(t, CH_3); mass spectrum m/e 261 (M^+).

Anal. Calcd for $C_{13}H_{11}NOS_2$: C, 59.74; H, 4.24; N, 5.36; S, 24.54. Found: C, 59.65; H, 4.24; N, 5.24; S, 24.05.

Benzothiazepinone **2** eluted next (2.50 g, 37%) and was purified from methylene chloride/petroleum ether to give the analytical product: mp 218–219 °C; UV 230, 250, 310 nm; ^1H NMR 10.30 (br s, 1 H, NH), 8.16 (d, 1 H, thiophene H), 7.61 (d, 1 H, thiophene H), 7.2 (m, 4 H, aromatic H); mass spectrum m/e calcd for $C_{11}H_7NOS_2$, 232.9969; m/e found, 232.9963.

Anal. Calcd for $C_{11}H_7NOS_2$: C, 56.63; H, 3.02; N, 6.00; S, 27.49. Found: C, 55.97; H, 3.12; N, 5.79; S, 27.21.

3-Chlorothieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one (23). A suspension of **1** (2.2 g, 0.01 mol) in chloroform (100 mL) was treated with sulfuryl chloride (0.9 mL, 0.01 mol) dropwise, and the mixture was stirred overnight. The product was collected by filtration (1.62 g, 64%) and melted at 258–260 °C: UV 210, 260 nm; ^1H NMR 10.28 (br s, 1 H, NH), 8.07 (s, 1 H, thiophene H), 7.20 (m, 4 H, aromatic H); mass spectrum m/e 251 (M^+).

Anal. Calcd for $C_{11}H_6ClNO_2S$: C, 52.49; H, 2.40; N, 5.57; S, 12.74; Cl, 14.09. Found: C, 52.66; H, 2.72; N, 5.44; S, 12.62; Cl, 14.03.

3-Chlorothieno[3,4-*b*][1,5]benzothiazepin-10(9*H*)-one (24). A suspension of **2** (2.33 g, 0.01 mol) in methylene chloride (40 mL) was treated with sulfuryl chloride (0.95 mL, 0.012 mol), and the mixture was refluxed for 2 h. After the mixture cooled to 0 °C, the precipitate was collected by filtration (2.15 g, 85%) and recrystallized from methylene chloride to give the analytical sample as white crystals: mp 287–288 °C; UV 205, 255 nm; ^1H NMR 10.40 (br s, 1 H, NH), 8.06 (s, 1 H, thiophene H), 7.25 (m, 4 H, aromatic H); mass spectrum m/e 267 (M^+).

Anal. Calcd for $C_{11}H_6ClNOS_2$: C, 49.34; H, 2.26; N, 5.23; S, 23.95; Cl, 13.24. Found: C, 49.34; H, 2.37; N, 5.33; S, 23.91; Cl, 13.50.

Acknowledgment. We acknowledge W. Fulmor and staff for spectral analyses, G. Morton for helpful insights on ^1H NMR spectra, and L. Brancone and staff for microanalytical elemental analyses.

Registry No. **1**, 70438-03-8; **2**, 70438-23-2; **4**, 2689-68-1; **5**, 95-55-6; **6**, 137-07-5; **7**, 72205-85-7; **8**, 72205-86-8; **9**, 72205-87-9; **10**, 72205-88-0; **11**, 72205-89-1; **12**, 70438-00-5; **13**, 70438-01-6; **14**, 70438-02-7; **16**, 72205-90-4; **17**, 72205-91-5; **18**, 72205-92-6; **19**, 1141-88-4; **20**, 70438-21-0; **21**, 70438-22-1; **22**, 72205-93-7; **23**, 70438-17-4; **24**, 70438-40-3; *N*-methyl-*o*-aminothiophenol, 21749-63-3; 2-(methylthio)aniline, 2987-53-3.

Synthesis of C-Ring-Functionalized A-Ring-Aromatic Trichothecane Analogues

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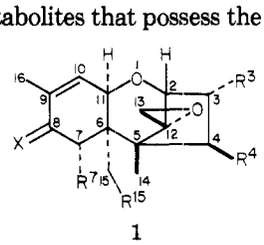
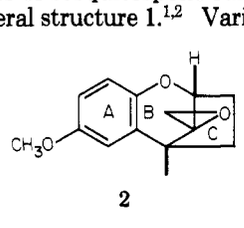
15,16-Dinor-4α-acetoxy-8-methoxy-6,8,10-trichothecatriene 12,13-epoxide (**11**) was prepared from 2α-(2-acetoxy-5-methoxyphenyl)-2β-methyl-3α-acetoxycyclopentanone (**8**) in three steps (bromination, DBN-induced cyclization, and spiroepoxidation). The cyclopentanone **8** was prepared from the hemiketal **6a** which was prepared from 2′-acetoxy-5′-methoxyacetophenone (**3f**) in a reaction sequence involving the boron trifluoride catalyzed aldol addition of 1,2-bis(trimethylsilyloxy)cyclobutene followed by a trifluoroacetic acid catalyzed pinacol rearrangement of the cyclobutanone intermediate.

The trichothecanes are a class of sesquiterpene fungal metabolites that possess the general structure **1**.[1,2] Various



1



2

members of this class have been demonstrated to possess a number of interesting biological properties, including significant antineoplastic activity.[1] We recently reported a synthesis of an A-ring aromatic trichothecane analogue, **2**,[3] and have subsequently shown that this compound possesses significant in vivo antileukemic activity (P388).[4]

We now wish to report a synthesis of A-ring aromatic trichothecane analogues that possess C-ring functionality analogous to the naturally occurring trichothecanes.

The strategy for the synthesis of C-ring functionalized compounds, like our previous approach, involves the assembly of the requisite A and C rings and subsequent cyclization of the B ring through the formation of the 1,2-ether bond. In the present approach, the A- and C-ring backbone was prepared using an aldol addition–pinacol rearrangement sequence.[5]

2′,5′-Dimethoxyacetophenone[6] (**3a**) was converted to the dimethyl ketal **3b** by treatment with 1 equiv of trimethyl orthoformate in refluxing absolute methanol containing a catalytic amount of *p*-toluenesulfonic acid monohydrate. A mixture of **3b** and 1,2-bis(trimethylsilyloxy)cyclobutene[7] in dichloromethane was treated with 2 equiv of boron trifluoride etherate at −78 °C, and the cyclopentadione **5a** was obtained in 39% yield along with 50–60% of the pi-

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(2) Baccharin has a β-epoxide in place of the 9,10-double bond.[1g]

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(4) Anderson, W. K.; Lee, G. E. *J. Med. Chem.*, in press.

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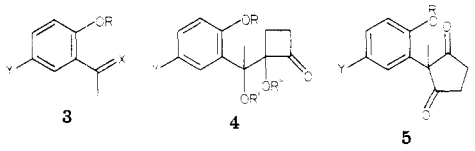
(6) (a) The Friedel–Crafts acylation of *p*-dimethoxybenzene in polyphosphoric acid–acetic acid gave **3a** in nearly twice the literature yield, **6b** when the reaction was conducted at 60–75 °C instead of 85 °C. (b) Horton, J. W.; Spence, J. J. *J. Am. Chem. Soc.* **1955**, *77*, 2894.

(7) Bloomfield, J. J.; Nolke, J. M. *Org. React.* **1976**, *23*, 259.

0022-3263/80/1945-0501$01.00/0

Table I



3 4 5

compd	R	R′	R″	X	Y
3a	CH_3			O	OCH_3
3b	CH_3			$(OCH_3)_2$	OCH_3
3c	CH_3			$(OCH_3)_2$	H
3d	$PhCH_2$			$(OCH_3)_2$	OCH_3
3e	CH_3SO_2			$(OCH_3)_2$	OCH_3
3f	CH_3CO			O	OCH_3
3g	CH_3CO			O	H
4a	CH_3	CH_3	$Si(CH_3)_3$		OCH_3
4b	CH_3	CH_3	H		OCH_3
4c	CH_3	CH_3	$Si(CH_3)_3$		H
4d	CH_3	CH_3	H		H
5a	CH_3				OCH_3
5b	CH_3				H
5c	H				H
5d	CH_3SO_2				OCH_3
5e	CH_3CO				OCH_3
5f	CH_3CO				H

nacols **4a** and **4b**. The ratio of **4a** to **4b**, as determined by ^1H NMR, was approximately 4:1. The mixture of **4a** and **4b** was dissolved in trifluoroacetic acid (TFA) and stirred for 1 h at 40 °C to give **5a** (19%) and **4b** (40%). The unsilylated pinacol **4b**, in contrast to systems studied by Nakamura and Kuwajima,[5] failed to rearrange to **5a** under a variety of conditions (refluxing TFA, refluxing methanolic hydrogen chloride, and acetic acid–hydrobromic acid). (See Table I for structures.)

Treatment of **3c** with 1,2-bis(trimethylsilyloxy)cyclobutene gave **4c** and **4d** in a ratio of approximately 3:1. In contrast to the preceding reaction with **3b**, only a minor amount of the cyclopentadione **5b** was produced. The crude mixture of **4c** and **4d** was treated with TFA to give **5b** (39%) and **4d** (44%). The unsilylated pinacol **4d**, as previously noted for **4b**, failed to rearrange to the dione.

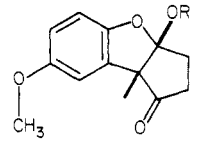
The methyl ether in **5b** proved difficult to cleave, and a number of standard conditions for effecting such a reaction failed in this instance. The cleavage was finally carried out using boron tribromide in dichloromethane at 23 °C for 2 h; the product, **5c**, existed exclusively as the hemiketal.

The stability of the 2′-methoxy group toward acid-catalyzed cleavage prompted us to explore other potential phenol protecting groups. 2′-Benzyloxy-5′-methoxyacetophenone dimethyl ketal (**3d**) yielded an intractable mixture under the preceding aldol conditions. The mesylated dimethyl ketal, **3e**, was smoothly converted to the pinacol which, without isolation, was converted to **5d** in 45% overall yield. Alkaline hydrolysis of the phenyl mesylate was accompanied by cleavage of the 1,3-diketone.

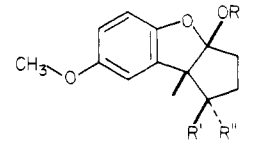
The most expedient protecting group was the acetate ester. The boron trifluoride catalyzed condensation of **3f**[8] with 1,2-bis(trimethylsilyloxy)cyclobutene failed to proceed at temperatures below 0 °C. The reaction did proceed when 2 equiv of boron tribromide was used and the reaction was carried out at 23 °C; no pinacols were obtained. The products were **5e** (7%), **6a** (12%), 2′-hydroxy-5′-methoxyacetophenone (56%), and 2-(β-carboethoxy)-3-methyl-5-methoxybenzo[*b*]furan. The acetate **5e** was converted to **6a** (90%) by treatment with potassium carbonate in absolute methanol–dichloromethane.

In a similar reaction, the acetophenone **3g** was converted to a mixture of **5f** (9%) and **5c** (19%) along with 14% 2-(β-carboethoxy)-3-methylbenzo[*b*]furan.

Reduction of the hemiketal **6a** with sodium cyanoborohydride under acidic conditions gave the alcohol **7a** (99%) with no trace (by TLC, ^1H NMR, and ^{13}C NMR) of the isomeric alcohol **7b**. The stereoselectivity of the



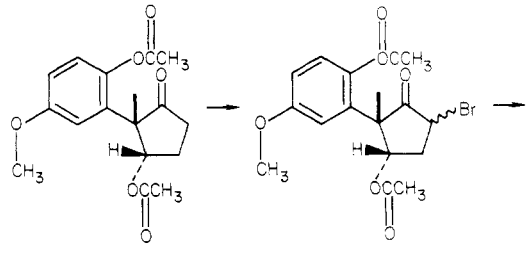
6a, R = H
b, R = CH_3



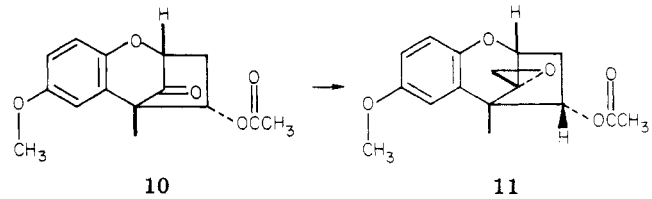
7a, R = R′ = H; R″ = OH
b, R = R″ = H; R′ = OH
c, R = CH_3; R′ = H; R″ = OH

reduction of **6a** was attributed to the fact that the α-face of the C-1 carbonyl is very hindered. The β-hydroxyl at C-3a could also have an effect upon the orientation in the reduction, but this was shown to be less significant since reduction of **6b** (prepared in quantitative yield from **6a** by treatment with absolute methanol containing a trace of hydrogen chloride) with lithium aluminum hydride afforded the C-1α alcohol **7c**. For purposes of comparison, the alcohol **7a** was converted to a mixed ketal which was identical in all respects (^1H NMR, ^{13}C NMR, IR, TLC, melting point, and mixture melting point) with **7c**. Aluminum isopropoxide–isopropyl alcohol reduction (Meerwein–Ponndorf–Verley conditions) of **6b** failed, even under forcing conditions, to give any reduction products, and starting material was recovered.

Acetylation of **7a** gave the diacetate **8** which, on treatment with cupric bromide in chloroform–ethyl acetate (1:1), was converted to an epimeric mixture of α-bromo ketones, **9**. Treatment of **9** with DBN (containing a trace



8 **9**



10 **11**

of water) effected hydrolysis of the phenyl acetate and concomitant cyclization to give 13,15,16-trinor-4α-acetoxy-8-methoxytrichotheca-6,8,10-trien-12-one (**10**). The ketone **10** was converted to the spiro epoxide **11** by the inverse addition of dimethylsulfonium methylide.

This synthesis exemplifies the use of 1,2-bis(trimethylsilyloxy)cyclobutene in conjunction with ortho-substituted acetophenones in an aldol addition–pinacol rearrangement sequence to generate the required eleven carbon backbone for ring-A aromatic trichothecanes. The two cyclopentadione carbonyls can be distinguished through the formation of an intramolecular hemiketal. The drawback of the present approach lies in the low yield of the initial aldol reaction, and further work will be re-

(8) The acetophenone **3f** was used rather than the corresponding dimethyl ketal because of difficulties encountered in the preparation of the ketal.

quired to improve upon this step. The cyclization of **9** was also a low-yield step; this was due to the instability of the tricyclic ketone **10**, and improved conditions for its isolation and purification will be required. The overall method is attractive because it is short (the spiro epoxide **11** was prepared in eight steps from the acetophenone) and versatile.

Experimental Section

Melting points (uncorrected) were determined on a Thomas–Hoover Unimelt apparatus in an open capillary. IR spectra were determined with a Perkin–Elmer 237 or 227B spectrophotometer. UV spectra were determined with a Beckman DB-G spectrophotometer using 1-cm matched cells. NMR spectra were determined for $CDCl_3$ solutions (unless otherwise specified) containing 1% (v/v) tetramethylsilane as an internal standard with a Varian T-60 or FT-80 spectrometer. Low-resolution mass spectra were determined with a Perkin–Elmer RMU-6 mass spectrometer at an ionizing voltage of 70 eV; high-resolution mass spectra were determined by the NIH Biomedical Technology Center at Cornell University. Elemental analyses were performed by Atlantic Microlabs Inc., Atlanta, GA.

2′,5′-Dimethoxyacetophenone (3a). A mixture of polyphosphoric acid (159 g, technical grade) and glacial acetic acid (8.0 g, 0.125 mol) was heated to 60 °C in a 250 mL wide-mouthed Erlenmeyer flask. *p*-Dimethoxybenzene (13.87 g, 1.0 mol) was added in 0.5-g portions, with vigorous stirring, at a rate which would maintain the reaction temperature between 70 and 75 °C. The dark-red reaction mixture was stirred (manually) for an additional 15 min at 75 °C, poured into ice water (800 mL), and extracted with ether (3 × 500 mL). The ethereal solution was washed with saturated NaCl solution (200 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. The residue was distilled to yield 12.4 g (69%) of 2′,5′-dimethoxyacetophenone (**3a**): bp 96 °C (0.25 torr) (lit.[6b] 155–158 °C (11 torr)); NMR (CCl_4) δ 2.48 (s, 3), 3.70 (s, 3), 3.78 (s, 3), and 6.67–7.18 (m, 3); IR (CCl_4) 2995, 2940, 2890, 2832, 1675, 1605, 1487, and 1215 cm^{-1}.

2′,5′-Dimethoxyacetophenone Dimethyl Ketal (3b). A stirred solution of 2′,5′-dimethoxyacetophenone (**3a**, 20.0 g, 0.11 mol), trimethyl orthoformate (11.8 g, 0.111 mol), and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol) dissolved in absolute methanol (300 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool to room temperature, treated with anhydrous sodium carbonate (5 g), and concentrated in vacuo. The residue was dissolved in dichloromethane (250 mL), washed with 1% aqueous sodium carbonate (2 × 100 mL), dried (anhydrous sodium carbonate), and concentrated in vacuo. Anhydrous potassium carbonate (1 g) was added, and the residue was distilled to yield 22.7 g (80%) of 2′,5′-dimethoxyacetophenone dimethyl ketal (**3b**): bp 88 °C (0.2 torr); IR (CCl_4) 2980, 2930, 2895, 2818, 1583, [1675 (no absorption)], 1490, 1218, and 1047 cm^{-1}; UV max 291 nm (ε 2920) and 227 (8125); NMR (CCl_4) δ 1.57 (s, 3), 3.10 (s, 6), 3.73 (s, 3), 3.77 (s, 3), and 6.67–7.25 (m, 3).

2′-Methoxyacetophenone Dimethyl Ketal (3c). 2′-Methoxyacetophenone was treated as before (for **3b**) to give **3c** (83%): bp 71 °C (0.4 torr); mp 39.5–40 °C (crystallized from hexane); IR (CCl_4) [1670 (no absorption)], 1600, 1580, 1486, 1460, 1435, 1290, 1246, and 870 cm^{-1}; UV max 278 nm (ε 1800), 272 (1930), and 229 (3070); NMR (CCl_4) δ 1.55 (s, 3), 3.05 (s, 6), 3.78 (s, 3), and 6.60–7.67 (m, 4).

2′-Benzyloxy-5′-methoxyacetophenone Dimethyl Ketal (3d). A stirred solution of 2′-benzyloxy-5′-methoxyacetophenone (10.0 g, 0.039 mol), trimethyl orthoformate (6.34 g, 0.059 mol), and anhydrous methanolic hydrogen chloride (1 mL) dissolved in anhydrous methanol (150 mL) was heated under reflux for 12 h. The reaction mixture was treated as before (for **3b**) and the residue was crystallized from carbon tetrachloride–petroleum ether (4:1) to yield 10.19 g (86%) of **3d**: mp 87–88 °C; IR (CCl_4) [no absorption 1740–1620), 1489, 1210, 1040, and 868 cm^{-1}; UV max 291 nm (ε 3340) and 228 (11 110); NMR (CCl_4) δ 1.65 (s, 3), 3.15 (s, 6), 3.72 (s, 3), 5.00 (s, 2), and 6.63–7.55 (m, 8).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.35; H, 7.37.

2′-Mesyloxy-5′-methoxyacetophenone Dimethyl Ketal (3e). A stirred solution of 2′-mesyloxy-5′-methoxyacetophenone (61.1 g, 0.25 mol), trimethyl orthoformate (53.1 g, 0.5 mol), and saturated anhydrous methanolic hydrogen chloride (5 mL) in absolute methanol (500 mL) was heated under reflux for 2 h. The cooled reaction mixture was diluted with dichloromethane (500 mL), treated with sodium bicarbonate (5 g), and vigorously shaken until neutral. The neutralized reaction mixture was filtered through analytical grade Celite and concentrated in vacuo to give a colorless oil which was crystallized from diisopropyl ether–petroleum ether (1:5) to yield 72.15 g (99%) of **3e**: mp 44.5–45.5 °C; IR (CCl_4) [3200–3600 (no absorption)], 3015, 2960, 2855, 1800–1625 (no absorption), 1495, 1368, 1200, 1167, 1075, 1043, 978, and 860 cm^{-1}; UV max 286 nm (ε 1850), 279 (2090), 227 (10 630), and 205 (12 050), NMR (CCl_4) δ 1.60 (s, 3), 3.15 (s, 9), 3.77 (s, 3), 6.73–7.22 (m, 3).

Anal. Calcd for $C_{12}H_{18}O_6S$: C, 49.64; H, 6.25. Found: C, 49.58; H, 6.24.

2′-Acetoxy-5′-methoxyacetophenone (3f). Acetic anhydride (112 g, 1.1 mol) was added to a stirred solution of 2′-hydroxy-5′-methoxyacetophenone (91.2 g, 0.549 mol) in pyridine (700 mL, dried over 4 A molecular seives). The mixture was heated to reflux (ca. 30 min), cooled, and concentrated in vacuo with the last traces of pyridine removed by azeotropic distillation with toluene. The residue was distilled to yield 113.2 g (99%) of **3f**: bp 135 °C (0.2 torr); mp 59.5–60.5 °C (crystallized from diisopropyl ether); IR (CCl_4) 1764, 1686, 1486, 1041, 909, 862, and 694 cm^{-1}; UV max 308 nm (ε 2200); NMR (CCl_4) δ 2.23 (s, 3), 2.45 (s, 3), 3.78 (s, 3), and 6.83–7.27 (m, 3).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.41; H, 5.81.

2′-Benzyloxy-5′-methoxyacetophenone. A stirred mixture of 2′-hydroxy-5′-methoxyacetophenone (19.3 g, 0.116 mol), anhydrous potassium carbonate (32.1 g, 0.232 mol), and benzyl bromide (29.8 g, 0.174 mol) in acetone (150 mL) was heated under reflux for 72 h. The cooled reaction mixture was filtered, the precipitate was washed with acetone (2 × 100 mL), and the combined acetone solution was concentrated in vacuo. The residue was dissolved in ether (500 mL), and the ethereal solution was washed with water (100 mL) and saturated NaCl solution (100 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. Anhydrous potassium carbonate was added, and the residue was distilled to yield 29.7 g (99%) of 2′-benzyloxy-5′-methoxyacetophenone: bp 156 °C (0.14 torr); IR (CCl_4) 1689, 1497, 1418, 1285, 1212, and 1047 cm^{-1}; UV max 335 nm (ε 3880) and 248 (6220); NMR (CCl_4) δ 2.47 (s, 3), 3.67 (s, 3), 4.97 (s, 2), 6.75–7.25 (m, 3), and 7.27 (s, 5).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.08; H, 6.33.

2-Methyl-2-(2′,5′-dimethoxyphenyl)cyclopentane-1,3-dione (5a). 2′,5′-Dimethoxyacetophenone dimethyl ketal (**3b**, 18.74 g, 0.0737 mol) dissolved in anhydrous dichloromethane (75 mL) was added (via syringe through a rubber injection septum) to a magnetically stirred solution of boron trifluoride etherate (21.0 g, 0.148 mol) in anhydrous dichloromethane (200 mL), and maintained at −78 °C under a nitrogen atmosphere to produce a dark-red BF_3–acetal complex. A solution of 1,2-bis(trimethylsilyloxy)cyclobutene (17.0 g, 0.0737 mol) in anhydrous dichloromethane (75 mL) was added via syringe, and the reaction mixture was maintained at −78 °C with stirring for 4 h. The cooling bath was removed, and the reaction was allowed to warm to 15 °C; the mixture was treated with water (100 mL), neutralized with saturated aqueous sodium carbonate solution (3 × 100 mL), dried (anhydrous sodium carbonate), and concentrated in vacuo. The residue was crystallized from carbon tetrachloride to give 7.19 g (39%) of 2-methyl-2-(2′,5′-dimethoxyphenyl)cyclopentane-1,3-dione (**5a**). The mother liquor was composed almost exclusively of the silylated pinacol benzylic methyl ether **4a**. Compound **5a** showed the following: mp 159.5 °C; IR ($CHCl_3$) 1730, 1504, 1274, 1235, and 1047 cm^{-1}; UV max 295 nm (ε 2680) and 227 (3810); NMR ($CDCl_3$) δ 1.43 (s, 3), 2.90 (s, 4), 3.63 (s, 3), 3.77 (s, 3), and 6.65–6.97 (m, 3).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.56; H, 6.51.

Trifluoracetic Acid Catalyzed Rearrangement of 4a. The silylated pinacol benzylic methyl ether (**4a**) (16 g, as a crude oil) was dissolved in trifluoracetic acid (25 mL, 99%) and stirred for 1 h at 40 °C. The reaction mixture was diluted with dichloromethane (500 mL), washed with water (2 × 100 mL) and then

with saturated NaCl solution (50 mL), dried (anhydrous sodium carbonate), and concentrated in vacuo. The residue was crystallized from carbon tetrachloride to give 3.41 g (19%) of 2-methyl-2-(2',5'-dimethoxyphenyl)cyclopentane-1,3-dione (**5a**); the mother liquor was concentrated in vacuo and distilled to give 8.32 g (40%) of unsilylated pinacol benzylic methyl ether (**4b**): bp 155 °C (0.175 torr); IR ($CHCl_3$) 3550, 2956, 2849, 1790, 1618, 1594, 1495, 1384, 1042 cm^{-1}; NMR (CCl_4) δ 1.22 and 1.33 (diastereomeric d, 3), 2.18–2.62 (m, 4), 3.55 (s, 3), 3.68 (s, 3), 3.75 (s, 3), 3.93 and 4.05 (diastereomeric d, 1, OH), and 6.43–6.78 (m, 3); mass spectrum, *m/e* (relative abundance) $M^+ + 1$, 281 (11.5), M^+, 280 (60), 248 (25), 247 (28), 220 (12), 219 (12), 207 (23), 196 (35), 195 (100), 193 (32), 185 (14), 181 (37), 180 (89), 179 (76), 178 (43), 177 (48), 166 (41), 165 (83), 164 (90), 163 (68), 162 (69), 161 (45), 160 (75), 152 (79), 150 (73), 148 (22), and 147 (22).

2-Methyl-2-(2'-methoxyphenyl)cyclopentane-1,3-dione (5b). 2'-Methoxyacetophenone dimethyl ketal (**3c**, 17.7 g, 0.0903 mol) dissolved in anhydrous methylene chloride (75 mL) was added to a solution of boron trifluoride etherate (19.7 g, 1.35 mol) in anhydrous dichloromethane (200 mL) under the conditions given for **5a** and treated with 1,2-bis[(trimethylsilyl)oxy]cyclobutene (20.8 g, 0.0903 mol) in anhydrous dichloromethane (75 mL) as described for **5a**. After workup, the residue was dissolved in carbon tetrachloride, and a maximum of 0.4 g (2%) of 2-methyl-2-(2'-methoxyphenyl)cyclopentane-1,3-dione (**5b**) was crystallized from solution. The mother liquor was almost exclusively silylated pinacol benzylic methyl ether (**4c**). Compound **5b** showed the following: mp 138.5–139.5 °C; IR ($CHCl_3$) 1730, 1504, 1274, 1258, 1109, and 1038 cm^{-1}; UV max 279 nm (ϵ 1810) and 272 (1870); NMR ($CDCl_3$) δ 1.47 (s, 3), 2.93 (s, 4), 3.68 (s, 3), and 6.65–7.48 (m, 4).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.68; H, 6.52.

Trifluoroacetic Acid Catalyzed Rearrangement of 4c. The silylated pinacol benzylic methyl ether was treated with TFA as described for **4a**. The crude product mixture was crystallized from carbon tetrachloride to give 7.63 g (39%) of 2-methyl-2-(2'-methoxyphenyl)cyclopentane-1,3-dione (**5b**). The mother liquor was concentrated in vacuo, and the residue was distilled to give 12.61 g (44%) of unsilylated pinacol benzylic methyl ether (diastereomeric mixture) (**4d**): bp 150–155 °C (0.35 torr); IR ($CHCl_3$) 3520, 2957, 2850, 1793, 1618, 1595, 1494, 1465, 1040, and 882 cm^{-1}; NMR ($CDCl_3$) δ 1.27 and 1.38 (diastereomeric d, 3), 2.20–2.67 (m, 4), 3.55 (s, 3), 3.78 (s, 3), 3.98 and 4.10 (diastereomeric d, 1, OH), and 6.60–7.33 (m, 4).

2-Methyl-2-(2'-hydroxyphenyl)cyclopentane-1,3-dione (5c) and *cis*-1-Oxo-3α-hydroxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan. A stirred solution of 2-methyl-2-(2-methoxyphenyl)cyclopentane-1,3-dione (**5b**, 1.5 g, 6.87 mmol) in dichloromethane (20 mL) was cooled to −78 °C under a nitrogen atmosphere and treated with boron tribromide (1.72 g, 6.87 mmol, added via syringe through a rubber injection septum). The reaction mixture was stirred at −78 °C for 1 h, the cooling bath was removed, and the reaction mixture was stirred at room temperature for an additional 2 h. The reaction mixture was poured over ice water (100 mL) and extracted with ether (2 × 100 mL). The ethereal extracts were combined, washed with water (50 mL) and then with saturated NaCl solution (50 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane–ether (97:3)) to yield 1.22 g (87%) of *cis*-1-oxo-3a-hydroxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzo[*b*]furan: mp 110–111 °C; IR ($CHCl_3$) 3559, 3289, 1742, 1475, 1253, 1149, 913, and 724 cm^{-1}; UV max 296 nm (ϵ 1210) and 284 (2260); NMR ($CDCl_3$) δ 1.40 (s, 3), 1.85–2.78 (m, 4), 3.58–3.85 (s, 1, OH), 6.57–7.37 (m, 4).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.58; H, 5.95.

***cis*-1-Oxo-3α-hydroxy-8b-methyl-2,3,3a,3b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan. Method A.** A solution of 2-methyl-2-(2'-acetoxyphenyl)cyclopentane-1,3-dione (**5f**, 11.6 g, 47.1 mmol) in reagent grade acetone (100 mL) was treated with 10% aqueous HCl (10 mL) and stirred under reflux for 18 h. The reaction mixture was concentrated in vacuo, diluted with dichloromethane (200 mL), washed with water (3 × 50 mL) and then with saturated NaCl solution (50 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo to leave a white crystalline residue which was crystallized from carbon tetrachloride to yield 9.6 g (99%) of *cis*-1-oxo-3a-hydroxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]furan: mp 110–111 °C; this material was spectroscopically identical with that obtained directly from the annelation reaction.

Method B. 2-Methyl-2-(2'-acetoxyphenyl)cyclopentane-1,3-dione (**5f**, 0.124 g, 0.5 mmol) dissolved in dichloromethane (1 mL) was added to a solution of saturated aqueous potassium carbonate (0.1 mL) in methanol (1 mL) and stirred under reflux for 30 min. The mixture was neutralized with 10% aqueous HCl and concentrated in vacuo. The remaining wet slurry was dissolved in dichloromethane (25 mL), washed with saturated NaCl solution (5 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. The residue was purified by silica gel chromatography [dichloromethane–ether (97:3)] to yield 0.0192 g (90%) of *cis*-1-oxo-3a-hydroxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta-[*b*]benzo[*b*]furan and 0.006 g (6%) of 2-(β-carbomethoxyethyl)-3-methylbenzo[*b*]furan.

2-Methyl-2-(2'-mesyloxy-5'-methoxyphenyl)cyclopentane-1,3-dione (5d). 2'-Mesyloxy-5'-methoxyacetophenone dimethyl ketal (**3e**, 29.0 g, 0.1 mol) was treated with boron trifluoride etherate (14.2 g, 0.1 mol) and 1,2-bis(trimethylsilyloxy)cyclobutene (23.0 g, 0.1 mol) as described for **5a** except the reaction was allowed to warm to room temperature over 12 h before it was worked up. The reaction mixture was treated with water (100 mL), washed with water (100 mL portions) until the washings were neutral, dried (anhydrous sodium sulfate), and concentrated in vacuo. The residue was dissolved in trifluoroacetic acid (50 mL, 99%) and stirred at 40 °C for 1 h. The reaction mixture was diluted with dichloromethane (500 mL), washed with water (100-mL portions until the washings were neutral) and then with saturated NaCl solution (100 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo. The residue was dissolved in chloroform (20 mL) and, upon the addition of carbon tetrachloride (100 mL), crystallized to give 14.1 g (45%) of 2-methyl-2-(2'-mesyloxy-5'-methoxyphenyl)cyclopentane-1,3-dione (**5d**). The mother liquor contained 5–10% of additional **5d**. On one occasion, the recovery of residual dione was successfully accomplished by fractional distillation on a microscale. The pot and distillation column were rapidly heated by means of a heating mantle and electrical heating tape. The first fraction was sufficiently pure to allow crystallization of **5d** in 5% yield. On subsequent attempts extensive pyrolysis occurred. Compound **5d** showed the following: mp 133–134 °C; bp 210 °C (0.3 torr); IR ($CHCl_3$) 1725, 1596, 1487, 1375, and 1163 cm^{-1}; UV max 283 nm (ϵ 2290), 223 (9920), and 204 (27 440); NMR ($CDCl_3$) δ 1.52 (s, 3), 2.95 (s, 3), 3.07 (s, 4), 3.83 (s, 3), and 6.70–7.65 (m, 3).

Anal. Calcd for $C_{14}H_{16}O_6S$: C, 53.84; H, 5.16. Found: C, 53.86; H, 5.21.

2-Hydroxy-2-(β-carbomethoxyethyl)-3-methyl-5-methoxy-2,3-dihydrobenzo[*b*]furan. A stirred solution of 2-methyl-(2'-mesyloxy-5'-methoxyphenyl)cyclopentane-1,3-dione (**5d**, 0.1 g, 0.32 mmol) in methanol (5 mL) was treated with 15% aqueous NaOH (0.1 mL) and heated under reflux for 15 min. The cooled reaction mixture was neutralized with 10% aqueous HCl and concentrated in vacuo, and the aqueous residue was extracted with dichloromethane (10 mL). The dichloromethane solution was washed with saturated NaCl solution (1 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo to give 0.09 g (100%) of 2-hydroxy-2-(β-carbomethoxyethyl)-3-methyl-5-methoxy-2,3-dihydrobenzo[*b*]furan: IR ($CHCl_3$) 3340 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (d, J = 7 Hz, 3), 2.27–2.95 (m, 4), 3.25 (s, 3), 3.45 (s, 1, OH), 3.60 (s, 3), 4.13 (q, J = 7 Hz, 1), and 6.63–7.37 (m, 3).

2-Methyl-2-(2-acetoxy-5-methoxyphenyl)cyclopentane-1,3-dione (5e). 2'-Acetoxy-5'-methoxyacetophenone (**3f**, 52.05 g, 0.25 mol) was treated with boron trifluoride etherate (35.5 g, 0.5 mol) and 1,2-bis(trimethylsilyloxy)cyclobutene (57.62 g, 0.25 mol) as described for **5a** and stirred at −40 °C for 1 h (TLC evaluation of the reaction mixture at this temperature showed no appreciable formation product). The temperature of the reaction mixture was allowed to rise slowly to room temperature over a 12-h period. The reaction mixture was diluted with ether (1 L) and washed with water (250-mL portions) until the washings were neutral. The organic phase was washed with saturated NaCl solution (250 mL), dried (anhydrous sodium sulfate), and con-

centrated in vacuo. The residue was dissolved in dichloromethane (50 mL), and the solution was diluted with carbon tetrachloride (250 mL); 2-methyl-2-(2-acetoxy-5-methoxyphenyl)cyclopentane-1,3-dione (**5e**) crystallized from solution to give 4.58 g (7%). The mother liquor was concentrated in vacuo and purified by silica gel chromatography; elution with dichloromethane gave 23.31 g (56%) of 2′-hydroxy-5′-methoxyacetophenone; elution with dichloromethane–ether (97:3) gave 2.62 g (5%) of *cis*-1-oxo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzobenzo[*b*]furan (**6a**) and 7.6 g (12%) of 2-(β-carboxyethyl)-3-methyl-5-methoxybenzo[*b*]furan.

5e: mp 178.5–179.5 °C; IR ($CHCl_3$) 1764, 1727, 1495, 1372, 1170, 1036, and 905 cm^{-1}; UV max 281 nm (ε 1680); NMR ($CDCl_3$) δ 1.50 (s, 3), 2.15 (s, 3), 2.95 (s, 4), 3.80 (s, 3), and 6.67–7.30 (m, 3).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.18; H, 5.84.

6a: mp 123–123.5 °C (CCl_4); IR ($CHCl_3$) 3623, 3279, 1727, 1475, 1176, 891, and 769 cm^{-1}; UV max 287 nm (ε 2620); NMR ($CDCl_3$) δ 1.38 (s, 3), 1.78–2.78 (m, 4), 3.73 (s, 3), 3.78–4.02 (s, OH, 1), and 6.57–6.88 (m, 3).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.74; H, 6.03.

2-Methyl-2-(2-acetoxyphenyl)cyclopentane-1,3-dione (5f). 2′-Acetoxyacetophenone (**3g**, 53.5 g, 0.3 mol) was treated with boron trifluoride etherate (42.6 g, 0.3 mol) as before. The mixture was then treated with 1,2-bis(trimethylsilyloxy)cyclobutene (69.1 g, 0.3 mol, dissolved in 200 mL of anhydrous dichloromethane) and allowed to warm slowly to room temperature (ca. 4 h). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for an additional 18 h, washed with water (100 mL portions until the washings were neutral) and then with saturated NaCl solution (100 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo to give a light-amber oil. The oil was placed on a silica gel column and eluted with dichloromethane (to remove the unreacted starting materials) followed by elution with dichloromethane–ether (9:1) to give a light-yellow oil. The oil was crystallized from carbon tetrachloride to yield 6.47 g (9%) of 2-methyl-2-(2-acetoxyphenyl)cyclopentane-1,3-dione (**5f**), and the mother liquor was purified by silica gel chromatography with dichloromethane–ether (97:3) to give 11.7 g (19%) of *cis*-1-oxo-3a-hydroxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzo[*b*]furan (**5c** hemiketal) and 8.5 g (14%) of 2-(β-carboxyethyl)-3-methylbenzo[*b*]furan.

5f: mp 162.5–163 °C; IR ($CHCl_3$) 1773, 1727, 1495, 1376, 1178, 1105, and 913 cm^{-1}; UV max 264 nm (ε 380) and 284 (220); NMR ($CDCl_3$) δ 1.50 (s, 3), 2.17 (s, 3), 2.93 (s, 4), and 7.03–7.58 (m, 4).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.27; H, 5.77.

5c hemiketal: mp mp 110–111 °C; IR ($CHCl_3$) 3359, 3289, 1742, 1475, 1253, 1149, 913, and 724 cm^{-1}; UV max 296 nm (ε 1200) and 284 (2260); NMR ($CDCl_3$) δ 1.40 (s, 3), 1.85–2.78 (m, 4), 3.58–3.85 (s, 1, OH), and 6.57–7.37 (m, 4).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.58; H, 5.95.

***cis*-1-Oxo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (6a).** 2-Methyl-2-(2-acetoxy-5-methoxyphenyl)cyclopentane-1,3-dione (**5e**, 4.58 g, 16.58 mmol) dissolved in dichloromethane (10 mL) was added to a solution of saturated potassium carbonate (5 mL) in methanol (40 mL) and stirred at room temperature for 8 h. The mixture was acidified with 10% aqueous HCl (pH 5) and concentrated in vacuo. The remaining wet slurry was taken up in dichloromethane (200 mL), washed with water (50 mL) and then with saturated NaCl solution (50 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo to give a yellow oil. The oil was crystallized from carbon tetrachloride to give a 3.49-g (90%) yield of *cis*-1-oxo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**6a**) and 0.39 g (9%) of 2-(β-carbomethoxyethyl)-3-methyl-5-methoxybenzo[*b*]furan.

***cis*-1-Oxo-3a,7-dimethoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (6b).** A stirred solution of *cis*-1-oxo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**6a**, 0.4 g, 1.7 mmol) in absolute methanol (20 mL) was treated with saturated methanolic hydrogen chloride (1 mL) and stirred under reflux for 12 h. The dark-red reaction mixture was allowed to cool to room temperature, and anhydrous potassium carbonate (1 g, finely ground) was added. The mixture was stirred vigorously for 5 min (upon neutralization the dark-red color was completely dissipated) and then concentrated in vacuo. The residue was dissolved in dichloromethane (10 mL), filtered through analytical grade Celite with rinsing (1 mL), concentrated under high vacuum, and purified by silica gel chromatography (dichloromethane) to give 0.42 g (99.5%) of *cis*-1-oxo-3a,7-dimethoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**6b**): IR (CCl_4) 1754, 1490, 1206, 1026, and 886 cm^{-1}; UV max 315 nm (ε 2980) and 225 (5210); NMR (CCl_4) δ 1.33 (s, 3), 1.83–2.77 (m, 4), 3.40 (s, 3), 3.68 (s, 3), and 6.47–6.72 (m, 3).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.64; H, 6.54.

***cis*-1α,3a-Dihydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (7a).** A stirred solution of *cis*-1-oxo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**6a**, 5.72 g, 24.4 mmol) dissolved in tetrahydrofuran (300 mL, freshly distilled over $LiAlH_4$) and maintained at pH 3–4 (by the dropwise addition of 10% aqueous HCl) was treated with sodium cyanoborohydride (2.8 g, 44.5 mmol, added in 0.5 g portions) at room temperature. The reaction was monitored every 15 min by TLC. Aliquots (0.2 mL) were removed, treated with water (2 mL), and extracted with 1 mL of dichloromethane. The dichloromethane phase was developed using silica gel with dichloromethane–ether (97:3). After 2 h the reduction was complete. The reaction mixture was poured into water (300 mL) and extracted with ether (3 × 100 mL). The ether–THF solution was concentrated in vacuo. The residue was dissolved in chloroform (100 mL), dried (anhydrous sodium sulfate), filtered (to remove the residual borate salts), and concentrated in vacuo. The residue was crystallized from carbon tetrachloride–chloroform (1:10) to yield 5.69 g (99%) of *cis*-1α,3a-dihydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**7a**): mp 126.5–127.5 °C; IR ($CHCl_3$) 3546, 3390, 1605, 1471, 960, 905, and 820 cm^{-1}; UV max 297 nm (ε 2120); NMR ($CDCl_3$) δ 1.38 (s, 3), 1.45 (s, 1, OH), 1.63–2.58 (m, 4), 3.17 (s, 1, OH), 3.73 (s, 3), 3.78–4.18 (m, 1), and 6.67 (s, 3).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.10; H, 6.85.

***cis*-1α-Hydroxy-3a,7-dimethoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (7c). Method A.** A stirred solution of *cis*-1α,3a-dihydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**7a**, 0.632 g, 2.68 mmol) in absolute methanol (20 mL) was treated with saturated anhydrous methanolic hydrogen chloride (1 mL) and stirred under reflux for 12 h. The dark-red reaction mixture was allowed to cool to room temperature, and anhydrous potassium carbonate (1 g, finely ground) was added. The mixture was vigorously stirred for 5 min (upon neutralization the dark-red color was completely dissipated) and then concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane) to give 0.66 g (98%) of *cis*-1-hydroxy-3a,7-dimethyloxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzo[*b*]furan (**7c**): mp 111–112 °C; IR ($CHCl_3$) 3584, 3448, 1493, 1163, 1031, 905, and 823 cm^{-1}; UV max 298 nm (ε 3770); NMR ($CDCl_3$) δ 1.37 (s, 1, OH), 1.38 (s, 3), 1.50–2.47 (m, 4), 3.43 (s, 3), 3.75 (s, 3), 3.77–4.17 (m, 1), and 6.67 (s, 3).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.06; H, 7.26.

***cis*-1α-Hydroxy-3a,7-dimethoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (7c). Method B.** *cis*-1-Oxo-3a,7-dimethoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**6b**, 0.2 g, 0.806 mmol) in anhydrous ether (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (16 mg, 0.42 mmol, 100% excess) in anhydrous ether (5 mL) under a nitrogen atmosphere at a rate which maintained the mixture under a gentle reflux. The reaction mixture was stirred at room temperature for 15 min, treated with water (1 mL), and stirred for an additional 5 min. The ethereal phase was separated, and the inorganic salts were washed with ether (2 × 20 mL). The ethereal solutions were combined, dried (anhydrous sodium sulfate), and concentrated in vacuo to give a clear colorless oil which crystallized under high vacuum. The product was purified by silica gel chromatography [dichloromethane–ether (97:3)] to give 0.194 g (98%) of *cis*-1α-hydroxy-3a,7-dimethoxy-

8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo[*b*]furan (**7c**): mp 109–110 °C. The product was spectroscopically identical with that obtained through the previous reduction ketalization procedure, although the observed melting point was 1 °C lower.

2-Methyl-3α-acetoxy-2-(2-acetoxy-5-methoxyphenyl)-cyclopentanone (8). Acetic anhydride (12.3 g, 120 mmol, 400% excess) was added to a stirred solution of *cis*-1α,3a-dihydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzo[*b*]furan (**7a**, 5.69 g, 24.1 mmol) in pyridine (50 mL, freshly distilled over CaH_2). The mixture was heated at reflux temperature under a nitrogen atmosphere for 4 h. The dark-brown reaction mixture was concentrated in vacuo, and the last traces of pyridine were removed by azeotropic distillation with toluene. The residue was purified by silica gel chromatography [dichloromethane–ether (9:1)] to give 3.96 g (51%) of 2-methyl-3α-acetoxy-2-(2-acetoxy-5-methoxyphenyl)cyclopentanone (**8**) as a viscous colorless oil: IR (CCl_4) 1770, 1739, 1475, 1370, 1238, 1185, 1058, 1044, and 866 cm^{-1}; UV max 261 nm (ε 220) and 202 (10 230); NMR (CCl_4) δ 1.38 (s, 3), 1.63 (s, 3), 1.87–2.72 [m, 7 (2.15, s, 3, OAc)], 3.73 (s, 3), 5.20–5.42 (m, 1), and 6.50–7.08 (m, 3).

5-Bromo-2-methyl-3α-acetoxy-2-(2-acetoxy-5-methoxyphenyl)cyclopentanone (9). A mixture of cupric bromide (2.61 g, 9.68 mmol) and 2-methyl-3α-acetoxy-2-(2-acetoxy-5-methoxyphenyl)cyclopentanone (**8**, 3.1 g, 9.68 mmol) in ethyl acetate (25 mL, dried by elution through basic activity grade I alumina) and chloroform (25 mL, dried by elution through neutral activity grade I alumina) was heated to reflux under a nitrogen atmosphere. After 2.5 h the dark-green cupric bromide had been completely consumed to give an amber solution containing the precipitated cuprous bromide. The reaction mixture was allowed to cool to room temperature and filtered through analytical grade Celite, and the cuprous salt washed with chloroform (50 mL). The combined filtrates were concentrated in vacuo, and the amber residue was purified by column chromatography (silica gel–dichloromethane) to give 2.7 g of the 5-bromo ketone. This oil was further purified by medium-pressure liquid chromatography (silica gel H/dichloromethane) to yield 2.61 g (68%) of 5-bromo-2-methyl-3-acetoxy-2-(2-acetoxy-5-methoxyphenyl)cyclopentanone (**9**, as an inseparable mixture of α-bromo epimers): IR ($CHCl_3$) 1760, 1618, 1596, 1505, 1378, 1190, 1048, and 763 cm^{-1}; UV max 281 nm (ε 1350) and 284 (1300); NMR ($CDCl_3$) δ 1.62 (s, 3), 1.72 (s, 3), 2.23 (s, 3), 2.47–3.03 (m, 2), 3.80 (s, 3), 4.57–5.10 (m, 1), 5.23–5.65 (m, 1), and 6.63–7.20 (m, 3); mass spectrum, *m/e* (rel abundance) 399 (70), 397 (70), 357 (1.6), 355 (1.6), 320 (11), 318 (28), 276 (26), 275 (25), 234 (34), 233 (97), 220 (11), 216 (16), 215 (56), 205 (26), 191 (74), 178 (95), 176 (31), 162 (21), 150 (54), 148 (23), 135 (46), 133 (18), 91 (21), 83 (23), 77 (31), and 43 (100).

Anal. Calcd for $C_{17}H_{19}O_6Br$: C, 51.14; H, 4.80; Br, 20.02. Found: C, 51.26; H, 4.85; Br, 20.22.

13,15,16-Trinor-4α-acetoxy-8-methoxytrichotheca-6,8,10-trien-12-one (10). DBN (0.23 g, 1.9 mmol) was added to a stirred solution of 5-bromo-2-methyl-3-acetoxy-2-(2-acetoxy-5-methoxyphenyl)cyclopentanone (**9**, 0.745 g, 1.87 mmol) in anhydrous benzene (10 mL). After 2 h at room temperature the consumption of **9** was complete (as judged by TLC). The precipitated amidine–HBr was removed by filtration through analytical grade Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography [dichloromethane–ethyl acetate (4:1)] to give 0.91 g (18%) of 13,15,16-trinor-4-acetoxy-8-methoxytrichotheca-6,8,10-trien-12-one (**10**): IR (CCl_4) 1772, 1745, 1484, 1228, and 1048 cm^{-1}; NMR (CCl_4) δ 1.37 (s, 3), 1.93 (s, 3), 2.20–3.00 (m, 2), 3.72 (s, 3), 4.03–4.25 (d, 1), 4.80–5.13 (d of d, 1), and 6.37–6.73 (m, 3).

15,16-Dinor-4α-acetoxy-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (11). A stirred mixture of NaH (98%, 0.16 g, 6.67 mmol) in Me_2SO (15 mL, dried over CaH_2) was heated to 80 °C (nitrogen atmosphere) for 7 h. The resultant gray solution, 6.67 mmol of sodium methylsulfinylmethide, was cooled to ambient temperature, THF (15 mL, freshly distilled over $LiAlH_4$) was added, and the solution was cooled to −10 °C. Trimethylsulfonium iodide (1.35 g, 6.67 mmol, dried under high vacuum over P_2O_5) was added, and the mixture stirred for 10 min at −10 °C. The ylide solution (2.5 mL, 0.556 mmol, 70% excess) was transferred via syringe through rubber injection septums to a stirred solution of 13,15,16-trinormethyl-4α-acetoxy-8-methoxytrichotheca-6,8,10-trien-12-one (**10**, 0.091 g, 0.329 mmol) in THF (5 mL, distilled over $LiAlH_4$) which was cooled to −40 °C and kept under a purge of nitrogen. The reaction mixture was allowed to warm to 20 °C over a 1-h period. The THF was removed under a stream of nitrogen, and the Me_2SO solution was diluted with water (100 mL) and extracted with ether (2 × 100 mL). The ethereal solution was washed with water (50 mL) and then with saturated NaCl solution (50 mL) and concentrated in vacuo. The residue was taken up in dichloromethane (100 mL), dried (anhydrous sodium sulfate), and concentrated in vacuo to give 0.109 g of crude brown residue. The residue was purified by preparative TLC silica gel [dichloromethane–ether (9:1)] to give 0.017 g (18%) of 15,16-dinor-4α-acetoxy-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (**11**) which by TLC silica gel [dichloromethane–ether (97:3)] showed a trace of chromatographically more mobile impurity. Purification of this material by preparative TLC on silica gel [dichloromethane–ether (97:3)] afforded 0.012 g (13%) of analytically pure (**11**): IR (CCl_4) 2920, 2820, 1740, 1483, 1460, 1423, 1368, 1230, 1192, 1047, and 860 cm^{-1}; NMR (CCl_4) δ 1.33 (s, 3), 1.52–1.85 (d of d, J = 6 Hz, 1), 1.90 (s, 3, OAc), 2.32–2.65 (d of d, J = 6 Hz, 1), 2.68–2.92 (d, $J_{12,13}$ = 5 Hz, 1), 2.95–3.12 (d, $J_{12,13}$ = 5 Hz, 1), 3.70 (s, 3), 3.87–4.05 (d, J = 6 Hz, 1), 4.77–5.10 (d of d, J = 6 Hz, 1), and 6.42–6.75 (m, 3); high-resolution mass spectrum, *m/e* (relative abundance) $M^+ + 1$, 291.1179 (18.27), M^+, 290.1155 (100.00), 247.0960 (27.01), 217.0867 (8.21), 205.0877 (20.82), 204.0783 (16.86), 203.0712 (29.69), 202.0982 (8.65), 201.0899 (5.67), 191.0710 (13.44), 189.0892 (8.26), 189.0541 (18.31), 188.0803 (10.72), 187.0763 (66.97), 178.0673 (15.06), 175.0773 (40.54), 174.0711 (10.85), 161.0599 (10.85), 159.0449 (9.00), 115.0543 (14.10), 103.0542 (7.33).

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Registry No. 3a, 1201-38-3; **3b**, 72229-44-8; **3c**, 72244-69-0; **3d**, 72229-45-9; **3e**, 72229-46-0; **3f**, 72229-47-1; **3g**, 7250-94-4; **4a**, 72229-48-2; **4b**, isomer 1, 72229-49-3; **4b**, isomer 2, 72229-50-6; **4c**, 72229-51-7; **4d**, isomer 1, 72229-52-8; **4d**, isomer 2, 72229-53-9; **5a**, 72229-54-0; **5b**, 72229-55-1; **5c** hemiketal, 72229-56-2; **5d**, 72244-70-3; **5e**, 72229-57-3; **5f**, 72229-58-4; **6a**, 72229-59-5; **6b**, 72229-60-8; **7a**, 72229-61-9; **7c**, 72229-62-0; **8**, 72229-63-1; **9**, isomer 1, 72229-64-2; **9**, isomer 2, 72258-25-4; **10**, 72229-65-3; **11**, 72229-66-4; *p*-dimethoxybenzene, 150-78-7; 2′-(benzyloxy)-5′-methoxyacetophenone, 65547-82-2; 2′-(mesyloxy)-5′-methoxyacetophenone, 72229-67-5; 2′-hydroxy-5′-methoxyacetophenone, 705-15-7; 1,2-bis[(trimethylsilyl)oxy]cyclobutene, 17082-61-0; 2-[β-(carbomethoxy)ethyl]-3-methylbenzo[*b*]furan, 72229-68-6; 2-hydroxy-2-[β-(carbomethoxy)ethyl]-3-methyl-5-methoxy-2,3-dihydrobenzo[*b*]furan, 72229-69-7; 2-(β-carboxyethyl)-3-methyl-5-methoxybenzo[*b*]furan, 72229-70-0; 2-(β-carboxyethyl)-3-methylbenzo[*b*]furan, 6836-90-4; 2-[β-(carbomethoxy)ethyl]-3-methyl-5-methoxybenzo[*b*]furan, 72229-71-1.