up by extraction with 2 *M* aqueous sodium hydroxide solution. The organic phase was dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (SiO_2; ethyl acetate/hexane, 1:9) afforded 0.156 g (63%) **2d**, identical in all respects (TLC, IR, NMR, and MS) with a sample obtained from the reaction of potassium ethyl nitronate with *p*-toluenesulfonyl azide.

Crossover Experiment. Preparation of 2b with Added *p*-Bromobenzenesulfinate. A suspension of the potassium salt of nitrocyclohexane (3.5 mmol) was prepared in 15 mL of THF as described above. Sodium *p*-bromobenzenesulfinate (3.5 mmol, 0.85 g) and tosyl azide (3.5 mmol, 0.69 g) were added, and the mixture was stirred for 20 h. The reaction mixture was partitioned between ether and 2 N NaOH. The organic phase was dried (Na_2SO_4), filtered, and evaporated. At this point, the reaction mixture was indistinguishable by TLC from the reaction which yielded **2b** alone. The product (0.49 g) was isolated by flash chromatography (SiO_2, ethyl/hexane, 1:20) and examined by ^1H NMR (200 MHz, $CDCl_3$). Integration of the doublet at δ 7.35 and the multiplet at δ 7.7 indicated that 33% of the *p*-bromobenzenesulfinate had been incorporated. As a control, tosyl azide (2 mmol, 0.42 g) and sodium *p*-bromo benzenesulfinate (2 mmol, 0.62 g) were stirred in THF at 25 °C for 46 h. Workup and chromatography as above gave 0.4 g (97%) of recovered tosyl azide and 0.01 g (2.4%) of *p*-bromobenzenesulfonyl azide.

Acknowledgment. This work was supported by a grant from the Research Corporation.

Registry No. **1a**, 84602-25-5; **1b**, 1122-60-7; **1c**, 79-46-9; **1d**, 79-24-3; **2a**, 108795-74-0; **2b**, 108795-75-1; **2c**, 108795-76-2; **2d**, 108795-77-3; 4-$H_3CCH_2SC_6H_4CH_3$, 622-63-9; 4-$H_3CCHClSC_6H_4CH_3$, 59480-99-8; 4-$H_3CC_6H_4SO_2N_3$, 941-55-9; 4-$BrC_6H_4SO_3Na$, 34176-08-4; 4-$H_3CC_6H_4SCHN_3CH_3$, 108795-78-4; 4-$BrC_6H_4SO_2N_3$, 6647-76-3.

Synthesis of HT-2 Toxin, Neosolaniol, T-2 Toxin, 3′-Hydroxy T-2 Toxin, and Sporotrichiol from Anguidine by Routes Involving Hydroxyl Inversion/Esterification

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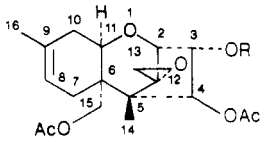
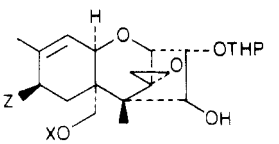
Trichothecenes are a group of more than 50 sesquiterpenoid mycotoxins produced by many fungi.[1] These mycotoxins have been responsible for human and animal toxicoses resulting from consumption of contaminated foodstuff.[1,2] Furthermore, in the recent past, there has been considerable interest in T-2 toxin (**11**) and related mycotoxins because of controversy over their alleged use in chemical/biological warfare in Afghanistan and Southeast Asia.[3]

In connection with our work on the preparation of antisera for the detection of trichothecene mycotoxins in the environment, we needed a hapten with a hemisuccinate ester at C-4 for coupling to the carrier protein. The synthesis of the 4α,8β-dihydroxy precursor **5** (Chart I) of the desired hapten was readily accomplished by selenium dioxide oxidation of the known compound **4**.[4] To convert

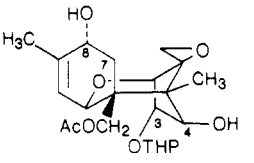
Chart I



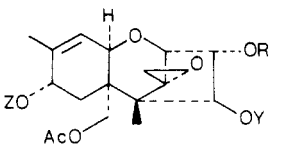
1, R=H
2, R=THP



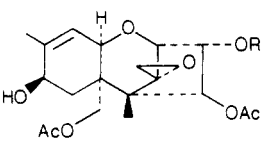
3, X=H, Z=H
4, X=Ac, Z=H



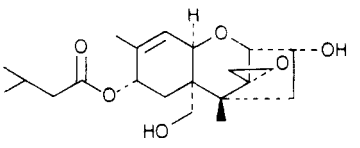
5



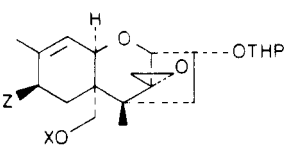
8, R=THP, Y=H, Z=
9, R=H, Y=H, Z=
10, R=H, Y=Ac, Z=H
11, R=H, Y=Ac, Z=
12, R=H, Y=Ac, Z=



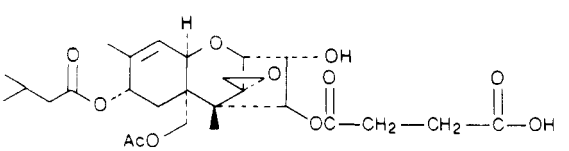
6, R=H
7, R=THP



17



13, X=Ac, Z=H
14, X=H, Z=H
15, X=formyl, Z=H
16, X=formyl, Z=OH



18

5 to the 8α-isovaleryloxy compound **8**, we examined a procedure used for the inversion of steroid alcohols to their formate esters of the opposite configuration.[5] Compound **5** reacted smoothly with diethyl azodicarboxylate (DEAD), triphenylphosphine, and isovaleric acid to yield **8**. This was succinylated and the THP ether cleaved to yield the desired hapten **18**.[6] The ease of inversion of configuration at C-8 led us to examine its applicability to the synthesis of other trichothecenes. In this paper, we report the synthesis of several naturally occurring mycotoxins including the recently isolated sporotrichiol[7] (**17**, 8α-[(3-methylbutyryl)oxy]scirpene-3α,15-diol) from the readily available trichothecene anguidine (**1**, 4β,15-diacetoxyscirpen-3β-ol) using the above methodology. The synthesis of **17** confirms the assigned structure of this natural product.

The synthesis of all the five trichothecenes, HT-2 toxin (**9**, 15-acetoxy-8α-[(3-methylbutyryl)oxy]scirpene-3α,4β-

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(6) Details of this work will be published elsewhere.
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0022-3263/87/1952-3468$01.50/0

diol), neosolaniol (**10**, 4β,15-diacetoxyscirpene-3β,8α-diol), T-2 toxin (**11**, 4β,15-diacetoxy-8α-[(3-methylbutyryl)-oxy]scirpen-3α-ol), 3′-hydroxy T-2 toxin[8] (**12**, 4β,15-diacetoxy-8α-[(3-hydroxy-3-methylbutyryl)oxy]scirpen-3α-ol), and sporotrichiol (**17**)[7] started with the known THP ether **2**[4] of anguidine (**1**).

In connection with the synthesis of HT-2 toxin (**9**), basic hydrolysis of diacetate **2** gave the diol **3**, which upon reacetylation with acetyl chloride and triethylamine in methylene chloride gave the primary acetate **4** in quantitative yield. This two-step procedure is preferable to the one involving selective hydrolysis of **2** with dilute ammonium hydroxide giving **4** in 38% yield.[4] Selenium dioxide oxidation of the primary acetate **4** led to the 4β,8β-diol **5** in 59% yield. Treatment of **5** with DEAD, triphenylphosphine, and isovaleric acid successfully effected inversion–esterification to give exclusively the 8α-isovalerate ester **8** in 35% yield. The hydroxyl function at C-4 was not affected under these conditions, probably due to steric hindrance. Cleavage of the THP ether function with pyridinium tosylate in refluxing 95% ethanol provided HT-2 toxin (**9**).

The trichothecenes **10–12** were also prepared in similar fashion from the 8β-hydroxy intermediate **7**, which in turn was obtained by the selenium dioxide hydroxylation of **2**. Thus, reaction of **7** with DEAD, triphenylphosphine, and formic acid followed by cleavage of the THP ether and selective removal of formate ester at C-8 yielded neosolaniol (**10**). An alternate synthesis of **10** from 8β-hydroxyanguidine **6** has been reported.[4] This procedure involves selective oxidation of the 8β-hydroxy function followed by diisobutylaluminium hydride reduction to give a mixture of 8β- (**6**) and 8α-hydroxy (**10**) compounds.

Substitution of isovaleric acid or 3-hydroxy-3-methylbutanoic acid[8] in the above reaction followed by cleavage of the THP ether yielded T-2 toxin (**11**) and its metabolite 3′-hydroxy T-2 toxin[8] (**12**), respectively. However, for the synthesis of T-2 toxin, it was later discovered that the protection of C-3 hydroxy function was not necessary during the inversion–esterification reaction.

The synthesis of the recently isolated mycotoxin sporotrichiol (**17**) was accomplished by the deoxygenation of the C-4 hydroxy function of **4**, employing a modification of the Barton procedure,[9] to give **13** in 56% yield. The primary acetate at C-15 was then hydrolyzed to the alcohol **14**, and the hydroxyl was subsequently protected as the formate ester **15**. Both of these steps proceeded in excellent yields. This intermediate was then subjected to selenium dioxide hydroxylation to give the 8β-hydroxy compound **16** in moderate (32%) yields. This was then treated with DEAD, triphenylphosphine, and isovaleric acid to effect inversion and esterification. Cleavage of both the THP ether and formate ester using pyridinium tosylate in refluxing 95% MeOH gave the target compound **17** in 22% yield from **16**. The spectral properties (IR, NMR) of **17** were identical with those reported in the literature.

Experimental Section

In view of the potential toxicity of anguidine, other mycotoxins, and intermediates, all operations were carried out in a well-ventilated hood by a chemist wearing protective clothing, double gloves, and goggles. A squeeze bottle containing Chlorox was kept handy in case of an accidental spill. Decontamination of all glassware and used silica gel was accomplished by soaking overnight in a solution of 0.25 N NaOH and 2.5% NaOCl. Additional safety data sheets on mycotoxins may be obtained from Sigma Chemical Company.

All reactions were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was freshly distilled prior to use from lithium aluminium hydride. Column chromatography was performed on slurry packed silica gel (Kieselgel 60, 70–230 mesh) columns or E. M. Merck lobar silica gel columns. GC analysis was performed by using a Varian Aerograph 1400 instrument equipped with a 3% SE 30 on 80/100 Chromosorb WHP column. The infrared spectra were determined in CH_2Cl_2 on a Perkin-Elmer 267 infrared spectrometer. Proton NMR spectra were obtained in $CDCl_3$ with a Bruker WM-250 spectrometer at 250 MHz. NMR data reported with an asterisk are due to the other diastereomer. Chemical shifts are expressed in ppm with tetramethylsilane as an internal standard. Mass spectra were determined with an AEI MS902 spectrometer at an ionizing voltage of 70 eV.

3α-(2-Tetrahydropyranyloxy)-15-acetoxyscirpen-4β-ol (4). To a cold (0 °C) solution of 3α-(2-tetrahydropyranyloxy)scirpene-4β,15-diol (**3**)[4] (0.96 g, 2.6 mmol) in Et_3N (1 mL) and CH_2Cl_2 (40 mL) was added AcCl (0.35 mL). After being stirred at 0 °C for 2 h, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and shaken with aqueous $NaHCO_3$ (2 × 50 mL), H_2O (50 mL), and brine (50 mL). Removal of the dried (Na_2SO_4) solvent in vacuo yielded 1.08 g (96%) of **4** as a foam with spectral properties (IR and ^1H NMR) identical with those reported.[4]

3α-(2-Tetrahydropyranyloxy)-15-acetoxyscirpene-4β,8β-diol (5). A solution of **4** (1.08 g, 2.4 mmol) and 333 mg (3.0 mmol) of freshly sublimed SeO_2 in dioxane (64 mL) and H_2O (2.8 mL) was refluxed for 17 h. After removal of the solvent in vacuo, the residue was eluted from silica gel (15 g) by using a gradient of 10% EtOAc in $CHCl_3$ to 50% EtOAc in $CHCl_3$ to yield 635 mg (59%) of **5** as a foam: IR 3600, 1735 cm^{-1}; NMR δ 0.85 (s, 3, H-14), 1.83 (s, 3, H-16), 2.00 (s, 3, OAc), 2.72 (d, 1, J = 4 Hz, H-13), 2.97 (d, 1, J = 4 Hz, H-13), 5.42 (m, 2, H-10); required for $C_{22}H_{32}O_8$ m/z 424.2097, found m/z 424.2094.

HT-2 Toxin (9). To a stirred solution of **5** (600 mg, 1.4 mmol), $(C_6H_5)_3P$ (750 mg, 2.9 mmol), and isovaleric acid (290 mg, 2.9 mmol) in THF (13 mL) was slowly (2 h) added a solution of diethyl azodicarboxylate (417 mg, 2.9 mmol) in THF (2 mL). After the mixture was stirred at room temperature for 3 h, the solvent was removed in vacuo and the residue taken up in CH_2Cl_2 (200 mL). The excess isovaleric acid was removed by shaking with aqueous $NaHCO_3$ (2 × 50 mL) and the organic layer dried over Na_2SO_4. The crude product obtained after removal of the solvent in vacuo was purified by elution from silica gel (10 g) with Et_2O in hexane (2:1) to give 223 mg (35%) of **8** as a foam. This compound was then treated with pyridinium tosylate (20 mg, 0.1 mmol) in refluxing 95% EtOH (6 mL) for 1 h. Removal of the solvent in vacuo gave the crude product, which was purified by elution from silica gel (10 g) with EtOAc to give 161 mg of HT-2 toxin (**9**) identical by GC and NMR with an authentic sample.

4β,15-Diacetoxy-3α-(2-tetrahydropyranyloxy)scirpene-8β-ol (7). A solution of 4β,15-diacetoxy-3α-(2-tetrahydropyranyloxy)scirpene (**2**)[4] (630 mg, 1.4 mmol) and SeO_2 (171 mg, 1.5 mmol) in dioxane (34 mL) containing water (1.4 mL) was refluxed for 22 h. The solvents were removed in vacuo and the residue dissolved in CH_2Cl_2 (3 mL) and filtered through Celite. This material was then eluted from a Merck Lobar silica gel column (size B) with a gradient of 10% EtOAc in CH_2Cl_2 to 50% EtOAc in CH_2Cl_2 to yield **7** (393 mg, 60%) as a foam: IR 3600, 1735 cm^{-1}; NMR δ 0.72 (s, 3, H-14), 1.78 (s, 3, H-16), 2.02 (s, 3, OAc), 2.05 (s, 3, OAc), 2.73 (d, 1, J = 4 Hz, H-13), 3.00 (d, 1, J = 4 Hz, H-13), 5.47 (m, 2, H-4, H-10); required for $C_{24}H_{34}O_9$ m/z 466.2203, found m/z 466.2201.

Neosolaniol (10). To a solution of **7** (163 mg, 0.35 mmol), $(C_6H_5)_3P$ (183 mg, 0.70 mmol), and 97% formic acid (32 mg, 0.70 mmol) in anhydrous THF (2 mL) was slowly (2 h) added a solution of diethyl azodicarboxylate (102 mg, 0.70 mmol) in THF (2 mL). After being stirred at room temperature for an additional 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and shaken with a saturated solution of $NaHCO_3$ (5 mL). After removal of the dried (Na_2SO_4) solvent in vacuo, the residue was passed through a clean-up column (silica gel, 4 g) by using 50% Et_2O in hexanes to remove $(C_6H_5)_3PO$ and unchanged starting material. The partially purified eluate was then treated with pyridinium

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tosylate (20 mg) in refluxing 95% EtOH for 1 h. After removal of the solvent in vacuo, the material was dissolved in CH_2Cl_2 and shaken with H_2O and dried (Na_2SO_4). Solvents were again evaporated in vacuo, and the residue was treated with 1% Et_3N in anhydrous MeOH at reflux temperature for 1 h to give crude **10**. This material was then eluted from silica gel (4 g) by using 20% EtOAc in Et_2O to give 23 mg (19%) of neosolaniol identical by GC and NMR with an authentic sample.

T-2-Toxin (11). To a solution of **7** (50 mg, 0.12 mmol), $(C_6H_5)_3P$ (59 mg, 0.24 mmol), and isovaleric acid (25 mg, 0.25 mmol) in anhydrous THF (1.5 mL) was slowly (1 h) added a solution of diethyl azodicarboxylate (42 mg, 0.24 mmol) in THF (1.5 mL). After being stirred at room temperature for an additional 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and shaken with a saturated solution of $NaHCO_3$ (5 mL). After removal of the dried (Na_2SO_4) solvent in vacuo, the residue was passed through a clean-up column (silica gel, 1 g) by using 50% Et_2O in hexanes to remove unchanged starting material and $(C_6H_5)_3PO$. The partially purified eluate was then refluxed with pyridinium tosylate (20 mg) in 95% EtOH (5 mL) for 1 h. Removal of the solvent in vacuo gave the crude product, which was purified by elution from silica gel (2 g) with 50% Et_2O in hexanes to yield 15 mg (25%) of T-2 toxin (**11**) identical by GC and NMR with an authentic sample.

T-2 toxin (**11**) could also be obtained in 30% yield from 4β,15-diacetoxyscirpene-3α,8β-diol (**6**) by use of the above procedure without protecting the 3α-hydroxy function.

3'-Hydroxy T-2 Toxin (12). To a solution of **7** (80 mg, 0.17 mmol), $(C_6H_5)_3P$ (80 mg, 0.34 mmol), and 3-hydroxy-3-methylbutanoic acid[8] (40 mg, 0.34 mmol) in anhydrous THF (2 mL) was slowly (1 h) added a solution of diethyl azodicarboxylate (50 mg, 0.34 mmol) in THF (1 mL). After being stirred at room temperature for an additional 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and shaken with a saturated solution of $NaHCO_3$ (5 mL). After removal of the dried (Na_2SO_4) solvent in vacuo, the residue was passed through a clean-up column (silica gel, 2 g) by using Et_2O to remove unchanged starting material and $(C_6H_5)_3PO$. The partially purified eluate was then refluxed with pyridinium tosylate (20 mg) in 95% EtOH (5 mL) for 1 h. Removal of the solvent in vacuo gave the crude product, which was purified by elution from silica gel (2 g) with Et_2O to give 17 mg (21%) of 3'-hydroxy T-2 toxin (**12**), whose spectral properties (IR and ^1H NMR) were identical with those reported.[8] Required for $C_{24}H_{34}O_{10}$ m/z 482.2152, found m/z 482.2149.

3α-(2-Tetrahydropyranyloxy)-15-acetoxyscirpene (13). To a solution of **4**[4] (250 mg, 0.62 mmol) and (*N*,*N*-dimethylamino)pyridine (293 mg, 2.4 mmol) in anhydrous CH_3CN (4 mL) was added phenyl chlorothionocarbonate (344 mg, 2.0 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with Et_2O (50 mL) and shaken with H_2O (3 × 20 mL). After removal of the dried (Na_2SO_4) solvent in vacuo, the crude residue was eluted from a silica gel (5 g) column with 40% Et_2O in hexanes to yield 193 mg of thionocarbonate, which was used as such in the next step.

To a solution of the above material in anhydrous toluene (8 mL) was added α,α'-azobisisobutyronitrile (62 mg, 0.38 mmol) and tri-*n*-butyltin hydride (420 mg, 1.44 mmol). After refluxing for 0.5 h, the solvent was removed in vacuo. The residue was eluted from silica gel (5 g) with 50% Et_2O in hexanes to yield 134 mg (56%) of **13** as a mixture of diastereomers: IR 1735 cm^{-1}; NMR δ 0.81, 0.82* (s, 3, H-14), 0.91, 0.94* (d, 2, J = 7 Hz, H-4), 1.72, 1.73* (s, 3, H-16), 2.05 (s, 3, OAc), 2.84 (d, 1, J = 4 Hz, H-13), 3.06, 3.07* (d, 1, J = 4 Hz, H-13), 5.45, 5.47* (d, 1, J = 6 Hz, H-10). Molecular ion was not observed; required for M^+ - THP ($C_{17}H_{23}O_5$) m/z 307.1545, found m/z 307.1543.

3α-(2-Tetrahydropyranyloxy)scirpen-15-ol (14). To a cold (0 °C) solution of **13** (113 mg, 0.29 mmol) in MeOH (3 mL) and THF (7 mL) was added cold (0 °C) aqueous NaOH (0.3 N, 10 mL). After standing at 5 °C for 18 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4). Removal of the solvent in vacuo yielded 95 mg (95%) of the THP ether **14** as a mixture of diastereomers: IR 3600 cm^{-1}; NMR δ 0.90, 0.92* (d, 2, J = 7 Hz, H-4), 0.91 (s, 3, H-14), 1.73, 1.74* (s, 3, H-16), 2.84, 2.85* (d, 1, J = 4 Hz, H-13), 3.06, 3.07* (d, 1, J = 4 Hz, H-13), 3.52 (m, 2, H-15), 5.46, 5.51* (d, 1, J = 4 Hz, H-10). Molecular ion was not observed; required for M^+ - THP ($C_{15}H_{21}O_4$) m/z 265.1440, found m/z 265.1436.

3α-(2-Tetrahydropyranyloxy)-15-(formyloxy)scirpene (15). To a solution of **14** (90 mg, 0.26 mmol) in anhydrous pyridine (2 mL) was added formylimidazole (180 mg, 2 mmol). After the mixture was stirred at room temperature for 4 h, the solvent was removed in vacuo. The resulting residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo yielded 96 mg (98%) of the THP ether **15** as a mixture of diastereomers: IR 1735 cm^{-1}; NMR δ 0.82, 0.83* (s, 3, H-14), 0.90, 0.92* (d, 2, J = 7 Hz, H-4), 1.73 (s, 3, H-16), 2.84 (d, 1, J = 4 Hz, H-13), 3.06, 3.07* (d, 1, J = 4 Hz, H-13), 3.94 (d, 1, J = 12 Hz, H-15), 4.21 (d, 1, J = 12 Hz, H-15), 5.46, 5.50* (d, 1, J = 6 Hz, H-10), 8.06 (s, 1, formyl). Molecular ion was not observed; required for M^+ - THP ($C_{16}H_{21}O_5$) m/z 293.1389, found m/z 293.1387.

3α-(2-Tetrahydropyranyloxy)-15-(formyloxy)scirpen-8β-ol (16). A solution of **15** (90 mg, 0.24 mmol) and SeO_2 (36 mg, 0.32 mmol) in dioxane (7 mL) containing H_2O (0.3 mL) was refluxed for 18 h. The solvents were removed in vacuo, and the residue eluted from silica gel (5 g) with 50% EtOAc in hexanes to yield 30 mg (32%) of the THP ether **16** as a mixture of diastereomers: IR 3600, 1735 cm^{-1}; NMR δ 0.75, 0.76* (s, 3, H-14), 0.83, 0.86* (d, 2, J = 7 Hz, H-4), 1.76 (s, 3, H-16), 2.81 (d, 1, J = 4 Hz, H-13), 3.01, 3.02* (d, 1, J = 4 Hz, H-13), 5.48 (m, 1, H-10), 7.99 (s, 1, formyl). Molecular ion was not observed; required for M^+ - THP ($C_{16}H_{21}O_6$) m/z 309.1338, found m/z 309.1342.

Sporotrichiol (17). To a stirred solution of **16** (25 mg, 0.06 mmol), $(C_6H_5)P$ (31 mg, 0.12 mmol), and isovaleric acid (12 mg, 0.12 mmol) in anhydrous THF (0.2 mL) was slowly (1 h) added a solution of diethyl azodicarboxylate (16 mg, 0.12 mmol) in THF (0.2 mL). After the mixture was stirred at room temperature for an additional 3 h, the solvent was removed in vacuo, and the residue eluted from a silica gel column (1 g) with Et_2O to remove $(C_6H_5)_3PO$. This partially purified material was refluxed with pyridinium tosylate (20 mg) in 95% aqueous MeOH (5 mL) for 20 h. Removal of the solvent gave the crude product, which was purified by elution from silica gel (1 g) with 20% hexanes in Et_2O to yield 4 mg (22%) of sporotrichiol (**17**), whose spectral properties (IR, ^1H NMR, and HRMS) were identical with those reported.[7]

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Detection of an Azomethine Ylide and Its Conversion to Aziridine

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The thermal ring opening of substituted aziridines to stabilized azomethine ylides has been extensively studied.[1-3] The reverse reaction is implicit in those cases where aziridine cis/trans equilibration occurs[3] and possibly also in the reactions of diazoalkanes with imines,[4] but we are not aware of previous examples where an ester-stabilized

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