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Note

One-pot Access to the 1,7a-Dihydro-1,3a-ethano-indene and 1,8a-Dihydro-1,3a-ethano-azulene Skeletons by Sequential Gold(I)-catalyzed Propargyl Claisen Rearrangement/ Nazarov Cyclization/[4+2] Cycloaddition Reaction

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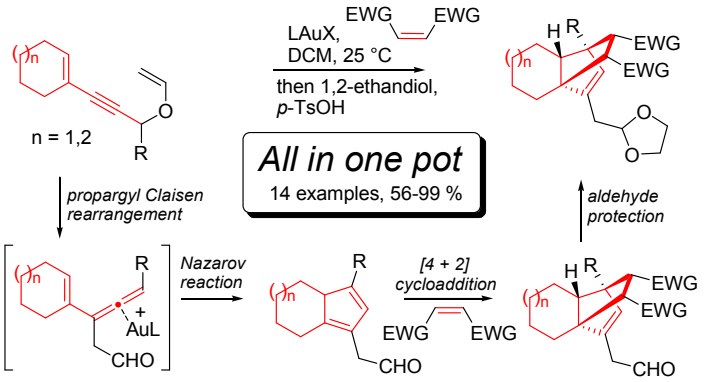
TOC/Abstract Graphic:



Abstract.

An efficient synthetic approach to the tricyclic 1,7a-dihydro-1,3a-ethano-indene and 1,8a-dihydro-1,3a-ethano-azulene skeletons from suitable propargyl vinyl ethers is based on a one-pot, multi-step process entailing a gold(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization, a [4 + 2] cycloaddition of the formed six- or seven-membered ring-fused cyclopentadiene system, and a final protection step for the easy isolation and purification of the products by chromatography.

The 1,7a-dihydro-1,3a-ethano-indene is an unusual tricyclic skeleton found in some natural products with up to three contiguous quaternary carbon atoms. Sesquiterpenes α-neoclovene,[1] β-neoclovene,[1,2] junicedranol,[3] and myltaylenol,[4] as well as the tetracyclic diterpene coronopifoliol,[5] are among the few examples of known

natural products with the 1,7a-dihydro-1,3a-ethano-indene skeleton (Figure 1). Guanacastapene K[6] and the dimeric guaianolides,[7,8] e.g. caruifolins B[7] and absinthin[7], are examples of the more numerous 1,8a-dihydro-1,3a-ethano-azulene-containing natural products (Figure 1). The latter in particular possess remarkable pharmacological activities, which include anti-HIV-1 protease activity, inhibition of cyclooxygenase-2, cytotoxic activity, inhibition of LPS-induced HF-κB activation and NO production, as well as selective inhibition of farnesyl protein transferase (FTPase).[8]

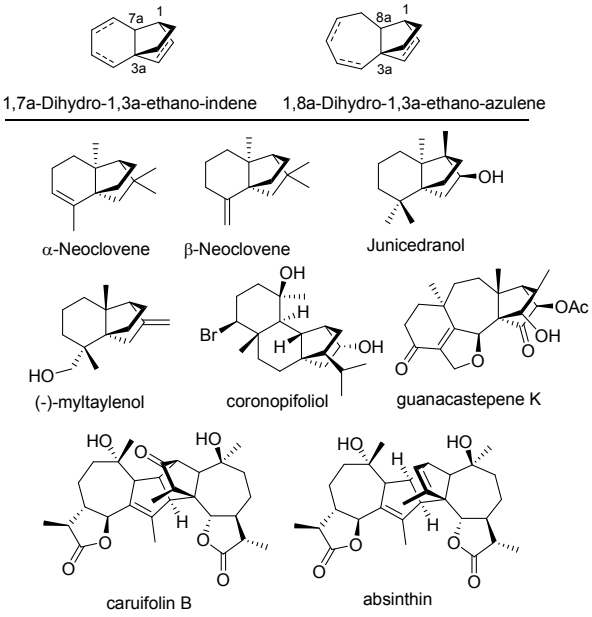


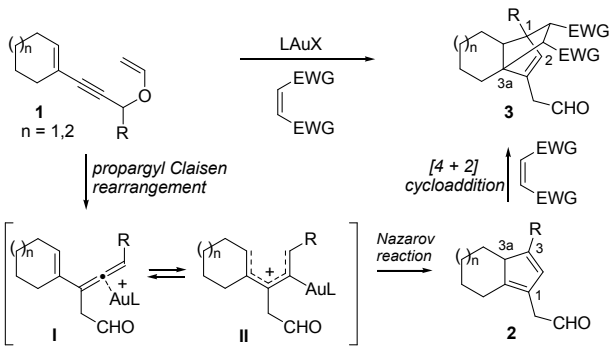
Figure 1. Some natural compounds embodying the 1,7a-dihydro-1,3a-ethano-indene and 1,8a-dihydro-1,3a-ethano-azulene skeletons

Either because these unique tricyclic structures represent a synthetic challenge or because their uncommon occurrence in nature, only a handful of approaches have been described for the construction of the 1,3a-ethano-indene skeleton, of which the most explored is based on the [4 + 2] cycloaddition reaction between suitable dienophiles and 4,5,6,7-tetrahydro-3a*H*-indene derivatives.[9,10,11] Despite their potential in medicinal chemistry, no examples of cycloadditions or alternative synthetic methods leading to 1,8a-dihydro-1,3a-ethano-azulene compounds have instead been reported, the only exception being the biomimetic dimerization of a guaiane-type precursor for the synthesis of absinthin.[12]

We have recently reported that suitably substituted enynyl vinyl ethers **1** undergo a propargyl Claisen rearrangement/Nazarov cyclization cascade process, when subjected to gold(I)-catalysis, to efficiently

provide functionalized cyclopentadienes fused with six- and seven-membered carbocycles (**2**) (Scheme 1).[13] The gold-allene complex (**I**) generated by the metal-catalyzed [3,3]-rearrangement of **1** immediately undergoes a 4π-electrocyclization via the corresponding pentadienyl cation (**II**). This cascade process provides cyclopentadiene **2** bearing, on one side chain, an aldehyde group which we have shown can be easily subjected to further in situ elaboration for incrementing the structural diversity of the products.[13,14]

Scheme 1. The cascade process leading to the target compounds 3

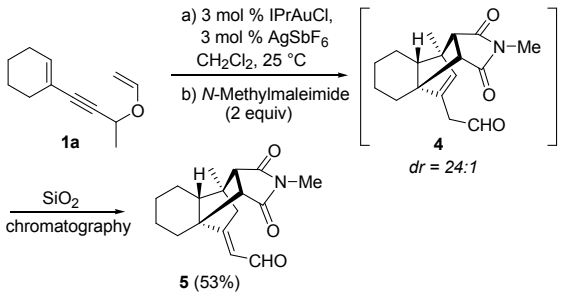


In order to establish a quick access to functionalized 1,7a-dihydro-1,3a-ethano-indene and 1,8a-dihydro-1,3a-ethano-azulene skeletons **3**, we decided to evaluate whether the diene system of aldehyde **2**, once generated through the rearrangement/cyclization step, could be trapped by a dienophile present *in situ* via a [4+2] cycloaddition process (Scheme 1).[15] This approach, which entails three steps in one pot, would also have the advantage of avoiding the isolation and purification of dienes of type **2**, which are in general susceptible of double bond isomerization and degradation during chromatography and thus very difficult to be isolated as such. In this Note we show that it is possible to perform such a multi-step process allowing for the rapid access to a variety of new products embodying the 1,7a-dihydro-1,3a-ethano-indene and 1,8a-dihydro-1,3a-ethano-azulene skeletons which could be useful in biological studies or as synthetic intermediates. Moreover, since no synthetic methods to 1,8a-dihydro-1,3a-ethano-azulenes have been reported so far, this would represent the first general approach to such a class of compounds.

Enynyl vinyl ether **1a**, prepared as reported,[13] was used for some preliminary experiments using $[IPrAu]^+SbF_6^-$ (3 mol %) as the catalyst prepared by mixing IPrAuCl and $AgSbF_6$ in CH_2Cl_2 (0.05 M in **1a**).[13] The first experiment (Scheme 2) was carried out by adding 2 equiv of *N*-methylmaleimide to the above solution *after* the rearrangement/cyclization step was complete (10 min) and leaving at room temperature.

We were glad to observe that the cyclopentadiene system generated by the former process was quickly consumed (in less than 15 min), giving rise with high diastereoselectivity (dr = 24:1 by integration of ^{1}H NMR signals of 2-H) to a cycloadduct possessing the β,γ-unsaturated aldehyde moiety of **4**.[16]

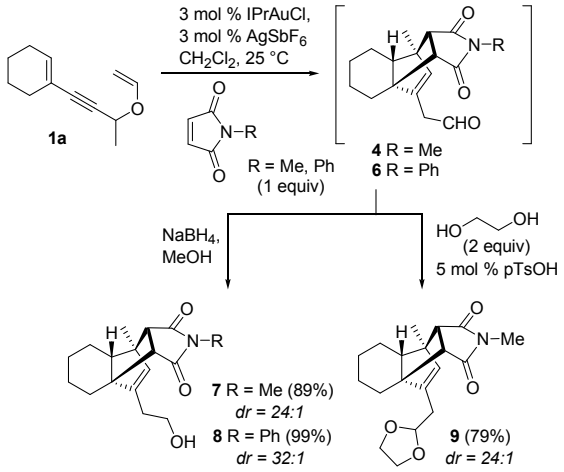
Scheme 2. Preliminary experiment leading to aldehyde 5



Chromatography of **4** on silica gel caused the expected migration of the double bond to the exocyclic position, providing α,β-unsaturated aldehyde **5** in 53% yield.[17] We then carried out a second experiment (Scheme 3) by adding a solution of **1a** and *N*-methylmaleimide (1 equiv.) in CH_2Cl_2 to a solution of the preformed catalyst. After 20 min the reaction was complete and the ^{1}H NMR analysis of a small fraction of the crude reaction mixture revealed the exclusive formation of aldehyde **4**. The rest of the solution was diluted with MeOH and treated with $NaBH_4$ to reduce the aldehyde to alcohol **7**, so to avoid isomerization of the double bond during chromatography.[13] Although vinyl allenes are known to readily react with dienophiles,[18] in fact no traces of products deriving from the reaction of the maleimide with the vinyl allene from **I** (Scheme 1) were detected, consistent with the fast ring closure step of the latter to give diene **2a** (R = Me, n = 1). While allene intermediates can be isolated in the tandem Claisen rearrangement/hydroarylation reaction of 3-arylsubstituted vinyl allenes,[14] with substrates of type **1** only the Nazarov product intermediate **2** can be observed while monitoring the reaction by ^{1}H NMR.

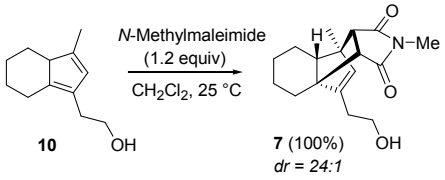
The same sequence was repeated by using *N*-phenylmaleimide as the dienophile (10 min for completion of the rearrangement/cycloaddition steps), which provided cycloadduct **8** in quantitative yield (99%) and with even higher facial selectivity (dr = 32:1). We also found that it was possible to protect the aldehyde functionality in the final product by adding, once the sequential process was complete, ethylene glycol (2 equiv.) and *p*-TsOH·H_2O (5 mol %), so that protected aldehyde **9** could be obtained in 79% yield after chromatography (Scheme 3).

Scheme 3. Preliminary experiments and synthesis of compounds 7-9



To prove that the metal cations present in the reaction mixture (Au^+ and residual Ag^+) have no role in the cycloaddition process, we prepared and purified by chromatography cyclopentadiene **10** (Scheme 4) obtained by reduction with $NaBH_4$ of intermediate **2a**.[13] Compound **10** was dissolved in CH_2Cl_2 in the presence of a slight excess of *N*-methylmaleimide (1.2 equiv) and, also under these conditions, the cycloaddition quantitatively provided alcohol **7** in 10 min in an 24:1 diastereomeric ratio.

Scheme 4. Cycloaddition reaction of the isolated diene 10



Compound **9** and α,β-unsaturated aldehyde **5** were fully characterized (Supporting Information) and used for NOE studies (Figure 2) after unambiguous assignment of all ^1H NMR signals.

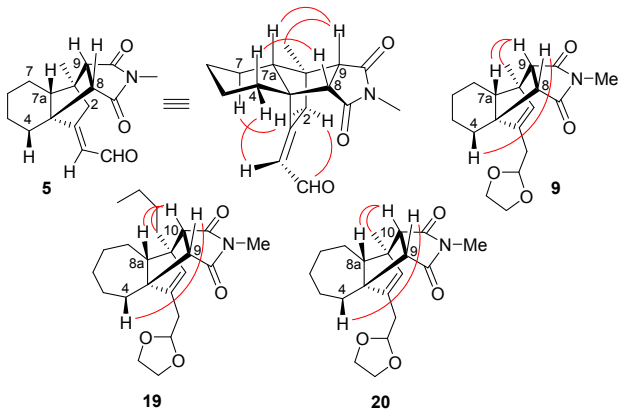
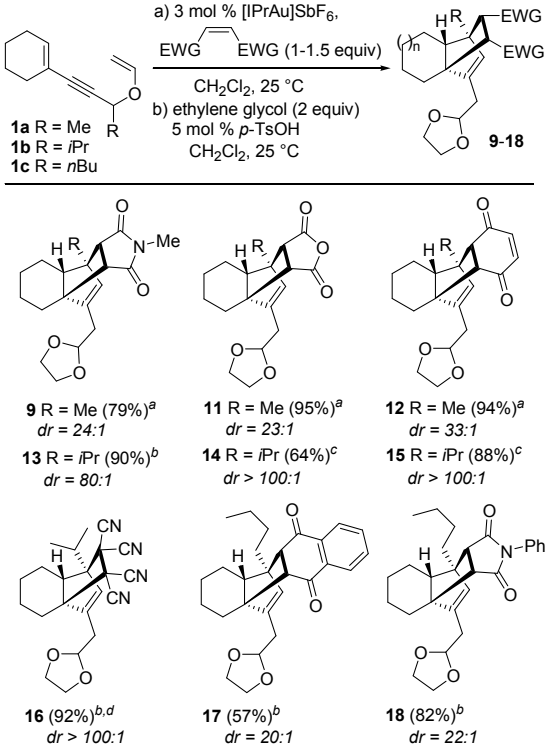


Figure 2. NOE studies on some the polycyclic compounds prepared

In compound **5** NOE cross-peaks between protons at position 9 (2.93 ppm) and 8 (3.2 ppm) with the bridgehead proton at position 7a (at about 1.6 ppm) and the axial 4a-H (at about 1.6 ppm), respectively, were diagnostic of the *endo* approach of the dienophile to the less hindered face of the diene **2**. The other NOE enhancements found in **5** were consistent with this stereochemical attribution, in particular the one between the *endo* proton on C2 (2.59 ppm) with axial proton on C7 (0.91 ppm) and that between the 1-methyl (1.37 ppm) with 9-H. Finally, two NOE cross-peaks, one between the CHO proton with *exo* 2-H (2.59 ppm) and the other between the double bond proton at 5.85 ppm with the equatorial 4-H (2.39 ppm), allowed us to establish the geometry of the double bond itself, as eventually confirmed by X-ray analysis of compound **5** (Supporting Information).[19] In compound **9**, NOE cross-peaks between 9-H and 8-H (isochronous at 2.91 ppm) with 7a-H (1.40 ppm) and 4-H_{ax} (1.48 ppm) were in accordance with the proposed structure. As expected, the approach of the dienophile to our 4,5,6,7-tetrahydro-3a*H*-indene intermediate is not different from that reported in literature for isolated six-membered ring-fused cyclopentadienes such as the Winterfeldt's cyclopentadiene (possessing a bridgehead methyl group at position 7a and a 4-methoxyphenyl group at C1), which undergoes an *endo* attack by dienophiles on the β face (i.e. on that containing the bridgehead methyl group at position 7a).[9c-d,f,h,j]

A series of dienophiles were then used to explore the scope of this sequential process with both six- and seven-membered ring carbocycles bearing a differently substituted propargyl vinyl ether moiety (compounds **1a-f**). The reactions were carried out in the presence of 1-1.5 equiv. of the dienophile and the aldehyde functionality was in most cases protected as dioxolane before work-up. As confirmed by NOE studies, with cyclohexene derivatives **1a-c** (Scheme 5) the reaction proceeded with an *endo* approach of the dienophile to the less hindered face (the β face) of the cyclopentadiene intermediate and the products – with a single exception – were obtained in good to excellent yield (57-95%) after chromatography and with high facial selectivity (d.r. from 20:1 to >100:1). Irrespective of the dienophile, the facial selectivity was very high with the isopropyl substituent at position 3 of the intermediate diene (compounds **13**-**16**). The time required for the cycloadditions varied from 5 min to 70 min, depending on the dienophile and its relative amount. In particular, with tetracyanoethylene it was not possible to perform the reaction by mixing the substrate and the dienophile as the latter underwent a nucleophilic attack by the vinyl moiety of the substrate. Thus tetracyanoethylene, in this case, was added after formation of the diene to form **16**.

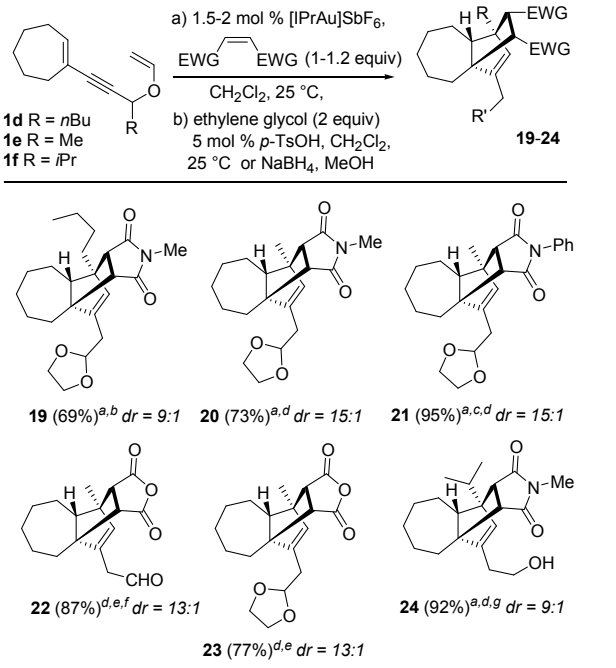
Scheme 5. Synthesis of 1,7a-dihydro-1,3a-ethano-indene derivatives 9-18



[a]With 1.0 equiv of dienophile; [b]with 1.2 equiv of dienophile; [c]with 1.5 equiv of dienophile;[d]dienophile added after the rearrangement/cyclization was complete

Double bond isomerization is a particularly serious issue when attempting to isolate aldehydes of type **2** in which the cyclopentadiene moiety is fused to a seven-membered ring.[13] Such isomerization even starts to take place during the gold(I)-catalyzed reaction of the enynyl vinyl ethers, so we were very glad to see that dienophiles present *in situ* quickly reacted (10 min) with the 3a,4,5,6,7,8-hexahydroazulenes once generated from **1d-f** (Scheme 6). However, the facial selectivity in the cycloaddition was somewhat lower than with the previous substrates. For example, *n*-butyl substituted compound **19** was obtained as a 9:1 mixture of diastereomers in 69% yield by using 2 mol % [IPrAu]SbF_6 as the catalyst.[20] The relative stereochemistry of major isomer **19**, consistent with an *endo* attack to the β face of the diene, was assigned by NOE studies (Figure 2). Changing the *n*-butyl group with a methyl group in the enynyl vinyl ether, the facial selectivity in the cycloaddition step increased and compound **20** (see Figure 2 for NOE correlations and Supporting Information) was obtained as a 15:1 mixture of diastereomers and in 73% yield when using 1.5 mol % [IPrAu]SbF_6 as the catalysts. The same facial selectivity was obtained reacting **1e** with 0.8 equiv. of *N*-phenylmaleimide under the same conditions (compound **21**).

Scheme 6. Synthesis of 1,8a-dihydro-1,3a-ethano-azulene derivatives 19-24



[a]With 1.2 equiv of dienophile; [b]with 2 mol % [IPrAu]SbF_6;[c]with 0.8 equiv. of dienophile; [d]with 1.5 mol % [IPrAu]SbF_6; [e]1.0 equiv of dienophile; [f]no protection was carried out; [g]reduction was carried out

With maleic anhydride, finally, we stopped the sequence at the cycloaddition step and in this case isolated cycloadduct **22** (13:1 mixture of isomers, 87% yield) with only traces of the corresponding α,β-unsaturated aldehyde after chromatography on silica gel. In any case, protected compound **23** was obtained according to the usual one-pot procedure in 77% yield.

In contrast to the results obtained with propargyl vinyl ether **1b**, the reaction of isopropyl substituted substrate **1f** in the presence of *N*-methylmaleimide occurred with much lower selectivity, providing alcohol **24** (after reduction instead of protection of the aldehyde group) as a 9:1 mixture of diastereomers. At the same time, cycloaddition was slow and with 1.2 equiv. of the dienophile it reached completion in 30 min.[21] From all these results it appears that with hexahydroazulenes **2** the facial selectivity decreases with the larger groups at C3.

In conclusion we have established a quick and efficient synthetic methodology to the 1,7a-dihydro-1,3a-ethano-indene and 1,8a-dihydro-1,3a-ethano-azulene skeletons based on a one-pot, multi-step process entailing a gold(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization sequence and a [4 + 2] *endo* cycloaddition of the formed diene system, readily occurring at room temperature. Since no synthetic methods to 1,8a-dihydro-1,3a-ethano-azulenes have been reported so far, this methodology represents the

first general approach to such a class of biologically interesting compounds.

Experimental Section

General information. 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) 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. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.4 MHz) spectra were recorded on Varian Inova and Mercury (400 MHz) spectrometers in the specified deuterated solvent at 25 °C. Solvent reference lines were set at 7.26 and 77.00 ($CDCl_3$) in ^{1}H 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 ion mode or by EI at 70 eV or by methanol CI 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. 1-Cyclohexenyl trifluoromethanesulfonate is commercially available; 1-heptenyl trifluoromethanesulfonate was prepared as reported.[22] Compounds **1a**, **1c** and **1e** are known.[13]

General Procedure for the Synthesis of Propargyl Vinyl Ethers 1.

A 3:1 (v/v) solution of anhydrous THF/Et_3N (6.6 mL) was added to a round-bottomed flask containing either 1-cyclohexenyl or 1-cycloheptenyl trifluoromethanesulfonate (1 mmol). The alkynol (1.0-1.1 equiv.), CuI (3.2 mol%) and $(Ph_3P)_2PdCl_2$ (1.6 mol%) were then added under nitrogen atmosphere and the reaction mixture stirred at room temperature for 3 h. Water (25 mL) was then added and the product extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude reaction mixture was purified by flash chromatography affording the intermediate enynyl alcohol which was used immediately in the next step. In a

screw cap vial, $Hg(OAc)_2$ (45 mol %) was added in one portion to a solution of the enynyl alcohol (1 mmol) in ethyl vinyl ether (5 mL) under nitrogen atmosphere and the reaction mixture was heated at 50 °C (external bath) for 1 day. The mixture was then cooled to room temperature and a solution of satd Na_2CO_3 (12.5 mL) was added. The product was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude reaction mixture was purified by flash column chromatography to give pure **1** which was stored at 4°C as a solution in the eluent containing 1% Et_3N. The solution of **1** in the eluent was concentrated and dried under *vacuum* just prior use.

1-(4-Methyl-3-viniloxypent-1-ynyl)cyclohexene (1b). Sonogashira coupling of 1-cyclohexenyl trifluoromethanesulfonate (525 μL, 3.0 mmol) and (±)-4-methyl-1-pentyn-3-ol (349 μL, 3.3 mmol), followed by purification by flash chromatography (*n*-hexane/EtOAc, 6:1 + 1% Et_3N; R_f = 0.36) afforded the enynyl alcohol intermediate which was used immediately in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.12–6.08 (m, 1 H), 4.30–4.25 (m, 1 H), 2.13–2.04 (m, 4 H), 1.96–1.79 (m, 1 H), 1.69–1.51 (m, 4 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H). Vinylation of the latter afforded **1b**, which was purified by flash chromatography (*n*-hexane/EtOAc, 60:1 + 1% Et_3N; R_f = 0.58). Pure **1b** was obtained as a yellow oil (246 mg, 46% over 2 steps from 1-cyclohexenyl trifluoromethanesulfonate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.45 (dd, J = 14.0, 6.8 Hz, 1 H), 6.13–6.10 (m, 1 H), 4.40 (dd, J = 14.0, 1.6 Hz, 1 H), 4.30 (d, J = 5.6 Hz, 1 H), 4.09 (dd, J = 6.8, 1.6 Hz, 1 H), 2.14–2.05 (m, 4 H), 2.05–1.96 (m, 1 H), 1.66–1.54 (m, 4 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.4 Hz, 3 H). ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 150.1, 135.3, 120.1, 89.1, 88.9, 83.0, 74.8, 33.1, 29.2, 25.6, 22.2, 21.4, 18.4, 17.7. GCMS (CI) *m/z* (%): 205 ([M + 1]$^+$, 100). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.45; H, 9.82.

1-(3-Viniloxyhept-1-ynyl)cycloheptene (1d). Sonogashira coupling of 1-cycloheptenyl trifluoromethanesulfonate (270 mg, 1.1 mmol) and (±)-1-heptyn-3-ol (146 μL, 1.1 mmol), followed by purification of the crude by flash chromatography (*n*-hexane/EtOAc, 9:1 + 1% Et_3N; R_f = 0.28) afforded the enynyl alcohol intermediate which was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (t, J = 6.8 Hz, 1 H), 4.47 (t, J = 6.8 Hz, 1 H), 2.33–2.30 (m, 2 H), 2.20–2.15 (m, 2 H), 1.76–1.67 (m, 4 H), 1.58–1.47 (m, 4 H), 1.45–1.31 (m, 4 H), 0.92 (t, J = 7.2 Hz, 3 H). Vinylation of the latter afforded **1d**, which was purified by flash chromatography (*n*-hexane/EtOAc, 2:1 + 1% Et_3N; R_f = 0.54). Pure **1d** was obtained as a colourless oil (187 mg, 73% over 2 steps from 1-cycloheptenyl trifluoromethanesulfonate). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 6.44 (dd, J = 14.0, 6.4 Hz, 1 H), 6.29 (t, J = 6.8 Hz, 1 H), 4.51 (t, J = 6.8 Hz, 1 H), 4.40 (dd, J = 14.0, 1.6 Hz, 1 H), 4.09 (dd, J = 6.4, 1.6 Hz, 1 H), 2.32–2.29 (m, 2 H), 2.19–2.15 (m, 2 H), 1.84–1.70 (m, 4 H), 1.58–1.40 (m, 6 H), 1.39–1.30 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 149.8, 140.5, 126.1, 89.8, 89.3, 84.2, 69.5, 35.3, 34.1, 32.0, 29.1, 27.3, 26.4, 22.3, 14.0. GCMS (EI) *m/z* (%): 232 (M^+, 13), 189 (11), 175 (100), 91 (17). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.55; H, 10.12.

1-(4-Methyl-3-vinyloxypent-1-ynyl)cycloheptene (1f). Sonogashira coupling of 1-cycloheptenyl trifluoromethanesulfonate (607 mg, 2.5 mmol) and (±)-4-methyl-1-pentyn-3-ol (263 μL, 2.5 mmol), followed by purification of the crude by flash chromatography (*n*-hexane/EtOAc, 5:1 + 1% Et_3N; R_f = 0.54), afforded the enynyl alcohol intermediate which was used immediately in the next step. ^1H NMR (400 MHz, $CDCl_3$): δ 6.28 (t, J = 6.8 Hz, 1 H), 4.27 (d, J = 5.6 Hz, 1 H), 2.33–2.30 (m, 2 H), 2.20–2.16 (m, 2 H), 1.93–1.82 (m, 1 H), 1.77–1.69 (m, 2 H), 1.59–1.47 (m, 4 H), 1.00 (t, J = 6.8 Hz, 6 H). Vinylation of the latter afforded **1f**, which was purified by flash chromatography (*n*-hexane + 1% Et_3N; R_f = 0.214). Pure **1f** was obtained as a colorless oil (305 mg, 56% over 2 steps from 1-cycloheptenyl trifluoromethanesulfonate). ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (dd, J = 14.4, 6.8 Hz, 1 H), 6.29 (t, J = 6.8 Hz, 1 H), 4.41 (dd, J = 14.0, 2.0 Hz, 1 H), 4.31 (d, J = 6.0 Hz, 1 H), 4.09 (dd, J = 6.8, 2.0 Hz, 1 H), 2.33–2.30 (m, 2 H), 2.20–2.14 (m, 2 H), 2.05–1.97 (m, 1 H), 1.76–1.69 (m, 2 H), 1.59–1.47 (m, 4 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 150.2, 140.3, 126.2, 90.5, 89.1, 82.9, 74.9, 34.2, 33.1, 32.0, 29.1, 26.5, 26.4, 18.4, 17.7. GCMS (EI) *m/z* (%): 218 (M^+, 11), 175 (100), 91 (13). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.31; H, 10.29.

General Procedure for the propargyl Claisen rearrangement/Nazarov cyclization/[4+2] cycloaddition reaction.

Gold(I) complex $IPrAuSbF_6$ was generated *in situ* by mixing equimolar quantities of IPrAuCl and $AgSbF_6$ and leaving the mixture under stirring for 5 minute at 25 °C before addition of the substrates. Gold(I) complex IPrAuOTf was generated *in situ* by mixing equimolar quantities of IPrAuCl and AgOTf (0.3 M solution in toluene) and leaving the mixture under stirring for 1 minute at 25 °C before addition of the substrates.

The solution of propargyl vinyl ether **1a-f** in *n*-hexane was concentrated and dried under *vacuum* just prior

use.

Method A. To a solution of gold(I) complex LAuX (3 mol%) in DCM (3 mL) stirred at 25 °C under nitrogen atmosphere was added a solution of propargyl vinyl ether **1** (0.3 mmol) and the dienophile (0.3-0.6 mmol) in DCM (3 mL; final concentration 0.05 M) and the reaction mixture was stirred at 25 °C until complete consumption of aldehyde **2** (TLC monitoring).

A.1. *Isolation of the unprotected aldehyde*: Water was added (6 mL) and the product extracted with DCM (2 x 5 mL). The combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the oily residue was purified by flash chromatography to afford the aldehyde in which complete isomerization of the double bond might also have occurred during the purification.

A.2. *Protection of the aldehyde as [1,3]dioxolane*: Ethylene glycol (0.6 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg) were added and the reaction mixture stirred at 25 °C for 1 h, before quenching by aqueous satd $NaHCO_3$ (15 mL); the product was extracted with DCM (3 x 10 mL) and 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 to afford the pure protected aldehyde.

A.3. *Reduction of the aldehyde*: The mixture was diluted with MeOH (12 mL) and $NaBH_4$ (12 mg, 0.3 mmol) immediately added. After 10 minutes the reduction was completed. The solvent was then evaporated, water added to the residue (15 mL) and the product extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude oil was purified by flash chromatography to afford the corresponding alcohol.

Method B. To a solution of gold(I) complex LAuX (3 mol %) in DCM (3 mL) stirred at 25 °C under nitrogen atmosphere was added a solution of propargyl vinyl ether **1** (0.3 mmol) in DCM (3 mL; final concentration 0.05 M) and the reaction mixture was stirred at 25 °C until complete consumption of **1** (TLC monitoring). The dienophile (0.3-0.6 mmol) was then added and the stirring continued until disappearance of the Nazarov reaction product **2** (TLC).

The mixture was then treated as described above in Method A, in order to obtain the final cycloadduct as either aldehyde (B.1) or [1,3]dioxolane (B.2).

Compound 5. Compound **5** was prepared following Method B.1, starting from **1a** (44 mg, 0.25 mmol) and

using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 10 minutes. Then *N*-methylmaleimide (56 mg, 0.50 mmol) was added and the reaction mixture stirred at 25 °C under nitrogen atmosphere for 15 minutes. The purification by flash chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.26) afforded **5** (38 mg, 53%), in which the double bond in the β,γ position with respect to the CHO functional group had completely isomerized to the α,β position, as also confirmed by X-ray analysis (see Supporting Information).[19] Colorless crystalline solid. M.p. = 144.9 – 146.1 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 24 : 1): δ 9.71 (d, J = 6.8 Hz, 1 H), 5.85 (dt, J = 6.8, 2.4 Hz, 1 H), 3.03 – 3.01 (m, 1 H), 2.94 – 2.91 (m, 1 H), 2.80 (s, 3 H), 2.65 – 2.51 (m, 2 H), 2.42 – 2.35 (m, 1 H), 1.77 – 1.70 (m, 1 H), 1.68 – 1.56 (m, 4 H), 1.37 (s, 3 H), 1.22 – 1.10 (m, 2 H), 0.95 – 0.84 (m, 1 H). ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 190.4, 177.0, 175.5, 165.8, 123.5, 59.6, 57.3, 54.7, 53.1, 47.7, 37.0, 28.4, 24.3, 24.1, 22.6, 21.4, 17.2. GCMS (CI) *m/z* (%): 289 ([M + 1]$^+$, 16), 288 (M$^+$, 100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.83; H, 7.51; N, 4.49.

Compound 7. Compound **7** was prepared following Method A.3, starting from **1a** (34 mg, 0.19 mmol), *N*-methylmaleimide (1 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 20 minutes. After this time, the mixture was diluted with MeOH (8.4 mL), $NaBH_4$ (8 mg, 0.21 mmol) was added and the reaction stopped after 10 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1:2; R_f = 0.36) afforded **7** (49 mg, 89%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 24 : 1): δ 5.36 (s, 1 H), 3.75–3.61 (m, 2 H), 2.94 (s, 3 H), 2.79 (s, 3 H) 2.44–2.37 (m, 1 H), 2.36–2.28 (m, 1 H), 2.13–2.05 (m, 1 H), 1.72–1.60 (m, 2 H), 1.54–1.42 (m, 2 H), 1.43–1.32 (m, 2 H), 1.39 (s, 3 H), 1.24–1.13 (m, 1 H), 1.13–0.94 (m, 2 H). ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 177.8, 177.3, 144.2, 128.4, 67.6, 60.3, 59.1, 55.4, 53.9, 53.3, 30.6, 28.6, 24.1, 23.9, 23.5, 21.7, 15.3. MS (ESI) *m/z* (%): 312 ([M + Na]$^+$, 100). HRMS (ESI/TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{23}NO_3Na$: 312.1570. Found: 312.1574.

Compound 8. Compound **8** was prepared following Method A.3, starting from **1a** (25 mg, 0.14 mmol), *N*-phenylmaleimide (1 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 15 minutes. After this time, the mixture was diluted with MeOH (5.6 mL), $NaBH_4$ (5 mg, 0.14 mmol) was added and the reaction stopped after 10 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.15) afforded **8** (49 mg, 99%) as a white solid. M.p. = 100.8 – 102.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 32 : 1): δ 7.43 – 7.39 (m, 2 H), 7.35 – 7.31 (m, 1 H), 7.17 – 7.12 (m, 2 H), 5.53 (s, 1 H), 3.82–3.67 (m, 2 H), 3.10 (AB system, J_{AB} = 7.2 Hz, 2 H), 2.47–2.42 (m, 1 H), 2.42–2.33 (m, 1 H), 2.19–2.11 (m, 1 H), 1.75–1.64 (m,

2 H), 1.59–1.47 (m, 2 H), 1.47–1.37 (m, 2 H), 1.45 (s, 3 H), 1.28–1.18 (m, 1 H), 1.18–1.01 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (100.4 MHz, $CDCl_3$): δ 176.6, 176.1, 144.6, 131.8, 129.0 (2 C), 128.5, 128.3, 126.3 (2 C), 67.8, 60.4, 59.6, 56.0, 53.8, 53.3, 30.8, 28.6, 23.8, 23.5, 21.7, 15.4. MS (ESI) *m/z* (%): 374 ($[M + Na]^+$, 100), 725 ($[2M + Na]^+$, 30). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{25}NO_3$: 352.1907. Found: 352.1904.

Compound 9. Compound **9** was prepared following Method A.2, starting from **1a** (30 mg, 0.17 mmol), *N*-methylmaleimide (1 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 20 minutes. After protection as [1,3]dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:8; R_f = 0.14) afforded compound **9** as a white solid (45 mg, 79%). M.p. = 113.8 – 115.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 24 : 1): δ 5.46 (s, 1 H), 4.91 (t, J = 5.0 Hz, 1 H), 3.97–3.86 (m, 2 H), 3.84–3.77 (m, 2 H), 2.92 (s, 2 H), 2.79 (s, 3 H), 2.44–2.32 (m, 3 H), 2.19–2.09 (m, 1 H), 1.72–1.58 (m, 2 H), 1.54–1.44 (m, 1 H), 1.43–1.31 (m, 2 H), 1.40 (s, 3 H), 1.13–0.92 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (100.4 MHz, $CDCl_3$): δ 177.8, 177.1, 141.6, 129.8, 102.7, 67.4, 64.8, 64.7, 59.1, 55.5, 53.8, 53.2, 32.4, 28.6, 24.2, 23.9, 23.5, 21.7, 15.3. MS (ESI) *m/z* (%): 354 ($[M + Na]^+$, 100), 685 ($[2M + Na]^+$, 45). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{25}NO_4$: 332.1856. Found: 332.1866.

Compound 11. Compound **11** was prepared following Method A.2, starting from **1a** (105 mg, 0.6 mmol), maleic anhydride (1 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 30 minutes. After protection as [1,3]dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.22) afforded compound **11** as a white solid (181 mg, 95%). M.p. = 85.7 – 87.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 23 : 1): δ 5.75–5.72 (m, 1 H), 4.99–4.96 (m, 1 H), 4.00–3.91 (m, 2 H), 3.90–3.81 (m, 2 H), 3.23 (s, 2 H), 2.42–2.36 (m, 2 H), 2.33–2.27 (m, 1 H), 1.73–1.63 (m, 2 H), 1.53–1.45 (m, 1 H), 1.45–1.35 (m, 2 H), 1.42 (s, 3 H), 1.29–1.22 (m, 1 H), 1.18–1.08 (m, 1 H), 1.04–0.94 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (100.4 MHz, $CDCl_3$): δ 171.3, 170.8, 142.9, 131.1, 102.7, 67.6, 65.0, 64.6, 60.5, 56.7, 54.7, 54.2, 32.2, 28.2, 23.6, 23.2, 21.7, 14.9. MS (ESI) *m/z* (%): 341 ($[M + Na]^+$, 28), 373 ($[M + Na + MeOH]^+$, 100), 723 ($[2M + Na + 2 MeOH]^+$, 86). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}O_5$: 319.1540. Found: 319.1542.

Compound 12. Compound **12** was prepared following Method A.2, starting from **1a** (45 mg, 0.26 mmol), 1,4-benzoquinone (1 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 35 minutes. After protection as dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:5; R_f = 0.13) afforded compound **12** as a colourless oil (80 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 33 : 1): δ

6.49 (d, J = 1.6 Hz, 2 H), 5.48 (s, 1 H), 4.89–4.86 (m, 1 H), 3.95–3.87 (m, 2 H), 3.84–3.76 (m, 2 H), 2.89 (AB system, J_{AB} = 8.0 Hz, 2 H), 2.34–2.24 (m, 2 H), 1.94–1.98 (m, 1 H), 1.70–1.60 (m, 2 H), 1.57–1.47 (m, 1 H), 1.38–1.28 (m, 2 H), 1.35 (s, 3 H), 1.26–1.14 (m, 1 H), 1.11–0.97 (m, 2 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 199.1, 198.7, 142.2, 141.7, 141.4, 130.9, 102.8, 64.9, 64.8, 64.6, 63.2, 59.3, 56.9, 56.5, 32.4, 28.1, 24.1, 23.4, 21.2, 14.8. MS (ESI) *m/z* (%): 351 ([M + Na]$^+$, 100), 383 ([M + Na + MeOH]$^+$, 40). HRMS (ESI/TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{24}O_4Na$: 351.1567. Found: 351.1569.

Compound 13. Compound **13** was prepared following Method A.2, starting from **1b** (35 mg, 0.17 mmol), *N*-methylmaleimide (1.2 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 70 minutes. After protection as dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:6; R_f = 0.15) afforded compound **13** as a white solid (55 mg, 90%). M.p. = 76.5 – 77.1 °C. ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 80 : 1): δ 5.66 (s, 1 H), 4.95–4.93 (m, 1 H), 3.97–3.86 (m, 2 H), 3.86–3.78 (m, 2 H), 3.20 (d, J = 7.2 Hz, 1 H), 2.87 (d, J = 7.2 Hz, 1 H), 2.79 (s, 3 H), 2.45–2.30 (m, 3 H), 2.17–2.11 (m, 1 H), 1.69–1.54 (m, 4 H), 1.53–1.43 (m, 1 H), 1.43–1.35 (m, 1 H), 1.31–1.19 (m, 1 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.01–0.96 (m, 1 H), 0.99 (d, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 178.0, 177.2, 141.1, 128.2, 102.7, 64.8, 64.7, 64.4, 64.2, 58.0, 53.1, 48.7, 32.6, 28.6, 26.9, 24.3, 24.2, 23.6, 23.3, 19.0, 18.3. MS (ESI) *m/z* (%): 382 ([M + Na]$^+$, 100), 741 ([2M + Na]$^+$, 14). HRMS (ESI/TOF) *m/z*: [M + H]$^+$ calc. for $C_{21}H_{29}NO_4$: 360.2169. Found: 360.2170.

Compound 14. Compound **14** was prepared following Method A.2, starting from **1b** (41 mg, 0.20 mmol), maleic anhydride (1.5 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 15 minutes. After protection as dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:6; R_f = 0.16) afforded compound **14** as a white solid (44 mg, 64%). M.p. = 125.4 – 127.2 °C. ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* >100 : 1): δ 5.95 (s, 1 H), 5.01–4.98 (m, 1 H), 4.01–3.91 (m, 2 H), 3.90–3.81 (m, 2 H), 3.50 (d, J = 8.0 Hz, 1 H), 3.17 (d, J = 7.6 Hz, 1 H), 2.44–2.24 (m, 4 H), 1.72–1.60 (m, 2 H), 1.60–1.54 (m, 1 H), 1.52–1.38 (m, 2 H), 1.34–1.22 (m, 1 H), 1.18–1.09 (m, 1 H), 1.14 (d, J = 6.8 Hz, 3 H), 1.04–0.98 (m, 1 H), 1.01 (d, J = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 171.4, 170.9, 142.4, 129.7, 102.8, 65.4, 65.0, 64.8, 64.6, 59.4, 54.1, 50.0, 32.3, 28.3, 26.8, 23.9, 23.2, 23.0, 18.7, 18.3. MS (ESI) *m/z* (%): 369 ([M + Na]$^+$, 100), 715 ([2M + Na]$^+$, 43). HRMS (ESI/TOF) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{26}O_5$: 347.1853. Found: 347.1855.

Compound 15. Compound **15** was prepared following Method A.2, starting from **1b** (31 mg, 0.15 mmol), 1,4-benzoquinone (1.5 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 1 h. After protection as dioxolane, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.12) afforded compound **10** as a colourless oil (47 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* >100 : 1): δ 6.51–6.44 (m, 2 H), 5.67 (s, 1 H), 4.93 (t, *J* = 4.8 Hz, 1 H), 3.96–3.87 (m, 2 H), 3.85–3.78 (m, 2 H), 3.15 (d, *J* = 8.0 Hz, 1 H), 2.86 (d, *J* = 8.0 Hz, 1 H), 2.45 (quintet, *J* = 7.2 Hz, 1 H), 2.34 (ddd, *J* = 17.6, 4.8, 2.4 Hz, 1 H), 2.28–2.22 (m, 1 H), 1.91 (ddd, *J* = 17.6, 4.8, 2.4 Hz, 1 H), 1.70–1.58 (m, 2 H), 1.55–1.44 (m, 3 H), 1.31–1.23 (m, 1 H), 1.08–0.96 (m, 2 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 199.6, 198.9, 142.4, 141.4, 140.8, 129.7, 102.9, 68.0, 64.8, 64.6, 62.5, 61.9, 56.7, 52.3, 32.6, 28.2, 26.2, 24.6, 23.7, 23.2, 19.7, 17.4. MS (ESI) *m/z* (%): 379 ([M + Na]$^+$, 100). HRMS (ESI/TOF) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{28}O_4Na$: 379.1880. Found: 379.1872.

Compound 16. Compound **16** was prepared following Method B.2, starting from **1b** (37 mg, 0.18 mmol) and using $IPrAuSbF_6$ as the catalyst. After 10 minutes, tetracyanoethylene (1.2 equiv.) was added and the cycloaddition was complete in 5 minutes. After protection as dioxolane, purification of the crude mixture by flash chromatography (EtOAc/*n*-hexane, 1:4; R_f = 0.20) afforded pure **16** as a white solid (62 mg, 92%). M.p. = 150.8 – 152.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* >100 : 1): δ 6.32 (s, 1 H), 5.14–5.11 (m, 1 H), 4.04–3.97 (m, 2 H), 3.94–3.87 (m, 3 H), 2.70–2.65 (m, 1 H), 2.49–2.43 (m, 1 H), 2.40–2.33 (m, 1 H), 2.32–2.25 (m, 1 H), 2.08–2.03 (m, 1 H), 1.98–1.86 (m, 2 H), 1.81–1.73 (m, 2 H), 1.35 (d, J = 7.2 Hz, 3 H), 1.33–1.27 (m, 1 H), 1.25 (d, J = 7.2 Hz, 3 H), 1.23–1.09 (m, 2 H). ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 145.0, 131.6, 112.1, 111.7, 111.4, 110.6, 102.0, 72.4, 66.1, 65.1, 64.8, 59.0, 53.4, 50.5, 32.3, 28.5, 24.8, 24.4, 23.0, 22.1, 20.0, 19.3. MS (ESI) *m/z* (%): 399 ([M + Na]$^+$, 100). HRMS (ESI/TOF) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{24}N_4O_2Na$: 399.1792. Found: 399.1784.

Compound 17. Compound **17** was prepared following Method A.2, starting from **1c** (50 mg, 0.23 mmol), naphtoquinone (1.2 equiv) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 50 minutes. After protection as dioxolane, purification of the crude mixture by flash chromatography (Et_2O/*n*-hexane, 1:10; R_f = 0.25) afforded pure **17** as a pale brown oil (55 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) (*d.r.* 20 : 1): δ 7.96–7.91 (m, 2 H), 7.68–7.61 (m, 2 H), 5.26 (s, 1 H) 3.98–3.95 (m, 1 H), 3.78–3.72 (m, 1 H), 3.63–3.56 (m, 2 H), 3.53–3.48 (m, 1 H), 3.38 (d, *J* = 8.0 Hz, 1 H), 3.12 (d, *J* = 8.0 Hz, 1 H), 2.34–2.27 (m, 1 H),

2.17–2.11 (m, 1 H), 2.03–1.93 (m, 1 H), 1.75–1.60 (m, 6 H), 1.56–1.49 (m, 1 H), 1.48–1.32 (m, 4 H), 1.12–1.02 (m, 3 H), 0.96 (t, J = 7.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 197.5, 197.0, 140.8, 136.9, 136.1, 133.9, 133.4, 131.5, 126.4, 126.3, 102.6, 64.7, 64.2, 63.9, 63.3, 62.4, 57.6, 53.4, 32.8, 28.2, 27.7, 26.5, 24.3, 23.6, 23.4, 21.3, 14.1. MS (ESI) *m/z* (%): 443 ($[M + Na]^+$, 100), 863 ($[2M + Na]^+$, 17). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{32}O_4$: 421.2373. Found: 421.2371.

Compound 18. Compound **18** was prepared following Method A.2, starting from **1c** (51 mg, 0.24 mmol), *N*-methylmaleimide (1.2 equiv.) and using $IPrAuSbF_6$ as the catalyst. The reaction was complete in 15 minutes. After protection as dioxolane, purification of the crude by flash chromatography (Et_2O/*n*-hexane, 1:6; R_f = 0.21) afforded compound **18** as a white solid (86 mg, 82%). M.p. = 121.9 – 123.2 °C. ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 22 : 1): δ 7.43 – 7.37 (m, 2 H), 7.34 – 7.30 (m, 1 H), 7.24 – 7.20 (m, 2 H), 5.71 (s, 1 H), 4.99 (t, J = 4.8 Hz, 1 H), 3.95 – 3.88 (m, 1 H), 3.86 – 3.72 (m, 3 H), 3.29 (d, J = 7.6 Hz, 1 H), 3.07 (d, J = 7.6 Hz, 1 H), 2.48 – 2.38 (m, 2 H), 2.28 – 2.20 (m, 1 H), 2.06 – 1.98 (m, 1 H), 1.84 – 1.76 (m, 1 H), 1.74–1.62 (m, 2 H), 1.62–1.46 (m, 3 H), 1.44–1.22 (m, 5 H), 1.22–0.97 (m, 2 H), 0.94 (t, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 176.6, 176.0, 141.7, 132.0, 129.9, 128.7 (2 C), 128.1, 126.7 (2 C), 102.8, 65.8, 64.7, 64.6, 60.2, 58.9, 53.1, 50.0, 32.6, 28.8, 28.6, 26.9, 24.0, 23.4 (2 C), 22.2, 14.0. MS (ESI) *m/z* (%): 458 ($[M + Na]^+$, 44), 893 ($[2M + Na]^+$, 100). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{33}NO_4$: 436.2482. Found: 436.2474.

Compound 19. Compound **19** was prepared following Method A.2, starting from **1d** (38 mg, 0.16 mmol), *N*-methylmaleimide (1.2 equiv.) and using $IPrAuSbF_6$ (2 mol%) as the catalyst. After 15 minutes, the reaction was complete. After protection as dioxolane, the crude mixture was purified by flash chromatography (Et_2O/*n*-hexane, 1:5; R_f = 0.18) to give pure **19** as a colorless oil (43 mg, 69%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 9 : 1): δ 5.46 (s, 1 H), 4.87 (t, J = 5.2 Hz, 1 H), 3.95 – 3.86 (m, 2 H), 3.84 – 3.77 (m, 2 H), 3.14 (d, J = 7.2 Hz, 1 H), 2.89 (d, J = 7.2 Hz, 1 H), 2.78 (s, 3 H), 2.41 (ddd, J = 17.2, 4.4, 2.0 Hz, 1 H), 2.19 – 1.98 (m, 4 H), 1.80 – 1.65 (m, 4 H), 1.65 – 1.54 (m, 2 H), 1.50 – 1.29 (m, 6 H), 1.26 –1.15 (m, 2 H), 0.93 (t, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 177.9, 177.6, 142.2, 129.6, 102.8, 69.9, 64.8, 64.7, 62.3, 59.0, 51.0, 49.1, 33.1, 30.2, 29.5, 28.4, 27.5, 26.2, 24.1, 23.3, 23.2, 22.1, 14.1. MS (ESI) *m/z* (%): 410 ($[M + Na]^+$, 100), 797 ($[2M + Na]^+$, 14). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{33}NO_4$: 388.2482. Found: 388.2492.

Compound 20. Compound **20** was prepared following Method A.2, starting from **1e** (37 mg, 0.19 mmol), *N*-methylmaleimide (1.2 equiv.) and using $IPrAuSbF_6$ (1.5 mol%) as the catalyst. The reaction was complete in 10 minutes. After protection as dioxolane, purification of the crude by flash chromatography (Et_2O/*n*-hexane, 1:5; R_f = 0.18) afforded compound **20** as a yellowish oil (44 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 15 : 1): δ 5.46 (s, 1 H), 4.87 (t, J = 5.2 Hz, 1 H), 3.94 – 3.86 (m, 2 H), 3.83 – 3.76 (m, 2 H), 2.92 (AB system, J_{AB} = 7.6 Hz, 1 H), 2.78 (s, 3 H), 2.41 (ddd, *J* = 17.6, 4.8, 2.0 Hz, 1 H), 2.19 – 2.07 (m, 2 H), 2.03 (ddd, *J* = 14.8, 9.6, 2.0 Hz, 1 H), 1.81 – 1.67 (m, 2 H), 1.64 – 1.53 (m, 2 H), 1.49 – 1.40 (m, 1 H), 1.38 (s, 3 H), 1.36 – 1.77 (m, 5 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 177.8, 177.4, 142.7, 129.5, 102.8, 72.8, 64.8, 64.7, 62.9, 55.2, 53.6, 51.2, 33.1, 30.2, 29.6, 27.5, 24.1, 23.2, 22.2, 16.0. MS (ESI) *m/z* (%): 368 ($[M + Na]^+$, 100). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{27}NO_4$: 346.2013. Found: 346.2007.

Compound 21. Compound **21** was prepared following Method A.2, starting from **1e** (35 mg, 0.18 mmol), *N*-phenylmaleimide (0.8 equiv.) and using $IPrAuSbF_6$ (1.5 mol%) as the catalyst. The reaction was complete in 10 minutes. After protection as dioxolane, purification of the crude by flash chromatography (Et_2O/*n*-hexane, 1:4; R_f = 0.16) afforded compound **21** as a pale yellow oil (56 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 15 : 1): δ 7.42 – 7.38 (m, 2 H), 7.34 – 7.30 (m, 1 H), 7.22 – 7.18 (m, 2 H), 5.68 (s, 1 H), 4.96 (t, *J* = 4.8 Hz, 1 H), 3.94 – 3.74 (m, 4 H), 3.10 (AB system, J_{AB} = 7.6 Hz, 2 H), 2.47 (ddd, *J* = 17.6, 4.8, 2.0 Hz, 1 H), 2.28 – 2.18 (m, 2 H), 2.12 (ddd, *J* = 16.8, 9.2, 2.0 Hz, 1 H), 1.85 – 1.71 (m, 2 H), 1.70 – 1.57 (m, 3 H), 1.45 (s, 3 H), 1.42 – 1.22 (m, 4 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 176.6, 176.3, 143.3, 132.0, 130.0, 128.7 (2 C), 128.1, 126.2 (2 C), 103.0, 73.2, 64.7, 64.6, 63.4, 55.9, 53.6, 51.3, 33.2, 30.2, 29.8, 27.6, 23.3, 22.0, 16.1. MS (ESI) *m/z* (%): 430 ($[M + Na]^+$, 60), 837 ($[2M + Na]^+$, 100). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{29}NO_4$: 408.2169. Found: 408.2184.

Compound 22. Compound **22** was prepared following Method A.1, starting from **1e** (62 mg, 0.33 mmol), maleic anhydride (1.0 equiv.) and using $IPrAuSbF_6$ (1.5 mol%) as the catalyst. The reaction was complete in 10 minutes. Purification of the crude mixture by flash chromatography (Et_2O/*n*-hexane, 1:4; R_f = 0.16) afforded pure **22** as a yellowish oil (82 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 13 : 1): δ 9.66 (t, *J* = 2.0 Hz, 1 H), 5.75 (s, 1 H), 3.28 (AB system, J_{AB} = 8.0 Hz, 2 H), 3.14 (t, *J* = 1.6 Hz, 2 H), 2.24 – 2.15 (m, 1 H), 1.97 – 1.90 (m, 1 H), 1.85 – 1.73 (m, 2 H), 1.71 – 1.65 (m, 1 H), 1.65 – 1.55 (m, 2 H), 1.43 (s, 3 H, Me), 1.39 – 1.31 (m, 2 H), 1.31 – 1.19 (m, 2 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 197.8, 171.1, 170.7, 140.8,

133.8, 73.4, 64.2, 56.8, 54.4, 52.4, 42.6, 30.1, 29.2, 27.6, 23.1, 22.2, 15.5. GCMS (EI) *m/z* (%): 288 (M^+, 5), 190 (100), 147 (5). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calc. for $C_{17}H_{20}O_4$: 289.1434. Found: 289.1434.

Compound 23. Compound **23** was prepared following Method A.1, starting from **1e** (41 mg, 0.22 mmol), maleic anhydride (1.0 equiv.) and using $IPrAuSbF_6$ (1.5 mol%) as the catalyst. The reaction was complete in 10 minutes. After protection as dioxolane, purification of the crude by flash chromatography (Et_2O/*n*-hexane, 1:4; R_f = 0.19) afforded compound **23** as a yellowish oil (56 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 13 : 1): δ 5.72 (s, 1 H), 4.94 (dd, J = 5.6, 4.0 Hz, 1 H), 3.99 – 3.91 (m, 2 H), 3.88 – 3.80 (m, 2 H), 3.22 (q, J = 8.0 Hz, 2 H), 2.44 – 2.41 (m, 1 H), 2.33 – 2.27 (m, 1 H), 2.12 – 2.08 (m, 2 H), 1.81 – 1.72 (m, 2 H), 1.66 – 1.55 (m, 3 H), 1.39 (s, 3 H, Me), 1.35 – 1.20 (m, 4 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 171.2, 171.1, 144.0, 131.0, 103.0, 73.0, 65.0, 64.6, 64.3, 56.4, 54.5, 52.5, 32.8, 30.0, 29.2, 27.4, 23.0, 22.1, 15.6. GCMS (EI) *m/z* (%): 234 (12), 233 (65), 147 (7), 73 (100). HRMS (ESI/TOF) *m/z*: $[M + H]^+$ calc. for $C_{19}H_{24}O_5$: 333.1697. Found: 333.1709.

Compound 24. Compound **24** was prepared following Method A.3, starting from **1f** (50 mg, 0.23 mmol), *N*-methyl maleimide (1.2 equiv.) and using $IPrAuSbF_6$ (1.5 mol%) as the catalyst. The reaction was complete in 30 minutes. After reduction, purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1:2; R_f = 0.13) afforded compound **24** as a colourless oil (70 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) (*d.r.* 9 : 1): δ 5.59 (s, 1 H), 3.71 – 3.58 (m, 2 H), 3.20 (d, J = 7.2 Hz, 1 H), 2.91 (d, J = 7.2 Hz, 1 H), 2.77 (s, 3 H), 2.38 – 2.30 (m, 1 H), 2.25 – 1.96 (m, 4 H), 1.84 – 1.76 (m, 1 H), 1.76 – 1.68 (m, 2 H), 1.66 – 1.57 (m, 2 H), 1.49 – 1.39 (m, 1 H), 1.39 – 1.21 (m, 3 H), 1.19 (d, J = 7.2 Hz, 3 H), 1.21 – 1.15 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H). 2.44–2.37 (m, 1 H), 2.36–2.28 (m, 1 H), 2.13–2.05 (m, 1 H), 1.72–1.60 (m, 2 H), 1.54–1.42 (m, 2 H), 1.43–1.32 (m, 2 H), 1.39 (s, 3 H), 1.24–1.13 (m, 1 H), 1.13–0.94 (m, 2 H). $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$): δ 177.6, 177.5, 144.8, 126.4, 70.4, 63.2, 61.8, 60.5, 50.8, 48.1, 31.4, 30.2, 29.0, 27.7, 26.9, 24.2, 23.0, 22.9, 18.7, 18.0. MS (ESI) *m/z* (%): 354 ($[M + Na]^+$, 100). HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{29}NO_3Na$: 354.2040. Found: 354.2036.

Associated contents. The Supporting Information is available free of charge:

Copies of ^1H and ^{13}C NMR spectra of all new compounds; Crystal structure determination and data of compound **5** (PDF).

Crystallographic data of compound **5** (CIF).

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Notes

The authors declare no competing financial interest.

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16) Diagnostic ^{1}H NMR signals are the dd at 9.56 ppm (J = 2.6 and 2.2 Hz) for the aldehyde proton, which couples with 2 diastereomeric protons (CH_2-CHO) resonating as dd between 3.16 and 2.88 ppm. The singlet at 5.56 ppm is assigned to the double bond proton at position 2 inside the five-membered ring.

17) Diagnostic ^{1}H NMR signals of the α,β-unsaturated moiety are the doublet at 9.75 ppm (J = 6.5 Hz) for the CHO proton, which couples with the double bond proton resonating at 5.85 ppm as a doublet of triplets (J = 6.5 and 2.4 Hz) because of a long-range coupling (^{4}J) with the diastereomeric CH_2 protons of the ring (C2).

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19) Crystallographic data for the structure of **5** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC 1970509, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

20) In an attempt to increase the facial selectivity, generating first the diene at 25 °C and then adding the *N*-methylmaleimide (1.2 equiv) to the crude solution of the diene cooled at 0, -20 or -40 °C, did not change this ratio. Even at the lowest temperature, cycloaddition was rather fast, being complete in 3 h.

21) A possible explanation for this result lies in the greater flexibility of the seven-membered ring in the 3a,4,5,6,7,8-hexahydroazulenes. A molecular mechanics (MMFF forcefield) Montecarlo conformational search on diene **2** (Scheme 1) from **1f,** showed a cluster of almost isoergonic conformations in which the 7-membered ring is bent downward (i.e. opposite to 3a-H), with one the methyl group of the isopropyl moiety pointing upward (and the other eclipsed to the C2-C3 bond of the five-membered ring), a situation which increases the steric hindrance on the β face of the diene.

22) Lim, B.-Y.; Jung, B.-E.; Cho, C.-G. Ene-hydrazide from Enol Triflate for the Regioselective Fischer Indole Synthesis. *Org. Lett*. **2014**, *16*, 4492–4495.