Total Synthesis of Dehydroaltenuene A. Revision of the Structure and Total Synthesis of Dihydroaltenuene B

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Total synthesis of alternaria toxins starting from previously synthesized altenuene (**3**) and isoaltenuene (**4**) is described. Dihydroaltenuene B (**9**) was prepared by hydrogenation of **3**, and the non-natural epimer 3-*epi*-dihydroaltenuene A was obtained analogously from **4**. Inspection of the spectroscopic data for **9** revealed that the originally proposed structure was in error. A revised structure (**11**), unambiguously proven by total synthesis, is reported herein. Oxidation of **4** with oxygen in the presence of palladium(II) acetate as catalyst led to the formation of dehydroaltenuene A (**8**), while oxidation of **3** using identical conditions yielded *ent*-dehydroaltenuene B (***ent*-9**). Oxidation of **4** with manganese(IV) oxide furnished dehydroaltenusin (**12**), although only impure material was obtained in low yield.

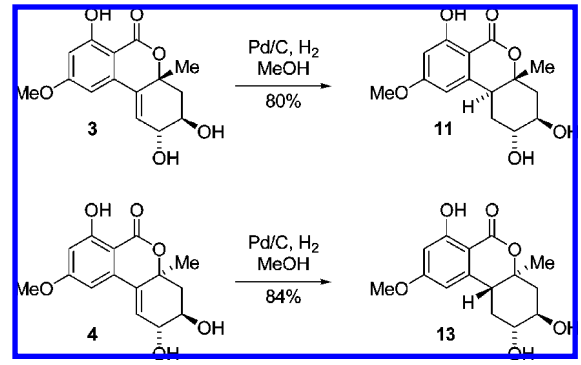
The resorcylic lactones alternariol (**1**) and alternariol 9-methyl ether (**2**) are important secondary metabolites of toxin-producing fungi of the genus *Alternaria*.[1] Although the toxicity of these mycotoxins is low as compared with others (e.g., aflatoxins),[2] infestation with *Alternaria* spp. leads to significant crop losses by fouling of tomatoes, apples, and other fruits.[3] Numerous investigations have been published on **1** and **2**,[4] and total syntheses have been provided for these compounds.[5] Much less is known about minor alternaria toxins such as altenuene (**3**),[1b,6−8] isoaltenuene (**4**),[7,9] neoaltenuene (**5**),[10] 5′-epialtenuene (**6**),[10−12] 4′-epialtenuene (**7**),[8,12] dehydroaltenuenes A and B (**8** and **9**), and dihydroaltenuenes A and B (**10** and **11**). The latter compounds **8**−**11**, which are oxidized or hydrogenated derivatives of **3** and **4**, have been isolated from an unidentified freshwater fungus by Gloer et al. in 2006.[11] Total syntheses of **3**,[13] **4**,[13] **5**,[14] and **9**[15] have been published previously. Neither detailed biological data[16] nor the absolute configuration was available for the latter compounds **5**−**11**. No total syntheses have been published for compounds **6**−**8**, **10**, and **11**. Dehydroaltenusin (**12**) was isolated from various fungi[17] and shows different interesting biological activities;[18] for example, it is a specific inhibitor of mammalian DNA polymerase α.[17d,19] Due to a ring open/ring closure mechanism it is not configurationally stable and occurs as a racemate.[20] Total syntheses for dehydroaltenusin have been published.[21] To provide sufficient amounts of material for toxicological and biological testing, we established total syntheses of **8** and of **11**, which are described herein.

Results and Discussion

All syntheses described herein were accomplished starting with synthetic **3** or **4**, respectively.[13] Structures and absolute configuration of these starting materials[22] with the respective natural products had been proven unambiguously by X-ray crystallographic analysis and by comparison of spectroscopic data[13,9a] including data from chiroptic methods.[13,11]

On the basis of the originally proposed structure of dihydroaltenuene B (***ent*-11**), hydrogenation of **3** was expected to lead to the mirror image of naturally occurring dihydroaltenuene B. Reduction with 10% palladium on charcoal led to a single diastereoisomer (**11**) since the methyl group allowed approach of the substrate to the catalyst in only one orientation (Scheme 1). Inspection of the NMR[23] and optical rotation data revealed that it was identical to natural dihydroaltenuene B. The published specific optical rotation for the natural compound was $[\alpha]^{25}_{D}$ +14[11] and was $[\alpha]^{20}_{D}$ +15

Scheme 1. Hydrogenation of Altenuene (**3**) and Isoaltenuene (**4**)



for the synthesized compound **11**. This unambiguously proved that the structure of the natural product was erroneously proposed as its mirror image. Consequently, we here give a revised structure **11** for dihydroaltenuene B. Hydrogenation of **4** under identical conditions led to an isomer not identified as a natural product up to now (3-*epi*-dihydroaltenuene A, **13**).

Dehydroaltenuene A (**8**) was expected to be accessible by allylic oxidation of **4**. This required a method suitable for the oxidation of an allylic alcohol in the presence of a further non-allylic alcohol function. Most tested methods led to a partial overoxidation, yielding dehydroaltenusin (**12**), where the resulting mixture was separable only by preparative HPLC (Scheme 2).

Oxidation using pyridinium chlorochromate (PCC)[24] yielded no oxidized product; only starting material was recovered. Oxidation with manganese(IV) oxide,[25] 2-iodoxybenzoic acid (IBX),[26] or Dess-Martin periodinane (DMP)[27] led to partial overoxidation with nonreacted starting material recovered from the product mixture. Small amounts of tetrapropylammonium perruthenate (TPAP)[28] in the presence of *N*-methylmorpholine-*N*-oxide (NMO) led to poor yields not exceeding 40%, while higher amounts of this reagent or prolonged reaction times again resulted in significant overoxidation. Nevertheless, a selective oxidation of **4** was achieved with 60% yield when oxygen in the presence of palladium(II) acetate as catalyst and triethylamine was used as oxidant.[29] This combination of reagents selectively oxidizes allyl alcohols only when the reaction is performed in the absence of molecular sieves. Comparison of spectroscopic and optical rotation data of synthesized dehydroaltenuene A (**8**) with the published data for the natural product gave unambiguous evidence for their constitutional and configurational identity.[23]

Application of identical conditions to the oxidation of **3** led to the clean formation of *ent*-dehydroaltenuene B (***ent*-9**). Optical

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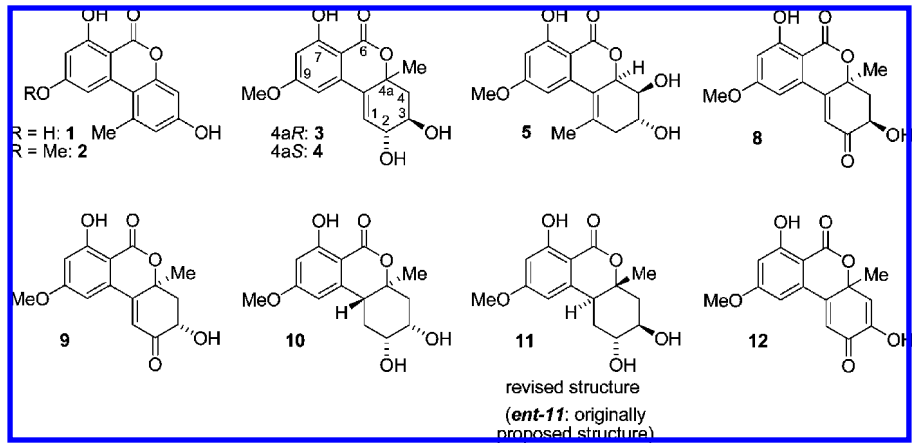
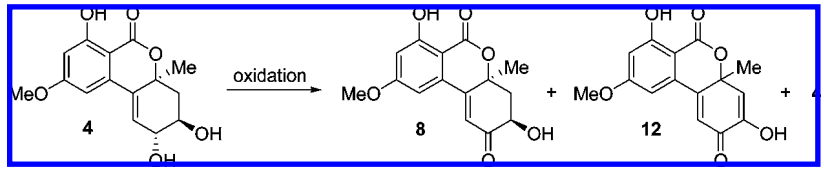
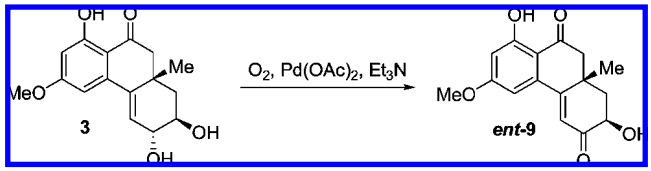


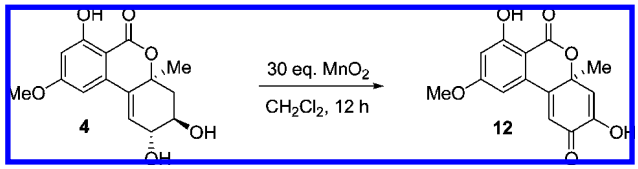
Scheme 2. Oxidation of Isoaltenuene (**4**)



Scheme 3. Oxidation of Altenuene (**3**)



Scheme 4. Synthesis of Dehydroaltenusin (**12**)



rotations of the natural product (**9**, $[\alpha]^{25}_D$ +65) and the synthesized material (***ent*-9**, $[\alpha]^{20}_D$ ~−22)[30] have opposite signs, giving strong evidence for the correctness of the originally proposed structure of dehydroaltenuene B (Scheme 3).

Attempts to oxidize **4** to **12** were successful with manganese(IV) oxide, although yields did not exceed 30%. Better yields (up to 60%) were obtained using DMP, but those higher yields were not reproducible. Nevertheless, only a very small amount of slightly impure **12** was obtained via these routes (Scheme 4).

Experimental Section

General Experimental Procedures. Altenuene (**3**) and isoaltenuene (**4**) were synthesized according to a published procedure.[13] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl radical, and CH_2Cl_2 was distilled from CaH_2. All moisture-sensitive reactions were carried out under an oxygen-free nitrogen atmosphere using oven-dried glassware and a vacuum line. Flash column chromatography[31] was carried out using Merck SiO_2 60 (230−400 mesh), and thin-layer chromatography (TLC) was carried out using commercially available Merck F_{254} precoated sheets. Preparative HPLC was performed using a binary high-pressure gradient system consisting of two Varian pumps (ProStar 210, fitted with 25 mL/min pump heads), manual injection valve (Rheodyne 7725i), Varian columns (Pursuit XRs-C18 5 μm, 250 × 21.4 mm), and a Varian diode array detector (ProStar 335). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Cryospek WM-250, an AM-400, or a DRX 500. Chemical shifts are given in ppm (δ) downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broadband proton decoupling. IR spectra were recorded on a Bruker IFS-88 spectrometer. EI, FAB, and high-resolution mass spectra were recorded on a Finnigan MAT-90 mass spectrometer. Specific optical rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. UV/vis spectra were recorded on a Perkin-Elmer Lambda 2 spectrometer. The extinction coefficient ε is given for quantitative measurements.

(2*R*,3*R*,4a*S*,10b*R*)-1,2,3,4,4a,10b-Hexahydro-2,3,7-trihydroxy-9-methoxy-4a-methyl-6*H*-benzo[*c*]chromen-6-one; 3-*epi*-Dihydroaltenuene A (13). Pd/C (5%, 19.0 mg) and a H_2 atmosphere were added to a mixture of isoaltenuene (**4**, 26 mg, 0.089 mmol) in MeOH (2 mL), and the mixture was stirred for 2 h at rt and filtered through Celite. The solvents were removed, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield **13** as a colorless solid (22 mg, 0.075 mmol, 84%); $[\alpha]^{20}_D$ ~4.0 (*c* 0.47, $CHCl_3$); UV (MeOH) λ_{max} 213, 269, 301 nm; IR (DRIFT) ν_{max} 3388, 1661, 1627, 1583, 1352, 1260, 1207, 1162 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.24 (1H, s, H-7), 6.44 (1H, d, ^4J = 2.1 Hz, H-8), 6.32 (1H, dd, ^4J = 1.3 Hz, ^4J = 2.1 Hz, H-10), 4.96−4.99 (2H, bm, OH-2, OH-3), 3.82 (3H, s, OCH_3), 3.36−3.48 (2H, m, H-2, H-3), 3.21, (1H, dd, ^3J = 12.7 Hz, ^3J = 3.2 Hz, H-10b), 2.38 (1H, dddd, ^2J = 13.3 Hz,^3J = 4.1 Hz, ^3J = 3.2 Hz, ^4J = 2.1 Hz, H-1$_{eq}$), 2.11 (1H, dd, ^2J = 11.7, ^3J = 4.1 Hz, H-4$_{eq}$), 1.79 (1H, dd, ^2J = 11.7 Hz, ^3J = 11.4 Hz, H-4$_{ax}$), 1.26 (1H, ddd, ^2J = 13.3 Hz,^3J = 12.7 Hz,^3J = 10.4 Hz, H-1$_{ax}$), 1.13 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.2 (C, C-6), 165.7 (C, C-9), 163.5 (C, C-7), 143.0 (C, C-10a), 103.7 (CH, C-10), 100.8 (CH, C-6a), 98.9 (CH, C-8), 83.1 (C, C-4a), 73.7 (CH, C-3), 70.9 (CH, C-2), 55.7 (CH_3, OCH_3-9), 44.2 (CH_2, C-4), 40.7 (CH, C-10b), 30.2 (CH_2, C-1), 18.7 (CH_3, CH_3-4a); FABMS *m*/*z* 295 $[M + H]^+$ (30), 136 (100), 107 (39), 91 (40); HRFABMS *m*/*z* 295.1185 (calcd for $C_{15}H_{19}O_6$, 295.1181).

(2*R*,3*R*,4a*R*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-2,3,7-trihydroxy-9-methoxy-4a-methyl-6*H*-benzo[*c*]chromen-6-one; Dihydroaltenuene B, Revised Structure (11). Pd/C (5%, 7.1 mg) and a H_2 atmosphere were added to a mixture of altenuene (**3**, 9.5 mg, 0.033 mmol) in MeOH (2 mL), and the mixture was stirred for 2 h at rt and filtered through Celite. The solvents were removed, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield **11** as a colorless solid (7.8 mg, 0.026 mmol, 80%); $[\alpha]^{20}_D$ +15 (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} 214, 261, 298 nm; IR (DRIFT) ν_{max} 3432, 2925, 1658, 1627, 1366, 1121 cm^1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.36 (1H, s, OH-7), 6.36 (1H, dd, ^3J = 2.3, ^6J = 0.7 Hz, H-8), 6.27 (1H, dd, ^4J = 2.3, ^4J = 1.4 Hz, H-10), 4.15−4.16 (1H, m, H-3), 4.09−4.11 (1H, m, H-2), 3.84 (3H, s, OCH_3), 3.57 (1H, dd, ^3J = 13.0 Hz, ^3J = 3.2 Hz, H-10b), 2.42 (1H, ddd, ^2J = 14.1 Hz, ^3J = 3.7 Hz, ^4J = 1.0 Hz, H-4$_{eq}$), 2.25 (1H, dddd, ^2J = 14.0 Hz, ^3J = 3.3 Hz, ^3J = 3.2 Hz, ^4J = 1.2 Hz, H-1$_{eq}$), 2.12 (1H, ddd, ^2J = 14.1 Hz,^3J = 2.6 Hz,^4J = 0.9 Hz, H-4$_{ax}$), 1.93 (1H, ddd, ^2J = 14.0 Hz, ^3J = 13.0 Hz, ^3J = 2.6 Hz, H-1$_{ax}$), 1.39 (3H, d, ^4J = 0.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz)

δ 168.8 (C, C-6), 166.0 (C, C-9), 164.6 (C, C-7), 143.3 (C, C-10a), 103.9 (CH, C-8), 102.0 (C, C-6a), 98.5 (CH, C-10), 83.6 (C, C-4a), 70.7 (CH, C-2), 69.3 (CH, C-3), 55.6 (CH_3, OMe-9), 39.6 (CH_2, C-4), 37.3 (CH, C-10b), 27.4 (CH_2, C-1), 20.5 (CH_3, CH_3-4a); EIMS (170 °C) *m/z* 294 $[M]^+$ (26), 240 (18), 220 (20), 149 (13), 84 (27), 83 (18), 82 (26), 71 (68), 58 (29), 57 (79), 56 (73), 43 (100); HREIMS (EI) *m/z* 294.1105 (calcd for $C_{15}H_{18}O_6$, 294.1103).

(3*R*,4a*S*)-4,4a-Dihydro-3,7-dihydroxy-9-methoxy-4a-methyl-3*H*-benzo[*c*]chromen-2,6-dione; Dehydroaltenuene A (8). Isoaltenuene (**4**, 10 mg, 0.034 mmol) was added to a solution of $Pd(OAc)_2$ (0.25 mg) and Et_3N (0.21 mg) in THF/toluene (3:1, 3 mL). The mixture was stirred under an O_2 atmosphere (balloon) for 36 h at 45 °C, concentrated, and filtrated over Celite. The crude mixture containing **8** and **4** (60:40) was separated by chromatography (silica gel, CH_2Cl_2/MeOH, 40:1) to yield **8** as a colorless solid (5.8 mg, 0.020 mmol); $[\alpha]^{20}_D$ +14.8 (*c* 0.45, $CHCl_3$); UV (MeOH) λ_{max} (ε) 199 (10 961), 217 (10 430), 251 (30 290), 295 (3044) nm; IR (DRIFT) ν_{max} 3416, 1656, 1624, 1579, 1263, 1207, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.38 (1H, s, OH-7), 6.70 (1H, d, ^4J = 2.2 Hz, H-10), 6.64 (1H, d, ^4J = 2.2 Hz, H-8), 6.53 (1H, s, H-1), 4.29 (1H, dd, ^2J = 13.3 Hz, ^3J = 5.5 Hz, H-3), 3.89 (3H, s, OCH_3), 3.57 (1H, br, OH-3), 2.82 (1H, dd, ^2J = 12.6 Hz, ^3J = 5.5 Hz, H-4_{eq}), 2.47 (1H, dd, ^3J = 13.3 Hz, ^2J = 12.6 Hz, H-4_{ax}), 1.74 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4 (C, C-2), 166.7 (C, C-6), 166.2 (C, C-9), 164.7 (C, C-7), 153.3 (C, C-10b), 134.3 (C, C-10a), 120.8 (CH, C-1), 105.0 (CH, C-10), 104.0 (CH, C-8), 100.1 (C, C-6a), 80.7 (C, C-4a), 70.6 (CH, C-3), 56.0 (CH_3, OMe-9), 44.1 (CH_2, C-4), 25.8 (CH_3, CH_3-4a); FABMS *m/z* 290 $[M + H]^+$ (42), 273 $[M + H - OH]^+$ (80), 94 (100); HRFABMS *m/z* 290.0789 (calcd for $C_{15}H_{14}O_6$, 290.0790).

(3*R*,4a*R*)-3,4,4a,6-Tetrahydro-3,7-dihydroxy-9-methoxy-4a-methyl-2*H*-benzo[*c*]chromen-2,6-dione; *ent*-Dehydroaltenuene B (*ent*-9). Altenuene (**3**, 4.5 mg, 0.015 mmol) was added to a solution of $Pd(OAc)_2$ (0.11 mg) and Et_3N (0.13 μL) in THF/toluene (3:1, 3 mL). The mixture was stirred under an O_2 atmosphere (balloon) for 36 h at 45 °C, concentrated, and filtrated over Celite. The crude mixture containing ***ent*-9** and **3** (55:45) was separated by preparative HPLC[23] to yield *ent*-dehydroaltenuene B (***ent*-9**) as a colorless solid (2.0 mg, 0.0069 mmol, 46%); $[\alpha]^{20}_D$ ~−22 (*c* ~0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 11.32 (1H, s, OH-7), 6.69 (1H, d, ^4J = 2.3 Hz, CH), 6.61 (1H, d, ^4J = 2.3 Hz, CH), 6.39 (1H, s, H-1), 4.44 (1H, dd, ^3J = 7.3 Hz, ^3J = 5.8 Hz, H-3), 3.89 (3H, s, OMe), 2.95 (1H, bs, OH-3), 2.82 (1H, dd, ^2J = 14.8 Hz, ^3J = 5.8 Hz, H-4_{eq}), 2.41 (1H, dd, ^2J = 14.8 Hz, ^3J = 7.3 Hz, H-4_{ax}), 1.72 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.3 (C), 167.6 (C), 166.3 (C), 164.8 (C), 152.1 (C), 135.7 (C), 121.7 (CH), 104.5 (2 × CH), 103.4 (C), 79.7 (C), 68.4 (C), 55.9 (CH_3), 40.7 (CH_2), 29.2 (CH_3).

4a,6-Dihydro-3,7-dihydroxy-9-methyoxy-4a-methyl-2*H*-benzo[*c*]-chromen-2,6-dione; Dehydroaltenusin (12). MnO_2 (37 mg, 0.43 mmol) was added to a solution of **4** (5 mg, 17 μmol) in CH_2Cl_2 and stirred at rt overnight. The mixture was filtered through Celite, and the filtrate was concentrated to yield product **12** (1.4 mg, 5 μmol, 30%) as a slightly impure colorless oil; ^1H NMR ($CDCl_3$, 250 MHz) δ 11.30 (1H, s, OH-6), 6.73 (1H, d, ^4J = 2.3 Hz, CH), 6.69 (1H, s), 6.64 (1H, d, ^4J = 2.3 Hz, CH), 6.39 (1H, bs, OH-2), 6.28 (1H, s), 3.91 (3H, s, OMe), 1.73 (3H, CH_3).

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Supporting Information Available: Detailed NMR spectroscopic data of the natural products and synthesized compounds **8**, **9**, and **11**; details on the purification of *ent*-dehydroaltenuene B (***ent*-9**) by preparative chromatography; spectra of compounds **13**, **11**, **8**, ***ent*-9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The name 5′-epialtenuene (**6**) is consistently used in the literature, although a correct IUPAC-conforming description would be 2-epialtenuene. 4′-Epialtenuene (**7**) would be more correctly 3-epialtenuene.

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