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# Total Synthesis of Altenuene and Isoaltenuene

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Total synthesis of altenuene and isoaltenuene, toxins produced by various *alternaria* fungi, were achieved for the first time in ten steps, starting with quinic acid and commercially available acetal-protected phloroglucinic acid, with the longest linear sequence consisting of seven steps. The key reactions are palladium-catalyzed Suzuki-type couplings between an arene boronate and iodinated cyclohexenes.



## Introduction

The resorcylic lactones alternariol (**1**) and alternariol 9-methyl ether (**2**) are main secondary metabolites of toxin-producing *alternaria* fungi (Figure 1).[1–3] Although the toxicities of these mycotoxins are low in comparison with others (such as aflatoxins),[4,5] infestation with *alternaria spp.* is a cause of significant crop losses through fouling of tomatoes, apples, and other fruits.[6–8] Numerous investigations on alternariol (**1**) and alternariol 9-methyl ether (**2**) have been published and total syntheses have been provided for these compounds.[9–11] Much less is known about minor *alternaria* toxins such as dehydroaltenusin (**3**),[12–14] altenuene (**4**),[2,13,15,16] isoaltenuene (**5**),[17–19] epialtenuene (**6**),[20] or neoaltenuene (**7**),[20] which have been isolated from infested fruits in sub-milligram amounts. While a total synthesis of dehydroaltenusin (**3**) has been published,[21,22] neither detailed biological data are available for the latter toxins, nor has their absolute configuration been reported. Altenuene was reported to show cytotoxicity,[13] and a more detailed investigation showed it to be active towards HeLa cells ($ID_{50}$: 0.5–28 μg $ml^{-1}$).[3] To provide sufficient amounts of material for toxicological and biological testing, we have established total syntheses of altenuene and isoaltenuene, which we wish to present in this paper.

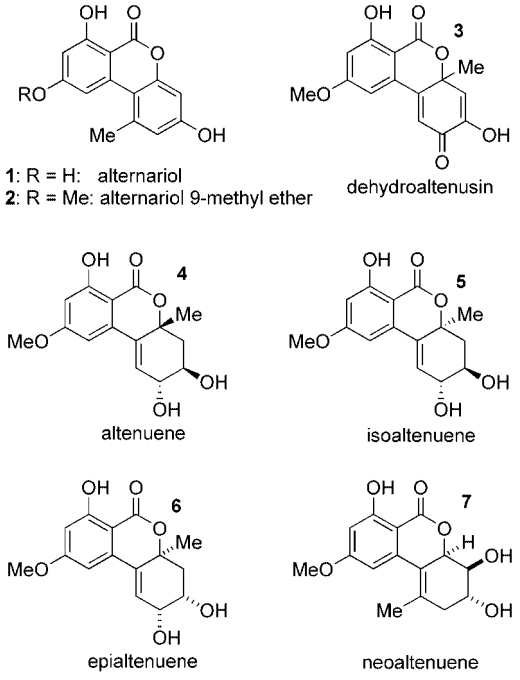


Figure 1. Toxins produced in *alternaria* fungi (absolute configurations for compounds **6** and **7** have not been reported; compound **3** racemizes under physiological conditions).

## Results and Discussion

Our intent was to develop a convergent synthesis, starting with identical building blocks, to give access to both altenuene and isoaltenuene. Since we had no reliable information on the absolute configurations of these natural products, we decided on a venture directed towards the enantiomers depicted in Figure 1, which would allow us to use inexpensive quinic acid as starting material. It was planned to construct the central C–C bond by Suzuki cross coupling between a boronic ester **A** and a cyclohexenyl iodide **B** (Scheme 1).

We chose acetals as protecting groups for both fragments, since these should be cleavable to liberate the final products without the acid-sensitive methyl ether being affected. It was expected that a boronic ester of type **A** should

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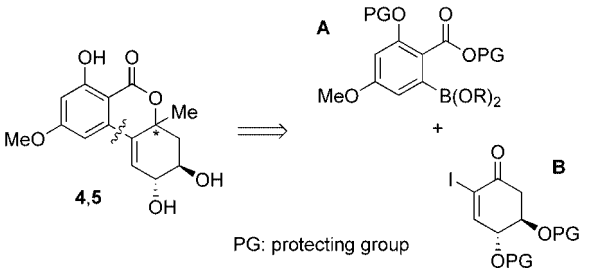
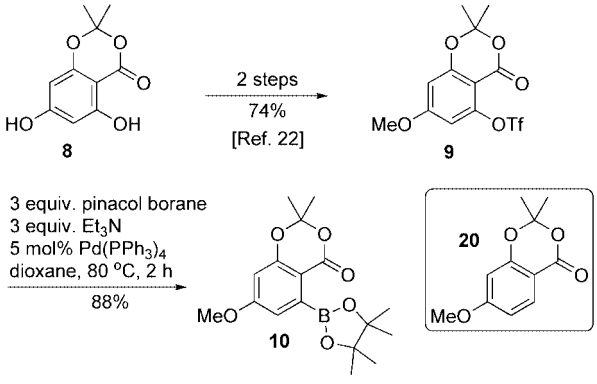



Scheme 1. Retrosynthetic analysis for altenuene and isoaltenuene.

be easily preparable from the corresponding triflate, used in the total synthesis of dehydroaltenusin (**3**).[21,22] A similar strategy was used by us in the synthesis of alternariol (**1**) and alternariol 9-methyl ether (**2**).[11] From the commercially available acetal **8**,[23] triflate **9** is prepared in two steps and in an overall yield of 74% (Scheme 2).[22,24] Triflates have frequently been used for the palladium-catalyzed preparation of boronic acids suitable for Suzuki cross coupling,[25,26] but reports on the preparation of *ortho*-substituted boronic acids from their corresponding triflates are nevertheless scarce.[27,28] Some efforts were necessary in order to optimize this reaction and to achieve a satisfying 88% yield of boronate **10** (Scheme 2 and Table 1). 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane ("pinacolborane", 3 equiv.) was used as boron source (Entries 3–5), and tetrakis(triphenylphosphane)palladium(0) [$Pd(PPh_3)_4$, 5 mol-%] proved to give significantly higher yields than dichloro[1,1′-bis(diphenylphosphanyl)ferrocene]palladium(II) [$PdCl_2$(dppf), Entries 1–3]. The suitability of triethylamine as base had previously been proposed by Masuda et al.,[29] and formation of the reduced side-product **20** could be suppressed by reducing the reaction time from 4 to 2 h (Entries 4, 5). Accumulation of this side product had already been reported by Suzuki.[25]

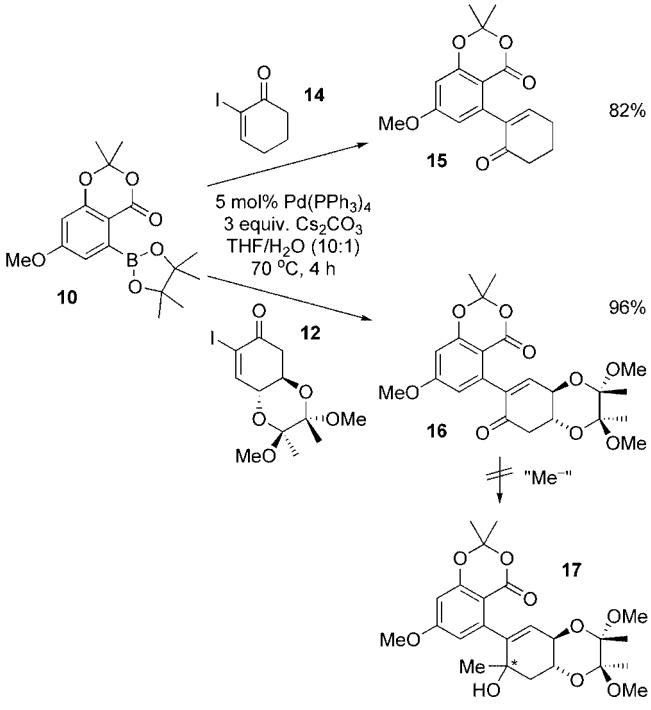



Scheme 2. Synthesis of the western building block **10**.

Iodinated substrate **12**, which should be suitable for Suzuki cross coupling was prepared in four steps by published procedures, starting with quinic acid (**11**) (37% overall yield, Scheme 4).[24,30,31] To establish the best conditions for cross coupling, we tested 2-iodocyclohex-2-enone (**14**)[32] in its reaction with boronate **10**. No reaction was observed with 5 mol-% $Pd(PPh_3)_4$ and potassium carbonate,[27] barium hydroxide,[25] or potassium phosphate as base, but utilization of cesium carbonate (3 equiv.) gave a satisfactory 82% yield of coupled substrate **15** (Scheme 3). An even higher 96% yield of chiral product **16** was obtained when these conditions were applied to the coupling of arylboronate **10** with chiral fragment **12**. However, no procedure for a clean formation of tertiary alcohol **17** could be established.

Table 1. Optimization in the preparation of boronate **10**.

| Entry | Boron compound | Catalyst | Conditions | Base | Yield [%] |
|---|---|---|---|---|---|
| 1 | 1.1 equiv. | 3 mol% $PdCl_2$(dppf) | DMSO, 80 °C, 10 h | 3 equiv. KOAc | no conversion |
| 2 | 1.1 equiv. | 3 mol% $PdCl_2$(dppf) | DMF, 80 °C, 4 h | 3 equiv. KOAc | no conversion |
| 3 | 3 equiv. | 5 mol% $PdCl_2$(dppf) | dioxane, 80 °C, 4 h | 3 equiv. $Et_3N$ | 34 |
| 4 | 3 equiv. | 5 mol% $Pd(PPh_3)_4$ | dioxane, 80 °C, 4 h | 3 equiv. $Et_3N$ | 53 |
| 5 | 3 equiv. | 5 mol% $Pd(PPh_3)_4$ | dioxane, 80 °C, 2 h | 3 equiv. $Et_3N$ | 88 |




Scheme 3. Suzuki coupling of iodocyclohexenones.

Consequently, we inverted the intended sequence and first methylated enone **12** to yield a product similarly applicable in a Suzuki coupling. Treatment of enone **12** with methylmagnesium bromide yielded adducts **13a** and **13b** with an 86:14 selectivity (Scheme 4) without the sensitive iodo substituent being affected. NMR spectroscopic investigations, including NOE spectroscopy, showed that the isomer bearing the methyl group in an axial orientation (**13a**) had been formed preferentially. (The conformation of the substrates is rigid in this *trans*-decalin-type system.) We as-

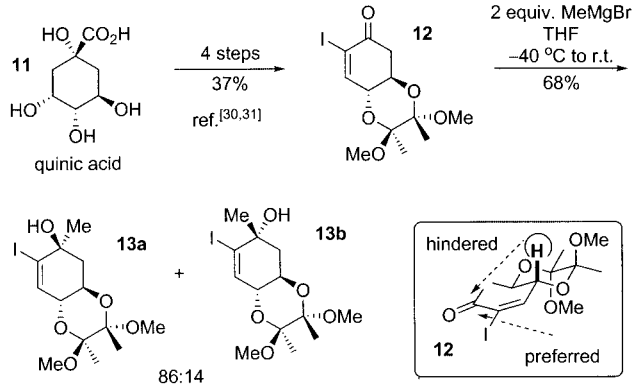
  

Table 2. Conditions tested for the Suzuki coupling of iodide **13a** and boronate **10**.

| Entry | Catalyst[a] | Conditions[b] | Yield [%] |
|---|---|---|---|
| 1 | 5 mol-% $Pd(PPh_3)_4$ | THF/$H_2O$ (10:1), 70 °C, 4 h | 45 |
| 2 | 5 mol-% $Pd(PPh_3)_4$ | THF/$H_2O$ (10:1), MW, 70 °C, 30 min | 55 |
| 3 | 5 mol-% $Pd(PPh_3)_4$ | dioxane/$H_2O$ (5:1), 80 °C, 4 h | 50 |
| 4 | 1.5 mol-% $Pd_2(dba)_3$, 3.6 mol-% $tBu_3P$ | dioxane, 80 °C, 2 h | 61 |
| 5 | 1.5 mol-% $Pd_2(dba)_3$, 3.6 mol-% $tBu_3P$ | dioxane/$H_2O$ (5:1), 80 °C, 2 h | 52 |
| 6 | 2 mol-% $Pd(OAc)_2$, 4 mol-% S-Phos | dioxane/$H_2O$ (5:1), 80 °C, 2 h | 72 |
| 7 | 2 mol-% $Pd(OAc)_2$, 4 mol-% S-Phos | dioxane/$H_2O$ (5:1), MW, 80 °C, 2 h | 55 |

[a] S-Phos: 2-(dicyclohexylphosphanyl)-2′,6′-dimethoxybiphenyl. [b] 1 equiv. iodinated compound, 1.3. equiv. boronate, 3 equiv. $Cs_2CO_3$, MW: microwave.

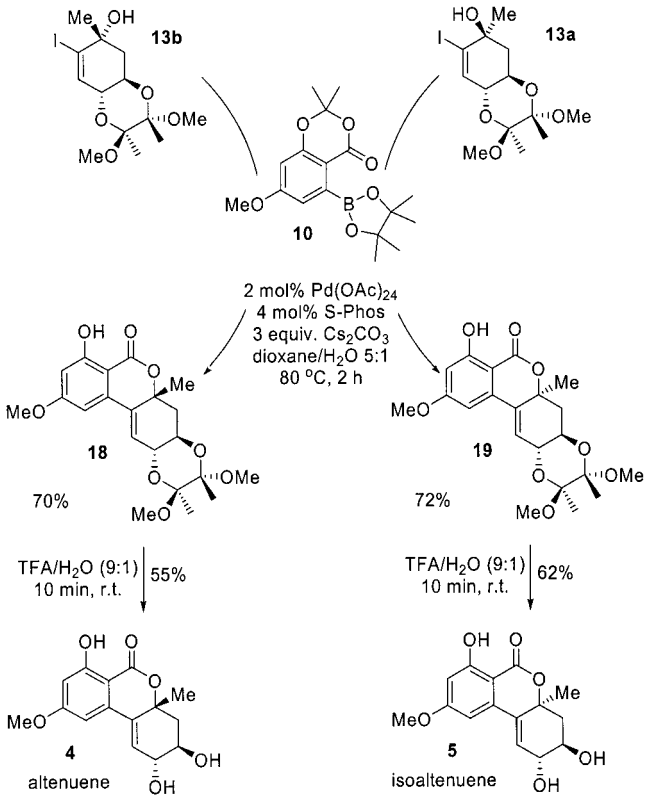
sume that the selectivity is best explained in terms of hindrance through the flagpole hydrogen atom in **12** preventing an approach of the nucleophile along the Bürgi–Dunitz trajectory (Scheme 4). The two isomers of **13** were easily separable by chromatographic methods, allowing for the utilization of both isomers in the further course of the sequence.




Scheme 4. Synthesis of the eastern building blocks **13a** and **13b**.

Compounds **13a** and **13b** proved to be suitable for Suzuki coupling, though the conditions described above (Scheme 3) gave only 40 and 45% yields for **18** and **19**, respectively. To our great surprise, however, we observed the formation not only of the C–C bond but also concomitantly of the corresponding lactones, with liberation of the phenolic hydroxy groups previously protected as acetals. We set out to optimize the Suzuki coupling, and obtained a 61% yield of protected isoaltenuene **19** when we used tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] together with tri-*tert*-butylphosphane (Table 2, Entry 4).[33] The best results, though, were obtained with palladium acetate in the presence of S-Phos as ligand (72%, Entry 6, Scheme 5).[34] These conditions were similarly applied to the formation of altenuene precursor **18** (70%). The fortunate formation of the lactone during the Suzuki coupling left only one step missing in the scheduled sequence – the cleavage of the remaining diol-protecting acetal group, which was achieved with trifluoroacetic acid (TFA)/water within 10 min, yielding altenuene (**4**) and isoaltenuene (**5**) in 55% and 62% yields, respectively.

The identities of altenuene (**4**) and isoaltenuene (**5**) were unambiguously established by comparison with published




Scheme 5. Suzuki coupling of iodo alcohols and liberation of the natural products.

data,[1,17] which, on the other hand, gave evidence for the constitutions and relative configurations proposed in the literature. The configuration of the product was verified not only through the configuration of the quinic acid starting material (**11**), but additionally through an X-ray crystallographic analysis of isoaltenuene precursor **19** (Figure 2).[35]

Since the absolute configurations of altenuene and isoaltenuene had not been known before our investigations, we measured the optical rotations of the synthesized substrates. While isoaltenuene (**5**) is not commercially available[36] and so could not be compared with the synthesized material, we found to our great stupefaction that purchased, microbiologically prepared altenuene (**4**, from Sigma–Aldrich) showed a specific rotation of about zero. On the other hand, altenuene synthesized by us showed a specific rotation of –4 (i.e., –0.4° $cm^2$ $g^{-1}$). For better quantification we measured

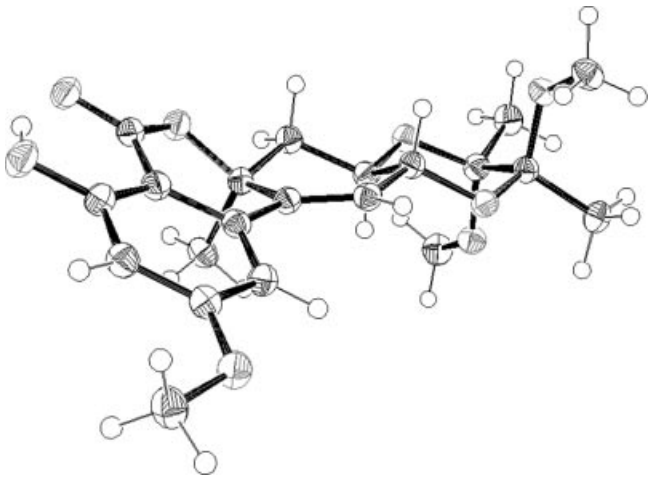


Figure 2. X-ray crystal structure of isoaltenuene derivative **19**.[35]

circular dichroism spectra and normalized the measured samples (for accurate comparison of the obtained data) by evaluation of their UV spectra.[37] From this, the enantiomeric excess of natural altenuene was determined to be only ca. 2%. The reason for this astonishing finding is completely unclear to us. Obviously we were lucky that the enantiomer synthesized by us represents the major isomer present in the genuine material. Since it is reasonable to assume that altenuene and isoaltenuene have common biosynthetic precursors (though this has yet to be confirmed) we infer that the isoaltenuene synthesized by us should also have the correct absolute configuration dominant in microbiologically produced isoaltenuene. Nevertheless, further investigations on, for example, the enantiopurity of natural isoaltenuene would be highly desirable.

## Experimental Section

**General Remarks:** An authentic sample of altenuene (**4**) was purchased from Sigma–Aldrich. Tetrahydrofuran (THF) and $Et_2O$ were distilled from sodium/benzophenone ketyl radical and $CH_2Cl_2$ was distilled from $CaH_2$. All moisture-sensitive reactions were carried out under oxygen-free argon or nitrogen with use of oven-dried glassware and a vacuum line. Flash column chromatography was carried out with Merck $SiO_2$ 60 (230–400 mesh) and thin layer chromatography was carried out with commercially available Merck $F_{254}$ pre-coated sheets. Medium-pressure liquid chromatography (MPLC): detection by UV absorption (Latek UVIS 200). $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker Cryospek WM-250, an AM 400, or a DRX 500. Chemical shifts are given in ppm downfield from tetramethylsilane. $^{13}C$ NMR spectra were recorded with broad-band proton decoupling and were assigned through DEPT 135 and DEPT 90 experiments. Melting points were measured with a Büchi apparatus and are not corrected. IR spectra were recorded with a Bruker IFS-88 spectrometer. Elemental analyses were performed with a Heraeus CHN-O-rapid instrument. Electrical ionization and high-resolution mass spectra were recorded with a Finnigan MAT-90 machine. MALDI-TOF spectra were recorded in negative, linear mode with a Bruker REFLEX IV spectrometer with a 2,5-dihydroxybenzoic acid (DHB) matrix. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter (with use of the sodium D line at 589 nm), and specific optical rotations $[\alpha]_D$ are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. UV/Vis spectra were recorded with a Perkin–Elmer Lambda 2 spectrometer. The extinction coefficient $\varepsilon$ is given for quantitative measurements. Circular dichroism spectra were recorded with a Jasco spectropolarimeter J-810.

**7-Methoxy-2,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*][1,3]dioxin-4-one (10):** Freshly distilled $Et_3N$ (210 mg, 1.50 mmol) and $Pd(PPh_3)_4$ (28 mg, 5 mol-%) were added to a solution of triflate **9** (178 mg, 0.500 mmol) in anhydrous dioxane (30 mL). The solution was degassed under argon in a ultrasonication bath, and "pinacolborane" (1.07 g, 8.42 mmol) was added dropwise over 5 min. The mixture was heated to 80 °C for 4 h and the solvent was removed in vacuo. Without further workup, the residue was purified by chromatography on $SiO_2$ (hexane/EtOAc, 10:1) to yield the boronate **10** (90 mg, 0.26 mmol, 54%) and a smaller fraction of the reduced side product **20** (23 mg, 22%). Compound **10**: Colorless solid, m.p. 108–110 °C. $R_f$ (hexane/EtOAc, 2:1) = 0.39. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 1.39 (s, 12 H, $CH_3$), 1.72 (s, 6 H, $CH_3$), 3.83 (s, 3 H, OMe), 6.40 (d, $^4J$ = 2.4 Hz, 1 H), 6.67 (d, $^4J$ = 2.4 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 24.8 (q), 25.8 (q), 55.7 (q), 84.5 (s), 101.6 (d), 106.2 (s), 108.7 (s), 113.7 (d), 157.7 (s), 161.8 (s), 165.6 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 2981 (s), 2947 (w), 2850 (w), 1725 (s, C=O), 1607 (m), 1582 (s), 1448 (m), 1378 (s), 1326 (m), 1297 (m), 1273 (w), 1208 (m), 1145 (m), 1051 (s), 962 (w) cm$^{-1}$. MS (EI, 70 °C): *m*/*z* (%) = 334 (14) [*M*]$^+$, 277 (15), 276 (100) [*M* – $C_3H_6O$]$^+$, 275 (24), 218 (34), 217 (20), 208 (13), 194 (42), 193 (10), 177 (12), 176 (12), 153 (15), 150 (42), 122 (13), 107 (23), 83 (16), 77 (28), 51 (13), 43 (31). $C_{17}H_{23}BO_6$ (334.16): calcd. C 61.45, H 6.94; found C 60.24, H 6.59. HRMS (EI): calcd. 334.1588 amu; found: 334.1585 amu. Compound **20**: solid, m.p. 47–48 °C. $R_f$ (hexane/EtOAc, 2:1) = 0.44. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.73 (s, 6 H, $CH_3$), 3.85 (s, 3 H, $CH_3$), 6.43 (d, $^4J$ = 2.4 Hz, 1 H, 8′-H), 6.65 (dd, $^4J$ = 2.4 Hz, $^3J$ = 8.8 Hz, 1 H, 6′-H), 7.87 (d, $^3J$ = 8.7 Hz, 1 H, 5′-H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 25.8 (q, 2 C), 55.7 (q), 101.0 (d), 106.2 (s), 106.3 (s), 110.3 (d), 131.2 (d), 157.9 (s), 161.0 (s); 166.3 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3003 (s), 2952 (w), 1730 (s), 1614 (s), 1503 (m), 1445 (w), 1379 (m), 1354 (w), 1301 (s), 1210 (m), 1155 (w), 1106 (m), 1050 (s), 1021 (m), 960 (m) cm$^{-1}$. MS (EI, 25 °C): *m*/*z* (%) = 208 (47) [*M*]$^+$, 151 (26) [*M* – $C_3H_5O$]$^+$, 150 (100) [*M* – $C_3H_6O$]$^+$, 122 (48) [*M* – $C_4H_6O_2$]$^+$, 107 (22) [$C_7H_7O$]$^+$, 79 (13). $C_{11}H_{12}O_4$ (208.07): calcd. C 63.45, H 5.81; found C 63.24, H 5.76. HRMS (EI): calcd. 208.0736 amu; found 208.0735 amu.

**7-Methoxy-2,2-dimethyl-5-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxin-4-one (15):** Iodocyclohexenone **14** (67 mg, 0.30 mmol), boronate **10** (130 mg, 0.390 mmol), $Cs_2CO_3$ (390 mg, 1.20 mmol), and $Pd(PPh_3)_4$ (17 mg, 5 mol-%) in THF/$H_2O$ (10:1, 10 mL) were heated under argon at 70 °C for 4 h and then cooled to room temp. Saturated $NH_4Cl$ solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), the solvents were removed in vacuo, and the residue was purified by chromatography on $SiO_2$ (hexane/EtOAc, 6:1) to yield product **15** (74 mg, 0.24 mmol, 82%). Compound **15**: brownish solid, m.p. 89–91 °C. $R_f$ (hexane/EtOAc, 2:1) = 0.21. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.74 (s, 6 H, 2 $CH_3$), 1.97–2.80 (m, 6 H, 3′-$H_2$, 4′-$H_2$, 5′-$H_2$), 3.84 (s, 3 H, OMe), 6.40, 6.82–6.85 (m, 3 H, 2′-H, 6-H, 8-H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 22.7 (t), 24.1 (q), 26.2 (t), 38.5 (t), 55.7 (q), 100.5 (d), 105.6 (s), 106.0 (s), 112.3 (d), 141.3 (s), 142.0 (s), 144.2 (d), 158.2 (s), 160.3 (s), 165.1 (s), 197.8 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3446 (w), 3081 (w), 3006 (w), 2982 (w), 2953 (m), 2893 (w), 2842 (w), 1733 (s), 1679 (s), 1611 (s), 1582 (m), 1469 (w), 1440 (w), 1425 (m), 1392 (w), 1381 (w), 1331 (m), 1284 (s), 1252 (m), 1204 (m), 1166 (s), 1095 (w), 1052

(w), 1033 (s) $cm^{-1}$. MS (EI, 30 °C): *m/z* (%) = 302 (12) $[M]^+$, 276 (42), 244 (56), 218 (20), 208 (25), 194 (28), 166 (25), 153 (43), 150 (100), 136 (24), 122 (35), 110 (33), 108 (37), 107 (60). $C_{17}H_{18}O_5$ (302.12): calcd. C 67.54, H 6.00; found C 66.54, H 6.05. HRMS (EI): calcd. 302.1154 amu; found 302.1153 amu.

**(2′*S*,3′*S*,4′a*R*,8′a*R*)-5-(2,3-Dimethoxy-2,3-dimethyl-6-oxo-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-7-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (16):** Iodo compound **12** (110 mg, 0.300 mmol), boronate **10** (154 mg, 0.420 mmol), $Cs_2CO_3$ (390 mg, 1.20 mmol), and $Pd(PPh_3)_4$ (17 mg, 5 mol-%) in THF/$H_2O$ (10:1, 10 mL) were heated under argon at 70 °C for 4 h and then cooled to room temp. Saturated $NH_4Cl$ solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($Na_2SO_4$), the solvents were removed in vacuo, and the residue was purified by chromatography on $SiO_2$ (hexane/EtOAc, 6:1) to yield product **16** (130 mg, 0.290 mmol, 96%). Compound **16**: yellowish solid, m.p. 90–93 °C. $R_f$ (hexane/EtOAc, 2:1) = 0.18. $[a]_D^{20}$ = +30.5 (*c* = 1.0, $CHCl_3$). $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$ = 1.25 (s, 3 H, $CH_3$), 1.27 (s, 3 H, $CH_3$), 1.68 (s, 6 H, $CH_3$), 2.53 (m, 1 H), 2.65–2.68 (m, 1 H), 3.19 (s, 3 H, OMe), 3.26 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.99–4.13 (m, 1 H), 4.52 (dd, *J* = 1.6 Hz, *J* = 9.2 Hz, 1 H), 6.64 (d, *J* = 2.4 Hz, 1 H), 6.56 (d, *J* = 1.9 Hz, 1 H), 6.78 (m, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): 2 rotamers, signals found at $\delta$ = 17.8, 24.1, 24.5, 24.9, 26.7, 27.0, 41.1, 43.0, 48.2, 48.3, 55.8, 67.2, 68.0, 69.2, 69.5, 75.0, 99.54, 99.9, 100.6, 100.8, 101.0, 101.6, 105.8, 111.4, 112.3, 140.1, 140.4, 140.8, 141.7, 141.8, 158.0, 158.3, 158.3, 160.0, 160.1, 160.4, 165.2, 194.6 ppm. IR (DRIFT): $\tilde{\nu}$ = 3519 (m), 2991 (s), 2949 (w), 2836 (w), 1731 (s), 1693 (m), 1610 (s), 1580 (m), 1431 (m), 1378 (m), 1328 (w), 1284 (s), 1229 (w), 1209 (m), (1165 (w), 1143 (s), 1082 (w), 1051 (w), 1051 (w) $cm^{-1}$. MS (EI, 90 °C): *m/z* (%) = 448 (2) $[M]^+$, 242 (37), 85 (16), 59 (100), 57 (18), 43 (24), 41 (10). $C_{23}H_{28}O_9$ (448.17): calcd. C 61.60, H 6.29; found C 61.17, H 7.02. HRMS (EI): calcd. 448.1733 amu; found 448.1739 amu.

**(2*S*,3*S*,4a*R*,6*S*,8a*R*)- and (2*S*,3*S*,4a*R*,6*R*,8a*R*)-7-Iodo-2,3-dimethoxy-2,3,6-trimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol (13a/13b):** MeMgBr (0.66 mL of a 3 M solution in $Et_2O$, 2 mmol) was added dropwise by syringe at –40 °C, with exclusion of moisture and air, to a solution of iodide **12** (368 mg, 1.00 mmol) in anhydrous THF (10 mL). The temperature was allowed to rise to room temp. over 6 h by removal of the cooling bath, and the mixture was hydrolyzed with saturated $NH_4Cl$ solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), the solvents were removed in vacuo, and the residue was purified by MPLC on $SiO_2$ (hexane/EtOAc, 8:1) to yield diastereomer **13a** (185 mg, 0.50 mmol, 50%) and diastereomer **13b** (69 mg, 0.18 mmol, 18%) as slightly yellow oils. Compound **13a**: $R_f$ (hexane/EtOAc, 2:1) = 0.41. $[a]_D^{20}$ = +141 (*c* = 1.0, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.30 (s, 3 H, $CH_3$), 1.30 (s, 3 H, $CH_3$), 1.44 (d, $^4J$ = 0.9 Hz, 3 H, C 6-$CH_3$), 2.04 (ddd, $^4J$ = 0.9 Hz, $^2J$ = 12.3 Hz, $^3J$ = 13.2 Hz, 1 H, 5-$H_{ax}H_{eq}$), 2.25 (dd, $^3J$ = 3.2 Hz, $^2J$ = 12.3 Hz, 1 H, 5-$H_{ax}H_{eq}$), 3.24 (s, 3 H, OMe), 3.25 (s, 3 H, OMe), 3.76 (ddd, $^3J$ = 3.2 Hz, $^3J$ = 8.9 Hz, $^3J$ = 13.2 Hz, 1 H, 4a-H), 4.21 (dd, $^3J$ = 1.9 Hz, $^3J$ = 8.9 Hz, 1 H, 8a-H), 6.26 (d, $^3J$ = 1.9 Hz, 1 H, 8-H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 17.8 (q), 30.1 (q), 39.6 (t), 47.9 (q), 48.0 (q), 66.4 (d), 71.2 (d), 75.0 (s), 100.1 (s), 100.6 (s), 114.2 (s), 137.4 (d) ppm. IR (film): $\tilde{\nu}$ = 3484 (s), 2990 (w), 2949 (s), 2832 (m), 1724 (s), 1683 (m), 1615 (w), 1452 (s), 1376 (s), 1299 (w), 1265 (w), 1205 (w), 1134 (s), 1037 (s), 1000 (s), 929 (w), 911 (s), 881(s) $cm^{-1}$. MS (EI, 60 °C): *m/z* (%) = 369 (25), 355 (32), 353 (24), 267 (22), 237 (38), 236 (97), 235 (38), 221 (84), 109 (100), 108 (64), 101 (81), 94 (81), 91 (19), 84 (47), 80 (31), 75 (30), 73 (37), 69 (28), 56 (36), 43 (99), 41 (50). MS (MALDI): *m/z* (%) = 410 (11) $[M + Na]^+$. Compound **13b**: $R_f$ (hexane/EtOAc, 2:1) = 0.40. $[a]_D^{20}$ = +125.2 (*c* = 1.0, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.30 (s, 3 H, $CH_3$), 1.32 (s, 3 H, $CH_3$), 1.37 (s, 3 H, $CH_3$), 1.87 (dd, $^2J$ = 12.8 Hz, $^3J$ = 13.1 Hz, 1 H, 5-$H_{ax}H_{eq}$), 2.28 (dd, $^3J$ = 3.6 Hz, $^3J$ = 13.1 Hz, 1 H, 5-$H_{ax}H_{eq}$), 3.25 (s, 3 H, OMe), 3.27 (s, 3 H, OMe), 3.91 (ddd, $^3J$ = 3.6 Hz, $^3J$ = 9.0 Hz, $^3J$ = 12.8 Hz, 1 H, 4a-H), 4.10 (dd, $^3J$ = 1.8 Hz, $^3J$ = 9.0 Hz, 1 H, 8a-H), 6.34 (d, $^3J$ = 1.8 Hz, 1 H, 8-H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 17.7 (q), 17.8 (q), 33.0 (t), 38.4 (q), 48.0 (q), 49.1 (q), 65.3 (d), 71.3 (d), 74.2 (s), 100.0 (s), 100.6 (s), 111.5 (s), 138.8 (d) ppm. IR (DRIFT): $\tilde{\nu}$ = 3471 (s), 2950 (s), 2833 (w), 2082 (w), 1612 (m), 1456 (m), 1375 (s), 1334 (w), 1301 (w), 1205 (m), 1135 (s), 1080 (w), 1039 (m), 987 (s), 881 (s) $cm^{-1}$. MS (FAB): *m/z* (%) = 353 (29), 236 (18), 154 (40), 115 (22), 101 (100), 89 (12). MS (MALDI): *m/z* (%) = 410 (28) $[M + Na]^+$.

**(6a*R*,7a*R*,9*S*,10*S*,11a*R*)-4-Hydroxy-2,9,10-trimethoxy-7a,9,10-trimethyl-6a,7,7a,9,10,11a-hexahydro-5*H*-benzo[*c*][1,4]dioxino[2,3-*g*]-chromen-5-one (18):** Iodide **13b** (384 mg, 1.00 mmol), boronate **10** (434 mg, 1.30 mmol), $Cs_2CO_3$ (98 mg, 3.0 mmol), $Pd(OAc)_2$ (5 mg, 2 mol-%), and 2-(dicyclohexylphosphanyl)-2′,6′-dimethoxybiphenyl (S-Phos, 17 mg, 4 mol-%) were dissolved in dioxane/$H_2O$ (5:1, 24 mL) and the mixture was heated under argon at 80 °C for 2 h. Hydrolysis with saturated $NH_4Cl$ solution (20 mL), extraction with EtOAc (3 × 20 mL), drying of the organic layer ($Na_2SO_4$), removal of the solvents in vacuo, and purification of the residue by MPLC on $SiO_2$ (hexane/EtOAc, 8:1) yielded lactone **18** (288 mg, 0.709 mmol, 71%) as a white solid. Compound **18**: $R_f$ (hexane/EtOAc, 2:1) = 0.56. $[a]_D^{20}$ = +68.1 (*c* = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.32 (s, 6 H, $CH_3$), 1.34 (s, 3 H, $CH_3$), 1.89 (dd, $^3J$ = 13.0 Hz, $^2J$ = 14.4 Hz, 1 H, 7-$H_{ax}H_{eq}$), 2.48 (dd, $^3J$ = 4.5 Hz, $^2J$ = 14.4 Hz, 1 H, 7-$H_{ax}H_{eq}$), 3.26 (s, 3 H, OMe), 3.31 (s, 3 H, OMe), 3.87–3.98 (m, 4 H, OMe, 9-H), 4.24 (dd, $^3J$ = 1.6 Hz, $^3J$ = 8.9 Hz, 1 H, 10-H), 6.14 (d, $^3J$ = 1.6 Hz, 1 H, 12-H), 6.42 (d, $^4J$ = 2.3 Hz, 1 H), 6.48 (d, $^4J$ = 2.3 Hz, 1 H), 11.32 (s, 1 H, OH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 17.7 (q), 17.8 (q), 28.2 (q), 38,8 (t), 48.1 (q), 48.2 (q), 55.6 (q), 66.0 (d), 69.5 (d), 81.3 (s), 99.9 (s), 100.3 (s), 100.4 (s), 100.7 (d), 102 (d), 128.6 (d), 138.9 (s), 164.0 (s), 166.1 (s), 168.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3434 (w), 2951 (s), 2835 (w), 2249 (w), 1667 (s), 1621 (m); 1579 (m), 1502 (w), 1440 (m),1378 (w), 1353 (m), 1314 (w), 1268 (m), 1229 (w), 1206 (m), 1164 (w), 1135 (s), 1089 (w), 1052 (m) $cm^{-1}$. UV/Vis (EtOH): $\lambda$ = 193, 242, 278, 319 nm. MS (EI, 90 °C): *m/z* (%) = 406 (0.6) $[M]^+$, 258 (58), 241 (30), 240 (100), 212 (17), 197 (9), 101 (12), 43 (8). HRMS (EI): calcd. 406.1628 amu; found 406.1632 amu.

**(6a*S*,7a*R*,9*S*,10*S*,11a*R*)-4-Hydroxy-2,9,10-trimethoxy-6a,9,10-trimethyl-6a,7,7a,9,10,11a-hexahydro-5*H*-benzo[*c*][1,4]dioxino[2,3-g]-chromen-5-one (19):** Iodide **13a** (95 mg, 0.25 mmol), boronate **10** (108 mg, 0.33 mmol), $Cs_2CO_3$ (244 mg, 0.75 mmol), $Pd(OAc)_2$ (1.20 mg, 2 mol-%), and 2-(dicyclohexylphosphanyl)-2′,6′-dimethoxybiphenyl (S-Phos, 4 mg, 4 mol-%) were dissolved in dioxane/$H_2O$ (5:1, 6 mL) and the mixture was heated under argon at 80 °C for 2 h. Hydrolysis with saturated $NH_4Cl$ solution (5 mL), extraction with EtOAc (3 × 5 mL), drying of the organic layer ($Na_2SO_4$), removal of the solvents in vacuo, and purification of the residue by MPLC on $SiO_2$ (hexane/EtOAc, 8:1) yielded lactone **19** (72 mg, 0.18 mmol, 72%) as a white solid. Compound **19**: yellowish solid, m.p. 196–200 °C. $R_f$ (hexane/EtOAc, 2:1) = 0.61. $[a]_D^{20}$ = +94.4 (*c* = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.36 (s, 3 H, $CH_3$), 1.38 (s, 3 H, $CH_3$), 1.62 (d, 3 H, $^3J$ = 3.5 Hz, $CH_3$), 2.27 (dd, 1 H, $^3J$ = 3.5 Hz, $^2J$ = 12.0 Hz, 7-$H_{ax}H_{eq}$), 2.36 (ddd, 1 H, $^4J$ = 0.9 Hz, $^2J$ = 12.0 Hz, $^3J$ = 13.0 Hz, 7-$H_{ax}H_{eq}$), 3.31 (s, 6 H, 2 OMe), 3.84 (s, 3 H, OMe), 3.89 (ddd, $^3J$ = 3.5 Hz, $^3J$ = 9.1 Hz, $^3J$ = 13.0 Hz, 1 H, 7a-H), 4.51 (dd, $^3J$ = 2.1 Hz, $^3J$ = 9.1 Hz, 1 H,

11a-H), 6.11 (d, $^3J$ = 2.1 Hz, 1 H, 12-H), 6.44 (d, $^4J$ = 2.3 Hz, 1 H), 6.52 (d, $^3J$ = 2.3 Hz, 1 H), 11.31 (s, 1 H, OH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 17.7 (q), 17.8 (q), 27.1 (q), 39.8 (t), 48.0 (q), 48.1 (q), 55.6 (q), 66.5 (d), 69.5 (d), 82.4 (s), 100.3 (s), 100.4 (s), 100.8 (s), 101.3 (d), 102.7 (d); 126.2 (d), 134.0 (s), 138.0 (s), 164 (s), 166.1 (s), 168.2 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3341 (w), 3018 (w), 2993 (w), 2947 (s), 2907 (w), 2863 (m), 2836 (m), 2081 (w), 1677 (s), 1621 (m), 1577 (m), 1501 (w), 1438 (m), 1379 (w), 1349 (m), 1258 (m), 1207(m), 1147 (s), 1075 (m), 1051 (m), 976 (s), 890 (s) cm$^{-1}$. UV/Vis (EtOH): $\lambda$ = 193, 243, 279, 322 nm. MS (EI, 70 °C): *m*/*z* (%) = 240 (50), 236 (39), 226 (26), 224 (30), 221 (18), 208 (25.63), 186 (35), 167 (15), 166 (93), 150 (90), 143 (34), 138 (33), 130 (68), 129 (21), 124 (23), 122 (29), 116 (53), 115 (19), 110 (38), 109 (41), 108 (18), 107 (18), 101 (72), 95 (24), 75 (25), 73 (23), 43 (100). $C_{21}H_{30}O_8$ (406.43): calcd. C 62.06, H 6.45; found C 61.49, H 6.48.

**(2*R*,3*R*,4a*R*)-2,3,7-Trihydroxy-9-methoxy-4a-methyl-2,3,4,4a-tetrahydrobenzo[*c*]chromen-6-one (Altenuene, 4):** The protected precursor **18** (169 mg, 0.42 mmol) was dissolved in TFA/$H_2O$ (5:1, 5 mL) and the mixture was stirred at room temp. for 10 min. The solvents were removed in vacuo and the residue was purified by MPLC on RP-18 $SiO_2$ (MeOH/$H_2O$, 3:2), yielding altenuene (**4**, 67 mg, 0.23 mmol, 55%) as a colorless, highly viscous oil. Compound **4**: $R_f$ ($CH_2Cl_2$/MeOH, 20:1) = 0.61. $[\alpha]_D^{20}$ = –4.0 (*c* = 0.1, MeOH). CD: $\lambda$ ($\Delta\varepsilon$ [l mol$^{-1}$ cm$^{-1}$]) = 232 (+7.6), 277 (–4.2) nm (synthesized). CD: $\lambda$ ($\Delta\varepsilon$ [l mol$^{-1}$ cm$^{-1}$]) = 232 (+0.75), 277 nm (–0.47) (purchased from Sigma–Aldrich). $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 1.47 (s, 3 H, $CH_3$), 1.95 (dd, $^3J$ = 7.4 Hz, $^2J$ = 14.0 Hz, 1 H, 4-$H_a$H$_b$), 2.26 (dd, $^3J$ = 3.4 Hz, $^2J$ = 14.0 Hz, 1 H, 4-H$_a$$H_b$), 3.67–3.72 (ddm, $^3J$ = 3.4 Hz, $^3J$ = 7.4 Hz, 1 H, 3-H), 3.86 (3 H, OMe), 3.93–3.97 (m, 1 H, 2-H), 5.16 (d, $^3J$ = 3.7 Hz, 1 H, 2-OH), 5.32 (d, $^3J$ = 6.1 Hz, 1 H, 3-OH), 6.30 (d, $^3J$ = 3.3 Hz, 1 H, 1-H), 6.50 (d, $^4J$ = 2.3 Hz, 1 H), 6.75 (d, $^4J$ = 2.3 Hz, 1 H), 11.30 (s, 1 H, 7-OH) ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 27.4 (q, $CH_3$), 38.5 (t, C-4), 55.8 (q, OMe), 68.7 (d, C-3), 69.4 (d, C-2), 81.1 (s, C-4a), 99.9 (s), 100.8 (d), 102.3 (d), 130.9 (d, C-1), 131.7 (s), 139.1 (s), 162.9 (s), 165.8 (s), 168.1 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3404 (s), 2980 (w), 2936 (w), 1757 (w), 1661(s), 1621 (w), 1578 (m), 1493 (w), 1438 (m), 1355 (m), 1316 (w), 1266 (w), 1210 (m), 1165 (s), 1129 (w), 1067 (m), 1043 (w) cm$^{-1}$. UV/Vis (EtOH): $\lambda$ = 194, 241, 278, 319 nm. MS (EI, 100 °C): *m*/*z* (%) = 293 (10) [*M* + 1]$^+$, 292 (48) [*M*]$^+$, 248 (30), 220 (34), 219 (32), 218 (24), 206 (30), 177 (34), 149 (32), 97 (26), 85 (24), 83 (27), 81 (26), 71 (24), 69 (51), 59 (75), 57 (53), 55 (43), 43 (100). HRMS (EI): calcd. 292.0947 amu; found 292.0947 amu. The spectroscopic data for altenuene (**4**) are in agreement with reported data, although one value for a signal in the $^{13}$C NMR was obviously misprinted in the original literature. Instead of 99.9 (s) for a quaternary carbon atom, 143.6 (s) was given there.[1]

**(2*R*,3*R*,4a*S*)-2,3,7-Trihydroxy-9-methoxy-4a-methyl-2,3,4,4a-tetrahydrobenzo[*c*]chromen-6-one (Isoaltenuene, 5):** The protected precursor **19** (90 mg, 0.22 mmol) was dissolved in TFA/$H_2O$ (5:1, 5 mL) and the mixture was stirred at room temp. for 10 min. The solvents were removed in vacuo and the residue was purified by MPLC on RP-18 $SiO_2$ (MeOH/$H_2O$, 3:2) yielding isoaltenuene (**5**, 71 mg, 0.18 mmol, 72%). Compound **5**: white solid, m.p. 102–105 °C. $R_f$ ($CH_2Cl_2$/MeOH, 20:1) = 0.7; $R_f$ (MeOH/$H_2O$, 1:1) = 0.27. $[\alpha]_D^{20}$ = +25.0 (*c* = 1.0, MeOH). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.62 (d, $^4J$ = 0.7 Hz, 3 H, $CH_3$), 2.31 (dd, $^4J$ = 0.7 Hz, $^3J$ = 6.7 Hz, $^2J$ = 12.5 Hz, 1 H, 4-$H_{ax}$H$_{eq}$), 2.37 (dd, $^3J$ = 3.8 Hz, $^2J$ = 12.5 Hz, 1 H, 4-H$_{ax}$$H_{eq}$), 2.33–2.69 (br., 2 OH), 3.79–3.90 (m, 4 H, $CH_3$, 3-H), 4.39 (dd, $^3J$ = 2.4 Hz, $^3J$ = 8.0 Hz, 1 H, 2-H), 6.12 (d, $^3J$ = 2.4 Hz, 1 H, 1-H), 6.46 (d, $^4J$ = 2.3 Hz, 1 H), 6.56 (d, $^4J$ = 2.3 Hz, 1 H), 11.35 (s, 1 H, OH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 26.8 (q), 42.8 (t), 55.7 (q), 71.7 (d), 73.79 (d), 82.1 (s), 100.3 (s), 101.3 (d), 103.0 (d), 127.3 (d), 134.0 (s), 137.3 (s), 164.3 (s), 166.2 (s), 168.1 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3409 (s), 2980 (w), 2944 (w), 1666 (s), 1620 (w), 1579 (m), 1496 (w), 1439 (m), 1357 (m), 1317 (w), 1263 (s), 1208 (m), 1165 (m), 1133 (w), 1060 (s), 955 (m) cm$^{-1}$. UV/Vis (EtOH): $\lambda$ ($\varepsilon$) = 193 (6.674), 243 (10.694), 279 (3.324), 323 (1.829) nm. MS (EI, 100 °C): *m*/*z* (%) = 293 (11) [*M* + 1]$^+$, 292 (65) [*M*]$^+$, 257 (20), 256 (100), 229 (25), 228 (63), 220 (21), 219 (30), 204 (28), 191 (20), 177 (31), 159 (25), 149 (23), 77 (29). HRMS (EI): calcd. 292.0947 amu; found 292.0946 amu. The spectroscopic data for isoaltenuene (**5**) are in full agreement with the reported data.[17]

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and $^1$H NMR spectroscopic data for all known substances. UV/Vis and CD spectra of authentic and synthesized altenuene. $^1$H and $^{13}$C NMR spectra of altenuene and isoaltenuene.

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[36] Specific rotations have not been published for altenuene (**4**) and isoaltenuene (**5**).
[37] UV/Vis and CD spectra of authentic and synthesized altenuene (**4**) are depicted in the Supporting Information.

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