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FURTHER STUDIES ON THE GOLD-CATALYZED OXIDATIVE DOMINO CYCLIZATION/CYCLOADDITION TO GIVE POLYFUNCTIONAL TETRACYCLES

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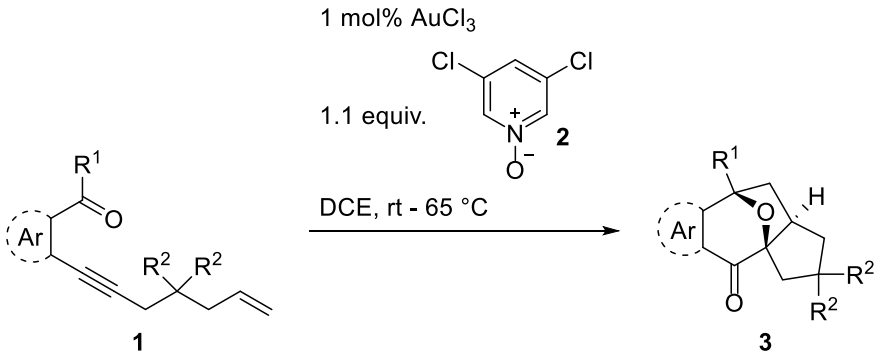
Abstract – Enyne aldehydes and ketones with ester and ether functions in the between the reactive functional groups were subjected to a gold(III)-catalyzed domino process in the presence of a pyridine *N*-oxide as external oxygen donor. The resulting tetracyclic ketoethers were formed in high yields under mild conditions and with excellent induced diastereoselectivity for substrates featuring stereogenic center within the enyne tether.

INTRODUCTION

Homogeneous gold catalysis[1] offers exciting opportunities for modern heterocyclic synthesis.[2] We communicated a mild and efficient gold-catalyzed oxidative domino cyclization/cycloaddition of enyne carbonyl compounds to give tetracyclic ketoethers embedding the hydrobenzoazulene ring systems of many naturally occurring diterpene families (Scheme 1).[3]

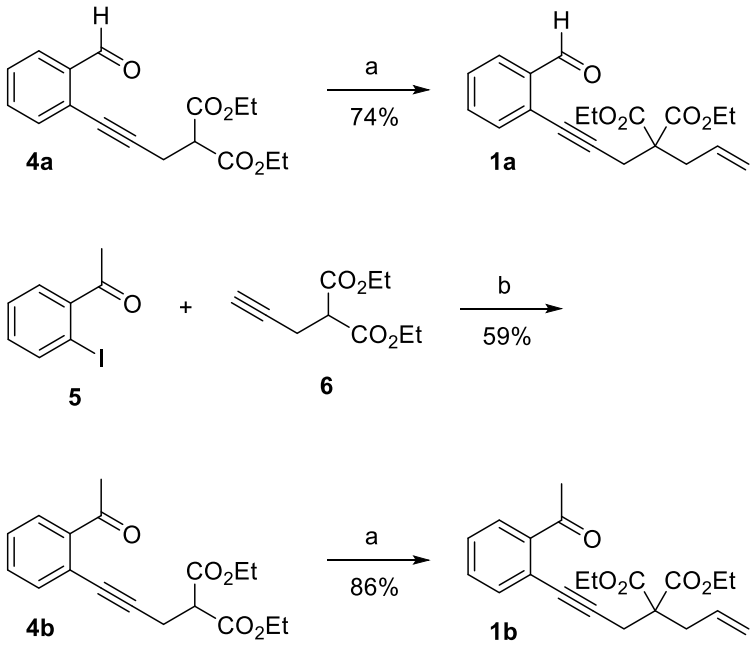


Scheme 1. Gold-catalyzed construction of tetracyclic ketoethers

Related transformations using rhodium,[4] platinum,[5] silver,[6] and gold[7] catalysis or stoichiometric amounts of iodine[8] have been reported as well.

RESULTS AND DISCUSSION

In order to compare the efficiency of our process with the alternative methodologies mentioned above, we decided to investigate the reaction of the known enyne benzaldehyde **1a** bearing a malonate unit within the tether between alkene and alkyne (Scheme 2). This substrate, which had already been studied in rhodium-,[4] platinum-,[5] and silver-catalyzed (CO_2Me instead of CO_2Et)[6] as well as iodine-mediated[8] transformations, was readily prepared by allylation of malonate **4a**.[9] The corresponding enyne ketone **1b** was synthesized as an additional substrate by Sonogashira coupling of the commercially available building blocks **5** and **6** to give malonate **4b** and subsequent allylation.

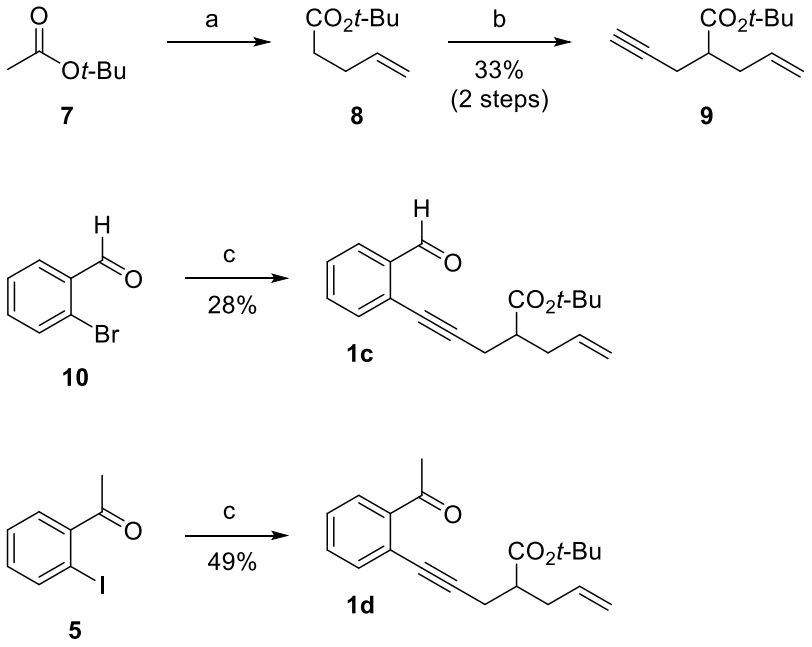


Synthesis of substrates **1a** and **1b**. *Reagents and conditions:* a) NaH, THF, 0 °C, then allyl bromide, THF, rt; b) 1.6 mol% $PdCl_2(PPh_3)_2$, 1.6 mol% CuI, Et_3N, rt.

Scheme 2

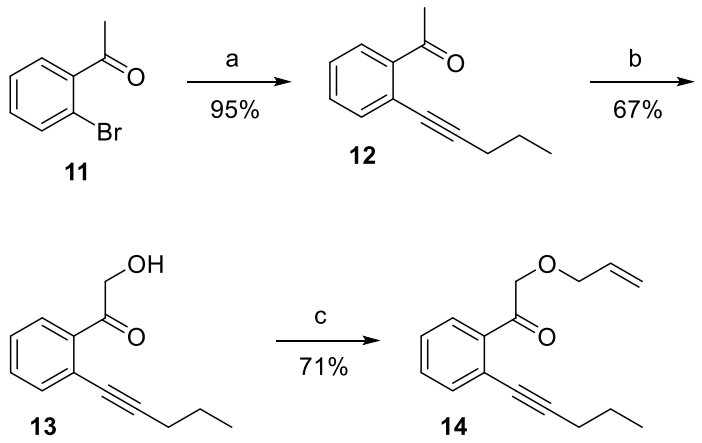
We were also interested in examining the substrate-controlled diastereoselectivity of the gold-catalyzed oxidative domino cyclization/cycloaddition for substrates containing a stereogenic center within the enyne tether. With this background, we synthesized the monoesters **1c** and **1d** (Scheme 3). In this case, the complete enyne portion was first prepared by sequential allylation and propargylation starting from ester **7** without purification of the known allylation product **8**.[10] Sonogashira coupling of alkyne **9** with bromo aldehyde **10** and iodo ketone **5** then yielded the desired enyne aldehyde **1c** and enyne ketone **1d**,

respectively. Both compounds turned out to be rather unstable and had to be used for the subsequent gold-catalyzed reaction rather quickly.



Synthesis of substrates **1c** and **1d**. *Reagents and conditions:* a) LDA, THF, –78 °C, then allyl bromide, –78 °C to rt; b) LDA, THF, –78 °C, then propargyl bromide, –78 °C to rt; c) **9**, 2 mol% $PdCl_2(PPh_3)_2$, 1-3 mol% CuI, Et_3N, rt.

Scheme 3

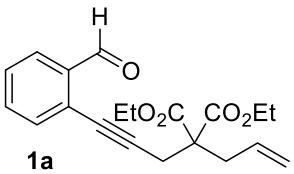
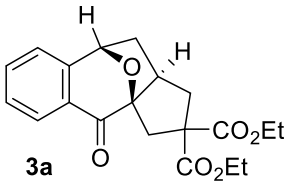
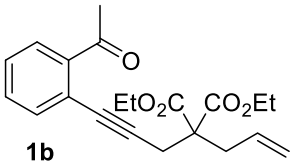
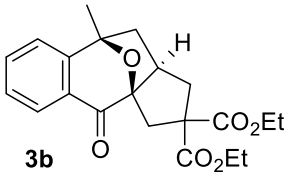
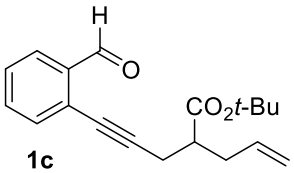
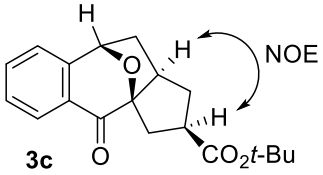
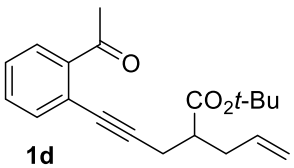
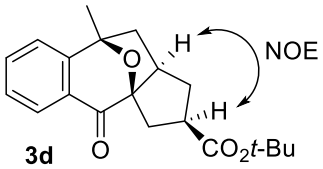
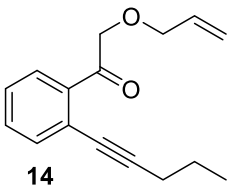
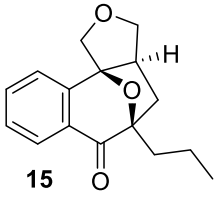


Synthesis of substrate **14** with alternative tethering of the reactive units. *Reagents and conditions:* a) 1-pentyne, 2 mol% $PdCl_2(PPh_3)_2$, 3 mol% CuI, *i*-Pr_2NH, microwave (300 W), 80 °C; b) TMSOTf, 2,6-lutidine, CH_2Cl_2, –10 °C to 0 °C, then MCPBA, CH_2Cl_2, 0 °C; c) Ag_2O, $CaSO_4$, allyl bromide, 0 °C to rt.

Scheme 4

Since the presence of a heteroatom between carbonyl group and alkene in the alternative tethering of the reactive units[3] had not been addressed yet, the acyclic ketoether **14** was chosen as another substrate (Scheme 4). Sonogashira coupling of bromo ketone **11** with 1-pentyne under microwave irradiation provided ynone **12** in superior yield compared with conventional heating.[11] Rubottom oxidation[12] of the silyl enol ether derived from **12** furnished α-hydroxy ketone **13**, which was *O*-allylated[13] to give the enyne ketone **14**.

Table 1. Gold-catalyzed domino cyclization/cycloaddition[a]

Entry	Substrate	Time	Product	Yield (%)
1	 **1a**	15 min	 **3a**	90
2	 **1b**	20 min	 **3b**	67
3	 **1c**	1 h	 **3c**	82
4	 **1d**	20 h	 **3d**	65
5	 **14**	2 h	 **15**	89

[a] *Conditions*: 1 mol% $AuCl_3$, 1.1 equiv **2**, DCE, rt.

Upon subjecting enyne benzaldehyde **1a** to our standard conditions for the gold-catalyzed oxidative domino cyclization/cycloaddition,[3] a clean reaction occurred to deliver the tetracyclic ketoether **3a** in 90% yield after only 15 min at room temperature (Table 1, Entry 1). This result compares favorably with the previously reported catalytic transformations of **1a** into **3a** using rhodium (5 mol% $[Rh(COD)Cl]_2$, 83% yield, 12 h 100 °C),[4] platinum (10 mol% $PtCl_2(PPh_3)_2$, 40% yield, 20 h 110 °C),[5] or silver (CO_2Me instead of CO_2Et: 0.75 mol% $AgSbF_6$, 57% yield, overnight at room temperature)[6] catalysis. While the iodine-mediated conversion of **1a** to **3a** proceeds in 95% yield (12 h at room temperature),[8] this methodology was only applied to benzaldehydes and might be problematic with ketones bearing α-C–H bonds. Similar to **1a**, the enyne ketone **1b** (Table 1, entry 2) reacted smoothly under our conditions to give the tetracycle **3b** in good yield. It is noteworthy that the treatment of an analogue substrate (Ph instead of Me in **1b**) with 5 mol% of a gold(I) catalyst in air only led to traces of the corresponding tetracyclic ketoether.[7a] Pleasingly, the gold-catalyzed transformations of **1c** and **1d** (Table 1, Entries 3 and 4) turned out to be highly diastereoselective. Thus, the tetracycles were formed with diastereomeric ratios of 96:4 for **3c** and 98:2 for **3d** according to GC-MS analysis of the crude products. The relative configuration of **3c** and **3d** was elucidated by 2D NMR measurements, which showed the NOEs depicted in Table 1 and additionally by X-ray diffraction analysis for **3c** (Figure 1). Gratifyingly, allyl ether **14** also underwent an efficient reaction at room temperature to yield the heterocyclic product **15** (Table 1, Entry 5), the relative configuration of which was assigned in analogy to earlier results with substrates containing an all-carbon linkage between ketone and olefin.[3]

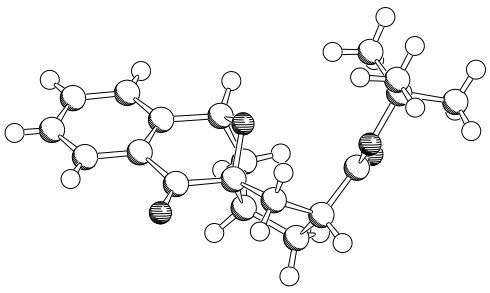
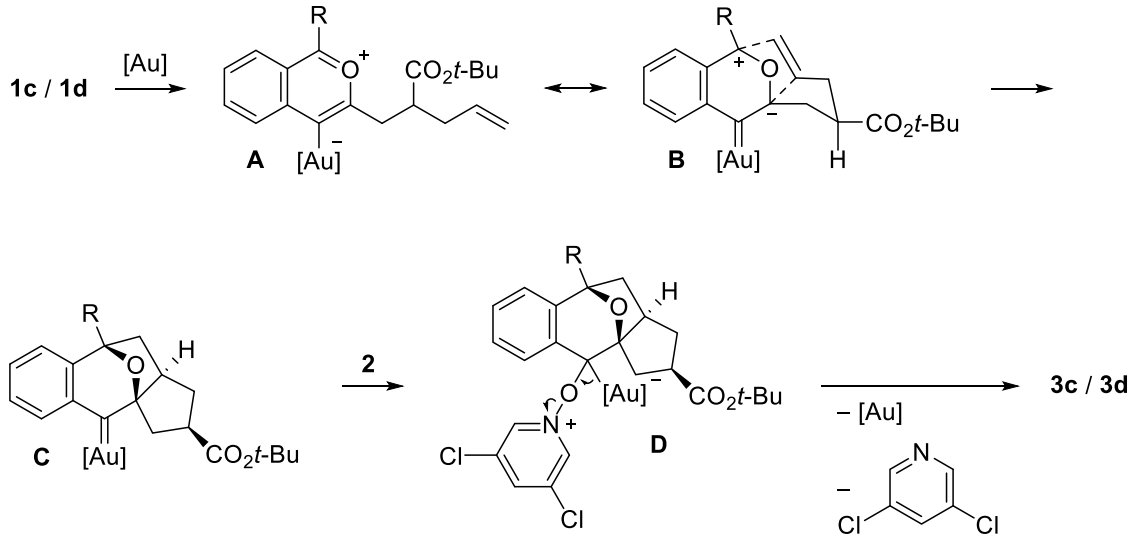


Figure 1. Crystal structure of tetracycle **3c**[14,15]

Scheme 5 illustrates a mechanistic rationale[3] for the diastereoselective formation of tetracycles **3c** and **3d** from enyne carbonyl compounds **1c** and **1d**, respectively. After intramolecular 6-*endo*-dig attack of the carbonyl oxygen atom on the gold-activated alkyne with generation of the isobenzopyrylium intermediate **A**, intramolecular 1,3-dipolar cycloaddition occurs preferentially via the chairlike folded transition state **B** with equatorially oriented *t*-butyl ester group. Subsequent intermolecular oxidation of the resultant gold

carbenoid **C** with *N*-oxide **2** gives rise to adduct **D**, which eventually decomposes to the products **3** with regeneration of the gold catalyst.



Scheme 5. Diastereoselective formation of the tetracyclic ketoethers **3c** and **3d**

In summary, novel tethers for the gold-catalyzed oxidative cyclization/cycloaddition of enyne carbonyl compounds were investigated. The resulting tetracyclic ketoethers were formed in high yields under mild conditions and with superior efficiency compared with alternative catalytic procedures. Excellent diastereoselectivity was observed for substrates featuring a stereogenic center within the enyne tether, and an ethereal oxygen atom was readily accommodated between ketone and olefin function in the alternative tethering mode.

EXPERIMENTAL

Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried and purified by passage through a *MBRAUN* SPS-800 device using molecular sieves. Triethylamine and 1,2-dichloroethane were distilled from CaH_2. All other solvents and reagents were used as received. Reactions were performed under an argon atmosphere. A *CEM* Discover apparatus was used for microwave reactions. Thin layer chromatography (TLC) was performed on *Merck* silica gel 60 F_{254} 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm and subsequently developed using anisaldehyde solution as appropriate. Flash column chromatography was carried out using silica gel (*Merck*, particle size 40–63 μm). Melting points were measured on a *Wagner & Munz* PolyTherm A and are uncorrected. Infrared spectra were recorded on a *Thermonicolet* Avatar 360 instrument using ATR. NMR spectra were recorded on a *Bruker* DRX 500 P (^{1}H 500 MHz, ^{13}C 125 MHz) spectrometer or else on an Avance III 600 (^{1}H 600 MHz, ^{13}C 150 MHz) or an AC-300-P (^{1}H 300 MHz, ^{13}C 75 MHz). Chemical shifts (δ) are quoted in parts

per million (ppm) downfield of tetramethylsilane, using residual proton-containing solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Mass spectra were recorded with an *Agilent* 5973N detector coupled with an *Agilent* 6890N GC (GC-MS, 70 eV) or a *Bruker* Esquire LC (direct injection as a methanolic NH_4OAc solution, ESI). HRMS spectra were recorded on a *Finnigan* MAT 95 (EI, 70 eV) or a *Bruker Daltonik* Impact II (ESI-TOF). Elemental analysis was performed on a *Hekatech* EA 3000. X-Ray diffraction analysis was carried out with a Bruker Kappa CCD diffractometer.

Allylation of malonate 4a to give enyne aldehyde 1a

To a solution of diester **4a**[9] (161 mg, 0.533 mmol) in THF (4 mL) at 0 °C was added NaH (60% in paraffin oil, 39.0 mg, 0.98 mmol). After stirring for 1 h at this temperature, the mixture was warmed to rt, and allyl bromide (800 μL, 9.25 mmol) was added. Stirring was continued for for 1 h, then water was added, and the mixture was extracted with pentane. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. Purification by flash chromatography on silica gel (isohexane/EtOAc, 9:1) gave **1a**[4-6,8,16] (134 mg, 74%) as a yellow oil.

Enyne aldehyde **1a**. R_f 0.51 (isohexane/EtOAc, 9:1); IR 3076 (w), 2982 (w), 2233 (w), 1918 (w), 1730 (s), 1698 (s), 1650 (m), 1594 (m), 1450 (m), 1290 (m), 1214 (s), 1191 (s), 1095 (m), 1067 (m), 926 (m), 857 (m), 824 (m), 765 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H), 7.47–7.58 (m, 2 H), 7.37–7.46 (m, 1 H), 5.59–5.81 (m, 1 H), 5.12–5.28 (m, 2 H), 4.25 (q, *J* = 7.2 Hz, 4 H), 3.11 (s, 2 H), 2.87 (d, *J* = 7.4 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 169.7, 136.1, 133.7, 133.5, 131.6, 128.4, 127.0, 126.8, 120.0, 92.0, 79.2, 61.8, 56.8, 36.8, 23.8, 14.1; GC-MS: *m/z* 342 $[M]^+$, 313, 297, 268, 239, 223, 195, 178, 165, 152, 139, 127, 115, 89, 77, 63.

Sonogashira coupling to give malonate 4b

To a solution of aryl iodide **5** (128 mg, 0.52 mmol) and malonate **6** (85.2 mg, 0.430 mmol) in triethylamine (4 mL) was added $PdCl_2(PPh_3)_2$ (4.8 mg, 0.007 mmol) and CuI (3.1 mg, 0.016 mmol) at rt. After stirring at rt for 2.5 h, the mixture was filtered over a pad of silica gel with Et_2O and concentrated in vacuum. Purification by flash chromatography on silica gel (isohexane/EtOAc, 9:1 then 4:1) yielded malonate **4b** (80.4 mg, 59%) as a yellow oil.

Malonate **4b**. R_f 0.33 (isohexane/EtOAc 4:1); IR 2983 (w), 2935 (w), 1728 (s), 1685 (m), 1446 (w), 1421 (w), 1368 (m), 1337 (m), 1276 (s), 1231 (s), 1152 (s), 1095 (m), 1030 (s), 959 (w), 857 (m), 162 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.70 (m, 1 H), 7.32–7.50 (m, 3 H), 4.21–4.30 (m, 4 H), 3.68 (t, *J* = 7.6 Hz, 1 H), 3.07 (d, *J* = 7.6 Hz, 2 H), 2.69 (s, 3 H), 1.29 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 167.9, 141.1, 134.2, 131.1, 128.3, 128.1, 121.5, 91.7, 81.4, 61.9, 51.1, 30.0, 19.7, 14.1;

GC-MS *m/z* 315 $[M–H]^+$, 287 $[M–Et]^+$, 271 [M–OEt], 259, 241, 215, 197, 185, 171, 159, 147, 127, 115, 101, 77, 43. HRMS *m/z* Calcd. for $C_{18}H_{20}O_5$ $[M]^+$: 316.1311. Found: 316.1305.

Allylation of malonate 4b to give enyne ketone 1b

To a solution of diester **4b** (75.3 mg, 0.238 mmol) in THF (2 mL) at 0 °C was added NaH (60% in paraffin oil, 13.5 mg, 0.34 mmol). After stirring for 1 h at this temperature, the mixture was warmed to rt, and allyl bromide (37.2 mg, 0.308 mmol) was added. Stirring was continued for 1 h, then water was added, and the mixture was extracted with pentane. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. Purification by flash chromatography on silica gel (isohexane/EtOAc, 4:1) gave **1b** (73.1 mg, 86%) as a yellow oil.

Enyne ketone **1b**. R_f 0.44 (isohexane/EtOAc 4:1); IR 3074 (w), 2981 (w), 2934 (s), 1917 (w), 1730 (s), 1698 (s), 1650 (m), 1479 (m), 1440 (m), 1363 (m), 1282 (m), 1212 (s), 1189 (s), 1143 (m), 1067 (m), 1036 (m), 925 (m), 857 (m), 763 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1 H), 7.48 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.41 (t, *J* = 7.9 Hz, 1 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 5.69 (ddt, *J* = 16.9, 10.2, 7.5 Hz, 1 H), 5.15–5.26 (m, 2 H), 4.23 (q, *J* = 7.2 Hz, 4 H), 3.09 (s, 2 H), 2.88 (d, *J* = 7.2 Hz, 2 H), 2.69 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.5, 169.8, 141.0, 134.4, 131.8, 131.1, 128.3, 128.0, 121.6, 119.9, 90.7, 82.4, 61.7, 56.9, 36.8, 30.0, 23.8, 14.1; GC-MS *m/z* 356 $[M]^+$, 327, 311, 283, 237, 209, 195, 178, 165, 152, 139, 128, 115, 103, 89, 77. HRMS *m/z* Calcd. for $C_{21}H_{24}O_5$ $[M]^+$: 356.1624. Found: 356.1621.

Synthesis of enyne 9

To a solution of diisopropylamine (0.53 mL, 3.8 mmol) in THF (20 mL) cooled to 0 °C was added BuLi (3.0 mL, 1.26 M in hexane, 3.8 mmol), and the mixture was stirred for 30 min at this temperature. After cooling to −78 °C, ester **7** (398 mg, 3.43 mmol) was added, and stirring was continued for 10 min. Then allyl bromide (360 μL, 4.16 mmol) was added, and the mixture was stirred overnight and slowly warmed to rt. Water (10 mL) and aqueous 1N HCl (5 mL) were added, and the mixture was extracted with EtOAc. After washing with water und brine, drying over Na_2SO_4, and concentration under reduced pressure, crude ester **8**[10] (274 mg) was obtained, which was used without further purification for the subsequent alkylation reaction.

To a solution of diisopropylamine (270 μL, 1.93 mmol) in THF (10 mL) cooled to 0 °C was added BuLi (1.2 mL, 1.6 M in hexane, 1.9 mmol), and the mixture was stirred for 30 min at this temperature. After cooling to −78 °C, a solution of crude ester **8** (274 mg) in THF (5 mL) was added, and stirring was continued for 20 min. Then propargyl bromide (380 μL, 80% solution in toluene, 3.53 mmol) was added, and the mixture was stirred for 3 d and slowly warmed to rt. Water (10 mL) and aqueous 1N HCl (5 mL) were added, and the mixture was extracted with EtOAc. After washing with water und brine, drying over

Na_2SO_4, and concentration under reduced pressure, flash chromatography on silica gel (isohexane/EtOAc, 9:1) gave enyne **9** (220 mg, 33% over 2 steps) as a colorless oil.

Enyne **9**. R_f 0.67 (isohexane/EtOAc, 9:1); IR 3308 (w), 2979 (w), 2055 (w), 1868 (w), 1725 (s), 1650 (m), 1456 (w), 1367 (m), 1241 (m), 1149 (s), 993 (w), 918 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66–5.82 (m, 1 H), 4.99–5.19 (m, 2 H), 2.54 (quin, *J* = 6.6 Hz, 1 H), 2.31–2.50 (m, 4 H), 1.99 (t, *J* = 2.5 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 134.6, 117.4, 81.5, 80.8, 69.8, 44.6, 35.2, 28.1, 20.4; GC-MS *m/z* 179 $[M–Me]^+$, 138, 121, 110, 93, 77, 57, 41.

Sonogashira coupling to give enyne aldehyde 1c

To a solution of aryl bromide **10** (104.2 mg, 0.563 mmol) and enyne **9** (126.0 mg, 0.649 mmol) in triethylamine (8 mL) was added $PdCl_2(PPh_3)_2$ (8.0 mg, 0.011 mmol) and CuI (3.0 mg, 0.016 mmol) at rt. After stirring at rt overnight, the mixture was filtered over a pad of silica gel with EtOAc and concentrated in vacuum. Purification by flash chromatography on silica gel (isohexane/EtOAc, 9:1) yielded enyne aldehyde **1c** (46.8 mg, 28%) as an unstable white solid that had to be used rather quickly.

Enyne aldehyde **1c**. R_f 0.58 (isohexane/EtOAc, 9:1); IR 3076 (w), 2977 (m), 2932 (w), 2234 (w), 2055 (m), 1723 (s), 1696 (s), 1651 (m), 1475 (m), 1367 (s), 1242 (m), 1148 (s), 992 (m), 918 (m), 845 (m), 760 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 7.49–7.56 (m, 2 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 5.73–5.84 (m, 1 H), 5.08–5.18 (m, 2 H), 2.63–2.82 (m, 3 H), 2.36–2.55 (m, 2 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.9, 136.0, 134.5, 133.7, 133.3, 128.1, 127.4, 126.9, 117.6, 94.9, 81.0, 77.7, 44.8, 35.6, 28.1, 21.6; GC-MS *m/z* 283 $[M–Me]^+$, 241 $[M–t\text{-}Bu]^+$, 225 $[M–Ot\text{-}Bu]^+$, 195, 179, 170, 144, 115, 102, 89, 77, 57. HRMS (EI) *m/z* Calcd. for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1647. Found: 299.1659.

Sonogashira coupling to give enyne ketone 1d

To a solution of aryl iodide **5** (80.2 mg, 0.326 mmol) and enyne **9** (71.6 mg, 0.369 mmol) in triethylamine (3 mL) was added $PdCl_2(PPh_3)_2$ (5.0 mg, 0.007 mmol) and CuI (0.5 mg, 0.003 mmol) at rt. After stirring at rt for 17 h, the mixture was filtered over a pad of silica gel with EtOAc and concentrated in vacuum. Purification by flash chromatography on silica gel (CH_2Cl_2) yielded enyne ketone **1d** (50.3 mg, 49%) as an unstable orange oil that had to be used rather quickly.

Enyne ketone **1d**. R_f 0.53 (CH_2Cl_2); IR 3064 (w), 2977 (m), 2932 (m), 2056 (w), 1724 (s), 1686 (m), 1453 (m), 1366 (m), 1278 (m), 1244 (m), 1150 (s), 918 (m), 846 (m), 762 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 3 H), 5.72–5.85 (m, 1 H), 5.03–5.18 (m, 2 H), 2.61–2.79 (m, 6 H), 2.36–2.55 (m, 2 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 173.0, 141.0, 134.6, 134.1, 131.1, 128.3, 127.8, 122.0, 117.6, 93.6, 81.0, 80.9, 44.8, 35.6, 30.1, 28.1, 21.7; GC-MS *m/z* 255 $[M–t\text{-}Bu]^+$, 239, 211, 195, 178, 157, 139, 128,

115, 88, 77, 57.

Sonogashira coupling to give alkyne 12

To a solution of aryl bromide **11** (199 mg, 1.00 mmol) and 1-pentyne (88.0 mg, 1.29 mmol) in diisopropylamine (3 mL) was added $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) and CuI (1.9 mg, 0.01 mmol). The mixture was heated to 80 °C for 90 min in a microwave oven (*CEM* Discover, 300 W). After cooling to rt, water was added, and the mixture was extracted with EtOAc (3x10 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuum. Flash chromatography on silica gel (isohexane/EtOAc, 9:1) afforded alkyne **12**[11] (177 mg, 95%) as a brown oil.

Alkyne **12**. IR 1679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 2.71 (s, 3 H), 2.41 (t, *J* = 7.4 Hz, 2 H), 1.71 (m, 2 H), 1.05 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 141.0, 134.0, 131.1, 128.3, 127.5, 122.4, 96.7, 79.8, 30.1, 21.9, 21.7, 13.6; GC-MS: *m/z* 186 (5) $[M]^+$, 185 (25), 171 (25), 158 (100), 128 (43), 115 (25), 77 (15). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.51; H, 7.62.

Oxidation of ketone 12 to give α-hydroxy ketone 13

To a stirred solution of ketone **12** (280 mg, 1.50 mmol) and 2,6-lutidine (430 mg, 4.01 mmol) in CH_2Cl_2 (15 mL) was added TMSOTf (0.35 mL, 1.93 mmol) at −10 °C to 0 °C. The mixture was stirred at this temperature for 30 min and then treated with a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4, and concentrated in vacuum to afford the crude silyl enol ether as a yellow oil. This was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, and MCPBA (70%, 1.00 g, 4.06 mmol) was added. After stirring the mixture at 0 °C for 2 h, a saturated aqueous solution of Na_2SO_3 was added. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography on silica gel (isohexane/EtOAc, 1:9) afforded α-hydroxy ketone **13** (203 mg, 67%) as a pale yellow oil.

α-Hydroxy ketone **13**. IR 3363, 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1 H), 7.43–7.57 (m, 2 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 4.92 (s, 2 H), 3.55 (br s, 1 H, OH), 2.45 (t, *J* = 7.4 Hz, 2 H), 1.62 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 135.8, 134.5, 132.4, 128.8, 127.7, 123.2, 97.7, 79.6, 68.2, 21.8, 21.7, 13.6; MS (ESI) *m/z* 203.1 $[M+H]^+$. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.93; H, 7.33.

Synthesis of allyl ether 14

To a solution of α-hydroxy ketone **13** (0.20 g, 0.99 mmol) in allyl bromide (5 mL) was added $CaSO_4$ (0.90 g). This mixture was cooled to 0 °C, and Ag_2O (0.20 g, 0.86 mmol) was added in several portions over 30 min with stirring. The mixture was warmed to rt and allowed to stir at rt for 10 h. Et_2O was added, and the reaction mixture was filtered through celite. The filtrate was evaporated under reduced pressure,

and flash chromatography on silica gel (isohexane/EtOAc, 9:1) afforded allyl ether **14** (0.17 g, 71%) as a colorless oil.

Allyl ether **14**. IR 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 7.7 Hz, 1 H), 7.42 (t, *J* = 7.7 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 5.90–6.00 (m, 1 H), 5.27–5.35 (m, 1 H), 5.20–5.25 (m, 1 H), 4.85 (s, 2 H), 4.13 (d, *J* = 7.5 Hz, 2 H), 2.42 (t, *J* = 7.4 Hz, 2 H), 1.60–1.70 (m, 2 H), 1.05 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 138.7, 134.2, 133.8, 131.3, 128.3, 127.7, 122.2, 118.0, 96.4, 79.5, 74.7, 72.4, 21.9, 21.7, 13.7; GC-MS *m/z* 242 (5) $[M]^+$, 241 (10), 228 (75), 171 (100), 128 (51), 77 (14). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.45; H, 7.38.

Gold-catalyzed oxidative cyclization/cycloaddition (general procedure)

A 0.1 M solution of the substrates **1a-d** or **14** (0.1-0.2 mmol), respectively, and 3,5-dichloropyridine *N*-oxide (1.1 equiv) in 1,2-dichloroethane (1-2 mL) was treated with $AuCl_3$ (1 mol%) at rt. The mixture was stirred for the time given in Table 1. After concentration of the mixture in vacuum, the residue was purified by flash chromatography on silica gel (isohexane/EtOAc mixtures) to give the tetracyclic ketoethers **3a-d** and **15**, respectively.

Ketoether **3a**. 65.6 mg (90%) white solid from 70.0 mg (0.204 mmol) **1a**. R_f 0.43 (isohexane/EtOAc, 4:1); mp 97 °C; IR 3066 (w), 2978 (w), 2928 (w), 2055 (w), 2030 (w), 1726 (s), 1695 (s), 1652 (m), 1454 (m), 1275 (m), 1238 (s), 1206 (m), 1176 (s), 1085 (s), 1045 (m), 995 (m), 868 (m), 754 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 1 H), 7.52 (t, *J* = 7.9 Hz, 1 H), 7.38 (t, *J* = 7.9 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 1 H), 5.31 (d, *J* = 6.9 Hz, 1 H), 4.18–4.29 (m, 4 H), 3.28 (d, *J* = 14.8 Hz, 1 H), 2.66–2.78 (m, 2 H), 2.53 (dd, *J* = 12.9, 4.4 Hz, 1 H), 2.36–2.47 (m, 2 H), 2.16 (dd, *J* = 12.1, 9.3 Hz, 1 H), 1.29 (t, *J* = 7.6 Hz, 3 H), 1.27 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 171.01, 170.98, 146.9, 133.8, 128.3, 127.9, 127.1, 123.9, 97.0, 79.9, 62.1, 61.8, 61.6, 43.8, 39.6, 39.3, 37.4, 14.04, 13.99; GC-MS *m/z* 358 $[M]^+$, 211, 195, 165, 144, 131, 115, 103, 89, 77, 63, 45. HRMS *m/z* Calcd. for $C_{20}H_{22}O_6$ $[M]^+$: 358.1416. Found: 358.1418.

Ketoether **3b**. 34.0 mg (67%) white solid from 48.9 mg (0.137 mmol) **1b**. R_f 0.44 (isohexane/EtOAc, 4:1); mp 75 °C; IR 2979 (w), 2939 (w), 1722 (s), 1696 (s), 1652 (m), 1600 (m), 1457 (m), 1372 (m), 1298 (m), 1262 (s), 1236 (s), 1213 (s), 1183 (s), 1113 (s), 1090 (s), 1016 (m), 929 (m), 863 (m), 845 (m), 776 (m), 749 (m), 700 (s), 674 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 4.20–4.28 (m, 4 H), 3.23 (d, *J* = 14.3 Hz, 1 H), 2.69–2.74 (m, 1 H), 2.67 (d, *J* = 14.3 Hz, 1 H), 2.60 (dd, *J* = 13.4, 3.4 Hz, 1 H), 2.31 (dd, *J* = 13.4, 10.0 Hz, 1 H), 2.24 (dd, *J* = 12.0, 9.8 Hz, 1 H), 2.18 (dd, *J* = 12.0, 6.0 Hz, 1 H), 1.75 (s, 3 H), 1.27–1.32 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.1, 171.0, 149.9, 133.9, 128.6, 127.6, 127.0, 122.8, 96.9, 84.7, 61.8, 61.7, 61.5, 46.2, 45.4, 39.3, 37.4, 23.0, 14.1, 14.0; GC-MS *m/z* 372 $[M]^+$, 344, 327, 309, 281,

253, 209, 179, 158, 145, 128, 115, 103, 91, 77, 43. HRMS *m/z* Calcd. for $C_{21}H_{24}O_6$ $[M]^+$: 372.1573. Found: 372.1563.

Ketoether **3c**. 35.5 mg (82%) white solid from 41.2 mg (0.138 mmol) **1c**. R_f 0.53 (isohexane/EtOAc, 4:1); mp 84 °C; IR 2979 (w), 2951 (w), 2928 (w), 1717 (s), 1696 (s), 1602 (w), 1349 (m), 1238 (m), 1152 (s), 1089 (m), 1019 (s), 872 (m), 854 (m), 767 (s), 747 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 5.38 (d, *J* = 6.6 Hz, 1 H), 3.04 (quin, *J* = 7.2 Hz, 1 H), 2.91 (dd, *J* = 14.2, 8.2 Hz, 1 H), 2.46–2.55 (m, 1 H), 2.29–2.37 (m, 1 H), 2.17–2.24 (m, 2 H), 2.03–2.15 (m, 2 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 173.4, 147.1, 133.7, 128.4, 127.9, 127.1, 123.8, 97.4, 80.7, 80.4, 47.6, 45.1, 39.0, 35.7, 33.9, 28.0; GC-MS *m/z* 314 $[M]^+$, 258, 241, 212, 195, 181, 167, 141, 131, 115, 103, 91, 77, 57. HRMS *m/z* Calcd. for $C_{19}H_{22}O_4$ $[M]^+$: 314.1518. Found: 314.1516.

Ketoether **3d**. 34.2 mg (65%) pale yellow oil from 50.3 mg (0.161 mmol) **1d**. R_f 0.50 (isohexane/EtOAc, 4:1); IR 2976 (w), 2937 (w), 2056 (w), 1722 (s), 1698 (s), 1652 (m), 1601 (m), 1454 (m), 1366 (m), 1293 (m), 1257 (m), 1151 (s), 1088 (m), 850 (m), 768 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 1 H), 7.52 (t, *J* = 7.9 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz, 1 H), 7.24 (d, *J* = 7.9 Hz, 1 H), 2.96–3.02 (m, 1 H), 2.84 (dd, *J* = 13.9, 8.3 Hz, 1 H), 2.45–2.52 (m, 1 H), 2.17–2.24 (m, 2 H), 2.12 (t, *J* = 7.0 Hz, 2 H), 2.05 (dd, *J* = 12.0, 6.8 Hz, 1 H), 1.77 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.4, 173.7, 150.1, 133.8, 128.8, 127.6, 127.0, 122.8, 97.4, 85.5, 80.4, 47.1, 46.7, 45.9, 35.3, 34.1, 28.1, 23.3; GC-MS *m/z* 328 $[M]^+$, 272, 254, 209, 181, 158, 145, 128, 115, 102, 91, 77, 57, 41. HRMS *m/z* Calcd. for $C_{20}H_{24}O_4$ $[M]^+$: 328.1675. Found: 328.1660.

Ketoether **15**. 110 mg (89%) pale yellow oil from 116 mg (0.479 mmol) **14**. IR 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.8 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 4.35 (d, *J* = 8.7 Hz, 1 H), 4.15–4.25 (m, 2 H), 3.70–3.80 (m, 1 H), 2.70–2.80 (m, 1 H), 1.35–2.28 (m, 6 H), 0.95 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 144.7, 133.7, 130.5, 128.2, 128.1, 121.4, 93.1, 75.0, 72.3, 52.3, 36.9, 36.0, 17.4, 14.5; GC-MS *m/z* 258 $[M]^+$ (65), 240 (10), 211 (75), 169 (100), 141 (51), 128 (45), 115 (54). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.52; H, 7.09.

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