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Synthesis of (±)-*epi*-Jungianol by the Gold(I)-Catalyzed Propargyl Claisen Rearrangement/Hydroarylation Cascade Reaction of Propargyl Vinyl Ethers

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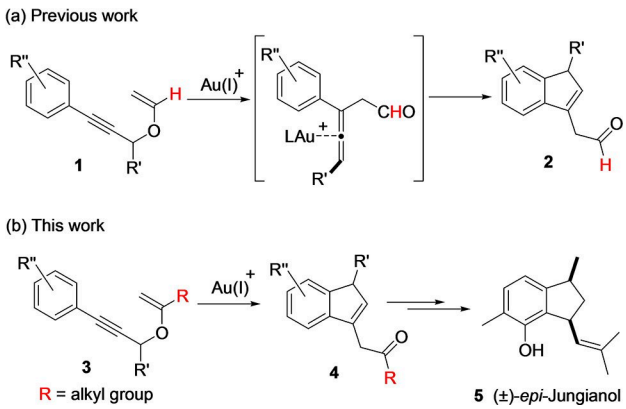
Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday.

The synthesis of (±)-*epi*-jungianol was successfully carried out by the gold(I)-catalyzed propargyl Claisen rearrangement/hydroarylation cascade reaction of suitably substituted propargyl vinyl ethers as the key step to form the indane skeleton. Two routes were compared, which involved substrates with a different degree of substitution on the vinyl moiety. The one based on a propargyl vinyl ether bearing an unsubstituted vinyl moiety, despite entailing two additional steps, provided the final compound in a higher overall yield. A method for the preparation of acid sensitive propargyl vinyl ethers with an α-alkyl-substituted vinyl moiety and their reactivity under gold catalysis is also reported.

1. Introduction

Cascade reactions allow for structural modifications on the organic compounds through the formation of several chemical bonds in one-pot, which results in the reduction of the number of steps in the synthesis of complex compounds. To this end, gold-catalysis,[1] has been extensively exploited, especially in cycloisomerization processes,[2] to construct various cyclic and heterocyclic frameworks through cascade reactions triggered by activation of a triple bond, which have ultimately led to the total synthesis of several natural compounds.[3] In the context of our studies on Au(I)-catalyzed synthesis of hetero- and carbacycles,[4] we have recently reported that propargyl vinyl ethers **1** (Scheme 1, a) are suitable substrates for a cascade process which entails the Au(I)-catalyzed propargyl Claisen rearrangement of **1** and the hydroarylation reaction of the Au(I)-allene complex intermediate to give differently substituted indenes **2** bearing an aldehyde appendage at C3.[5,6] To demonstrate the usefulness of this approach in the synthesis of target compounds, we focused our attention on *epi*-jungianol **5** (Scheme 1, b), an epimer of jungianol (which has 1,3-*trans* configuration) isolated in 1977 from a South American plant, *Jungia malvaefolia*, by Bolhmann et al.[7] To date, only two synthetic approaches of both epimers have been reported,[8,9] and in one of these, gold catalysis has been instrumental for the construction of the indane ring.[9] Although, as we will show later, *epi*-jungianol can be prepared *via* a suitably substituted aldehyde **2**, we envisaged that the corresponding ketone **4** (R = Me) would be a more advanced intermediate in the synthesis of **5**. However, ketones **4** (R = alkyl) would derive from the Au(I)-catalyzed propargyl Claisen rearrangement/hydroarylation reaction of propargyl vinyl ethers **3** bearing an α-alkyl group on the vinyl moiety for which there are no available synthetic methods.[10] In this paper we describe our approach to prepare such substituted vinyl ethers, their behavior under gold(I)-catalysis, and the application to the synthesis of *epi*-jungianol via Au(I) catalysis. The alternate approach from a propargyl vinyl ether of type **1** is also reported.



Scheme 1. Au(I)-catalyzed propargyl Claisen rearrangement/hydroarylation cascade reactions and synthetic approach to (±)-*epi*-jungianol.

2. Results and Discussion

In our previous studies, in most cases we prepared vinyl ethers **1** by treatment of the propargyl alcohols with ethyl vinyl ether in the presence of $Hg(OAc)_2$,[5,6] but to avoid the use of this toxic salt we also found convenient to react the corresponding propargyl acetates with 2-bromo-1-ethanol in the presence of

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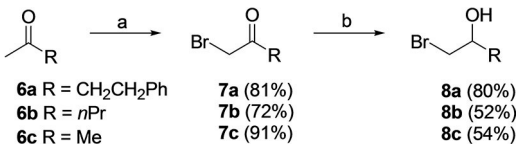
$InCl_3$ in nitromethane at 50 °C,[11] followed by elimination of HBr by *t*-BuOK in toluene.[12] In order to extend this approach to the synthesis of propargyl vinyl ethers **3** with an α-alkyl group on the vinyl moiety, we first prepared three 1-bromo-2-alkanols (**8a**–**c**, Scheme 2) according to reported procedures, i.e. by reacting the corresponding methyl ketones **6** with Br_2 in MeOH[13] and then reducing by $NaBH_4$ the formed α-bromoketones **7** to the bromoalcohols **8**.[14] Compounds **8a** and **8b** were used to find the best reaction conditions with model acetate **10** for the synthesis of the propargyl vinyl ethers **12** (Scheme 3) and to study the Au(I)-catalyzed reaction of the latter, while 1-bromo-2-propanol **8c** (R = Me) was used for the synthesis of *epi*-jungianol.

In the $InCl_3$-catalyzed reaction with acetate **10**, secondary alcohols **8a**–**b** proved less reactive than 2-bromo-1-ethanol.[5] By heating in nitromethane at 60 °C, with 5 mol% of the catalyst, the reaction of **10** with **8a** (2 equiv.) was slow and, after 2.5 h, only about 60% of the starting material was converted into **11a**, without reacting furtherly. The reaction was thus stopped and, after chromatography, **11a** was obtained in 50% yield, while recovering unreacted **10** (36%). This was reacted again under the same conditions obtaining at the end **11a** in 67% overall yield as a 1.4:1 mixture of diastereomers. With the same approach **11b** was obtained in 70% yield as 1.3:1 mixture of diastereomers. We tested many other conditions to carry out this coupling, including adding more $InCl_3$, changing the reactant ratios, using the corresponding α-chloroacetate instead of the acetate **10**, and using a different catalyst (pTsOH) with both alcohol **9** and acetate **10**, without any significant improvement.

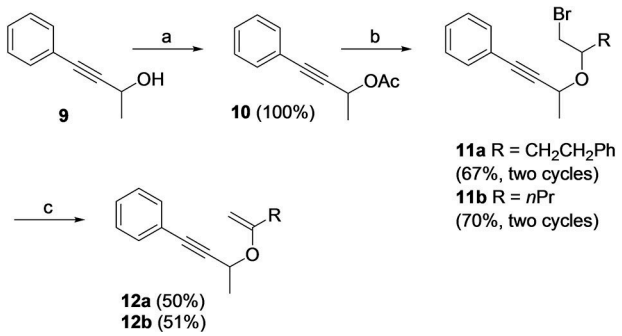
The next reaction with *t*-BuOK in toluene at 25 °C and in the presence of catalytic 18-crown-6 proved quite troublesome because we discovered that only one (the major) of the two diastereomers of **11a** underwent elimination of HBr. Also, in this case we tried many different reaction conditions, but it was always the same diastereomer that gave target product **12a**, while the other, whose relative stereochemistry could not be assigned, did not react and it was recovered unaltered. Under the best conditions (5 h at 25 °C, with 1.2 eq of *t*-BuOK and 5 mol% 18-crown-6) compounds **12a** and **12b** were obtained in 50 and 51% yield respectively after chromatography on alumina.[15] To explain the lack of reactivity of the minor diastereomer, as the process is likely an E_2 elimination in which the base removes a proton antiperiplanar to the leaving bromide anion, we reasoned that only with one of the two diastereomers of **11** a transition state without too much steric hindrance be possible. To prove this, we reacted dimethyl-substituted propargyl alcohol **13** with bromoalcohol **8a** in the presence of $FeCl_3$[16] to obtain ether **14** (44% yield) (Scheme 4).[17] This was subjected to the elimination conditions with *t*-BuOK and, as expected, it did not react at all.[18]

With model compound **12a** in hand we could finally study its behavior under gold(I)-catalysis and the results are reported in Table 1.

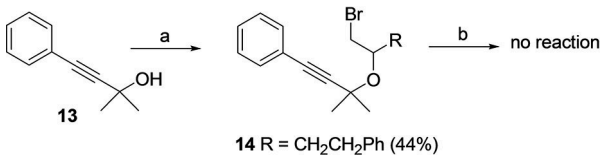
Compared to simple propargyl vinyl ethers of type **1**, substituted vinyl ether **12a** (i.e. of type **3**) was much more sensitive to the presence of acids, reasonably because of the α-alkyl group which makes the β position of the vinyl moiety



Scheme 2. (a) Br_2 (1.1 equiv.), MeOH, 0→10 °C, 2.5 h [ref. 13]; (b) $NaBH_4$ (6 equiv.), EtOH, 0 °C, 3 h [ref. 14].

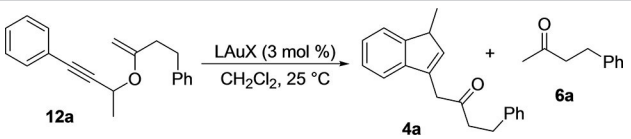


Scheme 3. (a) Ac_2O, DMAP, Et_3N, DCM, 25 °C, 2 h; (b) Bromohydrin **8a**–**b** (2 equiv.), $InCl_3$ (5 mol%), CH_3NO_2, 60 °C, 2.5 h; (c) *t*-BuOK (1.2 equiv.), 18-crown-6 (5 mol%), toluene, 25 °C, 5 h.



Scheme 4. (a) **8a**, $FeCl_3$ (5 mol%), CH_3NO_2, 25 °C, 7 h; (b) *t*-BuOK (1.2 equiv.), 18-crown-6 (5 mol%), toluene, 25 °C, 5 h.

Table 1. . Optimization of the reaction conditions.[a]



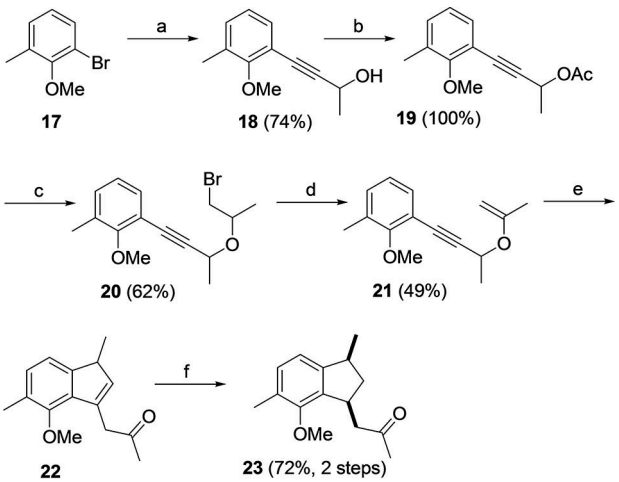
Entry	Catalyst	Solvent/additive	**4a** [%][b]	**6a** [%][b]
1	$IPrAu(CH_3CN)BF_4$	DCM[c]	50	50
2	$IPrAu(CH_3CN)BF_4$	DCM[c] / 0.25 eq K_2CO_3	74	26
3	$IPrAu(CH_3CN)BF_4$	DCM[c] / 1.0 eq K_2CO_3	87	13
4	$IPrAu(CH_3CN)BF_4$	toluene	(dec.)	-
5	$IPrAu(CH_3CN)BF_4$	DCM[d]	93	7
6	$IPrAu(CH_3CN)BF_4$	DCM[c]/4 Å MS	71	29
7	$IPrAuNTf_2$	DCM[d]	39	61
8[e]	[IPrAuCl]/AgOTf	DCM[d]	60	40
9[e]	[IPrAuCl]/$AgSbF_6$	DCM[d]	83	17

[a] Conditions: Reactions carried out on 0.2–0.3 mmol of **12a** in CH_2Cl_2 (0.05 M) at 25 °C under N_2 atmosphere. [b] Product ratio based on integration of ^1H NMR resonances in the crude reaction mixture. [c] From bottle. [d] Distilled from CaH_2 before use. [e] Catalyst prepared by mixing the silver salt (3 mol%) and the gold chloride (3 mol%) in CH_2Cl_2 before addition of the substrate unless otherwise noted. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

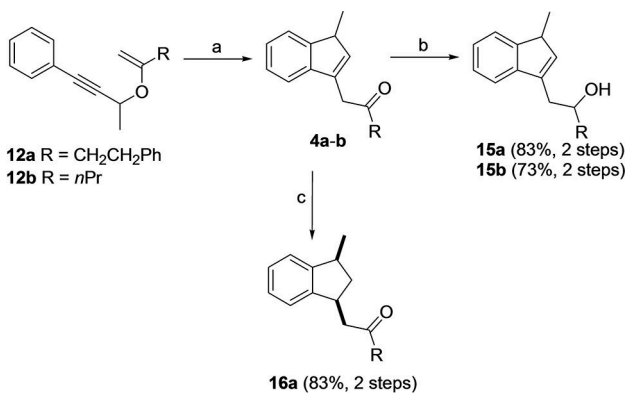
more electron-rich. In fact, during the gold-catalyzed reactions, we observed degradation of the substrate and formation of ketone **6a** (Table 1) because of the acidity of the reaction medium and, possibly, the concurrent presence of water. In analogy to substrates of type **1**, the only cationic gold complex capable to promote not only the propargyl Claisen rearrangement of **12a** but also the next hydroarylation of the formed allene intermediate to give **4a** was $[IPrAu]^+$. Under the standard conditions for the process (entry 1), the relative amount of ketone **6a** was about 50% (by ^1H NMR). To prevent the formation of ketone **6a** and thus degradation of the starting material before its Au(I)-catalyzed reaction, we carried out the reaction by adding to the mixture 0.25 and 1 equiv. of anhydrous K_2CO_3 (entries 2 and 3, respectively), in order to reduce the possible acidity deriving from the process and/or the solvent. With 1 eq. of K_2CO_3, the degradation of the substrate was reduced as the relative amount of ketone **6a** was 13%. Replacing the solvent with toluene caused an almost complete degradation of the substrate (entry 4). At the end we found that with no additives, but by simply employing as the solvent freshly distilled CH_2Cl_2 over CaH_2 (entry 5) we could abate the relative amount of ketone **6a** to 7% and obtain a conversion into product **4a** of 93% by ^1H NMR, whereas in the presence of molecular sieves (entry 6) results were again poor. In freshly distilled CH_2Cl_2, we also evaluated the efficiency of the catalyst by changing the counterion, as their conjugate acids possess a different acidity. With $IPrAuNTf_2$ (entry 7) an extensive degradation was observed (61% of ketone **6a**), and also with both [IPrAuCl]/AgOTf (entry 8) and [IPrAuCl]/$AgSbF_6$ (entry 9) we did not obtain acceptable results.

Since compound **4a**, and **4b** as well (Scheme 5), tend to isomerize during chromatography like the analogous aldehydes,[5] to give the α,β-unsaturated ketone, we decided to avoid trying to isolate products **4** as such and instead convert them as crude reaction mixtures into stable alcohols **15a**–**b** by reduction with $NaBH_4$ (83% and 73%, respectively, over the two steps after chromatography) or ketone **16a** by hydrogenation over dry Pd/C (83% yield after chromatography over the two steps). Interestingly, as reported for a closely related compound,[8b] the hydrogenation occurred with high stereoselectivity providing the *cis* isomers only, which was the one we hoped for in view of the *epi*-jungianol synthesis. This was demonstrated by analysis of a NOESY-2D spectrum of **16a** in which NOE cross-peaks between both the methyl group at 1.30 ppm and one of the protons of the appendage at position 3 (2.54 ppm) with the same proton at C2 (1.10 ppm) of the five-membered ring were consistent with the *cis* stereochemical attribution.

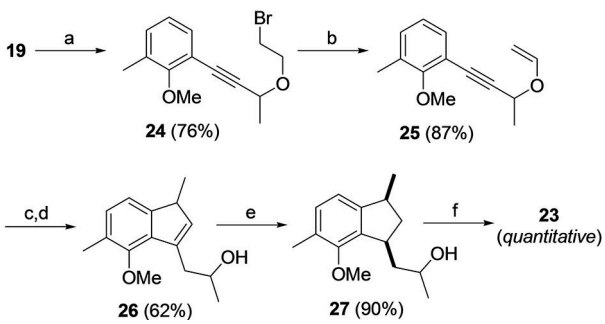
The synthesis of *epi*-jungianol is reported in Schemes 6–8. Starting from known 2-bromo-6-methylanisole **17**,[19] we prepared propargyl alcohol **18** (74%) by Sonogashira coupling (Scheme 6) and this was acetylated to quantitatively give **19**. Coupling with 1-bromo-2-propanol **8c** under the optimized conditions provided ether **20** in 62% yield and elimination with *t*-BuOK gave propargyl vinyl ether **21** in 49%. Also, in this case, only the major diastereomer reacted. The Au(I)-catalyzed reaction of **21**, followed by hydrogenation of the crude reaction



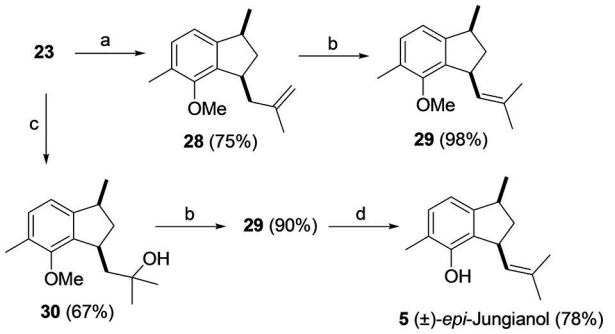
Scheme 6. (a) 3-Butyn-2-ol, $Pd(PPh_3)_4$, CuI, pyrrolidine, 70 °C, 16 h; (b) Ac_2O (2 equiv.), Et_3N, DMAP, DCM, 25 °C, 3 h; (c) 1-bromopropan-2-ol (2 equiv.), $InCl_3$ (5 mol%), CH_3NO_2, 60 °C, 2.5 h; (d) *t*-BuOK (1.2 equiv.), 18-crown-6 (5 mol%), toluene, 25 °C, 5 h; (e) $IPrAu(CH_3CN)BF_4$ (3 mol%), DCM, 25 °C, 50 min; (f) H_2, 10% Pd/C (16 mol%), $NaHCO_3$, THF, 25 °C, 1 h.



Scheme 5. (a) $IPrAu(CH_3CN)BF_4$ (3 mol%), DCM, 25 °C, 4.5 h; (b) $NaBH_4$ (4 equiv.), MeOH, 25 °C, 20 min; (c) H_2, 10% Pd/C (16 mol%), $NaHCO_3$, THF, 25 °C, 1 h.



Scheme 7. (a) 2-Bromo-1-ethanol, $InCl_3$ (5 mol%), CH_3NO_2, 50 °C, 1.5 h; (b) *t*-BuOK (1.2 equiv), 18-crown-6 (5 mol%), toluene, 25 °C, 16 h; (c) $IPrAu(CH_3CN)BF_4$ (3 mol%), DCM, 25 °C, 4 h; (d) CH_3MgBr (1.5 equiv.), THF, −65→-20 °C, 1.5 h; (e) H_2, 10% Pd/C (16 mol%), $NaHCO_3$, THF, 25 °C, 1 h; (f) Dess-Martin periodinane, DCM, 25 °C, 2 h.



Scheme 8. (a) Methyltriphenylphosphonium bromide (2 equiv.), *t*-BuOK, THF, 0 °C, 2 h; (b) cat. PTSA, DCM, 25 °C, 20 h; (c) CH_3MgBr (1.5 equiv.), THF, −65→−20 °C, 1.5 h; (d) NaH, propanethiol, DMF, 130 °C, 4.5 h.

mixture containing **22**, provided our key intermediate **23** as a single *cis* isomer in 72% yield after chromatography over two steps (16% overall yield from **17**).

The expected *cis* configuration was confirmed by the presence of NOE cross-peaks in a NOESY-2D spectrum as in compound **16a**, i.e. between both the methyl group at 1.27 ppm and one of the protons of the appendage at the relative position 3 (2.49 ppm) with the same proton at C2 (1.16 ppm) of the five-membered ring.

For the synthesis of **23** we relied also on the tandem Au(I)-catalyzed reaction of propargyl vinyl ethers of type **1** which would afford an aldehyde that must be consequently converted into ketone **23** (Scheme 7). Acetate **19** was thus reacted with 2-bromo-1-ethanol in the presence of $InCl_3$ which provided **24** in good yield (76%) after 1.5 h at 50 °C. As expected in this case, the next elimination step occurred smoothly giving vinyl propargyl ether **25** in 87% yield. This was subjected to gold(I) catalysis providing, after addition of 3.0 M MeMgBr solution in diethyl ether to the crude reaction mixture, indenyl alcohol **26** in 62% yield over the two steps. This was hydrogenated to furnish saturated alcohol **27** (as a 1:1 mixture of the *cis* diastereomers). However, the hydrogenation was not complete as 10% of the starting material remained in the crude reaction mixture and could not be separated by chromatography. Thus, **27** was subjected to the next oxidation with the Dess-Martin periodinane finally providing key intermediate **23** in 90% yield over the two steps. The overall yield in this sequence was 27% over 8 steps. Therefore, although, it requires two more steps than the previous route, this sequence seems a more efficient strategy for the synthesis of our target compound.

Eventually, we tried two routes to convert **23** into *epi*-jungianol (Scheme 8). In the first one, we carried out a Wittig olefination to generate compound **28** in 75% yield which however was difficult to purify by chromatography. This was subjected to isomerization to known **29**[8b] according to a procedure reported for a very similar compound (*p*-TsOH, CH_2Cl_2),[8a] but even after long reaction times, about 17% of the starting material remained unreacted. Instead, by reacting **23** with methyl magnesium bromide to give tertiary alcohol **30** (67%) followed by pTsOH-catalyzed elimination, compound **29** could be obtained in 90% yield with only 7% of the other isomer **28**. The final conversion of **29** into *epi*-jungianol by demethylation was carried out as described,[8b] providing pure (±)-**5** in 78% yield after chromatography with ^1H and ^{13}C NMR spectra as reported.[8b]

3. Conclusion

In conclusion, we have demonstrated that the gold(I)-catalyzed propargyl Claisen rearrangement/hydroarylation reaction is a cascade process useful for the synthesis of target compounds embodying a *cis* 1,3-disubstituted indane moiety, as in the case of *epi*-jungianol. Two types of propargyl vinyl ethers can be prepared and subjected to gold(I) catalysis, i.e. with or without an α-alkyl substituent on the vinyl moiety. Those bearing an α-alkyl group are less stable (acid sensitive) and generally obtained in lower yield than the unsubstituted ones, although they provide a more advanced intermediate in the total synthesis of the target compound. The route involving unsubstituted vinyl ethers is longer but allows for the preparation of a common intermediate in the synthesis of *epi*-jungianol in higher yield (27% over 8 steps).

Experimental Section

Anhydrous solvents were prepared accordingly to the standard techniques. Commercially available reagents were used without further purification. Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Chromatographic separations were performed under pressure on silica gel (Merck 70–230 mesh), unless otherwise stated, by using flash column techniques; R_f values refer to TLC carried out on 0.25 mm silica gel plates (F_{254}) with the same eluent as indicated for column chromatography. ^1H NMR (200 or 400 MHz) and ^{13}C NMR (100.4 MHz) spectra were recorded either on Varian Inova (400 MHz) or Mercury (200 or 400 MHz) spectrometers in the specified deuterated solvent at 25 °C. Solvent reference lines were set at 7.26 and 77.00 ($CDCl_3$), 2.05 and 29.84 (acetone-d6) in ^1H and ^{13}C NMR spectra, respectively. Mass spectra were carried out either by direct inlet of a 10 ppm solution in CH_3OH on a LCQ Fleet™ Ion Trap LC/MS system (Thermo Fisher Scientific) with electrospray ionization (ESI) interface in the positive or negative ion mode or by EI at 70 eV on a Varian GC/MS Saturn 2200 instrument equipped with a CP-sil8 Varian column. HRMS analyses were performed under conditions of ESI-MS through direct infusion of a 1 uM solution in MeOH in a TripleTOF® 5600+ mass spectrometer (Sciex, Framingham, MA, U.S.A.), equipped with a DuoSpray® interface operating with an ESI probe. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer. Compounds **10**,[5] **17**,[19] **5**[8] and **29**,[8] are known. Acetate **10**[5] and bromohydrines **8a–c**,[13,14] were prepared as reported. Bromohydrine **8c** is also commercially available.

[3-(1-Bromomethyl-4-phenylpropoxy)-but-1-ynyl]benzene (11a): To a solution of acetate **10** (800 mg, 4.3 mmol) and bromohydrin **8a** (1.95 g, 8.5 mmol) in nitromethane (17.0 mL), under nitrogen atmosphere, anhydrous $InCl_3$ (47 mg, 0.21 mmol, 5 mol%) was added. The resulting mixture was heated at 60 °C (external) for 2.5 h. After cooling, water (20 mL) was added, and the product extracted with DCM (3×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:30; R_f=0.36), affording pure **11a** as a

pale yellow oil (768 mg, 50%) and both starting materials. The so recovered acetate **10** (36%) was allowed to react again with the bromohydrin **8a** under the above reported conditions and a final 67% yield (1.03 g) was eventually obtained after the two cycles. ^{1}H NMR (400 MHz, $CDCl_3$) (1.4:1 mixture of diastereoisomers) δ (ppm): 7.47–7.15 (m, 10 H), 4.63 (q, J=6.8 Hz, 1 H, major), 4.48 (q, J=6.8 Hz, 1 H, minor), 4.02–3.95 (m, 1 H, major), 3.88–3.82 (m, 1 H, minor), 3.72 (dd, J=10.4, 6.4 Hz, 1 H, minor), 3.56 (dd, J=10.0, 6.8 Hz, 1 H, minor), 3.50 (dq, J=10.8, 5.6 Hz, 2 H, major), 2.95–2.88 (m, 1 H, major), 2.84–2.66 (m, 1 H major and 2 H minor), 2.16–2.07 (m, 1 H, minor), 2.04–1.95 (m, 1 H minor and 2 H major), 1.60 (d, J=6.4 Hz, 3 H, major), 1.56 (d, J=6.8 Hz, 3 H, minor). ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers) δ (ppm): 141.8 and 141.5, 131.6 (2 C), 128.5, 128.43 and 128.39 (2 C), 128.31 (2 C), 128.27 (2 C), 125.9 and 125.8, 122.5 and 122.4, 89.3 and 89.0, 85.2 and 85.0, 77.5 and 75.3, 65.8 and 64.4, 35.5 and 35.2, 34.8 and 34.5, 31.5 and 31.2, 22.6 and 22.5. MS (ESI) *m/z* (%): 381 ([M + Na]$^+$, 100) and 379 ([M + Na]$^+$, 96).

[3-(1-Bromomethylbutoxy)-but-1-ynyl]benzene (11b): Prepared as reported for **11a**, starting from acetate **10** (500 mg, 2.7 mmol) and bromohydrine **8b** (887 mg, 5.3 mmol). Purification of the crude was accomplished by flash chromatography (EtOAc/*n*-hexane, 1:30; R_f= 0.28) to afford the target compound **11b** (431 mg, 55%) as a pale yellow oil. Recovered starting material **10** (30%) was used to carry out the reaction again, affording eventually **11b** in the total yield of 70% (550 mg) after the two cycles. ^{1}H NMR (400 MHz, $CDCl_3$) (1.3:1 mixture of diastereoisomers) δ (ppm): 7.45–7.40 (m, 2 H), 7.32–7.30 (m, 3 H), 4.60 (q, J=6.8 Hz, 1 H, major), 4.48 (q, J=6.4 Hz, 1 H, minor), 3.95–3.89 (m, 1 H, major), 3.85–3.78 (m, 1 H, minor), 3.64 (dd, J=10.4, 4.4 Hz, 1 H, minor), 3.49 (dd, J=10.0, 6.4 Hz, 1 H, minor), 3.50–3.42 (m, 2 H, major), 1.74–1.60 (m, 2 H), 1.54 (d, J=6.8 Hz, 3 H, major), 1.53 (d, J=6.4 Hz, 3 H, minor), 1.50–1.34 (m, 2 H), 0.96 (t, J=7.6 Hz, 3 H, minor), 0.95 (t, J=7.2 Hz, 3 H, major). ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of diatereoisomers) δ (ppm): 131.64 and 131.58, 128.4 and 128.3 (2 C), 128.28 and 128.27 (2 C), 122.7 and 122.6, 89.5 and 89.2, 84.9 and 84.8, 77.9 and 76.0, 65.6 and 64.5, 36.0, 35.5 and 35.0, 22.6 and 22.5, 18.6 and 18.4, 14.1 and 14.0. GCMS (EI) *m/z* (%): 215 ([M - Br]$^+$, 49), 129 (100).

[3-(1-Methylene-3-phenylpropoxy)-but-1-ynyl]benzene (12a): To a solution of **11a** (572 mg, 1.6 mmol) and 18-crown-6 (21 mg, 0.08 mmol, 5 mol%) in anhydrous toluene (2.4 mL) under nitrogen atmosphere, solid *t*-BuOK (215 mg, 1.92 mmol) was added in one portion, and the mixture was left at room temperature under vigorous stirring for 5 h. Water (5 mL) was then added and the product extracted with *n*-hexane (3×5 mL). The combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the purification of the crude residue by flash chromatography on alumina (*n*-hexane; R_f=0.87) afforded pure **12a** as a pale yellow oil (221 mg, 50%). Compound **12a** was stored as a solution in *n*-hexane, concentrated and dried under *vacuum* just prior use. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49–7.45 (m, 2 H), 7.36–7.18 (m, 8 H), 4.85 (q, J=6.4 Hz, 1 H), 4.20 (d, J=1.6 Hz, 1 H), 4.05 (d, J=1.6 Hz, 1 H), 2.88 (t, J=7.2 Hz, 2 H), 2.46 (t, J=7.2 Hz, 2 H), 1.67 (d, J=6.4 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 160.5, 141.7, 131.7 (2 C), 128.6, 128.5 (2 C), 128.3 (2 C), 128.2 (2 C), 125.7, 122.7, 88.6, 84.9, 83.7, 62.9, 37.0, 33.7, 22.0. GCMS (EI) *m/z* (%): 276 ([M]$^+$, 14), 262 (100).

[3-(1-Methylenebutoxy)-but-1-ynyl]benzene (12b): Prepared as reported for **12a**, starting from **11b** (390 mg, 1.3 mmol) and obtaining, after purification of the crude by flash chromatography on alumina (*n*-hexane; R_f=0.88), pure **12b** as a pale yellow oil (144 mg, 51%). Compound **12b** was stored as a solution in *n*-hexane, concentrated and dried under *vacuum* just prior use. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44–7.41 (m, 2 H), 7.36–7.27 (m, 3 H), 4.81 (q, J=6.8 Hz, 1 H), 4.16 (d, J=1.6 Hz, 1 H), 4.04 (d, J=1.6 Hz, 1 H), 2.10 (t, J=7.6 Hz, 2 H), 1.62 (d, J=6.8 Hz, 3 H), 1.59–1.50 (m, 2 H), 0.94 (t, J=7.2 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 161.3, 131.7 (2 C), 128.6, 128.2 (2 C), 122.8, 88.7, 84.7, 83.1, 62.8, 37.0, 21.9, 20.5, 13.5. GCMS (EI) *m/z* (%): 214 ([M]$^+$, 33), 199 (84), 171 (100).

1-(3-Methyl-3*H*-inden-1-yl)-4-phenylbutan-2-ol (15a): To a solution of propargyl vinyl ether **12a** (120 mg, 0.43 mmol) in anhydrous DCM (8.7 mL) and under nitrogen atmosphere was added commercially available gold(I) complex $IPrAu(CH_3CN)BF_4$ (9.2 mg, 12.9 μmol, 3 mol%) and the reaction mixture was stirred at 25 °C. After complete consumption of starting material (TLC monitoring; 4.5 h), the mixture was diluted with MeOH (17.4 mL) and $NaBH_4$ (16 mg, 0.43 mmol) was immediately added. After 20 min, the reduction was completed. The solvent was then evaporated, water was added to the residue (10 mL), and the product extracted with DCM (3× 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:8; R_f=0.24) to give the corresponding indene **15a** as a colourless oil (99 mg, 83% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, J=7.2 Hz, 1 H), 7.32–7.27 (m, 4 H), 7.25–7.18 (m, 4 H), 6.28 (s, 1 H), 4.05–3.95 (m, 1 H), 3.48 (q, J=7.6 Hz, 1 H), 2.93–2.85 (m, 1 H), 2.83–2.71 (m, 2 H), 2.70–2.63 (m, 1 H), 1.95–1.88 (m, 2 H), 1.76 (d, J=2.8 Hz, 1 H, O*H*), 1.31 (d, J=7.6 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ (ppm): 149.9 and 149.8, 144.0 and 143.9, 142.0, 139.00 and 138.99, 138.2 and 138.1, 128.43 and 128.42 (2 C), 128.4 (2 C), 126.3, 125.8, 125.1, 122.8 and 122.7, 119.2 and 119.1, 69.2 and 69.1, 43.9, 38.7, 36.1 and 36.0, 32.1, 16.3 and 16.2. MS (ESI) *m/z* (%): 301 ([M + Na]$^+$, 100). HRMS (ESI/TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{22}ONa$: 301.1563. Found: 301.1554.

1-(3-Methyl-3H-inden-1-yl)-pentan-2-ol (15b): Prepared as reported for **15a**, starting from **12b** (120 mg, 0.56 mmol). The purification by flash chromatography (EtOAc/*n*-hexane, 1:15; R_f= 0.24) afforded pure **15b** as a colourless oil (88 mg, 73% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, J=7.2 Hz, 1 H), 7.35–7.21 (m, 3 H), 6.29 (s, 1 H), 4.01–3.92 (m, 1 H), 3.48 (q, J=7.6 Hz, 1 H), 2.80–2.74 (m, 1 H), 2.65–2.59 (m, 1 H), 1.71 (d, J=3.2 Hz, 1 H, O*H*), 1.61–1.52 (m, 3 H), 1.51–1.39 (m, 1 H), 1.32 (d, J=7.6 Hz, 3 H), 0.97 (t, J=7.2 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ (ppm): 149.94 and 149.92, 144.1 and 144.0, 139.30 and 139.28, 138.0 and 137.9, 126.3, 125.0, 122.73 and 122.70, 119.17 and 119.13, 69.7 and 69.6, 43.9, 39.3, 36.1 and 36.0, 19.0, 16.3 and 16.2, 14.1. MS (ESI) *m/z* (%): 239 ([M + Na]$^+$, 100). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.00; H, 9.56.

1-(3-Methylindan-1-yl)-4-phenylbutan-2-one (16a): To a solution of propargyl vinyl ether **12a** (80 mg, 0.28 mmol) in anhydrous DCM (5.6 mL) and under nitrogen atmosphere was added commercially available gold(I) complex $IPrAu(CH_3CN)BF_4$ (6.2 mg, 8.6 μmol) and the reaction mixture was stirred at 25 °C. After complete consumption of the starting material (TLC monitoring), a few drops of Et_3N were added and the solvent evaporated. The so obtained crude **4a** was used for the next step without further purifications. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.49–7.10 (m, 9 H), 6.27 (s, 1 H), 3.61 (s, 2 H), 3.48 (q, J=14.8 Hz, 1 H), 2.95–2.78 (m, 4 H), 1.30 (d, J=14.8 Hz, 3 H). Crude **4a** was dissolved in THF (1.6 mL) and added to a suspension of the activated 10% Pd/C (48 mg, 45 μmol, 16 mol%) and $NaHCO_3$ (62 mg, 0.74 mmol) in THF (7 mL). The reaction mixture was vigorously stirred at room temperature under hydrogen atmosphere (balloon). After completion (1 h), the reaction mixture was filtered over a celite pad and the solvent removed under reduced pressure. The resulting crude oil was purified by flash chromatography (EtOAc/*n*-hexane, 1:40; R_f=0.20) affording pure *cis*-indane **16a** (65 mg, 83% over two steps) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32–7.27 (m, 2 H), 7.22–7.13 (m, 6 H), 7.03 (d, J=7.6 Hz, 1 H), 3.57–3.49 (m, 1 H), 3.16–3.06 (m, 1 H),

3.02–2.91 (m, 3 H), 2.89–2.75 (m, 2 H), 2.60–2.50 (m, 2 H), 1.30 (d, $J=6.8$ Hz, 3 H), 1.10 (q, $J=10.4$ Hz, 1 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 209.3, 148.4, 145.8, 141.0, 128.5 (2 C), 128.4 (2 C), 126.7, 126.3, 126.1, 123.1, 122.8, 48.8, 44.8, 42.9, 38.8, 38.0, 29.8, 19.4. MS (ESI) *m/z* (%): 301 ($[M+Na]^+$, 100). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}O$: 279.1743. Found: 279.1746.

4-(2-Methoxy-3-methylphenyl)-but-3-yn-2-ol (18): To a solution of bromide **17** (2.27 g, 11.3 mmol) in pyrrolidine (22.6 mL), under nitrogen atmosphere, were added 3-butyn-2-ol (1.78 mL, 22.6 mmol), CuI (215 mg, 1.1 mmol) and tetrakis (triphenylphosphine)palladium (653 mg, 0.6 mmol). The reaction mixture was heated at 70 °C (external) and stirred overnight. The mixture was cooled to room temperature and water (25 mL) was added. The product was extracted with DCM (3×20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 for 30 min. After filtration and evaporation of the solvent, the crude reaction mixture was purified by flash column chromatography (*n*-hexane/EtOAc, 4:1; $R_f=0.37$), affording pure propargyl alcohol **18** (1.58 g, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 (d, $J=8.0$ Hz, 1 H), 7.12 (d, $J=7.6$ Hz, 1 H), 6.93 (t, $J=7.6$ Hz, 1 H), 4.82–4.75 (m, 1 H), 3.89 (s, 3 H), 2.67–2.56 (m, 1 H, O*H*), 2.26 (s, 3 H), 1.56 (d, $J=6.4$ Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 159.3, 131.5, 131.2, 131.1, 123.5, 116.1, 95.0, 80.4, 60.4, 58.8, 24.2, 16.0. MS (ESI) *m/z* (%): 213 ($[M+Na]^+$, 100). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.51; H, 7.68.

3-(2-Methoxy-3-methylphenyl)-1-methylprop-2-ynyl acetate (19): A solution of intermediate **18** (826 mg, 4.3 mmol) in anhydrous DCM (43 mL) under nitrogen atmosphere was cooled to 0 °C (ice bath); Et_3N (1.8 mL, 12.9 mmol) and 4-dimethylaminopyridine (26 mg, 0.22 mmol) were then added, followed by dropwise addition of Ac_2O (1.1 mL, 8.6 mmol). After 10 min, the ice bath was removed, and the resulting mixture was stirred at room temperature for 3 h. A satd solution of $NaHCO_3$ (40 mL) was added and the mixture left under vigorous stirring for 5 min; after separation of the phases, the product was extracted with DCM (2×20 mL) and the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude acetate was purified by flash chromatography (*n*-hexane/EtOAc, 7:1; $R_f=0.35$), affording pure acetate **19** (998 mg, quantitative) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.24 (d, $J=8.0$ Hz, 1 H), 7.13 (d, $J=7.6$ Hz, 1 H), 6.92 (t, $J=7.6$ Hz, 1 H), 5.70 (q, $J=6.8$ Hz, 1 H), 3.89 (s, 3 H), 2.25 (s, 3 H), 2.09 (s, 3 H), 1.59 (d, $J=6.8$ Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 169.9, 159.7, 131.7, 131.4, 131.2, 123.3, 115.6, 91.3, 81.2, 60.9, 60.4, 21.3, 21.0, 16.0. MS (ESI) *m/z* (%): 487 ($[2M+Na]^+$, 47), 255 ($[M+Na]^+$, 100). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.19; H, 7.15.

1-[3-(2-Bromo-1-methylethoxy)-but-1-ynyl]-2-methoxy-3-methylbenzene (20): Prepared as reported for **11a**, starting from acetate **19** (630 mg, 2.7 mmol) and 1-bromopropan-2-ol (**8c**, 754 mg, 5.4 mmol). The crude was purified by flash chromatography (*n*-hexane/EtOAc, 40:1; $R_f=0.34$) and pure **20** (336 mg, 40%) was obtained as pale yellow oil. By repeating the reaction on the recovered starting acetate **19**, compound **20** was obtained in the total amount of 523 mg and in 62% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) (1.1:1 mixture of diastereoisomers) δ (ppm): 7.25–7.22 (m, 2 H), 7.16–7.12 (m, 2 H), 6.95 (t, $J=7.6$ Hz, 2 H), 4.62 (q, $J=6.4$ Hz, 1 H, major), 4.57 (q, $J=6.4$ Hz, 1 H, minor), 4.13–4.05 (m, 2 H), 3.90 (s, 3 H, minor), 3.89 (s, 3 H, major), 3.58 (dd, $J=10.4$, 4.8 Hz, 1 H, major), 3.47–3.42 (m, 2 H, minor), 3.40 (dd, $J=10.4$, 6.4 Hz, 1 H, major), 2.27 (s, 6 H), 1.56 (d, $J=2.8$ Hz, 3 H, major), 1.55 (d, $J=3.6$ Hz, 3 H, minor), 1.38 (d, $J=6.4$ Hz, 3 H, major), 1.32 (d, $J=6.4$ Hz, 3 H, minor). ^{13}C NMR (100.4 MHz, $CDCl_3$) (1.1:1 mixture of diastereoisomers) δ (ppm): 159.5, 131.6 and 131.5, 131.4, 131.34 and 131.32, 123.53, 116.13, 93.0 and 92.9, 81.6 and 81.5, 73.0 and 72.8, 64.7 and 64.2, 60.5 and 60.4, 37.0 and 36.3, 22.6 and 22.4, 20.2 and 18.3, 16.0. MS (ESI) *m/z* (%): 333 ($[M+Na]^+$, 100).

1-(3-Isopropenyloxybut-1-ynyl)-2-methoxy-3-methylbenzene (21): Compound **21** was prepared as reported for **12a**, starting from **20** (225 mg, 0.72 mmol). Purification of the crude residue by flash chromatography on alumina (*n*-hexane; $R_f=0.90$) afforded pure **21** (81 mg, 49%) as a colourless oil. ^{1}H NMR (400 MHz, acetone-d6) δ (ppm): 7.23–7.18 (m, 2 H), 6.97 (t, $J=7.6$ Hz, 1 H), 4.91 (q, $J=6.8$ Hz, 1 H), 4.17 (d, $J=2.0$ Hz, 1 H), 4.04–4.03 (m, 1 H), 3.86 (s, 3 H), 2.23 (s, 3 H), 1.79 (d, $J=1.0$ Hz, 3 H), 1.59 (d, $J=6.8$ Hz, 3 H). ^{13}C NMR (100.4 MHz, acetone-d6) δ (ppm): 160.6, 158.5, 132.4, 132.2, 132.1, 124.3, 116.9, 93.5, 84.2, 82.1, 63.6, 60.7, 22.4, 21.2, 16.1. MS/MS (ESI) $[M+Na]^+$ *m/z* (%): 253 ($[M+Na]^+$, 10), 195 (100). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.98; H, 7.96.

1-(7-Methoxy-3,6-dimethylindan-1-yl)-propan-2-one (23): From 21. Indane **23** was prepared as reported for **16a**, starting from propargyl vinyl ether **21** (69 mg, 0.3 mmol) and obtaining intermediate **22** (reaction time: 50 minutes), which was used in the next step without purification. ^{1}H NMR (200 MHz, acetone-d6) δ (ppm): 7.11–6.99 (m, 2 H), 6.20 (s, 1 H), 3.79–3.76 (m, 1 H), 3.75 (s, 2 H), 3.70 (s, 3 H), 2.27 (s, 3 H), 2.15 (s, 3 H), 1.24 (d, $J=14.8$ Hz, 3 H). Hydrogenation of **22** was performed as reported for **16a**. Purification by flash chromatography (EtOAc/*n*-hexane, 1:20; $R_f=0.10$) afforded indane **23** (50 mg, 72% over 2 steps) as a pale yellow solid. **From 26**. Accordingly to the above reported hydrogenation procedure for compound **22**, compound **26** (79 mg, 0.34 mmol) was used to furnish the product **27** (72 mg, 90%) as a colourless oil, after purification by flash chromatography (EtOAc/*n*-hexane, 1:4; $R_f=0.22$). ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mixture of diastereoisomers) δ (ppm): 7.04 (d, $J=7.6$ Hz, 1 H), 7.03 (d, $J=7.6$ Hz, 1 H), 6.87 (t, $J=7.6$ Hz, 2 H), 4.01–3.87 (m, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.51–3.47 (m, 1 H), 3.34–3.26 (m, 1 H), 3.13–3.04 (m, 2 H), 2.65–2.51 (m, 2 H), 2.49–2.42 (m, 1 H), 2.31–2.20 (m, 1 H), 2.28 (s, 3 H), 2.27 (s, 3 H), 1.77–1.69 (m, 2 H), 1.49–1.35 (m, 2 H), 1.31 (d, $J=6.8$ Hz, 3 H), 1.30 (d, $J=7.2$ Hz, 3 H), 1.27 (d, $J=6.0$ Hz, 3 H), 1.26 (d, $J=6.0$ Hz, 3 H). MS (ESI) *m/z* (%): 257 ($[M+Na]^+$, 100). Dess-Martin periodinane (145 mg, 0.34 mmol) was added to an ice-bath cooled solution of alcohol **27** (72 mg, 0.31 mmol) in DCM (1.5 mL). The reaction mixture was stirred at room temperature for 2 h. Et_2O (0.8 mL) was added followed by an aqueous satd solution of $NaHCO_3$ containing 25% w/w $Na_2S_2O_3$ (1.5 mL) and the mixture was vigorously stirred for 5 min. After separation of the phases, the organic one was firstly dried over anhydrous Na_2SO_4 and then filtered and concentrated under *vacuum*. The crude was purified by flash chromatography (*n*-hexane/EtOAc, 20:1; $R_f=0.10$) affording pure ketone **23** (72 mg, quantitative) as a pale yellow solid. M.p. = 55.6–57.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.04 (d, $J=7.6$ Hz, 1 H), 6.86 (d, $J=7.6$ Hz, 1 H), 3.76–3.68 (m, 1 H), 3.66 (s, 3 H), 3.46 (dd, $J=17.2$, 4.0 Hz, 1 H), 3.13–3.04 (m, 1 H), 2.66 (dt, $J=12.8$, 7.6 Hz, 1 H), 2.49 (dd, $J=17.2$, 9.2 Hz, 1 H), 2.26 (s, 3 H), 2.20 (s, 3 H), 1.28 (d, $J=6.8$ Hz, 3 H), 1.16 (dt, $J=12.8$, 8.4 Hz, 1 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 208.4, 155.1, 148.7, 136.7, 130.2, 128.7, 118.9, 59.6, 49.1, 42.5, 38.0, 37.6, 30.5, 20.5, 15.6. MS (ESI) *m/z* (%): 255 ($[M+Na]^+$, 100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.99.

1-[3-(2-Bromoethoxy)but-1-ynyl]-2-methoxy-3-methylbenzene (24): Prepared as reported for **11a**, starting from acetate **19** (232 mg, 1.0 mmol) and 2-bromoethanol (213 μL, 3.0 mmol) but heating at 50 °C. The crude was purified by flash chromatography (*n*-hexane/EtOAc, 20:1; $R_f=0.29$) and pure **24** (226 mg, 76%) was obtained as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 (dd, $J=7.6$, 1.2 Hz, 1 H), 7.14 (dd, $J=7.6$ Hz, 0.8 Hz, 1 H), 6.95 (t, $J=7.6$ Hz, 1 H), 4.52 (q, $J=6.8$ Hz, 1 H), 4.12 (dt, $J=10.8$, 6.4 Hz, 1 H), 3.90 (s, 3 H), 3.84 (dt, $J=10.4$, 6.4 Hz, 1 H), 3.58–3.49 (m, 1 H), 2.27 (s, 3 H), 1.57 (d, $J=6.8$ Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 159.5, 131.6, 131.34, 131.33, 123.5, 116.0, 92.4, 82.0, 68.5,

66.2, 60.5, 30.4, 22.1, 16.0. MS (ESI) *m/z* (%): 321 ([M + Na]$^+$, 93) and 319 ([M + Na]$^+$, 100). Anal. Calcd for $C_{14}H_{17}BrO_2$: C, 56.58; H, 5.77. Found: C, 56.23; H, 5.51.

2-Methoxy-1-methyl-3-(3-vinyloxybut-1-ynyl)benzene (25): Prepared as reported for **12a**, starting from compound **24** (193 mg, 0.65 mmol) and leaving the reaction under stirring for 16 h at room temperature. The crude reaction mixture was filtered over a thin silica gel layer (165 mg) and the filter cake washed with *n*-hexane/EtOAc 20:1 (3 mL). After filtration and evaporation of the solvent, the so obtained crude was purified by flash column chromatography (*n*-hexane/EtOAc, 30:1 + 1% Et_3N; R_f = 0.14) to give pure **25** (122 mg, 87%) as a pale yellow oil, which was stored at 4 °C as a solution in the eluent containing 1% Et_3N until use. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26–7.23 (m, 1 H), 7.16–7.12 (m, 1 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 6.53 (dd, *J* = 14.0, 6.8 Hz, 1 H), 4.81 (q, *J* = 6.8 Hz, 1 H), 4.49 (dd, *J* = 14.0, 1.6 Hz, 1 H), 4.17 (dd, *J* = 6.4, 1.6 Hz, 1 H), 3.89 (s, 3 H), 2.27 (s, 3 H), 1.62 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 159.6, 149.7, 131.6, 131.4, 131.3, 123.4, 115.9, 91.9, 89.8, 82.3, 65.1, 60.5, 21.8, 16.00. MS/MS (ESI) [M + Na]$^+$ *m/z* (%): 239 ([M + Na]$^+$, 4), 195 (100). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.54; H, 7.60.

1-(7-Methoxy-3,6-dimethyl-3*H*-inden-1-yl)propan-2-ol (26): To a solution of propargyl vinyl ether **25** (46 mg, 0.56 mmol) in DCM (11.2 mL) under nitrogen atmosphere was added commercially available gold(I) complex $IPrAu(CH_3CN)BF_4$ (12 mg, 16.8 μmol, 3 mol%) and the reaction mixture was stirred at 25 °C. After complete consumption of **25** (TLC monitoring; 4 h), water (12 mL) was added and, after separation of the layers, the aqueous one was extracted with DCM (3 × 12 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the oily residue containing the intermediate aldehyde was used as such in the next step. ^{1}H NMR (200 MHz, acetone-d6) δ (ppm): 9.78 (t, *J* = 1.6 Hz, 1 H), 7.14–7.02 (m, 2 H), 6.30 (s, 1 H), 3.80–3.76 (m, 2 H), 3.72 (s, 3 H), 3.52–3.35 (m, 1 H), 2.29 (s, 3 H), 1.26 (d, *J* = 7.4 Hz, 3 H). Crude aldehyde was dissolved in anhydrous THF (5.6 mL) and, after cooling to −65 °C, treated with CH_3MgBr 3.0 M in Et_2O (280 μL, 0.84 mmol). The reaction mixture was allowed to warm to −20 °C, and completed in 1.5 h. The mixture was warmed at 0 °C and quenched by addition of aqueous satd NH_4Cl (6 mL). The product was extracted with EtOAc (3 × 6 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 5:1; R_f = 0.19) and pure alcohol **26** (81 mg, 62% over two steps) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.06 (q, *J* = 7.6 Hz, 2 H), 6.18 (s, 1 H), 4.19–4.12 (m, 1 H), 3.80 (s, 3 H), 3.41 (q, *J* = 7.2 Hz, 1 H), 2.92 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.47 (dd, *J* = 21.6, 2.0 Hz, 1 H, O*H*), 2.34 (s, 3 H), 1.28 (d, *J* = 6.4 Hz, 6 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers) δ (ppm): 152.4, 150.54 and 150.51, 138.8, 138.75 and 138.72, 135.61 and 135.57, 129.12 and 129.11, 128.4, 118.82 and 118.81, 66.9, 61.40 and 61.39, 43.43 and 43.41, 39.5 and 39.3, 23.04 and 23.00, 16.6 and 16.5, 15.8 and 15.7. MS (ESI) *m/z* (%): 487 ([2 M + Na]$^+$, 54), 255 ([M + Na]$^+$, 100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.32; H, 8.99.

4-Methoxy-1,5-dimethyl-3-(2-methylpropenyl)indan (29): From 23 *via* 28. A solution of commercially available methyltriphenylphosphonium bromide (143 mg, 0.4 mmol) in anhydrous THF (6.8 mL) was cooled to 0 °C and a 1.0 M solution of *t*-BuOK in THF (440 μL, 0.44 mmol) was then added dropwise. After 30 minutes, a solution of ketone **23** (47 mg, 0.20 mmol) in anhydrous THF (4 mL) was slowly added, and the resulting mixture stirred at 0 °C. After complete consumption of **23** (TLC monitoring; 2 h), the mixture was quenched by the addition of brine (20 mL) and the product extracted by Et_2O (2 × 15 mL) and DCM (15 mL); the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by flash chromatography (*n*-hexane; R_f = 0.20) affording **28** (35 mg, 75%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.05 (d, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 4.80 (s, 1 H), 4.75 (s, 1 H), 3.76 (s, 3 H), 3.48–3.40 (m, 1 H), 3.15–3.04 (m, 2 H), 2.43 (dt, *J* = 12.8, 8.0 Hz, 1 H), 2.28 (s, 3 H), 1.99 (dd, *J* = 14.0, 11.6 Hz, 1 H), 1.82 (s, 3 H), 1.34 (dt, *J* = 13.2, 8.0 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 155.3, 148.9, 144.7, 137.8, 129.9, 128.7, 118.9, 111.2, 59.5, 43.4, 40.7, 40.4, 38.0, 22.4, 21.1, 15.7. To a solution of **28** (18 mg, 0.08 mmol) in DCM (1 mL), cooled at 0 °C, a catalytic amount of PTSA was added. After 5 minutes the ice-bath was removed and the reaction mixture was stirred at room temperature for 20 h. Then, water (3 mL) was added and the product extracted with DCM (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and, after filtration and evaporation of the solvent, the oily residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:99; R_f = 0.20) affording 18 mg (98%) of a mixture of compound **29** (81%) and isomer **28** (17%), as a colourless oil. **From 30**. To a solution of **30** (37 mg, 0.15 mmol) in toluene (3 mL) was added a catalytic amount of PTSA and the reaction mixture was refluxed under vigorous stirring. After 20 min, the mixture was cooled, then water (5 mL) was added, and the product extracted with DCM (2 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (EtOAc/*n*-hexane, 1:99; R_f = 0.20) affording 35 mg (90%) of a mixture of compound **29** (97%) and isomer **28** (7%), as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.02 (d, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 5.30–5.27 (m, 1 H), 4.02 (q, *J* = 8.8 Hz, 1 H), 3.64 (s, 3 H), 3.11–3.01 (m, 1 H), 2.46 (dt, *J* = 12.4, 7.6 Hz, 1 H), 2.25 (s, 3 H), 1.79 (d, *J* = 1.2 Hz, 3 H), 1.76 (d, *J* = 1.2 Hz, 3 H), 1.36–1.27 (m, 1 H), 1.29 (d, *J* = 6.8 Hz, 3 H). MS/MS (ESI) [M + 1]$^+$ *m/z* (%): 231 ([M + 1]$^+$, 14), 189 (73), 175 (100), 161 (45).

1-(7-Methoxy-3,6-dimethylindan-1-yl)-2-methylpropan-2-ol (30): A solution of key intermediate **23** (45 mg, 0.19 mmol) in anhydrous THF (5.6 mL) was cooled to −65 °C and then treated with CH_3MgBr 3.0 M in Et_2O (97 μL, 0.29 mmol). The reaction mixture was allowed to warm at −20 °C, being completed in 1.5 h. After warming at 0 °C a saturated aqueous solution of NH_4Cl (6 mL) was added and the product extracted with EtOAc (3 × 6 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 10:1; R_f = 0.18) affording alcohol **30** (32 mg, 67%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.03 (d, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 3.74 (s, 1 H), 3.46–3.39 (m, 1 H), 3.15–3.05 (m, 1 H), 2.69 (dt, *J* = 12.8, 8.0 Hz, 1 H), 2.52 (dd, *J* = 14.4, 2.4 Hz, 1 H), 2.27 (s, 3 H), 1.62–1.54 (m, 1 H), 1.50–1.43 (m, 1 H), 1.33 (s, 6 H), 1.29 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 154.9, 148.6, 138.8, 130.0, 128.8, 119.1, 71.2, 59.8, 49.9, 43.8, 38.8, 38.6, 30.1, 29.8, 21.7, 15.7. MS (ESI) *m/z* (%): 271 ([M + Na]$^+$, 100). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.15; H, 10.02.

(±)-epi-Jungianol (5):[8b] In a round bottom flask NaH (128 mg, 3.19 mmol, 60% in mineral oil) was washed three times with anhydrous hexane, under nitrogen atmosphere. After few minutes, anhydrous DMF (2.9 mL) was added and the suspension cooled in an ice bath. Propanethiol (174 μL, 1.9 mmol) was then dropwise added and, after 5 minutes, the ice bath was removed and the mixture stirred at room temperature for 20 minutes. A solution of substrate **29** (15 mg, 0.064 mmol) in anhydrous DMF (1 mL) was dropwise added and the resulting mixture heated at 130 °C (external) for 4.5 h. After cooling to room temperature, the reaction was quenched by addition of satd NH_4Cl (39 mL) and the product extracted with Et_2O (4 × 15 mL). The combined organic extracts

were washed once with water (39 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 60:1; R_f= 0.17) affording (±)-*epi*-jungianol **5** (11 mg, 78%) as a white waxy solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.99 (d, J=7.4 Hz, 1 H), 6.68 (d, J=7.4 Hz, 1 H), 5.97 (s, 1 H), 5.35 (dm, J=10.2 Hz, 1 H), 4.0 (dt, J=10.2, 7.2 Hz, 1 H), 3.16–2.97 (m, 1 H), 2.42 (dt, J=12.2, 6.8 Hz, 1 H), 2.19 (s, 3 H), 1.88 (d, J=1.4 Hz, 3 H), 1.82 (d, J=1.4 Hz, 1 H), 1.35–1.23 (m, 1 H), 1.27 (d, J=4.8 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 151.6, 147.7, 136.0, 129.9, 127.7, 122.4, 114.6, 43.7, 41.1, 38.4, 25.9, 19.2, 18.2, 15.2. MS (ESI negative mode) *m/z* (%): 215 ([M−1]$^-$, 100).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: *epi*-Jungianol · Gold · Homogeneous catalysis · Rearrangement · Total synthesis

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