. Reductive removal of the benzyl group (Na, NH_3, THF/EtOH) provided the chromatographically separable (Waters Associates Prep 500) alcohols **26a** and **26b** in a ratio of 1:1. The assignment of structure to these alcohols again rests upon their ^1H NMR spectral data. Isomer **26b**, which probably exists in the conformation shown, exhibits a marked downfield shift for its vinyl proton nearer the dioxane ring. This effect, which can be attributed to the proximity of the vinyl hydrogen to the (deshielding) ring oxygens,[18] is absent in **26a**. Additionally, when the alcohols **26a** and **26b** were converted to their aldehydes by the Swern procedure, it became possible to examine the coupling constants between H(4) and H(5).



Aldehyde **27b** derived from alcohol **26b** displayed $J_{4,5}$ = 2.5 Hz, a value that lies in the generally accepted range of axial–equatorial coupling constants. The trans diaxial coupling in **27a**, although not measured precisely because of overlapping peaks, was appreciably larger.



Both aldehydes were converted individually to their oximes by treatment with hydroxylamine hydrochloride in pyridine. On exposure of **28b** to excess sodium hypochlorite in methylene chloride with triethylamine as catalyst at 0 °C, the isoxazoline **30b** was produced in good yield.[19] An examination of molecular models reveals that the required parallel plane approach of dipole and dipolarophile can be achieved only for the conformation of **29b** depicted. Overlaying of the dipole/dipolarophile orbitals requires no significant distortion of the dioxane ring.

Oxime **27a** of correct stereochemistry to produce a prostaglandin also reacted with sodium hypochlorite to produce a single isoxazoline. The reaction conditions had to be modified, however, for although the starting material was readily consumed at 0 °C, none of the desired isoxazoline could be detected. A very nonpolar spot was observed by TLC analysis. This intermediate, which is presumably the nitrile oxide, disappeared slowly with appearance of the desired isoxazoline **30a** when the reaction mixture was warmed to room temperature. The sodium hypochlorite oxidation was also conducted in the presence of several catalysts (Et_3N or Triton B), but the yields were optimum (65–75%) in the absence of a catalyst.

Having an equivalent of **4** in hand, we were now ready to examine its conversion to **3**. Removal of the acetonide (Amberlyst-15, methanol) from **30a** provided the diol **31**. A variety of methods and reagents were examined that might permit the selective conversion of the primary alcohol to its aldehyde. These included attempted oxidation with CrO_3/graphite,[20] derivatization of the primary alcohol as its tosylate followed by a Kornblum oxidation,[21]

(15) Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.

(16) (a) Kornblum, N.; Ungnade, H. E. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 724. (b) Kornblum, N. "Organic Reactions"; Wiley: New York, 1962; Vol. XII, p 101. (c) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497.

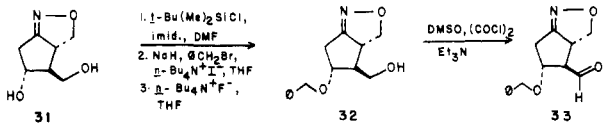
(17) (a) Grundmann, C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476. (b) Stevens, R. V.; Christensen, C. G.; Edmonson, W. L.; Kaplan, M.; Reid, E. B.; Wentland, M. P. *J. Am. Chem. Soc.* **1971**, *93*, 6629.

(18) Reference 13, p 81.

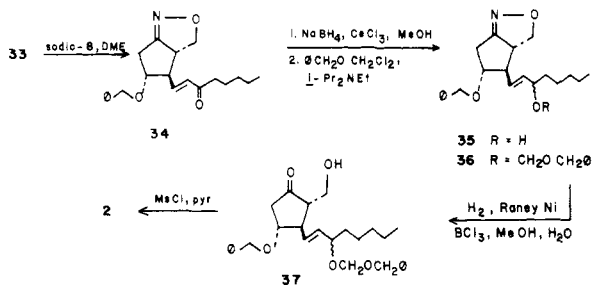
(19) Lee, G. A. *Synthesis* **1982**, 508.

(20) Lalancette, J.-M.; Rollin, G.; Dumas, P. *Can. J. Chem.* **1972**, *50*, 3058.

Ph_3PBr_2/DMF treatment to form primary bromide/secondary formate ester,[22] and even a direct Jones oxidation. Since none of these attempts met with success, we simply silylated (t-Bu(Me)$_2$SiCl, imidazole, DMF) the primary alcohol, benzylated (NaH, $PhCH_2Br$) the secondary alcohol, and then carried out a desilylation reaction ($Bu_4N^+F^-$) to provide alcohol **32** (80% overall yield from **30a**). A subsequent Swern oxidation cleanly afforded the aldehyde **33**.[23]



This aldehyde was condensed with the anion of the oxophosphonate **8** in DME at 0 °C to provide the enone **34**. Reduction of **34** in turn with sodium borohydride in the presence of $CeCl_3 \cdot 6H_2O$ gave a mixture of allylic alcohols **35** in 89% yield.[24,25] The hydroxyl group of **35** was protected as its (benzyloxy)methyl ether as described by Stork to provide the fully protected cyclopentane derivative **36**.

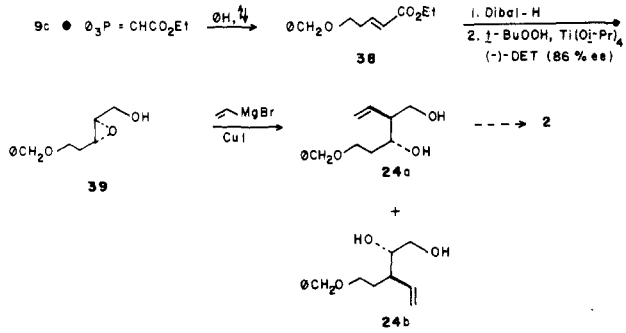


The final steps of the reaction sequence proceeded without incident. The isoxazoline ring of **36** was unmasked by exposure to W-2 Raney Ni/BCl_3/MeOH, H_2O[4] to reveal the β-hydroxy ketone **37**. The Raney nickel catalyst employed was deactivated prior to use by refluxing it for 3 h with acetone. This deactivation process was necessary in order to suppress hydrogenolysis of the benzylic protecting groups. Even so, some debenzylation was still found to occur. While chemical reduction of the isoxazoline ring using Ti^{3+} as first described by Torssell[5] also transformed **36** to **37**, the yield obtainable through such a procedure has not been optimized. The IR and ^1H NMR spectral data obtained for the β-hydroxy ketone **37** prepared by the hydrogenolysis reaction were identical with those kindly provided by Professor Stork. Dehydration of **37** to the enone **2** (R = $CH_2C_6H_5$, R′ = $CH_2OCH_2C_6H_5$) was accomplished by treatment with mesyl chloride in pyridine.[1]

A Chiral-Selective Route to 25

An alternate route to **25** was developed that produces this intermediate in optically active form. As diagrammed in the accompanying scheme, the aldehyde **9c** was reacted with carbethoxymethylenetriphenylphosphorane to provide **38**. The ester was reduced and the allylic alcohol was epoxidized under the Sharpless conditions by using unnatural diethyl tartrate as the chiral additive.[26] ^1H and ^{19}F NMR analysis of the (−)-α-methoxy-α-(trifluoromethyl)phenylacetate derivative of the epoxidation product revealed an enantiomeric excess of ~86%.[27] Ring opening of **39** with vinylmagnesium bromide in the presence of cuprous iodide led to the desired diol **24a** and the regioisomer **24b** in a ratio of ~85:15.[28] Control of the reaction temperature was crucial to the success of the ring-opening reaction, for at lower temperatures the reaction proceeded very slowly, whereas at higher temperatures magnesium bromide induced rearrangement of the epoxide to ketone was evident. Additionally, the use of lithium divinylcuprate in place of the Grignard reagent resulted in lower regioselectivity (~60/40).[29]

Diol **24a** was further transformed to the dioxanes **25a** and **26a**. While **26a** could be converted to the optically active prostaglandin intermediate **2** by steps identical with those described for the racemic diol, we chose not to carry the material on further.



Conclusion

Since **2** has been transformed to $PGF_{2\alpha}$ by Stork and Isobe, the present work constitutes a formal total synthesis of this prostaglandin.[3] The present synthesis does reveal the ability of an existing ring unit to steer the diastereofacial course of the INOC reaction during the creation of two new ring structures.[30] The complete regio- and stereocontrol that attend the cycloaddition processes described herein are, of course, entirely, or in part a consequence of the linear nature of the nitrile oxide group.[14b] Bridged products are not formed as is possible in cases where "bent" dipoles such as nitrones are employed in intramolecular cycloadditions.[31] Further aspects of stereocontrol in INOC reactions are under study and will be reported in due course.

Experimental Section

Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl prior to use. Benzene and toluene were distilled from CaH_2 prior to use. Methylene chloride was dried by passage through a column of activity I neutral alumina and

(21) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.
(22) Boeckman, R. K.; Ganem, B. *Tetrahedron Lett.* **1974**, 913 and 917.
(23) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(24) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. 1,4-Reduction of the enone was observed in the absence of $CeCl_3$.
(25) The diastereomeric alcohols **35** were separable by HPLC.
(26) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(28) The cuprous iodide used was purified as described by Kaufmann and Teter: Kaufmann, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(29) Other workers have reported similar ring opening reactions of epoxides. See, inter alia: (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (b) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *Ibid.* **1982**, *47*, 1378. (c) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (d) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (e) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377.
(30) For other examples of diastereoselection in nitrile oxide cycloaddition reaction, see: (a) Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. (c) Kozikowski, A. P.; Goldstein, S. *J. Org. Chem.* **1983**, *48*, 1139. (d) Kozikowski, A. P.; Kitagawa, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 1460.
(31) LeBel, N. A. *Trans. N.Y. Acad. Sci.* **1965**, *27*, 858.

stored over 4-Å molecular sieves. Ethanol and methanol were distilled from magnesium turnings and stored over 4-Å sieves. Dimethylformamide (DMF) and HMPA were distilled from CaO under reduced pressure and stored over 4-Å sieves. Me_2SO was distilled from CaH_2 under reduced pressure and stored over 4-Å sieves. Nitromethane was distilled from P_2O_5. Acetonitrile was stored over K_2CO_3.

Other reagents were used as supplied or purified as noted. *n*-Butyllithium in hexanes (Aldrich) was titrated at 0 °C in THF with *l*-menthol by using 1,10-phenanthroline as an end-point indicator.

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Boiling points refer to head temperatures (or oven temperatures for bulb-to-bulb distillations) and are uncorrected. Brine refers to a saturated NaCl solution. All reactions were carried out in oven or flame-dried glassware under a N_2 atmosphere with magnetic stirring unless noted otherwise. Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing dropping funnels where appropriate.

Solvents used for extraction and chromatography were purchased in 5-gal drums, redistilled from an all-glass apparatus, and stored in glass bottles. Infrared spectra were obtained on a Perkin-Elmer Model 247 or 231 spectrophotometer or a Beckman Acculab 4 spectrophotometer and were calibrated to a polystyrene absorption at 1602 cm^{-1} (6.43 μm). Spectra were obtained as dilute solutions in $CHCl_3$ or CCl_4, neat films, or KBr disks. The following qualitative descriptors are used: s = strong, m = medium, w = weak, v = very, br = broad, sh = shoulder.

Low-resolution mass spectra were determined on a LKB-9000 instrument operating at an ionizing potential of 15 or 70 eV. Usually all peaks greater than ~5% relative intensity are reported. High-resolution mass spectra were determined on a Varian MAT CH-5DF instrument by peak matching.

^1H NMR spectra were recorded at 60 MHz (Varian EM-360 or T-60A), 90 MHz (Varian EM-390), or at 300 MHz (Brüker WH-300) in the solvent(s) noted. Chemical shifts (δ) are reported downfield from internal Me_4Si (1% or ~0.5% for Fourier transform) at δ = 0.000 ppm. The following descriptions are used: AB q = AB quartet, br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

Apparent coupling constants (J) are reported in hertz (Hz). J values obtained on CW instruments are probably accurate to ±0.5 Hz. Due to data digitization on the FT instrument J values are ±0.40 Hz maximum but normally are accurate to ±0.20 Hz. First-order analysis of some complex absorptions may lead to J values correct to only ±1 Hz.

Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter in an unthermostatted glass microcell (100-mm pathlength, ~1 mL volume) at the sodium D line.

Silica gel 60 (Merck, 70–230 mesh or 230–400 mesh for flash chromatography), Mallinckrodt SilicAR CC-7, and Merck Aluminum Oxide 90 (70–230 mesh, deactivated with water to provide the necessary activity) were used for column chromatography. TLC was performed on Merck Silica Gel 60 F-254 (0.25 mm, precoated on glass) or Merck aluminum oxide F-254 type T (0.25 mm, precoated on aluminum, dried 1 h at 120 °C, and cooled in a dry atmosphere).

Preparative LC separations were performed on an updated Waters Prep-500 instrument by using standard silica PrepPAK cartridges. HPLC was carried out on a μ-Porasil column using a Waters Model 6000A solvent delivery system, a Waters UK-6 injector, and a Waters R401 refractive index detector with its associated electronics unit.

GC analysis was carried out on a Hewlett Packard Model 5710A instrument fitted with a TC detector. The helium carrier gas flow rate was generally ~60 mL/min. TC detector current was ~150 mA. The injection port was maintained at 250 °C, the detector at 300 °C. The oven temperature programs are noted where appropriate. Three columns were generally used: a 6 ft 10% OV-101 on 100–120 mesh Chromosorb W-HP, a 20 in. UC-W982 on 80–100 mesh Chromosorb W/AW/DMCS B4, or a 6 ft 10% OV-225 on 100–120 mesh Chromosorb W-HP.

2-Phenyl-1,3-dioxane. A mixture of benzaldehyde (16 mL, 158 mmol), 1,3-propanediol (9.5 mL, 131 mmol) and ~300 mg of *d,l*-10-camphorsulfonic acid in 100 mL of benzene was refluxed for 2.5 h in a flask fitted with a Dean–Stark trap. At this time ~2.5 mL (>100% theory) of water had collected. The reaction was cooled, diluted with 100 mL of ether, washed (2 × 100 mL of 2 N NaOH, 1 × 100 mL of water, 1 × 100 mL of saturated $NaHSO_3$, and brine), dried ($MgSO_4$), and concentrated in vacuo to an oil, which was distilled through a 7-cm Vigreux column to provide 18.4 g (85%) of a colorless oil: bp_4 100–101 °C; IR (neat film) 3049 (w), 2967 (m), 2857 (m), 1493 (w), 1449 (m), 1425 (w), 1385 (sh), 1374 (m), 1309 (w), 1274 (m), 1235 (m), 1214 (w), 1144 (m), 1103 (s), 1075 (w), 1050 (w), 1029 (w), 1006 (s), 989 (sh), 951 (w), 933 (w), 909 (m), 894 (w), 870 (w), 845 (m), 749 (br, s), 697 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.13–7.70 (m, 5 H), 5.45 (s, 1 H), 3.63–4.50 (m, 4 H), 1.72–2.67 (m, 1 H), 1.15–1.72 (m, 1 H).

3-(Phenylmethoxy)-1-propanol. Cold ether (250 mL) was added to $AlCl_3$ (24 g, 183 mmol) at 0 °C. After solution had occurred, LAH (1.73 g, 45.7 mmol) was added portionwise; the first few portions of which evolved some gas. After stirring for 30 min at 0 °C, 2-phenyl-1,3-dioxane (7.51 g, 45.7 mmol) dissolved in 50 mL of ether was added dropwise. The reaction was allowed to warm to room temperature, whereupon stirring was continued for 2 h. The reaction was cooled to 0 °C and quenched by the *slow* addition of 250 mL of 2 N H_2SO_4. The heavy preciptate necessitated some manual agitation. On a larger scale addition of ether was necessary to make up for loss from heat evolution. The mixture was warmed to room temperature and stirred until two layers resulted. The layers were separated, and the aqueous layer was extracted (2 × 50 mL of ether). The combined organic layers were dried (K_2CO_3) and concentrated in vacuo to an oil, which was bulb-to-bulb distilled to give 7.16 g (94%) of the expected alcohol: bp_1 115–125 °C (oven); IR (neat film) 3425 (s), 3077 (w), 3040 (w), 2941 (s), 2882 (s), 1961 (w), 1880 (w), 1818 (w), 1724 (w), 1701 (sh), 1608 (w), 1587 (w), 1493 (m), 1474 (w), 1447 (m), 1433 (w), 1408 (w), 1361 (m), 1307 (w), 1272 (w), 1202 (m), 1087 (br, s), 1026 (w), 972 (w), 741 (br, s) 696 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.26 (s, 5 H), 4.40 (s, 2 H), 3.38–3.83 (m, 5 H), 1.78 (quint, 2 H, J = 6 Hz).

3-(Phenylmethoxy)propanal (9c). To a stirred suspension of 19 g (86 mmol) of PCC in 175 mL of CH_2Cl_2 was added in one portion 3-(phenylmethoxy)-1-propanol (7.16 g, 43.1 mmol). The reaction was stirred for 2 h and poured into 800 mL of ether. The black tar-like residue was washed with several portions of ether until granular, and the combined organics were filtered through a short (10 cm) Florisil plug. The eluent was concentrated in vacuo and the resulting oil was bulb-to-bulb distilled to provide 5.28 g (75%) of an oil. The pot residue consisted mainly of 3-(phenylmethoxy)propyl 3-(phenylmethoxy)propionate, which could be reduced with LAH in ether to provide 3-(phenylmethoxy)-1-propanol for recycling. For the product: bp_1 100 °C (oven); IR (neat) 3012 (w), 2849 (m), 2725 (w), 1715 (s), 1689 (sh), 1590 (w), 1575 (w), 1484 (w), 1441 (m), 1377 (w), 1351 (m), 1299 (w), 1196 (m), 1089 (s), 1021 (w), 825 (w), 740 (s), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 9.68 (t, 1 H, J = 2 Hz), 7.28 (s, 5 H), 4.46 (s, 2 H), 3.74 (t, 2 H, J = 6 Hz), 2.60 (dt, 2 H, J = 6, 2 Hz); mass spectrum (70 eV), m/z 164, 120, 108, 107, 106, 105, 92, 91, 90, 89, 80, 79, 78, 77, 73, 65, 63.

Ethyl 2-Ethenyl-3-hydroxy-5-(phenylmethoxy)pentanoate (23). LDA was prepared by the dropwise addition of *n*-BuLi (84 mL, 117 mmol) to a −78 °C solution of diisopropylamine (distilled from CaH_2, 15.7 mL, 112 mmol) in 150 mL of THF and allowing the mixture to stir for 1 h. HMPA (84 mL, 117 mmol) was added dropwise, and the mixture was stirred for 30 min. After complete solution had occurred a solution of ethyl crotonate (distilled, 107 mmol, 13.3 mL) in ~50 mL of THF was added dropwise. After an additional 30 min the aldehyde **9c** (128 mmol, 21 g) in 20 mL of THF was added dropwise. The reaction was stirred for 3 h and quenched by adding 100 mL of 1:1 saturated NH_4Cl/H_2O. The aqueous phase was extracted twice with ether (100 mL each), and the combined organic layers were washed (H_2O), dried ($MgSO_4$), and concentrated in vacuo. The residue (35 g) could be used crude for the reduction or purified (PREP 500, 2 silica PrepPAK cartridges, 20% ethyl acetate–hexanes, 200 mL/min) if desired. The purified yield was 85–95%: IR ($CHCl_3$) 3521 (w), 2924 (m), 2857 (w), 1724 (s), 1639 (w), 1445 (w), 1412 (w), 1362 (w), 1294 (w), 1200 (m), 1176 (w), 1091 (m), 1026 (m), 996 (w), 928 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–7.40 (m, 5 H), 5.95 (ddd,

0.5 H, J = 17.2, 10.2, 9.2 Hz), 5.77 (ddd, 0.5 H, J = 17.2, 10.1, 9.3 Hz), 5.13–5.24 (m, 2 H), 4.44 (s, 2 H), 3.49–3.72 (m, 3 H), 3.02–3.12 (m, 1 H), 1.60–1.89 (m, 2 H), 1.19 and 1.20 (2 t, 2 H, J = 7.1 Hz); mass spectrum (70 eV), m/z 279, 233, 172, 171, 169, 165, 156, 155, 147, 144, 143, 126, 125, 123, 115, 114, 108, 107, 97, 92, 91 (base), 86, 82, 81, 80, 73, 69, 68.

2-Ethenyl-5-(phenylmethoxy)-1,3-pentanediol (24). A three-necked, round-bottomed 1000-mL flask was fitted with a magnetic stirring bar, and dropping funnel, and a condenser. The flask was charged with 400 mL of ether and 4.40 g of LAH (116 mmol). The crude aldol product **23** (24.8 g) was added dropwise to the stirred LAH suspension at a rate which maintained gentle reflux. Stirring was continued 5 min after the addition was complete, and the reaction mixture was cooled to 0 °C and quenched by the addition of wet sodium sulfate. After gas evolution had ceased the flask was warmed to room temperature and stirred until a white granular solid resulted. The solid was filtered and washed with several portions of ether. The combined filtrates were concentrated in vacuo to afford an oil, which was chromatographed (Prep 500, 2 PrepPAK columns, 500 mL/min, 40% ethyl acetate–hexanes) to provide 13.4 g of the diastereomeric diols as an oil. Threo diol: IR ($CHCl_3$) 3497 (m), 3086 (w), 3012 (w), 2941 (m), 2882 (m), 1639 (w), 1490 (w), 1451 (w), 1414 (w), 1353 (w), 1085 (s, br), 1047 (sh), 1025 (w), 923 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5 H), 5.60 (ddd, 1 H, J = 17.4, 10.5, 9 Hz), 5.12–5.18 (m, 2 H), 4.53 (s, 2 H), 3.63–3.94 (m, 6 H), 3.13 (m, 1 H), 2.30–3.14 (m, 1 H), 1.72–1.92 (m of AB q, J_{AB} ~14.5 Hz); mass spectrum (15 eV), m/z 218, 217 , 201, 188, 187, 166, 165, 164, 163, 160, 159, 149, 147, 146, 145, 144, 143, 131, 130, 129, 127, 121, 120, 118, 112, 109, 108, 107, 106, 105, 97, 95, 94, 93, 92, 91 (base), 85, 84, 83, 82, 81, 80, 79, 73, 71, 70, 69, 68, 67, 66; exact mass calcd for $C_{13}H_{15}O$ ($M^+ - H_2O - CH_2OH$) 187.1123, found 187.1122. Erythro diol: IR ($CHCl_3$) 3650 (sh), 3509 (m), 3077 (w), 2994 (sh), 2933 (m), 2874 (m), 1715 (w), 1634 (w), 1490 (w), 1445 (w), 1410 (w), 1353 (w), 1271 (w), 1089 (s), 1024 (w), 999 (w), 919 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.39 (m, 5 H), 5.88 (ddd, 1 H, J = 17.5, 10.5, 8.6 Hz), 5.12–5.24 (m, 2 H), 4.52 (s, 2 H), 4.08 (ddd, 1 H, J = 10.1, 5.5, 2.6 Hz), 3.63–3.83 (m, 4 H), 3.39 (br s, 1 H), 2.52 (br s, 1 H), 2.28–2.36 (m, 1 H), 1.83–1.96, 1.59–1.68 (m of AB q, 2 H, J_{AB} = 14.6 Hz); mass spectrum (15 eV), m/z 188, 187, 179, 165, 164, 163, 159, 147, 146, 143, 130, 129, 122, 120, 113, 112, 110, 109, 108, 107, 106, 105, 97, 95, 94, 93, 92, 91 (base), 85, 84, 83, 82, 81, 80, 79, 73, 71, 70, 69, 68, 67, 66; exact mass calcd $C_{13}H_{15}O$ ($M^+ - CH_2OH - H_2O$) 187.1123, found 187.1122.

***cis*- and *trans*-2,2-Dimethyl-4-[2-(phenylmethoxy)ethyl]-5-ethenyl-1,3-dioxane (25a and 25b).** Diol **24a** (6.5 g, 28 mmol) was dissolved in 300 mL of 2,2-dimethoxypropane (dried over sodium and then distilled). Amberlyst-15 resin (~500 mg) was added, and the mixture was stirred until the diol was consumed (~24 h). The resin was removed by filtration and washed with ether. The combined filtrates were concentrated in vacuo to provide a yellow oil, which was used without further purification for the debenzylation step. Chromatography (silica gel, 10% ethyl acetate–hexanes) provided a mixture of the diastereomers as a colorless to yellowish oil. Spectral data for the pure trans compound (**25a**) obtained from the epoxide route are as follows: IR ($CHCl_3$) 2985 (m), 2941 (sh), 2865 (m), 1712 (w), 1637 (w), 1445 (w), 1374 (m), 1359 (w), 1305 (w), 1261 (m), 1189 (w), 1163 (w), 1129 (w), 1111 (w), 1087 (w), 1052 (w), 1024 (w), 992 (m), 980 (sh), 921 (m), 865 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.38 (m, 5 H), 5.50 (ddd, 1 H, J = 17.2, 10.3, 8.9 Hz), 5.10–5.18 (m, 2 H), 4.50 (AB q, 2 H, J_{AB} = 12 Hz, ν_{AB} = 18 Hz), 3.85 (ddd, 1 H, J = 10, 9, <1 Hz), 3.69–3.72 (m, 2 H), 2.20–2.32 (m, 1 H, J = 10, 8.9 Hz), 1.92–2.03 and 1.54–1.65 (m of AB q, 2 H, J_{AB} = 14 Hz); mass spectrum (15 eV), m/z 275, 261, 232, 218, 191, 177, 165, 164, 163, 149, 146, 144, 122, 120, 113, 112, 108, 107 (base), 105, 101, 93, 92, 91, 84, 83, 80, 73, 59, 55, 54; exact mass calcd for $C_{16}H_{21}O_3$ ($M^+ - CH_3$) 261.1491, found 261.1491.

***cis*- and *trans*-2-(5-Ethenyl-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (26a and 26b).** A solution of crude acetonide **25** in 20 mL of THF was introduced into a 500-mL, round-bottomed, three-necked flask fitted with a dry ice/2-propanol condenser, mechanical stirrer, and N_2 balloon. One milliliter of absolute ethanol was added, the flask was cooled to −78 °C, and ~200 mL of liquid NH_3 (distilled from Na) was condensed into the flask. Sodium (~2 g, excess) was introduced into the well-stirred mixture piecewise until the characteristic blue color of excess sodium persisted. After stirring for an additional 5 min (TLC monitoring showed the reduction to be complete), solid NH_4Cl was added to discharge the color, the cooling bath and condenser were removed, and the ammonia was allowed to evaporate. The residue was partitioned between ether and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. High-pressure liquid chromatography (PREP 500, 2 PrepPAK cartridges, mass shave/recycle technique, 40% ethyl acetate/hexanes) provided the pure trans [faster moving isomer, 1.91 g (37%)] and cis (1.97 g) alcohols as oils.

Trans: IR ($CHCl_3$) 3559 (s), 2994 (s), 2874 (s), 1642 (w), 1453 (w), 1416 (w), 1377 (m), 1364 (sh), 1263 (w), 1192 (w), 1157 (w), 1130 (w), 1072 (m), 992 (w), 976 (m), 926 (m), 889 (m), 861 (m), 818 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (ddd, 1 H, J = 17.2, 10.1, 8.7 Hz), 5.13–5.21 (m, 2 H), 3.93 (ddd, 1 H, J = ~11, 9, 2.5 Hz), 3.70–3.82 (m, 4 H), 2.62 (br t, 1 H), 2.31–2.43 (m, 1 H, J = 11, 8.7, 8, 7 Hz), 1.63–1.93 (m of AB q, 2 H, J_{AB} = 14.8 Hz), 1.50 (s, 3 H), 1.41 (s, 3 H); mass spectrum (15 eV), m/z 172, 171, 141, 129, 128, 113, 112, 111, 110, 98, 93, 89, 83, 81, 80, 73, 70, 69, 68, 67, 59, 55, 54 (base); exact mass calcd for $C_9H_{15}O_3$ ($M^+ - CH_3$) 171.1021, found 171.1020.

Cis: IR ($CHCl_3$) 3436 (s), 3077 (w), 2994 (s), 2950 (s), 2874 (s), 1639 (w), 1471 (sh), 1456 (w), 1418 (w), 1374 (m), 1361 (sh), 1339 (sh), 1263 (m), 1233 (w), 1195 (w), 1168 (w), 1147 (w), 1119 (w), 1104 (w), 1058 (m), 1000 (m), 961 (w), 950 (w), 935 (sh), 916 (m), 890 (w), 864 (sh), 852 (m), 814 (w), 784 (w), 706 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (ddd, 1 H, J = 17.4, 10, 10 Hz), 5.07–5.20 (m, 2 H), 4.22–4.25 (m, 1 H), 4.19 (dd, 1 H, J = 11.5, 2.8 Hz), 3.67–3.73 (m, 3 H), 2.86 (br s, 1 H), 1.81–1.99 (m, 1 H, J = ~10, 3, 3, ~1 Hz), 1.69–1.79 and 1.46–1.55 (m of AB q, 2 H, J_{AB} = 14.5 Hz), 1.50 (s, 3 H), 1.40 (s, 3 H); mass spectrum (15 eV), m/z 172, 171, 128, 113, 112, 111, 98, 93, 89, 83, 81, 80, 73, 69, 68, 67, 59, 55, 54 (base); exact mass calcd for $C_9H_{15}O_3$ ($M^+ - CH_3$) 171.1021, found 171.1020.

***trans*-(5-Ethenyl-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (27a).** A solution of oxalyl chloride (distilled, 1.16 mL, 13.3 mmol) in 30 mL of CH_2Cl_2 was cooled to −78 °C. A solution of Me_2SO (1.89 mL, 26.7 mmol) in 6 mL of CH_2Cl_2 was slowly added over a 5-min period. After stirring for 5 min the alcohol **26a** (1.91 g, 10.3 mmol) in 5 mL of CH_2Cl_2 was added dropwise. After stirring for 35 min triethylamine (7.1 mL, 51.3 mmol) was added dropwise. The mixture was stirred for 5 min and allowed to warm to room temperature. Water (10 mL) was added, the layers were separated, and the aqueous layer was extracted with 10 mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude aldehyde **27a** (1.89 g) was obtained as an odorous yellow oil: IR (CCl_4) 2830 (s), 2732 (w), 1727 (s), 1642 (w) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.7 (t, 1 H, J <1 Hz), 5.10–5.90 (m, 3 H), 4.00–4.40 (m, 1 H), 3.75 (d, 2 H, J = 7.5 Hz), 2.11–2.81 (m, 3 H), 1.50 (s, 3 H), 1.38 (s, 3 H); mass spectrum (15 eV), m/z 169, 141, 131, 112, 73, 54. The cis alcohol (1.04 g, 5.58 mmol) was oxidized in the same manner as the trans alcohol by using 585 μL (6.70 mmol) of oxalyl chloride, 951 μL (13.4 mmol) of Me_2SO, and 3.9 mL (27.9 mmol) of triethylamine; ^1H NMR (60 MHz, $CDCl_3$) δ 9.70 (t, 1 H, J ~ 1 Hz), 5.90–6.60 (m, 1 H), 4.80–5.40 (m, 2 H), 4.60–5.40 (m, 2 H), 4.60 (dt, 1 H, J = 6, 2 Hz), 4.00 (d of AB q, 2 H, J_{AB} = 11.5 Hz, J_{AX} = 3 Hz, J_{BX} = 2 Hz, ν_{AB} = 30 Hz), 2.40–2.60 (m, 2 H), 1.90–2.30 (m, 1 H), 1.52 (s, 3 H), 1.40 (s, 3 H).

***(E)*-*trans*-(5-Ethenyl-2,2-dimethyl-1,3-dioxan-4-yl)acetoxime (28a).** The crude aldehyde **27a** (1.89 g) was dissolved in 100 mL of pyridine and recrystallized hydroxylamine hydrochloride (859 mg, 12.4 mmol) was added. The mixture was stirred for 1 h, poured into 300 mL of ether, washed with water (4×), dried ($MgSO_4$), and concentrated in vacuo to an odorous oil. Chromatography (flash, 10% then 25% ethyl acetate–hexanes) provided 1.36 (66%) of a white solid, initially a mixture of the syn and anti isomers which gradually isomerizes to only the anti form: mp 103.5–106 °C (raised to 110–111.5 °C after recrystallization from EtOH–H_2O); IR ($CHCl_3$) 3636 (m), 3333 (m), 3106 (w), 3012 (m), 2882 (w), 2653 (w), 2488 (w), 1706 (w), 1642 (w), 1605 (w), 1453 (w), 1412 (w), 1377 (m), 1370 (sh), 1359 (w), 1263 (w), 1189 (w), 1163 (w), 1122 (w), 1100 (w), 1050 (w), 990 (w), 928 (w), 882 (w), 858 (w), 833 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 8.53 (br s, 1 H), 7.50 (t, 1 H, J = 6.3 Hz), 5.48 (ddd, 1 H, J = 17.2, 10.1, 8.9 Hz), 5.15–5.22 (m, 2 H), 3.85 (m, 1 H), 3.72 (d, 2 H, J = 8.3 Hz), 2.26–2.54 (m, 3 H), 1.46 (s, 3 H), 1.40 (s, 3 H); mass spectrum (15 eV), m/z 185, 184, 166, 142, 141, 124, 113, 112 (base), 111, 107, 98, 97, 96, 94, 83, 81, 80, 79, 68, 67, 59, 58; exact mass calcd for $C_9H_{14}NO_3$ ($M^+ - CH_3$) 184.0974, found 184.0973. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.38; H, 8.70; N, 7.16.

(*E*)-*cis*-(5-Ethenyl-2,2-dimethyl-1,3-dioxan-4-yl)acetoxime (28b). The preceding crude aldehyde **27b** was dissolved in 20 mL of pyridine and hydroxylamine hydrochloride (465 mg, 6.70 mmol) was added. The reaction mixture was stirred for 1.5 h, and then worked up as described for **28a**. Chromatography (flash, 25% ethyl acetate–hexanes) provided 807 mg (73%) of an oil: IR (neat) 3378 (s, br), 3096 (w), 3003 (m), 2882 (m), 1855 (w), 1645 (w), 1456 (w), 1422 (w), 1377 (m), 1359 (sh), 1266 (m), 1238 (w), 1193 (w), 1168 (w), 1147 (w), 1116 (w), 1058 (m), 1012 (m), 968 (w), 932 (m), 852 (m), 813 (w), 767 (w), 735 (w), 704 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 8.40–9.20 (br s, 1 H), 7.40 (t, 0.5 H, J = 6 Hz), 6.80 (t, 0.5 H, J = 5.5 Hz), 5.90–6.60 (m, 1 H), 4.90–5.40 (m, 2 H), 3.90 (complex AB q, 2 H, J_{AB} = 11 Hz, J_{AX} = 3 Hz, ν_{AB} = 25 Hz), 4.00–4.40 (m, 1 H), 2.20–2.70 (m, 2 H), 1.80–2.20 (m, 1 H), 1.48 (s, 3 H), 1.42 (s, 3 H); mass spectrum (15 eV), m/z 185, 184, 166, 142, 141, 124, 113, 112, 111, 107, 98, 97, 96, 94, 93, 87, 83, 82, 81, 80, 79, 70, 69, 68, 67, 66, 59, 55, 54 (base).

4β,5α-5-Hydroxy-4-(hydroxymethyl)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole Acetonide (30a). To a vigorously stirred solution of 1.36 g (6.80 mmol) of the oxime **28a** in 150 mL of CH_2Cl_2 cooled to 0 °C was added 11.2 mL of commercial bleach (~5% NaOCl, ~0.7 M) dropwise. After the transient blue-green color had faded and TLC analysis revealed that the oxime had been consumed (~1 h), the stirrer was stopped, the ice bath was removed, and the reaction was allowed to stand overnight (~18 h). The layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting solid was chromatographed (silica, 50% ethyl acetate–hexanes) to provide 1.00 g (75%) of the isoxazoline as a white solid: mp 94–101 °C (recrystallization from ether–petroleum ether raised the mp to 98–103 °C); IR ($CHCl_3$) 2985 (s), 2933 (s), 2865 (s), 1706 (w), 1653 (w), 1456 (m), 1425 (w), 1376 (s), 1361 (s), 1307 (m), 1267 (w), 1247 (w), 1182 (w), 1156 (w), 1139 (w), 1116 (w), 1096 (w), 1062 (w), 1041 (w), 1018 (m), 989 (w), 963 (w), 934 (s), 910 (s), 847 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.50 (dd, 1 H, J = 9.10, 8.08 Hz), 4.23 (ddd, 1 H, J = 10.5, 10.3, 8.49 Hz), 4.04 (dd, 1 H, J = 11.1, 4.45 Hz), 3.90 (1 H, dd, J = 11.1, 11.1 Hz), 3.79 (dd, 1 H, J = 12.9, 8.08 Hz), 3.28 (ddddd, 1 H, J = 12.9, 10.5, 9.10, 2.43, 1.41 Hz), 2.95 (1 H, ddd, J = 17.4, 8.49, 1.41 Hz), 2.44 (ddd, 1 H, J = 17.4, 10.3, 2.43 Hz), 1.80 (dddd, 1 H, J = 11.1, 10.5, 9.7, 4.45 Hz), 1.53 (s, 3 H), 1.45 (s, 3 H); mass spectrum (15 eV), m/z 197, 183, 182, 141, 139 (base), 138, 137, 122, 112, 111, 110, 109, 108, 96, 95, 94, 93, 92, 85, 84, 83, 82, 81, 80, 79, 71, 70, 69, 68, 67, 66, 59; exact mass calcd for $C_9H_{12}NO_3$ ($M^+ - CH_3$) 182.0817, found 182.0818.

4β,5β-5-Hydroxy-4-(hydroxymethyl)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole Acetonide (30b). To a vigorously stirred solution of the oxime **28b** (40 mg, 0.20 mmol) in 1 mL of CH_2Cl_2 cooled to 0 °C was added dropwise commercial bleach (~5% NaOCl, ~0.7 M, 709 μL). The reaction was stirred for 40 min. The layers were separated, and the organic phase was dried ($MgSO_4$), concentrated in vacuo, and chromatographed (silica, 50% ethyl acetate–hexanes) to provide 27.7 mg of a white solid (70%): mp 102–104 °C; IR ($CHCl_3$) 2994 (m), 2941 (m), 2882 (w), 1453 (w), 1404 (w), 1376 (s), 1370 (s, sh), 1299 (w), 1284 (m), 1181 (w), 1166 (w), 1140 (m), 1121 (w), 1085 (s), 1072 (s), 1008 (w), 993 (m), 959 (m), 1032 (m), 894 (m), 873 (w), 847 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (dd, 1 H, J = 5.46, 3.63 Hz), 4.58 (dd, 1 H, J = 9.70, 7.88 Hz), 4.34–4.45 (m, 1 H), 4.20 (dd, 1 H, J = 12.3, 3.63 Hz), 3.83 (dd, 1 H, J = 12.3, 7.88 Hz), 3.74 (dd, 1 H, J = 12.3, <1 Hz), 2.65 (m of AB q, 2 H, J_{AB} = 18.4 Hz, ν_{AB} = 27.0 Hz, J_{AX} = 5.46, 1.82 Hz, J_{BX} <1 Hz), 1.68–1.74 (m, 1 H), 1.48 (s, 3 H), 1.40 (s, 3 H); mass spectrum (70 eV), m/z 198, 197, 183, 182, 169, 168, 154, 141, 140, 139, 138, 125, 124, 122, 111, 110, 109, 108, 107, 98, 96, 95, 94, 93, 92, 91, 85, 84, 83, 82, 81, 80, 79, 78, 77, 70, 69, 68, 67, 66, 65, 59 (base), 58, 57, 56, 55, 54, 53, 52, 51.

4β,5α-5-Hydroxy-4-(hydroxymethyl)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole (31). A 100-mL methanolic solution of the acetonide **30a** (1.00 g, 5.07 mmol) containing 20–30 beads of Amberlyst-15 was stirred for 1 h at room temperature. The Amberlyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to provide 797 mg of an oily product (100%). Chromatography, if desired, was accomplished by using ethyl acetate as eluent on SilicAR CC-7. The next reaction was generally carried out with the crude material: IR (neat) 3448 (s), 2994 (m), 2950 (m), 1664 (m), 1462 (w), 1416 (w), 1335 (w), 1287 (w), 1266 (w), 1239 (w), 1174 (w), 1056 (br, m), 1027 (sh, br), 955 (w), 927 (w), 876 (w), 835 (w), 800 (w) cm^{-1}; ^1H NMR (90 MHz, acetone-d_6) δ 4.35–4.70 (m, 2 H), 3.25–4.10 (m, 4 H), 2.80–3.22 (m, 3 H), 1.65–2.30 (m, 2 H, obscured by solvent); mass spectrum (15 eV), m/z 157, 139, 138, 129, 127, 126, 112, 111, 110, 99, 98 (base), 97, 96, 94, 93, 86, 85, 84, 83, 82, 81, 80, 79, 71, 70, 69, 68, 67, 66; exact mass calcd for $C_7H_{11}NO_3$ 157.0739, found 157.0739.

***tert*-Butyldimethylsilylation of 31.** A solution of 755 mg (4.81 mmol) of the diol **31**, 869 mg (5.77 mmol) of *tert*-butyldimethylsilyl chloride, and imidazole (818 mg, 12.0 mmol) in 2 mL of DMF was stirred for 3 h. The reaction was diluted with 50 mL of ether, washed with water (2×), dried ($MgSO_4$), and concentrated in vacuo to afford an oil (1.24 g, 95%), which was used in the next reaction without further purification. An analytical sample was prepared by chromatography (silica, 25% and then 50% ethyl acetate–hexanes) followed by recrystallization from hexanes: mp 84–84.5 °C; IR ($CHCl_3$) 3546 (w), 2959 (s), 2874 (s), 1462 (m), 1370 (w, br), 1250 (m), 1212 (w, br), 1087 (s, br), 1006 (w), 990 (w), 939 (w), 865 (w), 838 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.44 (dd, 1 H, J = 9.50, 8.08 Hz), 4.36–4.47 (m, 1 H), 3.75 (dd, 1 H, J = 12.5, 8.08 Hz), 3.70 (d of AB q, 2 H, J_{AB} = 10.3 Hz, J_{AX} = 5.4 Hz, J_{BX} = 6.3 Hz), 3.63 (br s, 1 H), 3.41 (ddddd, 1 H, J = 12.5, 9.7, 9.50, 1.82, 1.21 Hz), 2.91 (ddd, 1 H, J = 17.8, 9.10, 1.21 Hz), 2.34 (ddd, 1 H, J = 17.8, 6.5, 1.82 Hz), 1.84–1.94 (m, 1 H), 0.82 (s, 9 H), 0.00 (s, 6 H); mass spectrum (15 eV), m/z 272, 255, 216, 215, 214, 198, 197, 196, 187, 186, 185, 184, 180, 170, 169, 168, 167, 166, 156, 155, 154, 145, 143, 140, 139, 138, 131, 129, 127, 126, 122, 115, 111, 110, 106, 105, 98, 96, 95, 94, 93, 92, 89, 81, 80, 77, 76, 75 (base), 73, 72, 71, 70, 69, 67; exact mass calcd for $C_9H_{16}NO_3Si$ ($M^+ - t$-Bu) 214.0899, found 214.0899. Anal. Calcd for $C_{13}H_{25}NO_3Si$: C, 57.53; H, 9.28; N, 5.16; Si, 10.35. Found: C, 57.67; H, 9.33; N, 5.26; Si, 10.12.

4β,5α-5-(Phenylmethoxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole. To a suspension of a degreased sodium hydride (121 mg, 5.03 mmol) in THF (50 mL) was added dropwise a 1-mL THF solution of the preceding alcohol (1.24 g, 4.57 mmol). The mixture was stirred until hydrogen evolution ceased (~15 h). To the thick, brown suspension was added benzyl bromide (distilled, 0.652 mL, 5.48 mmol) and a catalytic amount of tetra-*n*-butylammonium iodide. The reaction was stirred until TLC analysis showed consumption of the alcohol (2–3 h). The mixture was poured into 200 mL of ether and washed with H_2O (3×). The organic layer was dried ($MgSO_4$) and concentrated. The crude material (>100% yield) was used directly in the next reaction. Chromatography (silica, 25% ethyl acetate–hexanes) provided an analytical sample: IR (neat) 2959 (m), 2890 (m), 2857 (m), 1490 (w), 1462 (w), 1453 (sh), 1381 (w), 1351 (w), 1247 (m), 1087 (s, br), 1026 (w), 1003 (w), 987 (w), 936 (w), 893 (w), 836 (s), 812 (w), 778 (m), 733 (w, br), 697 (m, br) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.32 (m, 5 H), 4.46 (dd, 1 H, J = 9.7, 8.08 Hz), 4.46 (AB q, 2 H, J_{AB} = 11.7 Hz, ν_{AB} = 35 Hz), 4.13 (ddd, 1 H, J = 8.69, 7.86, 5.86 Hz), 3.77 (dd, 1 H, J = 12.4, 8.08 Hz), 3.63 (d of AB q, 2 H, J_{AB} = 9.90 Hz, J_{AX} = 3.84 Hz, J_{BX} = 6.27 Hz, ν_{AB} = 41 Hz), 3.41–3.52 (m, 1 H), 2.61 (dd of AB q, 2 H, J_{AB} = 17.4 Hz, J_{AX} = 8.69, 1.41 Hz, J_{BX} = 5.86, 1.82 Hz, ν_{AB} = 109 Hz), 1.88–2.04 (m, 1 H), 0.81 (s, 9 H), −0.02 (s, 6 H); mass spectrum (15 eV), m/z 362, 361 (M^+), 346, 334, 333, 319, 318, 317, 307, 306, 305, 304, 286, 276, 275, 274, 270, 256, 244, 217, 216, 214, 212, 202, 201, 200, 199, 198, 196, 189, 188, 184, 182, 181, 180, 176, 175, 174, 173, 171, 170, 169, 168, 167, 166, 165, 158, 157, 156, 155, 146, 145, 144, 143, 142, 138, 131, 130, 129, 122, 117, 108, 107, 106, 105, 93, 92, 91 (base), 89, 79, 75, 73; exact mass calcd for $C_{20}H_{31}NO_3Si$ 361.2069, found 361.2073.

4β,5α-4-(Hydroxymethyl)-5-(phenylmethoxy)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole (32). The preceding

crude product was dissolved in 9.1 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF (Aldrich). The reaction mixture was stirred for 1 h, concentrated in vacuo, and chromatographed (silica, 90% ethyl acetate–hexanes) to provide 564 mg (45% from the acetonide **30a**) of an oil: IR (neat) 3448 (s), 3040 (w), 2941 (m), 2890 (m), 1653 (w), 1493 (w), 1460 (sh), 1447 (m), 1412 (w), 1391 (w), 1346 (w), 1304 (w), 1266 (w), 1208 (w), 1099 (br, m), 1068 (w), 1025 (w), 939 (w), 913 (w), 889 (w), 848 (w), 809 (w, br), 735 (s, br), 698 (m, br) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.39 (m, 5 H), 4.55 (dd, 1 H, J = 9.50, 8.08 Hz), 4.52 (AB q, 2 H, J_{AB} = 11.7 Hz, ν_{AB} = 34 Hz), 4.20 (ddd, 1 H, J = 8.69, 8.08, 5.86 Hz), 3.83 (dd, 1 H, J = 12.3, 8.08 Hz), 3.70 (d of AB q, 2 H, J_{AB} = 11 Hz, J_{AX} = 6.27 Hz, J_{BX} = 4.85 Hz, ν_{AB} = 48 Hz), 3.46–3.54 (m, 1 H), 2.67 (dd of AB q, 2 H, J_{AB} = 17.6 Hz, J_{AX} = 8.69, 1.41 Hz, J_{BX} = 5.86, 1.82 Hz, ν_{AB} = 115 Hz), 2.64 (br s, 1 H), 2.02–2.12 (m, 1 H); mass spectrum (15 eV), m/z 247, 219, 218, 216, 198, 190, 189, 188, 176, 175, 174, 159, 158, 150, 146, 132, 120, 108, 107, 106, 105, 104, 103, 98, 96, 93, 92, 91 (base), 80, 79, 69; exact mass calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1209.

4β,5α-5-(Phenylmethoxy)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole-4-carboxaldehyde (33). To a −78 °C solution of oxalyl chloride (distilled, 0.26 mL, 2.96 mmol) in 10 mL of CH_2Cl_2 was added dropwise Me_2SO (0.42 mL, 5.93 mmol) dissolved in the 0.5 mL of CH_2Cl_2. After stirring for 5 min, the alcohol **32** (564 mg, 2.28 mmol) in 1 mL of CH_2Cl_2 was added dropwise. After stirring for 30 min, triethylamine (1.6 mL, 11.4 mmol) was added dropwise. The reaction was stirred for an additional 5 min, allowed to warm to room temperature, and then diluted with 20 mL of ether, washed (H_2O and 5% $NaHCO_3$), dried ($MgSO_4$), and concentrated in vacuo. A crude yield of 565 mg (>100%) was obtained. This material could be used crude or purified by chromatography (silica, 50% ethyl acetate–hexanes). The chromatographed yield was ~84%: IR (neat) 3448 (w), 3030 (w), 2933 (w), 2874 (w), 2732 (w), 1721 (s), 1490 (w), 1460 (sh), 1447 (m), 1412 (w), 1342 (w), 1247 (w), 1205 (w), 1093 (br, m), 1065 (w), 1025 (w), 810 (br, m), 738 (br, m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.79 (d, 1 H, J = 1.0 Hz), 7.29–7.40 (m, 5 H), 4.48–4.65 (m, 4 H), 3.79–3.89 (m, 2 H), 2.88–2.94 (m, 1 H, obscured), 2.74 (dd of AB q, 2 H, J_{AB} = 17.38 Hz, J_{AX} = 8.49, 1.01 Hz, J_{BX} = 5.05, 1.21 Hz, ν_{AB} = 73 Hz).

4β,5α-4-[(*E*)-3-Oxo-1-octenyl]-5-(phenylmethoxy)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole (34). To a suspension of degreased NaH (54.7 mg, 2.28 mmol) in 25 mL of DME was added dropwise dimethyl 2-oxoheptylphosphonate (0.48 mL, 2.33 mmol). The mixture was stirred until hydrogen evolution ceased (~1 h) and the mixture became very thick. The mixture was cooled to 0 °C and the crude aldehyde (565 mg) in 1 mL of DME was added dropwise. After being stirred for 5 min, the reaction mixture was quenched with 10 mL of saturated NH_4Cl and extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to an oil. This oil could be used crude for the next reduction or chromatographed (SilicAR CC-7, 25% ethyl acetate–hexanes). The chromatographic yield was ~72%: IR (neat) 3509 (w), 3030 (w), 2950 (s), 2933 (s), 2865 (s), 1689 (m), 1669 (s), 1629 (m), 1490 (w), 1460 (w), 1447 (m), 1395 (w), 1368 (w), 1340 (w), 1266 (w), 1244 (w), 1200 (w), 1170 (w), 1099 (br, s), 1025 (w), 978 (br, m), 913 (w), 861 (w), 817 (m, br), 737 (br, s), 697 (br, s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.33 (m, 5 H), 6.78 (dd, 1 H, J = 16, 7 Hz), 6.14 (dd, 1 H, J = 16, 1 Hz), 4.55 (AB q, 2 H, J_{AB} = 11.7 Hz, ν_{AB} = 31 Hz), 4.53 (dd, 1 H, J = 10, 8.3 Hz), 4.16–4.25 (m, 1 H), 3.81 (dd, 1 H, J = 12.1, 8.3 Hz), 3.53 (br q, 1 H, J = 11 Hz), 2.97 (ddd, 1 H, J = 17.8, 8.9, 1.4 Hz), 2.60–2.70 (m, 1 H), 2.51 (t, 2 H, J = 7 Hz), 2.47–2.56 (m, obscured, 1 H), 1.56–1.66 (m, 2 H), 1.24–1.37 (m, 4 H), 0.90 (t, 3 H, J = 7 Hz).

4β,5α-4-[(*E*)-3-Hydroxy-1-octenyl]-5-(phenylmethoxy)-3,3aβ,5,6-tetrahydro-4*H*-cyclopent[*c*]isoxazole (35). To a solution of the crude enone (787 mg) and $CeCl_3 \cdot 6H_2O$ (816 mg, 2.30 mmol) in 6 mL of dry methanol was added in one portion $NaBH_4$ (87 mg, 2.30 mmol). After 5 min the reaction was diluted with ether, washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SilicAR CC-7, 35% ethyl acetate–hexanes) provided 425 mg of the pure allyl alcohol as a mixture of epimers. The C-15 epimers were separated by HPLC (μ-Porasil column, 40% ethyl acetate–hexanes, 2 mL/min). The lower R_f isomer was assigned the *S* configuration at C(15) in line with the general observation that most 15(*S*)prostanoids are more polar than the 15(*R*) compounds. 15(*S*)-Alcohol: IR ($CHCl_3$) 2950 (m), 2874 (m), 1721 (w), 1479 (w), 1445 (w), 1366 (w), 1335 (w), 1193 (w), 1094 (w), 967 (w), 909 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.39 (m, 5 H), 5.63 (m, 2 H), 4.48–4.59 (m, 3 H), 4.07–4.15 (m, 2 H), 3.82 (dd, J = 12.1, 8.1 Hz), 3.47 (br q, J = 11 Hz), 2.94 (ddd, 1 H, J = 17.6, 9.1, 1.5 Hz), 2.44–2.56 (m, 2 H), 1.20–1.63 (m, 8 H), 0.89 (3 H, m); mass spectrum (15 eV), m/z 343 (M^+), 323, 314, 272, 256, 252, 235, 214, 155, 149, 129, 127, 125, 113, 111, 107, 105, 99, 97, 95, 92, 91 (base), 85, 83, 81, 79, 77, 71, 70, 69, 68, 67, 65; exact mass calcd for $C_{21}H_{29}NO_3$ 343.2147, found 343.2149. 15(*R*)-Alcohol: IR ($CHCl_3$) 3650 (vw), 2959 (m), 2882 (m), 1742 (w), 1490 (w), 1453 (w), 1372 (w), 1340 (w), 1098 (m, br), 972 (w), 913 (w) cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.29–7.39 (m, 5 H), 5.65 (m of AB q, J_{AB} = 15.6 Hz, J_{AX} = 6, 1 Hz, J_{BX} = 6.5 Hz, ν_{AB} = 36 Hz), 4.50–4.64 (m, 3 H), 4.07–4.15 (m, 2 H), 3.82 (dd, 1 H, J = 12.1, 8.1 Hz), 3.46 (br q, J = 11 Hz), 2.94 (ddd, 1 H, J = 17.8, 8.9, 1.4 Hz), 2.44–2.56 (m, 2 H), 1.20–1.60 (m, 8 H), 0.89 (m, 3 H); mass spectrum (15 eV), m/z 344, 343, 326, 235, 315, 314, 300, 272, 254, 252, 244, 243, 242, 236, 235, 222, 219, 215, 214, 175, 166, 130, 108, 107, 106, 105, 100, 99, 95, 94, 93, 92, 91 (base), 85, 84, 83, 82, 81, 80, 79, 71, 67; exact mass calcd for $C_{21}H_{29}NO_3$ 343.2147, found 343.2149.

Benzyloxymethylation of 35. A solution of the alcohol **35** (425 mg, 1.24 mmol) and chloromethyl benzyl ether (0.34 mL, 2.47 mmol) in 5 mL of *i*-Pr_2NEt was stirred at room temperature for 18 h. The reaction was concentrated in vacuo and chromatographed (silica, 20–25% ethyl acetate–hexanes) to provide 469 mg (82%) of **36** as an oil: IR (neat) 3040 (w), 2933 (s), 2865 (s), 1745 (w), 1490 (w), 1458 (sh), 1447 (m), 1372 (w), 1346 (w), 1295 (w), 1255 (w), 1200 (w), 1166 (w), 1096 (s), 1040 (s), 1024 (w), 973 (w), 912 (w), 866 (w), 822 (m, br), 794 (s, br), 696 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.40 (m, 10 H), 5.64–5.77 (m, 1 H), 5.38–5.48 (m, 1 H), 4.45–4.82 (m, 7 H), 4.04–4.16 (m, 2 H), 3.75–3.82 (m, 1 H), 3.42 (m, 1 H), 3.87–3.97 (m, 1 H), 2.42–2.58 (m, 2 H), 1.30–1.70 (m, 8 H), 0.92 (m, 3 H); mass spectrum (15 eV), m/z 463, 462, 435, 434, 393, 392, 386, 376, 373, 372, 362, 361, 356, 355, 354, 342, 341, 327, 326, 325, 314, 312, 298, 297, 284, 272, 257, 256, 255, 248, 242, 241, 238, 235, 234, 228, 227, 226, 225, 220, 219, 214, 203, 191, 189, 181, 175, 166, 165, 163, 149, 137, 136, 127, 120, 109, 108, 107, 106, 105, 99, 95, 92, 91 (base), 82, 81, 79, 71, 69, 67; exact mass calcd for $C_{29}H_{36}NO_4$ (M^+ − H) 462.2644, found 462.2645.

2α,3β,4α-4-(Phenylmethoxy)-2-(hydroxymethyl)-3-[(*E*)-3-[(phenylmethoxy)methoxy]-1-octenyl]cyclopentanone (37). A mixture of ~50 mg of deactivated W-2 Raney nickel, 30 mg of the isoxazoline (0.065 mmol), and 0.065 mL of 1 M BCl_3 in CH_2Cl_2 in 6 mL of 5:1 $MeOH/H_2O$ was stirred under a hydrogen-filled balloon for 30 min. The reaction was filtered (Celite), the filter pad was washed with methanol, and the combined filtrates were concentrated in vacuo. The residue was partitioned between ether and water (5 mL each). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford a residue, which was chromatographed (silica, 35% ethyl acetate–hexanes) to provide 5.6 mg of debenzylated product and 13.6 mg (53%) of the desired β-hydroxy ketone: IR ($CHCl_3$) 3610 (w), 2950 (s), 2874 (m), 1742 (s), 1608 (w), 1493 (w), 1462 (sh), 1449 (w), 1399 (w), 1376 (w), 1346 (w), 1202 (w), 1159 (w), 1095 (m), 1033 (s), 1024 (s), 973 (m) cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.29–7.36 (m, 10 H), 5.50–5.71 (m, 2 H), 4.51–4.84 (m, 6 H), 4.06–4.15 (m, 1 H), 3.76–3.98 (m, 2 H), 3.63–3.70 (m, 1 H), 2.69–2.85 (m, 2 H), 2.15–2.40 (m, 3 H), 1.21–1.69 (m, 8 H), 0.89 (m, 3 H); mass spectrum (15 eV), m/z 365, 358, 347, 342, 335, 329, 328, 327, 315, 298, 287, 281, 279, 268, 269, 245, 239, 237, 229, 228, 227, 222, 221, 220, 219, 215, 208, 207, 204, 192, 181, 179, 165, 164, 151, 150, 149, 139, 121, 120, 112, 109, 108, 107, 99, 92, 91, 69; exact mass calcd for $C_{21}H_{29}O_4$ (M^+ − $PhCH_2OCH_2$) 345.2064, found 345.2066.

3β,4α-4-(Phenylmethoxy)-2-methylene-3-[(*E*)-3-[(phenylmethoxy)methoxy]-1-octenyl]cyclopentanone (2). To a solution of the β-hydroxy ketone (6.6 mg, 0.014 mmol) in 0.5 mL of pyridine at 0 °C was added mesyl chloride (0.002 mL, 0.024 mmol). After being stirred for 1 h the reaction mixture was diluted with ether, washed with water (2×), dried ($MgSO_4$), and concentrated in vacuo to an oil. Chromatography (silica, 25% ether–petroleum ether) provided 6.3 mg (100%) of the enone: IR ($CHCl_3$) 2941 (s), 2874 (m), 1727 (s), 1639 (m), 1490 (w), 1460 (sh),

1447 (m), 1374 (w), 1340 (w), 1234 (sh), 1199 (m), 1166 (w), 1094 (s), 1026 (br, s), 973 (w), 950 (w), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.38 (m, 10 H), 6.12–6.14 (m, 1 H), 5.49–5.64 (m, 2 H), 5.24–5.27 (m, 1 H), 4.51–4.84 (m, 6 H), 4.11–4.17 (m, 1 H), 3.86–3.95 (br quint, J = 6.5 Hz), 3.50–3.54 (m, 1 H), 2.57 (m of AB q, J_{AB} = 18.0 Hz, J_{AX} = 7.3, 1.4 Hz, J_{BX} = 6.5 Hz, ν_{AB} = 80.6 Hz), 1.23–1.71 (m, 8 H), 0.89 (t, J = 6.7 Hz).

(*E*)-5-(Phenylmethoxy)-2-penten-1-ol. To a −78 °C solution of the ester **38** (1.0 g, 4.27 mmol) in 40 mL of ether was added dropwise DIBAL-H (~0.8 M in hexanes, 13 mL). After an additional 5 min, several drops of 1 M citric acid were added. The reaction was warmed to 0 °C, and after gas evolution had ceased ~20 mL more of the aqueous acid was added dropwise. The mixture was warmed to room temperature and stirred until two layers formed. The layers were separated and the aqueous phase was extracted with ether (2 × 10 mL). The combioned organic phases were dried (Na_2SO_4), concentrated, and chromatographed (flash, 25% and then 50% ethyl 130, 121, to provide 743 mg of the alcohol as an oil (90%): IR ($CHCl_3$) 3636 (m), 3448 (w), 2994 (w), 2941 (sh), 2865 (s), 1488 (w), 1445 (m), 1370 (sh), 1091 (br, s), 1024 (w), 995 (sh), 971 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.42 (s, 5 H), 5.62–5.90 (m, 2 H), 4.56 (s, 2 H), 3.97–4.20 (m, 2 H), 3.52 (t, 2 H, J = 6 Hz), 2.18–2.58 (m, 2 H), 2.06 (br s, 1 H); mass spectrum (15 eV), m/z 192, 191, 175, 174, 173, 161, 159, 146, 145, 144, 138, 137, 133, 132, 131, 130, 121, 120, 117, 109, 108, 107, 105, 101, 93, 92, 91 (base), 85, 84, 83, 79; exact mass calcd for $C_{12}H_{14}O$ ($M^+ - H_2O$) 174.1045, found 174.1038.

Epoxide 39. To a −23 °C solution of the preceding olefin (200 mg, 1.04 mmol) in 25 mL of CH_2Cl_2 were added sequentially $Ti(O\text{-}i\text{-}Pr)_4$ (310 μL, 1.04 mmol), (−)-diisopropyl tartrate (265 μL, 1.24 mmol, stir 5 min before proceeding), and *tert*-butyl hydroperoxide (400 μL, 5.2 M in CH_2Cl_2, 2.08 mmol). After 5 min the reaction was transferred to a −20 °C cold room and allowed to stand for 20 h. The reaction was returned to −23 °C, and 5 mL of 10% aqueous tartaric acid was added. The mixture was stirred for 30 min, allowed to warm to room temperature, and then stirred until the layers were homogeneous. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (silica, 50% ethyl acetate–hexanes) provided 176 mg (81%) of an oil. Mosher analysis (MTPA ester) showed the product to be of 86% ee: IR ($CHCl_3$) 3636 (w), 3509 (w), 3003 (m), 2941 (m), 2874 (m), 1490 (w), 1471 (w), 1449 (m), 1383 (w), 1357 (m), 1199 (m, br), 1094 (s, br), 1026 (w, br), 885 (w, br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.50 (s, 2 H), 3.85 (A of AB q, m, 1 H, J_{AB} = 13 Hz, J_{AX} = 6, 3 Hz), 3.59 (obscured B of AB q, 1 H, and t, 2 H, J = 6.5 Hz), 3.08 (m, 1 H, J = 2.5 Hz) 2.95 (m, 1 H), 3.42 (t, 1 H, J = 6 Hz), 1.75–2.00 (m, 2 H); mass spectrum (15 eV), m/z 208, 207, 190, 189, 160, 159, 150, 149, 147, 146, 133, 131, 120, 119, 118, 117, 108, 107 (base), 106, 105, 92, 91, 87, 84, 83, 79, 71, 61; $[\alpha]_D$ +29.3° (*c* 1.70, $CHCl_3$); exact mass calcd for $C_{12}H_{15}O_3$ ($M^+ - H$) 207.1021, found 207.1021.

Vinyl Grignard Opening of Epoxide 39. Synthesis of *threo*-Diol 24 in Optically Active Form. To a stirred suspension of purified cuprous iodide (121 mg, 0.64 mmol) in 12 mL of THF at 0 °C was added dropwise vinylmagnesium bromide (1 M in THF, Aldrich, 6.4 mL). After being stirred for 10 min, a solution of epoxide **39** (265 mg, 1.27 mmol) in 1 mL of THF was added dropwise to the black solution. The reaction was allowed to stand in a 0 °C freezer for 2 days. At this time 5 mL of saturated NH_4Cl and 1 mL of 5% NH_4OH were added. The mixture was stirred vigorously until the aqueous phase had become a deep blue and all traces of the grey to black solid were gone. The mixture was extracted with three portions of ethyl acetate (10 mL each). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The product was chromatographed (flash, 50% ethyl acetate–hexanes) to provide 133 mg (44%) of *threo*-**24a** and 28 mg of a mixture of *threo*-**24a** and its 1,2-diol isomer **24b**. The ^1H NMR and IR data for **24a** are as reported for the racemic compound **24**; $[\alpha]_D$ −2.8° (*c* 1.24, $CHCl_3$). The diol **24a** was further transformed to the optically active dioxanes (+)-**25a** [$[\alpha]_D$ + 30.1° (*c* 1.43, $CHCl_3$)] and (+)-**26a** [$[\alpha]_D$ + 21.2° (*c* 0.735, $CHCl_3$)].

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Registry No. **1b**, 551-11-1; (±)-**2**, 89956-03-6; **8**, 36969-89-8; (±)-**9a**, 89922-81-6; (±)-**9a** (nitrile), 89923-32-0; **9b**, 89922-82-7; **9b** (nitrile), 89923-33-1; **9c**, 19790-60-4; **9c** (benzyl ether alcohol), 4799-68-2; (±)-**10**, 89922-83-8; **11**, 89922-84-9; (±)-**12a**, 89922-85-0; (±)-**12a** (silyl ether), 89923-34-2; (±)-**12b**, 89956-04-7; (±)-**12b** (silyl ether), 89956-15-0; (±)-**13a**, 89922-86-1; (±)-**13a** (tosylate), 89923-35-3; (±)-**13b**, 89922-87-2; (±)-**13b** (tosylate), 89923-36-4; (±)-**14** (isomer 1), 89922-88-3; (±)-**14** (isomer 2), 89956-05-8; (±)-(*R**,*R**)-**15**, 89922-89-4; (±)-(*R**,*S**)-**15**, 89922-90-7; (±)-(*R**,*R**)-**15** (tosylate), 89922-91-8; (±)-(*R**,*S**)-**15** (tosylate), 89922-92-9; (±)-*cis*-**16**, 89922-93-0; (±)-*trans*-**16**, 89936-14-1; (±)-(*R**,*R**)-**17**, 89922-94-1; (±)-(*R**,*S**)-**17**, 89922-95-2; (±)-(*R**,*R**)-**18**, 89922-96-3; (±)-(*R**,*S**)-**18**, 89922-97-4; (±)-(*R**,*R**)-**19**, 89922-98-5; (±)-(*R**,*S**)-**19**, 89922-99-6; (±)-(*R**,*R**)-**20**, 89923-00-2; (±)-(*R**,*S**)-**20**, 89923-01-3; (±)-(*R**,*R**)-**21**, 89923-02-4; (±)-(R*,*S**)-**21**, 89923-03-5; (±)-(*R**,*R**)-**22**, 89923-04-6; (±)-(*R**,*S**)-**22**, 89923-05-7; (±)-(*R**,*R**)-**23**, 89923-06-8; (±)-(*R**,*S**)-**23**, 89923-07-9; (±)-*threo*-**24**, 89923-08-0; (±)-*erythro*-**24**, 89923-09-1; (−)-**24a**, 89956-06-9; **24b**, 89923-10-4; (±)-**25a**, 89923-11-5; (+)-**25a**, 89956-07-0; (±)-**25b**, 89923-12-6; (±)-**26a**, 89923-13-7; (+)-**26a**, 89956-08-1; (±)-**26b**, 89923-14-8; (±)-**27a**, 89923-15-9; (±)-**27b**, 89923-16-0; (±)-*anti*-**28a**, 89923-18-2; (±)-*syn*-**28a**, 89923-17-1; (±)-*anti*-**28b**, 89923-19-3; (±)-**29a**, 89923-20-6; (±)-**29b**, 89923-21-7; (±)-**30a**, 89923-22-8; (±)-**30b**, 89956-09-2; (±)-**31**, 89923-23-9; (±)-**31** (silyl ether), 89923-24-0; (±)-**32**, 89923-26-2; (±)-**32** (silyl ether), 89923-25-1; (±)-**33**, 89923-27-3; (±)-**34**, 89923-28-4; (±)-(15*R*)-**35**, 89923-29-5; (±)-(15*S*)-**35**, 89956-10-5; (±)-(15*R*)-**36**, 89923-30-8; (±)-(15*S*)-**36**, 89956-11-6; (±)-(15*R*)-**37**, 89956-12-7; (±)-(15*S*)-**37**, 89956-13-8; **38**, 70542-83-5; **38** (alcohol), 89923-31-9; **39**, 89956-14-9; $HO(CH_2)_3OH$, 504-63-2; $HO(CH_2)_2CN$, 109-78-4; $CH_3CH{=}CHCO_2Et$, 10544-63-5; (±)-2-[(2-propenyl)oxy]tetrahydropyran, 69161-61-1; 2-phenyl-1,3-dioxane, 772-01-0; benzaldehyde, 100-52-7.