data is summarized in Table I. Three additional recrystallizations from hexane gave a pure sample of alcohol **3**, mp 162–164 °C. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.63; H, 9.71.

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Registry No. **1**, 63180-69-8; **2**, 97235-07-9; **3**, 105019-13-4; **4**, 105087-99-8; **5**, 105019-14-5; **9**, 105019-15-6; **10**, 105019-16-7; **11**, 105088-00-4.

A Short Efficient Synthesis of Trichodiene

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The trichothecene mycotoxins such as deoxynivalenol (vomitoxin, **1**) have been identified as harmful contaminants of grain in many parts of the world.[1] From precursor incorporation studies,[2] the hydrocarbon trichodiene, **2**, has been shown to be the first unique intermediate in the biosynthetic pathway leading to the trichothecenes. Since **2** has only been isolated in trace quantities from natural sources,[3] considerable effort has been directed toward the synthesis of this natural product. This interest is due both to the pivotal biosynthetic role occupied by **2** and to the synthetically challenging nature of the two contiguous quaternary centers inherent in the structure of **2** (Figure 1).

Some elegant and igenious total syntheses have been reported for racemic **2**[4] and also for its biogenetically divergent diastereomer bazzanene, **3**.[4b,f,5] To supplement our trichothecene biosynthetic studies,[6] a synthetic route to **2** was desired that would be amenable to isotopic labeling and was also as direct as possible from commercially available starting materials. The approach we devised employs an ester–enolate Claisen rearrangement as the key carbon–carbon bond-forming step enabling simultaneous introduction of the two quaternary centers.

Commercially available[7] methyl ketone **4** can be readily converted to allylic alcohol **5** via the two-step sequence[8]

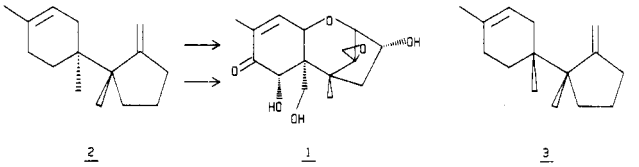


Figure 1. Outline of trichothecene iosynthesis.

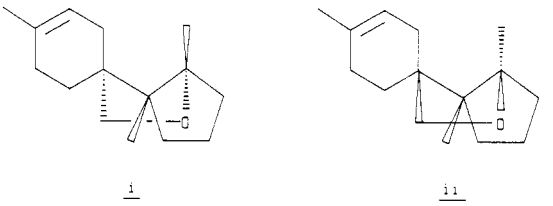
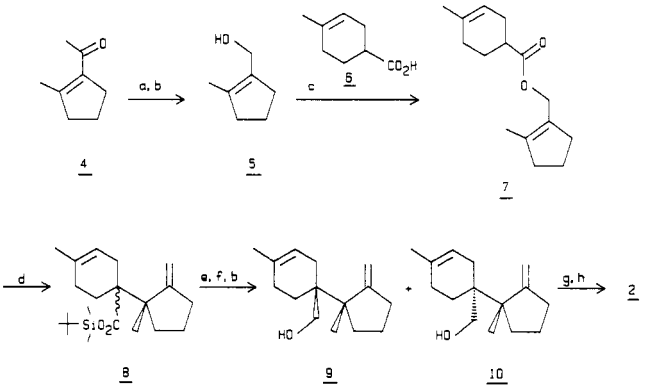


Figure 2. Structures of enol–ether byproducts.

Scheme I. Synthetic Route to Trichodiene[a]



[a] (a) KOCl; (b) $LiAlH_4$; (c) DCC, DMAP; (d) i. LDA, *t*-$BuMe_2SiCl$; ii. reflux; (e) *n*-Bu_4NF; (f) CH_2N_2; (g) PCC; (h) Me_3COK, NH_2NH_2.

shown in Scheme I. Diels–Alder adduct **6**[9] is then esterified with **5** under very mild conditions[10] in the presence of DCC to yield ester **7**. The complete carbon skeleton of trichodiene is then obtained in short order by subjecting ester **7** to the Ireland modification[11] of the Claisen rearrangement, which gives rise to **8** as a 60:40 mixture of diastereomers.

As has been observed[4g] for an analogous highly hindered neopentyl silyl ester, hydride reducing agents simply hydrogenolyzed **8** to the derived acid, necessitating the three-step route to alcohols **9** and **10** shown in Scheme I. By careful silica gel chromatography, diastereomers **9** and **10** could be separated with the desired **10** exhibiting the lower R_f. Alcohol **10** could then be converted to racemic trichodiene by PCC oxidation[12,13] to the aldehyde followed by Wolff–Kishner reduction using the reported conditions.[4f] In a comparison of its specral and chromatographic properties, the synthetic material proved identical in all respects (except optical rotation) with an authentic sample of natural trichodiene.[6b]

This direct synthesis of **2** has been employed to obtain standards of racemic trichodiene useful as carriers in on-

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going biosynthetic studies. Tritiated **2** has also been prepared by this route and its use in the elucidation of trichothecene biosynthetic intermediates is presently under investigation.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 1320 spectrophotometer. ^1H and ^{13}C nuclear magnetic resonance spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Bruker WM-300WB instrument with Me_4Si as the internal standard. All anhydrous reactions were run under a nitrogen atmosphere. Unless otherwise noted, all reagents and solvents were obtained from commercial sources and purified by standard methods. GC analyses were performed on a Spectra-Physics Model 7100 instrument equipped with a 0.25 mm i.d. × 30 m DB-1 capillary column and employing an oven temperature of 120 °C (2 min) followed by a gradient of 4°/min. High resolution mass spectra were performed by Shrader Laboratories.

1-(Hydroxymethyl)-2-methyl-1-cyclopentene (5). $LiAlH_4$ (2.1 g, 55 mmol) was suspended in dry ether and an ethereal solution of 2-methyl-1-cyclopentene-1-carboxylic acid[8] (6.2 g, 46 mmol) was added dropwise while cooling the reaction in an ice bath. After warming to ambient temerature and stirring 1 h, the reaction was carefully quenched by the dropwise addition of 1 N HCl. The pH was adjusted to 3 by the further addition of HCl. Ether was added and the layers were separated. The aqueous layer was extracted with ether (3×), the combined extracts were dried ($MgSO_4$), and ether was removed in vacuo leaving a crude yellow oil. Silica gel gravity chromatography using hexane–EtOAc (90:10 changing to 75:25) as eluent yielded **5** (2.1 g, 40%): bp 105–120 °C at 35 mmHg; R_f 0.43, hexane/EtOAc (3:1); ^1H NMR δ 1.63 (s, 3 H), 1.70–1.82 (m, 2 H), 2.05 (bs, 1 H), 2.23–2.44 (m, 4 H), 4.11 (s, 2 H); ^{13}C NMR: δ 13.7, 21.6, 34.2, 38.8, 59.1, 134.3, 135.7.

(2-Methyl-1-cyclopentenyl)methyl 4-Methyl-3-cyclohexene-1-carboxylate (7). To a CH_2Cl_2 solution of acid **6** (3.40 g, 24.3 mmol) and alcohol **5** (2.72 g, 24.3 mmol) were added 4-(dimethylamino)pyridine (600 mg, 4.9 mmol) and *N,N*-dicyclohexylcarbodiimide (6.26 g, 30.4 mmol). After stirring overnight at room temperature, the precipitate was filtered and the solvents were evaporated in vacuo. The residue was purified by gravity SiO_2 chromatography using hexane/EtOAc (100:0 to 85:15) as eluent. Thus **7** (4.68 g, 82%) was obtained as a clear colorless oil: bp 130–140 °C at 0.5 mmHg; R_f 0.54, hexane/EtOAc (9:1); IR ($CHCl_3$) 1705; ^1H NMR δ 1.64 (bs, 3 H), 1.70 (bs, 3 H), 4.64 (s, 2 H), 5.29–5.41 (m, 1 H); GC/MS (relative intensity) (EI), *m/z* 234 (M^+, 0.3), 95 (100).

***tert*-Butyldimethylsilyl 4-Methyl-1-(1-methyl-2-methylenecyclopentyl)-3-cyclohexene-1-carboxylate (8).** A THF solution of ester **7** (4.68 g 20.9 mmol) was slowly added to LDA [prepared from diisopropylamine (3.2 mL, 23 mmol) and *n*-butyllithium (14.8 mL of a 1.3 M soln., 19.2 mmol) in 40 mL of THF] while vigorously stirring and cooling the reaction at −78 °C. After 30 min, HMPA (3.7 mL, 21 mmol) was added to the reaction and after an additional 10 min, a THF solution of *tert*-butyldimethylsilyl chloride (3.19 g, 21.1 mmol) was added. The cooling bath was removed; the reaction mixture was allowed to warm to ambient temperature. The reaction was then refluxed overnight. Water and ether were added to the cooled reaction mixture, the layers were separated, and the aqueous layer was extracted with ether. The combined ether extracts were then washed with dilute HOAc and brine and dried ($MgSO_4$), and ether was removed in vacuo to leave 7.4 g of a crude oil: ^1H NMR δ 0.2 (s, 6 H), 0.9 (s, 9 H), 1.14 (s, 1.2 H), 1.17 (s, 1.8 H), 1.58 (bs, 1.8 H), 1.65 (bs, 1.2 H), 4.76–4.80 (m, 1 H), 4.96–4.99 (m, 1 H), 5.32–5.38 (m, 1 H).

1-(Hydroxymethyl)-4-methyl-1-(1-methyl-2-methylenecyclopentyl)-3-cyclohexene (9 and 10). The crude silyl esters **8** (7.4 g) from above were dissolved in THF at room temperature and a THF solution of tetra-*n*-butylammonium fluoride (23 mL of a 1.0M solution, 23 mmol) was added. After stirring 8 h at room temperature, the THF was removed in vacuo, and water and ether were added. The aqueous layer was extracted with ether and the ether extract was treated with excess diazomethane. After being kept overnight in the hood, the solvents were evaporated, and the residue was purified by SiO_2 chromatography using hexane/EtOAc (95:5) to yield a spectroscopically distinct mixture of diastereomeric methyl ester (4.29 g, 83% from **7**): R_f 0.44, hexanes/EtOAc (9:1); ^1H NMR δ 1.09 (s, 1.2 H), 1.12 (s, 1.8 H), 1.56 (bs, 1.8 H), 1.62 (bs, 1.2 H), 3.60 (s, 3 H), 4.72–4.78 (m, 1 H), 4.95–4.99 (m, 1 H), 5.30–5.34 (m, 1 H); HRMS, calcd for $C_{16}H_{24}O_2$ *m/z* 248.1776, found *m/z* 248.1788.

The mixture of diastereomeric methyl esters (1.2 g, 4.8 mmol) was dissolved in dry THF and slowly added to a THF suspension of $LiAlH_4$ (380 mg, 10 mmol). After stirring 6 h at room temperature, the reaction was carefully quenched by the slow addition of saturated NH_4Cl. Water and ether were added, the layers were separated, and the aqueous layer was extracted with ether (3×). The combined ether extracts were dried ($MgSO_4$), and the solvents were removed in vacuo. The residue was purified by SiO_2 gravity chromatography using hexane/EtOAc (98:2). Fractions were combined into four groups that were analyzed by GC to contain the following ratios of **9** to **10**: i, 92:8 (115 mg), ii, 60:40 (160 mg); iii, 20:80 (400 mg); iv, 5:95 (160 mg). The combined yield of **9** and **10** was 79%.

Alcohol **10**: R_f 0.21, hexane/EtOAc (9:1); ^{1},h NMR δ 1.11 (s, 3 H), 1.64 (bs, 3 H), 3.52 + 3.62 (dd, J = 12 Hz, 2 H), 4.81–4.84 (m, 1 H) 4.96–4.99 (m, 1 H), 5.20–5.24 (m, 1 H); ^{13}C NMR δ 22.7, 23.1, 24.6, 24.9, 27.7, 29.1, 37.3, 38.1, 41.3, 50.1, 64.0, 107.1, 119.5, 113.1, 161.8; HRMS, calcd for $C_{15}H_{24}O$ *m/z* 220.1827, found *m/z* 220.1830.

Alcohol **9**: 0.23, hexane/EtOAc (9:1); ^1H NMR δ 1.04 (s, 3 H), 1.64 (bs, 3 H), 3.47 (d, J = 12 Hz, 1 H), 3.70 (d, J = 12 Hz, 1 H) 4.98–5.02 (m, 1 H), 5.08–5.11 (m, 1 H), 5.25–5.28 (m, 1 H); ^{13}C NMR δ 23.1, 24.2, 24.8, 25.0, 27.7, 29.7, 36.9, 38.8, 41.2, 49.4, 64.0, 108.2, 119.1, 134.2, 161.1.

4-Methyl-1-(1-methyl-2-methylenecyclopentyl)-3-cyclohexene-1-carboxaldehyde (Trichodienal). A 95:5 mixture of alcohols **10** and **9** (121 mg, 0.55 mmol) was dissolved in 15 mL of CH_2Cl_2 and NaOAc (34 mg, 0.25 mmol) was added. The mixture was cooled to 0 °C and pyridinium chlorochromate (180 mg, 0.82 mmol) was added in one portion. After stirring 3 h at 0 °C, ether was added and the aldehyde was purified by suction filtration through a pad of SiO_2. The solvents were removed in vacuo, yielding trichodienal (107 mg, 0.49 mmol, 89%): R_f 0.49, hexane/EtOAc (9:1); ^1H NMR δ 1.04 (s, 3 H), 1.53 (bs, 3 H), 4.73 (d, J = 2.7 Hz, 1 H), 5.01 (d, J = 2.7Hz, 1 H), 5.35–5.37 (m, 1 H), 9.49 (s, 1 H); ^{13}C NMR 23.0, 23.1, 23.3, 24.7, 27.1, 27.5, 37.0, 37.8, 48.9, 52.5, 108.0, 119.4, 133.9, 157.5, 207.2.

This aldehyde was then dissolved in 15 mL of anhydrous EtOH and cooled to 0 °C, and NaB^3H_4 (25 mCi) was added. After reacting 30 min, unlabeled $NaBH_4$ (30 mg, 0.80 mmol) was added. After stirring an additional 3 h, ether and a saturated soln of NaCl were added. The layers were separated, the aqueous layer was extracted with ether (3×), and the extracts were combined and dried ($MgSO_4$); ether was removed in vacuo. The residual ^3H-**10** (101 mg, 94%) with specific activity 0.5 mCi/mmol was then subjected to the above PCC oxidation (160 mg PCC, 32 mg NaOAc), yielding crude [15-^3H]trichodienal (94 mg, 94%).

[15-^3H]Trichodiene (2). The above [15-^3H]trichodienal was dissolved in *n*-butanol (1 mL) and transferred under Argon to a 5-mL sealable high pressure vessel. A mixture of anhydrous hydrazine (46 μL, 1.46 mmol) and potassium *tert*-butoxide (112 mg, 1.0 mmol) in *n*-butanol (1 mL) was added and the reaction vessel was sealed at atmospheric pressure. The yellow reaction mixture was then heated 12 h at 180 °C. The resultant colorless solution was cooled to room temperature, diluted with hexane (5 mL), washed with H_2O, dried ($MgSO_4$), and concentrated. The residual yellow oil was chromatographed over SiO_2 using hexane as eluent to provide [15-^3H]trichodiene (62 mg, 71%) as a colorless oil with a specific activity of 0.3 mCi/mmol: R_f 0.50, hexane; ^1H NMR δ 0.85 (s, 3 H), 1.04 (s, 3 H), 1.64 (bs, 3 H), 4.73 (bs, 1 H), 4.96 (bs, 1 H), 5.27–5.32 (m, 1 H); ^{13}C NMR δ 18.1, 23.4, 23.6, 24.3, 28.0, 28.4, 33.2, 37.5, 39.0, 50.8, 107.0, 120.7, 132.5, 160.1; GC/MS (EI), *m/z* (relative intensity) 204 (M, 0.4), 109 (100), 108 (90), 67 (65).

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NMR spectra, and Dr. J. C. Gilbert for exchanging manuscripts after learning of our similar synthetic approaches.

Registry No. (±)-**2**, 61505-17-7; (±)-^{3}H-**2**, 105164-40-7; **5**, 81328-62-3; **6**, 4342-60-3; (±)-**7**, 104762-26-7; (±)-**8** (acid) (isomer 1), 105164-34-9; (±)-**8** (acid) (isomer 2), 105164-35-0; (±)-**8** (isomer 1), 105164-36-1; (±)-**8** (isomer 2), 105164-37-2; (±)-**8** (methyl ester) (isomer 1), 104762-29-0; (±)-**8** (methyl ester) (isomer 2), 104762-30-3; (±)-**9**, 104762-32-5; (±)-**10**, 104762-31-4; ^{3}H-**10**, 105164-38-3; (±)-^{3}H-**10**-al, 105164-39-4; 2-methyl-1-cyclopentene-1-carboxylic acid, 67209-77-2; (±)-trichodienal, 82096-03-5.

Asymmetric Synthesis of (*R*)- and (*S*)-[2-^{2}H$_1$]Glycine

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Chiral glycine[1] has become an increasingly important substance for the study of numerous biochemical reactions and serves as a starting material for stereospecific conversions into other important, labeled compounds such as chiral acetic[2] and chiral glycolic[3] acids. A number of syntheses of chiral glycine have been reported[1] that involve one or two enzyme-mediated transformations or involve unambiguous chemical syntheses from chiral, nonracemic starting materials such as other amino acids or sugars. The somewhat capricious nature of the enzyme-mediated syntheses and the tediousness of the multistep chemical syntheses make this deceptively simple molecule a challenging and important target for efficient asymmetric synthesis. We recently reported[4] a new asymmetric synthesis of α-amino acids based on the chiral electrophilic glycinate **2**. In this paper, we further demonstrate the utility of this method by reporting an efficient two-step stereospecific synthesis of (*R*)- and (*S*)-[2-^{2}H$_1$]glycine from the readily available[4] glycinates **1**.

Bromination of (−)-5(*S*),6(*R*)-**1** as previously described[4] furnishes the bromide **2** as a white solid (Scheme I). Reduction of **2** with D_2 at 40 psi in the presence of catalytic $PdCl_2$ in D_2O/THF at 25 °C for 40 h directly furnishes (*S*)-[2-^{2}H$_1$]glycine in 51–54% yield. The isotopic purity of this material at C-2 was determined to be at least 84–90% and the optical purity (% ee) was established at 77–82% according to the procedure of Armarego et al.[5] Specifically, acylation of **3** with (−)-camphanyl chloride (**4**) furnished the amides (**5a,b**, which were examined by ^{1}H NMR (Scheme II). Comparison of the resonances near δ 4 with that of the amides **5c** prepared from racemic [2-^{2}H$_1$]glycine obtained from racemic **1** rigorously established the stereochemical purities of (*S*)- and (*R*)-**3**. The isotopic purity was similarly obtained by comparing the ^{1}H NMR spectra of the camphanyl amide **5d** of glycine with those of the chiral glycine derivative (Figure 1).

The stereochemical outcome of the reduction clearly indicates that the C–D bond is formed from the sterically less encumbered face of the presumed putative imine **6** (Scheme III).

It is noteworthy that reduction of (−)-5(*S*),6(*R*)-**2** with Bu_3SnD followed by hydrogenolysis (H_2/Pd/C) produced

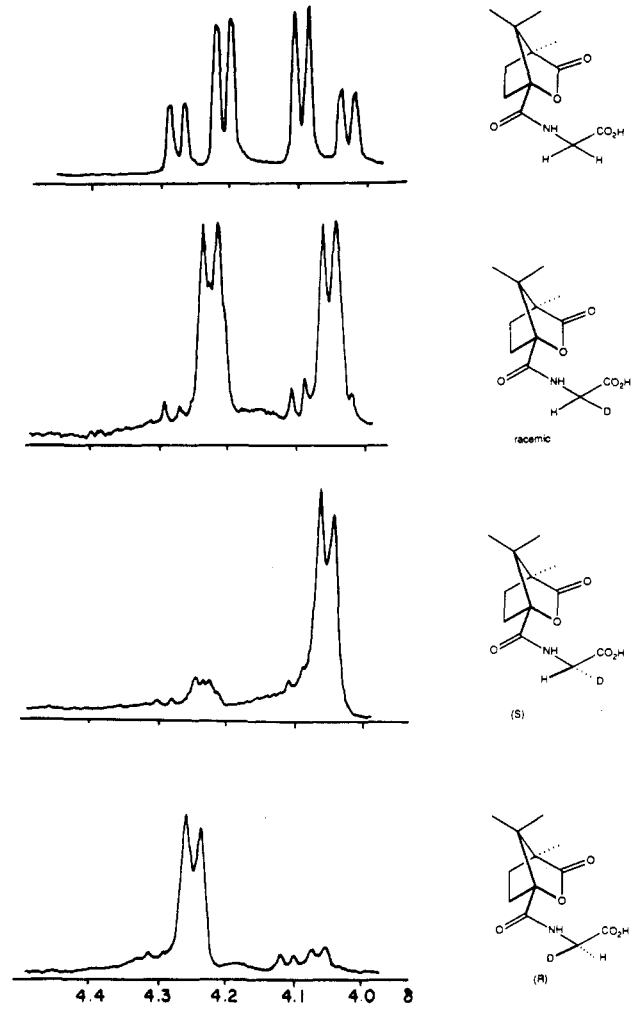

Figure 1. ^{1}H NMR spectra of camphanyl amides at 270 MHz between δ 4.0 and 4.4: (a) **5d**; (b) **5c**; (c) **5a**; (d) **5b**.

(*R*)-**3**, in 60% ee (ie., the *reverse* stereochemical outcome from the hydrogenolysis).

Similarly, the conversion of (+)-5(*R*),6(*S*)-**1** into (*R*)-**3** proceeds with equal efficiency. Although the optical purity of the chiral glycine obtained by the present method is slightly lower than that reported previously,[1,5] the relatively high overall chemical yield and experimental simplicity of this synthesis render this contribution a practical alternative to the significantly more laborious syntheses.[1] Furthermore, since the isotopic atom is introduced in the very last transformation, this methodology should be particularly appealing to those interested in synthesizing [2-^{3}H$_1$]glycine.

Experimental Section

(*S*)-[2-^{2}H$_1$]Glycine. The bromide (−)-5(*S*),6(*R*)-**2** (0.274 mmol, 1 equiv) is dissolved in dry THF (5 mL) and D_2O (1 mL) and placed in a pressure bottle that had been base washed with NaOD/D_2O. To this solution was added $PdCl_2$ (14.6 mg, 0.082 mmol, 0.3 equiv) and the vessel was charged with D_2 at 40 psi.

† Fellow of the Alfred P. Sloan Foundation, 1986–1988. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee, 1986–1988.

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