generous additional maintenance support.

Registry No. 1, 16755-07-0; **2**, 50-69-1; **7a**, 87709-10-2; **7c**, 99885-52-6; **7d**, 99885-53-7; **8a**, 28118-79-8; **8b**, 99885-66-2; **9d**, 99885-51-5; **12a**, 57129-69-8; **13**, 99885-54-8; **14**, 99885-55-9; **26a**, 5371-52-8; **26b** (isomer 1), 99885-56-0; **26b** (isomer 2), 99885-57-1; **27**, 54911-85-2; **28**, 99885-58-2; **29a**, 99885-59-3; **29b**, 99885-60-6; **30**, 99885-61-7; **31**, 100017-03-6; **32**, 99945-83-2; **33**, 99885-62-8; **34a**, 99885-64-0; **34b**, 99885-63-9; **35**, 92013-85-9; **36**, 79934-05-7; **37b**, 13199-25-2; **44a**, 99885-65-1; **44b**, 99885-68-4; **45**, 100017-04-7; **46**, 99885-69-5; **47**, 99885-70-8; PhSSPh, 882-33-7; succinimide, 123-56-8; *N*-benzylsuccinimide, 2142-06-5; *N*-phenylsuccinimide, 83-25-0; butyrolactone, 96-48-0; *N*-tritylmaleimide, 42867-31-2; 3-methylene-1-(triphenylmethyl)-2,5-pyrrolidinedione, 99885-67-3.

A Direct Synthesis of Trichodiene

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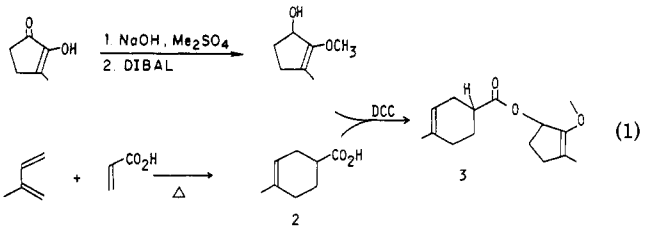
The synthesis of trichodiene via the Ireland modification of the Claisen rearrangement is described. The enol ether resulting from the rearrangement functions as a protecting group during two reduction steps. The enol ether diastereomers can be conveniently separated by flash chromatography.

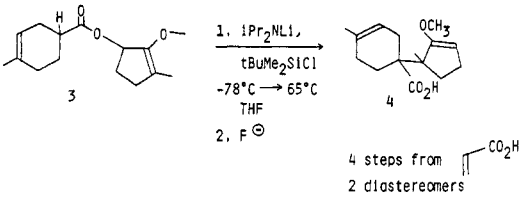
The trichothecene sesquiterpenes pose a fascinating challenge to synthetic organic chemists. With two adjacent quaternary centers plus an array of stereogenic carbon atoms of various oxidation states, complex trichothecenes such as deoxynivalenol and T-2 toxin have not been synthesized.[1] Less complex compounds such as verrucarol,[2] anguidin,[3] and calonectrin[4] have been prepared. The biogenetic precursor to all of the aforementioned compounds is trichodiene **1**. Because of its comparative simplicity and its pivotal role in trichothecene production in nature, several syntheses of trichodiene have been developed.[5-10] Recent syntheses have featured a nonstereospecific Claisen rearrangement,[6] a Nazarov cyclization/fragmentation strategy,[7] and a clever Diels–Alder-based approach.[8] In the context of developing a practical route to the complex trichothecenes, we recently employed the Ireland modification of the Claisen rearrangement[11] and now report a direct synthesis of **1**.

The synthesis starts with the commercially available 3-methylcyclopentane-1,2-dione (eq 1). Formation of the



(1)

enol ether with dimethyl sulfate and sodium hydroxide[12] followed by reduction of the ketone with diisobutylaluminum hydride provided an unstable allylic alcohol which was converted into a mixture of diastereomeric esters **3** with acid **2**[13] and dicyclohexylcarbodiimide.[14] Ester **3** was transformed into the *tert*-butyldimethylsilyl ester of **4** by deprotonation with lithium diisopropylamide (LDA), silylation with *tert*-butyldimethylchlorosilane, and then heating in refluxing THF to effect the Claisen rearrangement (eq 2). This rearrangement afforded two



(2)

products in essentially equal amounts. The lack of selectivity was expected and reflects the absence of steric or electronic direction in the formation of the ketene acetal.[15] Surprisingly, treatment of the silyl ester with lithium aluminum hydride resulted in desilylation rather than reduction. This must be a consequence of the highly crowded environment around the ester. Desilylation with tetrabutylammonium fluoride was more convenient and generated acid **4** in quantitative yield. Esterification with diazomethane followed by reduction of the ester with lithium aluminum hydride produced an unstable alcohol. This alcohol in the presence of even traces of acid formed an internal ketal by reaction with the enol ether. We solved this problem by forming the mesylate with methanesulfonyl chloride and triethylamine immediately after reduction.[16] The tosylate was also prepared. However, its formation was accompanied by significant amounts of the undesired internal ketal product (eq 3). Reduction of the mesylate was best accomplished with a zinc–copper couple and excess sodium iodide in dimethoxyethane with an equal volume of hexamethylphosphoric triamide.[17] The two enol ethers were distinct spots on TLC in pentane and

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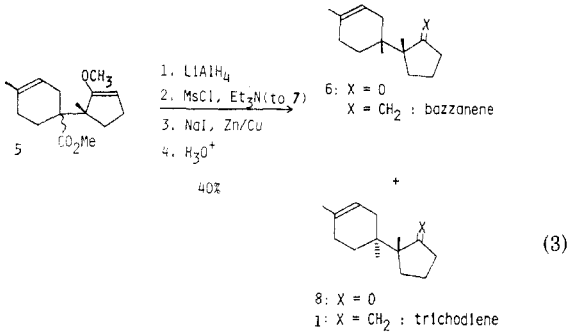

(3)

could be easily separated by using flash chromatography[18] with pentane. Hydrolysis of the less polar enol ether then gave bazzanenone (6). Its proton NMR was identical with that reported by Welch.[5] Hydrolysis of the more polar enol ether afforded trichoenone 8. Our C-13 spectrum of 8 was identical with that reported by Snowden.[9] Ketone 8 has been converted to 1 by treatment with methylenetriphenylphosphorane.[5,7]

This route is a convergent and very direct one. The synthesis of trichoenone represents a formal total synthesis of trichodiene. More improtantly, the structure of 4, a key intermediate in our approach to the complex trichothecenes, is secured.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 60-MHz instrument and on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument and the Nicolet 300 spectrometer. High-resolution mass spectra were determined on a Kratos mass spectrometer.

3-Methyl-2-methoxycyclopent-2-en-1-ol. To a stirred solution of the enone (8.6 g, 68 mmol) in anhydrous ether (125 mL) under a nitrogen atmosphere at 0° C was added dropwise a solution of DIBAL (135 mL in hexanes, 135 mmol). After the addition, the solution was stirred at 0° C for for an additional 4 h. One hundred milliliters of saturated sodium bicarbonate solution was then added slowly. After 30 min, the mixture was diluted with water (100 mL) and extracted 3 times with 150 mL of ether. The organic layer was washed with brine and then dried over sodium sulfate. Concentration in vacuo furnished 8.11 g of crude alcohol which was immediately taken on to the next step. This alcohol is *unstable* but can be stored overnight in solution in the refrigerator: NMR ($CDCl_3$) δ 0.80–2.30 (m, 4 H), 1.68 (br s, 3 H), 3.72 (s, 3 H), 4.56–4.92 (m, 1 H); IR (film) 3450, 1450, 1230.

Ester 3. To a solution of 3-methyl-2-methoxycyclopent-2-en-1-ol (4.55 g, 36 mmol), DMAP (0.86 g, 7 mmol), and the acid (5.16 g, 37 mmol) in dry methylene chloride (100 mL) was added DCC (9.2 g, 45 mmol). The solution was then stirred at room termperature for 4–5 h until thin layer chromatography (TLC) indicated that no alcohol remained. The suspension was then filtered. The filtrate was diluted with 250 mL of hexanes, filtered, and then concentrated. The residue was then purified by using flash chromatography with 9:1 hexanes/ethyl acetate. It is vital to use a column height of 3–4 in. and to pass the compound through the colum more rapidly than usual. The purified compound was obtained in 96% yield. 3: 300-MHz NMR ($CDCl_3$) δ 1.15–1.40 (m, 2 H), 1.52–1.80 (m, 3 H), 1.64 (s, 3 H), 1.68 (s, 3 H), 1.84–2.55 (m, 6 H), 3.59 (s, 3 H), 5.37 (br s, 1 H), 5.76–5.87 (m, 1 H); IR (film) 1735, 1700, 1650, 1460, 1223, 1165 cm^{-1}; HRMS; *m/e* calcd 250.15690, found 250.15654.

Claisen Rearrangement of 3. To a solution of lithium diisopropylamide (from 17 mmol of diisopropylamine and 16 mmol of *n*-butyllithium) in 30 mL of THF at −78 °C was added dropwise ester 3 (3.65 g, 15 mmol) in 10 mL of THF. After 30 min, HMPA (2.7 mL) was added followed by *tert*-butyldimethylchlorosilane (2.41 g, 16 mmol) in 10 mL of THF. The solution was stirred at −78 °C for 30 min. The reaction was then warmed to room temperature and then heated to reflux for 5 h. The solution was then cooled. The THF was removed in vacuo and 100 mL of ether was added. The ether layer was then washed sequentially with water, 5% acetic acid, and brine. The organic layer was dried and concentrated. The residue was diluted with 200 mL of hexanes. If a precipitate occurred, it was filtered and the filtrate was concentrated to afford 5.19 g of crude product: NMR ($CDCl_3$) δ 0.20 (s, 6 H), 0.90 (s, 9 H), 1.18 (s, 3 H), 1.60 (br s, 3 H), 3.49 (s, 3 H), 4.40–4.60 (m, 1 H), 5.23–5.56 (m, 1 H); IR (film) 1702, 1648, 1460, 1250, 835 cm^{-1}; HRMS, *m/e* calcd 364.24338, found 364.2431.

Preparation of 5. To a solution of the silyl ester of acid 4 (2 g, 5.4 mmol) in 10 mL of THF was added tetrabutylammonium fluoride (5.5 mL of a 1 M solution in THF, 5.5 mmol). The solution was stirred until TLC indicated that the silyl ether of 4 was no longer present (6–7 h). The solvent was removed. The residue was diluted with water and extracted with ether. The organic layer was washed with brine, dried, and concentrated to approximately 10 mL. This was treated with diazomethane in ether until gas evolution ceased. After 1 h, the solvent was removed and the methyl ester purified by flash chromatography with 9:1 hexanes/ethyl acetate. The purification yielded 1.2 g of 5: 300-MHz NMR ($CDCl_3$) δ 1.17 and 1.18 (s, 3 H), 1.30–2.68 (m, 10 H), 1.59 (br s, 3 H), 3.52 (s, 3 H), 3.61 (s, 3 H), 4.42–4.50 (m, 1 H), 5.30–5.40 (m, 1 H); IR (film) 1730, 1650, 1450, 1240, 1195 cm^{-1}; HRMS, *m/e* calcd 264.1725, found 264.1726.

Preparation of Mesylate 7 from Ester 5. To a stirred suspension of lithium aluminum hydride (0.70 g, 18.4 mmol) in anhydrous ether (50 mL) under an atmosphere of nitrogen was added ester 5 (1.00 g, 3.79 mmol) in 10 mL of ether. The mixture was stirred for 12 h. To this suspension was added dropwise *with care* a saturated solution of sodium sulfate until a white granular precipitate was obtained. The precipitate was filtered and washed with ether. One milliliter of triethylamine was added to prevent internal ketal formation. The solvent was removed and the resulting crude alcohol used *immediately*. To a stirred solution of the alcohol and triethylamine (1.3 mL, 9.3 mmol) in 20 mL of methylene chloride under nitrogen at −10 °C was added methanesulfonyl chloride (0.40 mL, 5.1 mmol) over a period of 10 min. The reaction mixture was stirred for another 20 min, diluted with 100 mL of ether, and wshed with ice–water and then brine. The solvent was removed in vacuo. The product was purified by flash chromatography with 9:1 hexanes/ethyl acetate. The overall yield of 7 from 5 was 73%. 7: 300-MHz NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.65 (br s, 3 H), 1.45–2.40 (m, 10 H), 2.96 (s, 3 H), 3.54 (s, 3 H), 4.09–4.49 (m, 3 H), 5.22–5.31 (m, 1 H); IR (film) 1640, 1355, 1170, 945 cm^{-1}; HRMS; *m/e* calcd 314.1552, found 314.1547.

Reduction of Mesylate 7. A solution of mesylate 7 (1.00 g, 3.2 mmol), zinc–copper couple (2.0 g) prepared by the method of Hassner[19] and sodium iodide (5.0 g) in dimethoxyethane (10 mL) and HMPA (10 mL) was heated under nitrogen at 83 °C for 48 h. The cooled mixture was filtered and the dimethoxyethane was removed. The residue was diluted with water and extracted with hexanes. The solution was dried and concentrated to provide a mixutre of the enol ethers of trichoenone and bazzanenone. This mixture could be readily separated by flash chromatography with pentane by using twice the amount of silica gel specified in ref 18. The yield was approximately 60%.

Enol ether (R_f 0.74): 300-MHz NMR ($CDCl_3$) δ 0.85 (s, 3 H), 1.05 (s, 3 H), 1.32–2.38 (m, 10 H), 1.64 (br s, 3 H), 3.52 (s, 3 H), 4.39 (br s, 1 H), 5.25–5.32 (m, 1 H); IR (film) 1640, 1450, 1220 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 18.17, 19.47, 23.37, 25.22, 27.76, 28.52, 32.86, 33.18, 36.00, 52.14, 56.42, 93.20, 120.78, 132.48, 166.61; mass spectrum, *m/e* 67, 79, 93, 112, 131, 145, 173, 188, 220; HRMS, *m/e* calcd 220.1827, found 220.1829.

Enol ether (R_f 0.65): 300-MHz NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.07 (s, 3 H), 1.38–2.25 (m, 10 H), 1.64 (br s, 3 H), 3.53 (s, 3 H), 4.39 (br s, 1 H), 5.27–5.32 (m, 1 H); IR (film) 1640, 1220 cm^{-1};

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^{13}C NMR ($CDCl_3$) δ 18.34, 20.61, 23.37, 25.76, 27.87, 28.36, 33.18, 34.05, 37.08, 52.63, 56.37, 93.53, 120.62, 132.32, 165.91; HMRS, m/e calcd 220.1827, found 220.1829.

Trichoenone and Bazzanenone. The enol ether (0.110 g) was dissolved in THF (5 mL). HCl (10% aqueous) (1 mL) was added and the mixture was stirred at room temperature for 12 h. The THF was removed in vacuo and the residue was extracted 3 times with 10 mL of ether. The organic layer was washed with brine and dried. The solvent was removed in vacuo and the crude product passed through a small silica gel column with 9:1 hexanes/ethyl acetate. Trichoenone was produced in 92% yield. Bazzanenone was similarly produced in 87% yield.

Bazzanenone (6): 300-MHz NMR ($CDCl_3$) δ 0.89 (s, 3 H), 1.00 (s, 3 H), 1.30-2.42 (m, 12 H), 1.63 (br s, 3 H), 5.23-5.29 (m, 1 H); IR ($CDCl_3$) 1728, 1450, 1407, 1370, 1160, 1058 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 17.65 (2 C), 18.58, 23.23, 27.25, 28.06, 31.95, 33.24, 35.71, 40.69, 53.22, 119.73, 132.38, 223.39; HRMS, m/e calcd 191.14359, found 191.14347.

Trichoenone (8): 300-MHz NMR ($CDCl_3$) 0.90 (s, 3 H), 1.01 (s, 3 H), 1.25-2.38 (m, 12 H), 1.63 (br s, 3 H), 5.23-5.30 (m, 1 H); IR ($CDCl_3$) 1729, 1450, 1407, 1380, 1162, 1058 cm^{-1}; ^{13}C NMR ($CDCl_3$) 18.28, 18.36, 18.71, 23.28, 27.37, 27.82, 33.10, 33.67, 36.30, 40.92, 53.89, 119.67, 132.36, 223.92; HRMS, calcd 191.14359, found 191.14339.

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Regioselective Addition of Butenyl Grignard Reagent to the Unactivated Double Bond of 2-(α-Methylallyl) Aza Aromatic Compounds

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The addition of the butenyl Grignard reagent to the unactivated double bond of 2-(α-methylallylic) aza aromatic compounds is completely regioselective, giving the 2-(1,4-dimethyl-5-hexen-1-yl) aza aromatics in good yield. A preliminary coordination of magnesium atom to nitrogen atom and the formation of a six-center transition state involving the butenyl Grignard and the vinyl group has been proposed in order to explain the selectivity of the reaction.

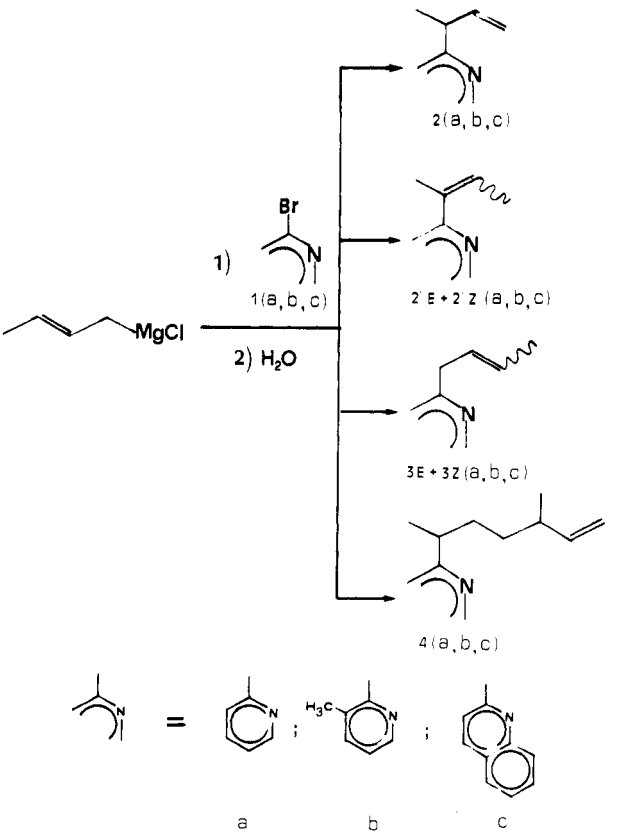
The butenyl Grignard reagent is known to react with many electrophilic substrates and to give crotyl or α-methylallyl derivatives depending on the reaction conditions and the substrates used.[1,2] Recently, we found[3] that the butenyl Grignard reagent is very reactive toward 2-bromo derivatives of aza aromatic heterocyclic compounds such as 2-bromopyridine (**1a**), 2-bromo-3-methylpyridine (**1b**), and 2-bromoquinoline (**1c**). Upon addition of Grignard reagent at 0 °C to the substrates **1a**, **1b**, and **1c** in a 1:1 molar ratio the isomerically pure α-methylallyl derivatives 2-(1-methyl-2-propen-1-yl)pyridine (**2a**), 2-(1-methyl-2-propen-1-yl)-3-methylpyridine (**2b**), and 2-(1-methyl-2-propen-1-yl)quinoline (**2c**) were obtained in good yield.

In the present paper we report the results obtained in the reaction between the aza aromatic compounds **1a**, **1b**, and **1c** and a large excess of butenyl Grignard reagent (molar ratio 1:6).

Results and Discussion

As shown in Scheme I, the most significant result is the formation of the 2-(1,4-dimethyl-5-hexen-1-yl) aza aromatic compounds **4**, arising from the addition of the α-methylallyl group to the CH_2 vinyl carbon atom of the α-methylallyl derivatives **2**. In addition to **4**, the α-methylallyl derivatives **2**, the isomers (*E*)-**2'** and (*Z*)-**2'**, and the crotyl derivatives **3** are obtained. The above compounds were separated by preparative VPC and identified by ^1H NMR and VPC-MS techniques; the results obtained are reported in Table I. The addition compound **4** is the main product in the case of **1a** and **1b**. In particular, **4b** is obtained in very good yield and high chemical purity, the other reaction products **2b**, **2'b**, and **3b** being formed in a very low amounts (<3%). In contrast, the product **4c** was obtained in a low yield (3%) from the substrate **1c**, the main

Scheme I



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