mixture was allowed to warm to room temperature and its volume then reduced to half on a rotary evaporator. When chilled in a −78 °C bath, the solution deposited 4.2 g (91%) of fine white solid. Recrystallization from methanol gave pure **2**: mp 131–134 °C; IR (KBr) $\nu_{C=O}$ 1690, ν_{SO_2} 1320 and 1130 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Table I. Anal. Calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; S, 15.70. Found: C, 46.91; H, 5.81; S, 15.67.

A bis(2,4-dinitrophenylhydrazone) precipitated instantly on mixing a hot solution of 0.8 g (0.004 mol) of 2,4-dinitrophenylhydrazine, 4 mL of concentrated H_2SO_4, and 6 mL of water with a solution of diketone **2** (0.4 g, 0.0020 mol) in 25 mL of ethanol. The difficultly soluble, bright orange solid, mp 204–206 °C, was analyzed directly.

Anal. Calcd for $C_{20}H_{20}N_8O_{10}S$: C, 42.55; H, 3.57; N, 19.85; S, 5.68. Found: C, 42.84; H, 3.53; N, 19.96; S, 5.58.

Crystal Data: $C_8H_{12}O_4S$ (**2**), mol wt 204.25; orthorhombic, a = 8.963 (4) Å, b = 15.403 (7) Å, c = 6.724 (3) Å, U = 928.3 Å^3, d_{measd}(flotation) = 1.45 g cm^{-3}, Z = 4, d_{calcd} = 1.461 g cm^{-3}, $F(000)$ = 432; Cu Kα radiation, λ = 1.5418 Å; absorption coefficient for Cu Kα radiation, μ = 28.9 cm^{-1}. Space group $P2_12_12_1$ (D_2^4) was uniquely established from the systematic absences $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

Crystallographic Measurements. Preliminary unit cell parameters and space group information were obtained from oscillation and Weissenberg photographs taken with Cu Kα radiation and precession photographs taken with Mo Kα (λ 0.7107 Å) radiation. For intensity measurements a crystal of dimensions ca. 0.20 × 0.36 × 0.40 mm was oriented on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu Kα radiation). Refined unit cell dimensions were derived by least-squares treatment of the θ, χ, and ϕ angles for 40 reflections widely separated in reciprocal space. One octant of intensity data to θ = 67° was surveyed by means of the θ–2θ scanning procedure with scan widths (0.90 + 0.40 tan θ)°; stationary background measurements were recorded at each end of the scan range for half the scan duration. Instrument and crystal stability were monitored throughout by remeasuring the intensity of a reference reflection after each batch of 99 reflections; no significant variation was noted. From a total of 1002 independent intensity measurements only those 913 for which $I > 2.0\sigma(I)$ [$\sigma^2(I)$ = scan count + total background count] were corrected for the usual Lorentz and polarization effects. Absorption corrections, derived from the ϕ dependence of the intensity of the 0,12,0 reflection measured at χ = 90°, were also applied to these data prior to their use in the structure analysis and refinement.

Structure Analysis. The structure was solved with difficulty by direct methods by use of MULTAN.[19] A seven-atom sulfur-containing fragment, obtained from the E map computed by using the phase angle set which gave the highest figure of merit and lowest residual, was used to phase a subsequent F_o Fourier map (R^{20} = 0.418) which yielded positions for the remaining nonhydrogen atoms. Full-matrix least-squares refinement of atomic positional and isotropic thermal parameters reduced R from 0.241 to 0.082, and, when allowance was made for anisotropic thermal motion, R decreased further to 0.063. Hydrogen atom positions were then obtained from a difference Fourier synthesis and their positional and isotropic thermal parameters were included as variables in the subsequent least-squares iterations. In addition, when the anomalous scattering corrections for sulfur were included in the structure factor calculations, R for the coordinates corresponding to those listed in Table II was significantly lower than for the mirror image and so all later refinement was based on this coordinate set. Following several further rounds of least-squares adjustment of positional and thermal parameters, the refinement converged at R = 0.032. A listing of observed and calculated structure amplitudes (Table VII) is available as supplementary material.

In all structure factor calculations the atomic scattering factor for hydrogen was taken from ref 21 and for carbon, oxygen, and sulfur from ref 22 with that of sulfur corrected for anomalous scattering effects.[12b] In the least-squares iterations, $\sum w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized with weights, w, assigned according to the following scheme: $(w)^{1/2} = 1$ when $|F_o| < 6.5$ and $(w)^{1/2} = 6.5/|F_o|$ when $|F_o| > 6.5$. The adequacy of this scheme was demonstrated by the fact that $\langle w\Delta^2 \rangle$ showed no systematic dependence when analyzed in ranges of $|F_o|$.

Registry No. **2**, 71138-48-2; **2** bis(DNP), 71138-49-3; *cis*-**3**, 610-09-3; *cis*-**4**, 71138-50-6; *cis*-**5**, 71138-51-7; *cis*-**6**, 71138-52-8; **7**, 2819-48-9; **8**, 55370-42-8.

Supplementary Material Available: Tables of anisotropic thermal parameters (Table IV), hydrogen atom parameters (Table V), and observed and calculated structure amplitudes (Table VII) and a packing diagram of molecules of **2** in the crystal (Figure 2) (9 pages). Ordering information is given on any current masthead page.

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Synthesis of (+)-*cis*-1-Methoxy-4β-carbomethoxy-4a,5,8,8a-tetrahydroisochroman, a Synthon for the Preparation of Alkaloids and Iridoids

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A synthesis of (+)-*cis*-1β-methoxy-4β-carbomethoxy-4a,5,8,8a-tetrahydroisochroman (**3b**) is carried out in seven steps from furfuryl alcohol in 8–16% overall yield. Detailed analyses of the ^{1}H NMR spectra of two intermediates prepared during this synthesis, **5b** and 1α-OMe-**6b**, plus other chemical evidence reveal that a preliminary report[7] concerning the preparation of **3b** and **5b** contained an incorrect assignment of relative stereochemistry. The results of the present study enable a correction of one literature report[8] describing the synthesis of **5b**. The bicyclic compound **3b** represents a potentially useful synthon for the preparation of certain indole alkaloids and iridoids.

Our continuing interest in the biosynthesis and pharmacology of several naturally occurring indole alkaloids and cyclopentanomonoterpenoids (iridoids) that have antitumor activity led us to consider the preparation of synthons that would be useful for the total synthesis of such natural products. Although our immediate objectives are the synthesis of the algucons of 16,17-dihydrostrictosamide (**1**) and of 3,4-dihydrosecologanin (**2**), we also

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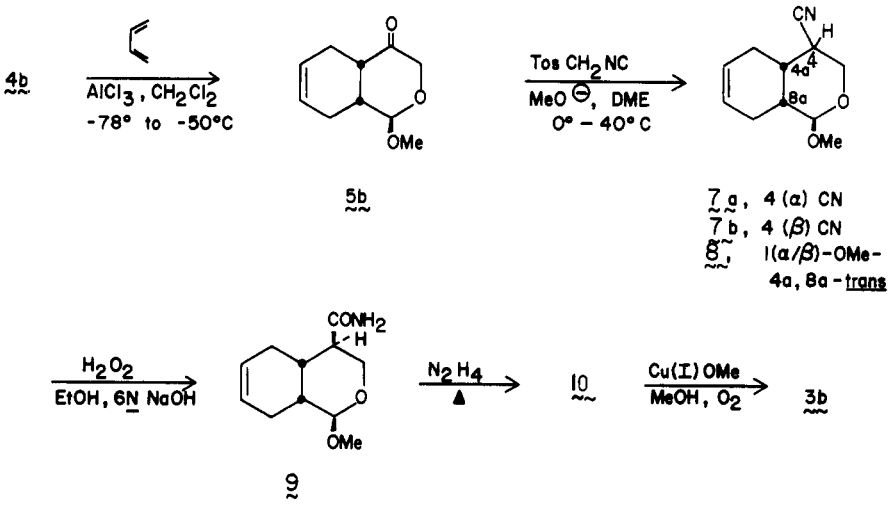
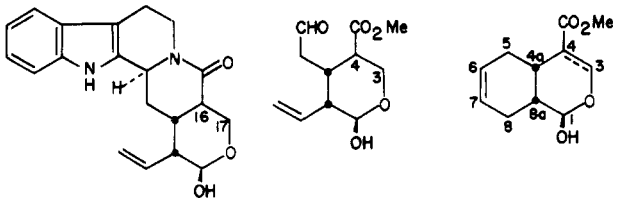
Scheme I



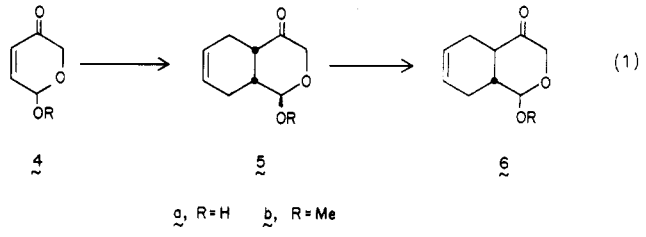
intend to use the synthons for preparation of camptothecin analogues,[2] xylomollin,[3] sarracenin,[4] and other biologically active iridoids.



We envision that a synthetic strategy should involve 4-substituted analogues of either the 1-hydroxy-4a,5,-8,8a-tetrahydroisochromene (**3a**) or -isochroman (**3b**) ring systems. This approach is attractive because it would give the desired relative stereochemistry at three key centers [C(1), C(4a), C(8a)] and because these two ring systems should be available by three different routes: from 1,4-cyclohexadiene and methyl diformylacetate by photochemical annulation,[5] from butadiene and 2-hydroxy-5-oxo-5,6-dihydro-2*H*-pyran by Diels–Alder annulation, and from (−)-*cis*-2-hydroxymethylcyclohex-4-enecarboxylic acid lactone[6] by suitable ring homologation reactions. Our synthesis of the secoiridoid aglucon acetals, (±)-1-methoxysecologanin and (±)-1-methoxysweroside, from **3a** in collaboration with a Hoffman–LaRoche group is a realization of the first synthetic strategy.[5] We report now the realization of the second synthetic strategy by a synthesis of the (+)-*cis*-1β-methoxy-4β-carbomethoxy-4a,5,8,8a-tetrahydroisochroman synthon (**3b**). New information obtained during the execution of this synthesis allows us also to report an important correction of results published in a preliminary account of some of this work.[7]

Results and Discussion

The synthesis of **3b** we described originally was based on the 1974 paper of Jones[8] in which 2-hydroxy-5-oxo-5,6-dihydro-2*H*-pyran (**4a**) was reported to react with several dienophiles in noncatalyzed Diels–Alder reactions (eq 1). Treatment of the primary Diels–Alder adducts (**5a**



(1)

and others) with methanol and acid give their 1-*O*-methyl acetals, which were characterized by their boiling points and GLC retention times and by partial spectral analyses.[8] A detailed analysis of the ^1H NMR spectrum of the bicyclic adduct of **4a** and cyclopentadiene revealed that this product had the expected cis-endo relative stereochemistry at the ring junction between the pyran ring and norbornene system, with the C(1) methoxy group oriented to the convex face of the molecule. The bicyclic adducts of **4a** and symmetrically substituted butadienes gave mixtures of C(1) epimers on conversion to their *O*-methyl acetals, whose spectral characteristics were stated to be consistent "with the stereochemistry of the ring junction [being] exclusively *cis* in all isomeric pairs".[8] On the basis of this report, we assumed that the C(4a) and C(8a) hydrogens of **5b**, prepared according to Jones, were cis when making the assignment of relative stereochemistry in **5b** and products derived from it under nonepimerizing conditions in our preliminary publication.[7] Subsequent work has revealed, however, that although the Diels–Alder adduct of **4a** and butadiene, compound **5a**, does have the cis-fused bridgehead proton relative stereochemistry, the 1-*O*-methyl acetals derived from **5a** (compounds **6b**) according to Jones' procedure[8] have their C(4a) and C(8a) hydrogens trans oriented.

Modification of our original synthetic route[7] to **3b** resulted in the development of a more efficient and con-

(1) Research Career Development Awardee of the National Institutes of Health (Grant No. CA 00253), 1976–1981.

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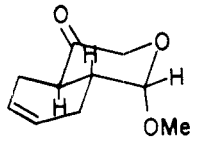
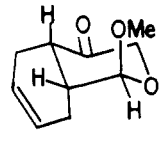
(8) Jones, G. *Tetrahedron Lett.* **1974**, 2231.

venient preparation of this key compound (Scheme I). We found that anodic oxidation of furfuryl alcohol in a methanolic solution of NH_4Br according to Clausen-Kaas[9] followed by treatment of the resulting distilled 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol with 97% formic acid in anhydrous methanol[10] gave **4b** in 52–62% overall yield. This 1-*O*-methyl acetal underwent a Lewis acid catalyzed Diels–Alder reaction with excess butadiene in CH_2Cl_2 at low temperature to give **5b** in 80–90% yield.

We presumed that **5b** obtained in this manner would be identical with the analogous bicyclic ketone *O*-methyl acetal prepared by the earlier route,[7] except for its C(1) relative stereochemistry. However, comparison of spectral and physical characteristics (VPC retention times, melting point of methoxysemicarbazole derivatives) indicated that the two routes resulted in bicyclic ketone *O*-methyl acetals that were epimeric at two positions, C(1) and C(4a). Detailed analysis of the high-field ^1H NMR spectra of **5b** and 1α-OMe-**6b** showed that the bridgehead hydrogens of **5b** are cis ($J_{4a,8a} \simeq 3.6$ Hz), whereas those of 1α-OMe-**6b** are trans ($J_{4a,8a} \simeq 8$ Hz).[11a] The small vicinal coupling constants for H(1) and H(8a) in both **5b** and 1α-OMe-**6b**, 2.4 and 2.6 Hz, respectively, are consistent with their cis relative stereochemistry. According to the aliphatic Karplus equation,[11b] these $^3J_{HH}$ values are consistent with the solution conformation A for **5b** and B for 1α-OMe-**6b**.



B



A

Thus, the relative stereochemistry of **5b** agrees with expectations based on the Diels–Alder endo rule,[8,12] whereas the relative stereochemistry of **6b** must be the result of thermodynamic control during acetalization of **5a** under acidic conditions.[7,8] Conversion of 1-*O*-acetyl-**5a**, prepared from **5a**[8] or **5b**, into all four possible C(1),C(4a) diastereomers of **5b** or **6b** by treatment with acidic methanol confirmed the latter interpretation.[13] Correspondingly, **5b** was epimerized to 1β-OMe-**6b** by NaOMe/MeOH-d_1, whereas **6b** was unchanged, although both ketones incorporated three deuterium atoms.

With the stereochemical relationships between **5b** and **6b** clarified, we attempted to carry **5b** through to **3b** by the homologation method of Ziegler and Wender[14] as was done earlier for 1α-OMe-**6b**.[7] Although this method works very well with either C(1) epimer of **6b**, neither it nor the related homologation method of Reese[15] gave the C(4) nitrile homologue of **5b**. In distinct contrast, reaction of **5b** with tosylmethyl isocyanide (TosMIC) according to Oldenziel et al.[16] smoothly gave **7** in excellent yield (67–75%) without detectable C(4a) epimerization. When the homologation reaction was conducted at ice-bath temperatures, **7a** was the predominant product; as the reaction temperature was raised, **7a** disappeared and **7b** became the major product. This was the only isomer formed when the reaction was run at room temperature or above. On the basis of the $^3J_{4,4a}$ values of 3.6 Hz for **7a** and 9.0 Hz for **7b**, it appears that the C(4) nitrile in **7a** is axial and in **7b** equatorial. Thus, **7a** must be the product of kinetic protonation of an intermediate C(4) carbanion,[16a] and **7b** the thermodynamic product, which is formed under the basic conditions of the TosMIC homologation reaction.[16] This interpretation is consistent with similar observations in other systems.[14,16a]

The conversion of the C(4) nitriles **7** and **8** to their carbomethoxy analogues was not a trivial process because of the compounding factor of a ring-opening alternative (eq 2) leading to UV-absorbing products such as **12**.[7] Our

(2)

11 12

original methods using strongly basic reaction conditions gave the two C(4) epimers of 4a,8a-*trans*-**3b** from **8** in 39% (4α CO_2Me) and 47% (4β CO_2Me) overall yield[7] but gave only UV-absorbing products when applied to **7b**. However, our requirements were met nicely by the method of Tsuji et al.[17] since **7b** gave its C(4) acyl hydrazide analogue **10** readily (66%) via the intermediate C(4) carboxamide **9**. Oxidative conversion of **10** by treatment with Cu^IOMe and air in methanolic solution[17] gave **3b** in 50% yield. Although the yield of the last step of this three-step process was moderate, it offers a useful alternative to the more familiar imidate method[18] for the CN → CO_2Me conversion. Both methods worked well (90%) for the preparation of 1-carbomethoxy-3-cyclohexene from 3-cyclohexene-1-carbonitrile.[13]

Conclusion

We have developed an efficient synthesis of a synthon, **3b**, that can be carried out in 8–16% overall yield from furfuryl alcohol in seven steps. This compound should be capable of elaboration into iridoids, secoiridoids, and certain indole alkaloids based on our literature precedent.[5] These are goals that we aim to achieve in extensions of the present study.

Experimental Section

General Methods. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. Mass spectra were obtained on a Finnigan Model 1015 spectrometer with a Model 6000 data processing unit. Mass spectra of selected samples were run on a DuPont 21-491B mass spectrometer interfaced to a Varian 2740 GC and a Nova 2 data system. Nuclear magnetic resonance spectra were taken in $CDCl_3$ on Varian EM-390 and Bruker 90- or 270-MHz NMR spectrometers. Chemical shifts are reported in ppm from Me_4Si. IR data were obtained from Perkin-Elmer Models 257 and 557 recording spectrophotometers. UV spectra were obtained from a Cary Model 14 recording spectrophotometer. Column chromatography utilized MN silica gel, 70–270 mesh. TLC was performed on Brinkman precoated silica gel F-254 plates, the spots being visualized under UV light or by potassium permanganate spray (2% in water). Organic

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extracts were dried over anhydrous $MgSO_4$. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Rotary evaporation was done on a Buchi rotary evaporator at reduced pressure with either a water aspirator or an oil pump.

2-Methoxy-5-oxo-5,6-dihydro-2*H*-pyran (4b). 2,5-Dimethoxy-2,5-dihydrofurfuryl alcohol (19.2 g, 0.12 mol), prepared by the method of Clausen-Kaas,[9] was mixed with 8 mL of anhydrous MeOH (0.25 mol) and the solution poured into a dropping funnel. HCO_2H (97%, 80 mL, 1.7 mol) was combined with 4 mL of freshly distilled MeOH in a single-necked, 250-mL, round-bottom flask. The system was protected from moisture with a drying tube on top of the addition funnel. The solution in the dropping funnel was added over a 15-min period to the rapidly stirred MeOH–HCO_2H solution at room temperature. After the addition was complete, the reaction was allowed to stir for 5 min more, and then it was poured into 200 mL of H_2O and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were washed with $NaHCO_3$ solution (100 mL) and then brine (100 mL) and dried. After filtration and removal of the solvent, crude **4b** was obtained as a colorless liquid (12.3 g, 0.096 mol, 80%).[20] The crude product was found to be pure enough for subsequent work, especially with regard to the low content of its C(4) ketal.

***cis*-1β-Methoxy-4a,5,8,8a-tetrahydroisochroman (5b).** The dienophile **4b** (7.523 g, 0.0587 mol) was dissolved in CH_2Cl_2 (75 mL) and poured into a jacketed dropping funnel, the jacket of which was cooled to −70 to −80 °C with dry ice and ethanol. The dropping funnel was connected to an oven-dried, three-necked, 500-mL, round-bottom flask into which butadiene (97 mL, 1.79 mol, 35 equiv) had been condensed and mixed with CH_2Cl_2 (redistilled, 175 mL) and $AlCl_3$ (3.0 g, 22.5 mmol, 0.38 equiv). The flask and dropping funnel were purged with dry nitrogen, and the reaction mixture was stirred magnetically. The round-bottom flask was cooled to −78 °C in an ethanol–dry ice bath. After sufficient time to allow for thorough cooling, the solution in the dropping funnel was run into the solution of butadiene and $AlCl_3$. This took about 10 min, care being exercised that good stirring and cooling were maintained during the addition. After completion of the addition of **4b**, the reaction mixture was stirred for an additional 10 min before being warmed to −50 °C by replacing the dry ice–ethanol bath with one containing chloroform–dry ice. The reaction mixture was stirred for about 1.0 h more at this temperature. The reaction's progress was followed by TLC using EtOAc–hexane (1:3) as a solvent system. Aliquots were quenched immediately with aqueous $NaHCO_3$ before TLC analysis; otherwise, the aliquots continued to react rapidly at room temperature and indicated premature progress of the reaction.

After completion of the reaction, the cold reaction mixture was poured into a magnetically stirred, 2-L beaker containing crushed ice and $NaHCO_3$ solution (1 L total). The quenched reaction mixture was allowed to warm up to room temperature, and then it was suction filtered through a 15-cm Buchner funnel containing 9.0 g of Celite. The aqueous filtrate was extracted with CH_2Cl_2 (3 × 175 mL), and the combined organics were washed once with $NaHCO_3$ solution (100 mL) and once with brine (100 mL). The organic solution was dried for 30 min and filtered and the solvent removed. The crude product was fractionally distilled through a 2.5-cm Vigreux column attached to a short-path distillation apparatus to give **5b** as a fraction distilling between 130 and 134 °C at 10–12 torr (9.11 g, 50.0 mmol, 84%): pale yellow liquid; TLC (EtOAc–hexane 1:3) R_f 0.70; IR ($CHCl_3$) ν 2900, 1720 (C=O), 1370 cm^{-1}; ^1H NMR δ ca. 2.15 (m, 3 H), 2.30–2.90 (m, 2 H), 2.47 (m, 1 H, H-8a), 3.11 (m, 1 H, H-4a), 3.47 (s, 3 H, OCH_3), 4.00 (A Bq, 2 H, J = 16.5 Hz, CCH_2O), 4.58 (d, 1 H, J = 3 Hz, acetal proton), 5.57 (s, 2 H, vinyl protons). Anal. ($C_{10}H_{14}O_3$) C, H.

***cis*-1-Methoxy-4-cyano-4a,5,8,8a-tetrahydroisochromans (7a and 7b).** Our experience with the tosylmethyl isocyanide reagent (TosMIC) has shown that this is a capricious reaction and one that can be controlled only by carefully defined experimental procedures.

TosMIC, as it comes from Aldrich Chemical Co., Inc., has been found to contain as much as 30% impurities. These impurities are deleterious and must be eliminated if present. Purification of this reagent was accomplished in the following manner. TosMIC (5.0 g, 0.026 mol) was dissolved in 50 mL of anhydrous MeOH at room temperature, and half of the solvent was removed by rotary evaporation at 35 °C. Crystallization occurred rapidly, and the mother liquor was filtered off and saved for recovery of additional crops of crystals. The first crop of crystals was collected quickly and dissolved in 20 mL of CH_2Cl_2. This solution was suction filtered through a pad of neutral alumina (9.0 g). After the primary filtration, the filter pad was washed with CH_2Cl_2 (8 × 15 mL) to remove the last traces of TosMIC. Rotary evaporation of the solvent led to the formation of a white, platelike solid which was broken up and dried by vacuum desiccation on the high-vacuum line for 6.0 h at 25 °C. The weight of recovered solid was 3.43 g (68% yield); mp 114–115 °C (lit.[16a] mp 114–116 °C).

A sample of **5b** (1.34 g, 7.4 mmol), purified TosMIC (1.575 g, 1.1 equiv), 1,2-dimethoxyethane (70 mL, freshly distilled over CaH or $LiAlH_4$), and 0.5 mL of anhydrous MeOH (2 equiv, relative to TosMIC) were added to a dry, 250-mL, round-bottom flask equipped with a stirring bar and flushed with N_2. After the flask was cooled to 0–5 °C with a water–ice bath, fresh, solid KO-*t*-Bu (1.814 g, 2 equiv, relative to TosMIC) was quickly added to the stirred solution. The reaction immediately turned a bright rusty red and was stirred at 0–5 °C for an additional hour. At this time TLC (EtOAc–hexane 1:3) showed one major non-UV-absorbing spot (R_f 0.67). If this reaction mixture was then allowed to warm to room temperature for 15 min, a second spot forms with a high R_f (0.78). If the solution was warmed for 15 min more at 40 °C, the lower R_f spot disappeared. This particular reaction was warmed to 22 °C and allowed to stir for an additional 30 min. The reaction mixture was then quenched with 20% HOAc (0.25 mL). The pH of the solution dropped to 6.5 (test paper), the treatment with dilute acid having solubilized the precipitated salts to form a brownish liquid. Then, 90% of the solvent was removed by evaporation. CH_2Cl_2 (75 mL) was added to remove the soluble material from the reaction flask, the reaction flask was then washed with H_2O (40 mL), and the organic and inorganic solutions were combined in a 250-mL separatory funnel. The aqueous phase was extracted with more CH_2Cl_2 (2 × 75 mL), and the combined organics were washed with $NaHCO_3$ solution (50 mL) and dried. After filtration, most of the solvent was removed and the yellowish concentrate (1.6 mL) put onto a 40 × 2 silica gel column and eluted with an Et_2O–hexane (1:1) solvent system. The fractions containing the desired products were evaporated to give **7b** (215 mg, R_f 0.78), **10a** (644 mg, R_f 0.67), and a mixed fraction of **7a** and **7b** (69 mg); total yield 67% (yields were found to vary from 40 to 75%).

7a: IR (film) ν 2900, 2830, 2240 (CN), 1650 (C=C), 1435 cm^{-1}; ^1H NMR δ 1.85–2.60 (m, 6 H), 2.82 (q, 1 H, J = 5 Hz, CHCN), 3.44 (s, 3 H, OCH_3), 3.97 (q of d, 2 H, J = 18 and 6 Hz, CCH_2O), 4.43 (d, 1 H, J = 5 Hz, acetal proton), 5.73 (s, 2 H, vinyl protons); mass spectrum, m/e (rel intensity) 193 (M^+, 22), 161 (24), 132 (20), 113 (50), 80 (100).

7b: IR ($CHCl_3$) ν 2242 (CN), 1600 (C=C), 1440 cm^{-1}; ^1H NMR δ 2.30–3.00 (m, 7 H), 3.39 (s, 3 H, OCH_3), 3.88 (d, 2 H, J = 8 Hz, CCH_2O), 4.42 (s, 1 H, acetal proton), 5.67 (s, 2 H, vinyl proton); mass spectrum, m/e (rel intensity) 193 (M^+, 22), 161 (16), 138 (8), 80 (100). Anal. ($C_{11}H_{15}O_2N$) C, H, N.

Amide of 7b (9). To a 50-mL round-bottom flask equipped with a stirring bar and reflux condenser were added a mixture of **7a** and **7b** (611 mg, 3.2 mmol), EtOH (15 mL, 100%, commercial), H_2O_2 (30%, 3 mL), and NaOH solution (6 N, 0.3 mL). The resulting pH of the reaction mixture was ca. 7.6. The reaction mixture was refluxed at 75–90 °C, the pH being monitored every 10 min. When the pH dropped below 7.5, enough 6 N NaOH was added to raise the pH to about 8.0. After 2.0 h, TLC indicated that the reaction was about 95% completed. The peroxides were reduced by addition of a saturated aqueous solution of $Na_2S_2O_3$ (15 mL), and the reaction mixture was reduced to one-third of its volume by rotary evaporation. The resulting mixture was mixed with CH_2Cl_2 (30 mL) and transferred to a 125-mL separatory funnel. Another 30 mL of CH_2Cl_2 was added, and the solution was washed with saturated NaCl solution (25 mL). The brine was extracted with CH_2Cl_2 (3 × 80 mL), and the combined organics were dried. After filtration, the solvent was removed to give only **9** (548 mg, 81%) as a white solid. The crude material

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was recrystallized from MeOH to give long, clear spar crystals: mp 200–204 °C; TLC (EtOAc–hexane, 1:1) R_f 0.33; IR ($CHCl_3$) ν 3520 (NH_2), 3405 (NH_2), 2900, 1680 (C=O), 1588 (C=C) cm^{-1}; ^1H NMR δ ca. 1.7 (br, 1 H), ca. 2.1 (s, 4 H), ca. 2.3 (br, 2 H), 3.40 (s, 3 H, OCH_3), 3.88 (d, 2 H, J = 8 Hz, CCH_2O), 4.40 (s, 1 H, acetal proton), 5.63 (s, 2 H, vinyl protons); mass spectrum, m/e (rel intensity) 211 (M^+, 10), 191 (9), 189 (14), 179 (40), 72 (100). Anal. ($C_{11}H_{17}O_3N$) C, H, N.

Acyl Hydrazide of 7b (10). A sample of **9** (200 mg, 0.95 mmol) was mixed with hydrazine hydrate (6 mL, 99%) and poured into a 20-mL, thick-walled Pyrex tube equipped with a stirring bar. After the tube was sealed under a water-aspirator vacuum, it was refluxed for 36 h in an oil bath at 160 °C. After the tube was opened, TLC (EtOAc–EtOH, 8:1) indicated that there was a 90% conversion of **9** and **10**. The solvent was removed by rotary evaporation at 75 °C, and the residue was dissolved into $CHCl_3$ (60 mL). This solution was transferred to a 125-mL separatory funnel and washed with brine (40 mL). The brine was then back-extracted with CH_2Cl_2 (2 × 50 mL), and the organics were combined and dried. After filtration, removal of the solvent gave **10** (176 mg, 82%) as a glassy liquid: TLC (EtOAc–EtOH, 8:1) R_f 0.50; IR ($CHCl_3$) ν 3440 (NH), 3320 (NH), 2959, 1668 (C=O), 1620 (C=C), 1500 cm^{-1}; ^1H NMR δ 1.80–2.90 (m, 9 H), 3.48 (s, 3 H, OCH_3), 4.03 (d, 2 H, J = 7 Hz, CCH_2O), 4.38 (d, 1 H, J = 7 Hz), 5.49 (s, 1 H, $NHNH_2$), 5.65 (s, 2 H, vinyl protons); mass spectrum, m/e (rel intensity) 210 (7), 194 (100), 179 (12), 163 (22), 69 (100). Anal. ($C_{11}H_{18}O_3N_2$) C, H.

***cis*-1β-Methoxy-4β-carbomethoxy-4a,5,8,8a-tetrahydroisochroman (3b).** Freshly cut sodium metal (60 mg, 0.0024 g-atom) was added to anhydrous MeOH (35 mL) in a dry, 100-mL, two-necked flask equipped with a stirring bar and protected by a N_2 atmosphere. Freshly prepared Cu^ICl[19] (240 mg, 2.4 mmol) was added to the mixture after complete solubilization of the sodium. The solution immediately turned blue. This solution was stirred for about 5 min, and a bubbler, connected to an oxygen tank, was inserted through the vertical neck of the flask. Into the side neck of the flask was placed a 25-mL, pressure-equalizing dropping funnel charged with **10** (333 mg, 1.47 mmol) dissolved in anhydrous methanol (15 mL). This solution was dripped into the reaction flask over a 30-min period, during which time the vessel was well stirred and a vigorous stream of O_2 bubbled through it. After the addition, the reaction flask was swept with O_2 for 1 h more. The solvent was removed, and the resulting residue was dissolved in Et_2O (75 mL). This solution was poured into a 250-mL separatory funnel and washed with brine (80 mL). The brine solution was back-extracted with Et_2O (2 × 60 mL), and the organic extracts were combined and dried. After filtration, most of the solvent was removed by rotary evaporation and the concentrated solution put onto a 30 × 1.5 cm silica gel column and eluted with an Et_2O–hexane (1:3) solvent system. Evaporation of the fractions containing the product gave **3b** (168 mg, 50%) as a clear glasslike material. Despite repeated attempts, **3b** could not be recrystallized: TLC (Et_2O–hexane, 1:3) R_f 0.85; IR ($CHCl_3$) ν 2900, 1725 (C=O), 1512, 1440 cm^{-1}; ^1H NMR δ 2.10 (m, 4 H), 2.50–2.80 (m, 3 H), 3.38 (s, 3 H, OCH_3), 3.68 (s, 3 H, CO_2CH_3), 3.78 (m, 2 H, CCH_2O), 4.38 (s, 1 H, acetal proton), 5.60 (s, 2 H, vinyl proton); mass spectrum, m/e (rel intensity) 226 (M^+, 19), 211 (4), 194 (30), 164 (14), 79 (100). Anal. ($C_{12}H_{18}O_4$) C, H.

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Registry No. 3b, 71117-60-7; **4b**, 60249-17-4; **5b**, 71117-61-8; **7a**, 71117-62-9; **7b**, 71117-63-0; **9**, 71117-64-1; **10**, 71097-05-7; 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol, 19969-71-2; butadiene, 106-99-0; tosylmethyl isocyanide, 36635-61-7.

Synthesis and Chemistry of 2,11-Dehydro-5-homoadamantanone

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Tiffeneau–Demjanov ring expansion of 8,9-dehydro-2-adamantanone gives 2,11-dehydro-5-homoadamantanone (**9**). Wolff–Kishner reduction of **9** provides 2,11-dehydrohomoadamantane. Alternatively, this hydrocarbon can be prepared by photoreduction of 5-acetoxy-2,11-dehydrohomoadamantane. Treatment of the tosylhydrazone of **9** with methyllithium affords 2,11-dehydro-4-homoadamantene which undergoes a thermal vinylcyclopropane–cyclopentene rearrangement to give tetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undec-4-ene. Perchloric acid catalyzed addition of acetic acid to **9** provides 2-*endo*-acetoxy-5-homoadamantanone (**17**). The structure proof of **17** follows in part from the photoisomerization of 2-*endo*-hydroxy-5-homoadamantanone to 3-oxa-*endo*-tricyclo[6.3.1.$0^{2,6}$]dodecan-4-one. Addition of bromine to **9** gives 2,11-*diendo*-dibromo-5-homoadamantanone.

The carbon skeleton of homoadamantane (**1**) allows for five "non-bridgehead" dehydrohomoadamantanes, **2–6** (Scheme I). Three of these hydrocarbons have been synthesized: 2,4-dehydrohomoadamantane[2] (**2**), 2,5-dehydrohomoadamantane[3] (**3**), and 2,9-dehydrohomoadamantane[4] (**4**). We now wish to report the preparation of 2,11-dehydro-5-homoadamantanone (**9**) and some of the aspects of its chemistry, including the synthesis of the parent hydrocarbon **6**.

Results and Discussion

Cyclopropyl ketone **9** was readily generated by Tiffeneau–Demjanov ring expansion of 8,9-dehydro-2-adamantanone[5] (**7**). Treatment of **7** with trimethylsilyl

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