Formal Total Synthesis of (±)-Trichodiene *via* Claisen Rearrangement and Robinson Annulation

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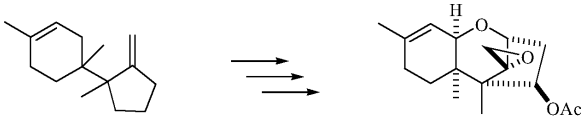
A facile formal total synthesis of (±)-trichodiene was achieved by employing Claisen rearrangement and Robinson annulation as synthetic key strategies.

Key words: (±)-Trichodiene, Claisen Rearrangement, Robinson Annulation

Introduction

(±)-Trichodiene (**1**) is a volatile sesquiterpene which was isolated from the extract of the mycelium of the fungus *Trichothecium roseum Link* [1]. The structure of (±)-trichodiene (**1**) was determined by Nozoe and Machida in 1970 *via* degradation reactions and by spectroscopic methods [2]. (±)-Trichodiene has been shown to be the biogenetic precursor of the trichothecane family of sesquiterpenoids as characterized by the cytotoxic fungal metabolite (–)-trichodermin (**2**, Fig. 1) [3]. The trichothecane family of sesquiterpenoids has stimulated significant interest due to its wide range of intriguing biological activities [4] such as antifungal [5], antibacterial [6], cytotoxic [7], and phytotoxic effects [8], and the inhibition of enzymes [9]. Several elegant synthetic approaches have been reported [10] in the literature; most of these methods are racemic syntheses, and only a few approaches are applicable to the stereocontrolled synthesis of (+)-trichodiene or (–)-trichodiene. The Lange group [11] has performed a synthesis of (±)-trichodiene using a free radical fragmentation approach. Meyer *et al.* [12] reported the asymmetric synthesis of (–)-trichodiene based on the generation of vicinal stereogenic quaternary centers *via* a thio-Claisen rearrangement. Gilbert *et al.* [13] described an enantioselective synthesis of (–)-trichodiene through Ireland-Claisen rearrangement of a ketene silyl acetal with excellent stereoselectivity.

Herein, we wish to report a formal total synthesis of (±)-trichodiene (**1**). Key synthetic steps of our strategy



1 (±)-Trichodiene **2** (-)-Trichodermin

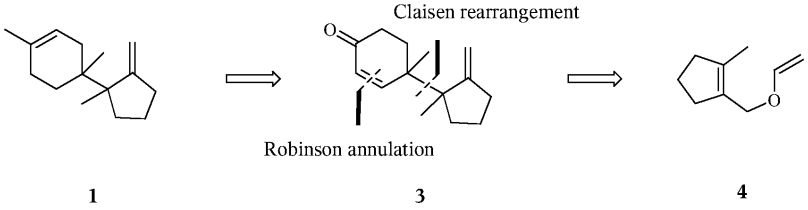
Fig. 1. Structures of (±)-trichodiene (**1**) and (–)-trichodermin (**2**).

are the Claisen rearrangement of vinyl ether **4** and the Robinson annulation of aldehyde **10a** in order to construct quaternary centers of enone **3** which has been converted into (±)-trichodiene (**1**).

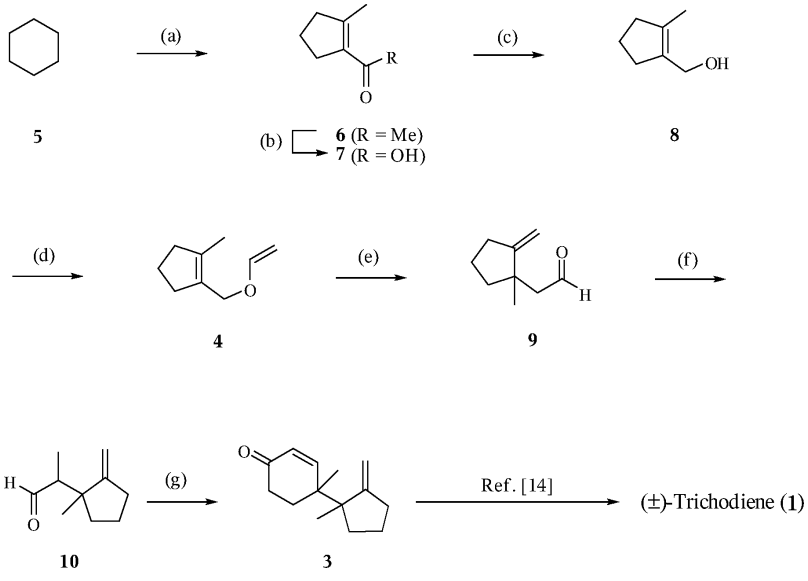
Results and Discussion

Our retrosynthetic analysis of (±)-trichodiene (**1**) is shown in Scheme 1. (±)-Trichodiene (**1**) has been synthesized from enone **3** by using a Wittig reaction and metal reduction [14]. We envisaged that the enone **3** would be accessible from the vinyl ether **4** *via* a Claisen rearrangement [15] and a Robinson annulation of aldehyde **10a** [16] (Scheme 2).

Cyclohexane was treated with acetyl chloride in the presence of aluminum chloride in chloroform to give 1-acetyl-2-methylcyclopentene (**6**) [17]. Compound **6** was oxidized with freshly prepared potassium hypochlorite (KOCl) solution (calcium hypochlorite was treated with 0.5 equiv. of potassium hydroxide and 0.75 equiv. of potassium carbonate in H_2O) to obtain 2-methyl-1-cyclopentenecarboxylic acid (**7**) in



Scheme 1. Retrosynthetic analysis of (±)-trichodiene (**1**).



Scheme 2. Synthesis of (±)-trichodiene (**1**): (a) $AlCl_3$, AcCl, $CHCl_3$, reflux, 2 h; then r.t., 48 h; then KOH, MeOH, r.t., 16 h (32 %); (b) KOCl [$Ca(OCl)_2$, KOH, K_2CO_3], H_2O, 0 °C, 16 h (80 %); (c) LAH, diethyl ether, r.t., 1 h (78 %); (d) $Hg(OAc)_2$, ethyl vinyl ether, reflux, 28 h (72 %); (e) neat, 235 – 240 °C, 1 h (83 %); or Ph_3P, Et_2AlCl, 1,2-dichloroethane, r.t., 1 h (51 %); (f) KH, CH_3I, THF, 5 °C, 30 min; then r.t., 6 h (70 %); (g) KH, 3-buten-2-one, r.t., 1 h; then 80 – 90 °C, 1 h (60 %).

80 % yield [18]. Subsequent reduction of compound **7** was accomplished by treatment with lithium aluminum hydride (LAH) in dry THF to give 2-methyl-1-cyclopentenylmethanol (**8**) in good yield [19]. Alcohol **8** was treated with freshly distilled ethyl vinyl ether in the presence of mercury acetate, [$Hg(OAc)_2$], to yield 1-methyl-2-vinyloxymethylcyclopentene (**4**) in 72 % yield, which was subjected to Claisen rearrangement at 235 – 240 °C for 1 h in a silicon oil bath to afford 1-methyl-1-formylmethyl-2-methylenecyclopentane (**9**) in 83 % yield (including recovered starting material).

Vinyl ether **4** was also treated with triphenylphosphine and diethyl aluminum chloride in 1,2-dichloroethane to give compound **9** in 51 % yield. Although the latter reaction condition was more convenient for handling, the thermal Claisen rearrangement method afforded a clean product and superior yield. Methylation of compound **9** was performed with KH (30 wt % dispersion in mineral oil) and CH_3I in dry THF to provide a 1 : 1 mixture of aldehyde **10**. Separation of the resulting mixture by preparative TLC (0.5 mm, 20 × 20 cm^2, silica gel, 2 % EtOAc in hexane) afforded **10a** and **10b** (1 : 1, 70 % combined yield). The desired component **10a** was subjected to Robinson annulation with 3-buten-2-one at 80 – 90 °C for 1 h in a steam bath to afford a 1.2 : 1 mixture of compound **3**. This mixture could be separated by flash chromatography [20] with 5 % EtOAc in hexane by using twice the amount of silica gel specified in [20] (1.2 : 1, 60 % combined yield). Most diagnostic for the assignment of the relative stereochemistry to the isomers were the singlets δ = 1.18 and 1.22 that are ascribable to the methyl group at C-4 of the cyclohexene ring: The resonance at higher field is assigned to **3a** by analogy to literature ^{1}H NMR data of **3a** [14].

Conclusion

In conclusion, we have developed a concise formal total synthesis of (±)-trichodiene (**1**), starting from 1-methyl-2-vinyloxymethylcyclopentene (**4**). The advantage of this synthesis over previously reported methods, that also employ a [3,3]-sigmatropic rearrangement, is that the starting materials can be prepared easily and from inexpensive reagents.

Experimental Section

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates from Analtech and visualized with 254 nm UV light. Flash chromatography was carried out on silica gel 60 (Scientific Adsorbents Incorporated (SAI), particle size 32 – 63 μm, pore size 60 Å). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 instrument at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J* values are given in Hz. Infrared (IR) spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded with a Waters Micromass ZQ LC-Mass system and high-resolution mass spectra (HRMS) were measured with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). When necessary, chemicals were purified according to the reported procedures [21].

*1-Methyl-2-vinyloxymethylcyclopentene (**4**)*

To a stirred solution of mercury acetate (3.20 g, 10.0 mmol) in freshly distilled ethyl vinyl ether (75 mL) was added alcohol **8** (1.70 g, 15.1 mmol) at r. t., and the mixture was refluxed for 28 h. The reaction mixture was cooled to r. t. and poured to a 5 % aqueous KOH solution (15 mL). The organic phase was separated and washed with a saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5 % ethyl acetate in hexanes) to give **4** (1.50 g, 72 %) as an oil. – IR (neat, NaCl): ν = 2976, 1465, 1100, 845 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.46 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.81 (dd, *J* = 15.6, 2.0 Hz, 1H), 4.52 (dd, *J* = 7.2, 2.0 Hz), 4.25 (s, 2H), 2.41 – 2.30 (m, 4H), 2.12 – 1.91 (m, 2H), 1.70 (br s, 3H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.1, 140.4, 131.7, 86.5, 65.2, 38.1, 31.2, 22.4, 17.1. – HRMS ((+)-ESI): *m/z* = 161.0925 (calcd. 161.0942 for $C_9H_{14}ONa$, $[M+Na]^+$). – $C_9H_{14}O_1$ (138.1): calcd. C 78.21, H 10.21; found C 78.15, H 10.12.

*2-Methyl-1-cyclopentenecarboxylic acid (**7**)*

To a stirred solution of potassium carbonate (2.5 g, 17.7 mmol) in H_2O (7 mL) was added potassium hydroxide (0.7 g, 12.5 mmol), followed by a suspension of calcium hypochlorite (3.5 g, 24.0 mmol) in H_2O (14 mL) at r. t. The mixture was stirred at r. t. for 1 h. The potassium hypochlorite solution (containing approximately 14.0 mmol) was then filtered to remove the calcium salts, and the filtered cake was rinsed with H_2O (5 mL). The residue was cooled to 0 °C, and compound **6** (1.0 g, 8.1 mmol) was added dropwise under argon atmosphere. The reaction mixture was stirred at 0 °C for 16 h and allowed to warm to r. t. The mixture was quenched by addition of sodium hydrogen sulfite (1.0 g) and extracted with diethyl ether (20 mL). The aqueous phase was acidified by using an 18 % aqueous HCl solution and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give **7** (0.81 g, 80 %). – IR (neat, NaCl): ν = 3460, 2960, 1461, 1280 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.9 (br s, 1H), 2.81 – 2.30 (m, 4H), 2.1 (s, 3H), 2.05 – 1.62 (m, 2H). – HRMS ((+)-ESI): *m/z* = 127.0773 (calcd. 127.0759 for $C_7H_{11}O_2$, $[M+H]^+$).

*2-Methyl-1-cyclopentenylmethanol (**8**)*

To a stirred suspension of LAH (1.70 g, 44.8 mmol) in anhydrous diethyl ether (100 mL) was added dropwise acid **7** (3.80 g, 30.0 mmol) at −45 °C, and the mixture was warmed to r. t. and stirred for 1 h. After the reaction was completed, the mixture was quenched with a 3 % aqueous HCl solution (20 mL), and the organic phase was separated and washed with a saturated aqueous NH_4Cl solution (30 mL) and brine (40 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10 % ethyl acetate in hexanes) to give alcohol **8** (2.60 g, 78 %) as a colorless oil. – IR (neat, NaCl): ν = 3320, 2940, 1450, l082 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.15 (s, 2H), 2.42 – 2.20 (m, 4H), 1.95 – 1.81 (m, 2H), 1.67 (s, 3H), 1.21 (s, 1H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.0, 134.5, 59.2, 38.4, 33.9, 21.8, 13.3.

*1-Methyl-1-formylmethyl-2-methylenecyclopentane (**9**)*

Method A: Vinyl ether **4** (1.38 g, 10.0 mmol) was heated at 235 – 240 °C for 1 h on a silicon oil bath. The mixture was cooled to r. t. and diluted with diethyl ether (55 mL) and then treated with a 10 % aqueous sodium bicarbonate solution (30 mL). The organic phase was separated and washed with a saturated aqueous NH_4Cl solution (25 mL) and brine (25 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 7 % ethyl acetate in hexanes) to give aldehyde **9** (1.15 g, 83 %) as a colorless oil. – IR (neat, NaCl): ν = 2960, 1720, 1460, 1122 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.70 (s, lH), 4.88 – 4.75 (m, 2H), 2.41 – 2.30 (m, 4H), l.70 – 1.61 (m, 4H), 1.12 (s, 3H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = l98.8, 170.1, 105.5, 55.6, 53.1, 52.3, 37.2, 25.1, 24.7. – HRMS ((+)-ESI): *m/z* = 139.1132 (calcd. 139.1123 for $C_9H_{15}O_1$, $[M+H]^+$). – $C_9H_{14}O_1$ (138.1): calcd. C 78.21, H 10.21; found C 78.11, H 10.15.

Method B: To a stirred solution of triphenylphosphine (1.20 g, 4.6 mmol) in 1,2-dichloroethane (5 mL) was added diethyl aluminum chloride (4 mL, 4.0 mmol, 1.0 M sol. in hexane), and the mixture was stirred at r. t. for 15 min. A solution of vinyl ether **4** (0.28 g, 2.0 mmol) in 1,2-dichloroethane (5 mL) was added dropwise to the reaction mixture, and the resulting reaction mixture was stirred at r. t. for 1 h. The mixture was diluted with dichloromethane (20 mL) and treated with a 5 % aqueous HCl solution (15 mL). The organic phase was separated and washed with a saturated aqueous NH_4Cl solution (15 mL) and brine (15 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 7 % ethyl acetate in hexanes) to give aldehyde **9** (0.14 g, 51 %) as a colorless oil.

*2-[1-Methyl-2-methylenecyclopentyl]propanal (**10**)*

A suspension of KH (0.44 g, 11.0 mmol, 30 wt.-% dispersion in mineral oil) in dry THF (15 mL) was added to a solution of **9** (1.38 g, 10.0 mmol) in dry THF (5 mL), and the mixture was stirred at r. t. for 30 min. After hydrogen evolution has ceased, a solution of CH_3I (1.56 g, 11.0 mmol) in THF (5 mL) was added dropwise at 5 °C, and the resulting mixture was stirred at 5 °C for 30 min. The reaction mixture was warmed to r. t. and stirred at same temperature for 6 h. The mixture was quenched with cold water (10 mL) and extracted with diethyl ether (2 × 20 mL). The organic phase was separated and washed with a saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5 % ethyl acetate in hexane) to give the products. Separation of the resulting mixture by preparative TLC (0.5 mm, 20 × 20 cm, silica gel, 2 % EtOAc in hexane) afforded **10a** (0.54 g, 35 %) and its diastereomer **10b** (0.54 g, 35 %) as pale yellow liquids. **10a**: IR (neat, NaCl): ν =1725, 1452, 1120, 1065 cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.70 (s, lH), 4.78 (br s, 1H), 5.05 (br s, 1H), 2.54 (m, 1H), 2.05 – 1.98 (m, 2H), l.78 – 1.42 (m, 4H), 1.16 (s, 3H), 1.08 (s, 3H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.1, 170.0, 102.1, 55.6, 49.8, 43.9, 36.4, 25.1, 21.9, 10.2. – HRMS ((+)-ESI): *m/z* = 153.1298 (calcd. 153.1279 for $C_{10}H_{17}O_1$, $[M+H]^+$). – $C_{10}H_{16}O_1$ (152.1): calcd. C 78.90, H 10.59; found C 78.61, H 10.53. **10b**: IR (neat, NaCl): ν = 1725, 1452, 1122, 1082 cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.60 (s, lH), 4.85 (d, *J* = 7.0 Hz, 2H), 2.49 – 2.31 (m, 1H), 2.29 – 2.18 (m, 2H), l.78 – 1.53 (m, 4H), 1.10 (s, 3H), 1.07 (s, 3H). – HRMS ((+)-ESI): *m/z* = 153.1291 (calcd. 153.1279 for $C_{10}H_{17}O_1$, $[M+H]^+$). – $C_{10}H_{16}O_1$ (152.1): calcd. C 78.90, H 10.59; found C 78.75, H 10.68.

*4-Methyl-4-[1-methyl-2-methylenecyclopent-1-yl]-2-cyclohexenone (**3**)*

To a stirred suspension of potassium hydride (0.20 g, 5.0 mmol, 30 wt.-% dispersion in mineral oil) in dry THF (10 mL) was added dropwise aldehyde **10a** (0.68 g, 4.5 mmol) in dry THF (5 mL) at 5 °C, and the mixture was stirred at r. t. for 30 min. A solution of 3-buten-2-one (0.35 g, 5.0 mmol) in dry THF (7 mL) was added to the mixture at r. t., and the resulting mixture was stirred at r. t. for 1 h and then heated on the steam bath (80 – 90 °C) for 1 h. The mixture was cooled to r. t. and treated with a 5 % aqueous HCl solution (5 mL). The mixture was concentrated under reduced pressure, and the residue was extracted with dichloromethane (20 mL). The organic phase was separated, washed with a saturated aqueous NH_4Cl solution (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 5 % EtOAc in hexane) to give **3a** (0.30 g, 33 %) and its epimer **3b** (0.25 g, 27 %) as pale yellow oils. **3a**: IR (neat, NaCl): ν = 1670, 1610 cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.98 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.93 (dd, *J* = 10.5, 0.7 Hz, 1H), 5.05 (d, *J* = 2.8 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 2.53 (ddd, *J* = 17.2, 14.2, 5.5 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.29 – 2.22 (m, 1H), 2.11 (dt, *J* = 13.8, 5.0 Hz, 1H) 1.85 – 1.64 (m, 3H), 1.53 – 1.37 (m, 2H), 1.18 (s, 3H), 1.12 (s, 3H). – HRMS ((+)-ESI): *m/z* = 205.1889 (calcd. 205.1592 for $C_{14}H_{21}O_1$, $[M+H]^+$). **3b**: IR (neat, NaCl): ν = 1670, 1610 cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.92 (dd, *J* = 10.2, 2.2 Hz, 1H), 5.95 (dd, *J* = 10.2, 0.7 Hz, 1H), 5.05 (d, *J* = 2.8 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 2.53 (ddd, *J* = 17.0, 14.2, 5.2 Hz, 1H), 2.48 – 2.35 (m, 2H), 2.30 – 2.25 (m, 1H), 2.11 (dt, *J* = 13.8, 5.0 Hz, 1H) 1.90 – 1.72 (m, 3H), 1.55 – 1.40 (m, 2H), 1.22 (s, 3H), 1.12 (s, 3H). – HRMS ((+)-ESI): *m/z* = 205.1877 (calcd. 205.1592 for $C_{14}H_{21}O_1$, $[M+H]^+$).

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