Synthesis of Analogues of Prostacyclin Containing a Thiazole Ring[1,2]

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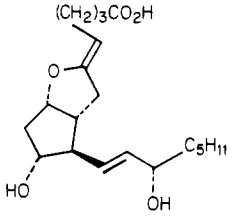
8,9-Dehydro-9,6-nitrilo-7-thiaprostaglandin F_1 (**2**) and related thiazole analogues of prostacyclin (PGI_2, 1) were prepared by a sequence involving conversion of 2β-[3α- and -β-hydroxy-1(*E*)-octenyl]-3-cyclopenten-1α-ol (**13**) to the bromo ketone **33** followed by condensation of this compound with a thioamide. Dehydration of the resulting hydroxythiazolines **35** and **36** to the fused thiazoles **40** and **42** was achieved by using the combination of triphenylphosphine and diethyl azodicarboxylate after conventional dehydrating agents failed to effect this transformation. Three routes to diol **13** from 3,4-epoxycyclopentene **6** are described, the most efficient of which utilizes a novel selective 1,2-opening of **6** by the lithioallyl pyridyl thioether **15**. Of these prostacyclin analogues the methoxy derivative **49** (0.16 × prostaglandin E_1, PGE_1) is the most potent inhibitor of ADP-induced human platelet aggregation.

Prostacyclin (PGI_2, 1) displays a wide range of biological properties,[4] including inhibition of human blood platelet aggregation,[5,6] deaggregation of platelet thrombi,[7] vasodilation,[5] and inhibition of gastric secretion.[8] However, the therapeutic usefulness of prostacyclin is limited by its rapid hydrolysis to 6-oxo-$PGF_{1\alpha}$,[9] and consequently a wide range of stable analogues of prostacyclin have been prepared.[4] Such compounds may have potential in the prevention of stroke, thrombosis, and heart attack[10] and in the treatment of arrthymia[11] and cancer.[12]

Prostacyclin analogues prepared to date may be regarded as involving formally the following general structural modifications of the natural compound: (1) stabilization of the acid-labile[9] enol ether 5,6-double bond by substitution at the 5-, 7-, or 10-positions;[13] (2) modification of the tetrahydrofuran ring by replacement of the enol ether oxygen with a different atom,[14] by introduction of an aromatic ring[15] or by ring expansion;[16] (3) manipulation of the 5,6-double bond by changing its position[17] or altering the oxidation level.[18]

Of these analogues the only reported "heteroaromatic" prostacyclins are 6,9-pyridazaprostacyclin[15a] and pyrazoloprostacyclin.[15b] The former possesses an sp^2 center at C-6, which has been postulated[15a] as being an important feature for biological activity. This paper describes[2] the synthesis of 8,9-dehydro-9,6-nitrilo-7-thia-PGF_1 (**2**), the



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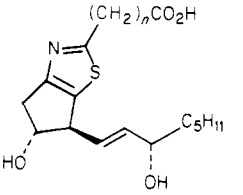
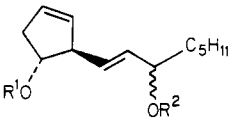


2, n = 4
3, n = 3



4

5, R^1 = $PhCH_2O$,
R^2 = $PhCH_2OCH_2O$

methoxy derivative **49**, and the nor analogue **3**, together with the corresponding methyl esters. In these compounds the tetrahydrofuran ring of 1 is formally replaced by a thiazole ring, and the sp^2 center at C-6 is retained. It was envisaged[19] that these and other heterocyclic prostacyclin analogues would be available from an intermediate, **4**, after selective functionalization of the cyclopentene double bond. A compound of this type was used in a synthesis of prostaglandin $F_{2\alpha}$, with hypobromite addition to **5** having been found to occur selectively in the desired fashion.[20]

(1) Contribution No. 627 from the Institute of Organic Chemistry.
(2) Preliminary communication: Bradbury, R. H.; Walker, K. A. M. *Tetrahedron Lett.* **1982**, *23*, 1335.
(3) Syntex Postdoctoral Fellow 1980–1981. Chemistry Department, ICI Ltd., Pharmaceuticals Division, Mereside Alderley Park, Macclesfield, Cheshire SK10 4TG, England.
(4) For reviews see: (a) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293. (b) Vane, J. R.; Bergstrom, S., Eds. "Prostacyclin"; Raven Press: New York, 1979. (c) Roberts, S. M.; Schienmann, F., Eds. "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids"; Pergamon Press: Oxford, 1979.
(5) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663.
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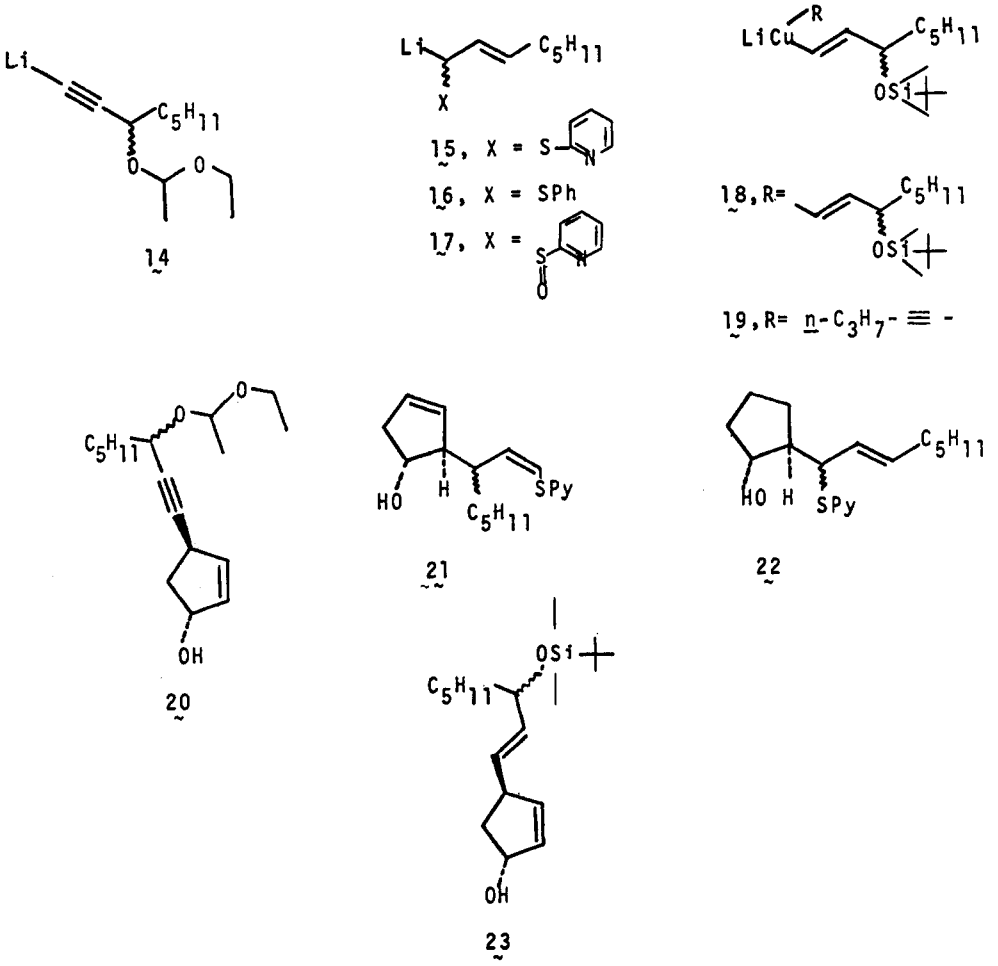
(7) (a) Gryglewski, R. J.; Korbut, R.; Ocetkiewicz, A. *Prostaglandins* **1978**, *15*, 637. (b) Moncada, S.; Gryglewski, R. J.; Bunting, S.; Vane, J. R. *Ibid.* **1976**, *12*, 715.
(8) Whittle, B. J. R; Boughton-Smith, N. K.; Moncada, S.; Vane, J. R. *Prostaglandins* **1978**, *15*, 955.
(9) Chiang, Y.; Kresge, A. J.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129.
(10) Moncada, S.; Vane, J. R. *J. Med. Chem.* **1980**, *23*, 591.
(11) Coker, S. J.; Parratt, J. R..; Ledingham, I. M.; Zeitlin, I. J. *Nature (London)* **1981**, *291*, 323.
(12) Honn, K. V.; Cicone, B.; Skoff, A. *Science* **1981**, *212*, 1270.
(13) (a) 5-Phenylthio-PGI_2: Toru, T.; Watanabe, K.; Oba, T.; Tanaka, T.; Okamura, N.; Bannai, K.; Kurozumi, S. *Tetrahedron Lett.* **1980**, *21*, 2539. (b) 5-Cyano-PGI_2: Schering, A. G. Ger. Offen. 2 801 846; Japan Kokai 54-81257. (c) 7-Hydroxy-PGI_2: Bannai, K.; Toru, T.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Kurozumi, S. *Tetrahedron Lett.* **1981**, *22*, 1417. (d) 10,10-Difluoro-13-dehydro-PGI_2: Freid, J.; Mitra, D. K.; Nagarajan, M.; Mehrotra, M. M. *J. Med. Chem.* **1980**, *23*, 234.
(14) (a) 6a-Carba-PGI_2: Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (b) 6a-Carba-Δ^6-PGI_1: Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 169. (c) 9,6-Nitrilo-PGF_1: Bundy, G. L.; Baldwin, J. M. *Tetrahedron Lett.* **1978**, 1371. (d) 5-Imino-, 5-oxa-, and 5-thia-9,6-nitrilo-PGF_1: Bartmann, W.; Beck, G.; Knolle, J.; Rupp, R. H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 819. (e) 6,9-Thia-PGI_2: Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3472. (f) 6,9-Thia-Δ^6-PGI_1: Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Chem. Lett.* **1980**, 1247.
(15) (a) 6,9-Pyridazaprostacyclin: Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 766. (b) Pyrazoloprostacyclin: Noyori, R. *Org. Synth.: Today Tomorrow, Proc. IUPAC Symp. Org. Synth., 3rd 1980* **1981**, 273.
(16) 6,9-Homo-PGI_2: Skuballa, W. *Tetrahedron Lett.* **1980**, *21*, 3261.
(17) (a) (5*E*)-PGI_2: Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182. (b) Δ^6-PGI_1: Shimoji, K.; Konishi, Y.; Arai, Y.; Hayashi, M.; *Ibid.* **1978**, *100*, 2547. (c) Δ^4-PGI_1: Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *Ibid.* **1981**, *103*, 3480.
(18) (a) PGI_1: See ref 17c and references therein. (b) 4,5,6,7-Tetradehydro-PGI_1: Ohno, K.; Nishiyama, H. *Tetrahedron Lett.* **1979**, 3003. (c) 6,7-Dehydro-5-oxo-PGI_1: Nishiyama, H.; Ohno, K. *Ibid.* **1979**, 3481.
(19) We thank Dr. M. Marx, Syntex Research, for valuable suggestions at the initiation of this work.

0022-3263/83/1948-1741$01.50/0

Chart I



Results and Discussion

Routes to Diol 13. Three routes to the diol **13** were investigated, each commencing with 1,2-opening of 3,4-epoxycyclopentene (**6**) by a carbanion[21] as outlined in Scheme I.

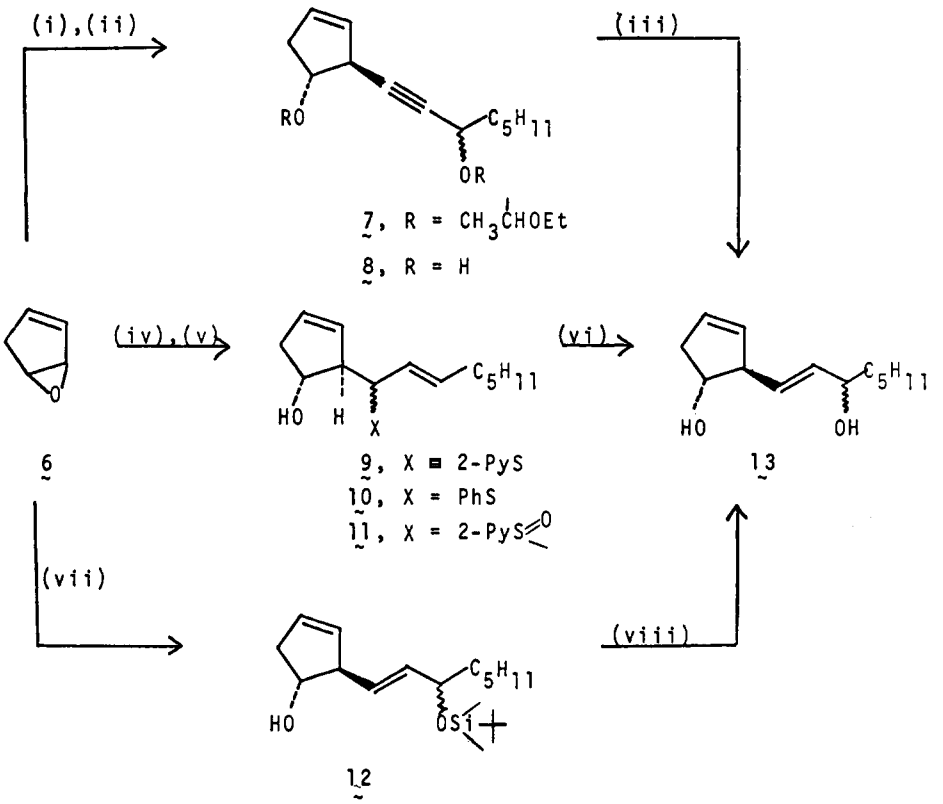
In the first approach, based on published work,[20] reaction of **6**[22] (2.6 equiv) with the lithium acetylide **14** (Chart I) in hexane at 25 °C gave the known[20] cyclopentenol **7** as the major product in 29% yield after chromatography. Several other products were formed, including a substance thought to be the cyclopentenol **20** from 1,4-opening of the epoxide.

Deprotection of **7** with *p*-toluenesulfonic acid in methanol and reduction of the resulting acetylenic diol **8** with lithium aluminum hydride in refluxing THF then provided the new diol **13** in 82% yield from **7**. Reduction was initially performed in the presence of sodium methoxide,[20] but it was found that a much cleaner conversion resulted from using lithium aluminum hydride alone.

The poor yield of epoxide opening in the above sequence prompted development of a superior route to diol **13**. 1-(2-Pyridylthio)-2(*E*)-octene was prepared in two steps from 1-octen-3-ol and deprotonated with *n*-butyllithium at −40 °C in THF to give the lithioallyl pyridyl thioether **15**. Treatment of **6** (1.2 equiv) with **15** at −78 °C then formed the cyclopentenol **9** as a 1:1 mixture of epimers at the carbon atom α to sulfur in 62% yield after chromatography.[23] In contrast to epoxide openings with the acetylide **14** or the cuprates **18** and **19** (vide infra), products from 1,4-cleavage of **6** were not evident in significant amounts. The sole minor product, isolated in less than 5% yield, was assigned structure **21**, resulting from γ-attack on the thioallyl anion. From the value of the vinylic coupling constant (9.8 Hz) for the side-chain double bond, it was concluded that γ-attack leads to formation of the *Z* isomer.[24] While quenching of thioallyl anions has been widely used with a variety of electrophiles, including alkyl halides,[25,26] ketones,[26,27] and enones,[24] no examples of their reaction with epoxides appear to have been reported.[28]

(20) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.
(21) Remarkably few examples of opening of **6** by carbon nucleophiles have been reported: see ref 20, 27, and 30, and: Crosby, G. A.; Stephenson, R. A. *J. Chem. Soc., Chem. Commun.* **1975**, 287. Stork, G.; Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258.
(22) Korach, M.; Nielsen, D. R.; Rideout, W. M. "Organic Syntheses"; Wiley: New York, 1973; Collect Vol. V, p 414.
(23) Compound **9** could be separated into its C-13 epimers (prostaglandin numbering) by layer chromatography. When these pure epimers were subjected to the sulfoxide–sulfenate rearrangement sequence described below, the more and less polar isomers gave the more and less polar isomers of the diol **13**, respectively. On the basis of chromatographic mobility, the latter epimers were provisionally assigned the 15α (more polar) and 15β (less polar) configurations. Consequently, since the sulfoxide–sulfenate rearrangement has been shown to be stereospecific,[25b] the stereochemistry of the epimers of **9** was assigned as being 13α for the more polar and 13β for the less polar isomer. In view of the disappointing biological activity of the ultimate analogues of prostacyclin, it was not considered worthwhile to repeat the synthesis with the pure epimers of **9** or **13**.
(24) Mixtures of *E* and *Z* isomers have been reported from γ-attack of enones on thioallyl anions: Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790.
(25) (a) Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* **1972**, 259. (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
(26) Hirai, K.; Kishida, Y. *Heterocycles* **1974**, *2*, 185.
(27) Kondo, K.; Matsui, K.; Negishi, A. *Chem. Lett.* **1974**, 1371.

Scheme I[a]



[a] Reagents: (i) 14/hexane/25 °C; (ii) *p*-TsOH/MeOH/25 °C; (iii) $LiAlH_4$/THF/Δ; (iv) 15 (to give 9) or 16 (to give 10)/THF/−78 °C; (v) MCPBA/CH_2Cl_2/−78 °C (to give 11); (vi) $(MeO)_3P$/MeOH/25 °C; (vii) 18 or 19/Et_2O/−50 °C; (viii) AcOH/H_2O/THF/25 °C.

Two related epoxide openings were carried out. With the epoxide **6**, the lithioallyl phenyl thioether **16** too gave predominantly 1,2-opening and α attack, with the cyclopentenol **10** being isolated in 58% yield. Thus in this case α attack is favored even in the absence of the α-directing[25] pyridine substituent. Also the less reactive cyclopentene oxide was cleaved by **15** to the cyclopentanol **22** in 32% yield (not optimized). Thus this methodology should be generally applicable for preparation of 2-ene-1,5-diols.[28]

Oxidation of **9** with *m*-chloroperbenzoic acid at −78 °C followed by rearrangement[25b] of the resulting crude allyl sulfoxide **11** in trimethyl phosphite and methanol afforded diol **13** (71% from **9**), identical in all respects with material from the previous route. 3,4-Epoxycyclopentene was found to be unreactive when preparation of sulfoxide **11** was attempted by using the lithiated sulfoxide **17** at 0 °C. Above this temperature considerable decomposition appeared to occur.

A potentially more direct approach to the diol **13** involves 1,2-opening of epoxide **6** by an (*E*)-octenyl cuprate reagent such as **18** or **19**. At the time of this work only one example of cleavage of **6** by a vinyl cuprate reagent had been reported, reaction with 1,1-diethoxy-2-propenylcuprate having resulted in predominantly 1,2-opening of the epoxide.[29] In the present study it was found that when the homocuprate **18** or the mixed cuprate **19**[30] was treated with **6** in ether, approximately equal proportions of the 1,2- and 1,4-opening products **12** and **23** were formed as shown in Table I. Similar observations have recently been reported by other workers,[31] and consequently this approach was not investigated further.

Table I. Cleavage of 6 by Octenyl Cuprates

cuprate	temp, °C	% yield 12	% yield 23
18 (Me_2S present)	−50	27	29
19 (HMP present)	−78	16	29
19 (HMP absent)	−78	18	38

Preparation of Bromo Ketone 33. As shown in Scheme II, diol **13** was protected as the bis[(benzyloxy)methyl] ether **24**, since it had been reported[20] that this protecting group was of significance in hindering electrophilic attack on the side chain double bond. Treatment of **24** with *N*-bromosuccinimide in aqueous Me_2SO[20] gave a mixture of two readily separable bromohydrins, to which the structures **27** (57%) and **30** (12%) were assigned on the basis of their ^1H NMR spectra. In each isomer the orientation of addition follows from D_2O exchange of the hydroxyl proton and decoupling experiments (see Experimental Section). The stereochemistry of addition is inferred from the chemical shifts of the protons at C-10 and C-12 (prostaglandin numbering) and is opposite that assigned to the corresponding known compound,[20] in which the ring hydroxyl is protected as a benzyl ether. Thus in isomer **27**, in which the 9- and 11-substituents are both on the α face, H-10α and H-10β resonate at δ 1.72 and 2.73, respectively, whereas in isomer **30**, in which the 9- and 11-substituents are on opposite faces, the H-10 signals appear much closer at δ 2.29 and 2.41. These observations

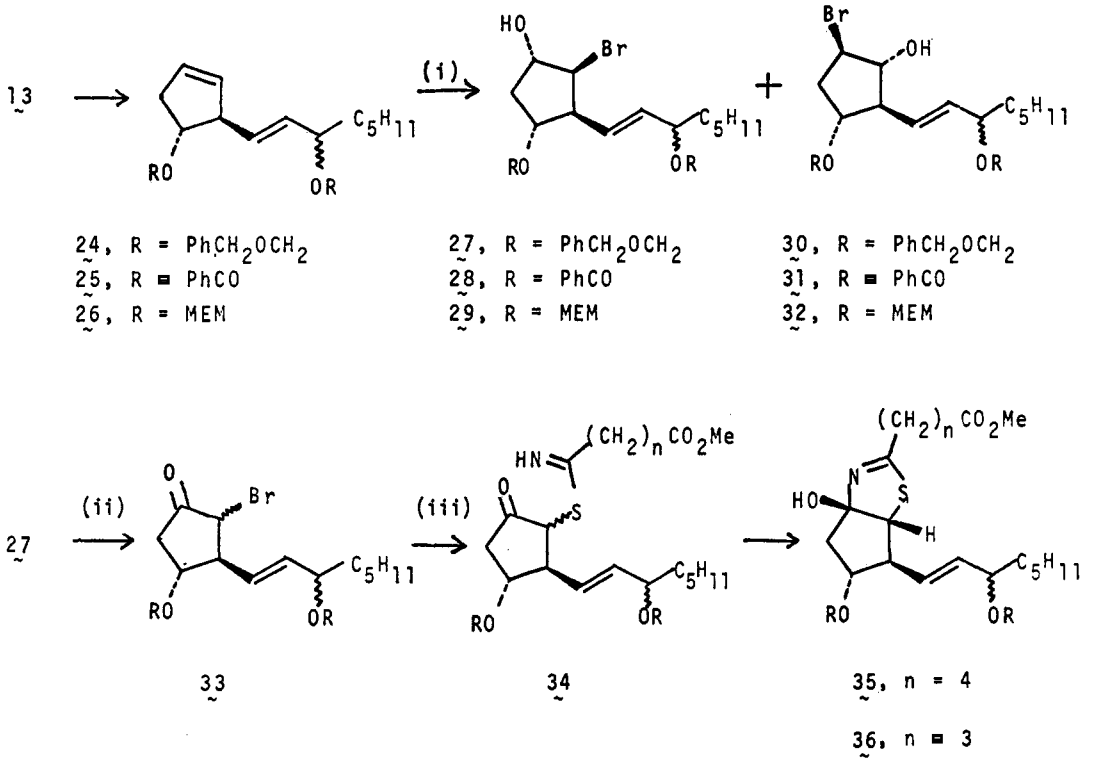
(28) After completion of this work cleavage of 1,2-epoxy-2-methyl-3-butene with a lithioallyl sulfoxide was described: Guittet, E.; Julia, S. *Synth. Commun.* **1981**, *11*, 723. **Added in Proof**: Since submission of this manuscript we became aware of the reported reaction of the lithio derivative of 4-thia-1-methylcyclohexene with an expoxide: Stotter, P. L.; Hornish, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 4444, and ref 2c therein.

(29) Marino, J. P.; Farina, J. S. *J. Org. Chem.* **1976**, *41*, 3213.

(30) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(31) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389.

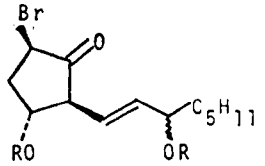
Scheme II[a,b]



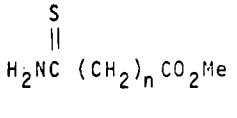
[a] Reagents: (i) NBS/H_2O/Me_2SO/25 °C; (ii) Py·HCl·CrO_3/CH_2Cl_2/25 °C; (iii) **38** or **39**/25 °C. [b] For **33**-**36** R = $PhCH_2OCH_2$.

are typical of those reported for 9-epimers of prostaglandin derivatives.[32] Furthermore, the same regioselectivity, orientation, and stereochemistry of addition were observed when benzoate or (methoxyethoxy)methyl (MEM) protecting groups were used.

By use of Jones reagent (60% yield for large-scale reactions) or, more efficiently, pyridinium chlorochromate[33] (94%), the major bromohydrin **27** was oxidized to the bromo ketone **33**. In a small-scale (200 mg) experiment with Jones reagent oxidation went to completion, with the ^1H NMR spectrum of the crude product showing that **33** was obtained as a single epimer (assumed β) at C-8. However, since oxidation was incomplete on a larger scale, isolation of the product by chromatography was required, and this caused partial epimerization at C-8 (α/β ratio of ca. 1:2). With pyridinium chlorochromate as an oxidant, **33** was also obtained as a mixture of epimers at C-8 even without chromatographic purification. Treatment of the isomeric bromohydrin **30** with a variety of reagents failed to provide the corresponding bromo ketone **37**. With



37 R = $PhCH_2OCH_2$



38, n = 4
39, n = 3

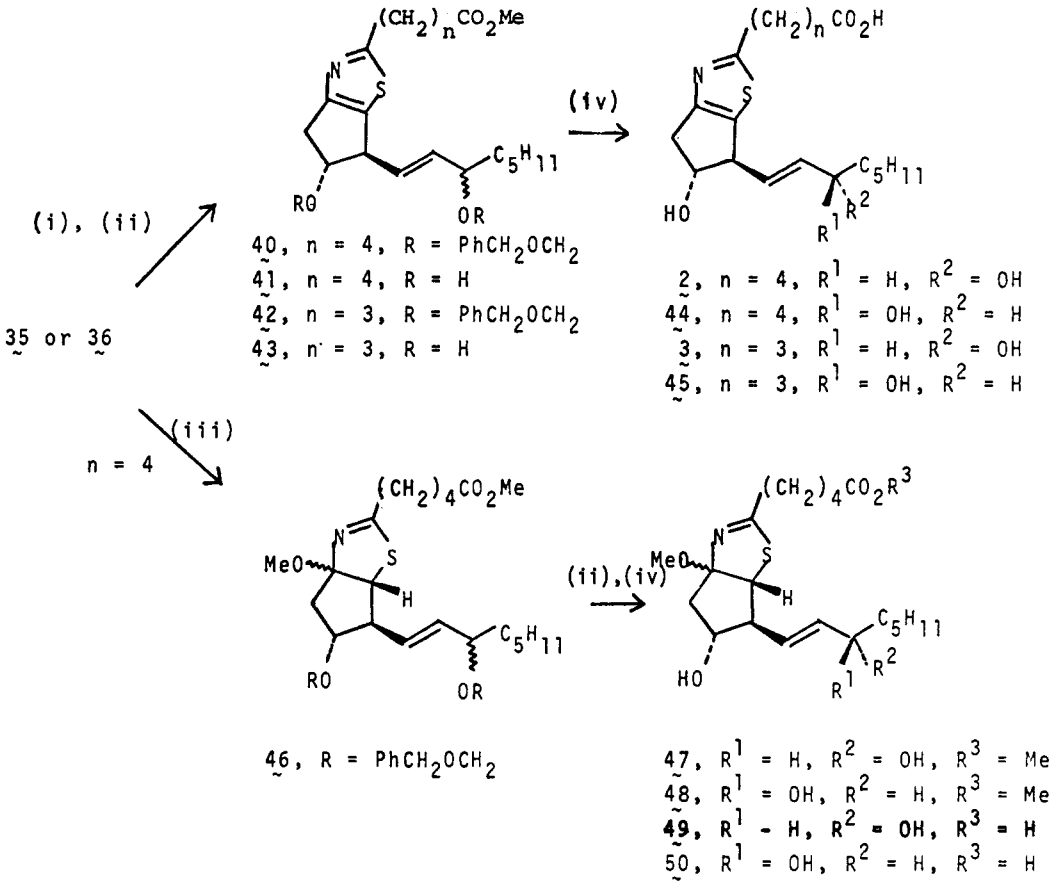
pyridinium dichromate or the Moffatt procedure no change was observed, while employment of Jones reagent, pyridinium chlorochromate, or Me_2SO/oxalyl chloride reagent led to complex mixtures of products, these possibly arising from movement of the double bond into conjugation with the carbonyl group in **37**.

Formation of Thiazoles. Reaction of bromo ketone **33** with the thioamide **38** (obtained by treatment of methyl adipamate with phosphorus pentasulfide) under standard conditions[34] failed to give the expected thiazole **40**. Heating **33** and **38** together in dioxane, acetone, or methanol caused both considerable decomposition and formation of several products. A much cleaner reaction ensued from mixing the two components in the absence of solvent at room temperature to form the fused hydroxythiazoline **35** (Scheme II). This compound exists as a single isomer, which was assigned α-cis stereochemistry from mechanistic reasoning and comparison of its ^1H NMR spectrum with that of the mixture of *cis*- and *trans*-methoxythiazolines **46** (vide infra). Thus, it was reasoned that the initially formed open-chain tautomer **34** would be expected to equilibrate to the more stable form in which the C-8 imino thioether substituent is in the α configuration, and this would then cyclize to give the thermodynamically more stable hydroxy-*cis*-α-thiazoline.

Although dehydration of **35** was not accomplished by a variety of standard reagents (e.g., thionyl chloride/pyridine, phosphoryl chloride/pyridine, mesyl chloride/pyridine, *p*-toluenesulfonic acid, acetic acid), treatment of **35** with the complex of triphenylphosphine and diethyl azodicarboxylate[35] resulted in clean elimination to the desired thiazole **40** (Scheme III) in 67% yield from **33**.

(32) De Clercq, P.; Samson, M.; Tavernier, D.; Van Haver, D.; Vandewalle, M. *J. Org. Chem.* **1977**, *42*, 3140. We thank Dr. M. Maddox, Syntex Research, for interpretation of this spectral data.
(33) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(34) Vernin, G. In "Thiazole and Its Derivatives"; Metzger, J. V., Ed.; Wiley: New York, 1979; p 165 (*Chem. Heterocycl. Compd.* **1979**, *34*, 165). The reaction of 2-chlorocyclopentenone with thioacetamide in refluxing ethanol has been reported: Erlenmeyer, H.; Bischoff, G. *Helv. Chim. Acta* **1946**, *29*, 280.
(35) For a review on the uses of this reagent see: Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme III[a]



[a] Reagents: (i) $EtO_2CN{=}NCO_2Et/Ph_3P$/THF/25 °C; (ii) *p*-TsOH/MeOH/25 °C; (iii) MeOH/50 °C; (iv) $NaOH/H_2O$/MeOH/25 °C.

Since some loss of material occurred when **35** was purified by chromatography, this transformation was performed by using crude hydroxythiazoline. This in turn led to contamination of **40** by an unidentified impurity believed to be derived from reaction of excess thioamide with triphenylphosphine and diethyl azodicarboxylate. Removal of this impurity was readily accomplished after the subsequent deprotection step.

Deprotection of **40** was effected in 52% yield with *p*-toluenesulfonic acid at 25 °C in methanol over 10 days. This procedure provides an alternative to the reductive conditions employed previously[20,36] for regeneration of alcohols from (benzyloxy)methyl ethers. Finally, alkaline hydrolysis of the resulting diol ester **41** afforded the prostacyclin analogue **2** together with its 15-epimer **44**. Neither this mixture of epimers nor the mixtures obtained for the preceding compounds subsequent to the diol **13** were readily separable by chromatographic means.

Inspection of molecular models suggests that, compared with prostacyclin itself, the presence of the bulky sulfur atom in **2** might serve to alter significantly the relative orientation of the C-1 carboxylic acid terminus and the heterocyclic ring. This effect could be counterbalanced by introduction of a shorter upper side chain, and consequently the nor prostacyclin analogue **3** was prepared. Compound **3** and its 15-epimer **45** were obtained from bromo ketone **33** and thioamide **39** via intermediates **36**, **42**, and **43**.

Heating the crude hydroxythiazoline **35** in methanol at 50 °C caused solvolysis to the methoxythiazoline **46** (62% from **33**) as a ca. 2:1 mixture of cis and trans ring-junction isomers. In the ^1H NMR spectrum the minor trans isomer displays resonances at δ 4.20 for H-8 and δ 3.26 for the C-9 methoxyl group, whereas for the major cis isomer, in which H-8 is shielded by the adjacent *cis*-methoxyl group, the corresponding signals appear at δ 3.50 and 3.15, respectively. The assignment of the H-8 signals is supported by decoupling experiments. Deprotection of **46** produced a mixture of diol esters, which could be separated into the individual 15-epimers **47** and **48**, although the ring-junction isomers remained inseparable. On the basis of chromatographic mobility and biological activity, the more and less polar isomers were provisionally assigned as being **47** and **48**, respectively.

The potency of these analogues relative to PGE_1 when tested in vitro for inhibition of ADP-induced human platelet aggregation[37] is given in parentheses as follows: **41** (0.0003×), **2** + **44** (0.07×), **43** (inactive), **3** + **45** (0.0001×), **47** (0.007×), **48** (0.0003×), **49** (0.16×), **50** (0.004×). Thus most of these analogues show weak to moderate biological activity, with the methoxy derivative **49** being the most potent. If this activity is derived primarily from the cis isomer, this observation may imply that for maximum activity in compounds of this type, the α-cis ring-junction present in prostacyclin itself should be retained. It is also noteworthy that whereas compound **2** displayed activity, the nor analogue **3** was almost inactive.

Experimental Section

IR spectra were obtained on a Perkin-Elmer 710B or a Sargent-Welch Pye Unicam 3-200 spectrophotometer. Abbreviations

(36) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

(37) We thank Dr. J. Bruno, Ms. D. Yang, and Ms. M. McSpadden, Institute of Biological Sciences, Syntex Research, for performing this assay.

used are strong (s), medium (m), weak (w), and broad (br). Only structurally important peaks are reported. ^1H NMR spectra were obtained on a Varian A60, a Varian EM-390, a Varian HA-100, or a Bruker WM-300 spectrometer with tetramethylsilane as an internal standard. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), double double doublet (ddd), multiplet (m), and broad (br). Assignments are reported on the basis of prostaglandin numbering for compounds containing a cyclopentane ring. Mass spectra were recorded on Finnigan MAT CH-7 or 112S mass spectrometers. The latter was used for obtaining chemical ionization (CI) spectra, with ammonia as the reagent gas. Only the strongest and/or structurally most important peaks are reported. Microanalyses were performed by the Syntex Analytical Department or Atlanta Laboratories.

Thin-layer chromatography (TLC) was carried out on 0.25-mm Analtech precoated silica gel plates (GF-250) with UV light and/or molybdic acid with heat as the developing agent. Preparative layer chromatography was performed on 1 mm × 20 cm × 40 cm Analtech silica gel plates. For column chromatography EM reagent silica gel 60 (70–230 mesh ASTM) was used. Hexane (Mallinckrodt nanograde) and tetrahydrofuran (THF, Mallinckrodt reagent grade) were dried by storage over 4A molecular sieves. Anhydrous ether (Mallinckrodt) was used from fresh containers as supplied. Reported boiling points are those observed during distillation and are uncorrected.

3-(1-Ethoxyethoxy)-1-octyne. Ethyl vinyl ether (19.1 mL, 14.4 g, 0.2 mol) was added dropwise over 15 min to a stirred solution of 1-octyn-3-ol (20.0 g, 0.159 mol) and *p*-toluenesulfonic acid (200 mg) in dry ether (200 mL). The solution was left at room temperature for 18 h and then washed with sodium carbonate solution (100 mL), water (100 mL), and brine (100 mL) and dried. After removal of the solvent, the residue was distilled under vacuum to give the octyne (26.8 g, 85%) as a clear liquid: bp 54–56 °C (0.3 torr); ^1H NMR (100 MHz, $CDCl_3$) δ 0.85–2.00 (17 H, m, C_5H_{11}, CH_3 of ethoxy, $CH_3C(OR)_2$), 2.40, 2.43 (ratio 1:1, 1 H, both d, J = 1 Hz, CH≡C), 3.58, 3.60 (ratio 1:1, 2 H, both q, CH_2O), 4.34 (1 H, m, CH(OR)C≡C), 4.90 (1 H, m, $CH(OR)_2$).

2β-[3α- and 3β-(1-Ethoxyethoxy)-1-octynyl]-3-cyclopenten-1α-ol (7). *n*-Butyllithium in hexane (102 mL of a 1.57 M solution, 0.16 mol) was added to a stirred solution of 3-(1-ethoxyethoxy)-1-octyne (30.6 g, 0.155 mol) in dry hexane (500 mL) at −78 °C under nitrogen. The solution was allowed to reach 0 °C over ca. 1 h and then recooled to −78 °C. After addition of 3,4-epoxycyclopentene (**6**;[22] 33.0 g, 0.40 mol) the cooling bath was removed, and the solution was left at 25 °C for 24 h. Saturated ammonium chloride solution (250 mL) was added, and the organic phase was separated. The aqueous phase was extracted with ether (2 × 200 mL), and the combined organic solutions were washed with water (300 mL) and brine (300 mL) and then dried ($MgSO_4$). Evaporation gave an oil (42.6 g), which was purified by column chromatography (1.6 kg of silica gel; 50% ether/hexane) to give the cyclopentenol **7**[20] (12.7 g, 29%) as a pale yellow oil: IR (liquid film) 3400 (s, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (0.89, 3 H, t, CH_3 of C_5H_{11}), 1.17–1.80 (14 H, m, $(CH_2)_4$, CH_3 of ethoxy, CH_3CO_2), 2.30 (1 H, m, CH_2-10α), 2.34 (1 H, br, exchanges with D_2O, OH), 2.78 (1 H, m, CH_2-10β), 3.40 (1 H, m, CH-12), 3.45–3.80 (2 H, m, CH_2O), 4.35 (1 H, m, CHOH-11), 4.46 (1 H, m, CHOR-15), 4.80–5.00 (1 H, m, $CH(OR)_2$), 5.62 (1 H, m, CH=C), 5.74 (1 H, m, CH=C); mass spectrum (CI), m/e 298 ($(M + NH_4)^+$), 263 ($MH^+ - H_2O$), 252, 226, 208, 191, 173, 134.

Also isolated was a product (20 mg) to which structure **20** was assigned on the basis of the NMR spectrum: IR (liquid film) 3400 (s, OH) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3 of C_5H_{11}), 1.10–1.90 (14 H, m, $(CH_2)_4$, ring CH_2, CH_3 of ethoxy, $CH_3C(OR)_2$), 2.25 (1 H, br, exchanges with D_2O, OH), 3.25–3.75 (3 H, m, ring CHC≡C, CH_2O), 4.32 (1 H, m, CH(OR)C≡C), 4.68–5.02 (2 H, m, ring CHOH, $CH(OR)_2$), 5.82 (2 H, m, CH=CH).

2β-(3α- and 3β-Hydroxy-1-octynyl)-3-cyclopenten-1α-ol (8). A solution of the cyclopentenol **7** (8.5 g, 30.4 mmol) and *p*-toluenesulfonic acid (300 mg) in methanol (100 mL) was left at 25 °C for 20 h. After removal of the solvent under reduced pressure at ambient temperature, the residue was dissolved in ether (100 mL). The solution was washed with sodium carbonate solution (50 mL), water (50 mL), and brine (50 mL) and dried. Evaporation gave the diol **8** as a clear oil: bp 70–75 °C (0.02 torr); IR ($CHCl_3$) 3590 (s, OH), 3400 (br, OH), 2220 (w, C≡C); ^1H NMR (300 MHz, $CHCl_3$) δ 0.90 (3 H, t, CH_3), 1.27–1.75 (8 H, m, $(CH_2)_4$), 2.31 (1 H, ddd, J = 17, 5, 2 Hz, CH_2-10α), 2.75 (1 H, m, CH_2-10β), 3.15 (1 H, br, OH), 3.42 (1 H, m, CH-12), 3.58 (1 H, br, OH), 4.35 (1 H, m, CHOH-15), 4.48 (1 H, m, CHOH-11), 5.61 (1 H, m, CH=C), 5.73 (1 H, m, CH=C); mass spectrum, m/e 190 ($M^+ - H_2O$), 134, 119, 105, 91, 79, 65, 55, 41.

1-(2-Pyridylthio)-2(*E*)-octene. Thionyl chloride (30.6 mL, 51.2 g, 0.43 mol) was added dropwise over 0.5 h to a stirred solution of 1-octen-3-ol (25.6 g, 0.20 mol) in dry ether (400 mL). After the solution had been allowed to stand at 20 °C for 20 h, water (200 mL) was added, and the mixture was stirred vigorously for 1 h. The organic phase was separated, washed with water (200 mL) and brine (200 mL), and then dried. Evaporation gave a brown liquid (29.2 g) which was distilled under vacuum to provide 1-chloro-2(*E*)-octene (23.05 g, 79%) as a clear liquid: bp 85–87 °C (40 torr) [lit.[38] bp 66–69 °C (11 torr)]; ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 (3 H, t, CH_3), 1.15–1.70 (6 H, m, $(CH_2)_3$), 2.10 (2 H, m, CH_2C=C), 4.08 (1 H, d, CH_2Cl), 5.75 (2 H, m, CH=CH).

Sodium (2.71 g, 0.118 mol) was dissolved in absolute ethanol and then 2-mercaptopyridine (13.1 g, 0.118 mol) was added. The solution was stirred for 5 min and then the foregoing chlorooctene (16.0 g, 0.109 mol) was added. After the solution had stood at 25 °C for 20 h, the precipitated sodium chloride was filtered off. The filtrate was evaporated, and the residue was partitioned between ether (150 mL) and water (150 mL). The organic phase was separated and washed with 1 M sodium hydroxide solution (50 mL), water (50 mL), and brine (50 mL) and then dried. Evaporation gave an oil, which was distilled under vacuum to yield 1-(2-pyridylthio)-2(*E*)-octene (21.5 g, 89%) as a pale yellow viscous liquid: bp 115–118 °C (0.6 torr); IR ($CHCl_3$) 1580 (s, C=N) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.86 (3 H, t, CH_3), 1.10–2.40 (8 H, m, $(CH_2)_4$), 3.82 (2 H, d, CH_2S), 5.68 (2 H, m, CH=CH), 6.85–7.70 (3 H, m, aromatic), 8.42 (1 H, m, aromatic). Anal. Calcd for $C_{13}H_{19}NS$: C, 70.59; H, 8.60; N, 6.33. Found: C, 70.51; H, 8.65; N, 6.31.

1-(Phenylthio)-2(*E*)-octene (84%) was obtained by the above procedure from thiophenol and the chlorooctene.

2β-[1α- and 1β-(2-Pyridylthio)-2(*E*)-octenyl]-3-cyclopenten-1α-ol (9). *n*-Butyllithium in hexane (89.0 mL of a 1.50 M solution, 0.134 mol) was added to a stirred solution of (2-pyridylthio)-2(*E*)-octene (27.6 g, 0.125 mol) in dry THF at −40 °C under nitrogen. The deep red solution was kept at −40 °C for 0.5 h and then cooled to −78 °C. 3,4-Epoxycyclopentene (**6**; 12.0 g, 0.146 mol) in dry THF (50 mL) was added dropwise over 0.5 h. The reaction mixture was then kept at −78 °C for 2 h, during which time the red coloration was almost completely discharged. The temperature was allowed to reach 0 °C, and the solution was added to saturated ammonium chloride solution (600 mL). Following separation of the organic phase, the aqueous phase was further extracted with ether (2 × 300 mL). The combined organic solutions were washed with water (500 mL) and brine (500 mL) and then dried. Evaporation gave an oil (37.2 g) which was purified by column chromatography (1.2 kg of silica gel; 3:2 ether/hexane) followed by bulb-to-bulb distillation to provide the cyclopentenol **9** (23.3 g, 62%) as a pale yellow oil: bp 70–75 °C (0.01 torr); IR (liquid film) 3350 (s, OH), 1580 (s, C=N) cm^{-1}; mass spectrum (CI), m/e 304 (MH^+), 286, 222, 194, 112. Anal. Calcd for $C_{18}H_{25}NOS$: C, 71.29; H, 8.25; N, 4.62. Found: C, 71.15; H, 8.30; N, 4.59.

A sample of cyclopentenol **9** was separated into its 13-epimers (PG numbering) by layer chromatography (silica gel, 2:1 ether/hexane). The more and less polar components were provisionally assigned the 13α and 13β configurations, respectively (see ref 23). More polar isomer: R_f 0.55 (silica gel, 2:1 ether/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3 H, t, CH_3), 1.10–1.35 (6 H, m, $(CH_2)_3$), 1.95 (2 H, dt, CH_2C=C), 2.32 (1 H, m, CH_2-10α), 2.75 (1 H, m, CH_2-10β), 2.98 (1 H, m, CH-12), 4.30 (1 H, dd, J = 8.5, 8.5 Hz), CHSPy), 4.53 (1 H, m, CHOH-11), 5.39 (1 H, m, side-chain CH=C), 5.58 (1 H, m, side-chain CH=C), 5.68 (1 H, m, ring CH=C), 5.76 (1 H, m, ring CH=C), 7.03, 7.22, 7.50, 8.44 (each 1 H, m, aromatic). Less polar isomer: R_f 0.60 (silica gel, 2:1 ether/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3 H, t, CH_3),

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1.10–1.34 (6 H, m, $CH_2)_3$), 1.97 (2 H, dt, CH_2C=C), 2.33 (1 H, m, CH_2-10α), 2.70 (1 H, m, CH_2-10β), 3.00 (1 H, m, CH-12), 4.41 (1 H, m, CHOH-11), 4.53 (1 H, dd, J = 8.5, 6.0 Hz, CHSPy) 5.48 (1 H, m, side-chain CH=C), 5.64 (1 H, m, side-chain CH=C), 5.72 (1 H, m, ring CH=C), 5.78 (1 H, m, ring CH=C), 7.00, 7.21, 7.48, 8.42 (each 1 H, m, aromatic). In the ^{1}H NMR spectrum of the bulk mixture of isomers, the signals at δ 4.30 and 4.53 are of equal intensity, thus demonstrating the presence of a 1:1 mixture.

Also isolated was a more polar product, to which was assigned structure **21**: IR (liquid film) 3400 (s, OH), 1580 (s, C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3 H, t, CH_3), 1.15–1.62 (8 H, m, $(CH_2)_4$), 2.24 (1 H, m, CH_2-10α), 2.38–2.55 (2 H, m, CH-12, side chain CHC=C), 2.66 (1 H, m, CH_2-10β), 2.60–2.85 (1 H, br, exchanges with D_2O, OH), 4.22 (1 H, m, CHOH-11), 5.72–5.82 (3 H, m, ring CH=CH, CH=CSPy), 6.82 (1 H, d, J = 9.8 Hz, *cis*-PySCH=C) 7.03, 7.21, 7.52, 8.44 (each 1 H, m, aromatic); mass spectrum, m/e 303 (M^+), 285, 270, 252, 220, 150, 136, 112. The ^{1}H NMR assignments were confirmed by decoupling experiments.

2β-[1α- and 1β-(Phenylthio)-2(*E*)-octenyl]-3-cyclopenten-1α-ol (10). Obtained by the above procedure from 1-(phenylthio)-2(*E*)-octene and **6** was the cyclopentenol **10** (58%) as a clear oil: IR (liquid film) 3375 (s, OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3 H, t, CH_3), 1.07–1.37 (6 H, s, $(CH_2)_3$), 1.92 (2 H, m, CH_2C=C), 2.32 (1 H, m, CH_2-10α), 2.72 (1 H, m, CH_2-10β), 2.82 (1 H, m, CH-12), 3.50, 3.57 (ratio 1:1, 1 H, each dd, J = 8.5, 8.5 Hz, CHSPy), 4.42 (1 H, m, CHOH-11), 5.24 (1 H, m, side-chain CH=C), 5.32 (1 H, m, side-chain CH=C), 5.62–5.82 (2 H, m, ring CH=CH), 7.20–7.42 (5 H, m, aromatic); mass spectrum, m/e 302 (M^+), 284, 219, 192, 175, 149, 109; exact mass, m/e 302.1689 (calcd for $C_{19}H_{26}OS$ 302.1704).

2β-[1α- and 1β-(2-Pyridylthio)-2(*E*)-octen-1-yl]cyclopentan-1α-ol (22). The lithioallyl thioether **15** in THF (15 mL) was obtained from 1-(2-pyridylthio)-2(*E*)-octene (0.55 g, 2.49 mmol) as described above. To this solution at −78 °C was added cyclopentene oxide (1.26 g, 15.00 mmol). The reaction mixture was then left at −25 °C for 16 h, after which the red coloration due to the thioallyl anion was completely discharged. The workup and chromatography as above gave the cyclopentenol **22** (240 mg, 32%) as an oil: IR (liquid film) 3400 (s, OH), 1580 (s, C=N) cm^{-1}; mass spectrum (CI), m/e 306 (MH^+), 280, 238, 221, 206, 177.

Cyclopentenol **22** was separated into its 13-epimers (PG numbering) by layer chromatography (silica gel, 50% ether/hexane). More polar isomer: R_f 0.30 (silica gel, 50% ether/hexane); ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.85 (3 H, t, CH_3), 1.20–2.15 (15 H, m, $(CH_2)_4$, ring $(CH_2)_3$, ring CH), 4.32 (2 H, m,CHOH, CHSPy), 5.48 (2 H, m, CH=CH), 6.85–7.62 (3 H, m, aromatic), 8.42 (1 H, m, aromatic). Less polar isomer: R_f 0.35 (silica gel; 50% ether/hexane); ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.85 (3 H, t, CH_3), 1.20–2.15 (15 H, m, $(CH_2)_4$, ring $(CH_2)_3$, ring CH), 3.85 (1 H, m, CHOH), 4.63 (1 H, dd, J = 7.5, 5.0 Hz, CHS), 5.58 (2 H, m, CH=CH), 6.85–7.55 (3 H, m, aromatic), 8.38 (1 H, m, aromatic).

2β-[3α- and 3β-(*tert*-Butyldimethylsiloxy)-1(*E*)-octenyl]-3-cyclopenten-1α-ol (12) and 4β-(3α- and 3β-(*tert*-Butyldimethylsiloxy)-1(*E*)-octenyl]-2-cyclopenten-1α-ol (23). Using Homocuprate 18. *n*-Butyllithium in hexane (2.73 mL of a 1.57 M solution, 4.29 mmol) was added to a solution of 3-(*tert*-butyldimethylsiloxy)-1-iodo-1(*E*)-octene[30] (1.50 g, 4.08 mmol) in dry hexane (15 mL) at −78 °C under nitrogen. The solution was kept at −78 °C for 1 h and then transferred by syringe to a vigorously stirred suspension of dimethyl sulfide–cuprous bromide complex[39] in dry ether (70 mL) at −78 °C under nitrogen. After the reaction mixture had been stirred at −78 °C for 1.5 h, a solution of **6** (0.50 g, 6.10 mmol) in dry ether (3 mL) was added. The temperature was allowed to reach −50 °C and then maintained there for 2 h. Saturated ammonium chloride solution (50 mL) was added, and the organic phase was separated. It was washed with water (50 mL) and brine (50 mL) and then dried. Evaporation gave an oil (1.27 g), which was purified by column chromatography (60 g silica gel, 50% ether/hexane) to provide the cyclopentenols **12** (176 mg, 27%) and **23** (188 mg, 29%). Spectral data for these compounds were identical with those reported in the literature.[31]

Using Heterocuprate 19. 3-(*tert*-Butyldimethylsiloxy)-1-iodo-1(*E*)-octene[30] (1.50 g, 4.09 mmol) was converted to its lithio derivative at −78 °C as described above. Meanwhile hexamethylphoshorus triamide (dried by distillation from calcium hydride and 4A molecular sieves; 1.33 g, 9.16 mmol) was added to a suspension of copper(I) pentyne[40] in dry ether (10 mL) under nitrogen. The mixture was stirred at 25 °C for 30 min, and then the resulting solution was added dropwise over 5 min to the solution of lithiooctene at −78 °C. After the reaction mixture had been maintained at −78 °C for 0.5 h, a solution of **6** (0.50 g, 6.1 mmol) in dry ether (5 mL) was added. The reaction mixture was kept at −78 °C for 3 h and then worked up as above to give **12** (210 mg, 16%) and **23** (384 mg, 29%).

The heterocuprate **19** was also generated in the absence of hexamethylphosphorous triamide. *n*-Butyllithium in hexane (1.36 mL of a 1.57 M solution, 2.15 mmol) was added to 1-pentyne (139 mg, 2.04 mmol) in dry ether (10 mL) at 0 °C under nitrogen. Anhydrous cuprous iodide (389 mg, 2.04 mmol) was added, and the mixture was stirred at 0 °C for 1 h. After the mixture had been cooled to −40 °C, a solution of the lithiooctene (2.04 mmol) at −78 °C was added. The mixture was stirred at −40 °C for 1 h and then cooled to −78 °C. A solution of **6** (250 mg, 3.05 mmol) in dry ether (5 mL) was added. The reaction mixture was kept at −78 °C for 3 h and then worked up as above to give **12** (120 mg, 18%) and **23** (250 mg, 38%).

2β-(3α- and 3β-Hydroxy-1(*E*)-octenyl)-3-cyclopenten-1α-ol (13). From Thioether 9. *m*-Chloroperbenzoic acid (85% pure; 14.7 g, 72.6 mmol) in dry dichloromethane (150 mL) was added dropwise over 0.5 h to a stirred solution of the thioether **9** (22.0 g, 72.6 mmol) in dry dichloromethane (600 mL) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1.5 h, allowed to warm to 0 °C, and added to 10% sodium sulfite solution (500 mL). The organic phase was separated, and washed with water (500 mL) and brine (500 mL). After being dried, it was evaporated to give the crude sulfoxide **11** (22.6 g, 98%) as a pale yellow oil: IR (liquid film) 3400 (s, OH), 1635 (w), 1580 (s), 1560 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3), 0.95–1.30 (6 H, m, $(CH_2)_3$), 1.78 (2 H, m, CH_2C=C), 2.26–2.50 (1 H, m, CH_2-10α), 2.70–2.90 (1 H, m, CH_2-10β), 3.35–3.60 (1 H, m, CH-12), 4.42–4.65 (1 H, m, CHOH-11), 4.90–5.06 (1 H, m, CHSOPy), 5.40–5.85 (4 H, m, CH=CH), 7.32 (1 H, m, aromatic), 7.80–8.00 (2 H, m, aromatic), 8.62 (1 H, m, aromatic); mass spectrum, m/e 320 (MH^+), 304, 253, 221, 210, 193, 175.

Sulfoxide **11** slowly decomposed on standing. It was therefore subjected to rearrangement without delay. A solution of **11** (22.6 g, 70.8 mmol) in methanol (60 mL) and trimethyl phosphite (120 mL; freshly distilled from sodium) was left at 25 °C for 20 h. The bulk of the methanol and trimethyl phosphite was removed at reduced pressure below 30 °C, and the residue was dissolved in ether (500 mL). The solution was washed successively with sodium carbonate solution (500 mL), water (500 mL), 1 M sulfuric acid (2 × 500 mL), water (500 mL), and brine (500 mL). It was then dried and evaporated to give an oil (14.6 g), which was purified by column chromatography (700 g of silica gel, 4:1 ether/hexane) to afford diol **13** (10.7 g, 72%). Distillation gave the analytical sample: bp 70–75 °C (0.05 torr); R_f 0.55, 0.60 (silica gel, ether); IR ($CHCl_3$) 3400 (s, OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3), 1.17–1.62 (8 H, m, $(CH_2)_4$), 2.28 (1 H, m, CH_2-10α), 2.66 (1 H, m, CH_2-10β), 3.01 (2 H, br s, exchanges with D_2O, OH), 3.18 (1 H, m, CH-12), 4.04 (1 H, m, CHOH-15), 4.13 (1 H, m, CHOH-11), 5.56 (3 H, m, CH=C), 5.72 (1 H, m, CH=C); mass spectrum (CI), m/e 228 ($(M + NH_4)^+$), 210, 193, 175. Anal. Calcd for $C_{13}H_{22}O_2$: H, 74.29; H, 10.48. Found: C, 74.09; H, 10.52.

When the pure 13-epimers of the starting thioether were oxidized and rearranged as above, the more polar thioether gave the more polar diol, and the less polar thioether gave the less polar diol.

From Reduction of Diol 8. A mixture of lithium aluminum hydride (104 mg, 3.0 mmol) and diol **8** (208 mg, 1.0 mmol) in dry THF (5 mL) was heated under reflux under nitrogen for 18 h. Saturated ammonium chloride solution (20 mL) was added, and the mixture was extracted with ether (2 × 20 mL). The extracts

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were washed with water (20 mL) and brine (20 mL) and then dried. Evaporation gave the diol **13** (176 mg, 85%) as a clear oil, identical in all respects with material obtained above.

From Desilylation of 12. Cyclopentenol **12** (105 mg) in THF/acetic acid/water (1:3:1; 10 mL) was left at 25 °C for 20 h. A workup by extraction with ether gave diol **13** (70 mg, 103%) containing about 20% of a silyl compound (by NMR). Column chromatography (silica gel, ether) gave diol **13** (15 mg, 22%).

[[[[2β-[3α- and 3β-[(Phenylmethoxy)methoxy]-1(*E*)-octenyl]-3-cyclopenten-1α-yl]oxy]methoxy]methyl]benzene (24). Benzyl chloromethyl ether (9.36 g, 60.0 mmol) was added to the diol **13** (3.25 g, 15.0 mmol) in *N,N*-diisopropylethylamine (20 mL). After the mixture had been stirred at 25 °C for 24 h, ether (250 mL) and 2% sulfuric acid (300 mL) were added. The organic phase was separated, washed with sodium carbonate solution (150 mL), water (150 mL), and brine (150 mL), and then dried. After removal of the solvent, the residue (9.6 g) was purified by column chromatography (silica gel, 12% ether/hexane) to give the bis[(benzyloxy)methyl] ether **24** (5.20 g, 77%) as a clear oil. Bulb-to-bulb distillation gave an analytical sample: bp 70–75 °C (0.02 torr); IR ($CHCl_3$) 2900 (s), 1460 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3 H, t, CH_3), 1.21–1.67 (8 H, m, $(CH_2)_4$), 2.36 (1 H, m, CH_2-10α), 2.68 (1 H, m, CH_2-10β), 3.35 (1 H, m, CH-12), 4.04 (1 H, m, CHOR-15), 4.18 (1 H, m, CHOR-11), 4.49–4.90 (8 H, m, CH_2OCH_2O), 5.36 (1 H, m, CH=C), 5.62 (2 H, m, CH=C), 5.74 (1 H, m, CH=C), 7.32 (10 H, m, aromatic); mass spectrum (CI), *m/e* 468 ($(M + NH_4)^+$), 330, 313, 283, 276, 246, 207, 192, 175. Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.34; H, 8.44. Found: C, 77.18; H, 8.47.

Treatment of **13** with benzoyl chloride/pyridine and (β-methoxyethoxy)methyl chloride/*N,N*-diisopropylethylamine/CH_2Cl_2[41] gave the benzoate **25** and MEM **26** derivatives, respectively.

2β-Bromo-4α-[(phenylmethoxy)methoxy]-3β-[3α- and 3β-[(phenylmethoxy)methoxy]-1(*E*)-octenyl]cyclopentan-1α-ol (27) and 5β-Bromo-3α-[(phenylmethoxy)methoxy]-2β-[3α- and 3β-[(phenylmethoxy)methoxy]-1(*E*)-octenyl]-cyclopentan-1α-ol (30). *N*-Bromosuccinimide (2.85 g, 16.00 mmol) was added to a solution of the bis[(benzyloxy)methyl] ether **24** (4.80 g, 10.67 mmol) in 5% aqueous Me_2SO (60 mL) at 10 °C. After the solution had stood at 25 °C for 3 h, brine (300 mL) was added, and the liberated emulsion was extracted with ether (3 × 150 mL). The extracts were washed with water (150 mL) and brine (150 mL) and then dried. Evaporation gave an oil (5.57 g), which was subjected to column chromatography (250 g of SiO_2, 50% ether/hexane). Initially eluted was the bromohydrin **30** (0.68 g, 12%) as a low-melting solid: IR (liquid film) 3450 (s, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.20–1.68 (8 H, m, $(CH_2)_4$), 2.29 (1 H, m, CH_2-10β), 2.41 (2 H, m, becomes 1 H on exchange with D_2O, CH_2-10α and OH), 2.50 (1 H, m, CH-12), 3.90 (1 H, m, becomes dd, *J* = 7.5, 7.5 Hz, on D_2O exchange, CHOH-8), 4.08 (2 H, m, CHOR-11, 15), 4.15 (1 H, m, CHBr-9), 4.50–4.90 (8 H, m, CH_2OCH_2O), 5.55 (1 H, dd, *J* = 14.8, 7.5 Hz, (CH=C)-14), 5.68 (1 H, dd, *J* = 14.8, 7.5 Hz, (CH=C)-13), 7.32 (10 H, m, aromatic). The following decoupling experiments after D_2O exchange established the relationship of the cyclopentane ring protons: irradiation at δ 2.50 caused collapse of the signals at δ 3.90 (becomes d), 4.08 (simplifies), and 5.68 (becomes d); irradiation at δ 3.90 caused collapse of the signals at δ 2.50 (simplifies) and 4.15 (simplifies); irradiation at δ 4.15 caused collapse of the signals at δ 2.29 (becomes dd), 2.41 (becomes dd), and 3.90 (becomes d); mass spectrum (CI), *m/e* 566, 564 (both $(M + NH_4)^+$), 484, 428, 426, 411, 409, 290, 288, 273, 271, 208, 191.

Further elution gave the bromohydrin **27** (3.34 g, 57%) as a clear oil: IR (liquid film) 3450 (s, OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, t, CH_3), 1.21–1.65 (8 H, m, $(CH_2)_4$), 1.72 (1 H, m, CH_2-10α), 2.29 (1 H, poorly resolved d, exchanges with D_2O, OH), 2.73 (1 H, m, CH_2-10β), 3.12 (1 H, m, CH-12), 4.09 (1 H, m, CHOR-15), 4.22 (2 H, m, CHBr-8, CHOR-11), 4.43 (1 H, m, simplifies on D_2O exchange, CHOH-9), 4.49–4.85 (8 H, m, CH_2OCH_2O), 5.52 (1 H, dd, *J* = 15.0, 7.2 Hz, (CH=C)-14), 5.82 (1 H, dd, *J* = 15.0, 7.0 Hz, (CH=C)-13), 7.34 (10 H, m, aromatic). The following decoupling experiments after D_2O exchange established the relationship of the cyclopentane ring protons: irradiation at δ 3.12 caused collapse of the signals at δ 4.22 (simplifies) and 5.82 (becomes d); irradiation at δ 4.09 caused collapse of the signal at δ 5.52 (becomes d); irradiation at δ 4.43 caused collapse of the signals at δ 1.72 (becomes dd), 2.73 (becomes dd), and 4.22 (simplifies); mass spectrum (CI), *m/e* 566, 564 (both $(M + NH_4)^+$), 484, 428, 426, 411, 409, 346, 329, 304, 281, 209, 191. Anal. Calcd for $C_{29}H_{39}BrO_5$: C, 63.62; H, 7.13; Br, 14.63. Found: C, 63.73; H, 7.17; Br, 14.15.

Also obtained by this procedure were bromohydrins **28** (71%)/**31** (11%) and **29** (60%)/**32** (19%).

2α- and 2β-Bromo-4α-[(phenylmethoxy)methoxy]-3β-[3α- and 3β-[(phenylmethoxy)methoxy]-1(*E*)-octenyl]cyclopentanone (33). The bromohydrin **27** (3.12 g, 5.70 mmol) in dichloromethane (30 mL) was added to a suspension of pyridinium chlorochromate (4.91 g, 22.80 mmol) in dichloromethane (30 mL) under nitrogen. The mixture was stirred at 25 °C for 20 h, and then anhydrous ether (400 mL) was added. The supernatant liquor was filtered through Florisil, and the insoluble material was extracted with a further portion of ether (100 mL). Evaporation of the combined solutions gave the bromo ketone **33** (2.92 g, 94%) as a clear oil: IR ($CHCl_3$) 1755 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, 10% $C_6D_6/CDCl_3$) δ 0.88 (3 H, t, CH_3), 1.22–1.70 (8 H, m, $(CH_2)_4$), 2.27 (dd, *J* = 19.5, 8.0 Hz, CH_2-10α of 8β-Br isomer), 2.32 (dd, *J* = 19.5, 9.0 Hz, CH_2-10α of 8α-Br isomer) (δ 2.27/δ 2.32 ratio of 2:1, total 1 H), 2.69–2.90 (2 H, m, CH_2-10β, CH-12), 3.77 (d, *J* = 11.5 Hz, CHBr-8β of 8α-Br isomer), 4.22 (d, *J* = 6.0 Hz, CHBr-8α of 8β-Br isomer) (δ 3.77/δ 4.22 ratio of 1:2, total 1 H), 3.86 (m, CHOR-11 of 8α-Br isomer), 4.30 (1 H, m, CHOR-11 of 8β-Br isomer) (δ 3.86/δ 4.30 ratio of 1:2, total 1 H), 4.09 (1 H, m, CHOR-15), 4.49–4.85 (8 H, m, CH_2OCH_2O), 5.56 (2 H, m, CH=CH), 7.32 (10 H, m, aromatic); mass spectrum (CI), *m/e* 564, 562 (both $(M + MH_4)^+$), 484, 482, 465, 426, 424, 409, 407, 327, 288, 286, 271, 269, 207, 191. Anal. Calcd for $C_{29}H_{37}BrO_5$: C, 63.85; H, 6.79; Br, 14.68. Found: C, 63.77; H, 6.88; Br, 14.58.

The assignments for the preceding ^1H NMR data were confirmed by decoupling experiments. When **27** (200 mg) was oxidized with Jones reagent (1.2 equiv) in acetone over 16 h, the crude product obtained after an aqueous workup showed signals due only to the 8β-Br isomer.

Methyl 6-Amino-6-thioxohexanoate (38). A solution of methyl hydrogen adipate (10.0 g, 62.5 mmol) in thionyl chloride (40 mL) was allowed to stand at 25 °C for 3 days. Excess thionyl chloride was removed under reduced pressure, and the residual acid chloride was dissolved in acetone (100 mL). Ammonium acetate (10.5 g, 136.0 mmol) was added, and the mixture was stirred at 25 °C for 3 h. The insoluble ammonium salts were filtered off, and the filtrate was stirred with excess anhydrous sodium carbonate for 3 h. Filtration and concentration of the filtrate gave a solid, which was recyrstallized from ethyl acetate to provide methyl adipamate: 4.3 g (43%); mp 92–93 °C. (lit.[42] mp 96 °C).

Phosphorus pentasulfide (0.49 g, 2.20 mmol) was added to a boiling solution of methyl adipamate (1.50 g, 10.00 mmol) in dry dioxane (35 mL). After the mixture had been heated under reflux for 1.5 h, the supernatant liquor was decanted off and concentrated under reduced pressure. The residue was eluted with ethyl acetate through a short column of silica gel to give the thioamide **38** as a low-melting solid: ^1H NMR (60 MHz, $CDCl_3$) 1.70–2.85 (8 H, m, $(CH_2)_4$), 3.78 (3 H, s, OCH_3), 8.00 (2 H, br, exchanges with D_2O, NH_2); mass spectrum, *m/e* 175 (M^+), 158, 144, 127, 109, 75.

Similarly prepared from glutaric acid monomethyl ester was thioamide **39**, recrystallized from ethyl acetate/hexane as a white solid: mp 73–75 °C; IR (KBr) 3170 (s, NH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.15 (2 H, q, CH_2), 2.44 (2 H, t, CH_2CS), 2.72 (2 H, t, CH_2CO), 3.68 (3 H, s, OCH_3), 7.0–8.0 (2 H, br, exchanges with D_2O, NH_2); mass spectrum, *m/e* 161 (M^+), 130, 102, 88, 75, 60. Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.95; H, 6.72; N, 8.86.

9β-Hydroxy-9α,6-nitrilo-7-thia-PGF$_1$ Methyl Ester 11,15-Bis[(phenylmethoxy)methyl] Ether and Its 15β-Epimer (35). Bromoketone **33** (1.78 g, 3.27 mmol) and thioamide **38** (0.63 g, 3.62 mmol) were mixed together by dissolution in ether followed

(41) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(42) Coffey, S.; Ed. "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Elsevier: London, 1965; Vol. 1D, p 319.

by evaporation under reduced pressure. The resulting oil was left at 25 °C for 3 days and then purified by column chromatography (100 g of silica gel, 2% MeOH/CH_2Cl_2) to give recovered **33** (0.25 g, 14%) and hydroxythiazoline **35** (0.84 g, 40%) as a clear oil: IR (liquid film), 3275, (br, OH), 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.20–1.75 (12 H, m, CH_2-3,4,16,17,18,19), 2.03 (1 H, dd, J = 14.0, 10.0 Hz, CH_2-10α), 2.29–2.56 (5 H, m, CH_2-2,5, CH-12), 2.75 (1 H, dd, J = 14.0, 6.0 Hz, CH_2-10β), 3.48, 3.52 (ratio 1:1, 1 H, both d, J = 7.2 Hz, CHS-8 of 15α and 15β isomers), 3.75 (3 H, s, CH_3O), 3.95–4.15 (2 H, m, CHOR-11,15), 4.49–4.83 (8 H, m, CH_2OCH_2O), 5.49 (1 H, dd, J = 15.0, 7.5 Hz, (CH=C)-14), 5.66 (1 H, m, (CH=C)-13), 7.32 (10 H, m, aromatic); mass spectrum (CI), m/e 622 ($MH^+ - H_2O$), 560, 502, 484, 364, 279, 160. Anal. Calcd for $C_{36}H_{49}NO_7S$: C, 67.61; H, 7.67; N. 2.19. Found: C, 67.37; H, 7.73; N, 2.10.

8,9-Dehydro-9,6-nitrilo-7-thia-PGF$_1$ Methyl Ester 11,15-Bis[(phenylmethoxy)methyl] Ether and Its 15β-Epimer (40). The crude material obtained from reaction of bromo ketone **33** (0.50 g, 0.90 mmol) and thioamide **38** (0.30 g, 1.70 mmol) as above was dissolved in dry THF (10 mL) under nitrogen. Diethyl azodicarboxylate (1.04 g, 6.00 mmol) was added, and the solution was cooled to 0 °C, followed by addition of triphenylphosphine (1.60 g, 6.10 mmol). After the reaction mixture had been allowed to stand at 25 °C for 20 h, the solvent was removed, and the residue was partitioned between ether (30 mL) and water (30 mL). The organic phase was separated and washed with brine (30 mL) and dried. Evaporation gave a gum (3.1 g), which was purified by column chromatography (100 g SiO_2, 33% ethyl acetate/hexane) to give the thiazole **40** (0.38 g, 67%) as a clear oil: IR ($CHCl_3$) 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.20–1.88 (12 H, m, CH_2-3,4,16,17,18,19), 2.37 (2 H, t, CH_2-2), 2.84 (1 H, dd, J = 16.0, 4.8 Hz, CH_2-10α), 2.98 (2 H, t, CH_2-5), 3.15 (1 H, dd, J = 16.0, 6.9 Hz, CH_2-10β), 3.68 (3 H, s, CH_3O), 3.86 (1 H, m, CH-12), 4.07 (1 H, m, CHOR-15), 4.58 (1 H, m, CHOR-11), 4.50–4.88 (8 H, m, CH_2OCH_2O), 5.48 (1 H, m, (CH=C)-14), 5.76 (1 H, m, (CH=C)-13), 7.33 (10 H, m, aromatic); mass spectrum (CI), m/e 622 (MH^+), 484, 408, 364. In the ^1H NMR spectrum the assignments for the cyclopentene ring protons were confirmed by decoupling experiments. TLC showed this compound to be contaminated by a slightly less polar impurity, and therefore a correct microanalysis was not obtained. When thioamide **38** was treated independently with triphenylphosphine/diethyl azodicarboxylate, this impurity was one of several components that were formed. The impurity displayed signals at δ 1.00–2.00, 1.32 (t), 2.38 (m), 3.72 (s), and 4.32 (q) in the ^1H NMR spectrum.

8,9-Dehydro-9,6-nitrilo-7-thia-2-nor-PGF$_1$ Methyl Ester 11,15-Bis[(phenylmethoxy)methyl] Ether and Its 15β-Epimer (42). Obtained as above from bromo ketone **33** (0.50 g, 0.92 mmol) and thioamide **39** (0.29 g, 1.80 mmol) (without isolation and characterization of intermediate **36**) was thiazole **42**: 0.39 g (70%); IR ($CHCl_3$) 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.68 (8 H, m, CH_2-16,17,18,19), 2.11 (2 H, m, CH_2-4), 2.42 (2 H, t, CH_2-3), 2.84 (1 H, dd, J = 16.0, 4.8 Hz, CH_2-10α), 3.02 (2 H, t, CH_2-5), 3.25 (1 H, dd, J = 16.0, 6.9 Hz, CH_2-10β), 3.68 (3 H, s, CH_3O), 3.85 (1 H, m, CH-12), 4.08 (1 H, m, CHOR-15), 4.57 (1 H, m, CHOR-11), 4.50–4.85 (8 H, m, CH_2OCH_2O), 5.47 (1 H, m, (CH=C)-14), 5.75 (1 H, m, (CH=C)-13), 7.32 (10 H, m, aromatic); mass spectrum (CI), m/e 608 (MH^+), 470, 394, 350.

8,9-Dehydro-9,6-nitrilo-7-thia-PGF$_1$ Methyl Ester and Its 15β-Epimer (41). The thiazole **40** (0.35 g, 0.56 mmol) and p-toluenesulfonic acid (0.35 g, 1.82 mmol) in methanol (20 mL) were left at 25 °C for 10 days. After removal of solvent, the residue was partitioned between ethyl acetate (20 mL) and sodium carbonate solution (20 mL). The organic phase was separated, washed with water (20 mL) and brine (20 mL), and then dried. Evaporation gave an oil (0.37 g), which was purified by column chromatography (25 g of silica gel, 5% MeOH/CH_2Cl_2) to provide the diol ester **41** (111 mg, 52%) as a clear oil: IR ($CHCl_3$) 3680 (m, OH), 3590 (m, OH), 3440 (m, OH), 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.88 (12 H, m, CH_2-3,4,16,17,18,19), 2.36 (2 H, t, CH_2-2), 2.78 (1 H, dd, J = 16.0, 4.8 Hz, CH_2-10α), 2.98 (2 H, t, CH_2-5), 3.24 (1 H, dd, J = 16.0, 6.0 Hz, CH_2-10β), 3.67 (3 H, s, CH_3O), 3.70 (1 H, m, CH-12), 4.10 (1 H, m, CHOH-15), 4.58 (1 H, m, CHOH-11), 5.59–5.79 (2 H, m, CH=CH); mass spectrum, m/e 381 (M^+), 364, 363, 350, 332, 310, 294, 278, 250, 227, 178; exact mass, m/e 381.1971 (calcd for $C_{20}H_{31}NO_4S$ 381.1974). Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67. Found: C, 62.56; H, 8.01; N, 3.66.

8,9-Dehydro-9,6-nitrilo-7-thia-2-nor-PGF$_1$ Methyl Ester and Its 15β-Epimer (43). Compcund **42** was deprotected with p-toluenesulfonic acid as above to give diol ester **43**: 33%; IR ($CHCl_3$) 3680 (m, OH), 3590 (m, OH), 3440 (m, OH), 1730 (s, C=O) cm^{-1}; ^1H NMR δ 0.88 (3 H, t, CH_3-20), 1.22–1.60 (8 H, m, CH_2-16,17,18,19), 2.11 (2 H, m, CH_2-4), 2.43 (2 H, t, CH_2-3), 2.30–2.60 (2 H, br, exchanges with D_2O, OH's), 2.79 (1 H, dd, J = 16.0, 4.8 Hz, CH_2-10α), 3.02 (2 H, t, CH_2-5), 3.25 (1 H, dd, J = 16.0, 6.0 Hz, CH_2-10β), 3.68 (3 H, s, CH_3O), 3.71 (1 H, m, CH-12), 4.11 (1 H, m, CHOH-15), 4.58 (1 H, m, CHOH-11), 5.59–5.79 (2 H, m, CH=CH); mass spectrum, m/e 367 (M^+), 350, 349, 336, 318, 296, 294, 276, 264, 236, 213; exact mass, m/e 367.1813 (calcd for $C_{19}H_{29}NO_4S$ 367.1817).

8,9-Dehydro-9,6-nitrilo-7-thia-PGF$_1$ (2) and Its 15β-Epimer (44). Sodium hydroxide solution (2.0 mL of 0.5 M solution, 1.00 mmol) was added to the ester **41** (83 mg, 0.22 mmol) in methanol (2 mL), and the solution was left at 25 °C for 24 h. Water (15 mL) was added, and the solution was washed with ether (10 mL). It was then acidified with 1 M sulfuric acid and extracted with ethyl acetate (3 × 10 mL). The extracts were washed with water (10 mL) and brine (10 mL) and dried. Evaporation gave crude **2** together with its 15-epimer **44** (64 mg, 79%). Pure material was obtained by layer chromatography (silica gel, 1:20:180 AcOH/MeOH/CH_2Cl_2): ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.90 (12 H, m, CH_2-3,4,16,17,18,19), 2.40 (2 H, t, CH_2-2), 2.78 (1 H, dd, CH_2-10α), 3.00 (2 H, t, CH_2-5), 3.24 (1 H, dd, CH_2-10β), 3.70 (1 H, m, CH-12), 4.11 (1 H, m, CHOH-15), 4.58 (1 H, m, CHOH-11), 5.59–5.79 (2 H, m, CH=CH); mass spectrum, m/e 267 (M^+), 350, 349, 296, 278; exact mass, m/e 367.1813 (calcd for $C_{19}H_{29}NO_4S$ 367.1817).

8,9-Dehydro-9,6-nitrilo-7-thia-2-nor-PGF$_1$ (3) and Its 15β-Epimer (45). Obtained by hydrolysis of **43** as above was **3** together with its 15-epimer **45**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.59 (8 H, m, CH_2-16,17,18,19), 2.11 (2 H, m, CH_2-4), 2.46 (2 H, t, CH_2-3), 2.20–2.90 (3 H, br, exchanges with D_2O, OH's and CO_2H), 2.78 (1 H, dd, CH_2-10α), 3.06 (2 H, t, CH_2-5), 3.26 (1 H, dd, CH_2-10β), 3.71 (1 H, m, CH-12), 4.12 (1 H, m, CHOH-15), 4.59 (1 H, m, CHOH-11), 5.59–5.79 (2 H, m, CH=CH); mass spectrum, m/e 353 (M^+), 336, 335, 282, 264; exact mass, m/e 353.1657 (calcd for $C_{18}H_{27}NO_4S$ 353.1661).

9α-Methoxy-9β,6-nitrilo- and 9β-Methoxy-9α,6-nitrilo-7-thia-PGF$_1$ Methyl Ester 11,15-Bis[(phenylmethoxy)methyl] Ether and Their 15β-Epimers (46). The crude material obtained as previously from reaction of bromo ketone **33** (0.50 g, 0.90 mmol) and thioamide **38** (0.30 g, 1.70 mmol) was heated in methanol (15 mL) at 50 °C for 1 h under nitrogen. After removal of the solvent, the residue was partitioned between ether (20 mL) and sodium carbonate solution (20 mL). The organic phase was separated, washed with water (20 mL) and brine (20 mL), and dried. Evaporation gave an oil (0.72 g), which was purified by column chromatography (40 g silica gel, 33% ethyl acetate/hexane) to provide the methoxythiazoline **46** (0.37 g, 62%) as a ca. 2:1 mixture of cis and trans ring-junction isomers: IR ($CHCl_3$) 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.80 (12 H, m, CH_2-3,4,16,17,18,19), 1.93 (dd, J = 13.5, 8.0 Hz, CH_2-10α of cis isomer), 2.13 (dd, J = 15.0, 7.5 Hz, CH_2-10α of trans isomer) (δ 1.93/δ 2.13 ratio of 1:2, total 1 H), 2.30–2.65 (5 H, m, CH_2-2,5, CH-12 at ca. 2.43 for cis isomer), 2.87 (dd, J = 13.5, 7.0 Hz, CH_2-10β of cis isomer), 3.00 (dd, J = 15.0, 8.0 Hz, CH_2-10β of trans isomer) (δ 2.87/δ 3.00 ratio of 2:1, total 1 H), 3.14, 3.16 (ratio 1:1, both s, CH_3O-9 of 15α- and 15β-epimers of cis isomer), 3.25, 3.26 (ratio 1:1, both s, CH_3O-9 of 15α- and 15β-epimers of trans isomer) δ 3.14,3.16/δ 3.25,3.26 ratio of 2:1), 3.49, 3.51 (ratio 1:1 both d, J = 9.0 Hz, CHS-8 of 15α- and 15β-epimers of cis isomer), 4.20 (d, J = 7.5 Hz, CHS-8 of trans isomer) (δ 3.49,3.51/δ 4.20 ratio of 2:1, total 1 H), 3.66 (s, CH_3OCO of trans isomer), 3.67 (s, CH_3OCO of cis isomer) (δ 3.66/δ 3.67 ratio of 1:2, total 3 H), 3.91 (1 H, m, CHOR-11), 4.08 (1 H, m, CHOR-15), 4.49–4.82 (8 H, m, CH_2OCH_2O), 5.49 (1 H, dd J = 16.0, 7.5 Hz, (CH=C)-14), 5.62 (1 H, m, (CH=C)-13), 7.32 (10 H, m, aromatic); mass spectrum (CI), m/e 654 (MH^+), 622, 578, 534, 516, 484, 364. Anal. Calcd for $C_{37}H_{51}NO_7S$: C, 67.99; H, 7.81; N, 2.14; S, 4.90.

Found: C, 67.77; H, 7.91; N, 2.11; S, 4.86.

The assignments for the preceding ^1H NMR data were confirmed by decoupling experiments, of particular significance being the observation that irradiation at δ 2.43 caused collapse of the signal at δ 3.49/3.51.

9α-Methoxy-9β,6-nitrilo- and 9β-Methoxy-9α,6-nitrilo-7-thia-PGF$_1$ Methyl Ester (47) and Their 15β-Epimers (48). Compound **46** was deprotected with *p*-toluenesulfonic acid as above to give **47** and **48** (73%), which were separated by column chromatography (silica gel, 2% methanol/ether).

47: R_f 0.25 (silica gel; ether); IR ($CHCl_3$) 3680 (m, OH), 3490 (m, OH), 3450 (m, OH), 1730 (s, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, s, CH_3-20), 1.24–1.78 (12 H, CH_2-3,4,16,17,18,19), 1.90 (dd, J = 14.0, 10.5 Hz, CH_2-10α of cis isomer), 2.10 (dd, J = 13.0, 9.0 Hz, CH_2-10α of trans isomer) (δ 1.90/δ 2.10 ratio of 2:1, total 1 H), 2.22 (m, CH-12 of cis isomer), 2.52 (m, CH-12 of trans isomer) (δ 2.22/δ 2.52 ratio of ca. 2:1, total 1 H), 2.36 (2 H, t, CH_2-2), 2.58 (2 H, m, CH_2-5), 2.78 (1 H, m, CH_2-10β), 3.14 (s, CH_3O-9 of cis isomer), 3.26 (s, CH_3O-9 of trans isomer) (δ 3.14/δ 3.26 ratio of 2:1, total 3 H), 3.51 (d, J = 10.0 Hz, CH-8 of cis isomer), 4.20 (d, J = 7.2 Hz, CH-8 of trans isomer) (δ 3.51/δ 4.20 ratio of ca 2:1, total 1 H), 3.94 (1 H, m, CHOH-11), 4.09 (1 H, m, CHOH-15), 5.55–5.70 (2 H, m, CH=CH); mass spectrum, m/e 413 (M$^+$), 395, 382, 364, 351, 310, 239, 221; exact mass, m/e 413.2226 (calcd for $C_{21}H_{35}NO_5S$ 413.2236).

48: R_f 0.30 (silica gel, ether); spectral data for this isomer were almost identical with those of **47**.

9α-Methoxy-9β,6-nitrilo- and 9β-Methoxy-9α,6-nitrilo-7-thia-PGF$_1$ (49). Saponification of **47** by the above procedure gave **49**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, t, CH_3-20), 1.22–1.80 (12 H, m, CH_2-3,4,16,17,18,19), 1.95 (dd, CH_2-10α of cis isomer), 2.08 (dd, CH_2-10α of trans isomer), 2.22 (m, CH-12 of cis isomer), 2.38 (2 H, t, CH_2-2), 2.53 (m, CH-12 of trans isomer), 2.62 (2 H, m, CH_2-5), 2.78 (1 H, dd, CH_2-10β), 3.12 (s, CH_3O-9 of cis isomer), 3.26 (s, CH_3O-9 of trans isomer), 3.49 (d, CH-8 of cis isomer), 3.90 (1 H, m, CHOH-11), 4.06 (1 H, m, CHOH-15), 4.18 (d, CH-8 of trans isomer), 4.40–4.90 (3 H, br, OH's, CO_2H), 5.50–5.68 (2 H, m, CH=CH); mass spectrum, m/e 339 (M$^+$), 381, 367, 349, 296, 278, 250, 221.

9α-Methoxy-9β,6-nitrilo- and 9β-Methoxy-9α,6-nitrilo-7-thia-15β-PGF$_1$ (50). Saponification of **48** as above gave **50** with spectral data almost identical with those of **49**.

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Supplementary Material Available: Experimental data for 1-(phenylthio)-2(*E*)-octene, **25**, **26**, **28**, **29**, **31**, and **32** (2 pages). Ordering information is given on any current masthead page.

Registry No. **2**, 82945-91-3; **3**, 82945-92-4; **6**, 7129-41-1; **7**, 85250-37-9; 3β-**8**, 85281-34-1; 3α-**8**, 82945-80-0; 1β-**9**, 82978-40-3; 1α-**9**, 82945-81-1; 1β-**10**, 85250-38-0; 1α-**10**, 85281-35-2; 1β-**11**, 85281-36-3; 1α-**11**, 85281-37-4; 3β-**12**, 85281-38-5; 3α-**12**, 85281-39-6; 3β-**13**, 82978-09-4; 3α-**13**, 82978-04-9; **14**, 53398-57-5; **15**, 82948-77-4; **16**, 85250-39-1; **17**, 85250-40-4; **18**, 74365-04-1; **19**, 56831-18-6; **20**, 85250-41-5; 1β-**21**, 85250-42-6; 1α-**21**, 85281-40-9; 1β-**22**, 85250-43-7; 1α-**22**, 85281-41-0; 3β-**23**, 85281-42-1; 3α-**23**, 85281-43-2; 3β-**24**, 82978-10-7; 3α-**24**, 82945-83-3; 3β-**25**, 85250-44-8; 3α-**25**, 85281-44-3; 3β-**26**, 85250-45-9; 3α-**26**, 85281-45-4; 3β-**27**, 82978-11-8; 3α-**27**, 82945-84-4; 3β-**28**, 85250-46-0; 3α-**28**, 85281-46-5; 3β-**29**, 85250-47-1; 3α-**29**, 85281-47-6; 3β-**30**, 82978-12-9; 3α-**30**, 82945-85-5; 3β-**31**, 85250-48-2; 3α-**31**, 85281-48-7; 3β-**32**, 85250-49-3; 3α-**32**, 85281-49-8; **33** (isomer 1), 82978-13-0; **33** (isomer 2), 82945-86-6; **33** (isomer 3), 82978-15-2; **33** (isomer 4), 82978-14-1; 15β-**35**, 85250-50-6; 15α-**35**, 85281-50-1; 15β-**36**, 85250-51-7; 15α-**36**, 85281-51-2; 3β-**37**, 85250-52-8; 3α-**37**, 85281-54-5; **38**, 82945-87-7; **39**, 82945-96-8; 15β-**40**, 82978-17-4; 15α-**40**, 82945-89-9; 15β-**41**, 82978-18-5; 15α-**41**, 82945-90-2; 15β-**42**, 85250-53-9; 15α-**42**, 85281-52-3; 15β-**43**, 85250-54-0; 15α-**43**, 85281-53-4; **44**, 82978-05-0; **45**, 82978-06-1; *cis*-15β-**46**, 82978-19-6; *cis*-15α-**46**, 82945-93-5; *trans*-15β-**46**, 82978-21-0; *trans*-15α-**46**, 82978-20-9; *cis*-**47**, 82945-94-6; *trans*-**47**, 82978-22-1; *cis*-**48**, 82978-07-2; *trans*-**48**, 82978-23-2; *cis*-**49**, 82945-95-7; *trans*-**49**, 82978-24-3; *cis*-**50**, 82978-08-3; *trans*-**50**, 82978-25-4; 3-(1-ethoxyethoxy)-1-octyne, 60741-07-3; 1-octyn-3-ol, 818-72-4; 1-octen-3-ol, 3391-86-4; 1-chloro-2(*E*)-octene, 68883-76-1; 2-mercaptopyridine–sodium, 13327-62-3; 1-(2-pyridylthio)-2-(*E*)-octene, 85250-55-1; 1-(phenylthio)-2(*E*)-octene, 85250-56-2; cyclopentene oxide, 285-67-6; 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodo-1(*E*)-octene, 39178-66-0; methyl hydrogen adipate, 627-91-8; monomethyl adipate acid chloride, 35444-44-1; methyl adipamate, 40760-22-3; glutaric acid monomethyl ester, 1501-27-5.

Stereoselective Deuterium Exchange of Methylene Protons in Methyl Tetrofuranosides: Hydroxymethyl Group Conformations in Methyl Pentofuranosides[1a]

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Methyl D-tetro- and pentofuranosides were treated with Raney nickel in hot ^2H_2O, and the resulting C-deuterated products were characterized by ^{13}C, ^1H, and ^2H NMR. In two tetrofuranosides, methyl β-D-erythrofuranoside (**1**) and methyl α-D-threofuranoside (**3**), ^1H–^2H exchange at C4 was stereoselective; the C4 protons of **1** and **3** were unequivocally assigned from this reaction with the aid of ^{13}C enrichment. Exchange at C4 occurs also in methyl β-D-ribofuranoside (**11**) and methyl β-D-xylofuranoside (**13**) but in none of the other pentofuranosides. Exchange occurs in all furanosides having H4 cis to O2 and trans to O1. A convenient synthesis of perdeuterated D-ribose is described on the basis of the Raney Ni exchange results with **11**. By use of the selectively C4-deuterated tetrofuranosides derived from **1** and **3**, eight pentofuranosides were prepared and the C5 protons stereochemically assigned. ^1H–^1H coupling constants and ^{13}C spin–lattice relaxation times (T_1) were measured and are interpreted in terms of the mobility and conformational preferences of the C4–C5 bond in these compounds, and factors affecting these preferences are discussed.

Carbohydrates enriched with deuterium have been widely used to elucidate reaction pathways,[2,3] interpret complex ^1H NMR spectra,[4,5] and assign ^{13}C chemical shifts.[6,7] In addition, deuterium spin–lattice relaxation

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