The Total Synthesis of Sarracenin[1]

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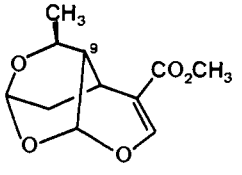
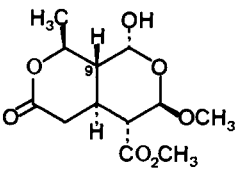
Abstract: The synthesis of the iridoid monoterpene sarracenin is described. The ketone **4**, prepared from 1,3-cyclooctadiene, was transformed by a ten-step sequence to the ketoester **15**. Baeyer-Villiger oxidation and diisobutylaluminum hydride reduction afforded the lactol **23**. Ozonolytic cleavage of **23** followed by zinc in acetic acid reduction of the ozonide afforded the penultimate skeleton **3** that, without isolation, was warmed in acetic acid to form sarracenin.

The realm of iridoid monoterpenes was enriched in 1976 by the separate reports of Miles[2] and Kubo[3] on the isolation and characterization of sarracenin and of xylomollin, respectively. While the structure of sarracenin, **1**, was established firmly by



sarracenin (**1**)



xylomollin (**2**)

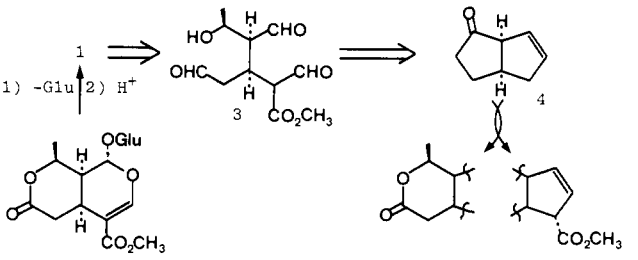
Miles using single-crystal, X-ray analysis, that reported for xylomollin was deduced from detailed, proton–proton coupling data. We[4] and others[5] noted that the stereochemical relationships depicted in **2** were more consistent with the reported information for xylomollin. In 1977, Hutchinson and Clardy[5] established this structure for the natural product by a combination of synthetic efforts (in the unnatural, *cis*-fused series) and an X-ray analysis of a derivative of xylomollin.

The stereochemical relationship between these two terpenes (they are epimeric at carbon 9, iridoid numbering) is intriguing as are the unique functionalities found in each.[6] We found the contiguous acetal–acetal–enol ether array in sarracenin especially fascinating and set about its construction from simpler compounds.

Results and Discussion

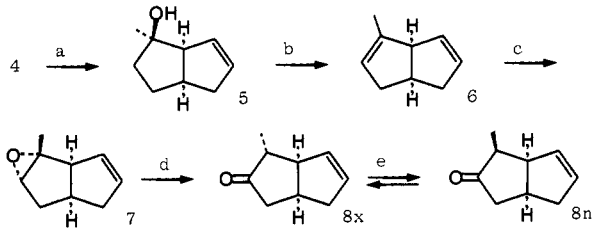
Our fundamental approached was based on the transformation of a simple and readily available bicyclo[3.3.0]octane, **4**,[7] into the functional equivalent of the trialdehyde **3**. Such a species had been obtained previously from morroniside and was reported to form sarracenin on treatment with acid.[8] The operations to be performed on **4** could then be divided into the conversion of the left-hand ring to a methyl-substituted lactone and the right-hand ring to a β,γ-unsaturated ester. The stage would then we set for reduction of the lactone on the one hand and oxidative cleavage of the alkene on the other leading to the desired trialdehyde **3**. Our method for effecting the first task is presented in Scheme II. Two points are worthy of note. First, dehydration of the tertiary alcohol **5** was quite sensitive to reaction conditions and

Scheme I



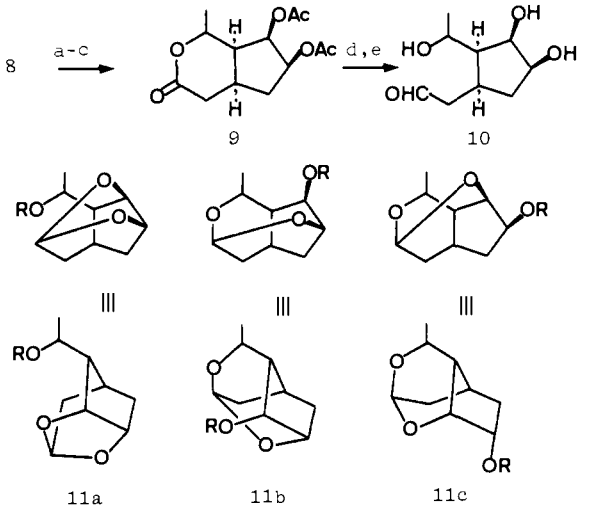
Morroniside

Scheme II



[a] CH_3–Li. [b] $K_2S_2O_7$. [c] mcpba. [d] $BF_3 \cdot Et_2O$. [e] $NaOCH_3$–CH_3OH.

Scheme III



[a] AcOAg, I_2; AcOAg. [b] Ac_2O, pyridine. [c] mcpba. [d] DiBAlH. [e] $NaOCH_3$–CH_3OH.

provided only moderate yields of the diene (**6**) with use of a wide variety of standard procedures. However, use of potassium pyrosulfate[9] for this reaction gave **6** with yields consistently in excess of 90%. Second, we had intended to effect the conversion of the

(1) A preliminary account of this research has been reported: Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784.
(2) Miles, D. H., Kokpol, U.; Bhattacharyya, J.; Atwood, J. L.; Stone, K. E.; Bryson, T. A.; Wilson, C. *J. Am. Chem. Soc.* **1976**, *98*, 1569.
(3) Kubo, I.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704.
(4) Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S.; Helbling, A. M. "Abstracts of Papers" 175th National Meeting of the American Chemical Society, Anaheim, CA, March 1978; American Chemical Society: Washington, DC, 1978; Abstract ORGN 176.
(5) Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079.
(6) The acetal–acetal–enol ether system in sarracenin and the mixed hemiacetal–acetal array in xylomollin do not appear in any other natural products.
(7) Crandal, J. K.; Chang, L.-H. *J. Org. Chem.* **1967**, *32*, 532.
(8) Souzu, I.; Mmitsuhashi, H. *Tetrahedron Lett.* **1969**, 2725.
(9) Plattner, Pl. A.; Fürst, A.; Jirasek, K. *Helv. Chim. Acta* **1946**, *29*, 740.

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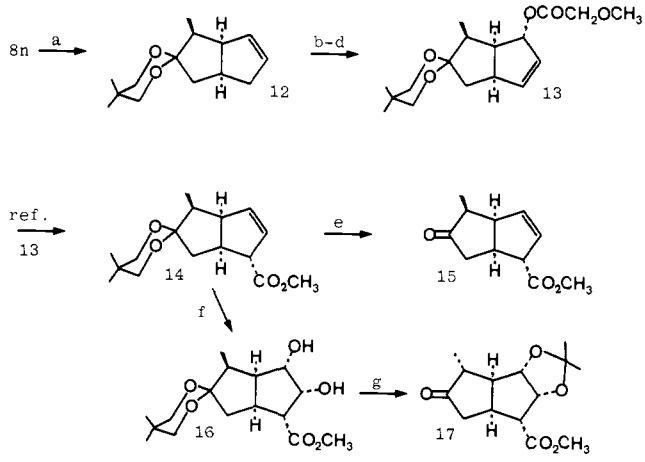
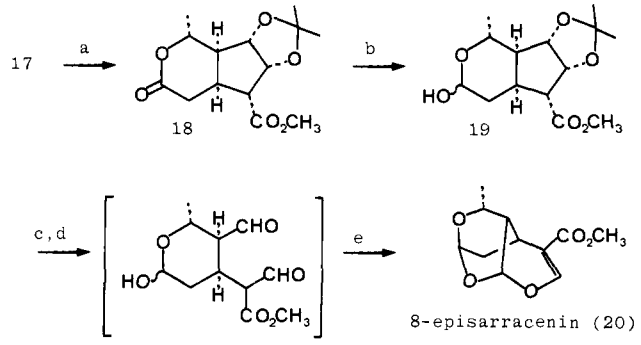
Scheme IV



[a] $(CH_3)_2C(CH_2OH)_2$, H^+, Sieves. [b] CH_3CO_2OH. [c] Li-N(*i*-Pr)$_2$. [d] CH_3OCH_2COCl, pyridine. [e] H^+, acetone. [f] OsO_4, NMO. [g] H^+, acetone.

Scheme V



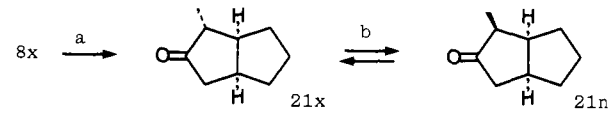
[a] mcpba. [b] DiBAlH. [c] HCl-H_2O. [d] $NaIO_4$. [e] HOAc.

exo-methyl ketone **8x** to the endo epimer **8n** by deprotonation–kinetic protonation but were surprised to find that the equilibrium mixture was composed of equal portions of each ketone. Since we had conceived of a scheme for the conversion of **8x** to xylomollin and since the isomers were readily separable in large quantities (50 g/run) by using high-performance liquid chromatography, we were content to prepare the mixture and effect separation.

Refunctionalization of the right-hand ring of the bicyclooctane required the addition of one carbon, as a carbomethoxy group. We examined two separate schemes for this conversion. The first was based on our expectation that of the three cyclic acetals that might form from the aldehyde triol **10,11c** would be the most stable. Oxidation of the remaining hydroxyl group would afford a ketone correctly positioned to permit facile addition of the carbomethoxy group. When the appropriate sequence was carried out by using the *exo* series (from **8x**) as a model, oxidation of the acetal produced provided a methyl ketone. Thus, **11a** is a more stable array than either **11b** or **11c**.

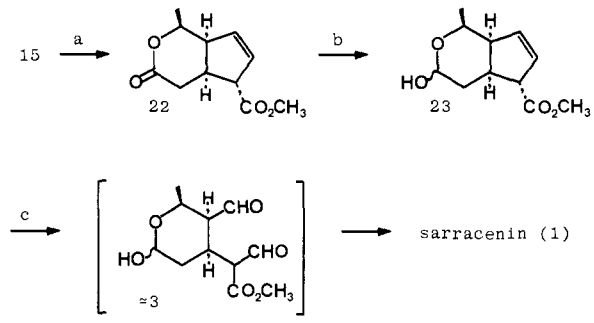
The second approach involved a combination of Ireland's ester enolate Claisen rearrangement[10] and Wasserman's oxidative decarboxylation sequence.[11] When combined with the conversion of an alkene to an allylic alcohol via the epoxide, these techniques incorporate a carbomethoxy group at the allylic position of the original alkene. The methodology has been described in detail elsewhere[12] and when applied to the ketal **12** (derived from **8n**) provided the desired ester **15**.

Scheme VI



[a] H_2, Pt/C. [b] $NaOCH_3$–CH_3OH.

Scheme VII



[a] mcpba. [b] DiBAlH. [c] OsO_4, NMO.

The remaining stages of the synthesis would require, on the one hand, formation of the lactol by Baeyer–Villiger oxidation followed by partial reduction and, on the other, oxidative cleavage of the alkene linkage to the dialdehyde. We were concerned about the selectivity of a peracid for the alkene vs. the ketone functionality of **15** because we had previously observed that the very similar keto–alkene **8x** underwent epoxidation to the virtual exclusion of lactone formation. We thus chose to initiate oxidation of the alkene in **14** by conversion to the glycol (**16**) with oxmium tetroxide. However, we were unable to effect hydrolysis of the ketal without concomitant epimerization at C-8, even with use of reaction conditions similar to those which had been used to convert **8n** to the ketal **12** without loss of stereochemical integrity. The exo ketone **17** was carried further by the sequence shown below to form 8-episarracenin (**20**).

The proportion of exo-methyl isomer to endo obtained in the formation of **17** was substantially higher than the equimolar, equilibrium mixture of **8x** and **8n**. We reasoned that the presence in **17** of sp^3 centers as opposed to the sp^2 carbons in **8** provided not only for a thermodynamic favoring of the exo configuration but also for an accelerated rate of conversion of the endo to the exo isomer. This reasoning was substantiated by two observations. First, equilibration of the saturated ketone **21**, derived from **8x** by catalytic hydrogenation, provided a 3:1 ratio of epimers, with exo predominating. Second, the ketal–olefin **14** was smoothly converted to ketone **15** with little loss of stereochemical integrity.

While we had previously observed that peracid oxidation of the keto–olefin **8x** provided the epoxide and not the lactone, we discovered that the converse selectivity obtained in the oxidation of **15** which afforded predominantly the lactone **22**. The use of heterogeneous bicarbonate in these oxidations effected a faster rate of oxidation (approximately twofold) and provided as well a lower level of byproduct formation.[13] It is not clear whether this selectivity difference in the oxidations of **8x** and **15** is due to a steric inhibition of the Baeyer–Villiger oxidation of **8x** by the exo-methyl group or a retardation of the rate of epoxidation of **15** by either steric or electronic influences of the allylically substituted carbomethoxy group.

Initial attempts to effect partial reduction of the lactone function in **22** with 1 equiv of diisobutylaluminum hydride led to the lactol **23** with quite variable success. It was only after some considerable investigation that we discovered that the first equivalent of reducing agent is consumed, nonproductively, by complexation with the carbomethoxy group. Early experiments were thus generating

(10) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *Ibid.* **1976**, *98*, 2868.
(11) Wasserman, H. H.; Lipshutz, B. *Tetrahedron Lett.* **1975**, 4611; **1976**, 4613.
(12) Whitesell, J. K.; Helbling, A. M. *J. Chem. Soc., Chem. Commun.* **1977**, 594; *J. Org. Chem.* **1980**, *45*, 4135.
(13) Dr. P. S. Stotter, University of Texas at San Antonio, had found that comparatively slow Baeyer–Villiger oxidations are accelerated in the presence of bicarbonate (private communication).

lactol only through the presence of adventitious hydride in excess of one equivalent. The use of two full equivalents afforded the lactol **23** with complete consumption of the lactone **22** with no apparent overreduction. Treatment of the crude lactol with 1 equiv of ozone and reduction of the ozonide with zinc in acetic acid afforded a species, presumably the functional equivalent of **3**, that was converted to sarracenin after 1 h at 70 °C in the same acid medium. The overall yield for the sequence from the lactone **22** to racemic sarracenin was 15%.[14] The synthetically produced sarracenin and an authentic sample of the natural product[15] were identical by ^{13}C, ^{1}H, infrared, and low-resolution mass spectral analysis.

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep blue solution resulting from benzophenone and sodium, and Skelly B was stirred with sulfuric acid and solid sodium carbonate and distilled before use. Ozone was generated by using a Welsbach generator, and the flow rate was determined prior to and after use by titration. Purified *m*-chloroperbenzoic acid was obtained by washing commerical, 85% material with a pH 7.5 buffer.[16] All other reagents and solvents were obtained from commercial sources and used without further purification.

Procedures. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of products were dried with molecular sieves prior to concentration in vacuo. Crude products were routinely run through a short column of silica gel prior to careful purification by using a Waters Prep 500 system with two Prep-Pak cartridges (HPLC). Reference to samples purified by HPLC is to material of 95% or greater purity (by ^{13}C analysis). All reported temperatures are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, AZ.

Spectra. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained with a Varian HA-100 instrument and are reported on the γ scale as follows: shift (number of hydrogens, multiplicity, coupling constant in hertz). ^{13}C NMR data were obtained with either a Brucker WD-90 or a Varian FT-80A instrument. Carbon magnetic resonance data for **4**, **5**, **6**, and **8x** have already been reported.[17] Assignments were made by using established α, β, and γ effects, our previous observations,[17] and off-resonance, continuous-wave decoupling techniques (to distinguish between methylene and methine carbons). Shift ranges for the ketal moiety carbons were as follows: CH_3, 21.2–22.8; CH_2, 70.6–72.9; C, 29.9–30.1. All NMR spectra were obtained on dilute, $CDCl_3$ solutions by using tetramethylsilane as internal standard. Infrared (IR) spectra were obtained on dilute, methylene chloride solutions by using a Perkin-Elmer 237B instrument. High-resolution mass spectra were recorded by using a Du Pont 21-110B instrument while low-resolution spectra were obtained with a Du Pont 21-491 instrument. Peak intensities are reported relative to the parent ion as 100%.

2-Methyl-*cis*-bicyclo[3.3.0]octa-2,7-diene (6). To a solution of 440 mL (0.90 mol) of 2.05 M methyl lithium–lithium bromide in ether was added 1 L of additional ether followed by the dropwise addition of 58.1 g (0.475 mol) of bicyclo[3.3.0]oct-7-en-2-one (**4**)[7] over 35 min with ice–salt cooling and magnetic stirring. The cooling bath was removed for 45 min and then replaced and the excess methyl lithium destroyed by the addition of water. The reaction mixture was partitioned between ether and water and the ether layer concentrated to 70 g (>100%, containing some ether) of *exo*-2-methyl-*cis*-bicyclo[3.3.0]oct-2-en-*endo*-2-ol (**5**) as a slightly yellow oil.

Potassium pyrosulfate was prepared by fusing potassium bisulfate. A mixture of 15 g of this material, finely ground, and 10 g (70 mmol) of crude alcohol **5** was heated at 120 °C for 2.5 h. The cooled, dark material was taken up in water and extracted with pentane. The organic layer was washed with 2 N aqueous sodium carbonate and then filtered through a short column of alumina. The bulk of the pentane was removed through a glass helices packed column to afford 8.6 g (100%) of diene contaminated by ~2% pentane but otherwise pure by ^{13}C and GLC analysis (SE-30): bp 145–150 °C; ^{1}H NMR δ 1.75 (3, s), 1.7–3.7 (6, m), 5.05–5.30 (1, m), 5.50–5.95 (2, m); mass spectrum calcd for C_9H_{12} 20.0939, found 20.0942.

***endo*- and *exo*-2-Methyl-*cis*-bicyclo[3.3.0]oct-7-en-3-one (8n and 8x).** The diene **6** obtained above was converted to the mono epoxide with technical *m*-chloroperbenzoic acid in methylene chloride at 0 °C. A portion (~70%) of the calculated amount of oxidant required was added dropwise as a solution in methylene chloride, and the extent of conversion was determined after 1 h by GLC analysis. This information was used to determine the amount of additional peracid needed to effect complete consumption of the starting diene. In a typical experiment, 9.5 g of diene required a total of 14.3 g of peracid. The reaction mixture was then washed with aqueous bicarbonate containing sodium sulfite, and concentration of the organic layer afforded the crude epoxide **7**.

Epoxide **7** (44 g) was dissolved in 750 mL of purified methylene chloride and then 5 mL of boron trifluoride etherate was added quickly with rapid stirring. After 1 min the reaction was quenched by the addition of excess aqueous bicarbonate solution. The organic layer was concentrated to 44 g of crude ketones, with an **8x**–**8n** ratio of approximately 10:1. All of this material was equilibrated by treatment with 1.6 g of sodium methoxide in 550 mL of dry methanol for 30 min. The mixture of ketones thus obtained (1:1 by HPLC analysis) was separated as a single batch by using the Waters Prep 500 system (10:1 Skelly B–ethyl acetate) and recycle and shaving techniques. There was obtained 11 g of **8n** and 12.2 g of **8x** plus a small, mixed fraction. The total yield from the diene **6** of separated, isomerically pure ketones was 50%.

For **8x**: ^{1}H NMR δ 1.16 (3, d, J = 7), 1.0–2.1 (7, m), 5.8 (2, br s); IR 1745 cm^{-1}; mass spectrum calcd for $C_9H_{12}O$ 136.0888, found 136.0884.

For **8n**: ^{1}H NMR δ 1.13 (3, d, J = 7), 1.7–2.1 (6, m), 3.4–3.7 (1, m) 5.6–5.9 (2, m); ^{13}C NMR δ 220.5 (C_3), 131.7, 129.7 (C_7, C_8), 52.3 (C_1), 46.4 (C_2), 44.1 (C_4), 40.7 (C_6), 34.5 (C_5), 11.3 (CH_3); IR 1740 cm^{-1}.

***endo*,*endo*-8,9-Diacetoxy-*exo*-2-methyl-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (9).** Woodward cis hydroxylation of ketone **8x** was effected by the standard procedure.[18] The resulting acetates were converted to the diacetate with acetic anhydride in pyridine for the purpose of purification. *endo*,*endo*-7,8-Diacetoxy-*exo*-2-methyl-*cis*-bicyclo[3.3.0]octan-3-one: ^{1}H NMR δ 1.1 (3, d), 1.5–2.9 (7, m), 2.05 (3, s), 2.06 (3, s), 5.2–5.4 (2, m). For ^{13}C data see ref 18.

To a solution of this diacetate (0.731 g, 2.80 mmol) in 40 mL of methylene chloride was added 0.745 g (4.3 mmol) of purified *m*-chloroperbenzoic acid and 0.725 g (8.6 mmol) of sodium bicarbonate. The mixture was stirred for 12 h at 25 °C and then partitioned between aqueous sodium bicarbonate–sodium sulfite and methylene chloride. Concentration afforded the crude lactone **9**, which was crystallized from ethyl acetate–pentane to give 0.642 g (83%): mp 119–120 °C; ^{1}H δ 1.36 (3, d, J = 7), 2.00 (3, s), 2.11 (3, s), 1.0–2.8 (9, m), 4.3–4.6 (1, m) 5.0–5.25 (1, m), 5.4–5.55 (1, m); mass spectrum calcd for $C_{13}H_{18}O_6$ 270.1103, found 270.1102; *m/e* 210 (150%, –HOAc), 227 (120%, $-CH_3CO$), 228 (150%, $-CH_2CO$). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.77; H, 6.85.

***exo*-4-(1-Hydroxyethyl)-2,8-dioxatricyclo[3.3.1.0^{3,7}]nonane (10a).** Lactone diacetate **9** was reduced with 1 equiv of diisobutylaluminum hydride in the same manner as described below for the conversion of **18** to **19**. The crude lactol (72%) was converted to a diol with excess methanolic sodium hydroxide. This diol was then treated, without purification, with glacial acetic acid at 60 °C for 5 h. Purification of the product thus obtained by preparative layer chromatography afforded the acetate **11a** (R = OAc) in 30% overall yield from the lactol: ^{1}H NMR δ 1.42 (3, d, J = 6), 2.03 (3, s), 1.2–2.3 (6, m), 4.4–4.6 (1, m), 4.6–4.8 (1, m), 5.35–5.45 (1, m), 5.52 (1, dd, J = 5, 10). Alcohol **11a** (R = H) was obtained in 89% yield from the acetate by hydrolysis with sodium hydroxide (2 equiv) in aqueous THF: ^{1}H NMR δ 1.41 (3, d, J = 6), 1.2–2.6 (7, m), 4.2–4.6 (2, m), 4.65–4.85 (1, m), 5.35–5.45 (1, m). This alcohol was converted to a methyl ketone with excess Collins reagent in methylene chloride (96%): ^{1}H NMR δ 1.2–2.8 (6, m), 2.36 (3, s), 4.6–5.0 (2, m), 5.35–5.45 (1, m); mass spectrum calcd for $C_9H_{14}O_3$ 168.0786, found 168.0782; 150 (50%, $-H_2O$), 140 (60%, –CO), 125 (75%, $-CH_3CO$).

***endo*-8-Methyl-7,7-(1,3-neopentanedioxy)-*cis*-bicyclo[3.3.0]oct-2-ene (12).** *endo*-Methyl ketone **8n** (16.8 g, 0.123 mol), 69.4 g (0.666 mol, 5.5 equiv.) of neopentyl glycol, and 70 mL of THF were stirred with warming until all of the glycol had dissolved. Sufficient 3-Å molecular sieves were added so that little solution remained above the sieves, and then 7.2 g (0.03 mol) of *d*-10-camphorsulfonic acid was added and the reaction stirred mechanically at room temperature for 3 h. Partitioning of the reaction mixture between aqueous sodium bicarbonate and pentane and concentration of the organic layer afforded 27.2 g of crude ketal with an endo/exo ratio of approximately 10:1. A portion of this material (18.8 g) was purified by HPLC (10:1 Skelly B–ethyl acetate) in two batches to afford 13 g (70%): ^{1}H NMR δ 0.82 (3, s), 0.91 (3, d, J = 7), 1.06 (3, s), 1.9–2.9 (6, m), 3.1–3.7 (5, m), 5.64 (2, s); ^{13}C NMR δ 130.9, 130.4

(14) Because the intermediate lactol **23** and dialdehyde **3** were rather unstable, it was not possible to determine at which stage(s) material was lost in the conversion of the lactone **22** to sarracenin.

(15) We thank Professor Miles for a sample of natural sarracenin.

(16) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

(17) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

(18) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209.

(C_2, C_3), 109.4 (C_7), 52.3 (C_1), 42.5 (C_8), 40.9 (C_6), 37.4, 36.4 (C_4, C_5), 10.9 (CH_3); mass spectrum calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1616; *m/e* 207 (25%, $-CH_3$), 192 (40%, $-(CH_3)_2$).

***exo*-4-(Methoxyacetoxy)-*endo*-6-methyl-7,7-(1,3-neopentanedioxy)-*cis*-bicyclo[3.3.0]oct-2-ene (13).** Ketal **12** (12 g, 54 mmol) and 13.5 g (127 mmol) of sodium carbonate were added to a flask containing 1 L of methylene chloride. This mixture was cooled with ice–salt to 0 °C, and then 15 mL (91 mmol) of commercial 40% peracetic acid containing 0.45 g (5.5 mmol) of sodium acetate was added dropwise over 5 min with stirring. After 0.5 h the cooling bath was removed and the reaction was then allowed to proceed at room temperature for an additional 2.5 h. The solution was washed first with aqueous sodium sulfite and then with aqueous sodium bicarbonate. Concentration afforded the crude epoxide which was purified by HPLC (10:1 Skelly B–ethyl acetate) to afforded 11.69 g (91%) of exo-epoxide: ^{1}H NMR δ 0.82 (3, s), 1.04 (3, d, J = 8), 1.08 (3, s), 2.1–2.9 (7, m), 3.3–3.7 (6, m); mass spectrum calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1577. There was also produced approximately 10% of the stereoisomer resulting from attack of the oxidant on the endo face of the molecule.

A solution of lithium diisopropyl amide was prepared from 13.2 g (96 mmol) of diisopropylamine, 8.5 mL (89 mmol) of 90% butyl lithium in hexane, and 100 mL of THF at 0 °C. To this solution was added 8.5 g (35.6 mmol) of the epoxide prepared above. After 5 min at 0 °C the cooling bath was removed and the reaction was heated to and then held at 60 °C for 2.5 h. The cooled reaction was diluted with 100 mL of ether and then extracted with aqueous hydrochloric acid, sodium bicarbonate solution, and then brine. Concentration afforded 7.9 g (93%) of allylic alcohol, pure by NMR, that was converted to the methoxyacetate ester **13** without further purification: ^{1}H NMR δ 0.7 (3, s), 1.05 (3, s), 1.1 (3, d, J = 7), 1.2–2.6 (4, m), 3.2–3.6 (5, m), 4.8–4.95 (1, m) 5.6–5.85 (2, m).

To a solution of the allylic alcohol (prepared from 1.86 g (7.8 mmol) of epoxide) in 10 mL of methylene chloride was added a solution of 2.5 mL of pyridine and 1.1 mL (12 mmol) of α-methoxyacetyl chloride. After being stirred overnight at room temperature the reaction was partitioned between water and ether. The organic layer was washed with aqueous hydrochloric acid, sodium bicarbonate, and brine and then concentrated. The crude product was purified by HPLC (5:1 Skelly B–ethyl acetate) to give 1.06 g (44% overall from the epoxide) of **13**: ^{1}H NMR δ 0.75 (3, s), 1.10 (3, d, J = 7), 1.09 (3, s), 2.66 (1, dd, J = 10, 13), 2.1–2.8 (3, m), 3.36 (1, d, J = 4), 3.45 (6, s), 4.00 (2, s), 5.6–5.8 (1, m), 5.96 (1, dd, J = 2,5); ^{13}C NMR δ 140.4 (C_3), 129.0 (C_2), 107.6 (C_7), 82.1 (C_4), 49.4 (C_5), 45.5, 42.9 (C_6, C_8), 32.4 (C_1), 9.0 (CH_3); mass spectrum calcd for $C_{17}H_{26}O_5$ 310.178; found, 310.179; *m/e* 221 ($-CH_3OCH_2CO_2$), 220 ($-CH_3OCH_2CO_2H$).

***endo*-2-Methyl-*exo*-6-(carbomethoxy)-*cis*-bicyclo[3.3.0]oct-7-en-3-one (15).** A solution of 0.946 g (3.35 mol) of ketal ester **14**[13] and 0.196 g (0.84 mmol) of *d*-10-camphorsulfonic acid in 30 mL of acetone was stirred at room temperature for 3.5 h. Solid sodium bicarbonate (0.28 g, 3.35 mmol) was then added and the reaction mixture stirred a further 2 h. The reaction was diluted with additional acetone and filtered through a short silica gel column. Concentration and purification by HPLC (3:1 Skelly B–ethyl acetate) afforded 0.57 g (88%) of ketone **15**: ^{1}H NMR δ 1.12 (3, d, J = 8), 1.94 (1, dd, J = 7, 19), 2.3–2.9 (2, m), 3.1–3.45 (2, m), 2.6–2.85 (1, m), 3.72 (3, s), 5.74–5.96 (2, m); IR 2850 (br), 1740 (s), 1425 (br), 1340, 1205, 1170 cm^{-1}; ^{13}C NMR δ 218.4 (C_3), 173.5 (CO_2), 133.4 c_7), 129.5 (C_8), 58.5 (C_6), 51.9, 51.8 (C_1, CH_3O), 45.6 (C_2), 43.0 (C_4), 38.3 (C_5), 11.3 (CH_3); mass spectrum calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0937; *m/e* 166 (400%, –CO), 162 (200%, $-CH_3OH$), 135 (300%, $-CH_2CH_3$). There was also obtained 0.060 g of the corresponding exo-methyl isomer: ^{13}C NMR δ 219.9 (C_3), 173.8 (CO_2), 136.9 (C_7), 128.7 (C_8), 58.0 (C_6), 54.9 (C_1), 52.0 (CH_3O), 47.7 (C_2), 42.9 (C_4), 39.3 (C_5), 15.4 (CH_3).

***exo*,*exo*-2,3-Dihydroxy-*exo*-4-(carbomethoxy)-*endo*-8-methyl-7,7-(1,3-neopentanedioxy)-*cis*-bicyclo[3.3.0]octane (16).** To a solution of 171 mg (0.612 mmol) of **14**[13] in 1 mL of water and 0.5 mL of acetone was added 111 mg of *N*-methylmorpholine *N*-oxide dihydrate (0.725 mmol) followed by 0.375 mL of *tert*-butyl alcohol containing 1.5 mg (1 mol%) of osmium tetroxide. After 12 h of stirring at room temperature the reaction was quenched by the addition of a slurry of 50 mg of sodium bisulfite, 0.5 mL of water, and 75 mg of celite. The mixture was then acidified with 2 N hydrochloric acid and extracted with three portions of ethyl acetate. Concentration afforded 191.3 mg (99%) of diol **16** (used without further purification): ^{1}H NMR δ 0.9 (3, s), 1.15 (3, d, J = 6), 1.18 (3, s), 1.3–3.7 (12, m), 3.77 (3, s), 4.05–4.2 (2, m).

***exo*-6-(Carbomethoxy)-*exo*-2-methyl-*exo*,*exo*-7,8-(isopropylidenedioxy)-*cis*-bicyclo[3.3.0]octan-3-one (17).** To a solution of 40.9 mg (0.13 mmol) of diol **16** in 2 mL of acetone was added 5 mg of camphorsulfonic acid. The reaction was stirred for 12 h, and then 20 mg of solid sodium carbonate was added. The supernatant was filtered through a short column of silica gel and concentrated to afford 33.0 mg (95%). Recrystallization from hexane gave white needles: mp 115–116 °C; ^{1}H NMR δ 1.16 (3, d, J = 7), 1.31 (3, s), 1.45 (3, s), 2.1–2.8 (5, m), 3.2–3.6 (1, m), 3.77 (3, s), 4.64 (1, d, J = 5), 5.0 (1, t, J = 5); mass spectrum, no M$^+$, *m/e* 253 ($-CH_3$). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.51; H, 7.42.

***exo*-7-(Carbomethoxy)-*exo*-2-methyl-*exo*,*exo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (18).** To a solution of 250 mg (1.30 mmol) of ketone **17** in 25 mL of methylene chloride was added 161 mg of sodium bicarbonate followed by 242 mg (1.4 mmol) of purified *m*-chloroperbenzoic acid. After being stirred at room temperature for 12 h, the reaction mixture was extracted with aqueous sodium sulfite plus sodium bicarbonate solution. Concentration afforded 264 mg (99%). Recrystallization from ethyl acetate–hexane provided a sample for analysis: mp 118–119 °C; ^{1}H NMR δ 1.31 (3, s), 1.44 (3, s), 1.47 (3, d, J = 6), 2.0–2.45 (3, m), 2.7–3.0 (2, m), 3.78 (3, s), 4.0–4.4 (1, m), 4.41 (1, dd, J = 2,5), 4.87 (1, t, J = 5); mass spectrum, no M$^+$, *m/e* 269 ($-CH_3$), 267 (–OH). Anal. Calcd for $C_{14}H_{20}O_5$: C, 59.14; H, 7.09. Found: C, 59.08; H, 7.25.

8-Episarracenin (20). To a solution of 180 mg (0.634 mmol) of lactone **18** in 3 mL of toluene and 3 mL of methylene chloride was added with stirring at –78 °C 0.64 mL of an approximately 1 M solution of diisobutylaluminum hydride in toluene. After 1 h at –78 °C the reaction was added quickly to 20 mL of 0.5 M aqueous hydrochloric acid. The aqueous layer was extracted with three portions of ethyl acetate, and the combined organic layers were concentrated to 165 mg of crude lactol **12**, still containing significant quantities of the starting lactone. To 82 mg of this material in 1 mL of THF was added 1 mL of 1 N aqueous hydrochloric acid. The resulting solution was heated at 65 °C for 2 h. The solution was then cooled and 80 mg (1 mmol) of sodium bicarbonate was added followed by 46 mg (0.2 mmol) of sodium metaperiodate in 4 mL of water. After the reaction had been stirred for 5 min at room temperature, one drop of ethylene glycol was added followed by 20 mg of sodium bicarbonate. The solvents were removed under high vacuum, and the white residue was taken up in 3 mL of glacial acetic acid. Camphorsulfonic acid (15 mg, 0.06 mmol) was then added and the resulting suspension stirred at 70 °C for 1 h. The solvent was removed under high vacuum, the residue was extracted with ethyl acetate, and excess ethereal diazomethane was added to the solution. The material was washed through a short column of silica gel with ethyl acetate and concentration afforded 56 mg of crude product. Purification was effected by preparative layer chromatography (3:1 Skelly B–ethyl acetate) and afforded 14.7 mg (21% overall from lactone **18**): ^{1}H NMR δ 1.39 (3, d, J = 0), 1.5–1.9 (2, m), 2.2–2.6 (1, m), 3.1–3.4 (1, m), 3.77 (3, s), 4.0–4.4 (1, m), 4.94–5.0 (1, m), 5.68–5.78 (1, m), 7.50 (1, s); IR 2950 (br), 1710, 1640, 1425 (br), 1380, 1370, 1300, 1250 (br), 1220, 1175, 1135, 1100, 925 (br) cm^{-1}; ^{13}C NMR δ 150.4 (C_3), 112.7 (C_4), 94.7 (C_1), 87.7 (C_7), 68.7 (C_8), 51.5 (OCH_3), 36.4, 31.9 (C_5, C_9), 19.2 (C_6), 16.9 (CH_3); mass spectrum calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0845; *m/e* 211 (40%, $-CH_3$).

***exo*-7-(Carbomethoxy)-*endo*-2-methyl-3-oxa-*cis*-bicyclo[4.3.0]non-8-en-4-one (22).** Baeyer–Villiger oxidation of ketone **15** (0.64 g) was effected exactly as described for the preparation of **18**, above. In addition to the desired lactone **22** (0.46 g, 70%) there was obtained by HPLC separation (1:1 Skelly B–ethyl acetate) 0.083 g (12%) of the *exo*-epoxy ketone and 0.77 g (10%) of the *exo*-epoxylactone. For **22**: mp 40–43 °C; ^{1}H NMR δ 1.42 (3, d, J = 6.5), 2.5 (1, d, J = 16), 2.79 (1, dd, J = 6, 16), 3.34 (3, m), 3.72 (3, s) 4.55 (1, qd, J = 2.5, 6.5), 5.88 (2, m); ^{13}C NMR δ 173.4 (CO_2), 172.5 (C_4), 131.7 (C_8), 129.7 (C_9), 74.7 (C_2), 58.0 (C_7), 52.2 (OCH_3), 49.2 (C_1), 36.0 (C_6), 34.7 (C_5), 18.0 (CH_3); IR 1735 cm^{-1}; mass spectrum calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0895. For the *exo*-epoxy ketone: ^{1}H NMR δ 1.28 (3, d, J = 7), 2.00 (1, dd, J = 6, 19), 2.3–3.2 (5, m), 3.6 (1, br s), 3.78 (3, s), 3.80 (1, br s); ^{13}C NMR δ 217.8 (C_7), 172.2 (CO_2), 60.3, 58.4 (C_2, C_3), 52.4 (C_4), 52.2 (OCH_3), 46.4 (C_1), 44.2, 43.8 (C_6, C_8), 36.4 (C_5), 11.4 (CH_3); IR 1737 cm^{-1}; mass spectrum calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0889. For the *exo*-epoxylactone: ^{1}H NMR δ 1.54 (3, d, J = 7), 2.6–3.1 (5, m), 3.66 (1, m), 3.79 (3, s), 3.80 (1, s), 4.54 (1, m); ^{13}C NMR δ 72.3, 7.2 (C_4, CO_2), 73.4 (C_2), 59.2, 56.5 (C_8,C_9), 52.4, 51.3 (C_7, OCH_3), 43.1 (C_1), 34.5, 33.4 (C_5, C_6), 17.2 (CH_3); mass spectrum calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0845.

***exo*-7-(Carbomethoxy)-*endo*-2-methyl-3-oxa-*cis*-bicyclo[4.3.0]non-8-en-4-ol (23).** To solution of 86.4 mg (0.41 mmol) of lactone **22** in 4 mL of THF was added rapidly and with stirring at –78 °C 0.82 mL (0.82 mmol, 2 equiv) of a 1 M solution of diisobutylaluminum hydride in hexane. After 1.5 h 1.0 mL of dry methanol, precooled to –78 °C, was added. After 20 min, the reaction was warmed slowly to 0 °C and then partitioned between water and ethyl acetate. The organic layer was washed twice with a saturated, aqueous solution of potassium sodium tartrate and then concentrated, leaving 62 mg (72%) of crude lactol **23**,

used without further purification. The ^{13}C spectrum was consistent with the presence of two isomers, epimeric at C-4, in approximately equal amounts.

(±)-Sarracenin (1). A solution of 91 mg (0.43 mmol) of crude lactol **23** in 20 mL of methylene chloride was ozonized with 1 equiv of ozone in oxygen at −78 °C. After removal of the solvent the oily residue was dissolved in 5 mL of glacial acetic acid and 84 mg (1.3 mmol) of zinc dust was added. After being stirred at room temperature for 70 min, the mixture was cooled and filtered through a layer of celite and then heated at 70 °C for 1 h. The solvent was removed under high vacuum to give 134 mg of an oil. Pure sarracenin was obtained by preparative layer chromatography (3:1 Skelly B–ethyl acetate) and could be crystallized from hot Skelly B to give very small white needles, mp 107–108 °C (lit.[2] for (+)-sarracenin, 127–128 °C dec), by ^1H and ^{13}C NMR, IR, and UV spectral analysis identikcal with that of an authentic sample.[16]

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Synthesis of (5*Z*)- and (5*E*)-6,9-Thiaprostacyclins

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Abstract: The stereospecific synthesis of (5*Z*)- and (5*E*)-6,9-thiaprostacyclins **1** and **2** from readily available prostanoid precursors is described. The key intermediates for the syntheses are the (5*Z*)- and (5*E*)-9-thia-$PGF_{2\alpha}$ methyl ester derivatives **3** and **4**, respectively, which undergo facile iodine-induced and stereospecific cyclization via sulfenyl iodide intermediates. Finally, base-induced E2 trans-type elimination of hydrogen iodide leads selectively to the desired (5*Z*)- and (5*E*)-thiaprostacyclin derivatives.

In 1976, Vane and his associates[2] reported that microsomal fractions of arterial walls transformed prostaglandin endoperoxides (PGG_2 and PGH_2) biosynthetically derived from arachidonic acid (AA) (Figure 1) into an unstable substance found to be an extremely potent inhibitor of blood platelet aggregation and a powerful vasodilator. This substance, initially termed PGX, is one of the most recently discovered[3] biosynthetic products of the arachidonic acid cascade[3,4] and together with thromboxane A_2[5] (Figure 1) constitutes two of the most important biomolecules of this metabolic pathway. The structure of PGX had first been postulated by Pace-Asciak and Wolfe[6] in 1971, but unfortunately it was neither isolated nor its biological importance recognized at that time. It was Johnson's elegant work[4,7,8] that led to the structural elucidation of PGX and its relationship to its degradation product 6-keto-$PGF_{1\alpha}$ previously reported by Pace-Asciak in 1976.[9] This important biomolecule is now recognized as 6,9α-oxido-11α,15α-dihydroprosta-5(*Z*),13(*E*)-dienoic acid and is referred to as prostaglandin I_2 (PGI_2) (Figure 1) or prostacyclin due to its second ring which distinguishes it from the primary prostaglandins.

Prostacyclin is a rather unstable molecule (chemical and biological half-lifes at pH 7.4 of a few minutes), its instability arising from the presence of the enol ether functionality and enhanced by the carboxyl group. The methyl ester of prostacyclin is more stable than prostacyclin itself, and its sodium salt is perfectly stable at ambient temperatures.

The discovery of prostacyclin and the recognition of its vasodilatory and antiaggregating properties together with the discoveries related to thromboxane A_2 and its biological actions revolutionized current concepts of thrombosis and hemostasis. Moncada and Vane[10] have shown that prostacyclin is continuously generated from the prostaglandin endoperoxides H_2 and G_2 by the inner walls of blood vessels and is responsible for the maintenance of the integrity of blood vessel walls by inhibiting the adherence of platelets as well as preventing thrombus formation. Thromboxane A_2 (TXA_2, Figure 1) is also generated from the endoperoxides H_2 and G_2, but its production is concentrated in the platelets. Its biological actions are opposite of those of prostacyclin, namely, aggregating and vasoconstricting.[5]

The potent and important physiological actions of prostacyclin on the cardiovascular system suggested its potential use as a therapeutic agent and its low natural abundance created a need for an efficient synthesis. Due to independent efforts of several groups[8,11] prostacyclin in various forms is now available in large quantities. Its instability, however, dictated the need for the design and synthesis of more stable analogues of prostacyclin. In this series of papers we describe the synthesis of a number of prostacyclins that fulfull this stability requirement. Most of these novel prostacyclins were constructed by new methodology specifically designed for their synthesis.

In this report we describe the synthesis of both the *Z* (natural) and the *E* isomers of 6,9-thiaprostacyclin in which the ring oxygen of prostacyclin has been replaced by a sulfur atom.[12] The ra-

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