$|F_c|)^2$ where $w = 1/[(\sigma(F))^2 + 0.25(0.05F)^2]$. Neutral-atom scattering factors with anomalous dispersion corrections for oxygen and carbon were used throughout.[11] Computing[12] was carried out on a UNIVAC-1100/82 computer.

Crystal Data. Compound 3: $2(C_{25}H_{40}O_4)\cdot 2.67H_2O$, M_r 857.27, orthorhombic, space group $P2_12_12_1$, a = 10.325 (1) Å, b = 14.856 (1) Å, c = 34.476 (3) Å, V = 5288.2 Å^3, D_{calcd} = 1.079 g cm^{-3}, Z = 4, μ(Cu Kα) = 5.58 cm^{-1}. The crystal was colorless and of dimensions 0.27 × 0.32 × 0.14 mm. θ–2θ scans were used to collect intensity data on 3753 unique reflections to $2\theta_{max}$ 110°, 3168 being "observed". The final R factor was R = 0.046, R_w = 0.064. The maximum shift/error ratio was <0.4 for "solvent molecules" and >0.2 for other atoms. All features in a final difference map were <0.16 e Å^{-3}.

Compound 4: $C_{25}H_{40}O_5$, M_r 420.59, monoclinic, space group $P2_1$, a = 11.553 (1) Å, b = 9.759 (1) Å, c = 11.900 (2) Å, β = 114.56 (1)°, V = 1220.3 Å^3, D_{calcd} = 1.144 g cm^{-3}, Z = 2, μ(Cu Kα) = 5.89 cm^{-1}. The crystal was colorless, 0.18 × 0.39 × 0.17 mm. Intensity data were collected by ω scans to $2\lambda_{max}$ 125°, yielding 2091 unique reflections, 1856 "observed". Six reflections suffering from extinction were removed from the data set. The final R factor was R = 0.059, R_w = 0.077. The maximum shift/error ratio was >0.1. All features in a final difference map were <0.19 e Å^{-3}.

Crystals of compound **3** were found to contain two independent molecules of $C_{25}H_{40}O_4$, showing essentially the same lengths and angles for equivalent bonds and very similar conformations, whithin the lattice. In addition, there were columns of electron density ($\rho_{max} \sim 1.2$ e Å^{-3}) running in the a direction through the crystal lattice, which would appear to correspond to disordered molecules of solvate, either H_2O or CH_3OH. Four oxygen atoms of occupancy 0.67 were introduced to model this region, though its exact nature was not determined.

Acknowledgment. Thanks go to Dr. E. Ball and Dr. R. Summons for assistance in specimen collection, to W. Wheate and M. Chapman for acquisition of mass spectral data, to J. Hooper for sponge taxonomy, and to M. Anderson and J. Rothschild for assistance in antimicrobial assaying of crude extracts and purified products.

Registry No. 1, 105969-64-0; **2**, 105969-65-1; **3**, 105969-66-2; **4**, 105969-67-3; **6**, 105969-68-4; **7**, 105969-69-5; **8**, 105969-70-8; **9**, 105969-71-9; **11**, 105969-72-0; **12**, 105969-73-1; 2,2-dimethoxypropane, 77-76-9.

Supplementary Material Available: Figure 3 (showing molecule 2 of **3**) and Tables III–IX (atomic parameters and selected bond lengths and angles for **3** and **4**) (20 pages). Ordering information is given on any current masthead page. Structure factor listings for **3** and **4** are available on request.

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O^5-Methyl-(±)-(2′*R*,3′*S*)-psorospermin

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Psorospermin (**1**), a novel xanthone isolated from the ethanolic extract of the root of the woody African plant *Psorospermum febrifugum* Spach. (Guttiferae), has shown biological activity in the 9KB cell culture and in vivo P388 mouse leukemia systems, leading to further investigation of **1** as a potential antineoplastic agent. Following the reisolation, studies were initiated to determine the absolute stereochemistry and to complete the total synthesis of **1**. O^5-Methyl-(±)-(2′*R*,3′*S*)-psorospermin (**2**) was chosen as our initial target to test the feasibility of the formation of the dihydrofuran and epoxide moieties in a stereoselective manner. The 4-allyl group of **7**, which was formed by an ortho-Claisen rearrangement, was oxidized to aldehyde **9**. A Wittig reaction gave the *E* allylic ester **10** as the predominant product. Reduction of **10** to **11**, epoxidation, mesylation, and deblocking gave the free phenol **14**. Compound **14** was cyclized with potassium *tert*-butoxide in one step to give (±)-**2**, an epimer of **1**, demonstrating that the epoxydihydrofuran system could be constructed in a concerted and stereoselective manner and providing indirect proof of the absolute stereochemistry of **1**.

Psorospermin (**1**) (NSC-266491) is an antitumor xanthone originally isolated by Kupchan and co-workers[1] as a result of an activity-directed fractionation of the ethanolic extract of the root of the African woody plant *Psorospermum febrifugum* Spach. (Guttiferae). The cytotoxicity of **1** in the in vitro 9KB cell culture system, and the significant activity in the in vivo P388 mouse leukemia system suggested further investigation of **1** as a potential antineoplastic agent. Research efforts in our laboratories have resulted in the reisolation[2] of **1** from *P. febrifugum* and the recent assignment of the absolute stereochemistry[3] to be 2′*R*,3′*R* as shown in Figure 1. We report here the total synthesis of (±)-**2**, an epimer of **1**, which serves both as a confirmation of the assignment of configuration of **1** and as a demonstration that the dihydrofuran and the epoxide moieties can be constructed in a concerted and stereoselective manner.[4]

Based on the retrosynthetic analysis in Figure 1, it is proposed that an intramolecular attack of an appropriate epoxide by a phenoxide ion would result in formation of

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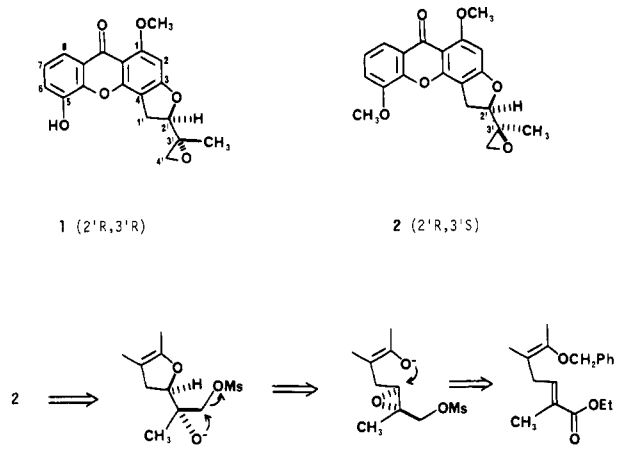


Figure 1.

a five-membered dihydrofuran ring[5] and generate an intermediate alkoxide ion. This intermediate ion could then form the terminal epoxide by displacing an appropriate leaving group. The success of this sequence which is outlined in Scheme I establishes the basis for the planned total synthesis of 1.

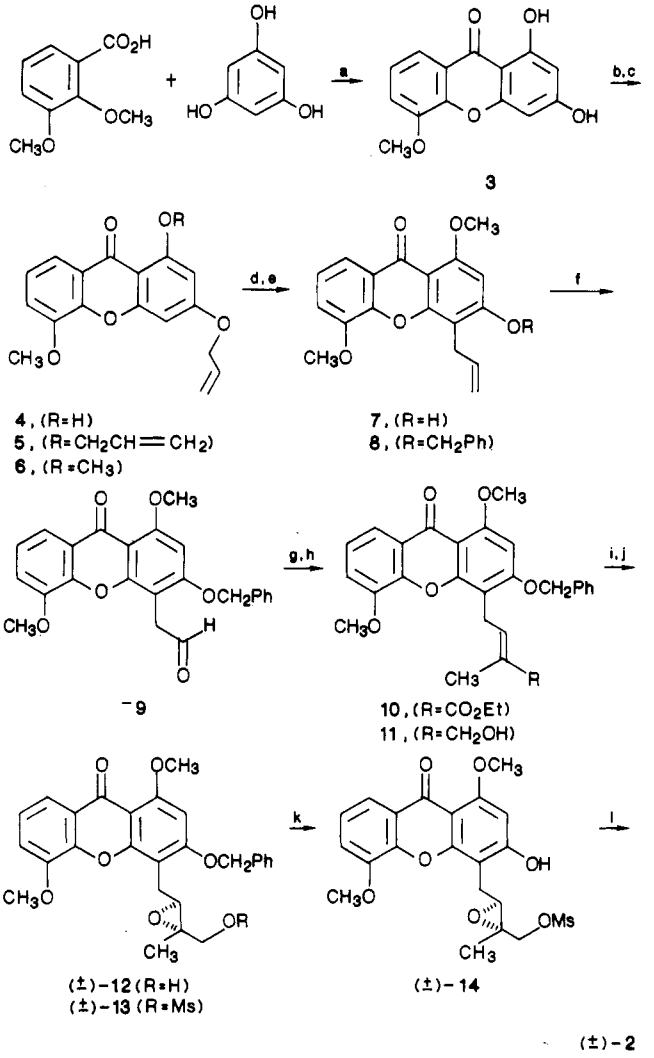
Results and Discussion

Synthesis of 7. A mixture of 2,3-dimethoxybenzoic acid, phloroglucinol, and zinc chloride was heated in phosphorus oxychloride at 80 °C for 2 h to give 1,3-dihydroxyxanthone **3**.[6] It was important to perform this Grover, Shah, and Shah[7] reaction under anhydrous conditions. Therefore, the phloroglucinol dihydrate was heated at 100 °C overnight, the phosphorous oxychloride was freshly distilled, and the zinc chloride was freshly fused. During workup the reaction mixture was poured slowly over ice with constant stirring in order to control the temperature and avoid polymerization. The precipitate isolated in 91% yield could be used without further purification. An alternate workup procedure[6] employing Soxhlet extraction with chloroform was also found to be effective.

Compound **3** underwent O-alkylation with allyl bromide and potassium carbonate in acetone to give the 3-(allyloxy)xanthone **4** as the major product and the 1,3-bis(allyloxy)xanthone **5** as the minor produce (12:1 ratio). The 1-hydroxyl group of **3** is chelated (appearing at δ 12.81 in the NMR) with the carbonyl function and therefore is much less susceptible to O-alkylation. The separation of **4** and **5** can be conveniently done by column chromatography on silica gel with CH_2Cl_2.

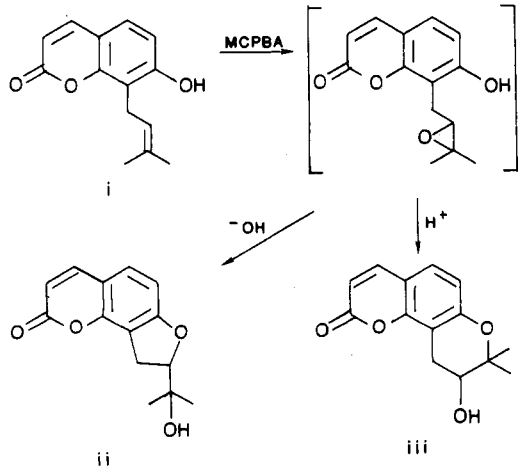
Methylation of compound **4** with dimethyl sulfate or methyl iodide gave **6** which was converted to **7** by an ortho-Claisen rearrangement. After cooling to room temperature, compound **7** was present as yellow crystals with only a small trace of the solvent which was removed by washing with chloroform. The attachment of the allyl group in **7** was proposed to be at the 4-position on the basis of ^1H NMR nuclear Overhauser effect (NOE) experiment. When the 1-methoxy group at 3.82 ppm was irradiated, the 2-H singlet at 6.48 ppm showed a 15% increase in signal. This proposal was confirmed by an X-ray crystallographic analysis of **7** which generated the final atomic coordinates and temperature factors, bond lengths, and

Scheme I[a]



[a] (a) $ZnCl_2$, $POCl_3$, 80 °C, 2 h; (b) allyl bromide, K_2CO_3, acetone, reflux; (c) MeI, K_2CO_3, acetone, reflux; (d) $PhN(Me)_2$, 200 °C; (e) benzyl bromide, K_2CO_3, acetone, reflux; (f) $OsO_4/NaIO_4$, dioxane-$/H_2O$ (3:1), 2 h; (g) $(Ph)_3P{=}C(CH_3)CO_2Et$, benzene; (h) $LiAlH_4$, THF, rt; (i) MCPBA, CH_2Cl_2; (j) MsCl, pyridine; (k) H_2, Pd/C, EtOH; (l) KO-*t*-Bu, *t*-BuOH.

(5) (a) It was shown by Murray et al.[5b] and Bohlmann and Franke[5c] that osthenol (i) reacted quantitatively with *m*-chloroperoxybenzoic acid in ethyl acetate to give only (±)-columbianetin (ii). When the solvent was chloroform which was acidified with HCl, (±)-lomatin (iii) was formed. (b) Murray, R. D.; Sutcliffe, M.; McCabe, P. H. *Tetrahedron* **1971**, *27*, 4901. (c) Bohlmann, F.; Franke, H. *Chem. Ber.* **1971**, *104*, 3229.



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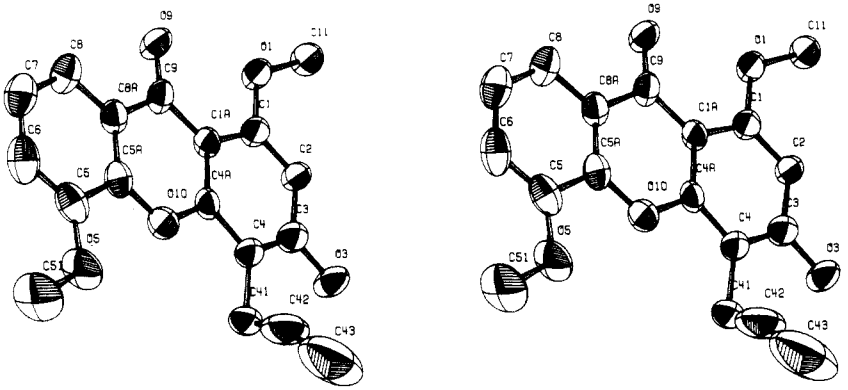

Figure 2. Stereoscopic view of **7**.

bond angles (see tables in supplementary material). It can be seen from the stereoscopic view of **7** (Figure 2) that the molecule is essentially flat other than the allyl group at the 4-position. This characteristic feature of the xanthone moiety is similar to that of a xanthotetralin reported by Lown and Sondi.[8]

In the next step of the synthetic route, efforts were directed to the protection of the 3-hydroxyl group of **7**. Numerous attempts to prepare a silyl derivative[9] which could be deprotected by sodium fluoride to generate a phenoxide ion for closure failed. It was possible to prepare derivative **8** in 80% yield by reacting **7** with benzyl chloride and potassium carbonate in acetone. Compound **8**, unlike **7**, was relatively soluble in many organic solvents.

Attempts to protect the carbonyl group of the xanthone system of **7** or **8** as a 1,3-dioxolane[10] with ethylene glycol and toluenesulfonic acid in refluxing benzene or as the 1,3-dithiane[11] failed.

Synthesis of 11. From compound **8**, the next target was the *E* allylic alcohol **11**. Our approach which employed the synthetic sequence of olefin to aldehyde to allylic ester to allylic alcohol was similar to routes used in syntheses of monensin,[12] chanoclavine I,[13] (±)-trihydroxydecipiadiene,[14] and erythromycin A.[15]

Therefore, **8** was oxidized with osmium tetraoxide and sodium periodate to the aldehyde **9**. It was found that in this case, the use of dioxane/water (3:1)[16] was a more suitable reaction medium than that of tetrahydrofuran/water (3:1).[17] When THF/water (3:1) was used, the side product due to partial oxidation was found at about a 1:4 ratio of the desired aldehyde, whereas the presence of the side product when dioxane/water (3:1) was used was negligible. The aldehyde proton of **9** appeared at 9.78 ppm as a triplet. Due to the unstable nature of **9**, it was used immediately after it was formed.

Compound **9** was allowed to react with (carbethoxyethylidene)triphenylphosphorane in refluxing benzene to give a solid which was purified on a chromatotron through several separate runs to give the ester (*E*)-**10** in 47% yield from **8**. The assignment to the *E* isomer was based on a ^{1}H NMR chemical shift correlation.[18] The vinyl proton in **10** occurs at δ 6.87 (calcd for *E* isomer, 6.60, and for *Z*, 6.03).

The allylic ester (*E*)-**10** was reduced in 50% yield to the allylic alcohol (*E*)-**11** by lithium aluminum hydride in THF at room temperature. The use of diisobutylaluminum hydride was ineffective for this reduction. Again, the configuration of the double bond was found to be *E* by ^{1}H NMR chemical shift correlation. In **11** the vinyl signal is at δ 5.59 (calcd for *E*, 5.41, and for *Z*, 5.01).

The allylic alcohol (*E*)-**11** was epoxidized with *m*-chloroperoxybenzoic acid (MCPBA) in chloroform to produce the racemic epoxy alcohols **12** in 70% yield. The stereochemistry of these intermediates control the stereochemical outcome of the cyclization process. Next, the epoxy alcohol **12** was derivatized by reaction with methanesulfonyl chloride in pyridine to give the methanesulfonate **13** in 65% yield. The methyl signal at 2.97 ppm was characteristic for the sulfonate moiety. The benzyl group in **13** was removed with palladium on charcoal at 40 psi of hydrogen in the presence of sodium bicarbonate[15] to give the phenol **14**.[19]

The phenol **14** was treated without further purification with potassium *tert*-butoxide in *tert*-butyl alcohol to give the target (±)-(2′*R*,3′*S*)-psorospermin methyl ether (**2**). As expected, the phenoxide ion attacked the epoxide in an S_N2 process to form a five-menbered ring,[5] and the intermediate alkoxide ion subsequently displaced the methanesulfonyloxy group to form the terminal epoxide.

The ^{1}H NMR spectrum of **2** showed the characteristic doublets of the 4′-protons at 2.75 and 2.87 ppm ($\Delta\delta$ 0.12), typical of the "higher R_f" series of epoxides.[3] Therefore, it was clear that **2** was diastereomeric with psorospermin (**1**). Since **1** has been shown to be 2′*R*,3′*R* on the basis of X-ray and NMR data, compound (±)-**2** is 2′*R*,3′*S* (2′*S*,3′*R*).

On the basis of this result, the enantioselective synthesis of **1** may be achieved by a route involving the *Z* alcohol and chiral epoxidation using the Sharpless conditions. Routes to **1** using this synthetic scheme are underway.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Melting points were taken on a Laboratory Devices Meltemp apparatus and are uncorrected. ^{1}H NMR data were collected on either a Varian FT-80 spectrometer (8K data points) or a Varian XL-200 spectrometer (32K data points). Chemical shifts are

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reported as parts per million from tetramethylsilane (Me_4Si). Electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a Finnigan 4023 mass spectrometer, and high resolution exact mass measurements were obtained from a Kratos MS 50 mass spectrometer. Centrifugal thin-layer chromatography is carried out by the Chromatotron which is manufactured by the Harrison and Harrison Company. High performance liquid chromatography was performed on a μ-Bondapak C_{18} column (30 cm) with a 6000A pump from Waters Associates.

1,3-Dihydroxy-5-methoxyxanthone (3). Compound **3** was prepared according to a literature procedure (Locksley et al., ref 6). To a flame-dried, three-necked, round-bottomed flask (500 mL) equipped with a mechanical stirrer were added in sequence freshly distilled phosphorus oxychloride (150 mL), freshly fused zinc chloride (46.9 g, 0.3 mol), 2,3-dimethoxybenzoic acid (9.11 g, 0.05 mol), and phloroglucinol (9.46 g, 0.075 mol) that was obtained from overnight heating of the dihydrate at 100 °C. After the reaction was stirred at 80 °C for 2 h, it was cooled to room temperature and poured slowly onto ice. The precipitate from overnight standing was collected, washed with water, and vacuum-dried to give **3** (11.7 g, 91%), a reddish brown solid: mp >300 °C; ^{1}H NMR (80 MHz, Me_2SO-d_6) δ 3.97 (s, 3 H, 5-OCH_3), 6.22 (d, J = 2.1 Hz, 1 H, H-4), 6.42 (d, J = 2.1 Hz, 1 H, H-2), 7.44 (m, 2 H, H-6 and H-7), 7.66 (dd, J = 7.1, 2.5 Hz, 1 H, H-8), 11.11 (br s, 1 H, 3-OH), 12.81 (s, 1 H, 1-OH); CIMS, m/z (rel intensity) 259 (M + H$^+$, 100); exact mass calcd for $C_{14}H_{10}O_5$ (M^+) 258.0528, found 258.0522.

3-(Allyloxy)-1-hydroxy-5-methoxyxanthone (4). A mixture of **3** (10.1 g, 0.0329 mol) and potassium carbonate (16.3 g, 0.118 mol) was stirred in acetone (400 mL) in a flame-dried, three-necked, round-bottomed flask (1000 mL). Allyl bromide (3.22 mL, 4.50 g, 0.0372 mol) in acetone (100 mL) was added dropwise at room temperature. Then the reaction was refluxed for 13 h. After being cooled to room temperature, the reaction mixture was filtered through a sintered glass filter with medium porosity. The filtrate was concentrated in vacuo to give a brown solid (8.82 g, 75.6%), which was further purified on a silica gel (Davidson gr. 62, 60–200 mesh, 600 g) column (6.5 cm in diameter, 40.5 cm in length) with methylene chloride. The isolated product was **4**, a yellow solid (8.33 g, 71.3%): mp 168–169 °C, R_f 0.53 (CH_2Cl_2); ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.02 (s, 3 H, 5-OCH_3), 4.62 (dt, J = 5.1, 1.4 Hz, 2 H, 3-OCH_2R), 5.34 (ddt, J = 10.2, 1.5, 1.5 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 5.43 (ddt, J = 17.2, 1.5, 1.5 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 6.08 (ddt, J = 17.2, 10.2, 5.1 Hz, 1 H, R(*H*)C=CH_2), 6.38 (d, J = 2.3 Hz, 1 H, H-4), 6.56 (d, J = 2.3 Hz, 1 H, H-4), 6.56 (d, J = 2.3 Hz, 1 H, H-2), 7.26 (m, 2 H, H-6 and H-7), 7.82 (dd, J = 6.5, 3.2 Hz, 1 H, H-8), 12.81 (s, 1 H, 1-OH); CIMS, m/z (rel intensity) 299 (M + H$^+$, 100), 259 (32); exact mass calcd for $C_{17}H_{14}O_5$ (M^+) 298.0841, found 298.0830.

1,3-Bis(allyloxy)-5-methoxyxanthone (5). From the same silica gel column that gave **4**, compound **5** was also obtained as a minor component (0.688 g, 5.9%): mp 110–111 °C; R_f 0.29 (CH_2Cl_2); ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.01 (s, 3 H, 5-OCH_3), 4.66 (t, J = 4.9 Hz, 4 H, 1-OCH_2R and 3-OCH_2R), 5.37 (d, J = 10.1 Hz, 2 H, 1-OCH_2C(H)=C(H_{cis})(H_{trans}) and 3-OCH_2C(H)=C(H_{cis})(H_{trans})), 5.61 (d, J = 17.2 Hz, 2 H, 1-OCH_2C(H)=C(H_{cis})(H_{trans}) and 3-OCH_2C(H)=C(H_{cis})(H_{trans})), 6.07 (ddt, J = 17.2, 10.1, 4.9 Hz, 2 H, 1-OCH_2C*H*=CH_2 and 3-OCH_2C*H*=CH_2), 7.16 (m, 2 H, H-6 and H-7), 7.88 (dd, J = 6.8, 2.7 Hz, 1 H, H-8); CIMS, m/z (rel intensity) 339 (M + H$^+$, 100), 298, (17), 258 (5); exact mass calcd for $C_{20}H_{18}O_5$ (M^+) 338.1154, found 338.1152.

3-(Allyloxy)-1,5-dimethoxyxanthone (6). In a one-necked, round-bottomed flask (1000 mL), a mixture of **4** (8.23 g, 0.0276 mol), potassium carbonate (15.2 g, 0.11 mol), and dimethyl sulfate (10.4 mL, 13.1 g, 0.11 mol) in acetone (500 mL) was refluxed for 8 h. The reaction was cooled to room temperature and filtered. The filtrate was concentrated in vacuo to give a yellow solid which was recrystallized from methanol to give a white solid (5.08 g). The filtered material was partitioned between water (300 mL) and methylene chloride (2 × 200 mL), washed with water (100 mL) and saturated sodium chloride solution (50 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a pale yellow solid, which was recrystallized from methanol to give a white solid (1.06 g). The combined yield of **6** was 71.2%: mp 158–160 °C; R_f 0.11 (CH_2Cl_2) and 0.69 (5% MeOH/CH_2Cl_2); ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.97 (s, 3 H, 1-OCH_3 or 5-OCH_3), 4.00 (s, 3 H, 1-OCH_3 or 5-OCH_3), 4.62 (dt, J = 5.1, 1.4 Hz, 2 H, 3-OCH_2R), 5.35 (ddt, J = 10.2, 1.5, 1.4 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 5.44 (ddt, J = 17.2, 1.5, 1.4 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 6.10 (ddt, J = 17.2, 10.2, 5.1 Hz, 1 H, R(*H*)C=CH_2), 6.39 (d, J = 2.4 Hz, 1 H, H-4), 6.62 (d, J = 2.4 Hz, 1 H, H-2), 7.13 (dd, J = 6.8, 2.8 Hz, 1 H, H-6), 7.27 (t, J = 6.8 Hz, 1 H, H-7), 7.87 (dd, J = 6.8, 2.8 Hz, 1 H, H-8); CIMS, m/z (rel intensity) 313 (M + H$^+$, 100), 273 (17); exact mass calcd for $C_{18}H_{16}O_5$ (M$^+$) 312.0998, found 312.0998.

Alternatively, compound **6** could be synthesized by using methyl iodide. A mixture of **4** (1.35 g, 0.00451 mol), potassium carbonate (2.49 g, 0.018 mol), and methyl iodide (1.12 mL, 2.56 g, 0.018 mol) in acetone (200 mL) was refluxed overnight in a three-necked, round-bottomed flask (500 mL). After the reaction was cooled to room temperature, it was mixed with water (200 mL), acidified with 3 N HCl, and extracted with ethyl acetate (300, 2 × 100 mL). The combined ethyl acetate fractions were washed with water (2 × 100 mL) and saturated sodium chloride solution (100 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a solid (1.40 g, 99.7%), which was recrystallized from methanol/water to give **6** with a yield of 86%.

4-Allyl-1,5-dimethoxy-3-hydroxyxanthone (7). Compound **6** (2.00 g, 0.0064 mol) was suspended in *N*,*N*-dimethylaniline (10 mL) in a test tube, which was then put in a stainless steel bomb, evacuated, flushed with nitrogen, sealed, and heated in an oil bath at 200 °C for 16 h. After cooling to room temperature, the yellow crystals inside the test tube were washed four times with chloroform and filtered to give **7** (1.74 g, 86.8%): mp 302–304 °C; R_f 0.23 (5% MeOH/CH_2Cl_2); ^{1}H NMR (80 MHz, Me_2SO-d_6) δ 3.50 (d, J = 6.2 Hz, 2 H, ArCH_2CH=CH_2), 3.82 (s, 3 H, 1-OCH_3), 3.96 (s, 3 H, 5-OCH_3), 4.95 (dd, J = 9.8, 2.4 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 5.11 (dd, J = 17.0, 2.4 Hz, 1 H, R(H)C=C(H_{cis})(H_{trans})), 5.96 (ddt, J = 17.0, 9.8, 6.2 Hz, 1 H, R(*H*)C=CH_2), 6.48 (s, 1 H, 2-H), 7.32 (t, J = 6.9 Hz, 1 H, 7-H), 7.39 (dd, J = 6.9, 2.7 Hz, 1 H, 6-H), 7.60 (dd, J = 6.9, 2.7 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 313 (M + H$^+$, 100), 299 (5), 285 (5); exact mass calcd for $C_{18}H_{16}O_5$ (M$^+$) 312.0998, found 312.0986.

Crystals of **7** suitable for single-crystal X-ray analysis were recrystallized from *N*,*N*-dimethylaniline.

Crystal data: $C_{18}H_{16}O_5$, M_r = 312, monoclinic, a = 7.154 (3) Å, b = 13.53 (2) Å, c = 16.69 (1) Å, β = 106.63 (6)°, V = 1547 (2) Å^3, Z = 4, ρ_{calcd} = 1.32 g/cm^3, $F(000)$ = 656, μ(Cu Kα) = 7.23, space group $P2_1/c$ from systematic absences.

Data collection: Crystallographic data were collected by using Cu Kα X-rays and a monochromater on a Nicolet P3 four-circle diffractometer with the θ–2θ scan technique out to a 2θ of 116.0°. A variable scan rate was used with a maximum of 29.30°/min and a minimum of 7.23°/min. The scan range was from 1.2° less than Kα_1 to 1.2° more than Kα_2; the times that the backgrounds at both ends of the scan range were counted was equivalent to the scan time. Three standard reflections were measured every 50 reflections. Of the 1960 reflections collected, 49 were rejected as systematically absent, leaving 1842 unique reflections, of which 1409 met the condition $F_o > 5\sigma(F_o)$ and were considered observed. The structure was solved by using the MULTAN80 program and refined by SHELX76 to a final R of 0.0880 with hydrogens fixed in calculated positions except OH which was found on a difference map and the 2H's off C43. In refinement the C42–C43 bond distance dropped to 1.17 Å, so it was fixed at 1.34 Å for the last three refinement cycles. The highest peaks on a final difference map were 0.69 and 0.37 e/Å^3, both in the C43 area.

4-Allyl-3-(benzyloxy)-1,5-dimethoxyxanthone (8). A mixture of 4-allyl-1,5-dimethoxyxanthone (**7**) (3.24 g, 0.0104 mol), benzyl bromide (1.86 mL, 2.67 g, 0.0156 mol), and potassium carbonate (3.75 g, 0.0416 mol) in acetone (250 mL) was refluxed overnight. After being cooled to room temperature, the reaction was mixed with water (250 mL), acidified with 3 N HCl, and extracted with ethyl acetate (500, 200, 100 mL). The combined ethyl acetate fraction was washed with water (2 × 200 mL) and saturated sodium chloride solution (150 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a beige solid (5.83 g). This solid was recrystallized from acetone/water to give **8** (3.63 g, 86.9%): mp 174–176 °C; R_f 0.69 (5% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.69 (d, J = 6.5 Hz, 2 H, ArCH_2CH=CH_2), 3.96 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.99 (s, 3 H, 5-OCH_3 or 1-OCH_3), 5.00 (dd, J = 9.9, 2.1 Hz, 1 H,

R(H)C=C(H_{cis})(H_{trans})), 5.19 (dd, J = 17.1, 2.1 Hz, 1 H, R(H)-C=C(H_{cis})(H_{trans})), 5.23 (s, 2 H, 3-OCH_2Ph), 6.03 (ddt, J = 17.1, 9.9, 6.5 Hz, 1 H, R(H)C=CH_2), 6.44 (s, 1 H, 2-H), 7.14 (dd, J = 7.9, 1.9 Hz, 1 H, 6-H), 7.21 (t, J = 7.9 Hz, 1 H, 7-H), 7.41 (m, 5 H, ArOCH_2C$_6H_5$), 7.84 (dd, J = 7.9, 1.9 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 403 (M + H$^+$, 100), 313 (40), 93 (18), 92 (37), 91 (33); exact mass calcd for $C_{25}H_{22}O_5$ (M$^+$) 402.1467, found 402.1422.

3-(Benzyloxy)-1,5-dimethoxy-4-(formylmethyl)xanthone (9). Compound **8** (3.63 g, 0.009 mol) was suspended in a dioxane/water (3:1) solution (300 mL) and cooled to 0 °C. An ether solution (0.1 M) of osmium tetraoxide (1.8 mL, 0.0458 g, 0.00018 mol) was added and stirred for 15 min. Sodium periodate (5.72 g, 0.027 mol) was added over a period of 15 min at 0 °C. Afterwards, the reaction was stirred at room temperature overnight. After being mixed with water (300 mL), the reaction was extracted with ethyl acetate (4 × 200 mL). The combined ethyl acetate fractions were washed with water (150 mL) and saturated sodium chloride solution (2 × 150 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude solid (4.38 g), which was carried through to the next step without further purification due to its instability. A homogeneous sample of **9** was obtained from the crude material by preparative TLC on silica gel: mp 185–186 °C; R_f 0.15 (1% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.96 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.99 (d, J = 1.7 Hz, 2 H, ArCH_2CHO), 5.19 (s, 2 H, ArOCH_2Ph), 6.45 (s, 1 H, 2-H), 7.11 (dd, J = 7.9, 1.8 Hz, 1 H, 6-H), 7.21 (t, J = 7.9 Hz, 1 H, 7-H), 7.39 (m, 5 H, ArOCH_2C$_6H_5$), 7.81 (dd, J = 7.9, 1.8 Hz, 1 H, 8-H), 9.78 (t, J = 1.7 Hz, 1 H, RCHO); CIMS, m/z (rel intensity) 405 (M + H$^+$, 100), 315 (7), 92 (29), 91 (26); exact mass calcd for $C_{24}H_{20}O_6$ (M$^+$) 404.1260, found 404.1221.

Ethyl (*E*)-4-[3-(Benzyloxy)-1,5-dimethoxy-9-oxoxanth-4-yl]-2-methyl-2-butenoate ((*E*)-10). A mixture of **9** (3.5 g, 0.00865 mol) and (carbethoxyethylidene)triphenylphosphorane (3.14 g, 0.00865 mol) was refluxed in benzene (250 mL) for 20 h. After concentrating in vacuo, a dark gray solid was obtained (7.69 g). Purification by centrifugal thin-layer chromatography on a silica gel coated rotor (4 mm) through seven separate runs resulted in (*E*)-**10**, an off white solid (1.97 g, 46.6% from **8**): mp 150–151 °C; R_f 0.14 (1% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H, RCO$_2$CH$_2$CH_3), 2.02 (br s, 3 H, R(H)-C=C(CH_3)CO$_2$Et), 3.81 (d, J = 7.3 Hz, 2 H, ArCH_2R), 3.96 (s, 6 H, 1-OCH_3 and 5-OCH_3), 4.15 (q, J = 7.1 Hz, 2 H, RCO$_2$CH_2CH$_3$), 5.23 (s, 2 H, ArOCH_2Ph), 6.45 (s, 1 H, 2-H), 6.87 (br t, J = 7.3 Hz, 1 H, R(H)C=C(CH$_3$)CO$_2$Et), 7.13 (dd, J = 7.9, 1.7 Hz, 1 H, 6-H), 7.21 (t, J = 7.9 Hz, 1 H, 7-H), 7.42 (m, 5 H, ArOCH_2C$_6H_5$), 7.83 (dd, J = 7.9, 1.7 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 489 (M + H$^+$, 100), 443 (3), 92 (18), 91 (9); exact mass calcd for $C_{29}H_{28}O_7$ (M$^+$) 488.1835, found 488.1847.

3-(Benzyloxy)-1,5-dimethoxy-4-((*E*)-4-hydroxy-3-methyl-2-butenyl)xanthone ((*E*)-11). Compound (*E*)-**10** (0.948 g, 0.00194 mol) was dissolved in THF (100 mL). Lithium aluminum hydride (0.0736 g, 0.00194 mol) was added and stirred at room temperature overnight. When TLC showed only partial completion of reaction, more lithium aluminum hydride (0.147 g, 0.00388 mol) was added. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (300, 2 × 100 mL). The combined ethyl acetate fractions were washed with saturated sodium chloride solution (150 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a brown solid (0.08 g). Purification by centrifugal thin-layer chromatography on a silica gel coated rotor (4 mm) yielded (*E*)-**11** (0.436 g, 50% yield): mp 163–165 °C; R_f 0.67 (5% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (br s, 3 H, R(H)C=C(CH_3)CH$_2$OH), 3.68 (d, J = 7.1 Hz, 2 H, ArCH_2R), 3.94 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.96 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.97 (br s, 2 H, CH_2OH), 5.20 (s, 2 H, ArOCH_2Ph), 5.59 (br t, J = 7.1 Hz, 1 H, R(H)C=C-(CH$_3$)CH$_2$OH), 6.43 (s, 1 H, 2-H), 7.12 (dd, J = 7.9, 1.8 Hz, 1 H, 6-H), 7.20 (t, J = 7.9 Hz, 1 H, 7-H), 7.40 (m, 5 H, ArOCH_2C$_6H_5$), 7.82 (dd, J = 7.9, 1.8 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 447 (M + H$^+$, 100), 430 (13), 429 (61), 92 (27), 91 (18); exact mass calcd for $C_{27}H_{26}O_6$ (M$^+$) 446.1729, found 446.1730.

(±)-3-(Benzyloxy)-1,5-dimethoxy-4-(2(*S*),3(*S*)-epoxy-4-hydroxy-3-methylbutyl)xanthone (12). To a solution of the allylic alcohol (*E*)-**11** in chloroform (40 mL) was added *m*-chloroperoxybenzoic acid (0.337 g, 0.00195 mol) in chloroform (50 mL) dropwise at 0 °C. The reaction was stirred for 40 h at room temperature, and the reaction mixture was then taken up in chloroform (200 mL) and washed with 1% aqueous sodium carbonate (100 mL). The aqueous portion was extracted with chloroform (2 × 100 mL), and then the combined chloroform fractions were washed with water (200 mL) and saturated sodium chloride solution (100 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a solid (0.48 g). This solid was purified by centrifugal thin-layer chromatography on a silica gel coated rotor (4 mm) with 4% MeOH/CH_2Cl_2 to give **12** (0.315 g, 69.7% yield): mp 175–177 °C; R_f 0.74 (5% MeOH/CH_2Cl_2); ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.45 (s, 3 H, CCH$_3$), 3.2–3.5 (m, 5 H, ArCH_2C$\overline{HOC}$(CH$_3$)CH_2OH), 3.94 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.95 (s, 3 H, 1-OCH_3 or 5-OCH_3), 5.23 (s, 2 H, ArOCH_2Ph), 6.44 (s, 1 H, 2-H), 7.12 (dd, J = 6.8, 2.7 Hz, 1 H, 6-H), 7.23 (t, J = 6.8 Hz, 1 H, 7-H), 7.41 (m, 5 H, ArOCH_2C$_6H_5$), 7.83 (dd, J = 6.8, 2.7 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 463 (M + H$^+$, 100), 405 (17), 375 (12); exact mass calcd for $C_{27}H_{26}O_7$ (M$^+$) 462.1678, found 462.1680.

(±)-3-(Benzyloxy)-1,5-dimethoxy-4-(2(*S*),3(*S*)-epoxy-4-methanesulfonoxy-3-methylbutyl)xanthone (13). To a solution of the epoxy alcohol **12** in pyridine (40 mL) was added methanesulfonyl chloride (0.076 mL, 0.112 g, 0.00098 mol) at 0 °C, and the reaction was stirred for 1 h at 0 °C and overnight at room temperature. More methanesulfonyl chloride (0.153 mL, 0.224 g, 0.00196 mol) was added to bring the reaction to completion. The reaction mixture was then taken up in water (200 mL), acidified to pH 7 with 3 N HCl, and extracted with ethyl acetate (2 × 200, 100 mL). The combined ethyl acetate was washed with water (200 mL) and saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give **13**, a solid (0.231 g, 65.3%): mp 183 °C dec; R_f 0.66 (5% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 3 H, CCH$_3$), 2.97 (s, 3 H, ROSO$_2$CH$_3$), 3.20–3.8 (m, 5 H, ArC$\overline{HOCH}$C(CH$_3$)CH_2OH), 3.95 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.96 (s, 3 H, 1-OCH_3 or 5-OCH_3), 5.23 (s, 2 H, ArOCH_2Ph), 6.44 (s, 1 H, 2-H), 7.12 (dd, J = 7.2, 1.8 Hz, 1 H, 6-H), 7.23 (t, J = 7.2 Hz, 1 H, 7-H), 7.43 (m, 5 H, ArOCH$_2$CH_5), 7.82 (dd, J = 7.2, 1.8 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 541 (M + H$^+$, 100), 445 (13), 375 (11), 355 (12); exact mass calcd for $C_{28}H_{28}O_9S$ (M$^+$) 540.1454, found 540.1465.

(±)-1,5-Dimethoxy-4-(2(*S*),3(*S*)-epoxy-4-methanesulfonoxy-3-methylbutyl)-3-hydroxyxanthone (14). In the Parr bottle, the benzyl ether **13** (0.10 g, 0.000185 mol) was dissolved in absolute ethanol (120 mL) and mixed with 10% palladium on charcoal (0.04 g) and sodium bicarbonate (0.008 g). Compound **13** was hydrogenolyzed at 40 psi at room temperature for 20 h. More palladium on charcoal (0.03 g) was used for a longer hydrogenolysis period (24 h) to bring the reaction to completion. Afterwards, the reaction mixture was filtered through a Celite pad and concentrated in vacuo to give **14**, a dark brown solid (0.085 g, quant.): mp 175 °C dec; CIMS, m/z (rel intensity) 451 (M + H$^+$, 87), 352 (13), 97 (100); exact mass calcd for $C_{21}H_{22}O_9S$ (M$^+$) 450.0984, found 450.0992.

***O*^{5}-Methyl-(±)-(2′*R*,3′*S*)-psorospermin (2).** To a solution of the phenol **14** (0.0833 g, 0.000185 mol) in *tert*-butyl alcohol (80 mL) was added potassium *tert*-butoxide (0.0830 g, 0.00074 mol), and the solution was stirred at 40 °C for 1 h and at room temperature overnight. Then the reaction was taken up in water (100 mL), acidified dropwise with 3 N HCl, and extracted with chloroform (200, 100, 50 mL). The combined chloroform fractions were washed with saturated sodium chloride solution (2 × 100 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give **2**, a yellow solid (0.0599 g, 91.5%). Purification of the solid by centrifugal thin-layer chromatography on a silica gel coated rotor (2 mm) with 3% MeOH/CH_2Cl_2 gave **2** (0.0354 g, 54%) as a pure compound by HPLC analysis on a C_{18} column with MeOH/H_2O/CH_3CN (6:3:1) as the solvent system: mp 165–167 °C; R_f 0.675 (5% MeOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 3 H, CCH$_3$), 2.75 (d, J = 4.5 Hz, 1 H, 4′-H$_a$), 2.87 (d, J = 4.5 Hz, 4′-H$_b$), 3.26 (dd, J = 15.3, 7.7 Hz, 1 H, 1′-H$_a$), 3.42 (dd, J = 15.3, 9.9 Hz, 1 H, 1′-H$_b$), 3.96 (s, 3 H, 1-OCH_3 or 5-OCH_3), 3.98 (s, 3 H, 1-OCH_3 or 5-OCH_3), 4.91 (dd, J = 9.9, 7.7 Hz, 1 H, 2′-H), 6.36 (s, 1 H, 2-H), 7.14 (dd, J = 7.8, 1.7 Hz, 1 H, 6-H), 7.23 (t, J = 7.8 Hz, 1 H, 7-H), 7.86 (dd, J =

7.8, 1.7 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 355 ($M + H^+$, 100), 297 (9); EIMS, m/z (rel intensity) 354 (M^+, 100), 323 (85); exact mass calcd for $C_{20}H_{18}O_6$ (M^+) 354.1103, found 354.1099.

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Supplementary Material Available: Tables of the atomic positions, temperature factors, bond lengths, and bond angles (2 pages). Ordering information is given on any current masthead page.

Biomimetic Alkaloid Syntheses. 15. Enantioselective Syntheses with Epichlorohydrin: Total Syntheses of (+)-, (-)-, and (±)-Vindoline and a Synthesis of (-)-Vindorosine

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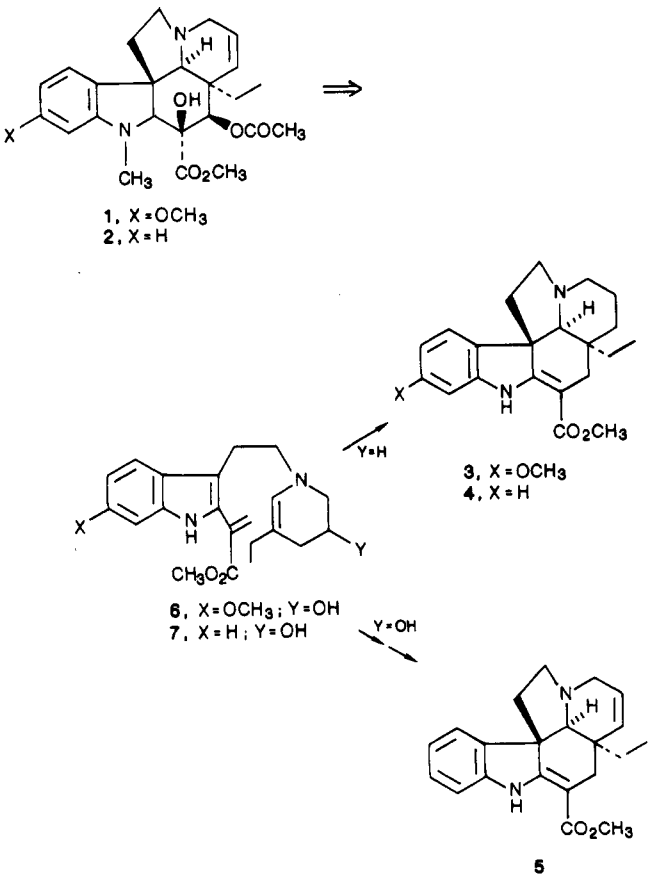
Total syntheses of vindoline (1) in racemic as well as in each enantiomeric form and of (-)-vindorosine (2) are described. They were achieved by generation and diastereoselective cyclizations of 14-hydroxysecodine intermediates **6** and **7**. The subsequent oxidative elaboration of ring E was also studied with 3-oxotabersonine (**24**), 3-oxovincadifformine (**26**), and 14β-hydroxyvincadifformine (**15**). N^a-Methyltabersonine (**22**) was oxidized to a ring-D-contracted α-keto lactam, **23**.

Vindoline (1), the major alkaloid obtained from *Vinca rosea* Linn, is of particular interest because of its biosynthetic[1] and synthetic[2-7] role as a precursor of the carcinostatic alkaloid drugs vinblastine and vincristine. In this report we describe some of our results leading to the first enantioselective total syntheses of vindoline (1) as well as reactions of related compounds. The compounds and structures in this paper are designated as **a** when racemic, as **b** when in the natural (-)-vindoline series, and as **c** when they are in the corresponding (+) enantiomeric series.

Previous studies, utilizing different synthetic strategies, had provided vindoline (1) and vindorosine (2) as racemates.[8-14] Our alternative approach was governed by a desire to utilize the biomimetic principles of secodine cyclizations, which had already provided us with syntheses of ervinceine (3), vincadifformine (4), and tabersonine (5), the latter two in an enantioselective as well as in a racemic

Scheme I



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