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Note

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Total Synthesis of the Plant Growth Promoter Auxofuran featuring a Gold(I) catalyzed Furan Formation

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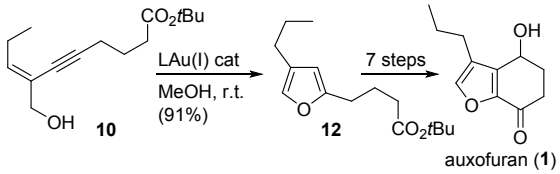
Supporting Information Placeholder



ABSTRACT: A concise synthesis of auxofuran (**1**) was developed. Starting with a Sonogashira cross-coupling reaction, enynol (**10**) was prepared. A gold(I) catalyzed cycloisomerization led to disubstituted furan **12**. Via an intramolecular Friedel-Crafts cyclization, a dihydrobenzofuranone was obtained. Functional group manipulations including benzylic oxidation led to the target molecule.

Most of the plants benefit from a symbiotic interaction with fungi, which is called mycorrhiza. The plant can supply compounds produced by photosynthesis to the fungus. The fungus, in turn, can aid in obtaining minerals from the soil surrounding the roots. Very often mycorrhiza additionally contain bacteria that may support this symbiotic relation between plant and fungus. These mycorrhiza helper bacteria stimulate mycorrhiza formation and fungal growth. Some years ago, the screening of actinomycetes from the hydrosphere of a sprue for positive effects on symbiotic and plant-pathogenic fungi led to the discovery of auxofuran (**1**) and two antifungal compounds.[1] Structural elucidation showed it to have a 5,6-dihydrobenzofuran-7(4*H*)-one core structure (Figure 1).[2]

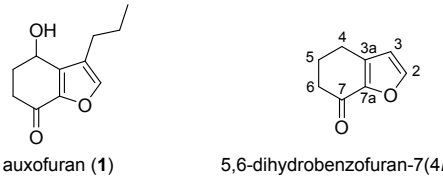
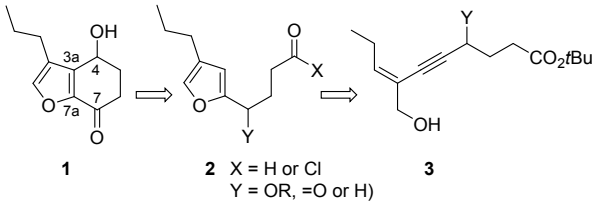


Figure 1. Structure of (–)-auxofuran (**1**).

So far one total synthesis of (–)-auxofuran was described by Boukouvalas et al.[3] They used a domino Diels-Alder reaction-cycloreversion between an alkyne and an oxazole to prepare a 3,4-disubstituted furan derivative. An intramolecular Friedel-Crafts cyclization formed the C7a-C7 bond.

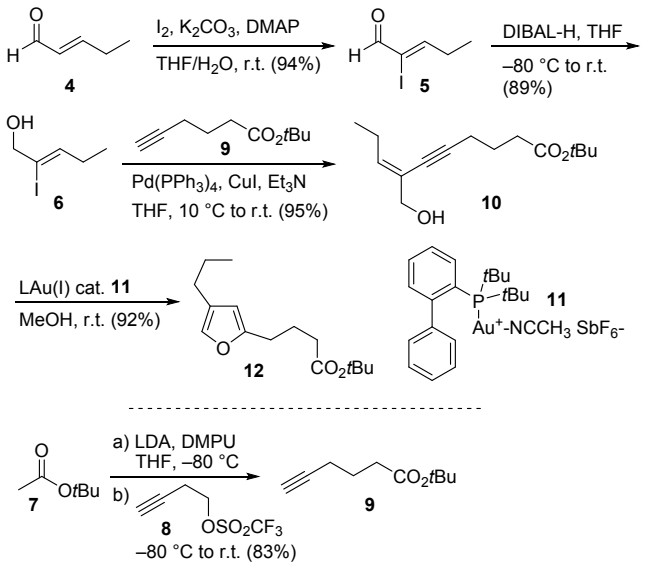
In principle, the synthesis of the fused ring system might start from a furan or a cyclohexanone derivative. In both cases, care must be taken to prevent the formation of benzofurans by elimination and/or tautomerization. Since we had some experience with the Liu furan synthesis[4] by gold(I)-catalyzed cycloisomerization of enynols,[5,6,7] we chose the furan first approach (Scheme 1).[8] In this case the second ring would be fashioned by closing the C3a-C4 bond.

Scheme 1. Plan for the synthesis of auxofuran



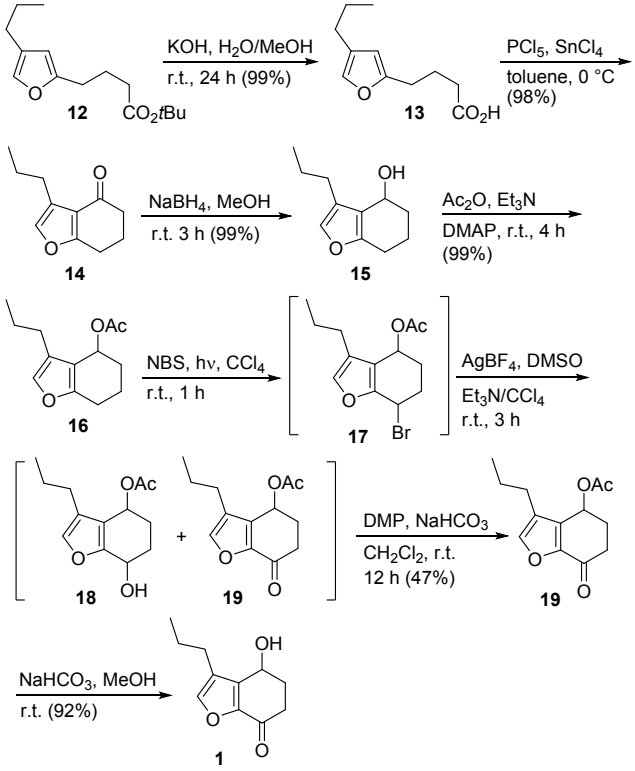
With this plan as a guideline, we started the synthesis of enynol **10** from 2-pentenal (**4**) (Scheme 2). Iodination of **4** in the α-position[9] followed by reduction of the aldehyde function using DIBAL-H delivered allylic alcohol **6**.[10] The 5-hexynoate **9** required for the ensuing Sonogashira coupling[11,12] was prepared by alkylation[13] of *tert*-butyl acetate (**7**) with the triflate[14] **8**, obtained from but-3-yn-1-ol. The cross-coupling between vinyl iodide **6** and hexynoate **9** delivered enynol **10** in excellent yield. Care must be taken that the reaction temperature is below 10 ºC and that oxygen is excluded from the mixture. Otherwise the diyne resulting from Glaser coupling of **9** is formed as a side product. Treatment of enynol **10** with gold(I) complex **11** (3 mol%) in methanol led to smooth formation of 2,4-disubstituted furan **12**. With catalyst **11** a yield of 92% was obtained. The simpler gold(I) complex $[Ph_3PAu(NCCH_3)SbF_6]$ gave furan **12** with 79%. Since reasonable yields were obtained with these two catalysts, no other gold(I) complexes were screened for the cycloisomerization of **10** to **12**.

Scheme 2. Synthesis of furan 12 from enynol 10



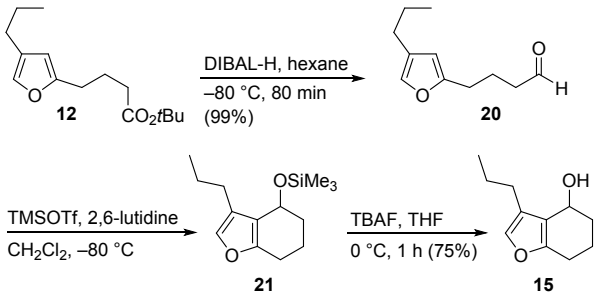
Next we focused on the formation of the 6,7-dihydrobenzofuran-4(5*H*)-one **14**. Saponification[15] of ester **12** gave carboxylic acid **13**. Cyclization to the dihydrobenzofuranone **14** was performed in a one-pot procedure by conversion of the acid to the corresponding acid chloride followed by addition of tin tetrachloride (0.2 equiv).[16] This way benzofuranone **14** was obtained in essentially quantitative yield (Scheme 3). We now had to adjust the oxidation levels at positions 4 and 7. First, ketone **14** was reduced to alcohol **15** which then was protected with an acetate group. The benzylic functionalization at C7 turned out to be not easy. Eventually, it was found that radical bromination using NBS and irradiation led to bromide **17**. This sensitive intermediate was not isolated but rather subjected to solvolysis with DMSO in presence of $AgBF_4$ and Et_3N.[17] These conditions delivered a mixture of alcohol **18** and ketone **19**. Treatment of this mixture with Dess-Martin periodinane converted alcohol **18** to ketone **19**. A final cleavage of the acetate under basic conditions furnished auxofuran (**1**). Its spectral data were in full agreement with the literature.[2,3]

Scheme 3. Friedel-Crafts cyclization of acid 13 to benzofuranon 14 and adjustment of the oxidation levels to give auxofuran (1)



Instead of annulation by intramolecular Friedel-Crafts reaction, it was also possible to form the cyclohexane ring by intramolecular hydroxyalkylation (Scheme 4). Thus, reduction of ester **12** using DIBAL-H in hexane provided aldehyde **20**. Upon treatment of this aldehyde with TMSOTf in presence of 2,6-lutidine, silyl ether **21** was obtained.[18] Cleavage of the silyl ether also led to key alcohol **15**.

Scheme 4. Alternative ring closure via hydroxyalkylation to give silyl ether 15



In conclusion, a concise synthesis of the plant growth promoting natural product auxofuran (**1**) was developed. The synthesis features a Liu furan synthesis whereby enynol **10** was converted to 4-(furan-2-yl)butanoate **12** using a gold(I) catalyst. A subsequent Friedel-Crafts cyclization of the derived butanoic acid **13** led to 6,7-dihydrobenzofuran-4(5*H*)-one **14**. Reduction of the keto function and benzylic oxidation provided the target molecule. Alcohol **15** could also be obtained by intramolecular hydroxyalkylation reaction. Since enantioselective reduction of furanone **14** might be possible, this route offers the possibility to prepare auxofuran in an enantioselective manner.

EXPERIMENTAL SECTION

General. All reactions were performed under nitrogen atmosphere. All solvents used in the reactions were purified before use. The progress of the reactions was followed by using TLC (POLYGRAM SIL G/UV254; petroleum ether/EtOAc). Flash chromatography was performed on silica gel Silica M, 0.04–0.63 mm, from Machery-Nagel GmbH & Co. KG, Germany. Distilled petroleum ether with a boiling range of 40−60 °C was used. Dry diethyl ether (Et_2O), tetrahydrofuran and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, hexane, DMSO, DMPU and all amines ($i$$Pr_2NH$, 2,6-lutidine, pyridine, Et_3N) were distilled from CaH_2. Furthermore, dry CCl_4 was distilled from P_2O_5 and dry methanol was distilled from magnesium turnings. All commercially available compounds (abcr, Acros, Aldrich, Fluka, Merck and TCI) were used without purification. Photochemical reactions were performed using a KESSIL A160WE TUNA BLUE LED lamp. The lamp was adjusted to full intensity, white light. The lamp was fixed around 5 – 10 cm away from the reaction flask and a cooling fan pointing towards the reaction flask was used to keep the temperature between 20 – 25 °C during the reaction. ^{1}H (400.160 MHZ) and ^{13}C (100.620 MHz) spectra were recorded on a Bruker Avance 400 III HD spectrometer. Some of the spectra were acquired on a Bruker Avance 700 spectrometer (^{1}H NMR at 700.29 MHz, ^{13}C NMR at 176.09 MHz). C_6D_6, $CDCl_3$, DMSO d6 were used as solvents at room temperature. Peak assignments were made by NMR spectroscopy (^{1}H, ^{13}C, DEPT-135, H,H−COSY, HSQC, and HMBC). HRMS (ESI-TOF) analysis was performed on Bruker maXis 4G system, whereas HRMS (EI-SEM) analysis was performed on a MasCom Bremen MAT 95 system.

*(Z)-2-Iodopent-2-enal (**5**)*. To a solution of aldehyde **4** (10.0 g, 119 mmol, 1.00 equiv) in a mixture of water (300 mL) and THF (300 mL), potassium carbonate (19.9 g, 144 mmol, 1.21 equiv), DMAP (2.91 g, 23.8 mmol, 0.20 equiv) und iodine (45.4 g, 179 mmol, 1.50 eq) were added successively while stirring the mixture. The resulting brown reaction mixture was stirred overnight at room temperature. Then the mixture was diluted with EtOAc (150 mL) and saturated $Na_2S_2O_3$ solution (200 mL) was added. After that, the layers were separated and the organic layer was washed with saturated $Na_2S_2O_3$ solution (200 mL) and hydrochloric acid (0.1 M, 200 mL). The combined aqueous layers were extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The aldehyde **5** was obtained as a light-brown oil (23.6 g, 112 mmol, 94%). It was sufficiently pure to be used for the next step without further purifications. If purification is necessary, it is possible via flash chromatography (petroleum ether/EtOAc, 10:1 + 0.1% triethylamine) or vacuum distillation (84 °C, 2 mbar). R_f = 0.50 (petroleum ether/EtOAc, 5:1) starting material and product show the same R_f value; ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 0.60 (t, ^3J = 7.5 Hz, 3H, 5-H), 1.96 (qd app quin, ^3J = 7.4 Hz, 2H, 4-H), 6.02 (t, ^3J = 6.9 Hz, 1H, 3-H), 8.08 (bs, 1H, 1-H); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ [ppm] = 11.9 (C-5), 30.2 (C-4), 112.2 (C-2), 162.5 (C-3), 187.3 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for C_5H_7OINa $[M + Na]^+$ 232.9434; found 232.9434.

*(Z)-2-Iodopent-2-en-1-ol (**6**)*. Under nitrogen atmosphere the crude aldehyde **5** (23.0 g, 110 mmol, 1 equiv) was dissolved in dry THF (460 mL). The yellowish solution was cooled down to –80 °C and then DIBAL-H (1M in hexane, 165 mL, 165 mmol, 1.5 equiv) was added dropwise. After complete addition, the mixture was stirred for 20 min at –80 °C, the cooling bath was removed, and the mixture stirred for 30 min at rt. The yellow-orange reaction mixture was poured on ice-cooled sodium potassium tartrate solution (1M, 500 mL) and stirred at rt until phase separation. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was carried out either by distillation (0.29 mbar, 90 °C oil bath, 45 °C steam temperature) or by flash chromatography (petroleum ether/EtOAc, 10:1 + 0.1% triethylamine). The allylic alcohol **6** (20.8 g, 98.1 mmol, 89%) was obtained as a yellow oil. R_f = 0.29 (petroleum ether/EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 0.78 (t, ^3J = 7.6 Hz, 3H, 5-H), 1.21 (t, ^3J = 6.7 Hz, 1H, OH), 2.01 (qdt app quint, ^3J = 7.5 Hz, ^5J = 1.1 Hz, 2H, 4-H), 3.86 (ddt als dd, ^3J = 6.6 Hz, ^4J = 1.3 Hz 1H, 1-H), 5.48 (tt, ^3J = 6.7 Hz, ^4J = 1.3 Hz, 1H, 3-H); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ [ppm] = 13.0 (C-5), 29.7 (C-4), 71.8 (C-1), 108.7 (C-2), 136.8 (C-3); HRMS (EI-SEM) *m/z*: calcd. for C_5H_9OI $[M]^{+\bullet}$ 211.9693; found 211.9713.

*But-3-yn-1-yl trifluoromethanesulfonate[14] (**8**)*. Under nitrogen atmosphere, but-3-yn-1-ol (5.00 mL, 65.9 mmol, 1 equiv) and dry pyridine (5.6 mL, 65.9 mmol, 1 equiv) were dissolved in dry CH_2Cl_2 (50 mL). This solution was added dropwise to a solution of trifluoromethanesulfonic anhydride (10.0 mL, 85.1 mmol,1.3 equiv) in dry CH_2Cl_2 (45 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3.5 h meanwhile the color changed from colorless to red brown. Then the reaction was quenched with water (250 mL). The layers were separated and the organic layer was washed with water (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (300 mbar, 25 °C). The triflate was obtained as a light-brown liquid (12.8 g, 63.3 mmol, 96%). It was pure enough to be used in the next step. Purification is possible by flash chromatography (pentane/CH_2Cl_2, 15:1) to give the triflate as a colorless liquid. R_f = 0.73 (petroleum ether/DE, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.10 (t, ^4J = 2.7 Hz, 2H, 4-H), 2.73 (dt, ^3J = 6.7 Hz, ^4J = 2.7 Hz, 2H, 2-H), 4.57 (t, ^3J = 6.7 Hz, 2H, 1-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ [ppm] = 19.9 (C-2), 71.8 (C-4), 73.5 (C-1), 76.9 (C-3), 113.8 – 123.3 (q, ^1J = 320 Hz, CF_3); ^{19}F NMR (377 MHz, C_6D_6): δ [ppm] = –75.23 (CF_3).

*tert-Butyl hex-5-ynoate[13] (**9**)*. Under nitrogen atmosphere, to a solution of $i$$Pr_2NH$ (12.3 mL, 87.4 mmol, 1.4 equiv) in dry THF (580 mL) was added at –80 °C n-BuLi (2.5M in hexane, 35.0 mL, 87.5 mmol, 1.4 equiv) in a dropwise fashion. The mixture was stirred at –80 °C for 45 min to form the LDA. Then *tert*-butyl acetate (9.50 mL, 71.2 mmol, 1.2 equiv) was added and the mixture stirred for 1 h. At this point DMPU (35.5 mL, 294 mmol, 4.8 equiv) was introduced and stirring continued for 10 min. The color of the reaction mixture turned from colorless to yellow. Finally, the crude triflate **8** (12.4 g, 61.3 mmol, 1 equiv), dissolved in dry THF (10 mL) was added. Then, the cooling bath was removed and the mixture stirred at room temperature overnight. The orange-red reaction mixture was quenched by adding saturated NH_4Cl solution (250 mL) and diluted with hexane (250 mL). The organic layer was washed with hydrochloric acid (1M, 2 × 250 mL) and water (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude ester could be purified by flash chromatography (pentane/Et_2O, 20:1) or distillation (2.5 mbar, 80 °C oil bath, b.p. 46 °C). The ester **9** (8.56 g, 50.9 mmol, 83%) was obtained as a colorless liquid. R_f = 0.42 (petroleum ether/DE, 10:1); ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 1.33 (s, 9H, C(CH_3)$_3$), 1.64 (tt (app quin), ^3J = 7.1 Hz, 2H, 3-H), 1.71

(t, ^4J = 2.7 Hz, 1H, 6-H), 1.95 (dt, ^3J = 7.0 Hz, ^4J = 2.7 Hz, 2H, 4-H), 2.17 (t, ^3J = 7.3 Hz, 2H, 2-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 18.3 (C-4), 24.5 (C-3), 28.4 ($C(CH_3)_3$), 34.5 (C-2), 69.8 (C-6), 80.0 ($C(CH_3)_3$), 83.8 (C-5), 172.2 (CO_2tBu).

*tert-Butyl (E)-7-(hydroxymethyl)dec-7-en-5-ynoate (**10**)*. To a solution of dry triethylamine (110 mL, 794 mmol, 30 equiv) in dry THF (120 mL) were added $Pd(PPh_3)_4$ (1.59 g, 1.38 mmol, 0.05 equiv), iodopent-2-enol **6** (5.61 g, 26.4 mmol, 1 equiv), dissolved in dry THF (60 mL), hexynoate **9** (5.00 g, 29.7 mmol, 1.13 equiv), dissolved in dry THF (60 mL), and CuI (1.25 g, 6.58 mmol, 0.25 eq) successively at 10 °C under an argon atmosphere. Then the yellow mixture was slowly allowed to warm to room temperature in the water bath, initially having a temperature of 10 °C. After 20 h, the dark-yellow mixture was diluted with hexane (200 mL), filtered (repeatedly rinsed with hexane), and concentrated in vacuo. The orange-brown oil was purified by flash chromatography (petroleum ether/EtOAc, 6:1, 0.1% triethylamine) to obtain enynol **10** (6.33 g, 25.1 mmol, 95%) as a light orange oil. R_f = 0.18 (petroleum ether/EtOAc, 5:1); ^1H NMR (400 MHz, C_6D_6): δ [ppm] = 0.93 (t, ^3J = 7.1 Hz, 3H, 10-H), 1.18 (t, ^3J = 6.6 Hz, 1H, OH), 1.35 (s, 9H, $C(CH_3)_3$), 1.70 (tt (app quin), ^3J = 7.1 Hz, 2H, 3-H), 2.19 (t, ^3J = 7.0 Hz, 2H, 4-H), 2.23 (t, ^3J = 7.3 Hz, 2H, 2-H), 2.33 (qd (app quin), ^3J = 7.6 Hz, 2H, 9-H), 3.97 (d, ^3J = 5.4 Hz, 2H, CH_2OH), 5.70 (t, ^3J = 7.3 Hz, 1H, 8-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 14.1 (C-10), 19.4 (C-4), 24.2 (C-9), 24.9 (C-3), 28.4 ($C(CH_3)_3$), 34.7 (C-2), 66.5 (CH_2OH), 78.8 (C-6), 80.1 ($C(CH_3)_3$), 95.0 (C-5), 124.1 (C-7), 138.0 (C-8), 172.4 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for $C_{15}H_{24}O_3Na$ $[M + Na]^+$ 275.1618; found 275.1619.

di-tert-Butyl dodeca-5,7-diynedioate. If the reaction was carried out at room temperature, the palladium catalyst was not good enough, or there was oxygen present, a significant amount of the dimeric side product as a light yellow sticky solid was observed , and thus, the yield of the enynol **10** decreased. R_f = 0.75 (petroleum ether/EtOAc, 5:1); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.43 (s, 18H, $C(CH_3)_3$), 1.79 (tt (app quin), ^3J = 7.3 Hz, 4H, 3-H), 2.31 (t, ^3J = 7.0 Hz, 4H, 4-H), 2.33 (t, ^3J = 7.5 Hz, 4H, 2-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 19.0 (C-4), 24.3 (C-3), 28.4 ($C(CH_3)_3$), 34.5 (C-2), 67.4 (C-6), 77.3 (C-5), 80.0 ($C(CH_3)_3$), 172.1 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for $C_{20}H_{30}O_4Na$ $[M + Na]^+$ 357.2036; found 357.2039.

*tert-Butyl 4-(4-propylfuran-2-yl)butanoate (**12**)*. Under nitrogen atmosphere enynol **10** (4.00 g, 15.9 mmol, 1 equiv) was dissolved in dry methanol (**11** c(**10**) = 0.1M, **B** c(**10**) = 0.08M) and then Au(I)-catalyst {0.477 mmol, 0.03 equiv [(acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**11**) (368 mg)] or [(acetonitrile)[triphenylphosphine]gold(I) hexafluoroantimonate (**B**) (351 mg)]} was added to the light orange solution. The reaction mixture was stirred for 19 h (**11**) or 24 h (**B**) at room temperature and then quenched with tetra-*n*-butylammonium bromide (TBAB)-solution in THF (1M, same quantity as methanol). Thereafter, Et_2O was added to reach phase separation, followed by extraction of the aqueous layer with Et_2O (4 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The light yellow oil was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give furan derivative **12** (using **11**: 3.69 g, 14.63 mmol, 92%; using catalyst **B**: 3.17 g, 12.56 mmol, 79%) as a colorless liquid. R_f = 0.77 (petroleum ether/EtOAc, 5:1); ^1H NMR (400 MHz, C_6D_6): δ [ppm] = 0.85 (t, ^3J = 7.3 Hz, 3H, 3''-H), 1.36 (s, 9H, $C(CH_3)_3$), 1.43 (qt (app sext), ^3J = 7.4 Hz, 2H, 2''-H), 1.89 (tt (app quin), ^3J = 7.2 Hz, 2H, 3-H), 2.11 (t, ^3J = 7.3 Hz, 2H, 2-H), 2.20 (dt, ^3J = 7.3 Hz, ^4J = 0.7 Hz, 2H, 1''-H), 2.50 (t, ^3J = 7.5 Hz, 2H, 4-H), 5.78 (bs, 1H, 3'-H), 6.97 (d, ^4J = 1.0 Hz, 1H, 5'-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 14.3 (C-3''), 23.8 (C-2''), 24.3 (C-3), 27.7 (C-1''), 28.0 (C-4), 28.5 ($C(CH_3)_3$), 35.1(C-2), 79.8 ($C(CH_3)_3$), 107.6 (C-3'), 126.3 (C-4'), 137.9 (C-5'), 156.1 (C-2'), 172.5 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for $C_{15}H_{24}O_3Na$ $[M + Na]^+$ 275.1618; found 275.1623.

*4-(4-Propylfuran-2-yl)butanoic acid (**13**)*. Ester **12** (2.50 g, 9.91 mmol, 1 eq) was treated with Claisen's alkali [66 mL of a mixture of KOH (21 g), water (15 mL) and methanol (60 mL)] and the resulting yellow solution was stirred at room temperature for 24 h. Then water (60 mL) was added and the mixture extracted with diethyl ether (3 × 60 mL). This was followed by acidification of the aqueous layer to pH = 1 using hydrochloric acid (1M). The acidic aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic extracts (only from the acidic phase) were dried over $MgSO_4$, filtered, and concentrated in vacuo. The acid (1.94 g, 9.89 mmol, >99%) was obtained as a light yellow viscous oil and was pure enough for the next step. R_f = 0.41 (petroleum ether/EtOAc, 3:1); ^1H NMR (400 MHz, DMSO d_6): δ [ppm] = 0.87 (t, ^3J = 7.3 Hz, 3H, 3''-H), 1.48 (qt (app sext), ^3J = 7.3 Hz, 2H, 2''-H), 1.76 (tt (app quin), ^3J = 7.3 Hz, 2H, 3-H), 2.22 (t, ^3J = 7.3 Hz, 2H, 2-H), 2.27 (t, ^3J = 7.3 Hz, 2H, 1''-H), 2.54 (t, ^3J = 7.5 Hz, 2H, 4-H), 5.98 (s, 1H, 3'-H), 7.23 (d, ^4J = 0.9 Hz, 1H, 5'-H), 12.05 (s, 1H, CO_2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO d_6): δ [ppm] = 13.7 (C-3''), 22.6 (C-2''), 23.0 (C-3), 26.4 (C-1''), 26.8 (C-4), 32.8 (C-2), 106.8 (C-3'), 125.1 (C-4'), 137.2 (C-5'), 154.9 (C-2'), 174.1 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for $C_{11}H_{16}O_3Na$ $[M + Na]^+$ 219.0992; found 219.0990; calcd. for $C_{11}H_{15}O_3$ $[M - H]^-$ 195.1027; found 195.1031.

*3-Propyl-6,7-dihydrobenzofuran-4(5H)-one (**14**)*. Under argon atmosphere, to a solution of furylbutanoic acid **13** (1.80 g, 9.17 mmol, 1 equiv) in dry toluene (92 mL) was added phosphorus pentachloride (2.29 g, 11.0 mmol, 1.2 equiv) at 0 °C in one portion while stirring the reaction mixture with a mechanical stirrer. The mixture was stirred at 0 °C for 1 h. Thereafter, $SnCl_4$ (0.1M in toluene, 18.5 mL, 1.85 mmol, 0.2 equiv) was added dropwise to the dark turquoise colored solution. A dirty green precipitate formed, and the reaction mixture was stirred at 0 °C for 17 h. The mixture was diluted with CH_2Cl_2 (100 mL), poured on a mixture of saturated $NaHCO_3$ solution (100 mL) and ice (100 g). This mixture was stirred at room temperature until phase separation was observed. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The light brown residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1), to give dihydrobenzofuranone **14** (1.60 g, 8.98 mmol, 98%) as a light yellow oil. R_f = 0.65 (petroleum ether/EtOAc, 3:1); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.93 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.59 (qt (app sext), ^3J = 7.3 Hz, 2H, 2'-H), 2.13 (tt (app quin), ^3J = 6.5 Hz, 2H, 6-H), 2.45 (t, ^3J = 7.0 Hz, 2H, 5-H), 2.57 (t, ^3J = 7.5 Hz, 2H, 1'-H), 2.82 (t, ^3J = 6.3 Hz, 2H, 7-H), 7.06 (s, 1H, 2-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ [ppm] = 13.8 (C-3'), 22.3 (C-2'), 22.7 (C-6), 23.7 (C-7), 26.1 (C-1'), 38.4 (C-5), 120.0 (C-3a), 124.2 (C-3), 138.6 (C-2), 167.6 (C-7a), 195.4 (C-

4); HRMS (ESI-TOF) *m/z*: calcd. for $C_{11}H_{14}O_2Na$ $[M + Na]^+$ 201.0886; found 201.0888.

*3-Propyl-4,5,6,7-tetrahydrobenzofuran-4-ol (**15**)*. To a solution of ketone **14** (650 mg, 3.65 mmol, 1 equiv) in dry methanol (15 mL), stirred at 0 °C and kept under nitrogen atmosphere, was added $NaBH_4$ (83.0 mg, 2.19 mmol, 0.6 equiv) portionwise. The mixture was stirred at room temperature for 3 h. Then water (15 mL) was added and CH_2Cl_2 to reach phase separation. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The alcohol **15** (657 mg, 3.64 mmol, >99%) was obtained as a colorless oil which can solidify in the freezer. If purification is necessary, it is possible via flash chromatography (petroleum ether/EtOAc, 6:1). R_f = 0.48 (petroleum ether/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 0.93 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.30 – 1.39 (m, 1H, 7-H), 1.41 – 1.46 (m, 1H, 5-H), 1.53 – 1.65 (m, 4H, 2'-H, 5-H, 7-H), 2.17 – 2.24 (m, 1H, 6-H), 2.32 – 2.45 (m, 3H, 1'-H, 6-H), 4.50 (t, ^3J = 4.0 Hz, 1H, 4-H), 6.95 (s, 1H, 2-H); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ [ppm] = 14.6 (C-3'), 18.9 (C-7), 23.4 (C-2'), 23.9 (C-6), 26.6 (C-1'), 33.4 (C-5), 63.3 (C-4), 120.8 (C-3), 125.2 (C-3a), 137.8 (C-2), 153.2 (C-7a); HRMS (EI-SEM) *m/z*: calcd. for $C_{11}H_{16}O_2$ $[M]^{+\bullet}$ 180.1145; found 180.1155.

*3-Propyl-4,5,6,7-tetrahydrobenzofuran-4-yl acetate (**16**)*. To a solution of alcohol **15** (584 mg, 3.24 mmol, 1 equiv) in dry Et_3N (5.90 mL, 42.6 mmol, 13.1 eq) was added acetic anhydride (0.86 mL, 9.10 mmol, 2.8 eq) under a nitrogen atmosphere. Finally, a spatula of DMAP was added and the reaction mixture was stirred at room temperature for 3.5 h. Then the mixture was diluted with methanol (10 mL) and water (60 mL) before ethyl acetate was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The yellow oil was purified by flash chromatography (petroleum ether/EtOAc, 30:1). The acetate **16** (717 mg, 3.23 mmol, >99%) was obtained as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 0.88 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.28 – 1.36 (m, 1H, 6-H), 1.44 – 1.55 (m, 3H, 2'-H, 5-H), 1.32 – 1.69 (m, 1H, 6-H), 1.72 (s, 3H, $OCOCH_3$), 1.75 – 1.81 (m, 1H, 5-H), 2.11 – 2.19 (m, 1H, 7-H), 2.24 – 2.32 (m, 2H, 1'-H), 2.33 – 2.39 (m, 1H, 7-H), 6.06 (t, ^3J = 3.7 Hz, 1H, 4-H), 6.92 (s, 1H, 2-H); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ [ppm] = 14.4 (C-3'), 19.3 (C-6), 21.2 ($OCOCH_3$), 23.4 (C-2'), 23.6 (C-7), 26.40 (C-1'), 30.0 (C-5), 65.6 (C-4), 117.2 (C-3a), 124.9 (C-3), 138.1 (C-2), 154.9 (C-7a), 170.2 ($OCOCH_3$); HRMS (EI-SEM) *m/z*: calcd. for $C_{13}H_{18}O_3$ $[M]^{+\bullet}$ 222.1250; found 222.1216.

*7-Oxo-3-propyl-4,5,6,7-tetrahydrobenzofuran-4-yl acetate (**19**)*. Under argon atmosphere acetate **16** (200 mg, 0.900 mmol, 1.1 equiv) was dissolved in dry CCl_4 (20 mL, dried over neutral aluminium oxide directly before use) at room temperature. This was followed by the addition of yellowish *N*-bromosuccinimide (NBS, 144 mg, 0.809 mmol, 1 equiv). The mixture was irradiated (white light including 621 nm) for 1 h during which succinimide appeared as a white precipitate on the top of the solution. The irradiation was discontinued and then DMSO (2 mL, 28.2 mmol, 34.8 equiv, dried over neutral aluminium oxide directly before use), and $AgBF_4$ (157 mg, 0.809 mmol, 1 equiv) were added. This caused immediate precipitation of silver bromide. The mixture was stirred at room temperature for 30 min before Et_3N (0.25 mL, 1.80 mmol, 2.2 equiv) was added. After that, the reaction mixture was stirred at room temperature for 2.5 h. The mixture was diluted with ethyl acetate (10 mL) and filtered through a plug of silica. The filtrate was concentrated in vacuo. The light brown residue was dissolved in dry CH_2Cl_2 (50 mL) and $NaHCO_3$ (340 mg, 4.05 mmol, 5 equiv) and DMP (515 mg, 1.21 mmol, 1.5 equiv) were added. The reaction mixture was stirred at room temperature overnight before it was quenched with saturated $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution (60 mL, 1:1). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The brown oil was purified by flash chromatography (petroleum ether/EtOAc, 8:1, 0.1% TEA). The ketone **19** (89.1 mg, 0.377 mmol, 47%) was isolated as a yellowish oil. R_f (alcohol) = 0.32 (petroleum ether/EtOAc, 3:1); R_f (ketone) = 0.38 (petroleum ether/EtOAc, 3:1); ^{1}H NMR (700 MHz, C_6D_6): δ [ppm] = 0.76 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.27 (qt (app sext), 2H, 2'-H), 1.61 (s, 3H, $OCOCH_3$), 1.70 – 1.76 (m, 2H, 5-H), 2.04 – 2.14 (m, 3H, 1'-H, 6-H), 2.42 (ddd, ^2J = 17.0 Hz, ^3J = 9.0 Hz, ^3J = 5.2 Hz, 1H, 6-H), 5.87 (dd (app t), ^3J = 4.6 Hz, 1H, 4-H), 6.77 (bs, 1H, 2-H); ^{13}C{^{1}H} NMR (176 MHz, C_6D_6): δ [ppm] = 14.2 (C-3'), 20.7 ($OCOCH_3$), 23.2 (C-2'), 25.7 (C-1'), 30.6 (C-5), 35.1 (C-6), 64.9 (C-4), 125.7 (C-3), 135.2 (C-3a), 144.6 (C-2), 149.3 (C-7a), 169.8 ($OCOCH_3$), 184.5 (C-7); HRMS (ESI-TOF) *m/z*: calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0941; found 259.0942.

*Auxofuran (**1**)*. Under nitrogen atmosphere, acetate **19** (29.6 mg, 0.125 mmol, 1 equiv) was dissolved in dry methanol (1.25 mL). $NaHCO_3$ (10.5 mg, 0.125 mmol, 1 equiv) was added and the mixture was stirred at room temperature for 4 h. The orange reaction mixture was quenched by adding saturated NH_4Cl solution (2 mL) and ethyl acetate was added to reach phase separation. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The yellow oil was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give auxofuran (**1**) (22.3 mg, 0.115 mmol, 92%) as a colorless oil. R_f = 0.39 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 0.96 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.62 (qt (app sext), 2H, 2'-H), 2.11 (bs, 1H, OH), 2.17 (dddd, ^2J = 18.1 Hz, ^3J = 10.6 Hz, ^3J = 6.0 Hz, ^3J = 4.5 Hz, 1H, 5-H), 2.38 (dddd (ddd), ^2J = 17.6 Hz, ^3J = 8.6 Hz, ^3J = 4.5 Hz, 1H, 5-H), 2.46 – 2.54 (m, 3H, 1'-H, 6-H), 2.86 (ddd, ^2J = 17.0 Hz, ^3J = 8.6 Hz, ^3J = 4.5 Hz, 1H, 6-H), 5.01 (dd, ^3J = 5.8 Hz, ^3J = 4.1 Hz, 1H, 4-H), 7.37 (bs, 1H, 2-H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ [ppm] = 13.9 (C-3'), 22.7 (C-2'), 25.4 (C-1'), 33.8 (C-5), 34.5 (C-6), 63.6 (C-4), 125.9 (C-3), 139.2 (C-3a), 144.8 (C-2), 147.0 (C-7a), 185.8 (C-7); HRMS (ESI-TOF) *m/z*: calcd. for $C_{11}H_{14}O_3Na$ $[M + Na]^+$ 217.0835; found 217.0836.

*4-(4-Propylfuran-2-yl)butanal (**20**)*. To a solution of furanylbutanoate **12** (690 mg, 2.73 mmol, 1 equiv) in dry hexane (30 mL) was added DIBAL-H (1M in hexane, 2.75 ml, 2.75 mmol, 1.01 equiv) dropwise at –80 °C under nitrogen atmosphere. The reaction mixture was stirred for 75 min at –80 °C. Then dry methanol (4 mL) was added and the light yellow solution was poured on ice-cooled sodium potassium tartrate solution (1M, 40 mL). This mixture was stirred at room temperature until phase separation was observed. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 6:1, 0.1% Et_3N) to give aldehyde **20** (492 mg, 2.73 mmol, > 99%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.92

(t, ^3J = 7.5 Hz, 3H, 3''-H), 1.53 (qt (app sext), ^3J = 7.5 Hz, 2H, 2''-H), 1.95 (tt (app quin), ^3J = 7.2 Hz, 2H, 3-H), 2.31 (t, ^3J = 7.3 Hz, 2H, 1''-H), 2.46 (dt, ^3J = 7.2 Hz, ^4J = 1.5 Hz, 2H, 2-H), 2.62 (t, ^3J = 7.2 Hz, 2H, 4-H), 5.88 (bs, 1H, 3'-H), 7.06 (d, ^4J = 1.0 Hz, 1H, 5'-H), 9.74 (t, ^4J = 1.6 Hz, 1H, 1-H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ [ppm] = 13.8 (C-3''), 20.6 (C-3), 23.1 (C-2''), 27.0 (C-1''), 27.3 (C-4), 43.0 (C-2), 107.2 (C-3'), 125.9 (C-4'), 137.2 (C-5'), 154.8 (C-2'), 202.1 (C-1);

^1H NMR (400 MHz, C_6D_6): δ [ppm] = 0.87 (t, ^3J = 7.3 Hz, 3H, 3''-H), 1.46 (qt (app sext), ^3J = 7.5 Hz, 2H, 2''-H), 1.64 (tt (app quin), ^3J = 7.3 Hz, 2H, 3-H), 1.77 (t, ^3J = 7.3 Hz, 2H, 2-H), 2.21 (t, ^3J = 7.3 Hz, 2H, 1''-H), 2.33 (t, ^3J = 7.5 Hz, 2H, 4-H), 5.72 (bs, 1H, 3'-H), 6.98 (d, ^4J = 1.0 Hz, 1H, 5'-H), 9.20 (t, ^4J = 1.3 Hz, 1H, 1-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 13.9 (C-3''), 20.7 (C-3), 23.5 (C-2''), 27.3 (C-1''), 27.5 (C-4), 42.8 (C-2), 107.3 (C-3'), 125.9 (C-4'), 137.5 (C-5'), 155.4 (C-2'), 200.1 (C-1); HRMS (ESI-TOF) *m/z*: calcd. for $C_{12}H_{20}O_3Na$ $[M + CH_3OH + Na]^+$ 235.1305; found 235.1304.

*3-Propyl-4,5,6,7-tetrahydrobenzofuran-4-ol (**15**) from aldehyde **20***.[18] To a solution of aldehyde **20** (180 mg, 0.999 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) was added 2,6-lutidine (0.780 mL, 4.99 mmol, 5 equiv) at –80 °C. This was followed by the dropwise addition of TMSOTf (1M in CH_2Cl_2, 2.50 mL, 2.50 mmol, 2.5 equiv) at –80 °C. The reaction mixture was stirred for 20 h at –80 °C. Then water (15 mL) was added and the mixture was warmed to room temperature. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

To the crude TMS-protected alcohol **21** (255 mg) in dry THF (20 mL) was added TBAF (1M in THF, 1.50 mL, 1.50 mmol, 1.5 equiv) dropwise at 0 °C under nitrogen atmosphere followed by stirring of the mixture for 1 h at 0 °C. Thereafter, the mixture was dry-loaded on silica and purified by flash chromatography (petroleum ether/EtOAc, 6:1) to provide alcohol **15** (135 mg, 0.749 mmol, 75 %) as a colorless viscous oil.

*Silyl ether **21***: R_f = 0.90 (petroleum ether/EtOAc, 5:1); ^1H NMR (400 MHz, C_6D_6): δ [ppm] = 0.17 (s, 9H, $Si(CH_3)_3$), 0.95 (t, ^3J = 7.3 Hz, 3H, 3'-H), 1.36 – 1.44 (m, 1H, 7-H), 1.53 – 1.68 (m, 4H, 2'-H, 5-H), 1.79 – 1.89 (m, 1H, 7-H), 2.36 – 2.34 (m, 1H, 6-H), 2.39 – 2.50 (m, 3H, 1'-H, 6-H), 4.75 (t, ^3J = 4.7 Hz, 1H, 4-H), 7.00 (s, 1H, 2-H); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ [ppm] = 0.7 ($Si(CH_3)_3$), 14.2 (C-3'), 19.2 (C-7), 23.2 (C-2'), 23.5 (C-6), 26.5 (C-1'), 33.6 (C-5), 64.7 (C-4), 120.5 (C-3), 124.9 (C-3a), 137.4 (C-2), 152.5 (C-7a); HRMS (ESI-TOF) *m/z*: calcd. for $C_{14}H_{24}O_2SiNa$ $[M + Na]^+$ 275.1438; found 275.1441.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.joc.yyyy.

Copies of ^1H and ^{13}C NMR spectra for the synthesized compounds (PDF)

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