Bisphenols from Furfurals by Organocatalysis and Gold Catalysis

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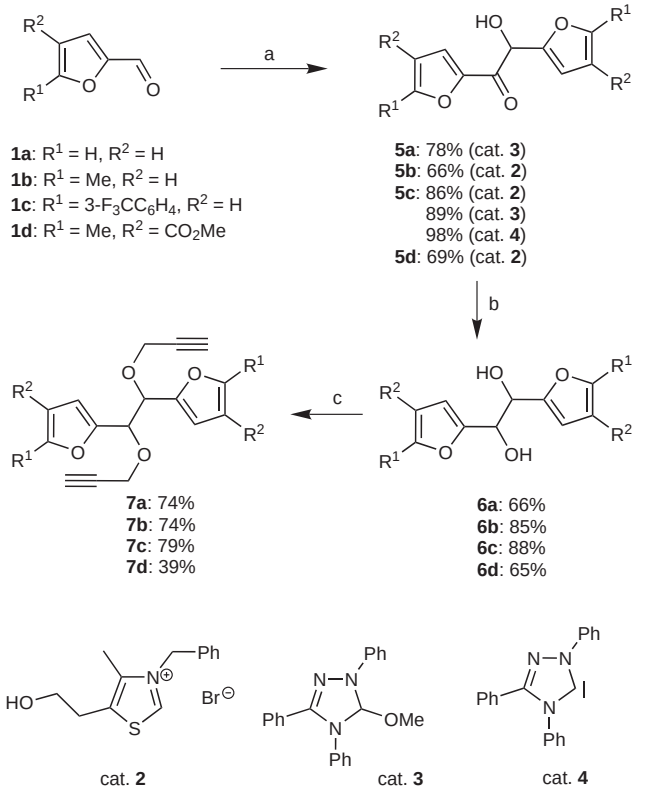
Abstract: Four different benzoins were formed from furfurals by organocatalysis with heterocyclic carbenes, reduced to the diols and converted into propargyl ethers. The gold-catalyzed cyclization exclusively gave bisphenols of the bisdihydroisobenzofuran type.

Key words: alkynes, furans, gold catalysis, organocatalysis, triazolium salts

Furfural and hydroxymethylfurufal are renewable resources from carbohydrate feedstocks,[2] and they can easily be converted into other furfural derivatives. Organocatalysis by N-heterocyclic carbenes derived from thiazolium salts and triazoles is an excellent tool for an efficient benzoin reaction.[3] In gold-catalyzed[4] reactions furans tethered to alkynes can efficiently be cycloisomerized to phenols.[5] We wanted to combine these principles in order to investigate the synthesis of more complex fine chemicals from furfurals.

We chose four substrates, the unsubstituted furfural **1a**, the alkyl derivative **1b**, the aryl derivative **1c**, and the acceptor-substituted **1d**. The organocatalyzed benzoin reaction delivered best results with catalyst **4**, but with catalyst **2** and catalyst **3** still much better results than with the classical cyanide catalyst were obtained (for example, with KCN only 15% of **5b** were isolated).[6] Next step was the reduction to the diols **6**, here mixtures of diastereomers were obtained; since a proof of principle was the aim, we did not try to optimize the ratio of diastereomers, especially as some explorative experiments showed that the furan oxygen atoms seem to interfere with the known diastereoselectivity of α-hydroxy ketone reduction. Then followed a two-fold ether synthesis to deliver the propargyl ethers **7**.[7] Only for **7d** the reaction conditions also caused partial transesterification to the propargyl ester, thus the reduced yield. In the propargylation step only terminal alkynes were used, from the previous work on the phenol synthesis it was known that internal alkynes do not react.[5]

A crystal structure analysis of the major diastereomer of **7d** could be obtained.[8] It allowed a safe assignment of the configuration for this *anti*-configurated test substrate.



Scheme 1 *Reagents and conditions*: a) cat. **2**: 5 mol% cat., Et_3N, EtOH, reflux; cat. **3** and **4**: 5 mol%, 10 mol% K_2CO_3, THF; b) $NaBH_4$, MeOH; for **6c**: $LiAlH_4$, Et_2O, with $NaBH_4$ only 60% yield; c) $HCCCH_2Br$, NaH, DMF.

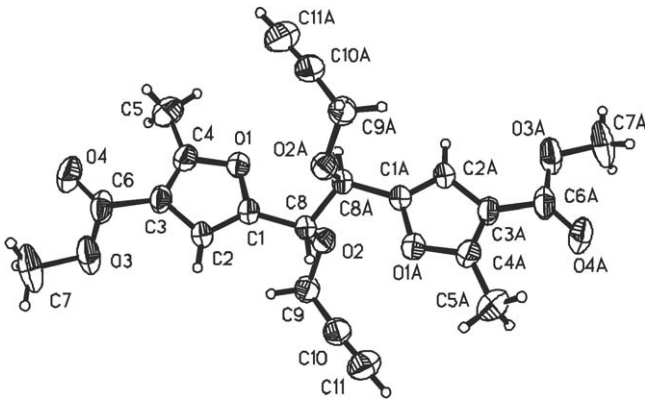


Figure 1 Solid-state structure of **7d**

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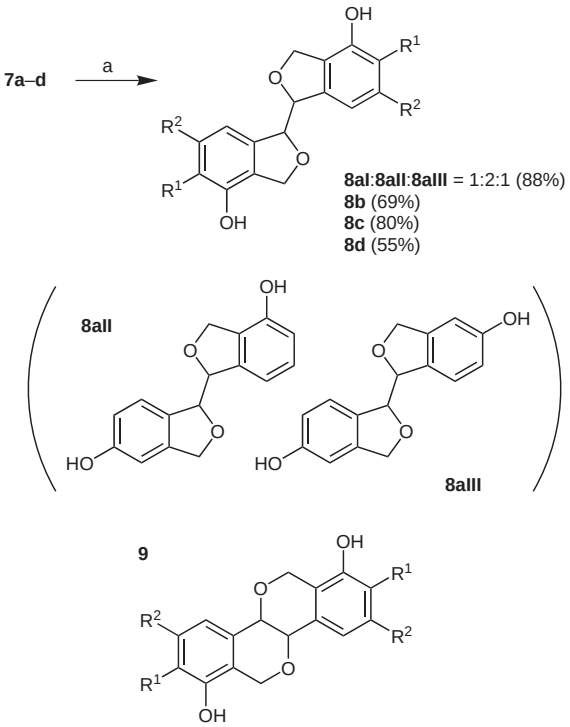
Then we investigated the gold-catalyzed cycloisomerization. All reactions readily proceeded with the simple $AuCl_3$ catalyst. The closure of the five-membered heterocyclic ring in **8** is the exclusive reaction pathway and we could not find products of type **9** with a six-membered heterocyclic ring. As one would expect for **7a**, a mixture of three constitutional isomers **8aI**, **8aII**, and **8aIII** was formed.[5a] No intramolecular hydroarylation[9] was observed. The assignment of the products to **8** is based on the mass spectra of these products. The strongest fragmentation is the symmetric cleavage [149 (100) for **8b**, 279 (100) for **8c** and 207 (100) for **8d**]. This process, generating a well-stabilized benzylic carboxonium ion, one would expect in **8**, but it would be very difficult to explain in **9**. The reaction of **7d** to **8d** gives an NMR conversion similar to the other reactions, but due to impurities that were difficult to remove two columns were necessary, which reduced the amount of isolated material.



Scheme 2 *Reagents and conditions*: a) 5 mol% $AuCl_3$, CH_2Cl_2.

Future challenges will be the enantioselective organocatalysis to deliver enantiomerically pure **5** and the diastereoselective reduction of **5** to diastereomerically pure **6**.

1,2-Di(furan-2-yl)-2-hydroxyethanon (5a)

To stirred furfural (1.00 g, 10.4 mmol) catalyst **3** (29.7 mg, 1.04 μmol, 1 mol%) was added. Significant heat was evolved and after 2 min a brown solid started to separate. After 30 min the latter was dissolved in CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and the solvent removed in vacuo to yield known **5a** (78%).[6]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19 (br s, 1 H), 5.80 (s, 1 H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.54 (dd, *J* = 3.7, 1.7 Hz, 1 H), 6.40 (d, *J* = 3.3 Hz, 1 H), 7.25 (dd, *J* = 3.7, 0.8 Hz, 1 H), 7.37 (dd, *J* = 1.8, 0.8 Hz, 1 H), 7.61 (dd, *J* = 1.7, 0.8 Hz, 1 H).

2-[2-(Furan-2-yl)-1,2-bis(prop-2-ynyloxy)ethyl]furan (7a)

Compound **5a** (577 mg, 3.00 mmol) was dissolved in MeOH (10 mL) and $NaBH_4$ (171 mg, 4.50 mmol) was added at 0 °C with stirring. Then stirring was continued for 1 h at r.t., H_2O was added, after extraction with CH_2Cl_2 the organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the crude product purified by column chromatography on silica gel (PE–EtOAc, 2:1, R_f = 0.15). Thus **6a** (384 mg, 66%) was obtained as a colorless liquid of two diastereomers in a ratio of 1:0.2.

Compound **6a** (384 mg, 2.00 mmol) was dissolved in DMF (10 mL), NaH (144 mg, 6.00 mmol) and after 10 min at 0 °C propargyl bromide (668 μL of a 80% solution in toluene, 6.00 mmol) were added. After 3 h at r.t. a sat. NH_4Cl solution was added and the product was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. After removal of the solvent the product was isolated by column chromatography on silica gel (PE–EtOAc, 5:1). Thus **7a** (401 mg, 74%) as a yellow solid was obtained as a 1:0.2 mixture of diastereomers.

Major Diastereomer of 7a

R_f = 0.30 (PE–EtOAc, 4:1).

Mp 82–85 °C.

IR (film): 3239, 2906, 2115, 1504, 1359, 1226, 1148, 1067, 1015, 924, 882, 753, 731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (t, *J* = 2.4 Hz, 2 H), 3.92 (dd, *J* = 16.0, 2.4 Hz, 2 H), 4.10 (dd, *J* = 16.0, 2.4 Hz, 2 H), 5.01 (s, 2 H), 6.37 (dd, *J* = 3.3, 1.9 Hz, 2 H), 6.45 (dd, *J* = 3.3, 0.9 Hz, 2 H), 7.44 (dd, *J* = 1.9, 0.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 55.95 (t, 2 C), 73.64 (d, 2 C), 74.69 (d, 2 C), 79.06 (s, 2 C), 110.32 (d, 2 C), 110.79 (d, 2 C), 142.80 (d, 2 C), 150.63 (s, 2 C).

Anal. Calcd for $C_{16}H_{14}O_4$ (270.28): C, 71.10; H, 5.22. Found: C, 70.86; H, 5.33.

MS/ESI-EM: *m*/*z* calcd $[C_{16}H_{14}O_4+Na]^+$: 293.0784; found: 293.0786.

Minor Diastereomer of 7a

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (t, *J* = 2.4 Hz, 2 H), 4.07 (dd, *J* = 15.9, 2.4 Hz, 2 H), 4.30 (dd, *J* = 15.9, 2.4 Hz, 2 H), 5.05 (s, 2 H), 6.22 (dd, *J* = 3.2, 1.8 Hz, 2 H), 6.24 (dd, *J* = 3.3, 0.9 Hz, 2 H), 7.32 (dd, *J* = 1.8, 0.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.53 (t, 2 C), 74.89 (d, 2 C), 75.00 (d, 2 C), 79.26 (s, 2 C), 110.07 (d, 2 C), 110.10 (d, 2 C), 142.74 (d, 2 C), 150.04 (s, 2 C).

MS (EI, 70 eV): *m*/*z* (%) = 270 (3) [M^+], 135 (100).

1,3-Dihydro-1-(1,3-dihydro-4-hydroxyisobenzofuran-1-yl)isobenzofuran-4-ol (8aI), 1,3-Dihydro-1-(1,3-dihydro-5-hydroxyisobenzofuran-1-yl)isobenzofuran-5-ol (8aII), and 1,3-Dihydro-1-(1,3-dihydro-5-hydroxyisobenzofuran-1-yl)isobenzofuran-4-ol (8aIII)

To **8a** (242 mg, 895 μmol) in CH_2Cl_2 (5 mL) a stock solution of $AuCl_3$ (81.4 mg of a 10% solution in MeCN, 26.8 μmol, 3 mol%) was added. After 10 min silica was added, the solvent was removed in vacuo, and the material was placed on top of a silica gel column. Chromatography (PE–EtOAc, 2:1) delivered **8aI**, **8aII**, and **8aIII** in a total yield of 214 mg (88%) and a ratio of 1:2:1. As pure fractions **8aI** (40 mg), **8aII** (80 mg), and **8aIII** (30 mg) could be separated as yellow-brown solids. All these products were mixtures of diastereomers.

Compound 8aI
R_f = 0.30 (PE–EtOAc, 1:1).

Mp >240 °C (dec.).

IR (film): 3230, 2867, 1601, 1468, 1290, 1003, 962, 828, 724, 658, 589 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 4.79 (d, *J* = 11.8 Hz, 2 H), 4.94 (d, *J* = 11.8 Hz, 2 H), 5.38 (d, 2 H), 6.43 (d, *J* = 7.4 Hz, 2 H), 6.75 (d, *J* = 7.9 Hz, 2 H), 7.03 (dd, *J* = 7.9, 7.4 Hz, 2 H), 8.48 (br s, 2 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 72.24 (t, 2 C), 87.97 (d, 2 C), 114.16 (d, 2 C), 115.03 (d, 2 C), 127.64 (s, 2 C), 141.49 (s, 2 C), 152.25 (s, 2 C).

MS (EI, 70 eV): *m*/*z* (%) = 270 (1) [M^+], 135 (100).

MS/ESI-EM: *m*/*z* calcd [$C_{16}H_{14}O_4$+Na]$^+$: 293.0784; found: 293.0775.

Compound 8aII
R_f = 0.25 (PE–EtOAc, 1:1).

Mp 215–218 °C.

IR (film): 3228, 2877, 1597, 1470, 1288, 1224, 1004, 917, 669 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 4.76 (d, *J* = 12.1 Hz, 1 H), 4.76 (d, *J* = 12.0 Hz, 1 H), 4.87 (d, *J* = 12.1 Hz, 1 H), 4.94 (d, *J* = 12.0 Hz, 1 H), 5.28–5.29 (m, 1 H), 5.33–5.34 (m, 1 H), 6.47 (d, *J* = 7.5 Hz, 1 H), 6.66 (d, *J* = 8.2 Hz, 1 H), 6.70–6.72 (m, 2 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 7.04 (dd, *J* = 8.0, 7.5 Hz, 1 H), 8.41 (br s, 1 H), 8.48 (br s, 1 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 72.18 (t), 73. 75 (t), 87.05 (d), 88.11 (d), 108.29 (d), 114.16 (d), 114.95 (d), 114.99 (d), 123.65 (d), 127.56 (s), 129.42 (d), 129.98 (s), 141.64 (s), 143 33 (s), 152.24 (s), 158.43 (s).

MS (EI, 70 eV): *m*/*z* (%) = 270 (0.3) [M^+], 135 (100).

MS/ESI-EM: *m*/*z* calcd [$C_{16}H_{14}O_4$+Na]$^+$: 293.0784; found: 293.0774.

Anal. Calcd for $C_{16}H_{14}O_4$ (270.28): C, 71.10; H, 5.22. Found: C, 70.63; H, 5.54.

Compound 8aIII
R_f = 0.22 (PE–EtOAc, 1:1).

Mp 231–233 °C.

IR (film): 3280, 2867, 1601, 1468, 1290, 1003, 962, 828, 724, 658, 589 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 4.72 (d, *J* = 12.2 Hz, 2 H), 4.86 (d, *J* = 12.2 Hz, 2 H), 5.23 (s, 2 H), 6.67 (d, *J* = 8.1 Hz, 2 H), 6.70–6.71 (m, 2 H), 6.75 (d, *J* = 8.1 Hz, 2 H), 8.41 (br s, 2 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 73.71 (t, 2 C), 87.23 (d, 2 C), 108.30 (d, 2 C), 114.96 (d, 2 C), 123.68 (d, 2 C), 130.22 (s, 2 C), 143.32 (s, 2 C) 158.44 (s, 2 C).

MS (EI, 70 eV): *m*/*z* (%) = 270 (0.4) [M^+], 135 (100).

MS/ESI-EM: *m*/*z* calcd [$C_{16}H_{14}O_4$+Na]$^+$: 293.0784; found: 293.0780.

2-Hydroxy-1,2-bis(5-methylfuran-2-yl)ethanone (5b)
Methylfurfural (10.0 g, 90.8 mmol) und catalyst **2** (142 mg, 4.52 mmol, 5 mol%) were dissolved in absolute EtOH (30 mL) and Et_3N (3.80 mL, 27.3 mmol) was added. The mixture was refluxed for 3 h and then placed in the freezer to crystallize the product. The crude product was recrystallized from EtOH. This yielded the known[6] **5b** (6.85 g, 69%) as pale-yellow crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (d, *J* = 1.0 Hz, 3 H), 2.38 (s, 3 H), 4.21 (br s, 1 H), 5.65 (s, 1 H), 5.91 (dq, *J* = 3.1, 1.0 Hz, 1 H), 6.14 (dq, *J* = 3.6, 0.9 Hz, 1 H), 6.25 (d, *J* = 3.1 Hz, 1 H), 7.12 (d, *J* = 3.6 Hz, 1 H).

2-Methyl-5-[2-(4-methylfuran-2-yl)-1,2-bis(prop-2-ynyloxy)ethyl]furan (7b)
Compound **5b** (2.52 g, 11.5 mmol) was dissolved in EtOH (30 mL), $NaBH_4$ (521 mg, 13.8 mmol) was slowly added and the mixture was stirred overnight at r.t. After hydrolysis with H_2O and extraction with Et_2O, the organic phase was washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The crude **6b** (2.18 g, 85%), a yellow liquid with a diastereomeric ratio of 1:0.4, was directly used in the next step.

To **6b** (2.17 g, 9.75 mmol) in absolute DMF (15 mL) NaH (705 mg, 29.3 mmol) was slowly added. After 25 min propargyl bromide (3.25 mL of a 80% solution in toluene, 4.36 g, 29.3 mmol) was added and the mixture was stirred at r.t. overnight. After quenching with H_2O, extraction with Et_2O and washing with brine, the organic phase was dried over $MgSO_4$, filtered, the solvent removed in vacuo, and the crude product purified by column chromatography on silica gel (PE–EtOAc–CH_2Cl_2, 30:1:2). Compound **7b** (2.15 g, 74%) was obtained as a slightly yellow solid. A small portion of pure diastereomer **7bI** could be isolated, the overall ratio of **7bI** and **7bII** is 1:0.4.

Compound 7bI
R_f = 0.13 (PE–EtOAc–CH_2Cl_2, 30:1:2).

Mp 120–121 °C.

IR (film): 3246, 2911, 2856, 2112, 1561, 1440, 1359, 1226, 1066, 1012, 933, 793, 686, 610 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 1.0 Hz, 6 H), 2.36 (t, *J* = 2.4 Hz, 2 H), 3.93 (dd, *J* = 15.9, 2.4 Hz, 2 H), 4.08 (dd, *J* = 15.9, 2.4 Hz, 2 H), 4.91 (s, 2 H), 5.95 (dq, *J* = 3.1, 1.0 Hz, 2 H), 6.33 (d, *J* = 3.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84 (q, 2 C), 55.76 (t, 2 C), 73.54 (d, 2 C), 74.48 (d, 2 C), 79.47 (s, 2 C), 106.37 (d, 2 C), 111.98 (d, 2 C), 148.83 (s, 2 C), 152.66 (s, 2 C).

Anal. Calcd for $C_{18}H_{18}O_4$ (298.33): C, 72.01; H, 6.10. Found: C, 72.47; H, 6.08.

MS (EI positive ion, 70 eV): *m*/*z* (%) = 298 (2) [M^+], 149 (100).

HRMS (EI positive ion, 70 eV): *m*/*z* calcd for $C_{18}H_{18}O_4$: 298.1205; found: 298.1198.

Compound 7bII
R_f = 0.09 (PE–EtOAc–CH_2Cl_2, 30:1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (d, *J* = 1.0 Hz, 6 H), 2.41 (t, *J* = 2.4 Hz, 2 H), 4.09 (dd, *J* = 15.9, 2.4 Hz, 2 H), 4.30 (dd, *J* = 15.9, 2.4 Hz, 2 H), 4.94 (s, 2 H), 5.79 (dq, *J* = 3.1, 1.0 Hz, 2 H), 6.10 (d, *J* = 3.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.71 (q, 2 C), 56.5 (t, 2 C), 74.77 (d, 2 C), 75.30 (d, 2 C), 79.68 (s, 2 C), 106.09 (d, 2 C), 111.10 (d, 2 C), 148.31 (s, 2 C), 152.55 (s, 2 C).

1,3-Dihydro-1-(1,3-dihydro-4-hydroxy-5-methylisobenzofuran-1-yl)-5-methylisobenzofuran-4-ol (8b)
To **7b** (60.0 mg, 200 μmol) in $CHCl_3$ (3 mL) a stock solution of $AuCl_3$ (25.4 mg of a 10% solution in MeCN, 8.38 μmol, 5 mol%) was added. After 15 min the solvent was removed in vacuo and the product was isolated by column chromatography on silica gel (PE–acetone–CH_2Cl_2,, 2:1:1). A portion of pure diastereomer **8bI** (13 mg) and a mixture of both diastereomers **8bI** and **8bII** (28 mg) was obtained as a pale-yellow solid (overall 69%, **8bI**:**8bII** = 1:0.4).

Compound 8bI

R_f = 0.37 (PE–acetone–CH_2Cl_2, 2:1:1)

Mp 230–232 °C.

IR (film): 3334, 2828, 1597, 1494, 1458, 1320, 1217, 1036, 927, 827, 769, 698 cm^{-1}.

^1H NMR (250 MHz, acetone-d_6): δ = 2.22 (s, 6 H), 4.78 (d, *J* = 11.9 Hz, 2 H), 4.94 (d, *J* = 11.9 Hz, 2 H), 5.31 (s, 2 H), 6.35 (d, *J* = 7.5 Hz, 2 H), 6.94 (d, *J* = 7.5 Hz, 2 H), 7.77 (br s, 2 H).

^{13}C NMR (62.9 MHz, acetone-d_6): δ = 15.84 (q, 2 C), 72.25 (t, 2 C), 87.94 (d, 2 C), 114.12 (d, 2 C), 124.36 (s, 2 C), 127.71 (s, 2 C), 130.88 (d, 2 C), 139.08 (s, 2 C), 149.82 (s, 2 C).

MS (EI positive ion, 70 eV): *m*/*z* (%) = 298 (0.8) [M^+], 149 (100).

HRMS (EI positive ion, 70 eV): *m*/*z* calcd for $C_{18}H_{18}O_4$: 298.1205; found: 298.1201.

Compound 8bII

R_f = 0.28 (PE–acetone–CH_2Cl_2, 2:1:1).

^1H NMR (300 MHz, acetone-d_6): δ = 1.19 (s, 6 H), 4.94 (d, *J* = 12.1 Hz, 2 H), 5.05 (d, *J* = 12.1 Hz, 2 H), 5.43 (s, 2 H), 6.77 (d, *J* = 7.5 Hz, 2 H), 6.98 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR (62.9 MHz, acetone-d_6): δ = 15.80 (q, 2 C), 72.50 (t, 2 C), 87.55 (d, 2 C), 113.60 (d, 2 C), 123.96 (s, 2 C), 127.30 (s, 2 C), 131.14 (d, 2 C), 139.85 (s, 2 C), 149.72 (s, 2 C).

1,2-Bis{5-[3-(trifluoromethyl)phenyl]furan-2-yl}ethane-1,2-diol (6c)

To 5-[3-(trifluormethyl)phenyl]furfural (500 mg, 2.08 mmol) and catalyst **3** (33.6 mg, 104 μmol) in EtOH (10 mL) at r.t. Et_3N (63.1 mg, 624 μmol) was added and the mixture was stirred overnight. The mixture was poured on ice water and extracted with CH_2Cl_2. After washing with aq $NaHCO_3$ and H_2O, drying over Na_2SO_4, filtration, and removal of the solvent in vacuo, the crude **5c** (430 mg, 86%), a yellow solid, was directly used in the next step.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.33 (br s, 1 H), 5.92 (s, 1 H), 6.57 (d, *J* = 3.5 Hz, 1 H), 6.72 (d, *J* = 3.5 Hz, 1 H), 6.87 (d, *J* = 3.8 Hz, 1 H), 7.44 (d, *J* = 3.5 Hz, 1 H), 7.42–7.54 (m, 4 H), 7.75–7.79 (m, 1 H), 7.81–7.83 (m, 1 H), 7.89 ('d', *J* = 8.1 Hz, 1 H), 7.93–7.95 (m, 1 H).

To **5c** (1.00 g, 2.08 mmol) in abs. Et_2O (50 mL) a suspension of $LiAlH_4$ (167 mg, 4.4 mmol) in Et_2O (20 mL) was added at 0 °C. Then the mixture was acidified with 0.1 N HCl and stirred until the colorless solid had dissolved. After extraction with Et_2O, the organic phase was dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Column chromatography on silica gel (PE–EtOAc, 3:1) delivered **6c** (880 mg, 88%) of a yellow solid with a diastereomeric ratio 1:0.22.

R_f = 0.15 (PE–EtOAc, 2:1).

IR (film): 3214, 1330, 1263, 1114, 1064, 1021, 785, 691 cm^{-1}.

Anal. Calcd for $C_{24}H_{16}F_6O_4$ (482.37): C, 59.76; H, 3.34. Found: C, 59.70; H, 3.52.

MS (EI positive ion, 70 eV): *m*/*z* (%): 482 (2) [M^+], 241 (100).

Compound 6cI

^1H NMR (300 MHz, $CDCl_3$): δ = 2.71 (br s, 2 H), 5.17 (s, 2 H), 6.46 (d, *J* = 3.6 Hz, 2 H), 6.69 (d, *J* = 3.6 Hz, 2 H), 7.41–7.47 (m, 4 H), 7.71 ('d', *J* = 7.5 Hz, 2 H), 7.77 (s, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 70.5 (d, 2 C), 107.2 (d, 2 C), 110.7 (d, 2 C), 120.5 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 124.0 (d, $J_{C–F}$ = 4 Hz, 2 C), 124.1 (s, $J_{C–F}$ = 274.0 Hz, 2 C), 126.8 (d, 2 C), 129.2 (d, 2 C), 131.2 (s, 2 C), 131.3 (s, $J_{C–F}$ = 33.0 Hz, 2 C), 152.5 (s, 2 C), 153.0 (s, 2 C).

Compound 6cII

^1H NMR (300 MHz, $CDCl_3$,): δ = 2.71 (br s, 2 H), 5.11 (s, 2 H), 6.44 (d, *J* = 3.6 Hz, 2 H), 6.65 (d, *J* = 3.6 Hz, 2 H), 7.41–7.47 (m, 4 H), 7.70 (d, *J* = 7.5 Hz, 2 H), 7.77 (s, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 70.6 (d, 2 C), 107.2 (d, 2 C), 110.5 (d, 2 C), 120.5 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 124.0 (d, $J_{C–F}$ = 3.9 Hz, 2 C), 124.1 (s, $J_{C–F}$ = 274.0 Hz, 2 C), 126.8 (d, 2 C), 129.2 (d, 2 C), 131.2 (s, 2 C), 131.3 (s, $J_{C–F}$ = 33.0 Hz, 2 C), 152.5 (s, 2 C), 153.0 (s, 2 C).

Reaction of 5-[3-(Trifluormethyl)phenyl]furfural with Catalyst 3

To 5-[3-(trifluormethyl)phenyl]furfural (540 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) catalyst **3** (41.2 mg, 125 μmol, 5 mol%) and the mixture was heated to reflux overnight. The solvent was removed in vacuo. The ^1H NMR showed 89% conversion to **5c**.

Reaction of 5-[3-(Trifluormethyl)phenyl]furfural with Catalyst 4

To 5-[3-(trifluormethyl)phenyl]furfural (480 mg, 2.00 mmol) in THF (5 mL) catalyst **4** (30.0 mg, 100 μmol, 5 mol%) was added and the mixture was refluxed overnight. After removal of the solvent the ^1H NMR showed >95% conversion to **5c**.

2-[3-(Trifluormethyl)phenyl]-5-{2-[5-(3-trifluormethyl)phenyl]furan-2-yl}-1,2-bis(prop-2-ynyloxy)ethylfuran (7c)

To **6c** (828 mg, 1.72 mmol) in DMF (10 mL), NaH (124 mg, 5.16 mmol) and after 10 min propargyl bromide (458 μL of a 80% solution in toluene, 5.16 mmol) were added. After stirring overnight and addition of H_2O, the product was extracted with Et_2O, the organic layer washed with brine, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. Column chromatography on silica gel (PE–EtOAc–CH_2Cl_2, 20:1:1) delivered one pure diastereomer **7cI** (215 mg, 22%) and a mixture of **7cI** and **7cII** (545 mg, 57%) as a colorless solid (overall ratio of **7cI**:**7cII** = 1:0.22).

Compound 7cI

R_f = 0.16 (PE–EtOAc–CH_2Cl_2, 20:1:1).

Mp 126 °C.

IR (film): 3307, 1611, 1448, 1331, 1264, 1227, 1160, 1121, 1068, 1019, 972, 934, 901, 791, 757, 696, 644 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 2.4 Hz, 2 H), 4.03 (dd, *J* = 16.1 Hz, *J* = 2.4 Hz, 2 H), 4.17 (dd, *J* = 16.1, 2.4 Hz, 2 H), 5.22 (s, 2 H), 6.65 (d, *J* = 3.5 Hz, 2 H), 6.75 (d, *J* = 3.5 Hz, 2 H), 7.47–7.50 (m, 4 H), 7.84 (d, 2 H), 8.0 (s, 2 H).

^{13}C NMR (62.9 MHz, $CDCl_3$,): δ = 55.87 (t, 2 C), 73.12 (d, 2 C), 75.04 (s, 2 C), 78.85 (d, 2 C), 106.99 (d, 2 C), 113.57 (d, 2 C), 120.69 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 123.92 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 124.07 (s, $J_{C–F}$ = 272.0 Hz, 2 C), 126.94 (d, 2 C), 129.09 (d, 2 C), 131.14 (s, $J_{C–F}$ = 32.0 Hz, 2 C), 131.39 (s, 2 C), 150.66 (s, 2 C), 152.82 (s, 2 C).

Anal. Calcd for $C_{30}H_{20}F_6O4$ (558.47): C, 64.52; H, 3.61. Found: C, 64.47; H, 3.73.

MS (EI, 70 eV): *m*/*z* (%) = 558 (1) [M^+], 279 (100).

Compound 7cII

R_f = 0.08 (PE–EtOAc–CH_2Cl_2, 20:1:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 2.4 Hz, 2 H), 4.21 (dd, *J* = 15.9, 2.4, 2 H), 4.39 (dd, *J* = 15.9, 2.4 Hz, 2 H), 5.12 (s, 2 H), 6.43 (d, *J* = 3.4 Hz, 2 H), 6.60 (d, *J* = 3.4 Hz, 2 H), 7.39 ('t', *J* = 7.7 Hz, 2 H), 7.44 (m, 2 H), 7.70 ('d', *J* = 7.7 Hz, 2 H), 7.76 (s, 2 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 57.01 (t, 2 C), 75.17 (d, 2 C), 75.85 (d, 2 C), 79.10 (s, 2 C), 106.92 (d, 2 C), 112.21 (d, 2 C), 120.38 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 123.88 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 123.99 (s, $J_{C–F}$ = 272.0 Hz, 2 C), 126.74 (d, 2 C), 129.07 (d, 2 C), 131.10 (s, 2 C), 131.11 (s, $J_{C–F}$ = 32.0 Hz, 2 C), 150.58 (s, 2 C), 152.60 (s, 2 C).

5-[3-(Trifluormethyl)phenyl]-1-{5-[3-(trifluormethyl)phenyl]-1,3-dihydro-4-hydroxyisobenzofuran-1-yl}-1,3-dihydroisobenzofuran-4-ol (8c)

To diastereomer **7cI** (120 mg, 215 μmol) in $CHCl_3$ (20 mL) a stock solution of $AuCl_3$ (32.6 mg of 10% $AuCl_3$ in MeCN, 10.7 μmol, 5 mol%) were added. After 2 h the solvent was removed in vacuo and the product was purified by column chromatography on silica gel (PE–EtOAc–CH_2Cl_2, 6:1:2). Compound **8cI** (95 mg, 80%) was obtained as pale-yellow solid.

R_f = 0.09 (PE–EtOAc–CH_2Cl_2, 4:1:1).

Mp 207 °C.

IR (film): 3300, 1754, 1585, 1453, 1422, 1333, 1266, 1221, 1160, 1123, 1066, 1002, 901, 805, 704, 660, 627 cm^{-1}.

^1H NMR (250 MHz, acetone-d_6,): δ = 4.97 (d, *J* = 12.1 Hz, 2 H), 5.12 (d, *J* = 12.1 Hz, 2 H), 5.47 (br s, 2 H), 6.72 (d, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 7.64–7.67 (m, 4 H), 7.83–7.87 (m, 2 H), 7.90 (m, 2 H), 8.25 (s, 2 H).

^{13}C NMR (62.9 MHz, acetone-d_6): δ = 72.5 (t, 2 C), 87.9 (d, 2 C), 115.2 (d, 2 C), 124.3 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 125.2 (s, $J_{C–F}$ = 272.0 Hz, 2 C), 126.9 (d, $J_{C–F}$ = 4.0 Hz, 2 C), 128.0 (s, 2 C), 129.1 (s, 2 C), 130.0 (d, 2 C), 130.7 (s, $J_{C–F}$ = 32.0 Hz, 2 C), 131.2 (d, 2 C), 134.1 (d, 2 C), 140.4 (s, 2 C), 141.8 (s, 2 C), 148.7 (s, 2 C).

MS (EI, 70 eV): *m*/*z* (%) = 558 (1) [M^+], 279 (100).

HRMS (EI positive ion, 70 eV): *m*/*z* calcd for $C_{30}H_{20}F_6O_4$: 558.1260; found: 558.1255.

Methyl 5-[1,2-Dihydroxy-2-(5-methyl-4-methoxycarbonyl-2-furyl)ethyl]-2-methyl-3-furoate (6d)

To methyl-5-formyl-2-methylfuran-3-carboxylate (500 mg, 2.97 mmol) and catalyst **2** (46.7 mg, 149 μmol, 5 mol%) in abs. EtOH (10 mL) Et_3N (90.4 mg, 894 mol) was added. After refluxing the mixture for 3 h, ice water was added and the product was extracted with CH_2Cl_2. The organic layer was washed with sat. aq $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. After purification by column chromatography on silica gel (PE–EtOAc, 3:1) **5d** (343 mg, 69%) was obtained as a yellow solid.

R_f = 0.16 (PE–EtOAc, 3:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 2.65 (d, *J* = 0.5 Hz, 3 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 5.66 (br s, 1 H), 6.64 (s, 1 H), 7.46 (q, *J* = 0.5 Hz, 1 H), 7.87 (q, *J* = 0.5 Hz, 1 H).

Compound **5d** was dissolved in MeOH (200 mL), and $NaBH_4$ (127 mg, 3.35 mmol) was added in portions. Then, the mixture was stirred at r.t. overnight. After hydrolysis with H_2O, the product was extracted with CH_2Cl_2, the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the product was purified by column chromatography on silica gel (PE–EtOAc, 2:1) **6d** (649 mg, 65% over 2 steps) was obtained as a yellow solid as a mixture of two diastereomers **6dI** and **6dII** in a ratio of 1:0.75.

R_f = 0.13 (PE–EtOAc, 2:1).

IR (film): 3446, 3127, 3011, 2956, 1686, 1449, 1229, 1086, 1031, 773 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_8$ (338.31): C, 56.80; H, 5.36. Found: C, 56.60; H, 5.39.

MS (EI, 70 eV): *m*/*z* (%) = 338 (4) [M^+], 169 (100).

Compound 6dI

^1H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 6 H), 2.83 (br s, 2 H), 3.79 (s, 6 H), 4.91 (s, 2 H), 6.53 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.91 (q, 2 C), 51.54 (q, 2 C), 69.40 (d, 2 C), 109.29 (d, 2 C), 114.11 (s, 2 C), 150.40 (s, 2 C), 159.51 (s, 2 C), 164.38 (s, 2 C).

Compound 6dII

^1H NMR (300 MHz, $CDCl_3$): δ = 2.44 (br s, 2 H), 2.55 (s, 6 H), 3.81 (s, 6 H), 4.92 (s, 2 H), 6.58 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.93 (q, 2 C), 51.56 (q, 2 C), 69.69 (d, 2 C), 109.52 (d, 2 C), 114.18 (s, 2 C), 150.58 (s, 2 C), 159.52 (s, 2 C), 164.39 (s, 2 C).

Methyl 5-[1,2-Bis(prop-2-ynyloxy)-2-(5-methyl-4-methoxycarbonyl-2-furyl)ethyl]-2-methyl-3-furoate (7d)

To **6d** (636 mg, 1.88 mmol) in DMF (10 mL), first NaH (99.3 mg, 4.14 mmol) and then propargyl bromide (460 μL of a 80% solution in toluene, 4.14 mmol) were added. After 3 h at r.t. a sat. NH_4Cl solution was added, the product was extracted with Et_2O, the organic phase was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. Column chromatography on silica gel (PE–EtOAc–CH_2Cl_2, 20:1:1) delivered **7d** (303 mg, 39%). The diastereomer **7dI** could be isolated and characterized by a crystal structure analysis, the other diastereomer **7dII** only as a mixture with **7dI** (overall ratio 1:0.3).

Compound 7dI

R_f = 0.05 (PE–EtOAc–CH_2Cl_2, 20:1:1).

Mp 135–136 °C.

IR (film): 3260, 2951, 2861, 1713, 1578, 1440, 1221, 1056, 771, 719, 660 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (t, *J* = 2.4 Hz, 2 H), 2.59 (s, 6 H), 3.83 (s, 6 H), 3.94 (dd, *J* = 16.0, 2.4 Hz, 2 H), 4.09 (dd, *J* = 16.0, 2.4 Hz, 2 H), 4.90 (s, 2 H), 6.72 (s, 2 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.92 (q, 2 C), 51.36 (q, 2 C), 55.82 (t, 2 C), 72.82 (d, 2 C), 74.90 (d, 2 C), 78.70 (s, 2 C), 112.04 (d, 2 C), 113.95 (s, 2 C), 148.04 (s, 2 C), 159.85 (s, 2 C), 164.35 (s, 2 C).

Anal. Calcd for $C_{22}H_{22}O_8$ (414.41): C, 63.76; H, 5.35. Found: C, 63.92; H, 5.54.

MS (EI, 70 eV): *m*/*z* (%) = 414 (1) [M^+], 207 (100).

Methyl 3-[6-(Methoxycarbonyl)-1,3-dihydro-4-hydroxy-5-ethylisobenzo-furan-1-yl]-1,3-dihydro-7-hydroxy-6-methylisobenzofuran-5-carboxylat (8d)

To **7d** (100 mg, 241 μmol) in CH_2Cl_2 (5 mL) a stock solution of $AuCl_3$ (36.6 mg of a 10% solution in MeCN, 12.1 μmol, 5 mol%) was added. After 30 min the solvent was removed and the product was purified by column chromatography on silica gel (PE–EtOAc–CH_2Cl_2, 2:1:1). One diastereomer **8dI** was isolated as a colorless solid (55 mg, 55%), the other diastereomer **8dII** was only obtained as a mixture with **8dI**.

Compound 8dI

R_f = 0.09 (PE–EtOAc–CH_2Cl_2, 2:1:1).

Mp 159–161 °C.

IR (film): 3298, 2950, 2847, 1715, 1435, 1324, 1246, 1209, 1045, 928 cm^{-1}.

MS (CI positive ion, reactand gas: CH_4): *m*/*z* (%) = 415 (7) [M^+], 397 (17), 383 (38), 223 (78), 207 (100).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 3.84 (s, 6 H), 4.99 (d, *J* = 12.9 Hz, 2 H), 5.07 (dd, *J* = 12.9 Hz, 2 H), 5.54 (s, 2 H), 7.42 (s, 2 H), 8.14 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.87 (q, 2 C), 52.08 (q, 2 C), 72.76 (t, 2 C), 87.37 (d, 2 C), 115.79 (d, 2 C), 126.28 (s, 2 C), 131.07 (s, 2 C), 132.46 (s, 2 C), 139.02 (s, 2 C), 150.17 (s, 2 C), 168.77 (s, 2 C).

HRMS (CI positive ion, reactand gas: CH_4): *m*/*z* calcd [$C_{22}H_{22}O_8$ + H]$^+$: 415.1387; found: 415.1376.

Compound 8dII

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 6 H), 3.80 (s, 6 H), 4.87 (d, *J* = 12.9 Hz, 2 H), 5.01 (dd, *J* = 12.9 Hz, 2 H), 5.32 (s, 2 H), 7.04 (s, 2 H), 8.18 (br s, 2 H).

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References and Notes

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(8) CCDC 638293 (**7d**) contains the supplementary crystallographic data for this paper. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk].

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