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Synthesis of analogues of natural antimitotic glaziovianin A based on dill and parsley seed essential oils

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General Experimental Procedures. Melting points were measured on a Boetius melting point apparatus and are uncorrected. Reaction mixtures were stirred magnetically. ^{1}H NMR spectra were recorded on Bruker DRX-500 (500.13 MHz) instrument. Chemical shifts (δ_H) are quoted in ppm and referenced to the appropriate NMR solvent peaks. 2D NMR experiments {^{1}H-^{1}H} NOESY, {^{1}H-^{13}C} HMBC-qs, {^{1}H-^{13}C} HSQC were used where necessary in assigning NMR spectra. Spin-spin coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded on Bruker DRX-500 (75.47 MHz) instrument. Chemical shifts (δ_C) were quoted in ppm and referenced to the appropriate solvent peaks and are assigned C, CH, CH_2, and CH_3 as determined using 2D NMR experiments HSQC and HMBC, where necessary. Low resolution mass spectra (*m*/*z*) were recorded on a Finnigan MAT/INCOS 50 mass spectrometer at 70 eV using direct probe inlet. Elemental analysis was performed on the automated Perkin-Elmer 2400 CHN microanalyzer. Flash chromatography was performed on silica gel (Acros 0.035–0.070 mm, 60 Å.). TLC was performed on Merck 60 F_{254} plates.

Non-anhydrous solvents and reagents were purchased at the highest commercial quality and used as received. Starting materials: 3,4-dimethoxybenzaldehyde (**2e**), 3,4,5-trimethoxybenzaldehyde (**2a**) and 2-bromo-4,5-dimethoxybenzaldehyde **(3e)** were purchased from Acros Organics (Belgium).

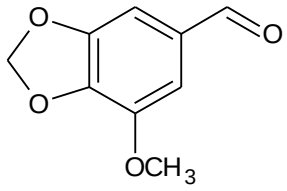
Isolation of Plant Allylpolyalkoxybenzenes 1a-d. Liquid CO_2 extraction of parsley and dill seeds was carried out by Company Karavan Ltd. (Krasnodar, Russia) [6]. Allylpolymethoxybenzenes **1a-d** with 98-99% purity were obtained by high-efficiency distillation using a pilot plant device at N.D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russia). The seed essential oils of parsley varieties cultivated in Russia contained 13% of **1a** (var. Astra), 40-46% of **1b** (var. Astra),

70-75% of **1d** (var. Sakharnaya). Indian dill seeds were purchased from Vremya & Co. (St. Petersburg, Russia). The dill seed essential oil contained 30-33% of **1c**.

General Procedure for the Synthesis of Aldehydes 2a-d[7]. Step 1: synthesis of styrenes. A mixture of allylbenzene (**1a-d**) (0.25 mol), freshly recrystallized tetrabutylammonium bromide (2.5 g, 0.0075 mol), and powdered KOH (10 g, 0.18 mol) was heated for 40 min on a water bath. The reaction mixture was cooled to rt and extracted with Et_2O (2 x 250 ml), and the combined organic extracts were washed with water (2 x 150 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The solid residue was recrystallized from petroleum ether to furnish 85-90% overall yields of target styrenes as mixtures of *trans*- (80-85%) and *cis*-isomers (15-20%).

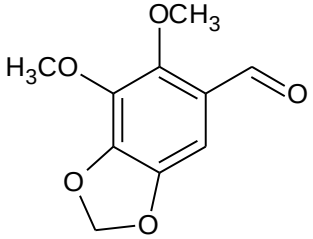
Step 2: ozonation of styrenes. Ozone (6.24 g, 0.13 mol) was bubbled through a solution of styrene (0.1 mol) in a mixture of $CHCl_3$-MeOH-pyridine (240:60:9 ml) for 1-2 h at -15 °C. The resulting solution was kept for an additional 3 h at 0 °C and concentrated *in vacuo* at 20 °C. The residue was treated with 150 ml of water, and the pH of the slurry was adjusted to *ca*. 3 with concentrated HCl. The resulting solid was filtered, washed with 3 x 70 ml of water, and dried to afford the desired aldehyde (60-80%).

*3-Methoxy-4,5-methylenedioxybenzaldehyde (Myristicin aldehyde, **2b**).*



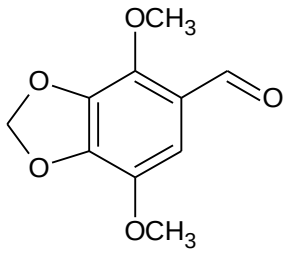
Yield 11 g (61.06 mmol, 61%); off-white solid; mp 133-135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.78 (1H, s, CHO), 7.26 (1H, s, H-Ph), 7.05 (1H, s, H-Ph), 6.12 (2H, s, OCH_2O), 3.95 (3H, s, OCH_3-3).

*2,3-Dimethoxy-4,5-methylenedioxybenzaldehyde (Dillapiol aldehyde, **2c**).*



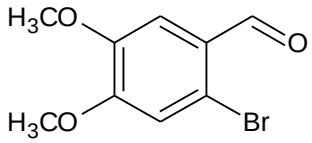
Yield 16.8 g (79.9 mmol, 80%); off-white solid; mp 75-77 °C; ^{1}H NMR (CDCl3, 500 MHz) δ 10.08 (1H, s, CHO), 6.85 (1H, s, H-6), 6.13 (2H, s, OCH_2O), 3.98 (3H, s, OCH_3), 3.87 (3H, s, OCH_3).

*2,5-Dimethoxy-3,4-methylenedioxybenzaldehyde (Apiol aldehyde, **2d**).*

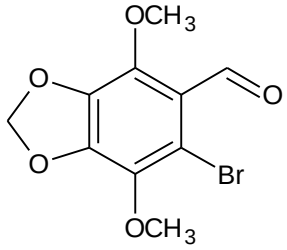


Reaction of 175 g (787 mmol) of crude isoapiol furnished 111 g (529 mmol, 67%) of product **2d** as an off-white solid: mp 102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.12 (1H, s, CHO), 7.00 (1H, s, H-6), 6.20 (2H, s, OCH_2O), 3.99 (3H, s, OCH_3), 3.83 (3H, s, OCH_3).

*2-Bromo-3,4-dimethoxylbenzaldehyde (**3c**):* purchased from Aldrich.



*6-Bromo-4,7-dimethoxy-2H-1,3-benzodioxole-5-carbaldehyde (**3d**)*

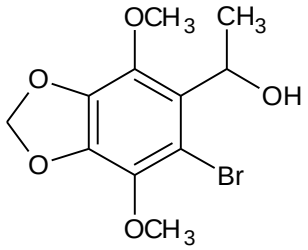


Freshly recrystallized and free from bromine *N*-bromosuccinimide (0.02 mol) was added to the solution of compound **2d** (0.02 mol) in DMF (30 ml) on cooling with ice water. The reaction mixture was stirred at room temperature for 8 hours, diluted with ice water (150 ml), the precipitate was filtered, washed with water (3x10 ml) and dried to afford *o*-bromo benzaldehyde **3d.** Yield 4.16 g (72%); colorless crystals; mp 112-113 ^{o}C (EtOH) (lit.[1] 94-95 ^{o}C); ^{1}H NMR (DMSO-d_6) δ 10.10 (1H, s, CH(O)), 6.23 (2H, s, OCH_2O), 3.92 (3H, s, OCH_3-6), 3.87 (3H, s, OCH_3-3); EIMS m/z 290

[M+1] (4), 288 (4), 133 (14), 131 (14), 107 (13), 95 (19), 93 (32), 92 (31), 77 (100), 76 (25); anal. C 41.55; H 3.14; Br 27.64%, calcd for $C_{10}H_9BrO_5$, C 41.63; H 3.17; Br 27.57%.

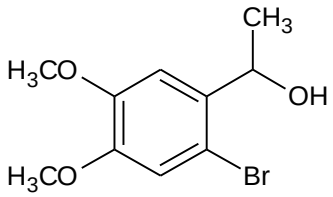
General Procedure for Synthesis of *o*-Bromo Benzylic Alcohols 4. A solution of *o*-bromobenzaldehyde **3** (0.1 mmol) in THF (140 ml) was added dropwise to methylmagnesium iodide (0.15 mol) in 50 ml of ether. The mixture was stirred for 0.5 h, evaporated till volume of 140-150 ml, boiled additionally for 1 h and poured onto ice (300 g) and aqueous NH_4Cl. The layers were separated and the aqueous one was extracted with ether. The combined organic extracts were washed with water and brine, dried, and concentrated to afford crude *o*-bromo alcohols **4** which were used on the next stage without purification.

*1-(6-Bromo-4,7-dimethoxy-2H-1,3-benzodioxol-5-yl)ethanol (**4d**)*:



Yield 1.95 g (64%); colorless crystals, mp 98-100 °C (EtOAc-hexane = 1:3); ^{1}H NMR (DMSO-d_6) δ 6.09, 6.07 (2H,2 s, OCH_2O), 5.20 (1H, p, J = 6.6 Hz, CH), 4.89 (1H, d, J = 6.0 Hz, OH), 3.83, 3.82 (6H, 2 s, 2 × OCH_3-3,6), 1.40 (3H, d, J = 6.6 Hz, CH_3); EIMS m/z 306 [M+1] (31), 305 $[M]^+$ (4), 304 (31), 292 (11), 291 (98), 290 (11), 289 (100), 276 (9), 274 (9), 261 (6), 259 (6), 210 (6), 182 (16); anal. C 43.30; H 4.29; Br 26.19%, calcd for $C_{11}H_{13}BrO_5$, C 43.40; H 4.32; Br 26.09%.

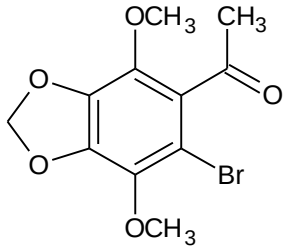
*1-(2-Bromo-4,5-dimethoxyphenyl)ethanol (**4e**):*



Yield 16.98 g (65%); colorless crystals; mp 59-60 ^{o}C (lit.[2] 60-62 °C).

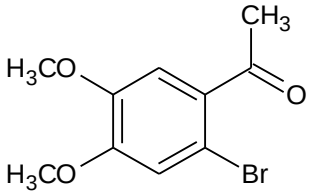
General Procedure for the Synthesis of *o*-Bromoacetophenones 5. A crude bromo alcohol **4** (0.01 mol) dissolved in CH_2Cl_2 (20 ml) was added rapidly to a suspension of pyridinium chlorochromate (3.23 g, 0.015 mol) in CH_2Cl_2 (10 ml) and the mixture was stirred for 18 h. The mixture was diluted with 15 ml of CH_2Cl_2 and filtered through Celite. The residual gum was digested with three portions of boiling CH_2Cl_2 and the combined organic extracts were washed with 15% aqueous KOH, aqueous NH_4I, and brine. The extracts were dried, concentrated, and crystallized from proper solvents (or separated by column chromatography) to yield the corresponding *o*-bromoacetophenones **5**.

*1-(6-Bromo-4,7-dimethoxy-2H-1,3-benzodioxol-5-yl)ethanone (**5d**):*



Yield 2.58 g (85%); colorless crystals; mp 55-57 °C (EtOAc-hexane = 1:1); ^{1}H NMR (DMSO-d_6) δ 6.14 (2H, s, OCH_2O), 3.86 (6H, s, 2 × OCH_3-3,6), 2.40 (3H, s, CH_3); EIMS m/z 304 [M+1] (51), 302 (51), 289 (100), 288 (11), 287 (100), 274 (13), 272 (13), 43 (19); anal. C 43.59; H 3.66; Br 26.36%, calcd for $C_{11}H_{11}BrO_5$, C 43.65; H 3.68; Br 26.29%.

*1-(2-Bromo-4,5-dimethoxyphenyl)ethanone (**5e**):*

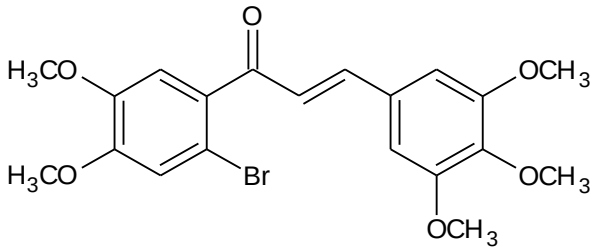


Yield 16.8 g (65%); colorless crystals; mp 75-77 °C (EtOAc-hexane=1:1) (lit.[2] 73-75 °C); ^{1}H NMR (DMSO-d_6) δ 7.28 (1H, s, H-6), 7.21 (1H, s, H-3), 3.83, 3,81 (6H, 2s, 2 × OCH_3-4,5), 2.57 (3H, s, CH_3); EIMS m/z 260 [M+1] (36), 258 (36), 245 (97), 243 (100), 108 (16), 93 (15), 77 (12);

General Procedure for the Synthesis of Chalcones 6. Sodium hydroxide (1.2 g, 30 mmol) was added to a vigorously stirred solution containing *o*-bromoacetophenone **5** (10 mmol) and benzaldehyde **2** (10 mmol) in EtOH (30 ml) at 20 °C. The mixture was stirred at room temperature

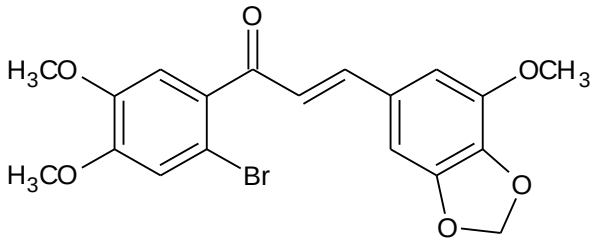
for 6 h, left overnight, then acidified with 10% HCl till pH = 3-4 and strirred 1 h. The residue was filtered, washed with water (3x20 ml) and crystallizedl from EtOAc to afford chalcone **6.**

*(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**6a**):*



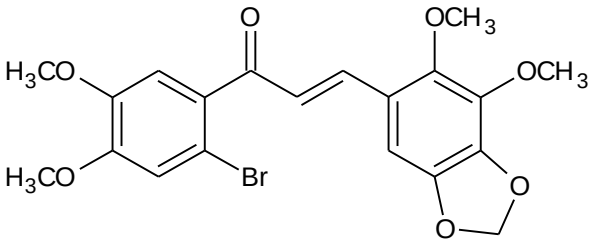
Yield 3.63g (83%); yellow solid; mp 148-150°C; ^{1}H NMR (DMSO-d_6) δ 7.35 (1H, d, *J* = 16.0 Hz, H-2), 7.25 (1H, s, H-6'), 7.24 (1H, d, *J* = 16.0 Hz, H-3), 7.11 (2H, s, H-2",6"), 7.09 (1H, s, H-3'), 3.85, 3.82, 3.80, 3.70 (15H, 4s, 5 × OCH_3-4',5',3",4",5"); EIMS m/z 439 [M+2] (21), 438 [M+1] (97), 437 $[M]^+$ (28), 436 (100), 423 (14), 421 (14), 407 (30), 405 (30), 358 (18), 357 (62), 314 (10), 299 (22), 298 (40), 283 (11), 271 (15), 245 (10), 243 (10), 221 (11), 157 (5), 149 (5); anal. C 54.93; H 4.84; Br 18.27%, calcd for $C_{20}H_{21}BrO_6$, C 54.84; H 4.80; Br 18.33%.

*(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-3-(7-methoxy-2H-1,3-benzodioxol-5-yl)prop-2-en-1-one (**6b**):*



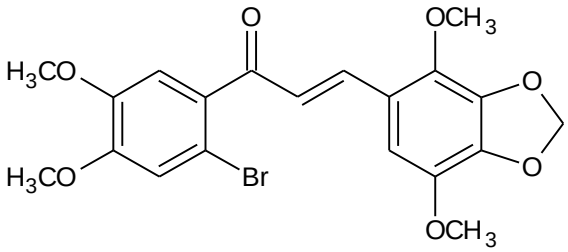
Yield 2.62 g (62%); yellow solid; mp 179-181°C; ^{1}H NMR (DMSO-d_6) δ 7.35 (1H, d, *J* = 16.0 Hz, H-2), 7.24 (1H, s, H-6'), 7.18 (1H, d, *J* = 16.0 Hz, H-3), 7.16 (1H, s, H-3'), 7.10 (2H, s, H-4",6"), 6.07 (2H, s, OCH_2O), 3.85, 3.80 (9H, 2s, 3 × OCH_3-4',5',7"); EIMS m/z 423 [M+2] (20), 422 [M+1] (100), 421 $[M]^+$ (31), 420 (97), 419 (10), 391 (16), 389 (16), 342 (9), 341 (29), 313 (8), 311(12), 298 (7), 284 (5), 283 (28), 245 (11), 243 (11), 205 (9); anal. C 54.17; H 4.07; Br 18.97%, calcd for $C_{19}H_{17}BrO_6$, C 54.25; H 4.09; Br 19.07%.

*(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-3-(6,7-dimethoxy-2H-1,3-benzodioxol-5-yl)prop-2-en-1-one (**6c**):*



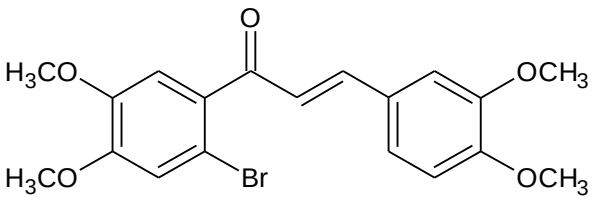
Yield 4.01 g (89%); yellow solid; mp 124-126°C; ^{1}H NMR (DMSO-d_6) δ 7.58 (1H, d, *J* = 16.1 Hz, H-2), 7.25 (1H, s, H-6'), 7.23 (1H, s, H-3'), 7.17 (1H, d, *J* = 16.1 Hz, H-3), 7.13 (1H, s, H-4"), 6/08 (2H, s, OCH_2O), 3.94 (3H, s, OCH_3-6"), 3.85, 3.80 (6H, 2s, 2 × OCH_3-4',5'), 3.70 (3H, s, OCH_3-7"); EIMS m/z 452 [M+1] (13), 450 (13), 422 (21), 421 (100), 420 (21), 419 (97), 405 (5), 404 (5), 245 (6), 243 (6), 209 (9); anal. C 53.23; H 4.24; Br 17.71%, calcd for $C_{20}H_{19}BrO_7$, C 53.27; H 4.27; Br 17.66%.

(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-3-(4,7-dimethoxy-2H-1,3-benzodioxol-5-yl)prop-2-en-1-one ***(6d)****:*



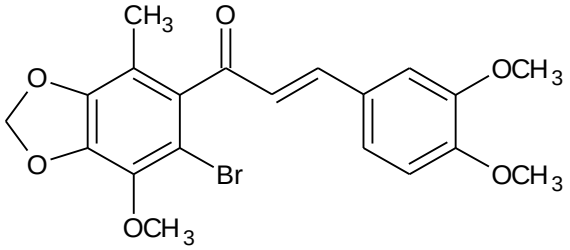
Yield 3.88 g (86%); yellow solid; mp 158-161°C; ^{1}H NMR (DMSO-d_6) δ 7.58 (1H, d, *J* = 16.0 Hz, H-2), 7.26 (1H, d, *J* = 16.0 Hz, H-3), 7.25 (1H, s, H-6'), 7.13 (1H, s, H-3'), 7.11 (1H, s, H-6"), 6.10 (2H, s, OCH_2O), 3.87, 3.85, 3.84, 3.80 (12H, 4s, 4 × OCH_3-4',5',4",7"); EIMS m/z 452 [M+1] (10), 450 (10), 422 (13), 421 (65), 420 (14), 419 (75), 306 (23), 292 (25), 245 (60), 243 (60), 235 (26), 220 (39), 206 (16), 205 (18), 192 (39), 191 (28), 181 (68), 177 (34), 175 (20), 165 (34), 164 (35), 157 (41), 149 (40), 147 (54), 135 (33), 121 (40), 119 (29), 108 (43), 107 (36), 106 (27), 105 (25), 93 (70), 92 (30), 91 (53), 90 (22), 79 (100), 78 (58), 77 (76), 75 (43); anal. C 53.23, H 4.24, Br 17.71%; calcd for $C_{20}H_{19}BrO_7$; C 53.29; H 4.28; Br 17.67%.

(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one ***(6e)***



Yield 3.51g (86%); light yellow solid; mp 146-148°C; ^{1}H NMR (DMSO-d$_6$) δ 7.39 (1H, s, H-2''), 7.36 (1H, d, *J* = 16.0 Hz, H-2), 7.30 (1H, d, *J* = 8.4 Hz, H-6''), 7.24 (1H, s, H-6'), 7.17 (1H, d, *J* = 16.0 Hz, H-3), 7.09 (1H, s, H-3'), 7.00 (1H, d, *J* = 8.4 Hz, H-5''), 3.85, 3.81, 3,80 (12H, 3s, 4 × OCH$_3$-4',5',3'', 4''); EIMS m/z 409 [M+2] (21), 408 [M+1] (100), 407 [M]$^+$ (37), 406 (98), 393 (15), 391 (15), 377 (14), 375 (14), 327 (26), 299 (15), 284 (15), 269 (14), 268 (29), 245 (15), 243 (15), 241 (15), 225 (10), 191 (79), 165 (15), 163 (23), 159 (12), 157 (12), 152 (10), 150 (20), 139 (22), 119 (21), 118 (16), 105 (15), 102 (13), 93 (15), 91 (26), 89 (23), 77 (41); anal. C 56.04; H 4.70; Br 19.62%, calcd for C$_{19}$H$_{19}$BrO$_5$, C 55.98; H 4.67; Br 19.67%.

(E)-1-(6-Bromo-7-methoxy-4-methyl-2H-1,3-benzodioxol-5-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one ***(6f)****:*

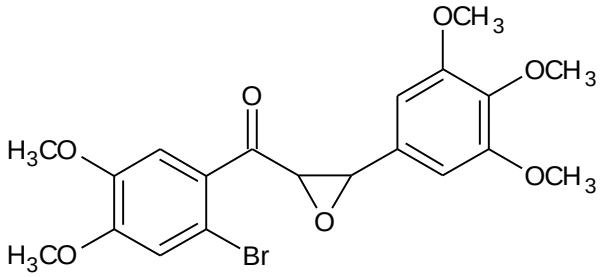


Yield 3.52 g (78%); yellow solid; mp 125-127°C; ^{1}H NMR (DMSO-d$_6$) δ 7.37 (1H, d, *J* = 2.0 Hz, H-2''), 7.28 (1H, dd, *J* = 8.4 Hz, *J* = 2.0 Hz, H-6''), 7.23 (1H, d, *J* = 16.1 Hz, H-2), 6.98 (1H, d, *J* = 8.4 Hz, H-5''), 6.97 (1H, d, *J* = 16.1 Hz, H-3), 6.17 (2H, s, OCH$_2$O), 3.90, 3.81, 3.80, 3.77 (12H, 4s, 4 × OCH$_3$-4',7',3'',4''); EIMS m/z 453 [M+2] (22), 452 [M+1] (96), 451 [M]$^+$ (31), 450 (96), 437 (10), 435 (10), 421 (10), 419 (10), 371 (45), 341 (17), 328 (22), 313 (58), 312 (79), 287 (16), 285 (16), 191 (100), 164 (27), 163 (21), 151 (15), 148 (10), 147 (10), 133 (11), 132 (8), 119 (8), 118 (7), 77 (7); anal. C 53.23; H 4.24; Br 17.71%, calcd for C$_{20}$H$_{19}$BrO$_7$, C 53.30; H 4.27; Br 17.63%.

General Procedure for the Synthesis of Epoxides 7 according to Patent.[3] Hydrogen peroxide (30%, 0.6 ml) was added to a vigorously stirred suspension of chalcone **6** (4 mmol) in EtOH (15 ml) and NaOH (1 *N*, 1.9 ml) at ~20 °C. The mixture was stirred at 30 °C for 3 h and left

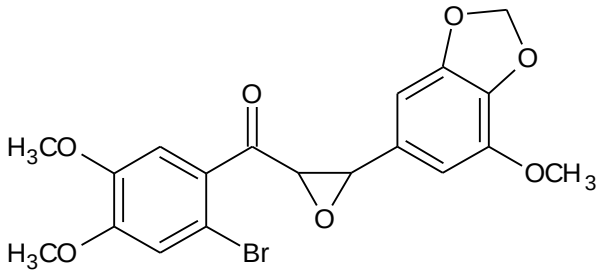
for 24 h at ~20 °C, then additional portions of NaOH (1 *N*, 1.9 ml) and H_2O_2 (30%, 0.6 ml) were added, and stirring was continued for 6 h at ~20 °C. Finally, the last portions of NaOH (1 *N*, 1.9 ml) and H_2O_2 (30%, 0.6 ml) were added followed by strirring for 24 h. The solid was filtered, washed with EtOH, water and dried at reduced pressure to afford epoxy ketones **7.**

*(2-Bromo-4,5-dimethoxyphenyl)[3-(3,4,5-trimethoxyphenyl)oxiran-2-yl]methanone (**7a**):*



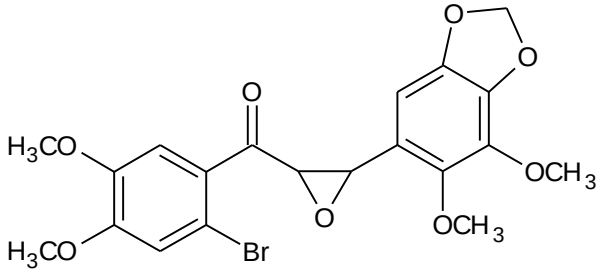
Yield 1.41 g (78%); yellow solid; mp 144-146°C; ^{1}H NMR (DMSO-d_6) δ 7.27 (1H, s, H-6'), 7.26 (1H, s, H-3'), 6.74 (2H, s, H-2",6"), 4.48 (1H, d, *J* = 1.6 Hz, H-2), 4.09 (1H, d, *J* = 1.6 Hz, H-3), 3.85, 3.80, 3,78, 3.66 (15H, 4s, 5 × OCH_3-4',5',3", 4", 5"); EIMS m/z 455 [M+2] (2), 454 [M+1] (12), 453 $[M]^+$ (2), 452 (12), 316 (15), 315 (13), 285 (14), 245 (95), 244 (11), 243 (100), 215 (10), 209 (34), 181 (66), 165 (18), 157 (11), 149 (25), 135 (10), 108 (24), 93 (13), 79 (14), 77 (11); anal. C 53.00; H 4.67; Br 17.63%, calcd for $C_{20}H_{21}BrO_7$, C 52.87; H 4.63; Br 17.73%.

*(2-Bromo-4,5-dimethoxyphenyl)[3-(7-methoxy-2H-1,3-benzodioxol-5-yl)oxiran-2-yl]methanone (**7b**):*



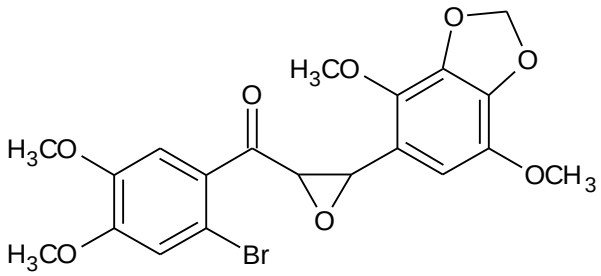
Yield 1.21 g, (69%), yellow solid, mp 148-150°C; ^{1}H NMR (DMSO-d_6) δ 7.27 (1H, s, H-6'), 7.26 (1H, s, H-3'), 6.78 (1H, d, *J* = 1.3 Hz, H-4"), 6.65 (1H, d, *J* = 1.3 Hz, H-6"), 6.01 (2H, br. s, OCH_2O), 4.47 (1H, d, *J* = 1.9 Hz, H-2), 4.07 (1H, d, *J* = 1.9 Hz, H-3), 3.85, 3.83, 3,80 (9H, 3s, 3 × OCH_3-4',5',7"); EIMS m/z 439 [M+2] (1), 438 [M+1] (8), 437 $[M]^+$ (1), 436 (8), 300 (24), 299 (16), 285 (6), 245 (96), 244 (10), 243 (100), 215 (10), 193 (19), 179 (21), 165 (42), 157 (11), 149 (25), 135 (11), 93 (12), 79 (12), 77 (15); anal. C 52.19, H 3.92, Br 18.27%, calcd for $C_{19}H_{17}BrO_7$, C 52.27; H 3.96; Br 18.21%.

*(2-Bromo-4,5-dimethoxyphenyl)[3-(6,7-dimethoxy-2H-1,3-benzodioxol-5-yl)oxiran-2-yl]methanone (**7c**):*



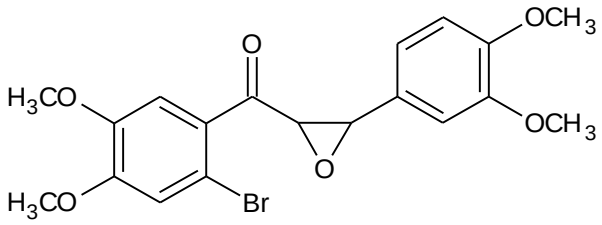
Yield 1.66 g (89%); yellow solid; mp 179-181°C; ^{1}H NMR (DMSO-d_6) δ 7.32 (1H, s, H-6'), 7.27 (1H, s, H-3'), 6.42 (1H, s, H-4''), 6.01 and 6.02(2H, 2s, OCH_2O), 4.44 (1H, d, J = 1.9 Hz, H-2), 4.15 (1H, d, J = 1.9 Hz, H-3), 3.94 (3H, s, OCH_3-6''), 3.85, 3,80 (6H, 2s, 2 × OCH_3-4',5'), 3.71 (3H, s, OCH_3-7''); EIMS m/z 469 [M+2] (8), 468 [M+1] (36), 467 [M]$^+$ (8), 466 (36), 421 (21), 419 (21), 411 (18), 409 (18), 245 (97), 244 (11), 243 (100), 223 (28), 195 (68), 180 (19), 165 (14), 157 (11), 149 (25), 121 (11), 93 (16), 79 (16), 77 (15); anal. C 51.41; H 4.10; Br 17.10%; calcd for $C_{20}H_{19}BrO_8$, C 51.44; H 4.12; Br 17.02%.

*(2-Bromo-4,5-dimethoxyphenyl)[3-(4,7-dimethoxy-2H-1,3-benzodioxol-5-yl)oxiran-2-yl]methanone (**7d**):*



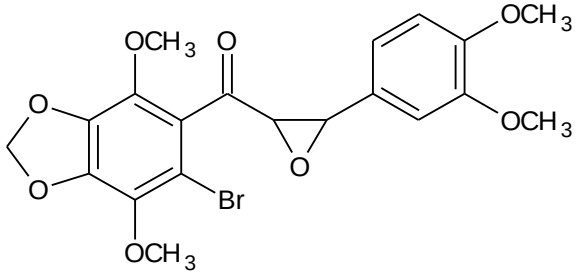
Yield 1.44 g (77%); yellow solid; mp 152-155°C; ^{1}H NMR (DMSO-d_6) δ 7.30 (1H, s, H-6'), 7.27 (1H, s, H-3'), 6.44 (1H, s, H-6''), 6.04 and 6.05(2H, 2s, OCH_2O), 4.45 (1H, d, J = 1.9 Hz, H-2), 4.16 (1H, d, J = 1.9 Hz, H-3), 3.85, 3,84, 3.81, 3.76 (12H, 4s, 4 × OCH_3-4',5', 4'', 7''); EIMS m/z 469 [M+2] (1), 468 [M+1] (11), 467 [M]$^+$ (1), 466 (11), 421 (3), 419 (3), 330 (12), 245 (97), 244 (10), 243 (100), 223 (45), 195 (72), 180 (11), 165 (14), 157 (8), 149 (20), 135 (15), 121 (10), 93 (28), 79 (20), 77 (24); anal. C 51.41; H 4.10; Br 17.10%, calcd for $C_{20}H_{19}BrO_8$, C 51.46; H 4.11; Br 17.04%.

*(2-Bromo-4,5-dimethoxyphenyl)[3-(3,4-dimethoxyphenyl)oxiran-2-yl]methanone (**7e**):*



Yield 1.10 g (65%); light yellow solid; mp 108-110°C; ^{1}H NMR (DMSO-d$_6$) δ 7.27 (1H, s, H-6'), 7.26 (1H, s, H-3'), 7.00 (1H, d, *J* = 8.2 Hz, H-6''), 6.96 (1H, d, *J* = 8.2 Hz, H-5''), 6.96 (1H, br. s, H-2''), 4.48 (1H, d, *J* = 1.5 Hz, H-2), 4.07 (1H, d, *J* = 1.5 Hz, H-3), 3.85, 3.79, 3,76 (12H, 3s, 3 × OCH_3-4',5',3'', 4''); EIMS m/z 425 [M+2] (4), 424 [M+1] (20), 423 [M]$^+$ (4), 422 (20), 367 (19), 365 (19), 286 (13), 245 (97), 244 (12), 243 (100), 241 (11), 179 (13), 165 (24), 151 (78), 149 (39), 121 (13), 119 (15), 107 (24), 93 (22), 92 (20), 79 (27), 77 (37); anal. C 53.92; H 4.52; Br 18.88%, calcd for $C_{19}H_{19}BrO_6$, C 53.87; H 4.50; Br 18.94%.

*(6-Bromo-4,7-dimethoxy-2H-1,3-benzodioxol-5-yl)[3-(3,4-dimethoxyphenyl)oxiran-2-yl]methanone (**7f**):*



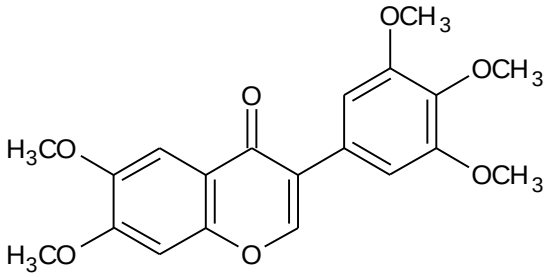
Yield 1.61 g (86%); yellow solid; mp 124-126°C; ^{1}H NMR (DMSO-d$_6$) δ 6.98 (1H, dd, *J* = 8.3 Hz, *J* = 1.8 Hz, H-6''), 6.94 (1H, d, *J* = 8.3 Hz, H-5''), 6.87 (1H, d, *J* = 1.8 Hz, H-2''), 6.15 and 6.16(2H, 2s, OCH_2O), 4.20 (1H, d, *J* = 1.8 Hz, H-2), 3.99 (1H, d, *J* = 1.8 Hz, H-3), 3.76, 3.75 (12H, 2s, 4 × OCH_3-4',7',3'',4''); EIMS m/z 469 [M+2] (7), 468 [M+1] (32), 467 [M]$^+$ (7), 466 (32), 411 (25), 409 (25), 387 (17), 330 (56), 329 (48), 289 (97), 287 (100), 285 (15), 274 (16), 272 (16), 262 (15), 260 (15), 206 (29), 192 (16), 178 (18), 165 (22), 151 (31), 135 (10), 133 (9), 107 (14), 92 (10), 77 (12); anal. C 51.41; H 4.10; Br 17.10%, calcd for $C_{20}H_{19}BrO_8$, C 51.49;
H 4.12; Br 16.97%.

General Rearrangement Procedure for the Synthesis of 2,3-Diaryl-3-oxopropanals (8) according to ref. 4. Boron trifluoride etherate (0.39 ml, 3 mmol) was added dropwise to an ice-

cooled solution of chalcone epoxide **7** (3 mmol) in absolute dichloromethane (15 ml) under argon and this was stirred for 3 h at 20 ^{o}C. The reaction was then quenched with 5% aqueous $NaHCO_3$ solution (15 ml) and extracted with chloroform (2 x 5 ml). The organic layer was washed with water (2 x 15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded crude keto aldehydes **8** as oils. The products were roughly-purified by column chromatography from CH_2Cl_2 extract (EtOAc–hexane = 1:4, R_f=0.6). Yields: **8a** (86%), **8b** (92%), **8c** (95%), **8d** (21%), **8e** (86%), **8f** (88%). Compounds **8** was used for the next step without further purification.

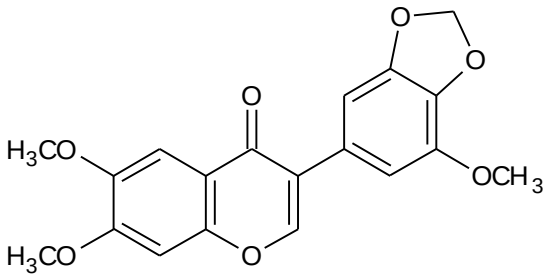
General Procedure for the Synthesis of Isoflavones according to ref. 5. A mixture of keto aldehyde **8** (5 mmol), CuI (95 mg , 0.5 mmol), K_2CO_3 (1.38 g, 10 mmol) and 2-picolinic acid (123 mg, 1 mmol) in dry DMF (30 ml) in a flask filled with argon was stired at 135-140 °C for 8 h. The mixture was diluted with H_2O (100 ml) and extracted by AcOEt (3x50 ml). The organic layer was dried (Na_2SO_4), filtered, evaporated under vacuum and purified by column chromatography (hexane/EtOAc=3/1, R_f=0.3-0.4) to afford the target izoflavones **9**.

*6,7-Dimethoxy-3-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one (**9a**):*



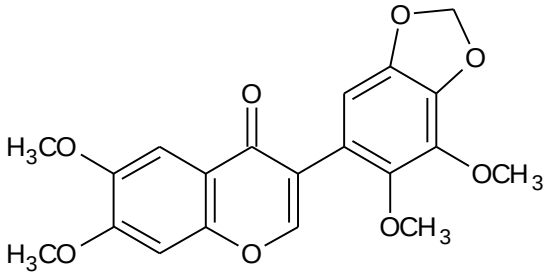
Yield 0.71 g (38%); yellowish solid; mp 172-174°C; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s, H-2), 7.64 (1H, s, H-5), 6.90 (1H, s, H-8), 6.82 (2H, s, H-2',6'), 4.01, 3.99 (6H, 2s, 2 × OCH_3-6,7), 3.91 (6H, s, 2 × OCH_3-3',5'), 3.89 (3H, s, OCH_3-4'); ^{13}C NMR ($CDCl_3$) δ 175.30, 154.44, 153.15, 152.27, 152.16, 147.77, 138.06, 127.55, 124.53, 117.81, 106.26, 104.73, 99.46, 60.80, 56.42, 56.30, 56.16; EIMS m/z 373 [M+1] (25), 372 [M]$^{+}$ (100), 358 (10), 357 (48), 329 (10), 271 (20), 171 (14), 149 (17), 134 (10); anal. C 64.51; H 5.41%, calcd for $C_{20}H_{20}O_7$, C 64.42; H 5.36%.

*6,7-Dimethoxy-3-(7-methoxy-1,3-benzodioxol-5-yl)-4H-chromen-4-one (**9b**):*



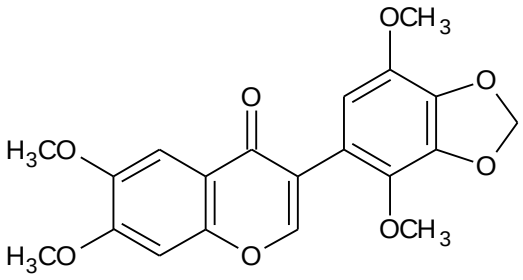
Yield 0.46 g (26%); white solid; mp 198-201°C; ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, s, H-2), 7.62 (1H, s, H-5), 6.88 (1H, s, H-8), 6.84 (1H, s, H-6'), 6.72 (1H, s, H-4'), 6.00 (2H, s, OCH_2O), 3.99 (6H, 2s, 2 × OCH_3-6,7), 3.94 (3H, s, OCH_3-7'); ^{13}C NMR ($CDCl_3$) δ 175.24, 154.37, 152.11, 148.78, 147.71, 143.49, 135.26, 126.20, 124.35, 117.77, 108.83, 104.77, 103.11, 101.50, 99.44, 56.57, 56.40, 56.29; EIMS m/z 357 [M+1] (23), 356 [M]$^{+}$ (100), 355 (21), 341 (1), 327 (3), 326 (2), 176 (5); anal. C 64.04; H 4.53%, calcd for $C_{19}H_{16}O_7$, C 63.96; H 4.48%.

*6,7-Dimethoxy-3-(6,7-dimethoxy-1,3-benzodioxol-5-yl)-4H-chromen-4-one (**9c**):*



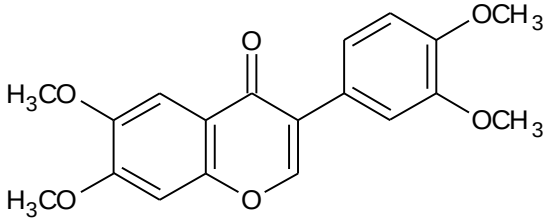
Yield 0.46 g (24%); yellow greenish solid; mp 204-206°C; ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, s, H-2), 7.62 (1H, s, H-5), 6.89 (1H, s, H-8), 6.56 (1H, s, H-4'), 5.96 (2H, s, OCH_2O), 4.05 (3H, s, OCH_3-6'), 4.00, 3.99 (6H, 2s, 2 × OCH_3-6,7),3.68 (3H, s, OCH_3-7'); ^{13}C NMR ($CDCl_3$) δ 175.37, 154.26, 153.76, 152.25, 147.59, 145.19, 144.57, 137.94, 137.65, 121.29, 118.28, 117.85, 104.88, 104.48, 101.45, 99.56, 61.22, 60.03, 56.39, 56.31; EIMS m/z 387 [M+1] (23), 386 [M]$^{+}$ (90), 371 (7), 357 (8), 356 (29), 355 (100), 343 (5), 340 (9), 313 (5), 181 (16), 178 (9); anal. C 62.18; H 4.70%, calcd for $C_{20}H_{18}O_8$, C 62.06; H 4.65%.

*6,7-Dimethoxy-3-(4,7-dimethoxy-1,3-benzodioxol-5-yl)-4H-chromen-4-one (Glaziovianin A (**9d**):*



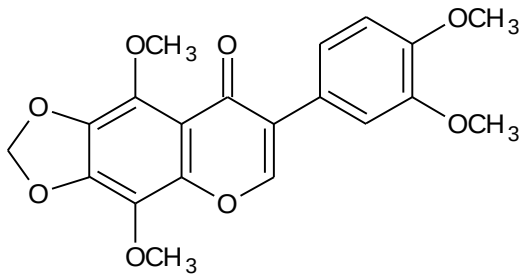
Yield 0.62 g (32%); yellowish solid; mp 139-141°C; ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, s, H-2), 7.62 (1H, s, H-5), 6.89 (1H, s, H-8), 6.53 (1H, s, H-6'), 6.03 (2H, s, OCH_2O), 4.00, 3.99 (6H, 2s, 2*OCH_3-6,7), 3.86, 3.87 (6H, 2s, 2 × OCH_3-4',7'); ^{13}C NMR ($CDCl_3$) δ 175.37, 154.27, 153.41, 152.28, 147.60, 139.10, 138.95, 137.04, 136.75, 121.68, 118.02, 117.79, 110.05, 104.88, 101.80, 99.52, 60.14, 56.83, 56.39, 56.32; EIMS m/z 387 [M+1] (24), 386 [M]$^{+}$ (100), 371 (7), 357 (7), 356 (12), 355 (49), 313 (10), 206 (12), 205 (15), 181 (50), 137 (10); anal. C 62.18; H 4.70%, calcd for $C_{20}H_{18}O_8$, C 62.08; H 4.66%.

*6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-4H-chromen-4-one (**9e**):*



Yield 0.41 g (24%); dark yellow solid; mp 172-174°C; ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, s, H-2), 7.64 (1H, s, H-5), 7.25 (1H, d, *J* = 2.0 Hz, H-2'), 7.06 (1H, dd, *J* = 2.0 Hz, *J* = 8.3 Hz, H-6'), 6.93 (1H, d, *J* = 8.3 Hz, H-5'), 6.89 (1H, s, H-8), 4.00, 3,99 (6H, 2s, 2 × OCH_3-6,7), 3.94, 3,92 (6H, 2s, 2 × OCH_3-3',4'); ^{13}C NMR ($CDCl_3$) δ 175.52, 154.35, 152.21, 151.95, 149.02, 148.71, 147.70, 124.81, 124.32, 120.88, 117.86, 112.51, 111.11, 104.79, 99.46, 56.41, 56.30, 55.90; EIMS m/z 343 [M+1] (19), 342 [M]$^{+}$ (100), 327 (13), 299 (6), 296 (5), 256 (7), 171 (6), 156 (5), 119 (9), 91 (8); anal. C 66;66, H 5.30%, calcd for $C_{19}H_{18}O_6$, C 66.71; H 5.33%.

7-(3,4-dimethoxyphenyl)-4,9-dimethoxy-8H-[1,3]dioxolo[4,5-g]chromen-8-one (iso-Glaziovianin A) ***(9f)****:*



Yield 0.95 g (49%); light-brown solid; mp 176-178 °C; ^{1}H NMR (DMSO-d_6) δ 7.15 (1H, s, H-2), 6.93 (1H, d, *J* = 8.2 Hz, H-5'), 6.89 (1H, d, *J* = 2.0 Hz, H-2'), 6.81 (1H, dd, *J* = 2.0 Hz, *J* = 8.1 Hz, H-6'), 6.22 (2H, s, OCH_2O), 3.89 (3H, s, OCH_3-9), 3.77, 3.73 (6H, 2s, 2 × OCH_3-3',4'), 3.25 (3H, s, OCH_3-4); ^{13}C NMR (DMSO-d6) δ 157.20, 148.05, 147.75, 146.13, 142.46, 140.41, 140.21, 134.25, 128.96, 127.18, 121.29, 117.14, 113.60, 110.88, 108.57, 103.41, 60.94, 60.01, 55.57; EIMS m/z 387 [M+1] (22), 386 $[M]^+$ (100), 371 (16), 358 (34), 357 (10), 356 (12), 344 (8), 343 (54), 328 (6), 193 (7), 135 (12), 128 (10), 127 (10); anal. C 62.18; H 4.70%, calcd for $C_{20}H_{18}O_8$, C 62.12; H 4.67%.

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