Total Syntheses of (+)-Pestaphthalide A and (–)-Pestaphthalide B

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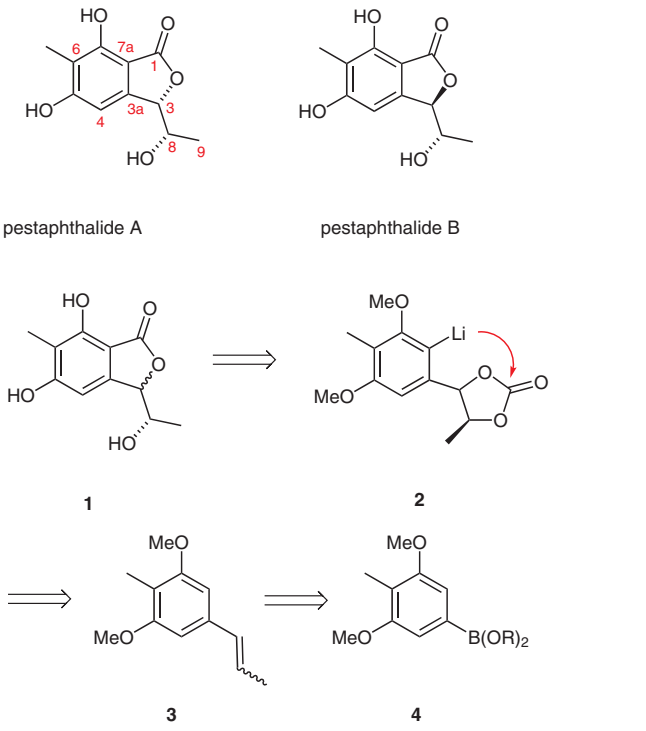
Abstract: Total syntheses of (+)-pestaphthalide A and (–)-pestaphthalide B were achieved. Key steps are an iridium-mediated *meta*-selective arylborylation, a Suzuki-coupling/Jacobsen-epoxidation sequence, a stereodivergent epoxide opening and an anionic cyclic carbonate/γ-lactone rearrangement.

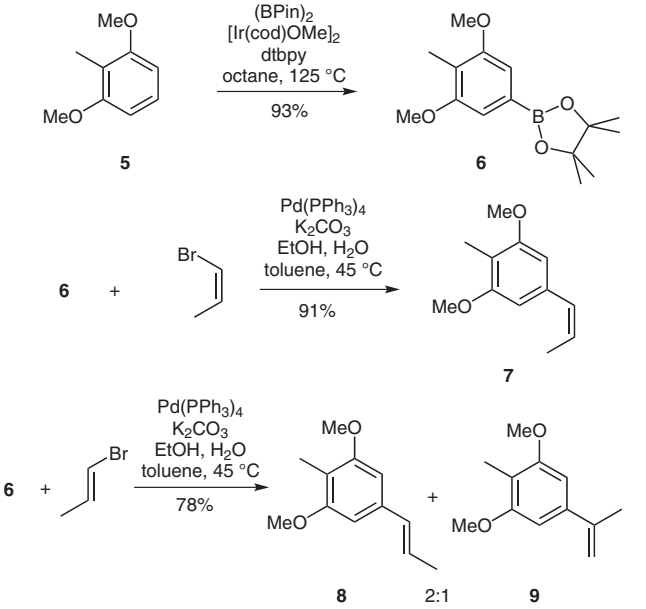
Key words: arylborylation, cyclic carbonate/γ-lactone rearrangement, natural products, total synthesis, pestaphthalide A and B

Pestaphthalide A and B were isolated from the endophytic fungus *Pestalotiopsis foedan* during a screening for antifungal activity against *Candida albicans* (ATCC 10231), *Geotrichum candidum* (AS2.498) and *Aspergillus fumigatus* (ATCC 10894).[1] The structures of both natural products were determined on the basis of HRESIMS analysis and NMR data while the absolute configuration was deduced by a comparison of CD data. The pestaphthalide skeleton consists of a 3*H*-isobenzofuran-1-one with a hydroxyethyl side chain at C3 (Scheme 1). Pestaphthalide A and B are epimers differing in the absolute configuration at the C3 stereocentre. Herein, we report our results on an efficient synthesis of both pestaphthalides.

Our synthetic plan for the pestaphthalide structure **1** relied on the introduction of the γ-lactone via an intramolecular attack of an aryllithium function **2** at the carbonyl group of a cyclic carbonate at the late stage of the synthesis (Scheme 1). Compound **2** should be accessible by asymmetric epoxidation or dihydroxylation of an alkene **3**, which could be prepared by a Suzuki cross-coupling from the arylboronate **4**. A *meta*-selective arylborylation should be the reaction of choice for the preparation of the arylboronate **4**. Miyaura, Hartwig and co-workers introduced the catalyst system $[Ir(cod)OMe]_2$, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), bis(pinacolato)diboron $[(BPin)_2]$ to achieve a *meta*-selective arylborylation.[2,3] The synthetic potential of the CH borylation of arenes was expanded by Maleczka, Smith and Marder.[4–6] Applications of this reaction in the total synthesis of natural products[7,8] and in bioorganic chemistry[9] have been reported. The reaction of the resorcine dimethyl ether **5** under Miyaura's borylation conditions gave the arylboronate **6** in very good yield (Scheme 2). Subsequent Suzuki cross-coupling worked well with (*Z*)-1-bromoprop-1-ene to deliver the *Z*-alkene **7**. In contrast, the reaction with (*E*)-1-bromoprop-1-ene led to a mixture of the desired *E*-alkene **8** and the 1,1-disubstituted alkene **9** which were not separable by chromatography.



Scheme 1 Structures and retrosynthetic analysis of the pestaphthalides



Scheme 2 Arylborylation and Suzuki cross-coupling

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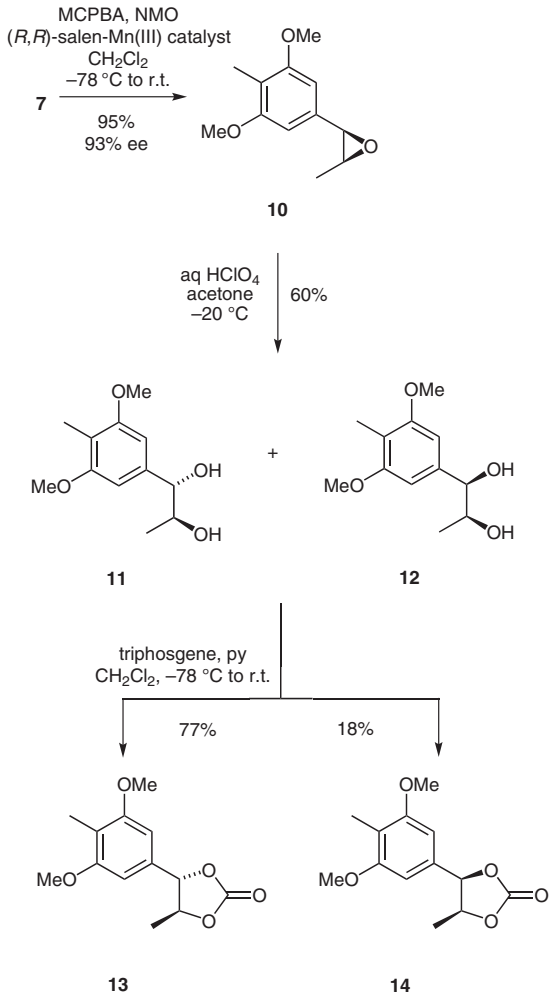
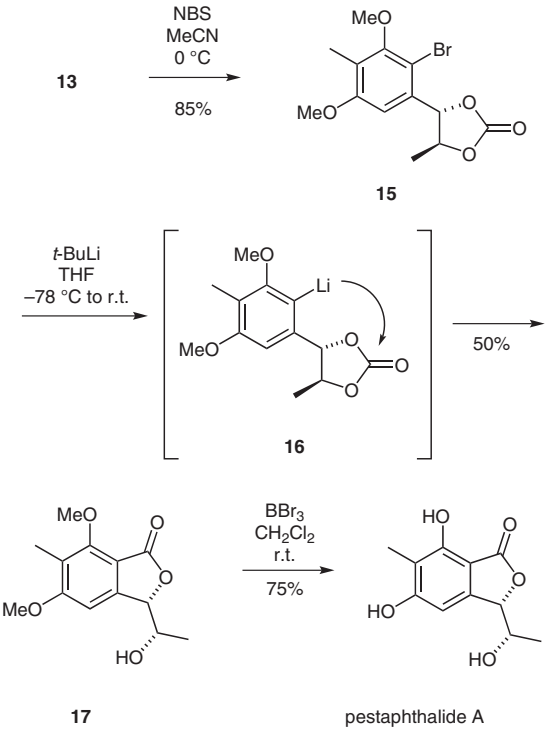
Having synthetic access to the pure *Z*-alkene **7** only, we disfavoured dihydroxylation for the functionalisation of the double bond, which is known to give low enantioselectivities under Sharpless conditions for these type of substrates.[10] In contrast, *Z*-alkenes such as **7** are ideal candidates for the asymmetric Katsuki–Jacobsen epoxidation.[11,12] With the (*R*,*R*)-salen–Mn(III) catalyst and *m*-chloroperoxybenzoic acid/*N*-methylmorpholine *N*-oxide as oxidant, the epoxide **10** was obtained with 93% ee (Scheme 3). The acid-catalysed opening of the epoxide **10** in the benzylic position by aqueous perchloric acid led to a 4:1-mixture of diols **11** and **12**. Subsequent treatment of the mixture of diols with triphosgene resulted in the cyclic carbonates **13** and **14**, which were separated by chromatography. The epoxide opening of compound **10** with aqueous 10-camphorsulfonic acid led to a 1:3 mixture of diols **11** and **12**, which after conversion into the cyclic carbonates resulted in compound **14** as the major product. The stereodivergent opening of the epoxide gave access to both precursors for pestaphthalide A and B.

The final sequence of the syntheses consists of an anionic rearrangement of the cyclic carbonate into a hydroxyethyl-substituted γ-lactone. For pestaphthalide A, the bromination of **13** gave the aryl bromide **15** (Scheme 4). A bromine–lithium exchange using *tert*-butyllithium at –78 °C gave the aryllithium intermediate **16**, which rearranged upon warming to 20 °C into the desired 3*H*-isobenzofuran-1-one **17**. No formation of the six-membered lactone was observed. Boron tribromide cleavage of the two methyl ethers in **17** provided the target compound pestaphthalide A. The analytical data of synthetic pestaphthalide A (optical rotation, NMR) matched those reported for the natural product.[1]



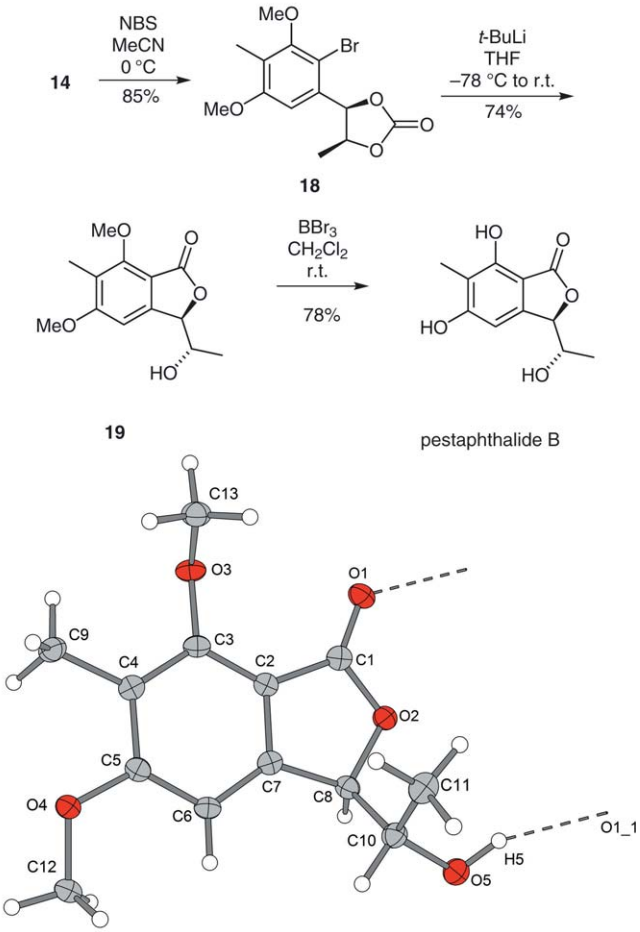
Scheme 3 Asymmetric epoxidation and stereodivergent synthesis of the carbonates



Scheme 4 Synthesis of pestaphthalide A

The cyclic carbonate **14** was the starting point for the final sequence to pestaphthalide B (Scheme 5). *N*-Bromosuccinimide bromination yielded the aryl bromide **18**. Treatment of **18** with *tert*-butyllithium at –78 °C resulted in a bromine–lithium exchange. Upon warming to room temperature the aryllithium group attacked the cyclic carbonate intramolecularly and delivered the isobenzofuranone **19**. The assignment of the relative configuration in compound **19** was possible via an X-ray structure of compound *rac*-**19** (Scheme 5), which was obtained in the racemic series (epoxidation of the *Z*-alkene **7** with MCPBA only). The unambiguous structural assignment of **19** in the pestaphthalide B series also allows the clear assignment of the epimeric compound **17** in the pestaphthalide A series. Deprotection of the two methyl ethers in **19** gave the target compound pestaphthalide B, which was identical with respect to its spectroscopic and analytical data with the natural product.[1]

In conclusion, the first syntheses of pestaphthalide A and B have been accomplished. Key steps were a *meta*-selective arylborylation, an asymmetric epoxidation/stereodivergent epoxide opening and an anionic carbonate/isobenzofuranone rearrangement. This work confirms the



Scheme 5 Synthesis of pestaphthalide B and X-ray structure of *rac*-**19**[13]

structural assignment of the natural products and opens synthetic access to derivatives with potential antifungal/antibiotic applications.

All nonaqueous reactions were carried out using flame-dried glassware under argon atmosphere. All solvents were distilled by rotary evaporation. Solvents for nonaqueous reactions were dried as follows prior to use: THF was dried with KOH and subsequently distilled from sodium/benzophenone, and Et_2O similarly from a potassium/sodium alloy (K–Na, 4:1). CH_2Cl_2 was distilled from CaH_2. *n*-Octane was dried by refluxing with sodium (5 g/L) and subsequent distillation. All commercially available reagents and reactants were used without purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{245} plates and visualised by fluorescence quenching under UV light. In addition, TLC plates were stained using a $KMnO_4$ stain. Chromatographic purification of products was performed on Merck silica gel 60 (230–400 mesh) using a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and the appropriate pressure. Yields refer to purified and spectroscopically pure products unless otherwise noted. IR spectra were recorded on a Bruker Alpha-P FT-IR spectrometer. The absorption bands are given in wave numbers (cm^{-1}). NMR spectra were recorded on a Bruker DPX250, AV300B, DRX400, or DRX500 spectrometer at room temperature. Chemical shifts are reported in ppm with the solvent resonance as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, pq = pseudoquartet. Mass spectra were recorded on a Finnigan MAT TSQ 700 or MAT 95S mass spectrometer. Specific rotations were recorded on a Perkin-Elmer 241 polarimeter. X-ray crystallographic measurements were performed at 100 K on a STOE IPDS 2T diffractometer using MoKα radiation.

2-(3,5-Dimethoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6)

$[Ir(cod)OMe]_2$ (261 mg, 0.39 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy; 212 mg, 0.79 mmol) and bis(pinacolato)diboron [$(BPin)_2$; 13.3 g, 52.6 mmol] were dissolved in *n*-octane (526 mL) and the resulting solution was stirred at r.t. for 15 min. 2,6-Dimethoxytoluene (**5**; 8.00 g, 52.6 mmol) was added to the reaction vessel and the reaction mixture was heated to reflux for 3 d. After complete consumption of the starting material, the reaction mixture was allowed to cool to r.t. and transferred into a separatory funnel with MTBE (200 mL) and brine (100 mL). The organic phase was removed and the aqueous phase was extracted with MTBE (3 × 200 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel (*n*-pentane–Et_2O, 10:1) to give the boronate **6**.

Yield: 13.6 g (93%); colourless, crystalline solid; mp 108–109 °C.

R_f = 0.31 (*n*-hexane–MTBE, 10:1).

IR (film): 2983, 2841, 1574, 1461, 1443, 1400, 1357, 1325, 1294, 1263, 1240, 1212, 1182, 1165, 1130, 1003, 965, 914, 847, 830, 711, 691, 517, 402 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 12 H, 4 × Me_{BPin}), 2.12 (s, 3 H, 4_{Ar}-Me), 3.87 (s, 6 H, 2 × OMe), 6.97 (s, 2 H, 2-H and 6-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.6 (4_{Ar}-Me), 24.9 (4 C, 4 × Me_{BPin}), 55.9 (2 C, 2 × OMe), 83.8 (2 C, C_{BPin}4 and 5), 109.5 (2 C, C2 and 6), 118.4 (C_{Ar}4), 126.8 (C1), 158.1 (2 C, C_{Ar}3 and 5).

^{11}B NMR (160 MHz, $CDCl_3$): δ = 31.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{23}BO_4Na$: 301.1584; found: 301.1584.

1,3-Dimethoxy-2-methyl-5-[(*Z*)-prop-1-enyl]benzene (7)

Boronate **6** (1.00 g, 3.60 mmol), K_2CO_3 (12.7 g, 92.2 mmol) and $Pd(PPh_3)_4$ (208 mg, 0.18 mmol) were dissolved in a mixture of toluene (69.0 mL), EtOH (23.0 mL) and H_2O (46.0 mL), and the mixture was degassed twice by freezing in liquid N_2 under vacuum. (*Z*)-1-Bromoprop-1-ene (0.93 mL, 10.79 mmol) was added and the biphasic reaction mixture was heated to 45 °C for 16 h under vigorous stirring. Then, the reaction mixture was allowed to cool to r.t. and poured into a mixture of H_2O (100 mL) and MTBE (150 mL). The organic phase was removed and the aqueous phase was extracted with MTBE (3 × 100 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel (*n*-pentane–Et_2O, 20:1) to give the olefin **7**.

Yield: 0.63 g (91%); colourless oil.

R_f = 0.53 (*n*-hexane–MTBE, 9:1).

IR (film): 2998, 2834, 1601, 1580, 1451, 1412, 1400, 1235, 1182, 1133, 1047, 964, 893, 839, 713, 602, 586 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (dd, *J* = 7.2, 1.7 Hz, 3 H, 3-H_{Pr}), 2.13 (s, 3 H, 2_{Ar}-Me), 3.85 (s, 6 H, 2 × OMe), 5.79 (dq, *J* = 11.6, 7.2 Hz, 1 H, 2-H_{Pr}), 6.44 (dd, *J* = 11.6, 1.4 Hz, 1 H, 1-H_{Pr}), 6.52 (s, 2 H, 4-H and 6-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.1 (2_{Ar}-Me), 14.7 (C_{Pr}3), 55.7 (2 C, 2 × OMe), 104.4 (2 C, C4 and 6), 113.1 (C_{Ar}), 126.2 (C_{Pr}2), 130.3 (C_{Pr}1), 135.8 (C_{Ar}), 158.0 (2 C, C_{Ar}1 and 3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_2$: 193.1223; found: 193.1224.

1,3-Dimethoxy-2-methyl-5-[(*E*)-prop-1-enyl]benzene (8) and 1,3-Dimethoxy-2-methyl-5-(prop-1-en-2-yl)benzene (9)

In an argon atmosphere boronate **6** (200 mg, 0.72 mmol) was dissolved in a mixture of toluene (14.0 mL), EtOH (4.5 mL) and H_2O (9.0 mL). K_2CO_3 (2.49 g, 18.0 mmol) was added and the mixture was degassed twice by freezing in liquid N_2 under vacuum. $Pd(PPh_3)_4$ (42.0 mg, 0.04 mmol) and (*E*)-1-bromoprop-1-ene (0.22 mL, 2.5 mmol) were added and the reaction mixture was heated to 45 °C for 16 h under vigorous stirring. The reaction mixture was then cooled to r.t. and poured into a mixture of H_2O (12 mL) and MTBE (20 mL). The aqueous phase was removed and extracted with MTBE (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure. The remaining crude product was purified by chromatography on silica (*n*-pentane–Et_2O, 19:1) to give the isomeric olefins **8** and **9** as an inseparable 2:1 mixture (according to ^{1}H NMR analysis).

Yield: 109 mg (78%); colourless oil.

R_f = 0.50 (*n*-hexane–MTBE, 9:1).

IR (film): 2933, 2836, 1691, 1584, 1464, 1408, 1370, 1314, 1279, 1248, 1181, 1124, 1024, 969, 915, 840, 764, 708, 588, 533, 496, 444 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (olefin **8**) = 1.89 (dd, *J* = 6.4, 1.5 Hz, 3 H, 3-H_{Pr}), 2.07 (s, 3 H, 2_{Ar}-Me), 3.83 (s, 6 H, 2 × OMe), 6.21 (dq, *J* = 15.6, 6.5 Hz, 1 H, 2-H_{Pr}), 6.38 (dq, *J* = 15.7, 1.5 Hz, 1 H, 1-H_{Pr}), 6.52 (s, 2 H, 4-H and 6-H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (olefin **9**) = 2.09 (s, 3 H, 2_{Ar}-Me), 2.16 (dd, *J* = 1.3, 0.8 Hz, 3 H, 3-H_{Pr}), 3.85 (s, 6 H, 2 × OMe), 5.06 (pq, *J* = 1.5 Hz, 1 H, 1-$H_{Pr,a}$), 5.33 (dq, *J* = 1.1, 0.6 Hz, 1 H, 1-$H_{Pr,b}$), 6.63 (s, 2 H, 4-H and 6-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (olefin **8**) = 8.3 (2_{Ar}-Me), 18.5 ($C_{Pr}3$), 55.8 (2 C, 2 × OMe), 101.6 (2 C, C4 and 6), 113.6 ($C_{Ar}2$), 125.1 ($C_{Pr}2$), 131.6 ($C_{Pr}1$), 136.5 (C5), 158.5 (2 C, $C_{Ar}1$ and 3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (olefin **9**) = 8.3 (2_{Ar}-Me), 22.1 ($C_{Pr}3$), 55.8 (2 C, 2 × OMe), 101.5 (2 C, C4 and 6), 112.0 ($C_{Pr}1$), 113.5 ($C_{Ar}2$), 140.1 (C5), 143.9 ($C_{Pr}2$), 158.0 (2 C, $C_{Ar}1$ and 3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_2$: 193.1223; found: 193.1227.

(2*R*,3*S*)-2-(3,5-Dimethoxy-4-methylphenyl)-3-methyloxirane (10)

Olefin **7** (100 mg, 0.52 mmol), (*R*,*R*)-(–)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride [(*R*,*R*)-salen–Mn(III) catalyst; 26.4 mg, 0.04 mmol] and 97% NMO (132 mg, 1.13 mmol) were dissolved in CH_2Cl_2 (10 mL) and the solution was cooled to –78 °C. Then, a soln of MCPBA (257 mg, 1.49 mmol) in a mixture of CH_2Cl_2 (5 mL) and EtOH (1 mL) was added dropwise and the reaction mixture was allowed to warm to r.t. and stirred for 24 h. CH_2Cl_2 (20 mL) was added and the mixture was transferred into a separatory funnel. The organic phase was washed with 1 M NaOH (3 ×) and dried ($MgSO_4$), and the solvents were removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel (*n*-pentane–Et_2O, 19:1) to give the desired oxirane **10**.

Yield: 103 mg (95%); yellow oil; 93% ee [the enantioselectivity was determined at the stage of the carbonate **13** (*vide infra*)].

R_f = 0.29 (*n*-hexane–MTBE, 9:1).

IR (film): 2996, 2959, 2936, 2869, 1692, 1587, 1453, 1407, 1356, 1233, 1133, 1059, 1021, 979, 935, 892, 846, 817, 685, 584, 390 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 5.4 Hz, 3 H, 3-H_{Pr}), 2.08 (s, 3 H, 4-Me), 3.32 (dq, *J* = 4.2, 5.4 Hz, 1 H, 2-H_{Pr}), 3.83 (s, 6 H, 2 × OMe), 4.04 (d, *J* = 4.2 Hz, 1 H, 1-H_{Pr}), 6.48 (s, 2 H, 2-H_{Ar} and 6-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.1 (4-Me), 12.6 ($C_{Pr}3$), 55.2 ($C_{Pr}2$), 55.7 (2 C, 2 × OMe), 57.9 ($C_{Pr}1$), 101.8 (2 C, $C_{Ar}2$ and C6), 113.5 (C4), 133.9 ($C_{Ar}1$), 158.0 (2 C, $C_{Ar}3$ and C5).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_3$: 209.1172; found: 209.1176.

(1*S*,2*S*)-1-(3,5-Dimethoxy-4-methylphenyl)propane-1,2-diol (11) and (1*R*,2*S*)-1-(3,5-Dimethoxy-4-methylphenyl)propane-1,2-diol (12)

Oxirane **10** (50.0 mg, 0.24 mmol) was dissolved in acetone (5 mL) and H_2O (0.10 mL) was added. The resulting solution was cooled to –20 °C and 5% aq $HClO_4$ (0.10 mL, 0.05 μmol) was added. After 24 h, the reaction mixture was diluted with NaH_2PO_4/Na_2HPO_4 buffer (pH 6.5, 10 mL), acetone was removed under reduced pressure and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (EtOAc–*n*-pentane, 4:1) to yield diastereomeric diols **11** and **12** as an inseparable 4:1 mixture (according to ^{1}H NMR analysis).

Yield: 32.5 mg (60%); white solid.

R_f = 0.31 (EtOAc–*n*-hexane, 4:1).

IR (film): 3362, 2989, 2931, 2839, 1588, 1461, 1413, 1312, 1236, 1076, 1049, 1020, 975, 920, 829, 646, 547 cm^{-1}.

^{1}H NMR (250 MHz, CD_3OD): δ (diol **11**) = 0.98 (d, *J* = 6.4 Hz, 3 H, 3-H_{Pr}), 2.01 (s, 3 H, 4-Me), 3.81 (s, 6 H, 2 × OMe), 3.81 (m, 1 H, 2-H_{Pr}), 4.30 (d, *J* = 6.9 Hz, 1 H, 1-H_{Pr}), 6.59 (s, 2 H, 2-H_{Ar} and 6-H).

^{1}H NMR (250 MHz, CD_3OD): δ (diol **12**) = 1.13 (d, *J* = 6.4 Hz, 3 H, 3-H_{Pr}), 2.16 (s, 3 H, 4-Me), 3.81 (s, 6 H, 2 × OMe), 3.81 (m, 1 H, 2-H_{Pr}), 4.46 (d, *J* = 5.4 Hz, 1 H, 1-H_{Pr}), 6.61 (s, 2 H, 2-H_{Ar} and 6-H).

^{13}C NMR (62.9 MHz, CD_3OD): δ (diol **11**) = 8.1 (4-Me), 18.8 ($C_{Pr}3$), 55.8 (2 C, 2 × OMe), 72.2 ($C_{Pr}2$), 79.8 ($C_{Pr}1$), 102.0 (2 C, $C_{Ar}2$ and C6), 114.3 (C4), 139.5 ($C_{Ar}1$), 158.3 (2 C, $C_{Ar}3$ and C5).

^{13}C NMR (62.9 MHz, CD_3OD): δ (diol **12**) = 8.1 (4-Me), 17.7 ($C_{Pr}3$), 55.8 (2 C, 2 × OMe), 71.4 ($C_{Pr}2$), 78.2 ($C_{Pr}1$), 101.8 (2 C, $C_{Ar}2$ and C6), 114.0 (C4), 139.0 ($C_{Ar}1$), 158.3 (2 C, $C_{Ar}3$ and C5).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_4Na$: 249.1097; found: 249.1098.

(4*S*,5*S*)-4-(3,5-Dimethoxy-4-methylphenyl)-5-methyl-1,3-dioxolan-2-one (13) and (4*R*,5*S*)-4-(3,5-Dimethoxy-4-methylphenyl)-5-methyl-1,3-dioxolan-2-one (14)

The diastereomeric mixture of diols **11** and **12** (658 mg, 2.91 mmol) was dissolved in CH_2Cl_2 (50 mL) and pyridine (1.41 mL, 17.5 mmol) was added. The resulting solution was cooled to –78 °C and a soln of triphosgene (432 mg, 1.45 mmol) in CH_2Cl_2 (5 mL) was added dropwise. Once the addition was complete, the reaction mixture was allowed to warm to r.t. and was then quenched with sat. aq NH_4Cl (50 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was washed with 1 M HCl (20 mL), sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product containing the two diastereomeric carbonates was purified and separated by flash column chromatography (MTBE–*n*-pentane, 2:1).

IR (film): 3362, 2989, 2931, 2839, 1588, 1461, 1413, 1373, 1312, 1236, 1132, 1076, 1049, 1020, 975, 920, 829, 646, 547, 450 cm^{-1}.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_5Na$: 275.0891; found: 275.0892.

Carbonate 13

Yield: 565 mg (77%); white solid; mp 131 °C.

$[\alpha]_D^{20}$ +4.5 (*c* 1.0, $CHCl_3$).

R_f = 0.50 (MTBE–*n*-hexane, 2:1).

HPLC: CHIRALPAK® IA (Daicel Chemical Industries), eluent: *i*-PrOH–*n*-hexane (5:95), flow: 1.0 mL/min, λ = 200–650 nm, temperature = 25 °C, t_R[*RR*] = 17.23 min and t_R[*SS*] = 22.84 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 6.2 Hz, 3 H, 3-H_{Pr}), 2.08 (s, 3 H, 4-Me), 3.84 (s, 6 H, 2 × OMe), 4.60 (dq, *J* = 8.1, 6.2 Hz, 1 H, 2-H_{Pr}), 5.08 (d, *J* = 8.1 Hz, 1 H, 1-H_{Pr}), 6.48 (s, 2 H, 2-H_{Ar} and 6-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.2 (4-Me), 18.4 (C_{Pr}3), 55.9 (2 C, 2 × OMe), 80.8 (C_{Pr}2), 85.4 (C_{Pr}1), 101.0 (2 C, C_{Ar}2 and C6), 116.2 (C4), 133.3 (C_{Ar}1), 154.4 (CO_3), 158.8 (2 C, C_{Ar}3 and C5).

Carbonate 14

Yield: 129 mg (18%); white solid; mp 102 °C.

$[\alpha]_D^{21}$ –43.3 (*c* 1.04, $CHCl_3$).

R_f = 0.34 (MTBE–*n*-hexane, 2:1).

HPLC: CHIRALPAK® IA (Daicel Chemical Industries), eluent: *i*-PrOH–*n*-hexane (5:95), flow: 1.0 mL/min, λ = 200–650 nm, temperature = 25 °C, t_R[*RS*] = 12.90 min and t_R[*SR*] = 17.71 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.6 Hz, 3 H, 3-H_{Pr}), 2.08 (s, 3 H, 4-Me), 3.82 (s, 6 H, 2 × OMe), 5.06 (dq, *J* = 7.7, 6.6 Hz, 1 H, 2-H_{Pr}), 5.70 (d, *J* = 7.7 Hz, 1 H, 1-H_{Pr}), 6.38 (s, 2 H, 2-H_{Ar} and 6-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.2 (4-Me), 16.0 (C_{Pr}3), 55.9 (2 C, 2 × OMe), 77.2 (C_{Pr}2), 81.0 (C_{Pr}1), 101.1 (2 C, C_{Ar}2 and C6), 115.6 (C4), 131.5 (C_{Ar}1), 154.7 (CO_3), 158.6 (2 C, C_{Ar}3 and C5).

Synthesis of (+)-Pestaphthalide A

(4*S*,5*S*)-4-(2-Bromo-3,5-dimethoxy-4-methylphenyl)-5-methyl-1,3-dioxolan-2-one (15)

A soln of carbonate **13** (415 mg, 1.64 mmol) in MeCN (30 mL) was cooled to 0 °C. NBS (439 mg, 2.47 mmol) was added and the resulting mixture was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel (MTBE–*n*-pentane, 2:1) to give the desired bromide **15**.

Yield: 465 mg (85%); white solid; mp 102 °C.

$[\alpha]_D^{24}$ +22.6 (*c* 1.07, $CHCl_3$).

R_f = 0.35 (MTBE–*n*-hexane, 3:1).

IR (film): 2937, 1800, 1570, 1451, 1386, 1364, 1319, 1185, 1159, 1116, 1075, 1027, 994, 902, 769, 580, 426 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (d, *J* = 6.3 Hz, 3 H, 3-H_{Pr}), 2.20 (s, 3 H, 4-Me), 3.78 (s, 3 H, 3_{Ar}-OMe), 3.84 (s, 3 H, 5-OMe), 4.59 (dq, *J* = 6.3, 5.1 Hz, 1 H, 2-H_{Pr}), 5.58 (d, *J* = 5.1 Hz, 1 H, 1-H_{Pr}), 6.69 (s, 1 H, 6-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.7 (4-Me), 19.7 (C_{Pr}3), 56.0 (3_{Ar}-OMe), 60.6 (5-OMe), 80.9 (C_{Pr}2), 82.5 (C_{Pr}1), 103.8 (C6), 107.2 (C_{Ar}2), 122.9 (C4), 134.0 (C_{Ar}1), 154.5 (CO_3), 156.1 (C_{Ar}3), 158.6 (C5).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{15}BrO_5Na$: 354.9975; found: 354.9979.

(*S*)-3-[(*S*)-1-Hydroxyethyl]-5,7-dimethoxy-6-methylisobenzofuran-1(3*H*)-one (17)

A soln of *t*-BuLi in *n*-pentane (1.6 M, 0.77 mL, 1.23 mmol) was added slowly to a stirred soln of bromide **15** (325 mg, 0.98 mmol) in THF (40.0 mL) at –78 °C, and the mixture was stirred for 3 h. Then, the reaction mixture was allowed to warm to r.t. and sat. aq NH_4Cl (20 mL) was added. The mixture was stirred for 30 min, then the THF was evaporated and the remaining aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (MTBE–*n*-pentane, 5:1) to yield the desired isobenzofuranone **17**.

Yield: 123 mg (50%); white solid; mp 113 °C.

$[\alpha]_D^{22}$ +32.1 (*c* 1.03, $CHCl_3$).

R_f = 0.40 (MTBE–*n*-hexane, 5:1).

IR (film): 2968, 2928, 1740, 1600, 1470, 1454, 1419, 1319, 1236, 1133, 1045, 999, 974, 831, 780, 685, 523, 436 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 [d, *J* = 6.4 Hz, 3 H, 3-CH(OH)CH_3], 2.14 (s, 3 H, 6-Me), 3.92 (s, 3 H, 7-OMe), 4.03 (s, 3 H, 5-OMe), 4.15 [qd, *J* = 6.4, 3.9 Hz, 1 H, 3-C*H*(OH)CH_3], 5.20 (d, *J* = 3.9 Hz, 1 H, 3-H), 6.68 (s, 1 H, 4-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.8 (6-Me), 18.9 [3-CH(OH)*C*H_3], 56.3 (7-OMe), 62.3 (5-OMe), 69.0 [3-*C*H(OH)CH_3], 83.0 (C3), 99.2 (C4), 110.8 (C7a), 121.3 (C6), 148.5 (C3a), 157.9 (C7), 164.4 (C5), 168.3 (C1).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_5Na$: 275.0890; found: 275.0893.

(+)-Pestaphthalide A

To a soln of isobenzofuranone **17** (33.0 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) was added 1 M BBr_3 in CH_2Cl_2 (0.78 mL, 0.78 mmol) at 0 °C and the mixture was stirred at r.t. for 3 d. When TLC showed complete consumption of the starting material, 1 M HCl (10 mL) was added and the mixture was extracted with EtOAc (4 × 20 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel ($CHCl_3$–MeOH, 12:1) to give (+)-pestaphthalide A.

Yield: 22.0 mg (75%); brown oil.

$[\alpha]_D^{21}$ +36.7 (*c* 0.06, MeOH) [Lit.[1] $[\alpha]_D$ +51 (*c* 0.05, MeOH)].

R_f = 0.24 ($CHCl_3$–MeOH, 12:1).

IR (film): 3301, 2967, 1708, 1617, 1460, 1346, 1292, 1258, 1131, 1089, 977, 798, 548 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 [d, *J* = 6.4 Hz, 3 H, 3-CH(OH)CH_3], 2.07 (s, 3 H, 6-Me), 4.14 [qd, *J* = 6.4, 3.5 Hz, 1 H, 3-C*H*(OH)CH_3], 5.26 (d, *J* = 3.5 Hz, 1 H, 3-H), 6.52 (s, 1 H, 4-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9 (6-Me), 18.5 [3-CH(OH)*C*H_3], 68.8 [3-*C*H(OH)CH_3], 85.5 (C3), 102.1 (C4), 105.0 (C7a), 112.8 (C6), 148.3 (C3a), 156.6 (C7), 164.7 (C5), 173.5 (C1).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{12}O_5Na$: 247.0577; found: 247.0575.

Synthesis of (–)-Pestaphthalide B

(4*R*,5*S*)-4-(2-Bromo-3,5-dimethoxy-4-methylphenyl)-5-methyl-1,3-dioxolan-2-one (18)

A soln of carbonate **14** (120 mg, 0.476 mmol) in MeCN (10 mL) was cooled to 0 °C. NBS (127 mg, 0.714 mmol) was added and the resulting mixture was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure and the remaining crude product was purified by flash column chromatography on silica gel (MTBE–*n*-pentane, 2:1) to give the desired bromide **18**.

Yield: 134 mg (85%); white solid; mp 132 °C.

$[\alpha]_D^{24}$ –79.6 (*c* 1.08, $CHCl_3$).

R_f = 0.4 (MTBE–*n*-hexane, 3:1).

IR (film): 2940, 2857, 1819, 1568, 1452, 1386, 1334, 1306, 1193, 1163, 1117, 1095, 1023, 998, 900, 837, 797, 749 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.6 Hz, 3 H, 3-H_{Pr}), 2.20 (s, 3 H, 4-Me), 3.77 (s, 3 H, 3_{Ar}-OMe), 3.85 (s, 3 H, 5-OMe), 5.33 (dq, *J* = 7.7, 6.6 Hz, 1 H, 2-H_{Pr}), 6.01 (d, *J* = 7.7 Hz, 1 H, 1-H_{Pr}), 6.77 (s, 1 H, 6-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.7 (4-Me), 16.1 ($C_{Pr}3$), 56.0 (3_{Ar}-OMe), 60.6 (5-OMe), 76.2 ($C_{Pr}2$), 79.9 ($C_{Pr}1$), 104.5 (C6), 106.7 ($C_{Ar}2$), 122.4 (C4), 131.8 ($C_{Ar}1$), 154.2 (CO_3), 156.0 ($C_{Ar}3$), 158.4 (C5).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}BrO_5Na$: 354.9975; found: 354.9965.

(*R*)-3-[(*S*)-1-Hydroxyethyl]-5,7-dimethoxy-6-methylisobenzofuran-1(3*H*)-one (19)

A soln of *t*-BuLi in *n*-pentane (1.6 M, 0.13 mL, 0.21 mmol) was added slowly to a stirred soln of bromide **18** (55.0 mg, 0.17 mmol) in THF (10.0 mL) at –78 °C, and the mixture was stirred for 3 h. Then, the reaction mixture was allowed to warm to r.t. and sat. aq NH_4Cl (10 mL) was added. The mixture was stirred for 30 min, then the THF was evaporated and the remaining aqueous mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (MTBE–*n*-pentane, 5:1) to yield the desired isobenzofuranone **19**.

Yield: 31.0 mg (74%); white solid; mp 125 °C.

$[\alpha]_D^{24}$ –18.8 (*c* 1.01, $CHCl_3$).

R_f = 0.30 (MTBE–*n*-hexane, 7:1).

IR (film): 3422, 2949, 2891, 1728, 1599, 1414, 1394, 1324, 1235, 1135, 1099, 1065, 985, 770, 611 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 [d, *J* = 6.4 Hz, 3 H, 3-CH(OH)CH_3], 2.14 (s, 3 H, 6-Me), 3.91 (s, 3 H, 7-OMe), 4.02 (s, 3 H, 5-OMe), 4.06 [qd, *J* = 6.4, 4.9 Hz, 1 H, 3-C*H*(OH)CH_3], 5.23 (d, *J* = 4.9 Hz, 1 H, 3-H), 6.71 (s, 1 H, 4-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 8.7 (6-Me), 18.4 [3-CH(OH)*C*H_3], 56.3 (7-OMe), 62.3 (5-OMe), 69.7 [3-*C*H(OH)CH_3], 83.1 (C3), 99.6 (C4), 110.4 (C7a), 121.3 (C6), 148.8 (C3a), 157.9 (C7), 164.4 (C5), 168.4 (C1).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_5Na$: 275.0890; found: 275.0893.

(–)-Pestaphthalide B

To a soln of isobenzofuranone **19** (11.0 mg, 0.04 mmol) in CH_2Cl_2 (3.0 mL) was added 1 M BBr_3 in CH_2Cl_2 (0.26 mL, 0.26 mmol) at 0 °C and the mixture was stirred at r.t. for 3 d. When TLC showed complete consumption of the starting material, 1 M HCl (5.0 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The remaining crude product was purified by flash column chromatography on silica gel ($CHCl_3$–MeOH, 12:1) to give (–)-pestaphthalide B.

Yield: 7.6 mg (78%); brown oil.

$[\alpha]_D^{21}$ –44.1 (*c* 0.05, MeOH) [Lit.[1] $[\alpha]_D$ –41 (*c* 0.05, MeOH)].

R_f = 0.30 ($CHCl_3$–MeOH, 12:1).

IR (film): 3293, 2982, 2927, 1716, 1616, 1344, 1293, 1132, 1088, 773, 726, 640, 548 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 [d, *J* = 6.5 Hz, 3 H, 3-CH(OH)CH_3], 2.07 (s, 3 H, 6-Me), 4.00 [qd, *J* = 6.5, 4.6 Hz, 1 H, 3-C*H*(OH)CH_3], 5.23 (d, *J* = 4.6 Hz, 1 H, 3-H), 6.54 (s, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8 (6-Me), 18.0 [3-CH(OH)*C*H_3], 69.8 [3-*C*H(OH)CH_3], 85.9 (C3), 102.3 (C4), 104.5 (C7a), 112.8 (C6), 148.2 (C3a), 156.7 (C7), 164.8 (C5), 173.5 (C1).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}O_5Na$: 247.0577; found: 247.0577.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^1H and ^{13}C NMR spectra of compounds **6**, **7**, **8** and **9**, **10**, **11** and **12**, **13**, **14**, **15**, **17**, (+)-pestaphthalide A, **18**, **19** and (–)-pestaphthalide B.

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(13) The crystal data of compound *rac*-**19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 831699. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033; E-mail: deposit@ccdc.cam.ac.uk] or via www.ccdc.cam.ac.uk/data_request/cif. Crystal data: $C_{13}H_{16}O_5$, *M* = 252.26, triclinic, *P*1, *a* = 8.5193 (5) Å, *b* = 9.3779 (7) Å, *c* = 9.4830 (6) Å, α = 62.355 (5)°, β = 66.112 (5)°, γ = 67.335 (5)°, *V* = 595.13 (7) Å^3, *Z* = 2, D_{calcd} = 1.408 Mg/m^3, 6344 reflections collected, 2500 independent (R_{int} = 0.0306), *R*1 = 0.0325, *wR*2 = 0.0791 (all data).