was no indication of the presence of a second diastereomeric allene.

**(1S,3S,6R)-9,10-Secocholesta-5(10),6,7,9(11),25-pentaene-1,3-diol (47).** Tetra-*n*-butylammonium fluoride (1 M in THF, 11 mL, 11 mmol) was added dropwise to a solution of stannylallene **46** (~978 mg, partially purified material from previous reaction) in THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 20 min, slowly warmed to room temperature, and then stirred for 14 h. Water (15 mL) was added, the mixture was extracted with diethyl ether (3 × 30 mL), and then the combined organic extracts were washed with brine (1 × 10 mL) and dried ($MgSO_4$). The crude material obtained after evaporation was purified by flash chromatography (silica gel, 4/1 ethyl acetate/hexanes) to obtain in order of elution a mixture of the 3-TBDMS protected diol and its 6*S* isomer (~297 mg) and a mixture of diol **47** and its 6*S* isomer **48** (192 mg). The partially protected material was dissolved in THF (5 mL) and stirred with fresh tetra-*n*-butylammonium fluoride (1 M in THF, 3.3 mL) at room temperature for 38 h. A similar workup as described above yielded an additional 120 mg of the diol mixture **47** and **48** (total crude yield, 312 mg). The ratio of 6*R* vinylallene to its 6*S* isomer was 10:1 [by $^1H$ NMR integration of the $C_{18}$-$CH_3$ signals at $\delta$ 0.74 (major 6*R* isomer) and $\delta$ 0.67 (minor 6*S* isomer)]. This mixture was separated by HPLC (Rainin Dynamax 2.24 × 25 cm, 5 μm silica gel column, 4/1 ethyl acetate/hexanes, 8 mL/min) to give in order of elution the desired 6*R* vinylallene **47** (183 mg) and slightly impure ($^1H$ NMR spectrum) 6*S* vinylallene **48** (~19 mg). The overall yield of the desired (1*S*,3*S*,6*R*)-vinylallene **48** was 47% from propargyl alcohol **44** (three steps).

**(1S)-9,11,25,26-Tetradehydro-1-hydroxyvitamin $D_3$ (49).** A solution of vinylallene **47** (43 mg, 0.108 mmol) in isooctane (11 mL) was refluxed under an argon atmosphere for 3.25 h. After cooling, the solvent was evaporated, and the residue was purified by HPLC (Rainin Dynamax 1 × 25 cm, 8 μm silica gel column, 7/3 ethyl acetate/hexanes, 3 mL/min) to afford in order of elution the vitamin **49** (28 mg, 65%) and an inseparable mixture of 7*Z*-pentaenes **50** and **51** (13 mg, 30%). The 7*Z* fraction was a mixture of $C_{10}$ epimers (10*S* and 10*R*) analogous to **27** and **28**. These minor components were not separated (they appeared under optimized conditions as overlapping peaks on the HPLC trace), but were characterized as a mixture: the major component eluted slightly faster than the minor component; the major and minor components were identified as the 10*S* and 10*R* isomers, respectively, by $^1H$ NMR analysis of the mixture (2.7:1.0 ratio by $^1H$ NMR integration). The ratio of vitamin **49** to 7*Z* isomers (by integration of the HPLC trace) was 2.3:1.0. The overall mass balance of the reaction after separation was 95%.

**1α,25-$(OH)_2$-$D_3$ Receptor Competition Assays.** The assay of competitive binding was performed using the hydroxylapatite batch assay.[31a,32] Increasing amounts of unlabeled 1α,25-$(OH)_2$-$D_3$ or analogue were added to a constant amount of [$^3H$]-1α,25-$(OH)_2$-$D_3$ and incubated with chick intestinal cytosol. The relative competitive index (RCI) for **5a** or **5b** was calculated by plotting the percent maximum 1α,25-$(OH)_2$-[$^3H$]-$D_3$ bound × 100 on the ordinate versus [competitor]/[1α,25-$(OH)_2$-[$^3H$]-$D_3$] on the abscissa. The slope of the line obtained for the analogue is divided by the slope of the line obtained for 1α,25-$(OH)_2$-$D_3$; multiplication of this value by 100 results in the RCI.[31a] By definition, the RCI for 1α,25-$(OH)_2$-$D_3$ is 100. For the preparation of intestinal cytosol from vitamin D-deficient chicks, the duodenal loop was removed after decapitation, stripped of contents, and washed at 4 °C in 0.9% NaCl solution. All subsequent steps were carried out at 4 °C as previously described.[31a]

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**Supplementary Material Available:** Spectral data for all new compounds and general experimental details (19 pages). Ordering information is given on any current masthead page.

# Total Synthesis of (±)-Dimethyl Secologanoside *O*-Methyl Ether

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The synthesis of the iridoid monoterpene (±)-dimethyl secologanoside *O*-methyl ether is described. The key steps include the anionic oxy-Cope rearrangement of an *endo*-vinylnorbornenol, lead tetraacetate oxidative cleavage of an α-hydroxy ketone to an aldehyde ester, and ozonolytic cleavage of a β,γ-unsaturated ester followed by zinc–acetic acid reduction of the ozonide to a hemiacetal.

The iridoids,[1] with ca. 300 known naturally occurring compounds, represent a large class of natural products. They usually occur as the glucoside and are important for the biosynthesis of some types of indole alkaloids.[2] In addition, some possess significant biological activity of their own.[3] Most of the members of these iridoids, such as secologanoside (**1a**),[4] sweroside (**2**),[5] loganin (**3**),[6] allamandin (**4**),[7] and specionin (**5**),[8] are highly oxygenated and densely functionalized. These characteristics may explain

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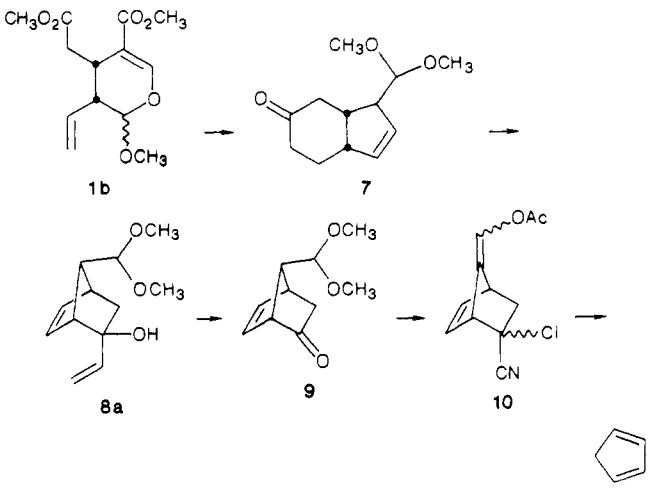
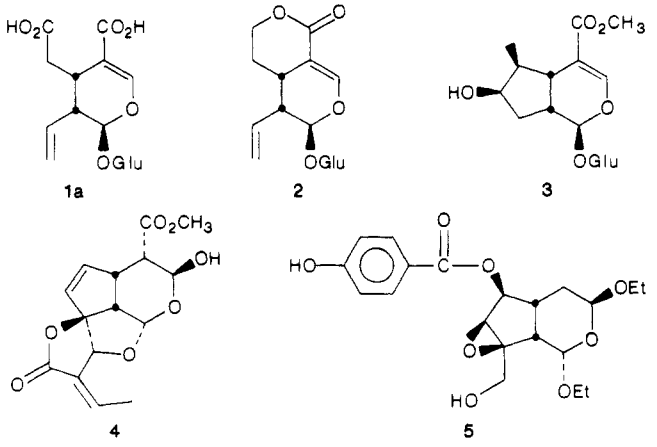
0022-3263/89/1954-4083$01.50/0 

**Scheme I**

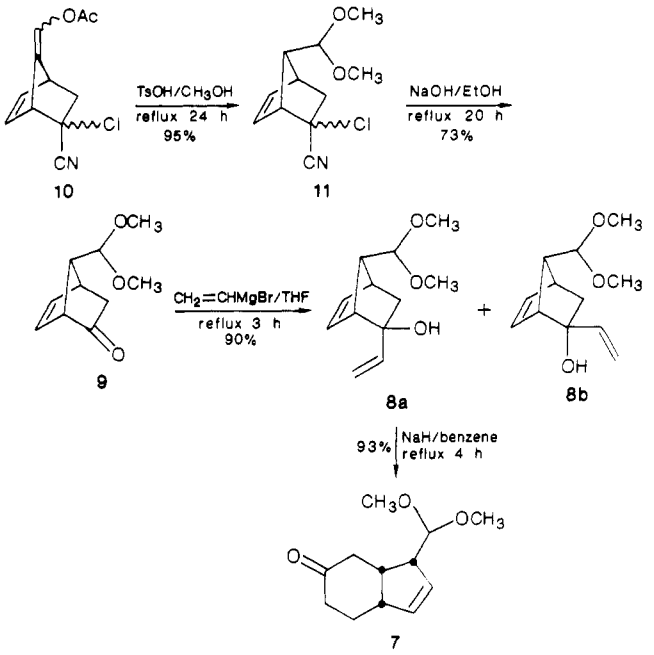


the considerable interest of synthetic organic chemists in these compounds.[9] We wish to describe here an efficient synthesis of (±)-dimethyl secologanoside *O*-methyl ether (**1b**).[4]

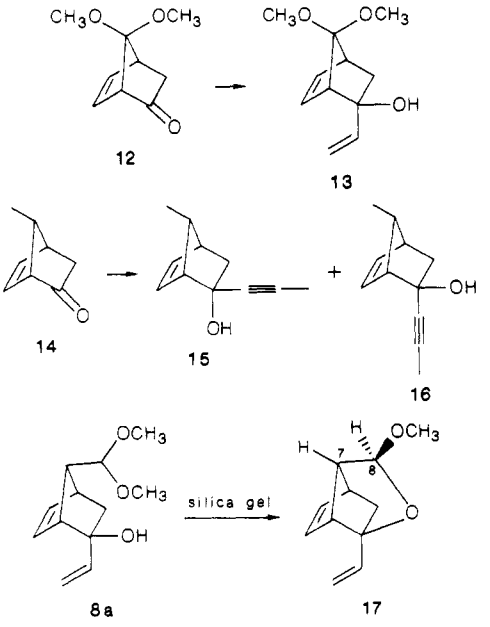


Our approach to secologanoside ether **1b** is based on the anionic oxy-Cope rearrangement of an *endo*-vinylnorbornenol **8a**, a method which had previously been reported to be an efficient means for construction of substituted *cis*-hydrindanones.[10,11] As shown in Scheme I, it was anticipated that **1b** would be available from **7**, which in turn would be produced upon anionic oxy-Cope rearrangement of the bicyclo[2.2.1]heptenol **8a**. The synthetic precursor of alcohol **8a** can be seen to be the bicyclo[2.2.1]heptenone **9**. The logical precursor of **9** was 7-(acetoxymethylene)bicycloheptenes **10**, and our synthesis thus began with the readily available **10**.[12]

**Scheme II**



**Scheme III**



The most convenient synthesis of **8a** is presented in Scheme II. In order to obtain the desired allyl alcohol (**8a**) for oxy-Cope rearrangement, the organometallic reagent should attack the carbonyl group of **9** from the endo face. Therefore the presence of a carbomethoxy equivalent substituent at C-7 syn to this carbonyl group was necessary. Treatment of the enol acetate of **10** with methanol in the presence of a catalytic amount of toluene-*p*-sulfonic acid provided the dimethyl acetal **11** in 95% yield.[13] Hydrolysis of the α-chloro nitrile in **11** with sodium hydroxide gave a single ketone **9**, the structure assignment of which is based on its $^{13}C$ and $^{1}H$ NMR spectra. There was no evidence that the 7-epimer was formed.

Vinylmagnesium bromide (1.2 equiv) was added to ketone **9** at 0 °C, and the mixture was stirred at 25 °C for 20 h or refluxed in tetrahydrofuran solution for 3 h and furnished a 2:1 endo/exo ratio of **8a**:**8b** in 90% yield. This

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(10) (a) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1984**, *25*, 5103. (b) Chang, N.-C.; Lu, W.-F.; Tseng, C.-Y. *J. Chem. Soc., Chem. Commun.* **1988**, 182.

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(13) Too much acid or prolonged reaction time enriched the 7-epimer.

result was unexpected since in a similar system reported by Jung,[11] compound **12** gave excluxively the endo vinyl adduct **13**, (Scheme III). The reason for our observed result is unclear. However, it is apparent that the bulky *exo*-7-(dimethyl acetal) group did not totally block exo approach to the carbonyl.[14] Nevertheless, this result did provide evidence that ketone **9** has the assigned structure, since in Fleming's report,[10] addition of a Grignard reagent to compound **14** gave 90% of the exo adduct **15**, with only 4% of the epimer **16**.

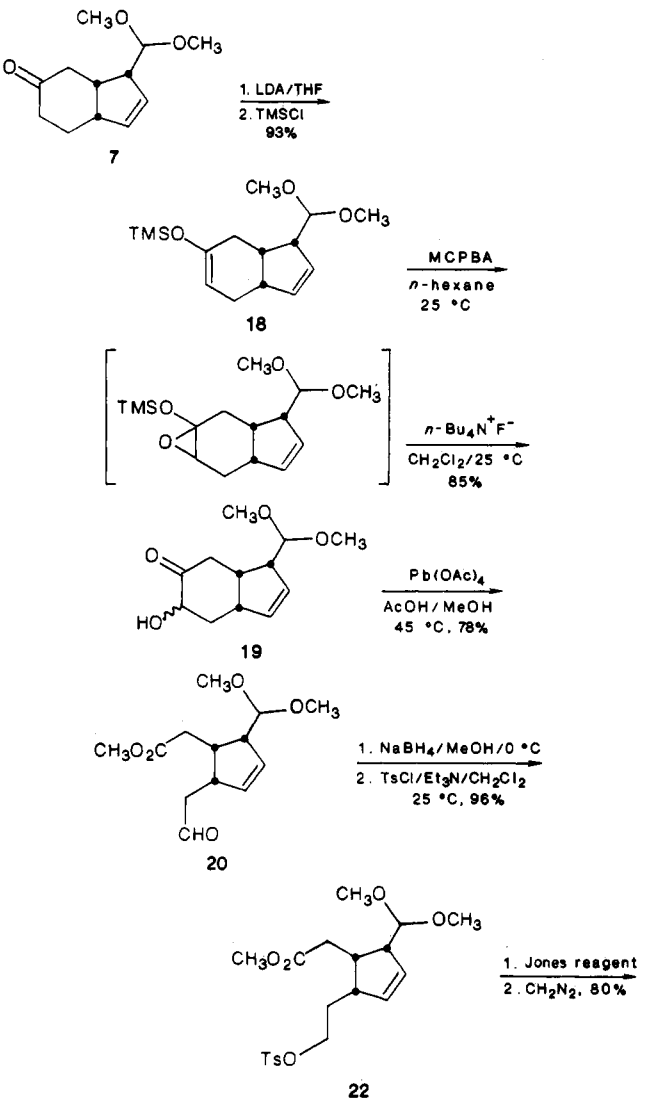
Passage of **8a** over unactivated silica gel gave a very nonpolar product. The structure of this compound is assigned as **17**, since in the $^1$H NMR spectrum there is only one methoxy peak and the 0-Hz coupling observed in **17** between protons H-7 and H-8 is in agreement with the structure. The formation of **17** provided further evidence that the dimethyl acetal function is **9** in "syn" to the carbonyl group. When allyl alcohol **8a** was treated with sodium hydride in boiling benzene for 4 h,[15] it underwent anionic oxy-Cope rearrangement to give the desired ketone **7** in 93% yield.[16] It was not surprising that the epimeric alcohol **8b** was recovered unchanged when subjected to the same conditions.

The conversion of **7** to the target molecule **1b** is shown in Scheme IV. Addition of ketone **7** to excess lithium diisopropylamide in tetrahydrofuran at −78 °C, followed by treatment with freshly distilled trimethylsilyl chloride, cleanly afforded the silyl enol ether **18**. Reaction of **18** with *m*-chloroperbenzoic acid (mCPBA), followed by desilylation with tetrabutylammonium fluoride or excess of aqueous sodium bicarbonate solution, furnished an α-hydroxy ketone **19** in 66–85% yield.[17] Attention was now directed to the ring cleavage of **19**. The α-hydroxy ketone **19** was oxidatively cleaved by treatment with lead tetraacetate in acetic acid and methanol solution. The resulting aldehyde ester **20** was subsequently reduced with sodium borohydride to yield hydroxy ester **21**.

Once in hand, the hydroxy ester (**21**) was converted into the corresponding tosylate **22** and purified by preparative TLC. It is crucial to perform the tosylation at this stage, since the alcohol group is protected from the oxidation reaction needed in the following procedure. A further advantage is that the tosylate function can be converted into the double bond, which is present in the target molecule.

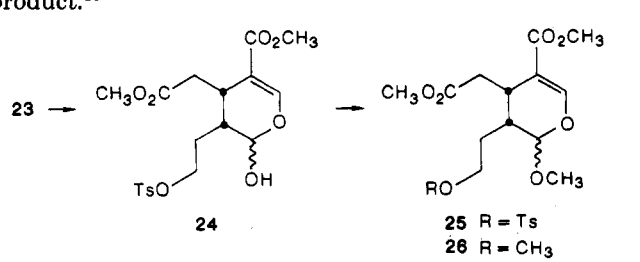
At this juncture, the remaining stages of the synthesis would require the formation of a carboxylic acid and oxidative cleavage of the alkene linkage to the dialdehyde. We were concerned about double bond migration during

**Scheme IV**



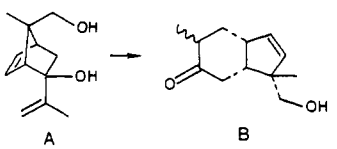

the acetal hydrolysis; however, after considerable effort it was found that addition of Jones reagent to **22** at 25 °C with stirring for 15 min led to rapid and clean hydrolysis and oxidation without migration of the double bond. Prolonged reaction time only enriched the undesired conjugated acid. Reaction of the β,γ-unsaturated acid with diazomethane furnished diester **23** in 75% yield.

It now seemed that the conversion of **23** to **1b** would be quite straightforward. However, it was initially problematic. Ozonolytic cleavage of **23** followed by zinc–acetic acid reduction of the ozonide afforded a hemiacetal (**24**). Treatment of **24** with a catalytic amount of acid in methanol at 24 °C resulted in the formation of **25** and **26** in which the undesired methyl ether **26** was the major product.[18]




(14) When **9** was treated with vinylmagnesium bromide in the presence of 1.5 equiv of HMPA a 7:1 endo/exo ratio of **8a**:**8b** in 60% yield was observed.

(15) Treatment of **8a** with potassium hydride in boiling THF gave only starting material. One possible explanation of the observation was that the presence of the bulky dimethyl acetal group on the exo face makes the endo face even more congested; thus, a higher temperature is required to force the vinyl group to enter the endo face and commence the proceed the rearrangement. Furthermore, compound A can be converted into B (unpublished result) at 25 °C. This result seems support our argument.

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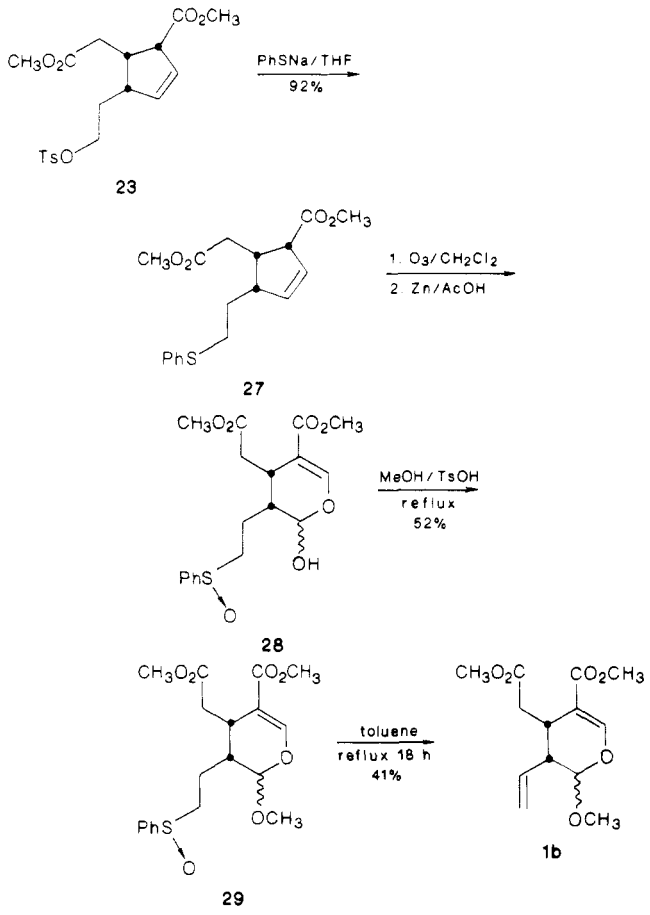
(17) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

(18) (a) Hutchinson, C. R.; Mattes, K. C.; Nakane, M. *Helv. Chim. Acta* **1978**, *61*, 1221. (b) Furnichi, K.; Abe, K.; Miwa, T. *Tetrahedron Lett.* **1974**, 3685.

**Scheme V**




In view of this disappointing but not totally unexpected result, it was apparent that the tosyl group should be replaced to avoid the undersired substitution. It is widely recognized that a sulfide cannot be substituted easily and that the corresponding sulfoxide can be pyrolyzed to form a double bond. When tosylate **23** was treated with sodium thiophenoxide, **27** was isolated in 92% yield. Exposure of the sulfide **27** to excess ozone at −78 °C followed by zinc–acetic acid reduction of the ozonide generated hemiacetal **28**. Without purification, **28** was treated directly with a catalytic amount of acid in methanol solution to give the acetal sulfoxide **29** in 52% yield from **27**. As anticipated, the sulfide in **27** was oxidized to sulfoxide in the ozonolysis procedure. Pyrolysis of **29** gave **1b** in 41% yield (see Scheme V).

The successful syntheses of (±)-dimethyl secologanoside *O*-methyl ether **1b** demonstrates the utility of the oxy-Cope rearrangement of *endo*-vinylnorbornenols for the synthesis of iridoids. Efforts directed toward the synthesis of other natural occurring iridoids are currently under way in our laboratories.

## Experimental Section

**Materials.** Ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzophenone and sodium. 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 anhydrous magnesium sulfate prior to concentration in vacuo. Crude products were purified by preparative TLC or column chromatography on silica gel. All reported temperatures are uncorrected. Elemental analyses were performed by Heraeus CHN-O-Rapid Analyzer. $^1H$ and $^{13}C$ NMR spectra were recorded on either a Varian EM 390 or a VXR 300-MHz instrument. The purity of all titled compounds was established to be >90% by inspection of $^1H$ and $^{13}C$ NMR spectra unless otherwise stated.

***anti*-7-(Dimethoxymethyl)bicyclo[2.2.1]hept-5-en-2-one (9).** A solution of **10** (55.6 g, 248.8 mmol), with a catalytic amount of *p*-toluenesulfonic acid (1.3 g) in methanol (150 mL) was heated at reflux for 24 h. After cooling to room temperature, an excess of solid $NaHCO_3$ was added. The mixture was stirred for 30 min, filtered, and concentrated. The residue was diluted with ethyl acetate (350 mL), washed with water, dried ($MgSO_4$), and concentrated to give 53 g (94%) of crude **11**, which was used immediately in the next step.

A mixture of crude **11** (50.0 g, 233 mmol), ethanol (300 mL), and solid sodium hydroxide pellets (19.8 g, 498 mmol) was heated at reflux for 20 h. After cooling, the solution was concentrated. The residue was diluted with water (300 mL) and extracted with ethyl acetate (4 × 300 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated. Purification of the residue by flash column chromatography (silica gel, 5:1 *n*-hexane–ethyl acetate) furnished 30.9 g (73%) of **9** as an oil: IR ($CHCl_3$) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.80 (dd, $J$ = 16.5, 2.0 Hz, 1 H), 2.1 (dd, $J$ = 16.5, 3.0 Hz, 1 H), 2.70 (m, 1 H), 2.90 (m, 1 H), 3.10 (br s, 1 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 4.23 (d, $J$ = 9.0 Hz, 1 H), 6.16 (m, 1 H), 6.60 (dd, $J$ = 6.0, 3.0 Hz, 1 H) ppm; $^{13}C$ NMR ($CDCl_3$) 33.45, 40.78, 52.54, 54.13, 56.78, 63.44, 102.35, 131.08, 144.05, 214.01 ppm; MS $m/z$ (relative intensity) 182 (8, $M^+$), 151 (24), 123 (32), 108 (48), 109 (43), 91 (100), 45 (35); HRMS $m/e$ calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0950.

**2-*endo*-Vinyl-7-*anti*-(dimethoxymethyl)bicyclo[2.2.1]-hept-5-en-2-ol (8a) and 2-*exo*-Vinyl-7-*anti*-(dimethoxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (8b).** To a solution of the ketone **9** (9.42 g, 51.8 mmol) in dry THF (20 mL) at 0 °C was added vinylmagnesium bromide (1.00 M, 62.0 mL). After 15 min the solution was warmed to room temperature (25 °C) and stirred for 20 h or refluxed for 3 h. The solution was quenched with saturated ammonium chloride and extracted with ether. The ether layer was dried and concentrated to give a mixture of **8a** and **8b** (11.0 g). The crude products were separated by chromatography on silica gel using *n*-hexane/ethyl acetate (2:1) and 1% of triethylamine as eluent to give pure **8a** (6.25 g) as an oil and **8b** as an oil (3.26 g) in 90% yield. **8a**: IR ($CHCl_3$) 3600, 3200–3580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.50–2.30 (m, 3 H), 2.40 (br s, 1 H), 2.60 (m, 1 H), 2.84 (m, 1 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 4.92 (d, $J$ = 9.0 Hz, 1 H), 4.98 (dd, $J$ = 11.0, 2.0 Hz, 1 H), 5.23 (dd, $J$ = 17.0, 2.0 Hz, 1 H), 5.84 (dd, $J$ = 11.0, 17.0 Hz, 1 H), 6.10 (m, 1 H), 6.25 (m, 1 H) ppm; $^{13}C$ NMR ($CDCl_3$) 40.2, 43.4, 52.4, 53.4, 55.6, 61.3, 81.1, 103.2, 111.9, 135.5, 139.4, 145.4 ppm; MS $m/z$ (relative intensity) 179 ($M^+ - OCH_3$, 3), 123 (20), 108 (14), 91 (17), 75 (100), 55 (10). Anal. Calcd for **8a** $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.20; H, 8.64. **8b**: IR ($CHCl_3$) 3300–3640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.20–1.50 (m, 1 H), 1.50–1.80 (m, 1 H), 2.20–2.33 (m, 2 H), 2.73–3.00 (m, 2 H), 3.25 (br s, 6 H), 4.28 (d, $J$ = 10.0 Hz, 1 H), 5.10–5.60 (m, 2 H), 6.10–6.60 (m, 3 H) ppm; $^{13}C$ NMR ($CDCl_3$) 40.6, 43.7, 52.0, 52.7, 72.9, 79.8, 101.1, 114.6, 135.4, 140.7, 143.6 ppm; MS $m/z$ (relative intensity) 179 ($M^+ - OCH_3$, 3), 123 (16), 108 (16), 91 (10), 75 (100), 55 (12).

**9-*endo*-(Dimethoxymethyl)-*cis*-bicyclo[4.3.0]non-7-en-3-one (7).** A solution of **8a** (3.39 g, 19.0 mmol) and dry benzene (5 mL) was added to a rapidly stirred suspension of sodium hydride (683 mg, 28.5 mmol) and dry benzene (60 mL). The resulting mixture was heated at reflux under nitrogen for 4 h. After cooling to room temperature, saturated ammonium chloride solution was added slowly, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The brown residue was purified by flash chromatography (silica gel, 2:1 *n*-hexane–ethyl acetate) to give 3.15 g (93%) of **7** as an oil: IR ($CHCl_3$) 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.60–3.35 (m, 9 H), 3.36 (s, 6 H), 4.23 (d, $J$ = 8.0 Hz, 1 H), 5.73 (br s, 2 H) ppm; $^{13}C$ NMR ($CDCl_3$) 25.44, 37.24, 37.29, 38.03, 44.04, 51.29, 52.70, 53.56, 104.09, 130.12, 135.07, 213.82 ppm; MS $m/z$ (relative intensity) 179 ($M^+ - OCH_3$, 5), 121 (5), 75 (100), 47 (8); HRMS $m/e$ calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1242.

**9-*endo*-(Dimethoxymethyl)-3-[(trimethylsilyl)oxy]-*cis*-bicyclo[4.3.0]nona-3,7-diene (18).** A solution of **7** (730 mg, 3.48

mmol) and dry THF (5 mL) was added dropwise at −78 °C to an excess of LDA prepared from dry diisopropylamine (0.98 mL, 6.95 mmol), *n*-BuLi (2.54 mL of a 1.64 M solution in hexane, 4.16 mmol), and dry THF (15 mL) at −78 °C for 20 min. After an additional 15 min at −78 °C, freshly distilled chlorotrimethylsilane (0.51 mL, 4.0 mmol) was added in one portion. The reaction mixture was warmed to 0 °C in 2 h, quenched with water, and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 910 mg (93%) of crude **18**, which was used immediately in the next step. An analytical sample was purified by flash chromatography: $^1H$ NMR ($CDCl_3$) 0.15 (s, 9 H), 1.60–3.20 (m, 7 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 4.35 (d, $J$ = 9.0 Hz, 1 H), 4.83 (m, 1 H), 5.63 (m, 2 H) ppm; $^{13}C$ NMR ($CDCl_3$) 0.0, 26.0, 28.6, 38.9, 41.9, 51.3, 52.1, 52.7, 101.7, 103.7, 128.8, 138.2, 150.5 ppm. Anal. Calcd for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28. Found: C, 64.16; H, 9.30.

**4-Hydroxy-9-*endo*-(dimethoxymethyl)-*cis*-bicyclo[4.3.0]non-7-en-3-one (19).** A solution of purified *m*-chloroperbenzoic acid (216 mg, 1.26 mmol) and *n*-hexane (15 mL) was stirred at room temperature for 20 min and cooled to −15 °C (ice–methanol bath), and a solution of **18** (323 mg, 1.10 mmol) in *n*-hexane (5 mL) was added over 5 min. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and filtered. The filtrate was dried ($MgSO_4$) and concentrated to give a yellow oil. The yellow oil was dissolved in $MeOH/H_2O$ (1:1, 20 mL), and excess of $NaHCO_3$ (>4 equiv) was added. The reaction mixture was stirred vigorously at room temperature for 24 h and concentrated. The residue was diluted with water (20 mL) and extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (silica gel, ethyl acetate–*n*-hexane, 2:1) gave 170 mg (66%) of pure **19** as an oil: IR ($CHCl_3$) 3200–3700, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.70–3.30 (m, 8 H), 3.34 (s, 6 H), 4.00–4.35 (m, 2 H), 5.60–6.30 (m, 2 H) ppm; MS $m/z$ (relative intensity) 195 ($M^+ - OCH_3$, 77), 163 (100), 75 (94); HRMS $m/e$ calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1187.

**Methyl 2-(Dimethoxymethyl)-5-(2-oxoethyl)-3-cyclopenteneacetate (20).** Lead tetraacetate (2.31 g, 5.20 mmol) was added at room temperature to a solution of **19** (1.07 g, 4.73 mmol) and 1:1 methanol–acetic acid (15 mL). The resulting solution was heated at 45–50 °C for 25 min and concentrated at reduced pressure. The residue was treated with water (30 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (silica gel, 2:1 *n*-hexane–ethyl acetate) to give 939 mg (78%) of **20** as an oil: IR ($CHCl_3$) 2715, 1730, 1715 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 2.20–3.30 (m, 5 H), 3.34 (s, 6 H), 3.68 (s, 3 H), 4.14 (d, $J$ = 6.0 Hz, 1 H), 5.72 (m, 1 H), 5.92 (m, 1 H), 9.78 (m, 1 H) ppm; $^{13}C$ NMR ($CDCl_3$) 31.73, 37.68, 41.18, 46.37, 49.30, 51.55, 53.83, 54.77, 105.86, 130.61, 135.55, 173.37, 201.70 ppm; HRMS $m/e$ calcd for $C_{13}H_{18}O_6$ 256.1311, found 256.1367.

**Methyl 2-(Dimethoxymethyl)-5-(2-hydroxyethyl)-3-cyclopenteneacetate (21).** To a solution of **20** (195 mg, 0.76 mmol) in methanol (10 mL) at ice bath temperature was added excess sodium borohydride. After 25 min, the mixture was concentrated and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 1:1 *n*-hexane–ethyl acetate) to give 181 mg (92%) of **21** as an oil: IR ($CHCl_3$) 3200–3700, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.30–1.45 (m, 1 H), 1.60–1.80 (m, 2 H), 2.37 (dd, $J$ = 7.2, 16.8 Hz, 1 H), 2.52 (dd, $J$ = 8.4, 16.8 Hz, 1 H), 2.72 (m, 1 H), 2.92 (m, 2 H), 3.28 (s, 3 H), 3.30 (s, 3 H), 3.67 (s, 3 H), 3.60–3.71 (m, 2 H), 4.13 (d, $J$ = 7.0 Hz, 1 H), 5.68 (m, 1 H), 5.93 (m, 1 H) ppm; $^{13}C$ NMR ($CDCl_3$) 31.54, 35.16, 38.29, 43.56, 48.98, 51.42, 52.93, 53.82, 61.63, 105.70, 130.36, 136.06, 173.80 ppm; MS $m/z$ (relative intensity) 257 ($M^+ - 1$, 0.5), 195 (43), 75 (100).

**Methyl 2-(Dimethoxymethyl)-5-[2-[(4-methylphenyl)sulfonyl]ethyl]-3-cyclopenteneacetate (22).** A stirred solution of **21** (833 mg, 3.23 mmol), triethylamine (1.34 mL, 9.69 mmol), and $CH_2Cl_2$ (20 mL) was cooled to 0 °C, and *p*-toluenesulfonyl chloride (1.23 g, 6.46 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and concentrated, and a solid precipitated. The mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 2:1 *n*-hexane–ethyl acetate) to afford 1.28 g (96%) of **22** as an oil: IR ($CHCl_3$) 1730, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.03–3.10 (m, 10 H), 2.45 (s, 3 H), 3.29 (s, 6 H), 3.68 (s, 3 H), 4.05 (m, 3 H), 5.74 (m, 2 H), 7.36 (d, $J$ = 9.0 Hz, 2 H), 7.80 (d, $J$ = 9.0 Hz, 2 H) ppm; $^{13}C$ NMR ($CDCl_3$) 21.61, 31.23, 31.45, 38.05, 43.05, 49.04, 51.49, 53.33, 54.32, 69.22, 105.70, 127.92, 129.88, 131.18, 134.85, 144.79, 173.40 ppm. Anal. Calcd for $C_{20}H_{28}O_7S$: C, 58.24; H, 6.84; S, 7.77. Found: C, 58.06; H, 6.84; S, 7.83.

**Methyl 2-Carbomethoxy-5-[2-[(4-methylphenyl)sulfonyl]ethyl]-3-cyclopenteneacetate (23).** To a solution of **22** (1.13 g, 2.75 mmol) in acetone (25 mL) at room temperature was added excess Jones reagent. The mixture was stirred for 15 min and treated with 2-propanol to destroy the unreacted oxidation reagent. The mixture was cooled to 0 °C, neutralized with 0.2 N NaOH solution, and concentrated. The residue was recooled to 0 °C and acidified with 0.2 N HCl to pH = 2. The mixture was extracted with ethyl acetate (3 × 40 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in ether and treated with $CH_2N_2$. After 15 min, the solution was bubbled with nitrogen to eliminate the excess of $CH_2N_2$, the ether solution was concentrated, and the residue was purified by flash chromatography (silica gel, 2:1 *n*-hexane–ethyl acetate) to furnish 872 mg (80%) of **23** as an oil: IR ($CHCl_3$) 1730, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.65 (m, 1 H), 1.80 (m, 1 H), 2.42 (s, 3 H), 2.30–2.70 (m, 6 H), 2.77 (m, 1 H), 2.95 (m, 1 H), 3.59 (s, 3 H), 3.65 (s, 3 H), 4.03 (m, 2 H), 5.71 (m, 1 H), 5.87 (m, 1 H), 7.33 (d, $J$ = 8.4 Hz, 2 H), 7.76 (d, $J$ = 8.4 Hz, 2 H) ppm; $^{13}C$ NMR ($CDCl_3$) 21.52, 30.43, 31.62, 39.53, 42.66, 51.57, 52.16, 68.85, 127.90, 129.40, 129.88, 133.10, 137.10, 144.82, 172.88, 173.64 ppm. Anal. Calcd for $C_{19}H_{24}O_7S$: C, 57.56; H, 6.10; S, 8.09. Found: C, 57.58; H, 6.18; S, 8.23.

**Methyl 2-Carbomethoxy-5-[2-(phenylthio)ethyl]-3-cyclopenteneacetate (27).** A solution of thiophenol (0.1 mL, 0.91 mmol) and dry THF (3 mL) was added to a rapidly stirred suspension of sodium hydride (20 mg, 0.83 mmol) in dry THF (20 mL). The resulting mixture was stirred for 5 min, and **23** (120 mg, 0.30 mmol) in THF (5 mL) was added. After being stirred for 25 min at room temperature, the mixture was quenched with water. The organic layer was separated, the aqueous layer extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (silica gel, 5:1 *n*-hexane–ethyl acetate) furnished 93 mg (92%) of **27** as an oil: IR ($CHCl_3$) 1730, 1590 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.70 (m, 2 H), 2.41 (dd, $J$ = 16.7, 8.3 Hz, 1 H), 2.53 (dd, $J$ = 16.7, 8.3 Hz, 1 H), 2.86 (m, 2 H), 3.02 (m, 2 H), 3.59 (m, 1 H), 3.60 (s, 3 H), 3.62 (s, 3 H), 5.80 (m, 1 H), 6.10 (m, 1 H), 7.18 (m, 1 H), 7.31 (m, 4 H) ppm; $^{13}C$ NMR ($CDCl_3$) 29.66, 30.51, 31.71, 31.92, 39.87, 45.69, 51.56, 52.34, 125.82, 128.83, 128.90, 129.08, 136.56, 137.54, 173.03, 173.61 ppm. Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63. Found: C, 64.44; H, 6.62.

**Oxidation of 27.** A solution of **27** (100 mg, 0.30 mmol) in $CH_2Cl_2$ (8 mL) was treated with excess ozone at −78 °C. After a nitrogen purge, the solution was concentrated at 23 °C under high vacuum. The residue was dissolved in acetic acid (15 mL), excess zinc dust was added, and the mixture was heated at 45 °C for 45 min. After the acetic acid was evaporated in vacuo, the residue was treated with water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried and concentrated to give 110 mg of crude **28**, which was used immediately in the next step. A solution of the crude **28** (110 mg), a catalytic amount (10 mg) of *p*-toluenesulfonic acid, and methanol (15 mL) was heated at reflux for 5 h. After being cooled to room temperature, the solution was concentrated and purified by preparative TLC (silica gel, 1:2 *n*-hexane–ethyl acetate) to give 60 mg (52%) of **29** as an oil: IR ($CDCl_3$) 1730, 1705, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.70–3.30 (m, 8 H), 3.39, 3.41, 3.46, 3.49 (s, total 3 H), 3.64, 3.65, 3.69, 3.70 (s, total 6 H), 4.80–4.93 (m, 1 H), 7.40–7.75 (m, 6 H); MS $m/z$ (relative intensity) 396 ($M^+$, 14), 239 (49), 165 (100), 85 (99); HRMS $m/e$ calcd for $C_{19}H_{24}O_7S$ 396.1243, found 396.1252.

**Dimethyl Secologanoside O-Methyl Ether (1b).** A solution of **29** (50 mg, 0.13 mmol) in toluene (10 mL) was heated at reflux for 18 h. After cooling to room temperature, toluene was evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, 4:1 *n*-hexane–ethyl acetate) to give 14 mg (41%) of **1b** as an oil: IR ($CHCl_3$) 1731, 1705, 1630, 1600

cm$^{-1}$; $^1$H NMR ($CDCl_3$) 2.20–3.00 (m, 3 H), 3.10–3.35 (m, 1 H), 3.46 and 3.52 (s, total 3 H), 3.66 and 3.67 (s, total 3 H), 3.70 and 3.71 (s, total 3 H), 4.80–5.00 (m, 1 H), 5.10–5.30 (m, 2 H), 5.50–5.95 (m, 1 H), 7.48 (m, 1 H) ppm; MS $m/z$ (relative intensity) 270 ($M^+$, 20), 238 (21), 178 (77), 165 (20), 84 (100). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.02; H, 6.65.

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# Total Synthesis of (±)-Dihydropinidine, (±)-Monomorine I, and (±)-Indolizidine 223AB (Gephyrotoxin 223AB) by Intramolecular Nitroso Diels–Alder Reaction

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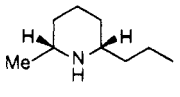
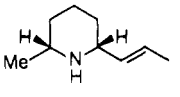
The total synthesis of alkaloids possessing saturated nitrogen heterocyclic ring systems such as (±)-dihydropinidine (**1**), (±)-monomorine I (**3**), and (±)-indolizidine 223AB (gephyrotoxin 223AB) (**4**) is described. The synthetic strategy for a general approach to these alkaloids is based on highly regio- and stereoselective intramolecular acyl nitroso Diels–Alder cycloaddition leading to bicyclic oxazinolactams **13** and **36**. Subsequent introduction of the C-8 alkyl side chain was elaborated by means of a completely stereocontrolled process involving Grignard reaction followed by reduction. The bicyclic oxazines **22**, **39**, and **49** thus obtained were then subjected to reductive N–O bond cleavage, affording the *cis*-2,6-dialkylpiperidines **17**, **40**, and **50**, which were led to the alkaloids **1**, **3**, and **4**, respectively, through intramolecular ring closure in the latter two cases.

Hetero Diels–Alder reactions in which the *C*-nitroso moiety (RN=O) functions as a heterodienophile provide cyclic derivatives of hydroxylamine, namely, 3,6-dihydro-1,2-oxazines.[1-3] A synthetically important feature of this cycloaddition is the simultaneous introduction of nitrogen and oxygen functionalities into a 1,3-diene at the positions 1 and 4 with both regiochemical and stereochemical control. Compared to the intramolecular imino Diels–Alder reaction,[2] the intramolecular variant of the nitroso Diels–Alder reaction has received far less attention,[3b,h,4] despite the enormous potential it holds for alkaloid synthesis. With this in mind, we proceeded to investigate application of the intramolecular nitroso Diels–Alder cycloaddition in the synthesis of alkaloids possessing saturated nitrogen heterocyclic ring systems such as the piperidine and octahydroindolizidine skeletons. In this paper, we describe the development of a successful new approach to (±)-dihydropinidine (**1**), (±)-monomorine I (**3**), and (±)-indolizidine 223AB (gephyrotoxin 223AB)[5] (**4**) based on an intramolecular nitroso Diels–Alder strategy involving a high degree of stereocontrol.[7]



**1**



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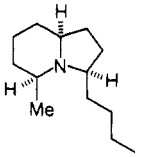

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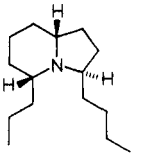
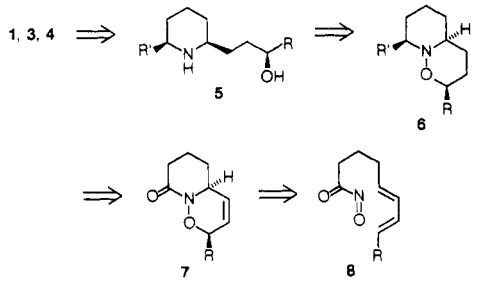


**4**

Our synthetic strategy for a general approach to these nitrogen-containing natural products **1**, **3**, and **4** is illustrated in Scheme I. Key features involved in this approach are an intramolecular Diels–Alder cycloaddition of

**Scheme I**



**5** **6** **7** **8**

† Deceased Nov 12, 1988.

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(4) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.

(5) We comply with the proposal by Daly[6] that it is preferable to discontinue use of the term gephyrotoxin for the simple indolizidine class of dendrobatid alkaloids and to refer to it simply as indolizidines. Thus the former conventional name gephyrotoxin 223AB is termed indolizidine 223AB in this paper.

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