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Gold Catalysis: Dihydroisobenzofurans and Isochromanes by the Intramolecular Furan/Alkyne Reaction

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Abstract: A series of furyl alcohols and homofuryl alcohols was synthesized by reduction of furfurals or reaction of furyllithium compounds with epoxides and subsequent propargylation. The gold-catalyzed cycloisomerization of these products furnished dihydroisobenzofurans and isochromanes. Crystal structure analyses proved the sequence of the substituents for both classes of products. Unsaturated dicarbonyl compounds as side-products show the mechanistic relationship to the analogous platinum-catalyzed reactions. Neither ester groups, even on the 4-position of the furan ring, nor aryl bromides hinder the catalysis by gold. In the case of a substrate with an allyl ether in the side chain, a side-product, which provides evidence for a reaction of the alkyne with an inverse regioselectivity, was observed.

Keywords: alkynes; furans; gold; heterocycles; homogeneous catalysis; oxepines

Introduction

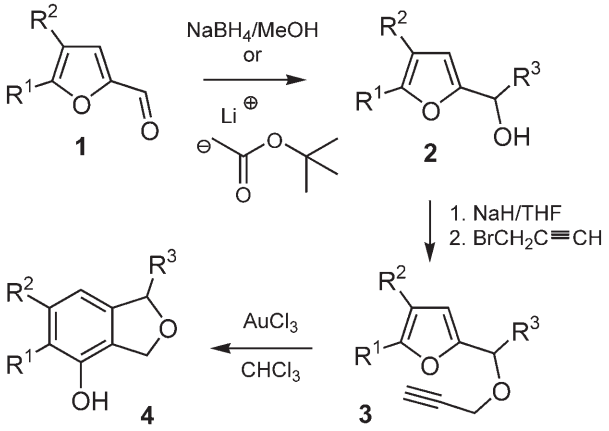
Gold currently is a hot spot in catalysis research.[1] Among homogeneous gold-catalyzed reactions,[2] the gold-catalyzed phenol synthesis by Hashmi et al.[3] provides an easy entry to numerous benzo-anellated heterocycles, among them dihydroisoindol-4-ols and 8-hydroxytetrahydroisoquinolines.[3a,4]

So far, only four examples for the synthesis of a dihydroisobenzofuran have been reported,[3a,5] the method has not been used for the synthesis of the corresponding isochromanes. Here we report the efficient synthesis of these heterocyclic systems and the observation of side-products which, for the first time in gold-catalyzed reactions, are similar to the side products observed by Echavarren et al.[6,7] in the analogous platinum-catalyzed reactions.

Results and Discussion

The most direct access to substrates **3** was the reduction of furfural derivatives **1a–c** and the subsequent propargylation of the furyl alcohols **2a–c** (Scheme 1 and Table 1). Another approach is the aldol reaction of 2-methylfurfural (**1a**) with *tert*-butyl acetate, leading to the furfurol derivative **2d**, propargylation then furnished **3d**.

The individual substrates **3a–d** readily reacted in the gold-catalyzed cycloisomerization step, the corresponding phenols were obtained in good yields, with the exception of **3d**. The latter is prone to elimination of propargyl alcohol, which not only reduces the yield of **4d** but is already a problem in the synthesis of **3d** and **2d**. With other catalysts like pyridine-2-carboxylates,[4a] chloro-bridged gold(I)[4b] complexes and $Na[AuCl_4]$ no superior results were obtained. Testing

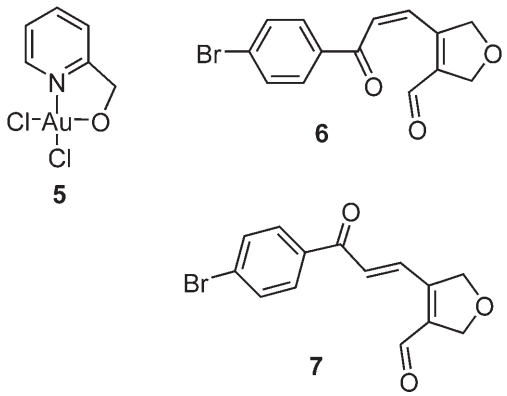


Scheme 1. Nucleophilic additions to furfural derivatives as the basis for the synthesis of dihydroisobenzofurans **4**.

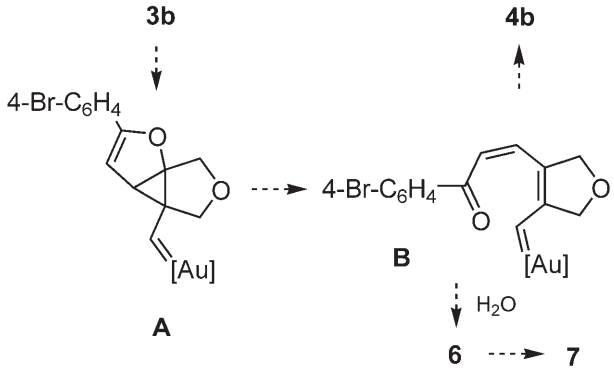
Table 1. Synthesis and gold-catalyzed conversion of propargyl furfuryl ethers **3**.

Entry	R^1	R^2	R^3	Yield of **2**	Yield of **3**	Yield of **4**[a]
1	Me	H	H	**2a** (83%)	**3a** (42%)	**4a** (71%)
2	4-Br-C_6H_4	H	H	**2b** (78%)	**3b** (81%)	**4b** (79%)
3	Me	CO_2Me	H	**2c** (55%)	**3c** (52%)	**4c** (65%)
4	Me	H	CH_2CO_2Me	**2d** (26%)	**3d** (15%)	**4d** (29%)

[a] Using $AuCl_3$ in $CHCl_3$ at room temperature.



Scheme 2. Side-products **6** and **7** obtained from **2b** with catalyst **5**.



Scheme 3. Echavarren's mechanistic suggestion for the formation of side-products of type **6**.

different catalysts for the other substrates **3**, three interesting observations were made: (a) $AuCl_3$ in $CHCl_3$ is a more efficient catalyst for the cycloisomerization than $AuCl_3$ in MeCN, the known conversion of **3a** (entry 1) to **4a** was previously reported to deliver a 69% yield with 2 mol% $AuCl_3$ in MeCN at room temperature[3a] and a 75% yield with 5 mol% $PtCl_2$ (MeCN) in refluxing acetone. (b) **3c**, a derivative derived from Feist–Benary synthesis,[8] reacts in the gold-catalyzed step (entry 3). This is remarkable, as many other furan substrates, bearing acceptor substituents in 2- or 5-position of the furan ring, were unreactive.[9] In **3c** the acceptor in 3-position of the furan is not a problem, an observation of both mechanistic and synthetic applicative significance. (c) The reaction of **3b** furnished two side-products when catalyst **5** was used in order to observe arene oxide intermediates as previously described for other substrates.[3f] In addition to the desired **4b** (46%) the two geometric isomers **6** and **7** (Scheme 2) were obtained. No reaction of the aryl bromide functionality was detected.

This is remarkable, given that Echavarren et al. with $PtCl_2$ in aqueous acetone obtained related products (Scheme 3). However, they observed the (*E*)-isomer exclusively (e.g., **7**) and not the (*Z*)-isomer (e.g., **6**). This ultimately led to a mechanistic proposal of an initial formation of cyclopropyl carbenoids **A** which then rearrange to the *cis*-configurated **B** and finally are hydrolyzed to **6**. This proposal was in agreement with computational studies for the platinum-catalyzed reaction.[11] Now the observation of **6** and **7** is not only the first experimental evidence for this pathway for gold, but **6** also for the first time shows the (*Z*)-geometry (coupling constant of the two hydrogen atoms on the olefin is 12.7 Hz) which is necessary for the subsequent steps of the phenol synthesis. It is reasonable to assume that **7** is formed from **6** by subsequent isomerization but it is unclear, why these side-products are observed with oxygen heteroatoms in tether between the furan and the alkyne in the substrate.

From **3b** single crystals suitable for a X-ray crystal structure analysis could be obtained (Figure 1).[10] In the biaryl axis the bromophenyl group is not coplanar with the benzoanellated heterocycle. Intermolecular hydrogen bonds between the phenolic hydroxy groups and the dihydrofuran oxygen atoms are observed.

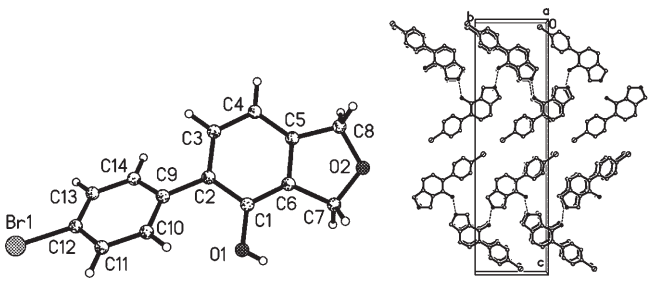
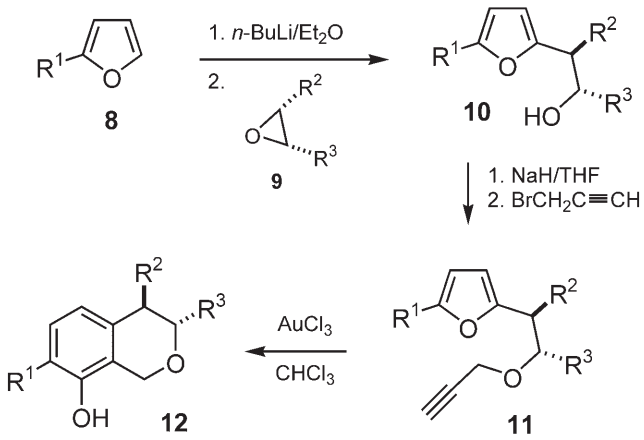


Figure 1. Structure of **3b** and hydrogen intramolecular hydrogen bonding of the phenolic hydroxy group.[12]



Scheme 4. Ring-opening of oxiranes as the basis for the synthesis of isochromanes **12**.

The substrates **11** were conveniently prepared by ring-opening of oxiranes **9** with the 2-furyllithium compounds obtained by metallation of furans **8** with *n*-BuLi and the propargylation of the homofuranols **10** (Scheme 4 and Table 2). In the case of monosubstituted oxiranes, the ring opening was regioselective, affording substrates **9** with $R^2 = H$ (entries 1–4). Oxiranes derived from cyclic olefins in a diastereoselective reaction furnished the *trans*-1,2-disubstituted derivatives, in which ultimatively the presence of both side-chains in a bis-equatorial position places the furan and the alkynyl group in the proximity necessary for the cyclization.

The conversion of **11a** to **12a** worked quite well (entry 1). A crystal structure analysis (Figure 2)[10] showed the connectivity of **12a**, the sequence of the four substituents on the central benzene ring was unambiguously proven.[12]

Without a substituent in the 5-position of the furan ring, **11b** (entry 2) provided a second constitutional isomer: **14** was formed (Scheme 5), the low yield of pure material was caused by separation problems.[3a] With the phenyl substituent **12c** was the only product (entry 3). The reactions of **11d** and **11e** nicely indicate the higher reactivity of the alkynyl groups (entries 4 and 5), the allyl ethers remain untouched. But they seem to be able to influence the outcome of the reaction, in the reaction of **11d** in addition to **12d** (structure also clearly proven by a crystal structure analysis, see Figure 2)[10] the seven-membered heterocycle **15** was formed (Scheme 5).

The α,β-unsaturated ketone in the side-chain resembles the side-products **6** and **7**, but the formation of the seven-membered ring can only be expained when a different regioselectivity in the reaction of the alkyne is assumed, a cyclopropyl carbenoid **C** might be formed, which can rearrange to intermediate **D** (Scheme 6).

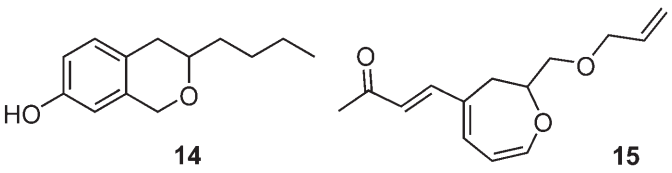
With **11f** and **11g** the expected benzo- and *trans*-cycloalkyl-anellated products **12f** and **12g** were formed.

Table 2. Synthesis and gold-catalyzed conversion of propargyl homofurfuryl ethers **11**.

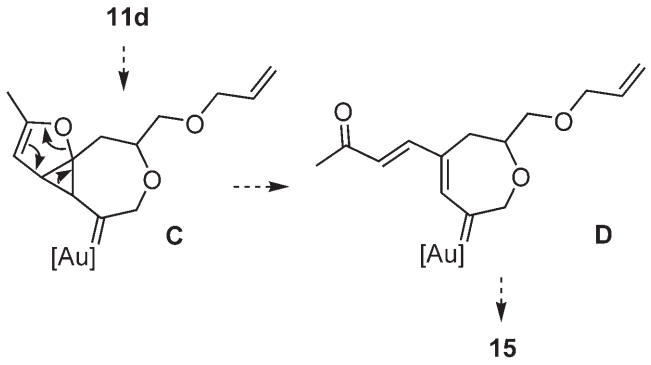
Entry	R^1	R^2	R^3	Yield of **10**	Yield of **11**	Yield of **12**[a]
1	Me	H	H	**10a** (68%)	**11a** (62%)	**12a** (65%)
2	H	H	Bu	**10b** (45%)	**11b** (76%)	**12b** (33%)[b]
3	Me	H	Ph	**10c** (77%)	**11c** (64%)	**12c** (89%)
4	Me	H	$CH_2OAllyl$	**10d** (97%)	**11d** (55%)	**12d** (64%)
5	n-C_5H_{11}	H	$CH_2OAllyl$	**10e** (96%)	**11e** (63%)	**12e** (96%)[c]
6	Me	$-(CH_2)_3-$		**10f** (48%)	**11f** (63%)	**12f** (34%)
7	Me	$-(CH_2)_4-$		**10g** (66%)	**11g** (51%)	**12g** (78%)

[a] Using $AuCl_3$ in $CHCl_3$ at room temperature.
[b] As described previously for other furans without substituents in the 5-position, the constitutional isomer, **14** was obtained, too (17%).
[c] **15** (7%, Scheme 5) was obtained, too.

Figure 2. Proof of the constitution of **12a** (*left*) and **12d** (*right*) by X-ray crystal structure analysis.



Scheme 5. Side-products **14** and **15** observed in the formation of isochromanes.



Scheme 6. Possible explanation for the formation of **15**.

Conclusions

The gold-catalyzed phenol synthesis is an efficient tool for the synthesis of dihydroisobenzofurans and isochromanes. With the oxygen atom in the tether connecting the furan and the alkyne in the substrate, interesting side-products are obtained. The latter provide the first experimental proof for a mechanistic analogy with the related platinum-catalyzed reactions of ω-alkynyl furans.

Experimental Section

Characterization data for the compounds made can be found in the Supporting Information.

Synthesis of Methyl 5-Formyl-2-methylfuran-3-carboxylate (1c)

Methyl 2-methylfuran-3-carboxylate (10.0 g, 71.4 mmol) was dissolved in DMF (30 mL), cooled to 0 °C and $POCl_3$ (21.9 g, 143 mmol) was added slowly. After 30 min the mixture was warmed to 40 °C and stirred at that temperature over night. Then it was cooled and hydrolyzed with ice/water then hydrolyzed with 5 N NaOH. The aqueous phase was extracted with diethyl ether, the organic layers were washed with $NaHCO_3$ solution, water and dried over Na_2SO_4. The solvent was removed under vacuum and the product purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford **1c** as a yellow solid; yield: 10.9 g (90%).[13]

Synthesis of [5-(4-Bromophenyl)furan-2-yl]methanol (2b)

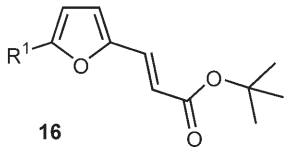
5-(4-Bromphenyl)furfural **1b** (2.16 g, 8.43 mmol) was dissolved in boiling ethanol (350 mL) and small portions of $NaBH_4$ (360 mg, 9.27 mmol) were added. After 2 h more $NaBH_4$ (100 mg, 2.64 mmol) was added, after 3 h the reaction mixture was hydrolyzed with water (100 mL), stirred for 10 min and then extracted with Et_2O. The organic layer was dried over $MgSO_4$, the solvent removed under reduced pressure and the residue purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to afford **2b** as a colourless solid; yield: 1.67 g (78%).

Synthesis of Methyl 5-(Hydroxymethyl)-2-methylfuran-3-carboxylate (2c)

Compound **1c** (3.50 g, 20.8 mmol) was dissolved in methanol (50 mL), $NaBH_4$ (994 mg, 25.0 mmol) was added in portions and the mixture was stirred overnight.Then the reaction was quenched with water and stirring was continued for 15 min. The aqueous phase was extracted with dichloromethane and the combined organic phases dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to afford **2c** as yellow solid; yield: 3.10 g (88%).[14]

Synthesis of *tert*-Butyl 3-Hydroxy-3-(5-methylfuran-2-yl)propionate (2d)

Under an atmosphere of nitrogen *tert*-butyl acetate (5.06 g, 43.6 mmol) was added drop by drop to a stirred solution of LDA (9.00 g, 51.5 mmol) in THF (70 mL) at −78 °C. The solution was stirred for 1 hour at −78 °C, after which 5-methyl-2-furaldehyde (**1a**; 4.36 g, 39.6 mmol) was added dropwise and the mixture was again stirred for 1 hour at −78 °C. Then the resulting mixture was allowed to warm to room temperature and was quenched with 2 M HCl (50 mL) and diluted with Et_2O (30 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried over $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 20:1 and petroleum ether/EtOAc, 3:1) to give **16** (yield: 3.05 g, 36%) and **2d** (yield: 2.31 g, 26%).



Synthesis of 2-Methyl-5-prop-2-ynyloxymethylfuran (3a)

5-Methylfurfurol **2a** (2.00 g, 17.8 mmol) in DMF (20 mL) was stirred with NaH (510 mg, 21.4 mmol) at 0 °C for 10 min, then propargyl bromide (80% in toluene, 3.18 g, 21.4 mmol) was added. After 3 h the mixture was quenched with water, extracted with Et_2O, the organic layer washed

with brine and dried over $MgSO_4$. Column chromatrography on silica gel (petroleum ether/ethyl acetate 50:1) furnished **3a** as a pale yellow oil; yield: 1.13 g (42%).[10]

Synthesis of 2-(4-Bromphenyl)-5-prop-2-ynyloxymethylfuran (3b)

Compound **2b** (1.67 g, 6.59 mmol) was dissolved in absolute DMF (20 mL) and at 0°C NaH (190 mg, 7.91 mmol) was added. After stirring for 10 min, propargyl bromide (80% in toluene, 1.18 g, 7.91 mmol) was added drop by drop. After 3 h NaH (100 mg, 4.17 mmol) was added again and stirring was continued overnight. Water was added (100 mL) and the product was extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$ and the solvent removed under vacuum. Column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) furnished **3b** as a yellowisch solid; yield: 1.55 g (81%).

Synthesis of Methyl 2-Methyl-5-[(prop-2-ynyloxy)-methyl]furan-3-carboxylate (3c)

Compound **2c** (1.00 g, 5.88 mmol) was dissolved in absolute DMF (2 mL) and cooled to 0°C. NaH (155 mg, 6.46 mmol) was added. After 10 min of stirring, a solution of propargyl bromide (80% in toluene, 961 mg, 6.46 mmol) was added drop by drop. After 3 h more NaH (155 mg, 6.46 mmol) was added and stirring continued overnight. The reaction mixture was hydrolyzed with water and the product extracted with ether. The combined organic layer was dried over magnesium sulfate, the solvent was removed under vacuum and the product purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to afford **3c** as a yellow solid; yield: 633 mg (52%).

Synthesis of *tert*-Butyl 3-(5-Methylfuran-2-yl)-3-prop-2-ynyloxypropionate (3d)

Under an atmosphere of nitrogen to a solution of **2d** (213 mg, 939 μmol) in dry THF (3.5 mL) was added sodium hydride (27.0 mg, 1.13 mmol) at 0°C. Propargyl bromide (80% solution in toluene, 251 μL, 2.82 mmol) was then added and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (20 mL for 1.10 mmol) and the resulting solution was extracted with diethyl ether (3×10 mL for 1.10 mmol). The combined organic phases were dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to furnish **3d**; yield: 350 mg (15%).

Synthesis of 5-Methyl-1,3-dihydroisobenzofuran-4-ol (4a)

Compound **3a** (200 mg, 1.33 mmol) was dissolved in chloroform (5 mL) and $AuCl_3$ (10% solution in acetonitrile, 20.2 mg, 66.5 μmol, 5 mol%) added. After 90 min the solvent was removed and the crude product purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1). Furanol **4a** was isolated as a colourless solid; yield: 142 mg (71%).[10]

Synthesis of 5-(4-Bromphenyl)-1,3-dihydroisobenzofuran-4-ol (4b)

Compound **3b** (226 mg, 776 μmol) was dissolved in DCM (10 mL) and $AuCl_3$ (10% solution in acetonitrile, 11.8 mg, 38.8 μmol, 5 mol%) was added. After 1 hour the solvent was removed under vacuum and the product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to furnish **3b** as a light brown solid; yield: 179 mg (79%).

Synthesis of Methyl 1,3-Dihydro-7-hydroxy-6-methylisobenzofuran-5-carboxylate (4c)

Compound **3c** (200 mg, 961 μmol) was dissolved in chloroform (5 mL) and $AuCl_3$ (14.6 mg, 48.0 μmol, 5 mol%) was added. After 90 min the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1).

Synthesis of Methyl 1,3-Dihydro-4-hydroxy-5-methylisobenzofuran-1-carboxylate (4d)

Compound **3d** (20.0 mg, 76.0 μmol) was dissolved in deuterated acetonitrile (700 μL) and $AuCl_3$ in acetonitrile (1.15 mg, 3.78 μL, 5 mol%) was added. The reaction was monitored by ^1H NMR spectroscopy. After complete consumption of **3d**, the reaction was worked up by column chromatography on silica gel (SiO_2, pentane/ethyl acetate/dichloromethane, 5:1:1) to afford **4d**; yield: 5.8 mg (29%).

Synthesis of 2-(*Z*)-2-[3-(4-Bromophenyl)-3-oxopropenyl]cyclopent-1-enecarbaldehyde (6) and 2-(*E*)-2-[3-(4-Bromophenyl)-3-oxopropenyl]cyclopent-1-enecarbaldehyde (7)

Compound **3b** (96.0 mg, 330 μmol) was dissolved in chloroform (1 mL) and water (12 mg, 666 μmol) was added. With stirring the catalyst **5** (6.2 mg, 17 μmol, 5 mol%) was added with strong stirring. When TLC showed the consumption of the substrate the solvent was removed and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1). In addition to **4b** (yield: 44 mg, 46%) the aldehydes **6** (11%) and **7** (8%) were obtained.

Synthesis of 1-Furan-2-ylhexan-2-ol (10b)

To a solution of furan (3.00 g, 44.0 mmol) in THF (30 mL) at 0°C, *n*-butyllithium (1.6 M solution in hexane, 15.0 mL, 24.2 mmol) was added. The reaction mixture was stirred for two hours at room temperature before the mixture was cooled to −78°C, then hexene oxide (2.80 mL, 22.0 mmol) was added. The reaction mixture was warmed to room temperature and 10 mL $NaHCO_3$ were added. The mixture was neutralized with a 2 M solution of HCl then extracted with diethyl ether (2×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 20:1) resulting in **10b**; yield: 1.38 g (45%).

Synthesis of 2-(5-Methylfuran-2-yl)-1-phenylethanol (10c)

Under nitrogen *n*-butyllithium in *n*-hexane (1.6 M, 38.1 mL, 61.0 mmol) was added dropwise to a solution of methylfuran (5.00 g, 61.0 mmol) in dry THF (60 mL) at 0 °C. After stirring for 4 h epoxystyrene (13.9 mL, 122 mmol) was added dropwise at 0 °C and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (80 mL) and the resulting solution was extracted with DCM (3 × 60 mL). The combined organic phase was dried over Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to give **10c**; yield: 9.50 g (77 %).

Synthesis of 1-Allyloxy-3-(5-pentylfuran-2-yl)propan-2-ol (10e)

Under nitrogen *n*-butyllithium in *n*-hexane (1.6 M, 22.6 mL, 36.2 mmol) was added dropwise to a solution of pentylfuran (5.00 g, 36.2 mmol) in dry THF (50 mL) at 0 °C. After stirring for 4 h, allyl glycidyl ether (8.50 mL, 72.4 mmol) was added dropwise at 0 °C and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (30 mL) and the resulting solution was extracted with DCM (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1); yield: 8.6 g (96 %).

Synthesis of 2-(5-Methyl-furan-2-yl)-cyclopentanol (10f)

n-Butyllithium in *n*-hexane (1.6 M, 36.1 mL, 57.7 mmol) was added dropwise under nitrogen to a solution of methylfuran (4.74 g, 57.7 mmol) in dry THF (20 mL) at 0 °C. After stirring for 4 h, cyclopentenoxide (5.00 mL, 57.7 mmol) was added dropwise at 0 °C and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (20 mL) and the resulting solution was extracted with DCM (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1); yield: 2.27 g (48 %).

Synthesis of 2-(5-Methylfuran-2-yl)-cyclohexanol (10g)

Under nitrogen *n*-butyllithium in *n*-hexane (23.1 mL, 36.9 mmol) was added dropwise to a solution of 2-methylfuran (3.03 g, 36.9 mmol) in dry THF (20 mL) at 0 °C. After stirring for 4 h cyclohexene oxide (3.70 mL, 36.9 mmol) was added dropwise at 0 °C and stirring was continued over night at room temperature. The reaction mixture was hydrolyzed with water (20 mL) and the resulting solution was extracted with DCM (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1); yield: 1.99 g (66 %).

Synthesis of 2-(2-Prop-2-ynyloxyhexyl)furan (11b)

To furyl alcohol **10b** (744 mg, 4.42 mmol) in DMF (15 mL), sodium hydride (106 mg, 4.42 mmol) was added at 0 °C. The mixture was stirred at room temperature for 30 min and propargyl bromide (80 wt % solution in toluene, 492 μL, 4.42 mmol) was added. The mixture was stirred at room temperature overnight, then hydrolyzed with water and extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 20:1) to furnish product **11b**; yield: 685 mg (76 %).

Synthesis of 2-(2-Ethynyloxy-2-phenylethyl)-5-methylfuran (11c)

To a solution of **10c** (5.00 g, 25.0 mmol) in dry THF (50 mL) was added sodium hydride (372 mg, 30.0 mmol) at 0 °C. Propargyl bromide (80 wt % solution in toluene, 3.53 g, 30.0 mmol) was then added and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (50 mL) and the resulting solution was extracted with DCM (3 × 50 mL). The combined organic phases were dried over $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1); yield: 3.80 g (64 %).

Synthesis of 2-(3-Allyloxy-2-prop-2-ynyloxypropyl)-5-pentylfuran (11e)

To a solution of **10e** (250 mg, 990 μmol) in dry THF (3 mL) was added sodium hydride (30.0 mg, 1.19 mmol) at 0 °C. Propargyl bromide (80 wt % solution in toluene, 142 mg, 1.19 mmol) was then added and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (5 mL), then the resulting solution was extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1); yield: 180 mg (63 %).

Synthesis of 2-Methyl-5-(2-prop-2-ynyloxycyclopentyl)furan (11f)

To a solution of **10f** (1.19 g, 7.15 mmol) in dry THF (20 mL) was added sodium hydride (343 mg, 14.3 mmol) at 0 °C. Propargyl bromide (80 wt % solution in toluene, 142 mg, 1.19 mmol) was then added and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (15 mL) and the resulting solution was extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1); yield: 744 mg (63 %).

Synthesis of 2-Methyl-5-(2-prop-2-ynyloxycyclohexyl)furan (11g)

To a solution of **10g** (926 mg, 5.14 mmol) in dry THF (10 mL) was added sodium hydride (370 mg, 15.4 mmol) at 0 °C. Propargyl bromide (80 wt % solution in toluene, 1.83 g, 15.4 mmol) was then added and stirring was continued overnight at room temperature. The reaction mixture was hydrolyzed with water (5 mL) and the resulting solution was extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1); yield: 180 mg (51 %).

Synthesis of 3-Butylisochroman-7-ol (14) and 3-Butylisochroman-8-ol (12b)

To **11b** (28.0 mg, 135 μmol) in $CDCl_3$ (700 μl), $AuCl_3$ (2.01 mg, 6.75 μmol; 10 wt % in CD_3CN) was added. The reaction was monitored by TLC. After consumption of the substrate, purification of the crude product by column chromatography (hexanes/ethyl acetate, 8:1) afforded **14** (yield: 4.6 mg, 17 %) and **12b** (yield: 9.2 mg, 33 %).

Synthesis of 7-Methyl-3-phenylisochroman-8-ol (12c)

To **12c** (80.0 mg, 354 μmol) in CD_3CN (500 μL) was added $AuCl_3$ in CD_3CN (5.40 mg $AuCl_3$, 17.7 μmol, 5 mol %). Purification of the product by column chromatography (petroleum ether/ethyl acetate, 50:1) afforded **12c**; yield: 71.0 mg (71 %).

Synthesis of 3-Allyloxymethyl-7-pentylisochroman-8-ol (12e)

To **11e** (50.0 mg, 172 μmol) in CD_3CN (500 μL), $AuCl_3$ in CD_3CN (2.6 mg $AuCl_3$, 8.6 μmol, 5 mol %) was added. Purification of the product by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) afforded **12e**; yield: 48.0 mg (96 %).

Synthesis of 7-Methyl-2,3,5,9b-tetrahydro-1*H*,3a*H*-cyclopenta[*c*]isochromen-6-ol (12f)

To **11f** (100 mg, 489 μmol) in CD_3CN (500 μl) was added $AuCl_3$ in CD_3CN (7.42 mg $AuCl_3$, 24.5 μmol, 5 mol %). Purification of the product by column chromatography (petroleum ether/ethyl acetate, 20:1) afforded **12f**; yield: 34.0 mg (34 %).

Synthesis of 8-Methyl-1,2,3,4,6,10b-hexahydro-4a*H*-benzo[*c*]chromen-7-ol (12g)

To **11g** (160 mg, 733 μmol) in CD_3CN (500 μL) was added $AuCl_3$ in CD_3CN (2.2 mg $AuCl_3$, 7.3 μmol, 5 mol %). Purification of the product by column chromatography (petroleum ether/ethyl acetate, 50:1) afforded **12g**; yield: 124.0 mg (78 %).

Synthesis of 2-(5-Methylfuran-2-yl)ethanol (10a)

In a 250-mL three-necked flask with dry ice/acetone condenser, dropping funnel and a gas-inlet, 2-methylfuran (10.0 g, 122 mmol) was dissolved in THF (100 mL) and cooled to 0 °C. *n*-BuLi (1.6 M in hexane, 76.1 mL, 122 mmol) was slowly added, then stirring was continued for 3 h at room temperature. The reaction mixture was cooled to 0 °C again and oxirane (5.37 g, 122 mmol) was condensed at the dry ice/acetone cooler at −78 °C. After stirring at room temperature over night, the reaction mixture was quenched with water, the organic layer was separated and the aqueous layer extracted with DCM. The combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum to afford **10a** as a colourless liquid; yield: 10.5 g (68 %).

Synthesis of 2-Methyl-5-(2-(prop-2-ynyloxy)ethyl)-furan (11a)

To **10a** (740 mg, 5.86 mmol) in DMF (10 mL) at 0 °C NaH (169 mg, 7.03 mmol) was added, followed after 10 min by slow addition of propargyl bromide (80 % in toluene, 1.05 g, 7.03 mmol). After 2 h more NaH (80.0 mg, 3.33 mmol) was added and stirring was continued overnight. After quenching with water and extraction with Et_2O, washing of the organic layer with brine, drying with $MgSO_4$ and removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to afford **11a** as a slightly yellow liquid; yield: 597 mg (62 %) .

Synthesis of 3,4-Dihydro-7-methyl-1*H*-isochromen-8-ol (12a)

To **11a** (300 mg, 1.83 mmol) in $CHCl_3$ (10 mL), $AuCl_3$ (10 % solution in acetonitrile, 11.1 mg, 36.5 μmol, 2 mol %) was added, After stirring at room temperature for 90 min, the solvent was removed under vacuum and the crude product was purified by column chromatography (petroleum ether/acetone/dichloromethane, 10:1:1). Thus **12a** was obtained as a pale yellow solid; yield: 221 mg (65 %).

Synthesis of 1-Allyloxy-3-(5-methylfuran-2-yl)propan-2-ol (10d)

2-Methylfuran (1.00 g, 12.2 mmol) was dissolved in THF (20 mL) and cooled to 0 °C.Then slowly *n*-BuLi (1.6 M in hexane, 7.60 mL, 12.2 mmol) was added and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C again, quickly allyl glycidyl ether (2.80 mL, 24.4 mmol) was added. Stirring was continued for 8 h, then the reaction mixture quenched with water and extracted with DCM. The organic layer was dried over $NaSO_4$ and then the solvent removed under vacuum. By column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) **10d** was obtained as a yellow oil; yield: 2.33 g (97 %).

Synthesis of 2-(2-Allyloxymethylhex-5-ynyl)-5-methylfuran (11d)

Compound **10d** (1.98 g, 10.1 mmol) was dissolved in THF (25 mL) and NaH (270 mg, 11.1 mmol) was added. After 10 min propargyl bromide (80 % in toluene, 1.32 g, 11.1 mmol) was added. After 12 h more NaH (100 mg, 4.17 mmol) was added. Then water was added, the mixture was extracted with dichloromethane and dried over $MgSO_4$.

After removal of the solvent under vacuum, a column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) afforded **11d** as a yellowish oil; yield: 1.31 g (55%).

Synthesis of 3-Allyloxymethyl-7-methylisochroman-8-ol (12d)

Compound **11d** (200 mg, 853 μmol) was dissolved in chloroform and reacted with $AuCl_3$ (10% in acetonitrile; 104 mg, 17.1 μmol, 5 mol%). After 8 h the solvent was removed under vacuum and column chromatography on silica (petroleum ether/ethyl acetate/dichloromethane, 10:1:2) furnished **12d** (yield: 128 mg, 64%) as a pale yellow solid and **15** (yield: 13.5 mg, 7%) as a yellow-brownish liquid.

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[10] CCDC nos. 615252 (**3b**), 615254 (**12a**) and 615253 (**12d**) contain 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)-1223–336–033; ormailto:deposit@ccdc.cam.ac.uk).

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