155.6, 133.1, 129.7, 127.9, 122.7, 84.5, 20.4. Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.60; H, 4.64; N, 8.98.

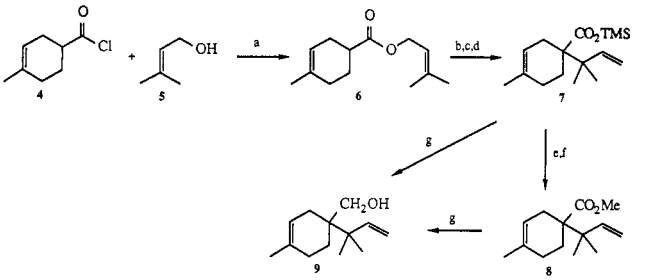
**2-Anilino-1,3-diphenylimidazolidine-4,5-dione (9).** To a solution of 7.5 g (0.08 mol) of aniline in 50 mL of chloroform was added dropwise a solution of crude **5** (obtained from 7.8 g of **1**) in 100 mL of chloroform at 0 °C. The solid product formed during the reaction was filtered off and thoroughly washed with methanol. Recrystallization from acetonitrile gave 9.3 g (68%) of **9**: colorless crystals; mp 230–233 °C; IR (KBr) 1710 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 7.7–6.5 (complex m); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 156.4, 143.5, 134.4, 129.0, 128.9, 126.9, 123.9, 118.9, 114.2, 78.0. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.19; H, 5.04; N, 12.16.

**2-(*N*-Phenyl-*N*-benzylamino)-1,3-diphenylimidazolidine-4,5-dione (10).** A solution of crude **5** (obtained from 7.8 g of **1**) in 100 mL of chloroform was added dropwise to a cold solution of 15 g (0.082 mol) of *N*-phenyl-*N*-benzylamine in 75 mL of chloroform. The resulting reaction solution was stirred for 1 h at room temperature, washed with aqueous sodium hydroxide and water, and concentrated. The solid residue was recrystallized from toluene to give 12.0 g (71%) of **10**: mp 207–209 °C; IR ($CHCl_3$) 1730 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 7.3–6.4 (complex m, 20 H), 4.2 (s, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.4, 145.0, 135.9, 133.9, 129.3, 129.0, 128.1, 127.6, 127.3, 126.8, 124.4, 122.5, 119.7, 85.0, 46.5. Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.61; H, 5.28; N, 9.75.

**1,3-Diphenyl-2-[4-(dimethylamino)phenyl]imidazolidine-4,5-dione (11).** A solution of crude **5** (obtained from 7.8 g of **1**) in 100 mL of chloroform was added dropwise to a cold solution of 9.7 g (0.08 mol) of *N,N*-dimethylaniline in 100 mL of chloroform. The resulting solution was heated to reflux for 3 h, cooled, diluted with 500 mL of chloroform, and washed with aqueous sodium hydroxide and water. Concentration of the dried ($MgSO_4$) solution left 9.4 g of a colorless residue which was recrystallized from acetonitrile to yield 7.6 g (51%) of **11**: mp 221–223 °C; IR (KBr) 1715 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 7.7–7.1 (m, 13 H), 6.5–6.3 (d, 8 Hz, 2 H), 2.7 (s, 6 H); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 156.0, 150.5, 134.8, 128.8, 126.5, 123.2, 119.4, 111.5, 71.9, 39.4. Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.10; H, 5.78; N, 11.20.

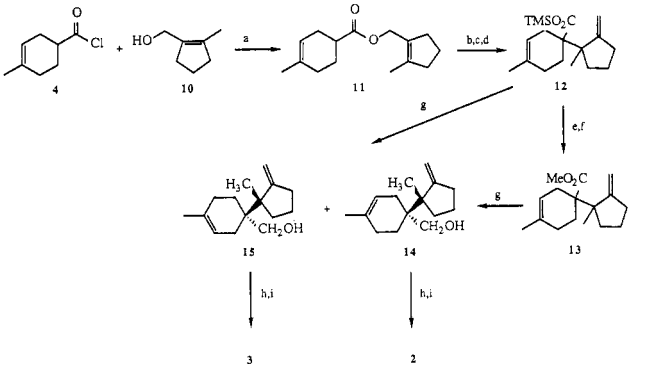
**Registry No.** **1**, 622-15-1; **2**, 104716-64-5; **3**, 104716-65-6; **4**, 104716-66-7; **5**, 104716-67-8; **6**, 104716-68-9; **7**, 104716-69-0; **8**, 104716-70-3; **9**, 104716-71-4; **10**, 104716-72-5; **11**, 104716-73-6; $COCl_2$, 75-44-5; PhN=C=O, 103-71-9; $PhNH_2$, 62-53-3; PhN(CHO)CONHPh, 92148-97-5; 4-$MeOC_6H_4OH$, 150-76-5; $PhNHCH_2Ph$, 103-32-3; $PhN(CH_3)_2$, 121-69-7; PhNHCOCONHPh, 620-81-5; oxalyl chloride, 79-37-8; 1,3-diphenylimidazolidine-2,4,5-trione, 6488-59-1.

**Scheme I. Preparation, Rearrangement, and Reduction of Model Substrate 6[a]**



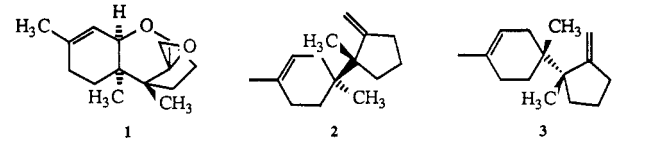

[a] (a) Pyridine; (b) LDA/−78 °C; (c) $Me_3SiCl$; (d) 25 °C; (e) *n*-$Bu_4NF$; (f) $CH_2N_2$; (g) $LiAlH_4$.

**Scheme II. Preparation of Trichodiene (2) and Bazzanene (3)[a]**




[a] (a) Pyridine/0 °C; (b) LDA/−78 °C; (c) $Me_3SiCl$; (d) reflux; (e) *n*-$Bu_4NF$; (f) $CH_2N_2$; (g) $LiAlH_4$; (h) *n*-BuLi, $(Me_2N)_2P(O)Cl$; (i) $EtNH_2$/Li/*t*-BuOH.

antifungal,[3] and cytotoxic[4] biological activity. Their biosynthetic precursor is the simple diene trichodiene (**2**).[5] Considerable effort has been expended in the synthesis of **2**, which is isolable in only trace quantities from natural sources,[6] because of its pivotal biosynthetic role and the synthetic challenge associated with the presence of the two contiguous quaternary centers in the molecule.




These efforts have borne fruit in that several total syntheses have previously been reported for racemic **2**[7] and its biogenetically divergent diastereomer bazzanene (**3**).[7bf,8]

As part of a program directed toward the total synthesis of trichothecenes, a route to **2** was developed to test the

## Creation of Contiguous Quaternary Centers by way of [3,3] Sigmatropic Rearrangements: Synthesis of Trichodiene and Bazzanene

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The trichothecenes (**1**) are a class of almost four dozen fungal metabolites[1] that possess among them insecticidal,[2]

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applicability of an ester–enolate Claisen rearrangement[9] in the key carbon–carbon bond-forming step that creates the two quaternary centers. The results of Denmark[10] and Kraus[7g] showing that the ester–enolate Claisen rearrangement will in fact produce contiguous quaternary centers of the type contained in **2** had not been published when we undertook this approach. Therefore, the feasibility of such a reaction was first evaluated by examining the model system **6** (Scheme I). This compound was readily prepared from Diels–Alder adduct **4**[11] and the commercially available 3-methyl-2-buten-1-ol (**5**). Subjection of it to the Ireland modification of the Claisen rearrangement gave rise to the trimethylsilyl ester **7** which was converted to the methyl ester **8** in 84% yield. This ester was then reduced in 76% yield to the alcohol **9** by using lithium aluminum hydride. Alternately, the crude trimethylsilyl ester **7** could be treated in situ with an excess of lithium aluminum hydride to give the alcohol **9** directly in 72% yield.

With the success of the model study, we turned our attention to the synthesis of the natural product **2** (Scheme II). Ester **11** was prepared in 81% yield by condensation of alcohol **10**[12] with 4-methyl-3-cyclohexenecarbonyl chloride (**4**). Rearrangement of **11**, followed by reduction of the resulting silyl esters, afforded, in 76% yield, a 60:40 mixture of the diastereometric alcohols **14** and **15** designated as trichodien-15-ol and bazzanen-15-ol, respectively. These alcohols possess the *complete* carbon skeletons of trichodiene (**2**) and bazzanene (**3**). Isolation of **14** by silica gel chromatography followed by its reduction through its *N,N,N′,N′*-tetramethylphosphorodiamidic derivative[14] afforded in 96% yield, a diene shown to be spectroscopically identical with trichodiene (**2**). Application of similar procedures to alcohol **15** gave bazzanene, as expected. The stereochemical assignments of alcohols **14** and **15** were thus confirmed. The overall yield of **2** and **3** from the starting acid chloride **4** was 58%.

The advantages of this synthesis of **2** over previously reported methods that also employ [3,3] sigmatropic rearrangements[7bfg] are that the starting esters are simple to prepare from inexpensive starting materials and the exocyclic methylene group is created in the same step as the two quaternary centers. In addition, the overall yield of the two diastereomers (58%), is significantly higher than the previously reported yields of 16–37%.[7g,b]

## Experimental Section

Infrared spectra were recorded with a Beckman IR-5A spectrophotometer as liquid samples between salt plates. $^1H$ and $^{13}C$ nuclear magnetic resonance spectra were recorded at 360 MHz on a Nicolet NT-360 instrument with $CDCl_3$ used as an internal standard and deuterium lock. Chemical shifts are reported in ppm. Low-resolution mass spectra were obtained with a Du Pont (CEC) 21-471 double focusing mass spectrometer operating at 70 eV. Exact mass measurements were obtained on a Du Pont (CEC) 21-110 instrument. High-pressure liquid chromatography was performed on a Waters 6000A instrument with two contiguous 2 ft × $^1/_4$ in. columns packed with LC Porasil (type A) silica gel.

All anhydrous reactions were run under a nitrogen atmosphere. Trimethylsilyl chloride was dried by distillation followed by centrifugation of a 3:1 mixture of it and triethylamine. Skelly B was stirred over sulfuric acid for 24 h, over sodium carbonate for 12 h, and then filtered and distilled. All other reagents and solvents were obtained from commercial sources and purified by standard methods.

**4-Methyl-3-cyclohexene-1-carbonyl Chloride (4).** To a mixture of 14.3 mL (0.220 mol) of isoprene and 4 drops of propylene oxide was added 6.0 mL (0.075 mol) of acryloyl chloride.[15] The mixture was stirred in the dark at room temperature for 24 h. The flask was then equipped with a fractionating column, and, following distillation of unchanged starting materials, 10.6 g (89%) of the acid chloride was collected: bp 45–47 °C (0.5 mmHg) [lit.[11] 89–91 °C (20 mmHg)]; $^1H$ NMR 1.65 (s, 3 H), 1.85–2.40 (m, 6 H), 2.95 (m, 1 H), 5.40 (br s, 1 H); $^{13}C$ NMR 23.3, 24.7, 27.9, 28.9, 51.4, 118.2, 134.0, 164.7; IR 1815 (s) $cm^{-1}$.

**3-Methyl-2-butenyl 4-Methyl-3-cyclohexene-1-carboxylate (6).** A solution of 5.0 g (32 mmol) of the acid chloride **4** in 50 mL of methylene chloride was cooled in an ice bath under a stream of nitrogen. Pyridine (5 mL) was added dropwise followed by the slow addition of 3-methyl-2-buten-1-ol (4.3 g, 50 mmol). After warming to room temperature, the mixture was stirred for 12 h and quenched by the addition of 10 mL of water. The organic layer was washed sequentially with 25-mL portions of cold 10% sulfuric acid, saturated sodium bicarbonate, and water and then dried ($Na_2SO_4$). Removal of solvent by rotary evaporation followed by distillation of the residue gave 4.3 g (66%) of a colorless oil: bp 87–88 °C (4 mmHg); $^1H$ NMR 1.63 (s, 3 H), 1.70 (s, 3 H), 1.75 (s, 3 H), 1.90–2.30 (m, 6 H), 2.40–2.50 (m, 1 H), 4.58 (d, 2 H), 5.35 (m, 2 H); $^{13}C$ NMR 18.0, 23.4, 25.5, 25.9, 27.8, 29.3, 39.4, 61.4, 119.0, 119.4, 133.8, 138.6, 176.2; IR 1740 (s) $cm^{-1}$; LRMS, *m/z* (relative intensity) 208 ($M^+$, 0.03), 139 (0.39), 122 (0.31), 93 (1.00), 69 (0.91); HRMS, $C_{13}H_{20}O_2$ calcd 208.14632, found 208.14689.

**Methyl 4-Methyl-1-(1,1-dimethyl-2-propenyl)-3-cyclohexene-1-carboxylate (8).** To a stirred solution of 5.2 mmol of lithium diisopropylamide in 10 mL of dry THF at −78 °C and under a dry nitrogen atmosphere was added 1 g (0.005 mol) of ester **6** in 5 mL of THF. After the mixture had been stirred for 10 min, 1.32 mL (0.010 mol) of trimethylsilyl chloride was added, and the reaction mixture was allowed to warm to room temperature over 3 h. Stirring was maintained for an additional 12 h to complete the rearrangement and produce the crude trimethylsilyl ester **7**. The trimethylsilyl group was then cleaved by treatment with 7 mL of a 1 M solution of tetrabutylammonium fluoride to yield a solution of the carboxylic acid. The trimethylsilyl group was then cleaved by treatment with 7 mL of a 1 M solution of tetrabutylammonium fluoride to yield a solution of the carboxylic acid. The acid was then purified by dilution of the reaction mixture with 100 mL of ether followed by two washings with 50-mL portions of saturated sodium chloride that had been acidified to pH 2 with 12 M HCl. Extraction of the aqueous washings with ether, drying ($MgSO_4$), and removal of solvents from the combined ethereal extracts gave the crude acid as a white solid. This was treated with ethereal diazomethane to yield the methyl ester **8** (0.89 g, 89%). Purification of **8** was achieved by silica gel chromatography (5% EtOAc/95% Skelly B): $^1H$ NMR 1.05 (s, 3 H), 1.08 (s, 3 H), 1.61 (s, 3 H), 1.90–2.30 (m, 6 H), 3.65 (s, 3 H), 5.00 (m, 2 H), 5.38 (br s, 1 H), 5.93 (m, 1 H); $^{13}C$ NMR 23.0, 23.2, 25.6, 26.4, 28.4, 29.1, 29.9, 41.1, 50.9, 112.0, 120.0, 133.1, 145.0, 175.4; IR 1740 (s) $cm^{-1}$; LRMS, *m/z* (relative intensity) 222 ($M^+$, 0.13), 153 (1.00), 93 (0.84); HRMS, $C_{14}H_{22}O_2$ calcd 222.16197, found 222.16259.

**4-Methyl-1-(1,1-dimethyl-2-propenyl)-1-(hydroxymethyl)-3-cyclohexene (9). Method A.** The solution containing the crude trimethylsilyl ester **7**, prepared from **6** as described above, was treated directly with 0.4 g of $LiAlH_4$ (0.010 mol); the reaction was allowed to proceed for 6 h. Careful quenching with water, followed by filtration and washing of the lithium salts with ether, drying ($MgSO_4$) of the combined organic solutions, and removal of solvent gave a yellow oil. This oil was purified by

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chromatography on silica gel (10% EtOAc/90% Skelly B) or distillation [bp 90–91 °C (4.8 mmHg)] to yield 0.67 g (72%) of the alcohol **9**.

**Method B.** Alternately, a solution of 0.5 g of the methyl ester **8** in 5 mL of THF could be treated with 0.2 g of $LiAlH_4$ and allowed to stir 3 h. Workup as described in Method A gave 0.34 g (76%) of the expected alcohol **9**.

$^1H$ NMR 0.95 (s, 3 H), 0.98 (s, 3 H), 1.60 (s, 3 H), 1.70–2.05 (m, 6 H), 3.62 (m, 2 H), 4.95 (m, 2 H), 5.20 (m, 1 H), 5.30 (br s, 1 H), 6.15 (q, 1 H); $^{13}C$ NMR 22.0, 23.2, 24.1, 27.7, 28.6, 29.6, 41.0, 41.6, 62.4, 111.6, 119.5, 133.9, 147.8; IR 3360 (br) $cm^{-1}$; LRMS, *m/z* (relative intensity) 194 ($M^+$, 0.02), 176 (0.19), 163 (0.19), 143 (0.16), 125 (0.21), 107 (1.00), 93 (0.83), 79 (0.84), 69 (0.76); HRMS, $C_{13}H_{22}O$ calcd 194.16706, found 194.16761.

**(2-Methyl-1-cyclopentenyl)methyl 4-Methyl-3-cyclohexene-1-carboxylate (11).** To a solution of alcohol **10**[12] (1.0 g, 8.9 mmol) in 100 mL of pyridine and at 0 °C was slowly added the acid chloride **4** (2.0 g, 12.6 mmol). After warming to room temperature and stirring for 12 h, the reaction was quenched by the addition of 5 mL of water. Dilution with 50 mL of methylene chloride followed by sequentially washing the organic layer with 25-mL portions of cold 10% sulfuric acid, saturated sodium bicarbonate, and water gave, upon drying ($MgSO_4$) and solvent evaporation, a clear, sweet smelling oil. This oil was purified by silica gel chromatography using hexane/EtOAc (100:0 to 85:15) as eluent to yield 1.7 g (81%) of the desired ester **11**: bp 96–98 °C (0.1 mmHg); $R_f$ 0.54 (90% hexane/10% EtOAc); $^1H$ NMR 1.65 (s, 3 H), 1.71 (s, 3 H), 1.80 (m, 2 H), 1.98 (m, 4 H), 2.22 (m, 2 H), 2.35 (m, 4 H), 2.50 (m, 1 H), 4.64 (s, 2 H), 5.35 (s, 1 H); $^{13}C$ NMR 13.6, 21.3, 23.1, 25.2, 27.6, 29.1, 34.2, 38.5, 39.4, 60.8, 119.3, 129.9, 133.6, 137.8, 175.8; IR 1710 (s) $cm^{-1}$; LRMS, *m/z* (relative intensity) 234 ($M^+$, 0.01), 139 (0.14), 122 (0.11), 95 (1.00), 79 (0.68), 67 (0.50); HRMS, $C_{15}H_{22}O_2$ calcd 234.16197, found 234.16239.

**Methyl 4-Methyl-1-(1-methyl-2-methylenecyclopentyl)-3-cyclohexene-1-carboxylate (13).** To a solution of LDA (2.35 mmol) in 5 mL of THF cooled to −78 °C under an atmosphere of dry nitrogen was slowly added a mixture of ester **8** (0.5 g, 2.1 mmol) in 2 mL of THF. After this solution was stirred for 15 min, 0.7 mL (5.0 mmol) of $Me_3SiCl$ was added, and the reaction was allowed to warm to room temperature. The reaction vessel was then equipped with a reflux condenser and the mixture was heated in an oil bath at 70 °C, taking care to keep the system under a nitrogen atmosphere. The rearrangement to the crude trimethylsilyl esters **12** was complete after 12 h. After being cooled to room temperature, the reaction mixture was treated with 7.0 mL of a 1 M solution of tetra-*n*-butyl ammonium fluoride and diluted with 100 mL of diethyl ether. The ethereal solution was then washed twice with 25-mL portions of saturated sodium chloride that had been acidified to a pH of 2. The aqueous washings were extracted with a 50-mL portion of ether, and the combined ether fractions were treated with an excess of ethereal diazomethane. The diazomethane reaction was quenched after 2 h with 2 mL of glacial acetic acid, and the ether layer was washed carefully with two 50-mL portions of saturated sodium bicarbonate solution. Drying of the ether layer with $MgSO_4$ followed by rotary evaporation gave an oil that was purified by silica gel chromatography (5% EtOAc/95% Skelly B) to yield a 60:40 mixture of the diastereometric methyl esters **13** as a clear colorless liquid in 86% yield overall: $^1H$ NMR 1.12 (s, 1.2 H), 1.15 (s, 1.8 H), 1.65 (s, 3 H), 2.00–2.50 (m, 12 H), 3.62 (s, 3 H), 4.76 (dd, 1 H), 5.00 (s, 1 H), 5.30–5.41 (br s, 1 H); $^{13}C$ NMR 23.1, 25.0, 25.8, 28.5, 29.6, 37.7, 38.0, 38.1, 49.1, 50.9, 51.7, 107.6, 120.2, 132.9, 158.3, 175.5; IR 1750 (s) $cm^{-1}$; LRMS, *m/z* (relative intensity) 248 ($M^+$, 0.03), 152 (0.59), 95 (1.00), 81 (0.20); HRMS $C_{16}H_{24}O_2$ calcd 248.17762, found 248.17703.

**4-Methyl-1-(hydroxymethyl)-1-(1-methyl-2′-methylenecyclopentyl)-3-cyclohexene (14 and 15). Method A.** Reduction of the crude trimethylsilyl ester **12** obtained above in the preparation of **13** was done directly by treating the solution of **12** at 25 °C with 0.8 g (0.020 mol) of $LiAlH_4$ and stirring the resulting slurry for 12 h. The reaction mixture was carefully quenched with a small amount of water, and the lithium salts were removed by filtration. The salts were washed with 50 mL of ether, and the ether fractions were dried ($MgSO_4$) and concentrated by rotary evaporation. Purification and separation was achieved by HPLC using 98% hexane/2% EtOAc.[16] The combined yield of **14** and **15** was 76%.

**Method B.** The diasteremetric methyl esters **13** (0.1 g, 0.4 mmol) could be reduced by treating them with 0.4 g (0.010 mol) of $LiAlH_4$ in 50 mL of dry diethyl ether. The reaction was worked up and purified as described above in Method A to yield the alcohols in 79% yield.

Trichodien-15-ol (**14**): $^1H$ NMR 1.12 (s, 3 H), 1.30–1.45 (m, 4 H), 1.65 (s, 3 H), 1.70–1.80 (m, 2 H), 1.90–2.10 (m, 4 H), 2.40 (m, 2 H), 3.68 (q, 2 H), 4.94 (s, 1 H), 5.08 (s, 1 H), 5.32 (s, 1 H); $^{13}C$ NMR 22.8, 23.2, 25.0, 25.1, 27.9, 29.2, 37.5, 38.2, 41.6, 50.4, 64.5, 107.3, 119.8, 133.5, 162.2; IR 3500 (br) $cm^{-1}$; LRMS, *m/z* (relative intensity) 220 ($M^+$, 0.03), 189 (0.13), 124 (1.00), 107 (0.73), 95 (0.98); HRMS, $C_{15}H_{24}O$ calcd 220.18270, found 220.18302.

Bazzanen-15-ol (**15**): $^1H$ NMR 1.08 (s, 3 H), 1.30–1.50 (m, 4 H), 1.66 (s, 3 H), 1.75–2.00 (m, 2 H), 2.05–2.15 (m, 4 H), 2.35–2.42 (m, 2 H), 3.50 (t, 1 H), 3.60 (d, 1 H), 5.02 (s, 1 H), 5.13 (s, 1 H), 5.25 (s, 1 H); $^{13}C$ NMR 23.1, 23.2, 24.3, 24.9, 27.8, 29.3, 37.0, 38.8, 41.3, 49.5, 64.1, 108.1, 119.2, 134.2, 161.4; IR 3500 (br) $cm^{-1}$; LRMS, *m/z* (relative intensity) 220 ($M^+$, 0.06), 189 (0.48), 124 (1.00), 107 (0.97), 95 (0.99); HRMS, $C_{15}H_{24}O$ calcd 220.18270, found 220.18343.

**Trichodiene (2).** To a stirred solution of 0.2 g of alcohol **14** (0.9 mmol) in 5 mL of a 4:1 mixture of dimethoxyethane and *N,N,N′,N′*-tetramethylethylenediamine at 0 °C was slowly added 0.8 mL (1 mmol) of a 1.3 M solution of *n*-butyllithium in hexanes. After being stirred 5 min the mixture was treated with 0.74 mL (4.5 mmol) of *N,N,N′,N′*-tetramethylphosphorodiamidic chloride,[14] and the resulting reaction mixture was stirred at room temperature for 1 h. The mixture was then transferred to a vessel containing 0.3 g of *tert*-butyl alcohol, 0.1 g of lithium wire, and 25 mL of dry ethylamine held at 0 °C. After being stirred for 2 h, this reaction mixture was carefully quenched with water, and the product was isolated by extraction into diethyl ether. Drying ($MgSO_4$) followed by solvent removal gave an oil which was easily purified by chromatography on silica gel with Skelly B as the eluent: yield, 0.18 g (96%); $^1H$ NMR 0.88 (s, 3 H), 1.08 (s, 3 H), 1.35–1.50 (m, 4 H), 1.65 (s, 3 H), 1.80–2.05 (m, 4 H), 2.15–2.35 (m, 4 H), 4.75 (s, 1 H), 5.00 (s, 1 H), 5.33 (s, 1 H); $^{13}C$ NMR 18.0, 23.2, 23.4, 24.1, 27.9, 28.3, 33.1, 36.9, 37.4, 38.8, 50.8, 106.9, 120.6, 132.3, 159.9; IR 3065 (w), 1640 (m) $cm^{-1}$; LRMS, *m/z* (relative intensity) 204 ($M^+$, 0.28), 148 (0.22), 107 (0.53), 93 (1.00), 79 (0.65); HRMS, $C_{15}H_{24}$ calcd 204.18779, found 204.18817.

**Bazzanene (3).** Alcohol **15** was treated as described above for the preparation of trichodiene **2**. After similar workup bazzanene **3** was obtained in 93% yield: $^1H$ NMR 0.86 (s, 3 H), 1.04 (s, 3 H), 1.35–1.50 (m, 4 H), 1.65 (s, 3 H), 1.80–2.05 (m, 4 H), 2.15–2.35 (m, 4 H), 4.82 (s, 1 H), 5.00 (s, 1 H), 5.33 (s, 1 H); $^{13}C$ NMR 17.8, 23.2, 23.7, 24.1, 28.0, 28.2, 32.5, 36.9, 37.1, 38.7, 50.6, 106.3, 120.2, 132.5, 159.8; IR 3065 (w), 1640 (m) $cm^{-1}$; LRMS, *m/z* (relative intensity) 204 ($M^+$, 0.26), 148 (0.19), 107 (0.56), 93 (1.00), 79 (0.68).

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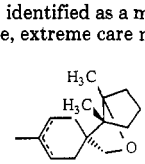
(16) A byproduct of the reaction was observed if the alcohols were exposed to the acidic medium of the chromatographic column for too long a period. This material was identified as a mixture of the diastereometric internal ethers i. Therefore, extreme care must be exercised during this




i

separation. Spectral data for i: $^1H$ NMR 0.88 (2 s, 3 H), 1.26 (2 s, 3 H), 1.40–1.50 (m, 2 H), 1.65 (s, 3 H), 1.70–2.10 (m, 10 H), 3.35 (d, 1 H), 3.50 (d, 1 H), 3.70 (d, 1 H), 3.80 (d, 1 H), 5.38 (s, 1 H); $^{13}C$ NMR 17.4, 18.2, 23.0, 23.1, 23.7, 23.9, 25.3, 25.4, 26.2, 26.4, 28.2, 28.9, 30.0, 31.3, 37.6, 37.9, 43.3, 43.4, 45.6, 46.3, 54.5, 54.7, 71.5, 72.9, 91.8, 92.7, 120.6, 120.7, 132.8, 133.1; IR, no hydroxyl or carbonyl absorptions; LRMS, *m/z* (relative intensity) 220 ($M^+$, 0.02), 178 (0.43), 124 (1.00), 110 (0.90); HRMS, $C_{15}H_{24}O$ calcd 220.18270, found 220.18322.

with us his results for a similar approach to **2** and **3** prior to publication.

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## Tetrahydropyran as an Efficient Alcohol Protecting Group for the Synthesis of Penems: Synthesis of Sch 34343

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In the past few years, syntheses leading to (3*S*,4*R*)-3-[(R)-hydroxyethyl]-4-[(triphenylmethyl)thio]-2-azetidinone (**1**) have become available.[1] The conversion of azetidinone **1** to broad-spectrum antibiotic penems has been established by various groups.[2] This conversion usually requires the protection of the secondary hydroxy group. The trimethylsilyl ($Me_3Si$) group has been used for this purpose,[2a] but this group is not sufficiently stable. Though the *tert*-butyldimethylsilyl (TBDMS) group is stable,[2b] the group itself as well as the reagent reported for its removal, $(Bu)_4N^+F^-$, are not cost effective.

The analysis of the penem synthesis reported above[2a,b] indicated that the alcohol protecting group should be stable to basic conditions and that this group should be cleaved under mild acidic conditions. We report here that the tetrahydropyranyl group meets the above needs and that it can be used for an efficient synthesis of penems such as **9**. This synthesis is outlined in Scheme I.

The N-alkylation of **1** progressed smoothly in good yield to give **2** as a white foam. The protection of the hydroxy moiety of **2** with dihydropyran under the standard conditions[3] gave a 1:1 mixture of diastereomeric hydroxy-protected **3** as an oil in quantitative yield. The removal of the triphenylmethyl group of **3** was capricious. The quantity of methanol used in this reaction and the reaction time determined the yield of the reaction. When the reaction was run in methanol, the formation of **4** appeared to take place in the beginning of the reaction as judged by TLC, but **4** decomposed with time. An excellent yield for the removal of the triphenylmethyl group was realized when the reaction was carried out in $CH_3CN$ with only 1 equiv of MeOH. The silver thiolate **4** was not isolated but was converted to the next intermediate.

Imidazole has been reported as a leaving group for the synthesis of penems.[2a] The reaction of azetidinone **4** with 1,1′-carbonothioylbis(1*H*-imidazole) (CTBI) proceeded in moderate yield to give **5** as a yellow oil. The reaction of azetidinone **4** with *O*-2-naphthalenyl carbonochloridothioate (NCCT) progressed in excellent yield to give **6** as an oil. The cyclization of **5** as well as **6** proceeded smoothly at low temperatures. In the case of **5**, after cyclization, the removal of the resultant imidazole from unstable and acid-sensitive **7** was necessary in order to avoid complications in the subsequent reactions. Some deprotection and some decomposition of **7** resulted during this workup as judged by TLC and NMR. Removal of β-naphthol from a solution of **7** after the cyclization of **6** was not necessary. Only some deprotection was apparent in the latter case as judged by TLC and NMR. Since NCCT is a stable solid, is readily available, and reacts with **4** in excellent yield whereas CTBI is an unstable solid, is difficult to purify, reacts with **4** in only moderate yield, and necessitates the removal of imidazole from a solution of **7**, NCCT is preferable over CTBI in the penem synthesis.

Compound **7**, derived from **5** or **6** (partially decomposed when derived from **5**), was S-alkylated in excellent yields to give **8** as an oil. For the purpose of characterization, **8** derived from **6** was chromatographed on a column of silica gel to separate it from β-naphthol. This resulted in some loss of material on the column and some deprotection that resulted in lowering of the yield.[4] Though the THP deprotection (of **8**) was possible with acetic acid in aqueous ethanol,[5] this reaction was very sluggish. THP deprotection with pyridinium *p*-toluenesulfonate (PPTS)[3] was rapid in the beginning of the reaction, but it slowed down considerably with time and hence at the end of 8 h *p*-toluenesulfonic acid (PTSA)[6] was added to the reaction mixture to accelerate the conversion of the remaining amount of **8** to **9**. This conversion progressed in excellent yield. Compound **9** thus obtained was similar to authentic **9** in melting point, NMR, IR, and TLC behavior.[7] The technique for the removal of the allyl protecting group from penems **9** to give the sodium salt of penems **10** has been reported previously.[7,8]

In conclusion, the synthesis of penems via the use of THP for the protection of the hydroxy group gave excellent overall yield. THP is compatible with the above synthesis, and it is cost effective. The use of β-naphthol was found to be superior to the use of imidazole as a leaving group in the above synthesis.

### Experimental Section

The $^1H$ NMR spectra were recorded on a Varian FT-80 or Varian XL 200. Chemical shifts are expressed in parts per million downfield from $Me_4Si$, and coupling constants are recorded in hertz. The infrared spectra were recorded on a Perkin-Elmer 1320 or Nicolet MX-IE FTIR spectrophotometer. Elemental microanalyses were conducted by Schering Analytical Research Services. Melting points were recorded on a Fisher-Johns hot-plate apparatus. The term flash chromatography refers to the method described by Still.[9] Dry THF was obtained by distillation from sodium benzophenone ketyl.

**(3*S*,4*R*)-1-[[(Allyloxy)carbonyl]methyl]-3-[(*R*)-1-hydroxyethyl]-4-[(triphenylmethyl)thio]-2-azetidinone (2). Step a.** To a stirred solution of 0.38 g (0.97 mmol) of **1** in 7 mL of $CH_3CN$ at 25 °C under $N_2$ was added 0.44 g (1.95 mmol) of allyl iodoacetate followed by 0.40 g (1.23 mmol) of $Cs_2CO_3$. The reaction mixture was stirred at room temperature for 2 h and then at 40 °C for 1 h, then diluted with 90 mL of ether, and washed

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