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Total Synthesis of Neoaltenuene

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Dedicated to Professor Dr. János Rétey on the occasion of his 75th birthday

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The total synthesis of neoaltenuene, a toxin produced by alternaria fungi, has been achieved for the first time in 14 steps in a yield of 10 % starting from quinic acid and phloroglucinic acid, the longest linear sequence consisting of 10 steps. The key reaction was a palladium-catalyzed Suzuki-type coupling of an arene boronate with an iodinated cyclohexene. 4a-*epi*-Neoaltenuene, a non-natural isomer has been synthesized similarly.

Introduction

The resorcylic lactones alternariol (**1**) and alternariol 9-methyl ether (**2**) are the main secondary metabolites of toxin-producing *Alternaria* fungi (Figure 1).[1] Although the toxicity of these mycotoxins is low compared with others (e.g., aflatoxins),[2] infestation with *Alternaria* sp. leads to significant crop losses through the fouling of tomatoes, apples, and other fruit.[3]

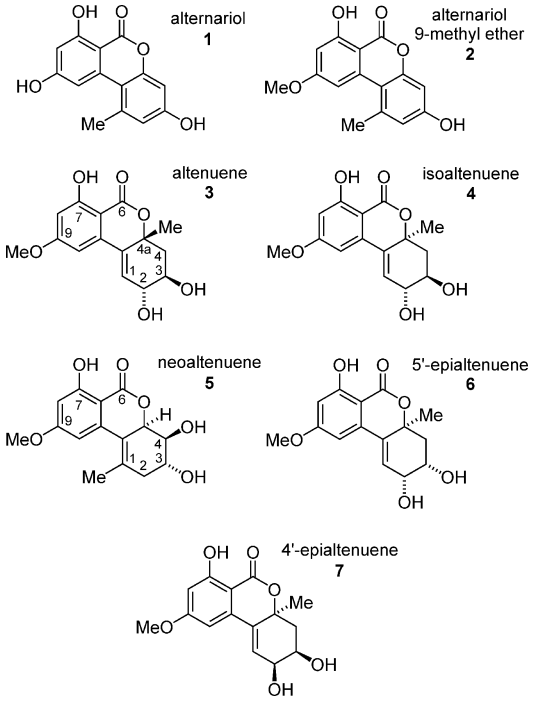

Figure 1. Metabolites in *Alternaria* fungi.

Numerous investigations have been published on alternariol (**1**) and alternariol 9-methyl ether (**2**),[4] and total syntheses have been reported for these compounds.[5] Much less is known about minor *Alternaria* toxins such as altenuene (**3**),[1b,6–9] isoaltenuene (**4**),[8,10] neoaltenuene (**5**),[11] 5′-epialtenuene (**6**),[11–13] or the recently isolated 4′-epialtenuene (**7**),[9,13] which have been isolated from infested fruits in submilligram amounts. Although we have previously published the total syntheses of altenuene (**3**) and isoaltenuene (**4**),[14] neither report details biological data[15] or their absolute configurations, nor have the total syntheses of the compounds **5**–**7** been published. To provide sufficient amounts of material for toxicological and biological testing, we have established a total synthesis of neoaltenuene (**5**), which is described herein.

Results and Discussion

A retrosynthetic analysis of neoaltenuene revealed that a Suzuki coupling of an arene boronate and an iodoalkene should be promising.[16] The synthesis of boronate **A** has been published previously[14] and an approach to halide **B** should be possible starting from tartaric acid (**9**) or, alternatively, quinic acid (**10**, Scheme 1). The use of tartaric acid would have the advantage of both enantiomers being available as starting materials.

Marco-Contelles et al. published a synthesis of cyclohexenone **13** starting from tartaric acid (*ent*-**9**).[17] The key step was the radical cyclization of iodo alkyne **12**. We planned to use a similar approach using a cyclization precursor **14**

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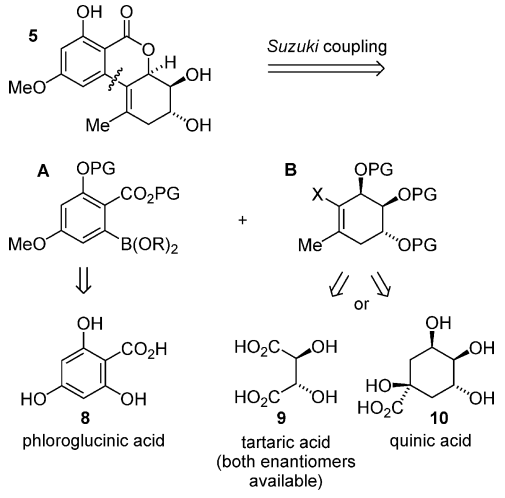
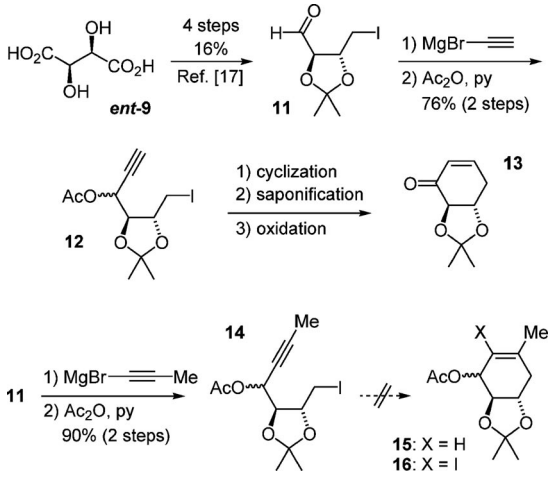


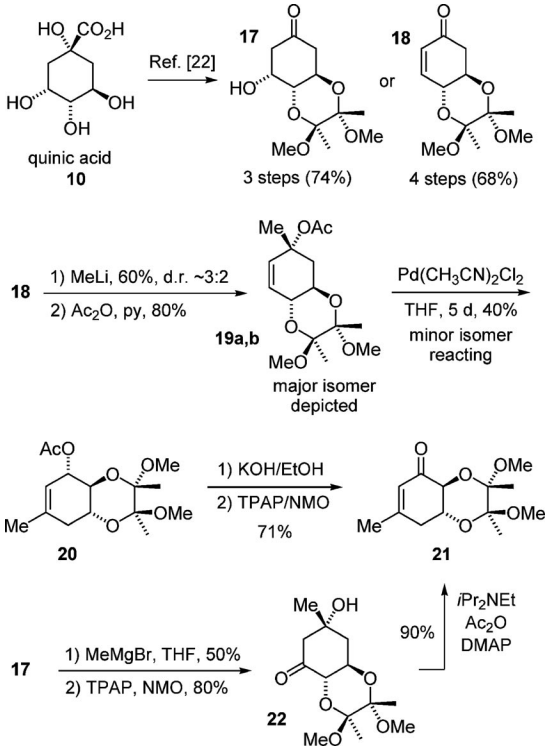
Scheme 1. Retrosynthetic analysis of neoaltenuene (PG: protecting group).

bearing an additional methyl group, which was available from tartaric acid in six steps in 14% yield (Scheme 2). A 6-*endo*-*dig* cyclization yielding a six-membered ring should be favored according to Baldwin's rules,[18] whereas the alternative 5-*exo*-*dig* cyclization to give a five-membered ring is hardly possible due to the unfavored formation of two *trans*-fused five-membered rings. Depending on the cyclization conditions we expected to obtain allyl acetate **15** or its iodinated derivative **16**. Unfortunately, none of the various conditions[19] tested, including atom-transfer conditions,[20] led to the clean formation of a six-membered ring suitable for further use.



Scheme 2. Attempted synthesis of neoaltenuene starting from tartaric acid.

Consequently we used an alternative approach starting from quinic acid (**10**). Compound **17** bearing a free hydroxy group and enone **18**, both suitably protected as 2,3-butane diacetals (BDA),[21] were accessible by synthesis according to a previously published procedure (Scheme 3).[22] 1,2-Addition of methyllithium[23] to enone **18** followed by acylation led to allyl acetate **19** suitable for a palladium(II)-catalyzed rearrangement.[24] As only the minor isomer **19b** formed in the methyllithium addition was prone to isomerization, a poor yield of 40% was achieved and isomer **19a** was cleanly recovered. The reason for the observed difference in reactivity is not quite clear. Inspection of the structures of **19a** and **19b** obtained from molecular modeling optimizations revealed that the steric hindrance at the allyl acetate moiety should be essentially the same in both **19a** and **19b**.[24e,25] Nevertheless, formation of the *S*-configured isomer **20** was confirmed by NOE experiments. Saponification of allyl acetate **20** and subsequent oxidation of the intermediate allyl alcohol with tetrapropylperruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO) led to enone **21** (9% from quinic acid).



Scheme 3. Synthesis of enone **21** starting from quinic acid.

Enone **21** was alternatively obtained by a sequence starting from β-hydroxy ketone **17**. Addition of methylmagnesium bromide led to a single isomer,[23] most likely because attack from the bottom is prevented by steric hindrance (Figure 2).[26] Oxidation and elimination furnished cyclohexenone **21** in a superior 27% yield starting from quinic acid.

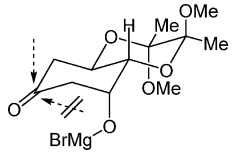
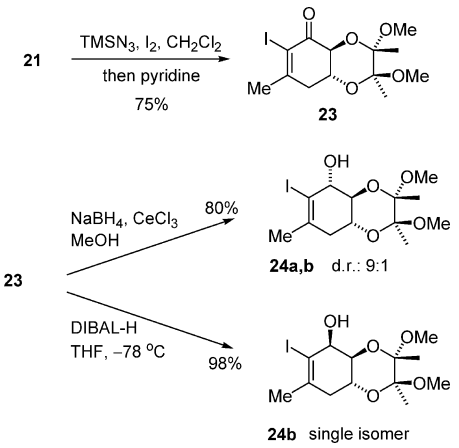


Figure 2. Proposed rationale for the addition of methylmagnesium bromide to ketone **17**.

We tested the iodination of the commercially available 3-methylcyclohex-2-enone with iodine, pyridine, and phenyl-

iodine(III) bis(trifluoroacetate)[27] and achieved a 50% yield. Although application of these conditions to enone **21** was not successful, a satisfactory 75% yield for the preparation of iodo enone **23** was obtained with trimethylsilyl azide ($TMSN_3$) and iodine followed by the addition of pyridine (Scheme 4).[28]



Scheme 4. Identification of the "southeastern" coupling partner.

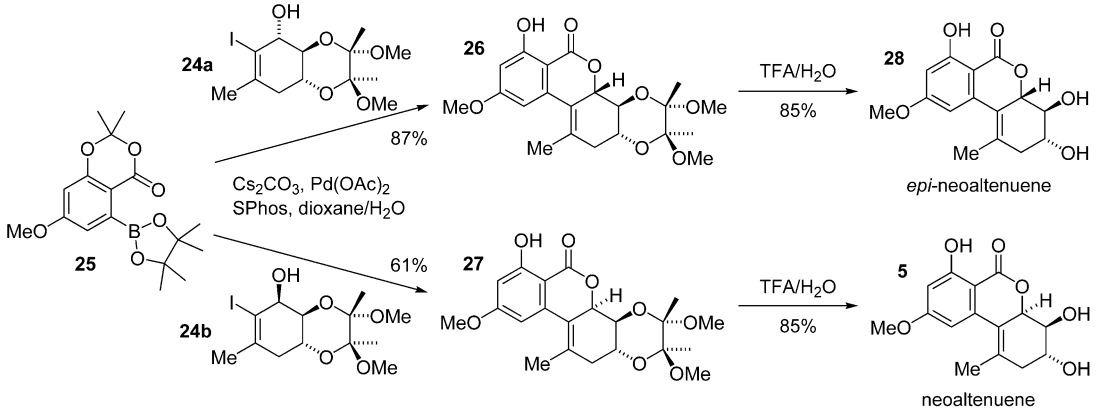
Reduction of iodo enone **23** with sodium borohydride in the presence of cerium(III) chloride[29] yielded the neoaltenuene precursor **24a**,**b** with 9:1 diastereoselectivity. The use of diisobutylaluminium hydride (DIBAL-H)[30] as reducing agent on the other hand gave alcohol **24b** suitable for the synthesis of non-natural 4a-*epi*-altenuene as a single isomer in an excellent 98% yield. K-Selectride, which has proven successful in similar transformations,[31] led to significant over-reduction when applied to iodo enone **23**.

The "northwestern" boronate **25** was prepared according to a published procedure starting from phloroglucinic acid in four steps.[14] For the Suzuki coupling[32] we used a protocol that has already proven to be successful in the syntheses of altenuene and isoaltenuene.[14] The coupling of boronate **25** with iodide **24b** in the presence of palladium(II) acetate, caesium carbonate, and SPhos (2-dicyclohexylphoshanyl-2′,6′-dimethoxybiphenyl)[32b] yielded biaryl **26** in which the lactone was concomitantly formed under these conditions (Scheme 5). Deprotection with trifluoroacetic acid yielded neoaltenuene (**5**). Starting from the diastereomeric iodide **24** these reaction conditions provided 4a-*epi*-neoaltenuene (**28**), a derivative that has not been identified as a natural product to date. The total synthesis of neoaltenuene has thus been achieved in 14 steps and in 10% yield starting from quinic acid and phloroglucinic acid, the longest linear sequence consisting of 10 steps.

Synthetic neoaltenuene (**5**) shows a specific optical rotation of +66.4 ($CHCl_3$). Nevertheless, because no data were given in the original communication reporting this compound,[11] a comparison with the natural product is not possible. The specific optical rotation of 4a-*epi*-neoaltenuene (**28**) was measured to be –311.3 (DMSO). The NMR spectroscopic data are significantly dependent on the solvents used. Changing the solvent from $CDCl_3$/[D_6]DMSO to $CDCl_3$ caused a shift in the coupling constants from, for example, 6.2 to 8.8 Hz ($^3J_{3H–4H}$). A detailed comparison of published and measured NMR spectroscopic data, given in the Supporting Information, conclusively proves that the herein synthesized neoaltenuene (**5**) is identical to the compound previously reported in the literature, which was isolated from a microbiological preparation.[11]

Experimental Section

General: 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 oxygen-free argon using oven-dried glassware and a vacuum line. Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh) and thin-layer chromatography was carried out by using commercially available Merck F_{254} pre-coated sheets. ^1H and ^{13}C NMR spectra were recorded with Bruker Cryospek WM-250, AM-400, and DRX 500 spectrometers. Chemical shifts are given in ppm downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad-band proton-decoupling and were assigned by using DEPT 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 apparatus. Electrical ionization and high-resolution mass spectra were recorded with a Finnigan MAT-90 spectrometer. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter [using the sodium D line (589 nm) or Hg



Scheme 5. Suzuki coupling and synthesis of neoaltenuene and *epi*-neoaltenuene.

lines (365 and 436 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 spectrophotometer. The extinction coefficient ε is given for quantitative measurements.

General Procedure for the Grignard Reactions (GP 1): The Grignard reagent (2.5 equiv.) was added at –78 °C under argon to a solution of the carbonyl compound (1 mmol) in anhydrous THF (20 mL). The mixture was stirred and warmed slowly until TLC indicated complete consumption of the starting material. A saturated aqueous NH_4Cl solution (15 mL) was added and the solution was extracted with EtOAc (3 × 15 mL), dried (Na_2SO_4), concentrated, and purified by chromatography.

General Procedure for the Suzuki Cross-Coupling Reactions (GP 2): Degassed solvent (dioxane/H_2O, 6:1) was added under argon to a mixture of aryl bromide (1 equiv.), boronate **25** (1.3 equiv.), Cs_2CO_3 (3 equiv.), $Pd(OAc)_2$ (0.03 equiv.), and SPhos (0.06 equiv.). The solution was heated at 80 °C for 2–6 h (monitoring with TLC). After cooling to room temp., a saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated and the residue was purified by chromatography (silica gel).

(4′*S*,5′*R*)-1-(5-Iodomethyl-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (29): Aldehyde **11** (2.10 g, 7.78 mmol, 1.0 equiv.) was treated with propynylmagnesium bromide (0.5 M in Et_2O, 46.6 mL, 23.3 mmol, 3.0 equiv.) in accord with GP 1. After stirring for 5 h, warming to room temp., work-up, and concentration, the residue was purified by chromatography (silica gel, hexanes/EtOAc, 4:1) to yield the title compound (57:43) as a colorless oil (2.01, 6.48 mmol, 83%). The isomers could not be separated. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.88 (d, ^5J = 2.2 Hz, 3 H, 4-CH_3), 2.27 (d, ^3J = 4.5 Hz, 1 H, 1-OH), 3.40 (dd, ^2J = 10.8, ^3J = 5.4 Hz, 1 H, 1′′-H_AH$_B$), 3.53 (dd, ^2J = 10.8, ^3J = 4.0 Hz, 1 H, 1′′-H$_A H_B$), 3.87 (dd, ^3J = 7.5, ^3J = 4.1 Hz, 1 H, 4′-H), 4.01 (ddd, ^3J = 7.5, ^3J = 5.4, ^3J = 4.0 Hz, 1 H, 5′-H), 4.57 (ddq, ^3J = 4.5, ^3J = 4.1, ^5J = 2.2 Hz, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.6 (q), 7.8 (t), 27.2 (q), 27.6 (q), 62.0 (d), 75.7 (d), 75.8 (s), 82.9 (d), 83.9 (s), 109.9 (s) ppm. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.88 (d, ^5J = 2.2 Hz, 3 H, 4-CH_3), 2.34 (d, ^3J = 5.6 Hz, 1 H, 1-OH), 3.34 (dd, ^2J = 10.7, ^3J = 5.4 Hz, 1 H, 1′′-H_AH$_B$), 3.46 (dd, ^2J = 10.7, ^3J = 4.7 Hz, 1 H, 1′′-H$_A H_B$), 3.86 (dd, ^3J = 7.0, ^3J = 5.8 Hz, 1 H, 4′-H), 3.95 (ddd, ^3J = 7.0, ^3J = 5.4, ^3J = 5.4 Hz, 1 H, 5′-H), 4.44 (ddq, ^3J = 5.8, ^3J = 5.6, ^5J = 2.2 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): d = 3.6 (q), 6.9 (t), 27.4 (q), 27.6 (q), 63.6 (d), 75.8 (s), 76.3 (d), 83.7 (s), 83.9 (s), 110.4 (s) ppm. Mixture of isomers: R_f = 0.22 (hexanes/EtOAc, 2:1). IR (film): $\tilde{\nu}$ = 3447 (s, OH), 2986 (s), 2934 (m), 2917 (m), 2227 (w), 1.664 (w), 1412 (w), 1373 (s), 1308 (w), 1238 (s), 1151 (m) cm^{-1}. MS (FAB): *m*/*z* (%) = 311 (77) [M + H]$^+$, 295 (56) [M – CH_3]$^+$, 241 (100) [M – C_4H_5O]$^+$, 235 (30), 183 (36) [M – I]$^+$, 137 (50), 108 (46). HRMS (FAB): calcd. for $^{12}C_{10}{}^1H_{16}{}^{127}I^{16}O_3$ 311.0141; found 311.0144. $^{12}C_{10}{}^1H_{15}{}^{127}I^{16}O_3$: C 38.73, H 4.88; found C 38.90, H 5.07.

(4′*S*,5′*R*)-1-(5-Iodomethyl-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ynyl Ethanoate (14): Ac_2O (1.23 mL, 12.9 mmol, 2.0 equiv.), pyridine (1.05 mL, 12.9 mmol, 2.0 equiv.), and DMAP (10 mol-%) were added to the alkyne as synthesized above (mixture of isomers, 2.01 g, 6.48 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (15 mL) at 0 °C and the mixture was stirred for 2 h at 0 °C. The mixture was concentrated and purified by chromatography (silica gel, hexanes/EtOAc, 6:1) to yield **14** (1.90 g, 5.90 mmol, 91%) as a yellowish oil. The isomers could not be separated. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.88 (d, ^5J = 2.3 Hz, 3 H, 4-CH_3), 2.13 (s, 3 H, OAc), 3.36 (dd, ^2J = 10.8, ^3J = 5.3 Hz, 1 H, 1′′-H_AH$_B$), 3.49 (dd, ^2J = 10.8, ^3J = 4.3 Hz, 1 H, 1′′-H$_A H_B$), 3.97 (dd, ^3J = 7.3, ^3J = 3.4 Hz, 1 H, 4′-H), 4.03 (ddd, ^3J = 7.3, ^3J = 5.3, ^3J = 4.3 Hz, 1 H, 5′-H), 5.60 (dq, ^3J = 3.4, ^5J = 2.3 Hz, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.7 (q), 6.9 (t), 20.9 (q), 27.0 (q), 27.6 (q), 63.2 (d), 76.1 (d), 73.0 (s), 81.6 (d), 84.4 (s), 110.4 (s), 169.5 (s) ppm. Minor isomer (selected data): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 3 H, CH_3), 3.36 (dd, ^2J = 10.8, ^3J = 5.3 Hz, 1 H, 1′′-H_AH$_B$), 5.50 (dq, ^3J = 6.6, ^5J = 2.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.7 (q), 7.4 (t), 20.9 (q), 27.1 (q), 17.6 (q), 64.9 (d), 73.2 (s), 76.9 (d), 81.3 (d), 84.5 (s), 110.7 (s), 169.5 (s) ppm.

Mixture of Isomers: R_f = 0.21 (hexanes/EtOAc, 2:1). IR (film): $\tilde{\nu}$ = 2987 (m), 2935 (m), 2239 (w), 1746 (s, C=O), 1433 (m), 1371 (s), 1325 (w), 1226 (s), 1156 (m), 1069 (m), 1022 (m) cm^{-1}. MS (FAB): *m*/*z* (%) = 353 (15) [M + H]$^+$, 337 (32) [M – CH_3]$^+$, 241 (32) [M – $C_6H_7O_2$]$^+$, 235 (39), 123 (100), 85 (83). HRMS (FAB): calcd. for $^{12}C_{12}{}^1H_{18}{}^{127}I^{16}O_4$ 353.0249; found 353.0247. $C_{12}H_{17}IO_4$: C 40.93, H 4.87; found C 41.27, H 5.14.

(2*S*,3*S*,4a*R*,6*S*,8a*R*)- and (2*S*,3*S*,4a*R*,6*R*,8a*R*)-2,3-Dimethoxy-2,3,6-trimethyl-2,3,4a,5,6,8a-hexahydro-1,4-benzodioxin-6-ol: MeLi (1.6 M in Et_2O, 10.7 mL, 17.1 mmol) was added at –78 °C under argon to a solution of ketone **18** (3.19 g, 13.2 mmol) in anhydrous THF (40 mL) and the solution was stirred for 3 h at this temperature. The mixture was extracted after addition of a saturated aqueous NH_4Cl solution (30 mL) with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated and the residue was purified by chromatography (silica gel, hexanes/EtOAc, 6:1 to 3:1) to give the title compound (2.04 g, 7.89 mmol, 60%) as a mixture of isomers (60:40). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.33 (s, 3 H, 6-CH_3), 1.56 (s, 3 H, CH_3), 1.70 (dd, ^3J = 13.1, ^2J = 12.5 Hz, 1 H, 5-H_{ax}H$_{eq}$) 1.98 (br. s, 1 H, OH), 2.08 (ddd, ^2J = 12.5, ^3J = 3.4, ^4J = 1.2 Hz, 1 H, 5-H$_{ax}H_{eq}$), 3.26 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 3.72 (ddd, ^3J = 13.1, ^3J = 9.0, ^3J = 3.4 Hz, 1 H, 4a-H), 4.26 (dd, ^3J = 9.0, ^3J = 2.2 Hz, 1 H, 8a-H), 5.47 (dd, ^3J = 10.1, ^3J = 2.2 Hz, 1 H, 8-H), 5.50 (dd, ^3J = 10.1, ^4J = 1.2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9 (q, 2 C), 29.5 (q), 42.5 (t), 47.9 (q, 2 C), 68.1 (d), 69.7 (d), 72.1 (s), 100.0 (s), 100.4 (s), 126.3 (d), 135.5 (s) ppm. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.38 (s, 3 H, 6-CH_3), 1.70 (br. s, 1 H, OH), 1.86 (dd, ^2J = 13.2, ^3J = 12.8 Hz, 1 H, 5-H$_{ax}$H$_{eq}$), 2.00 (ddd, ^2J = 13.2, ^3J = 3.6, ^4J = 1.3 Hz, 1 H, 5-H$_{ax}$H$_{eq}$), 3.27 (3 H, OCH_3), 3.28 (3 H, OCH_3), 3.90 (ddd, ^3J = 12.8, ^3J = 9.0, ^3J = 3.6 Hz, 1 H, 4a-H), 4.12 (dd, ^3J = 9.0, ^3J = 2.3 Hz, 1 H, 8a-H), 5.59 (ddd, ^3J = 9.9, ^3J = 2.3 Hz, 1 H, 7-H), 5.65 (dd, ^3J = 9.9, ^3J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9 (q, 2 C), 29.9 (q), 40.6 (t), 47.9 (q), 48.0 (q), 66.4 (d), 69.7 (d), 70.5 (s), 100.0 (s), 100.5 (s), 127.9 (d), 134.2 (d) ppm. Both isomers: R_f = 0.50 (hexanes/EtOAc, 1:1). IR (DRIFT): $\tilde{\nu}$ = 3316 (s, OH), 2996 (s), 2946 (s), 2865 (s), 2833 (m), 2585 (w), 2079 (w), 1900 (w), 1734 (w), 1645 (w), 1463 (s), 1373 (s), 1324 (w), 1275 (s), 1119 (s) cm^{-1}. MS (FAB): *m*/*z* (%) = 258 (35) [M + H – CH_3OH]$^+$, 101 (100). HRMS (FAB): calcd. for $^{12}C_{12}{}^1H_{19}{}^{16}O_4$: 227.1283; found 227.1281. $C_{13}H_{22}O_5$ (258.31): calcd. C 60.45, H 8.58; found C 60.26, H 8.46.

(2*S*,3*S*,4a*R*,6*R*,8a*R*)- and (2*S*,3*S*,4a*R*,6*S*,8a*R*)-2,3-Dimethoxy-2,3,6-trimethyl-2,3,4a,5,6,8a-hexahydro-1,4-benzodioxin-6-yl Ethanoate (19a,b): Ac_2O (2.40 mL, 25.4 mmol), pyridine (1.54 mL, 19.1 mmol), and DMAP (155 mg, 1.27 mmol) were added at 0 °C to a solution of the tertiary alcohol as synthesized above (3.28 g, 12.7 mmol) in anhydrous CH_2Cl_2 (15 mL) and the mixture was

stirred overnight. The solution was concentrated and the residue was purified by chromatography (silica gel, hexanes/EtOAc, 5:1) to give **19** as a mixture of isomers (3.07 g, 10.2 mmol, 80%). Major isomer **19a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.56 (d, ^4J = 1.0 Hz, 3 H, 6-CH_3), 1.98 (s, 3 H, 6-OAc), 2.19 (ddd, ^2J = 12.2, ^3J = 3.8 Hz, 1 H, 5-$H_{ax}H_{eq}$), 2.33 (ddd, ^3J = 13.1, ^2J = 12.2, ^4J = 1.0 Hz, 1 H, 5-$H_{ax}H_{eq}$), 3.26 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 3.72 (ddd, ^3J = 13.1, ^3J = 9.0, ^3J = 3.8 Hz, 4a-H), 4.35 (d, ^3J = 9.0 Hz, 1 H, 8a-H), 5.66–5.68 (m, 2 H, 7-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q, 2 C), 22.2 (q), 27.5 (q), 38.3 (t), 47.9 (q), 48.0 (q), 67.5 (d), 69.3 (d), 81.2 (s), 100.0 (s), 100.3 (s), 127.8 (d), 131.6 (d), 169.9 (s) ppm. Minor isomer **19b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.60 (s, 3 H, 6-CH_3), 1.63 (d, ^2J = 13.3, ^3J = 12.9 Hz, 1 H, 5-$H_{ax}H_{eq}$), 1.94 (s, 3 H, 6-OAc), 2.26 (ddd, ^2J = 13.3, ^3J = 3.4, ^4J = 1.7 Hz, 1 H, 5-$H_{ax}H_{eq}$), 3.27 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 3.96 (ddd, ^3J = 12.9, ^3J = 9.1, ^3J = 3.4 Hz, 1 H, 4a-H), 4.13 (ddd, ^3J = 9.1, ^3J = 2.5, ^3J = 3.4 Hz, 1 H, 8a-H), 5.17 (dd, ^3J = 10.1, ^4J = 1.7 Hz, 1 H, 7-H), 6.19 (ddd, ^3J = 10.1, ^3J = 2.5, ^4J = 1.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q, 2 C), 22.1 (q), 25.9 (q), 39.6 (t), 47.8 (q), 47.9 (q), 65.8 (d), 69.5 (d), 80.2 (s), 100.1 (s), 100.5 (s), 129.3 (d), 130.8 (d), 170.0 (s) ppm. Both isomers: R_f = 0.58 (hexanes/EtOAc, 1:1). IR (DRIFT): $\tilde{\nu}$ = 3012 (s), 2991 (s), 2831 (m), 2075 (w), 1870 (w), 1733 (s, C=O), 1449 (s), 1370 (s), 1242 (s), 1207 (s), 1121 (s) cm^{-1}. MS (FAB): *m*/*z* (%) = 301 (1) $[M + H]^+$, 269 (52) $[M + H - CH_3OH]^+$, 123 (29), 115 (42), 101 (100), 93 (89) $[C_7H_9]^+$. HRMS (FAB): calcd. for $^{12}C_{14}{}^1H_{21}{}^{16}O_5$: 269.1389; found 269.1388. $C_{15}H_{24}O_6$: C 59.98, H 8.05; found C 59.88, H 7.96.

(2*S*,3*S*,4a*S*,5*R*,8a*R*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,4a,5,8,8a-hexahydro-1,4-benzodioxin-5-yl Ethanoate (20): $[Pd(CH_3CN)_2Cl_2]$ (86.0 mg, 0.33 mmol) was added under argon to **19** (mixture of isomers, see above, 1.00 g, 3.33 mmol, 1.0 equiv.) in anhydrous THF (16.2 mL) and the mixture was stirred for 5 d at room temp. The catalyst was removed by filtration through Celite and the filtrate was concentrated and purified by chromatography (silica gel) to yield a diastereomerically pure product **20** (392 mg, 1.31 mmol, 40%) as a colorless oil. R_f = 0.74 (hexanes/EtOAc, 2:1). $[\alpha]_D^{20}$ = –36.8 (*c* = 0.5, $CHCl_3$) ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3, 7-CH_3), 2.08 (s, 3 H, CH_3, OAc), 2.15 (dd, ^2J = 17.4, ^3J = 10.4 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.32 (dd, ^2J = 17.4, ^3J = 6.3 Hz, 1 H, 8-$H_{ax}H_{eq}$), 3.25 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 3.69 (dd, ^3J = 10.6, ^3J = 4.4 Hz, 1 H, 4a-H), 4.13 (ddd, ^3J = 10.6, ^3J = 10.4, ^3J = 6.3 Hz, 8a-H), 5.37 (dd, ^3J = 5.4, ^3J = 4.4 Hz, 1 H, 5-H), 5.51 (dm, ^3J = 5.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (q), 17.9 (q), 21.3 (q), 23.3 (q), 35.6 (t), 47.8 (q), 47.9 (q), 63.2 (d), 67.7 (d), 69.2 (d), 99.0 (s), 99.5 (s), 118.4 (d), 139.8 (s), 170.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3448 (w), 2992 (m), 2949 (s), 2832 (m), 1733 (s, C=O), 1663 (w), 1444 (s), 1376 (s), 1241 (s), 1218 (s), 1120 (s) cm^{-1}. MS (EI, 40 °C): *m*/*z* (%) = 300 (5) $[M]^+$, 109 (18), 101 (37), 94 (20), 93 (74), 92 (62), 91 (27), 75 (100), 43 (32). HRMS (EI): calcd. for $^{12}C_{15}{}^1H_{24}{}^{16}O_6$: 300.1573; found 300.1579.

(2*S*,3*S*,4a*S*,5*R*,8a*R*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,4a,5,8,8a-hexahydro-1,4-benzodioxin-5-ol: A solution of acetate **20** (300 mg, 1.00 mmol) in 10% KOH (EtOH/H_2O, 1:1, 5 mL) was stirred for 2 h and neutralized with 1 N HCl. The mixture was extracted with EtOAc (3 × 10 mL) and the organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes/EtOAc, 6:1) to yield the title compound (230 mg, 0.89 mmol, 89%) as a colorless solid. R_f = 0.31 (hexanes/EtOAc, 1:1). M.p. 82–82 °C. $[\alpha]_D^{20}$ = +60.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.74 (m, 3 H, CH_3), 2.14 (ddq, ^2J = 16.8, ^3J = 10.4, ^3J = 1.2 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.27 (ddq, ^2J = 16.8, ^3J = 10.4, ^3J = 0.6 Hz, 1 H, 8-$H_{ax}H_{eq}$), 3.25 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 3.59 (ddd, ^3J = 10.8, ^3J = 4.0, J = 0.5 Hz, 1 H, 4a-H), 4.17 (dddd, ^3J = 10.8, ^3J = 10.4, ^3J = 6.1, J = 0.5 Hz, 1 H, 8a-H), 4.20–4.21 (m, 1 H, 6-H), 5.54–5.57 (m, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q), 17.9 (q), 23.4 (q), 35.5 (t), 47.8 (q), 47.9 (q), 62.7 (d), 65.7 (d), 71.2 (d), 99.0 (s), 99.9 (s), 120.9 (d), 137.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3481 (s, OH), 2990 (s), 2948 (s), 2831 (s), 1086 (w), 1667 (s), 1440 (s), 1375 (s), 1331 (m), 1296 (w), 1221 (m), 1196 (m), 1122 (s) cm^{-1}. MS (EI, 70 °C): *m*/*z* (%) = 258 (1) $[M]^+$, 227 (28) $[M - CH_3OH]^+$, 110 (81) $[M - C_6H_{12}O_4]^+$, 109 (59), 101 (55), 92 (24), 95 (100), 81 (43), 75 (33), 58 (14), 43 (45). HRMS (EI): calcd. for $^{12}C_{13}{}^1H_{22}{}^{16}O_5$ 258.1467; found 258.1465.

(2*S*,3*S*,4a*S*,8a*R*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,8,8a-tetrahydro-4a*H*-1,4-benzodioxin-5-one (21) by Oxidation: The secondary alcohol as synthesized above (250 mg, 0.91 mmol), NMO (183 mg, 1.35 mmol), and molecular sieves (4 Å, 4.75 mg) were dissolved in anhydrous CH_2Cl_2 (10 mL) and stirred for 10 min. TPAP (16.0 mg, 0.045 mmol) was added and the mixture was filtered through a Celite pad and concentrated. The residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH, 50:1) to yield enone **21** as a colorless solid (198 mg, 0.73 mmol, 80%). R_f = 0.46 (CH_2Cl_2/MeOH, 20:1). M.p. 140–143 °C. $[\alpha]_D^{20}$ = +106.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.98 (s, 3 H, 7-CH_3), 2.49 (dd, ^2J = 17.6, ^3J = 5.9 Hz, 8-$H_{ax}H_{eq}$), 2.59 (dddd, ^2J = 17.6, ^3J = 10.2, ^4J = 2.4, ^4J = 1.2 Hz, 8-$H_{ax}H_{eq}$), 3.23 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 4.05 (dddd, ^3J = 11.3, ^3J = 10.1, ^3J = 5.9, ^4J = 1.2 Hz, 8a-H), 4.19 (dd, ^3J = 11.4, ^4J = 1.0 Hz, 1 H, 4a-H), 5.88 (dd, ^4J = 2.4, ^4J = 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (q), 17.7 (q), 24.3 (q), 36.3 (t), 48.0 (q), 48.4 (q), 65.8 (d), 74.1 (d), 99.2 (s), 100.2 (s), 126.2 (d), 157.9 (s), 193.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3349 (m), 2991 (s), 2956 (s), 2852 (s), 2832 (s), 2080 (w), 2038 (w), 1896 (m), 1686 (s, C=O), 1625 (s), 1440 (s), 1376 (s), 1272 (s), 1120 (s) cm^{-1}. MS (FAB): *m*/*z* = 279 $[M + Na + H]^+$, 225 (100). HRMS (FAB): calcd. for $^{12}C_{13}{}^1H_{20}{}^{16}O_5Na$ 279.1208; found 279.1206. $C_{13}H_{20}O_5$ (256.30): calcd. C 60.92, H 7.87; found C 60.78, H 7.77.

(2*S*,3*S*,4a*R*,5*R*,7*S*,8a*R*)-2,3-Dimethoxy-2,3,7-trimethyloctahydro-1,4-benzodioxine-5,7-diol: Ketone **17** (3.00 g, 11.5 mmol, 1.0 equiv.) was treated with MeMgBr (3 M in Et_2O, 15.4 mL, 46.3 mmol) in accord with GP 1 and the reaction was quenched after 4 h at 0 °C. Purification by chromatography (silica gel) yielded the title compound as a single isomer (1.60 g, 5.79 mmol, 50%). R_f = 0.20 (hexanes/EtOAc, 1:1). M.p. 113–115 °C. $[\alpha]_D^{20}$ = +155.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, J = 0.5 Hz, 3 H, 7-CH_3), 1.30 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.50 (dd, ^2J = 12.8, ^3J = 12.6 Hz, 1 H, 8-$H_{ax}H_{eq}$), 1.56 (ddd, ^2J = 14.9, ^3J = 3.0, ^3J = 1.8 Hz, 1 H, 6-$H_{ax}H_{eq}$), 1.98 (ddd, ^2J = 12.8, ^3J = 4.5, ^4J = 3.1 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.07 (ddd, ^2J = 14.9, ^3J = 3.2, ^4J = 3.1 Hz, 1 H, 6-$H_{ax}H_{eq}$), 2.87 (dd, ^3J = 1.8, ^2J = 1.5 Hz, 1 H, 5-OH), 3.25 (s, 3 H, OCH_3), 3.26 (s, 3 H, OCH_3), 3.52 (dd, ^3J = 10.1, ^3J = 2.9 Hz, 1 H, 4a-H), 4.08 (br. s, 1 H, 7-OH), 4.15 (dddd, ^3J = 3.2, ^3J = 2.9, ^2J = 1.5, J = 0.5 Hz, 1 H, 5-H), 4.26 (dddd, ^3J = 12.6, ^3J = 10.1, ^3J = 4.6, J = 0.4 Hz, 1 H, 8a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (q), 17.9 (q), 30.1 (q), 40.9 (t), 42.4 (t), 47.9 (q), 48.0 (q), 63.1 (d), 70.0 (d), 71.7 (s), 73.2 (d), 99.6 (s), 100.3 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3430 (s, OH), 3258 (s, OH), 2950 (s), 2828 (s), 1717 (w), 1449 (s), 1405 (m), 1378 (m), 1296 (w), 1201 (s) cm^{-1}. MS (FAB): *m*/*z* = 299 $[M + Na]^+$, 245 (100), 101 (85). HRMS (FAB): calcd. for $^{12}C_{13}{}^1H_{24}{}^{16}O_6Na$ 299.1470; found 299.1467. $C_{13}H_{24}O_6$ (276.33): calcd. C 56.51, H 8.75; found C 56.50, H 8.54.

(2*S*,3*S*,4a*S*,7*R*,8a*R*)-7-Hydroxy-2,3-dimethoxy-2,3,7-trimethylhexahydro-4a*H*-1,4-benzodioxin-5-one (22): A mixture of the tertiary alcohol as synthesized above (500 mg, 1.81 mmol), NMO (366 mg, 2.71 mmol), and molecular sieves (4 Å, 905 mg) in anhydrous CH_2Cl_2 (15 mL) was stirred for 10 min and TPAP (31.8 mg, 0.09 mmol) was added. The mixture was filtered after 12 h through Celite and the filtrate was concentrated and purified by chromatography (silica gel, CH_2Cl_2/MeOH, 50:1) to yield ketone **22** (397 mg, 1.45 mmol, 80%) as a colorless solid. R_f = 0.51 (CH_2Cl_2/MeOH, 10:1). M.p. 131–133 °C. $[\alpha]_D^{20}$ = +271.3 (c = 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, OCH_3), 1.40 (s, 3 H, OCH_3), 1.42 (s, 3 H, 7-CH_3), 1.70 (br. s, 1 H, 7-OH), 1.96 (dd, ^2J = 13.3, ^3J = 11.7 Hz, 1 H, 8-$H_{ax}H_{eq}$) 2.12 (ddd, ^2J = 13.3, ^3J = 4.6, ^4J = 2.9 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.45 (dd, ^2J = 14.3, ^4J = 2.9 Hz, 1 H, 6-$H_{ax}H_{eq}$), 2.58 (dd, ^2J = 14.3, ^4J = 1.4 Hz, 1 H, 6-$H_{ax}H_{eq}$), 3.24 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 4.24 (ddd, ^3J = 11.7, ^3J = 10.2, ^3J = 4.6 Hz, 1 H, 8a-H), 4.36 (dd, ^3J = 10.2, ^4J = 1.4 Hz, 4a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (q), 17.8 (q), 31.0 (q), 41.4 (t), 48.0 (q), 48.3 (q), 53.2 (t), 67.3 (d), 71.8 (s), 77.2 (d), 99.5 (s), 100.5 (s), 201.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3489 (s, OH), 2951 (s), 2246 (s), 1735 (s, C=O), 1452 (s), 1379 (s), 1310 (m), 1273 (m), 1209 (m), 1136 (s) cm^{-1}. MS (FAB): m/z = 297 [M + Na + H]$^+$, 243 (100). HRMS (FAB): calcd. for $^{12}C_{13}{}^1H_{22}{}^{16}O_6Na$ 297.131; found 297.131.

(2*S*,3*S*,4a*S*,8a*R*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,8,8a-tetrahydro-4a*H*-1,4-benzodioxin-5-one (21) by Elimination of Alcohol 22: Ac_2O (100 μL, 1.06 mmol), iPr$_2$EtN (282 μL, 1.71 mmol), and DMAP (5.0 mg, 0.041 mmol) were added at 0 °C to a solution of alcohol **22** (223 mg, 0.813 mmol) in anhydrous CH_2Cl_2 (10 mL) and the mixture was stirred overnight. Aqueous saturated $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, CH_2Cl_2/MeOH, 50:1) to yield enone **21** (187 mg, 0.73 mmol, 90%) as a colorless solid. For spectroscopic data see above.

(2*S*,3*S*,4a*S*,8a*R*)-6-Iodo-2,3-dimethoxy-2,3,7-trimethyl-2,3,8,8a-tetrahydro-4a*H*-1,4-benzodioxin-5-one (23): $TMSN_3$ (325 μL, 2.47 mmol) was added at 0 °C to a solution of enone **21** (253 mg, 0.99 mmol) in CH_2Cl_2 (5 mL). After 2 h at 0 °C I_2 (625 mg, 2.47 mmol) in pyridine/CH_2Cl_2 (1:1, 10 mL) was added. The mixture was allowed to warm to room temp. overnight and diluted with Et_2O (20 mL), washed with H_2O (20 mL), 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and an aqueous $Na_2S_2O_3$ solution (20 mL). The organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes/EtOAc, 6:1) to yield iodide **23** (282 mg, 0.740 mmol, 75%) as a yellowish solid. R_f = 0.53 (hexanes/EtOAc, 1:1). M.p. 131–132 °C. $[\alpha]_D^{20}$ = +2.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.29 (dd, ^4J = 1.2, ^4J = 0.5 Hz, 3 H, 7-CH_3), 2.72 (ddd, ^2J = 17.7, ^3J = 10.3, ^4J = 1.2 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.80 (ddd, ^2J = 17.7, ^3J = 5.8, ^4J = 0.5 Hz, 1 H, 8-$H_{ax}H_{eq}$), 3.24 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 4.05 (ddd, ^3J = 11.5, ^3J = 10.3, ^3J = 5.8 Hz, 1 H, 8a-H), 4.29 (d, ^3J = 11.5 Hz, 1 H, 4a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6. (q), 17.7 (q), 31.3 (q), 38.2 (t), 48.1 (q), 48.5 (q), 66.2 (d), 72.9 (d), 99.3 (s), 100.4 (s), 104.8 (s), 160.9 (s), 187.7 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 2993 (m), 2949 (s), 2834 (m), 2247 (w), 2107 (w), 1701 (s, C=O), 1589 (s), 1457 (m), 1429 (m), 1376 (s), 1116 (s) cm^{-1}. MS (FAB): m/z = 381 [M + H]$^+$, 351 [M – CH_3OH]$^+$ (100). HRMS (FAB): calcd. for $^{12}C_{12}{}^1H_{16}{}^{127}I^{16}O_5$ 351.0093; found 351.0089. $C_{13}H_{19}IO_5$ (382.19): calcd. C 40.85, H 5.01; found C 40.66, H 5.28.

(2*S*,3*S*,4a*R*,5*R*,8a*R*)- and (2*S*,3*S*,4a*R*,5*S*,8a*R*)-6-Iodo-2,3-dimethoxy-2,3,7-trimethyl-2,3,4a,5,8,8a-hexahydro-1,4-benzodioxin-5-ol (24a,b): $CeCl_3{\cdot}7H_2O$ (780 mg, 2.09 mmol) and $NaBH_4$ (87.1 mg, 2.30 mmol) were added at –40 °C to a solution of iodo enone **23** (800 mg, 2.09 mmol) in MeOH (25 mL) and the mixture was stirred for 1 h at this temperature. H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes/EtOAc, 2:1) to yield a mixture of isomers (90:10, 642 mg, 1.67 mmol, 80%) as a solid. Recrystallization (Et_2O/hexanes) yielded the major isomer **24a** (526 mg, 1.37 mmol, 65%). Major isomer **24a**: R_f = 0.61 (hexanes/EtOAc, 1:1). M.p. 155–158 °C. $[\alpha]_D^{20}$ = +97.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3), 2.35–2.40 (m, 2 H, 8-H), 2.64 (d, ^3J = 3.9 Hz, 1 H, 5-OH), 3.27 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 3.72 (dd, ^3J = 10.8, ^3J = 7.8 Hz, 1 H, 4a-H), 3.84 (ddd, ^3J = 10.8, ^3J = 8.1, ^3J = 8.1 Hz, 1 H, 8a-H), 4.26 (dddd, ^3J = 7.8, ^3J = 3.9, ^5J = 3.8, ^5J = 1.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (q, 2 C), 29.1 (q), 36.6 (t), 48.0 (q), 48.1 (q), 64.7 (d), 73.3 (d), 75.0 (d), 99.2 (s), 99.3 (s), 102.2 (s), 138.6 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3539 (s, OH), 2953 (s), 2908 (s), 2889 (s), 2835 (s), 2075 (w), 1894 (w), 1634 (m), 1436 (s), 1374 (s), 1337 (m), 1310 (m), 1208 (s) cm^{-1}. MS (FAB): m/z (%) = 383 (1) [M – H]$^+$, 353 (75) [M – CH_3OH]$^+$, 154 (35), 136 (28), 101 (100). HRMS (FAB): calcd. for $^{12}C_{13}{}^1H_{20}{}^{127}I^{16}O_5$ 383.0355; found 383.0351. $C_{13}H_{21}IO_5$ (384.21): calcd. C 40.64, H 5.51; found C 40.65, H 5.51.

(2*S*,3*S*,4a*R*,5*S*,8a*R*)-6-Iodo-2,3-dimethoxy-2,3,7-trimethyl-2,3,4a,5,8,8a-hexahydro-1,4-benzodioxin-5-ol (24b): DIBAL-H (1 M in toluene, 1.69 mL, 1.69 mmol) was added slowly at –78 °C to a solution of iodo enone **23** (322 mg, 0.84 mmol) in anhydrous THF (10 mL). The reaction was quenched after 1.5 h by the addition of a saturated aqueous NH_4Cl solution (10 mL) at –78 °C. The mixture was extracted with EtOAc (3 × 15 mL) and the organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes/EtOAc, 2:1) to yield diastereoisomer **24b** (320 mg, 0.83 mmol, 98%) as a colorless solid. R_f = 0.61 (hexanes/EtOAc, 1:1). M.p. 152–154 °C. $[\alpha]_D^{20}$ = +34.4 (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 2.28 (dd, ^2J = 17.0, ^3J = 10.4 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.50 (ddd, ^2J = 17.0, ^3J = 6.0 Hz, 1 H, 8-$H_{ax}H_{eq}$), 2.73 (br. s, 1 H, 5-OH), 3.25 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 3.74 (dd, ^3J = 11.0, ^3J = 4.0 Hz, 1 H, 4a-H), 4.17 (ddd, ^3J = 11.0, ^3J = 10.2, ^3J = 6.0 Hz, 8a-H), 4.45 (d, ^3J = 4.0 Hz, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (q), 17.8 (q), 28.9 (q), 31.0 (t), 48.0 (q), 48.1 (q), 62.0 (d), 70.8 (d), 76.3 (d), 95.0 (s), 99.1 (s), 100.1 (s), 141.2 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3513 (s, OH), 2995 (s), 2937 (s), 2867 (s), 2830 (s), 2086 (w), 1899 (w), 1634 (m), 1448 (m), 1375 (s), 1332 (s), 1290 (w), 1218 (m), 1197 (m), 1133 (s) cm^{-1}. MS (FAB): m/z (%) = 407 (8) [M + Na]$^+$, 353 (47) [M – CH_3OH]$^+$, 235 (32) [M – $C_6H_{12}O_4$]$^+$, 136 (57), 101 (100). HRMS (FAB): calcd. for $^{12}C_{13}{}^1H_{21}{}^{127}I^{16}O_5Na$ 407.0331; found 407.0329. $C_{13}H_{21}IO_5$ (384.21): calcd. C 40.64, H 5.51; found C 40.70, H 5.51.

(2*S*,3*S*,4a*S*,4b*S*,12a*R*)-7-Hydroxy-2,3,9-trimethoxy-2,3,11-trimethyl-2,3,4a,4b,12,12a-hexahydro-6*H*-benzo[*c*][1,4]dioxino[2,3-*h*]-chromen-6-one (26): Iodide **24a** (209 mg, 0.55 mmol) was treated with boronate **25** (273 mg, 0.816 mmol) in accord with GP 2. Work-up after 2.5 h and purification by MPLC (silica gel, hexanes/EtOAc, 8:1) yielded protected *epi*-neoaltenuene **26** (190 mg, 0.47 mmol, 87%) as a colorless solid. R_f = 0.56 (hexanes/EtOAc, 1:1). M.p. 153–155 °C. $[\alpha]_D^{20}$ = –49.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 2.02 (d, ^5J = 1.4 Hz, 3 H, 11-CH_3), 2.43 (dd, ^2J = 17.9, ^3J = 9.8 Hz, 1 H, 12-$H_{ax}H_{eq}$), 2.48 (dd, ^2J = 17.9, ^3J = 6.5 Hz, 1 H, 12-$H_{ax}H_{eq}$), 3.27 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.83 (ddd, ^3J = 11.0, ^3J

= 9.8, ^3J = 6.5 Hz, 1 H, 12a-H), 4.04 (dd, ^3J = 11.0, ^3J = 7.4 Hz, 1 H, 4a-H), 5.01 (ddq, ^3J = 7.4, ^5J = 2.5, ^5J = 1.4 Hz, 1 H, 4b-H), 6.39 (d, ^4J = 2.4 Hz, 1 H, Ar-H), 6.41 (d, ^4J = 2.4 Hz, 1 H, Ar-H), 11.31 (s, 1 H, 7-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (q), 17.7 (q), 21.4 (q), 37.1 (t), 48.1 (q), 48.3 (q), 55.6 (q), 63.9 (d), 72.1 (d), 76.7 (s), 80.3 (d), 99.2 (s), 99.3 (d), 99.8 (s), 107.4 (d), 120.8 (s), 137.0 (s), 138.4 (s), 164.2 (s), 165.0 (s), 169.1 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 2949 (s), 2834 (m), 1674 (s, C=O), 1616 (s), 1576 (s), 1521 (m), 1431 (m), 1365 (s), 1309 (s), 1258 (s), 1230 (s), 1202 (s), 1163 (s), 1136 (s) cm^{-1}. MS (FAB): *m*/*z* (%) = 407 (15) $[M + H]^+$, 375 (30) $[M + H - CH_3O]^+$, 275 (42), 257 (100), 240 (85), 229 (57), 133 (95), 101 (57). HRMS (FAB): calcd. for $^{12}C_{21}{}^1H_{27}{}^{16}O_8$ 407.1706; found 407.1701.

(3*R*,4*S*,4a*R*)-3,4,7-Trihydroxy-9-methoxy-1-methyl-2,3,4,4a-tetrahydro-6*H*-benzo[*c*]chromen-6-one, *epi*-Neoaltenuene (28): Acetal **26** (88 mg, 0.22 mmol) was dissolved in TFA/H_2O (6:1) and stirred for 15 min at room temp. The mixture was concentrated and purified by chromatography (silica gel, CH_2Cl_2/MeOH, 30:1) to yield *epi*-neoaltenuene (**28**; 54 mg, 0.18 mmol, 85%) as a colorless solid. R_f = 0.23 (CH_2Cl_2/MeOH, 20:1). M.p. 202–205 °C. $[\alpha]_D^{20}$ = –311.3 (*c* = 0.275, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 3 H, CH_3), 2.25 (ddm, ^2J = 18.1, ^3J = 10.0 Hz, 1 H, 2-$H_{ax}H_{eq}$), 2.51 (dd, ^2J = 18.1, ^3J = 4.9 Hz, 1 H, 2-$H_{ax}H_{eq}$), 3.51 (dddd, ^3J = 10.5, ^3J = 10.0, ^3J = 4.9, ^3J = 4.9 Hz, 1 H, 3-H), 3.62 (ddd, ^3J = 10.5, ^3J = 6.9, ^3J = 4.9 Hz, 1 H, 4-H), 3.84 (s, 3 H, OMe), 4.82–4.86 (dm, ^3J = 6.9 Hz, 1 H, 4a-H), 5.06–5.08 (br. m, 1 H, 4-OH), 6.48–6.50 (m, 2 H, 10-H, 8-H), 11.28 (br. s, 1 H, 7-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (q, CH_3-1), 40.7 (t, C-2), 55.7 (q, 9-OMe), 66.9 (d, C-3), 74.8 (d, C-4), 83.9 (d, C-4a), 99.9 (d, C-8), 100.9 (s, C-7), 106.5 (d, C-10), 119.9 (s, C-10b), 138.2 (s, C-1), 138.8 (s, C-10a), 163.1 (s, C-6a), 164.7 (s, C-9), 169.0 (s, 6) ppm. UV/Vis (MeOH): λ (ε) = 195 (18311), 241 (38600), 281 (5540), 319 (2890 dm^3 mol^{-1} cm^{-1}) nm. IR (DRIFT): $\tilde{\nu}$ = 3320 (m, OH), 2979 (w), 2916 (m), 2883 (w), 1668 (s, C=O), 1620 (s), 1578 (s), 1493 (m), 1460 (m), 1438 (s), 1365 (s), 1302 (m), 1257 (s), 1222 (s), 1206 (s), 1164 (s) cm^{-1}. MS (FAB): *m*/*z* (%) = 293 (60) $[M + H]^+$, 257 (25), 154 (100), 136 (63). HRMS (FAB): calcd. for $^{12}C_{15}{}^1H_{17}{}^{16}O_6$ 293.1025; found 293.1028.

(2*S*,3*S*,4a*S*,4b*R*,12a*R*)-7-Hydroxy-2,3,9-trimethoxy-2,3,11-trimethyl-2,3,4a,4b,12,12a-hexahydro-6*H*-benzo[*c*][1,4]dioxino[2,3-*h*]-chromen-6-one (27): Iodide **24b** (232 mg, 0.60 mmol) was treated with boronate **25** (262 mg, 0.79 mmol) in accord with GP 2. Work-up after 2.5 h and purification by chromatography (silica gel, hexanes/EtOAc, 10:1 to 3:1) and recrystallization (Et_2O/hexanes) gave a biaryl side-product as colorless needles. Concentration of the mother liquor yielded protected neoaltenuene **27** (mg, 0.37 mmol, 61%) as a colorless solid. R_f = 0.32 (hexanes/EtOAc, 2:1). M.p. 116–119 °C. $[\alpha]_D^{20}$ = +68 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.97 (s, 3 H, 11-CH_3), 2.36 (dd, ^2J = 17.2, ^3J = 5.6 Hz, 1 H, 12-$H_{ax}H_{eq}$), 2.47 (ddd, ^2J = 17.2, ^3J = 10.4, ^5J = 1.2 Hz, 1 H, 12-$H_{ax}H_{eq}$), 3.25 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.87 (dd, ^3J = 10.8, ^3J = 4.8 Hz, 1 H, 4a-H), 4.12 (ddd, ^3J = 10.8, ^3J = 10.4, ^3J = 5.6 Hz, 1 H, 12a-H), 4.82 (ddq, ^3J = 4.8, ^5J = 1.2, ^5J = 1.0 Hz, 1 H, 12a-H), 6.35 (d, ^4J = 2.4 Hz, 1 H, Ar-H), 6.38 (s, ^4J = 2.4 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (q), 17.9 (q), 20.8 (q), 37.8 (t), 47.9 (q), 48.1 (q), 53.5 (q), 63.1 (d), 68.5 (d), 76.0 (d), 99.3 (s), 99.5 (d), 100.7 (s), 102.4 (s), 106.4 (d), 122.1 (s), 136.8 (s), 140.8 (s), 164.3 (s), 164.8 (s), 169.9 (s) ppm. IR (DRIFT): $\tilde{\nu}$ = 3500 (w, OH), 2992 (m), 2948 (m), 2833 (m), 2247 (w), 1665 (s, C=O), 1620 (s), 1577 (s), 1435 (m), 1369 (s), 1335 (m), 1294 (m), 1254 (s), 1224 (s), 1203 (s), 1133 (s) cm^{-1}. MS (FAB): *m*/*z* (%) = 429 (20) $[M + Na]^+$, 407 (20) $[M + H]^+$, 375 (97) $[M - CH_3OH]^+$, 343 (36), 275 (38), 257 (70), 240 (80) $[M - C_8H_6O_4]^+$, 115 (100), 101 (61). HRMS (FAB): calcd. for $^{12}C_{21}{}^1H_{27}{}^{16}O_8$ 407.1706; found 407.1701. **7,7′-Dimethoxy-2,2,2′,2′-tetramethyl-5,5′-bi[1,3-benzodioxinyl]-4,4′-dione (Side Product):** R_f = 0.37 (hexanes/EtOAc, 2:1). Mp. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (s, 6 H, CH_3), 1.76 (s, 6 H, CH_3), 3.85 (s, 6 H, OMe), 6.46 (d, ^4J = 2.5 Hz, 2 H, Ar-H), 6.48 (d, ^4J = 2.5 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0 (q, 2 C), 27.1 (q, 2 C), 55.7 (q, 2 C), 100.7 (d, 2 C), 112.3 (d, 2 C), 105.7 (s, 4 C), 145.2 (s, 2 C), 158.3 (s, 2 C), 159.9 (s, 2 C), 164.9 (s, 2 C) ppm. IR (DRIFT): $\tilde{\nu}$ = 3279 (w), 3086 (m), 3001 (m), 2943 (m), 2847 (m), 1744 (s, C=O), 1718 (s, C=O), 1609 (s), 1582 (s), 1431 (m), 1377 (s), 1327 (s), 1283 (s), 1215 (s), 1175 (s) cm^{-1}. MS (FAB): *m*/*z* = 415 (60) $[M + H]^+$, 91 (100) $[C_7H_7]^+$. HRMS (FAB): calcd. for $^{12}C_{22}{}^1H_{23}{}^{16}O_8$ 415.1392; found 415.1388. $C_{22}H_{22}O_8$ (414.41): calcd. C 63.76, H 5.35; found C 63.32, H 5.24.

(3*R*,4*S*,4a*S*)-3,4,7-Trihydroxy-9-methoxy-1-methyl-2,3,4,4a-tetrahydro-6*H*-benzo[*c*]chromen-6-one, Neoaltenuene (5): Acetal **27** (33 mg, 0.08 mmol) was dissolved in TFA/H_2O (6:1) and stirred for 15 min at room temp. The mixture was concentrated and purified by chromatography (silica gel, CH_2Cl_2/MeOH, 30:1) yielding neoaltenuene **5** (20 mg, 0.07 mmol, 85%) as a colorless solid. R_f = 0.31 (CH_2Cl_2/MeOH, 30:1). M.p. 171–174 °C. $[\alpha]_D^{20}$ = +66.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (br. s, 1 H, OH), 2.04 (s, 3 H, CH_3), 2.39 (dd, ^2J = 17.9, ^3J = 7.5 Hz, 1 H, 2-$H_{ax}H_{eq}$), 2.64 (dd, ^2J = 17.9, ^3J = 4.9 Hz, 2-$H_{ax}H_{eq}$), 2.78 (br. s, 1 H, OH), 3.86 (s, 3 H, OMe), 3.94 (dd, ^3J = 8.8, ^3J = 4.7 Hz, 1 H, 4-H), 4.05 (ddd, ^3J = 8.8, ^3J = 7.5, ^3J = 4.9 Hz, 1 H, 3-H), 5.00 (dm, ^3J = 4.7 Hz, 4a-H), 6.41 (d, ^4J = 2.4 Hz, 1 H, 8-H), 6.43 (d, ^4J = 2.4 Hz, 1 H, 10-H), 11.06 (br. s, 1 H, 7-OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (q, 1-CH_3), 39.1 (t, C-2), 55.7 (q, 9), 67.5 (d, C-3), 71.0 (d, C-4), 77.2 (d, C-4a), 99.6 (d, C-8), 101.7 (s, C-6a), 107.2 (d, C-10), 120.6 (s, C-10b), 137.2 (s, C-1), 140.1 (s, C-10a), 164.5 (s, C-7), 165.3 (s, C-9), 169.3 (s, C-6) ppm. UV/Vis (MeOH): λ (ε) = 196 (12993), 241 (18940), 282 (4501), 318 (2357) nm. IR (DRIFT): $\tilde{\nu}$ = 3404 (s. OH), 3011 (w), 2969 (w), 2923 (m), 2261 (w), 2128 (w), 1673 (s, C=O), 1654 (s), 1622 (s), 1579 (s), 1433 (s), 1337 (m), 1301 (s), 1256 (s), 1224 (s), 1206 (s), 1163 (m), 1133 (m) cm^{-1}. MS (FAB): *m*/*z* (%) = 292 (37) $[M + H]^+$, 136 (63). HRMS (FAB): calcd. for $^{12}C_{15}{}^1H_{17}{}^{16}O_6$ 293.1025; found 293.1023.

Supporting Information (see also the footnote on the first page of this article): Comparison of NMR spectroscopic data for the originally proposed and synthesized neoaltenuene (**5**) and *epi*-neoaltenuene (**28**). Experimental details, spectroscopic data, and spectra for all synthesized compounds.

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