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Gold(I)-catalyzed Cycloisomerization/Hetero Diels-Alder Reaction/Ring Opening Cascade to Functionalized Cyclopentadienes

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Abstract

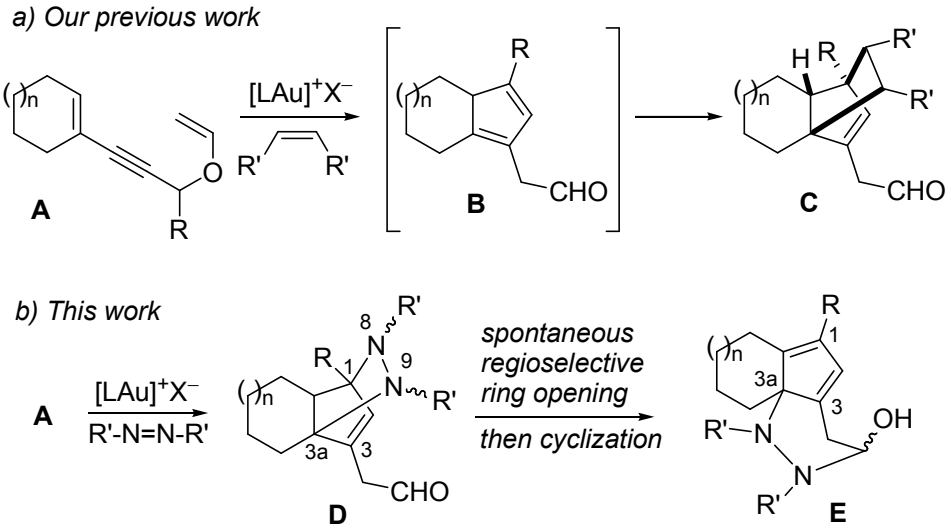
Six- and seven-membered-ring-fused, functionalized cyclopentadienes can be obtained in moderate to excellent yields by a cascade process entailing the Au(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization of propargyl vinyl ethers, the hetero-Diels-Alder reaction with dialkylazodicarboxylates, and the spontaneous conversion of the cycloaddition products into the cyclopentadienes by a highly regioselective cleavage of a C-N bond. Depending on the treatment of the crude reaction mixtures, two types of products can be obtained: cyclopentadienes with pendant hydrazine and aldehyde moieties which intramolecularly react to form hemiaminals are obtained in 43-52% overall yields when the crude reaction mixtures are left over K_2CO_3 in a DCM solution. Instead, by reducing *in situ* the aldehyde group just after addition of the heterodienophile, the regioselective C-N bond cleavage generates the corresponding cyclopentadienes bearing a hydrazine and an alcohol appendage in excellent yields (66-82%) over four steps, all in one pot. Two examples from the latter class of compounds were also converted into ring-fused, functionalized cyclopentadienes, bearing a protected amino group, by the selective N-N cleavage of the hydrazine moiety.

Introduction

New synthetic methods for the preparation of functionalized cyclopentadienes are highly sought after as these valuable compounds find applications in many areas of chemistry. In organic synthesis, they are useful partners in Diels–Alder reactions for the construction of complex natural and biologically active products.[1] In organometallic chemistry, they are widely used as ligands in transition-metal complexes, with cyclopentadiene coordination complexes reported for a number of different elements not only in the area of catalysis, where they empower a broad spectrum of

reactions,[2] but also in medicinal chemistry, where particularly ferrocene derivatives have shown promising activities in the treatment of diseases such as malaria and cancer.[3] In addition, the cyclopentadiene moiety is present in natural compounds,[1,4] which furtherly renders the discovery of new strategies for the synthesis of diversely functionalized cyclopentadienes a very attractive target.[5]

Scheme 1. Previous and current works on cycloisomerization/cycloaddition reactions.

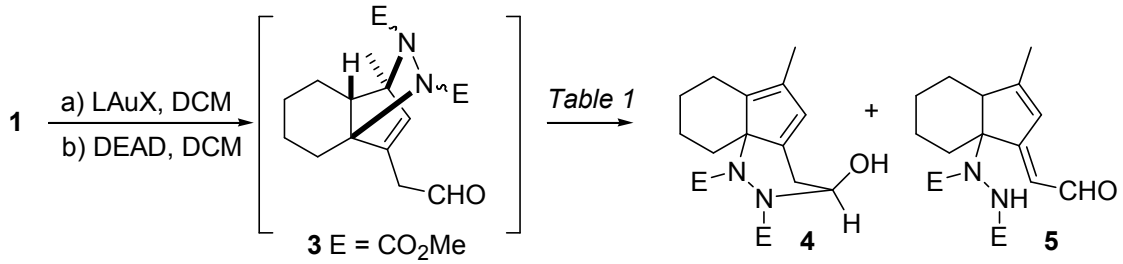


Since the pioneering works of Toste[6] and Zhang[7] on the cycloisomerization of vinyl allenes and enynyl acetates, respectively, gold catalysis has not failed to show its strength in enabling the construction of functionalized cyclopentadienes by a variety of approaches based on intra- and intermolecular reactions.[8,9] Some of these methods, in particular, involved an initial Au(I)- or Au(III)-catalyzed rearrangement of propargyl alcohol or amine derivatives to form a proper intermediate capable of cyclization. In Zhang's work,[7] it was the 1,3-migration of an acetyloxy group, whereas both Gagosz[8g] and Helaja[8c,h] exploited a 1,5-hydride shift involving the benzylic position of propargyl benzyl ethers and the α position to the N atom in propargyl amines, respectively. Because of our interest in gold-catalyzed synthesis of pentannulated compounds,[10] we contributed to this field with the recently reported gold(I)-catalyzed Claisen rearrangement/Nazarov cyclization tandem reaction of propargyl vinyl ethers, a process which forms functionalized cyclopentadienes fused with both carba- and heterocyclic rings,[11] and which we have exploited to prepare indenes, too.[12] We have also shown that this cascade reaction, which involves the initial 1,3-shift of the vinyloxy moiety, can be further extended by one step with

propargyl vinyl ethers **A** (Scheme 1, a) as substrates if a dienophile is present in the reaction mixture to trap the cyclopentadiene intermediate (**B**) (and by two steps if *in situ* protection of the aldehyde group is carried out) thus forming complex polycyclic structures (**C**) found in a few natural compounds.[13]

In continuation of this study, we decided to evaluate whether the same process, if carried out in the presence of heterodienophiles such as dialkylazodicarboxylates (Scheme 1, b),[14] would lead to strained diazabicycle cycloadducts **D** which could be used to further functionalize the cyclopentene ring by reductive cleavage of the N-N bond or by ring-opening with organometallic nucleophiles.[15] However, this was not the case, as the major reaction products in our first experiments with DEAD (diethyl azodicarboxylate) were the ring-fused cyclopentadienes **E**, bearing a diaza moiety at the C3a bridgehead position, which derived from the spontaneous, regioselective C1-N8 bond cleavage.[16] This serendipitous discovery led us to study mechanistically this process and extend the scope to a variety of substrates and azodicarboxylates in order to establish a protocol for the synthesis of such complex, polyfunctionalized cyclopentadiene structures bearing a N functionality (a masked amino group) at the bridgehead position otherwise very difficult to synthesize.[17]

Table 1.[a] Survey of reaction conditions influencing the **4**:**5** ratio



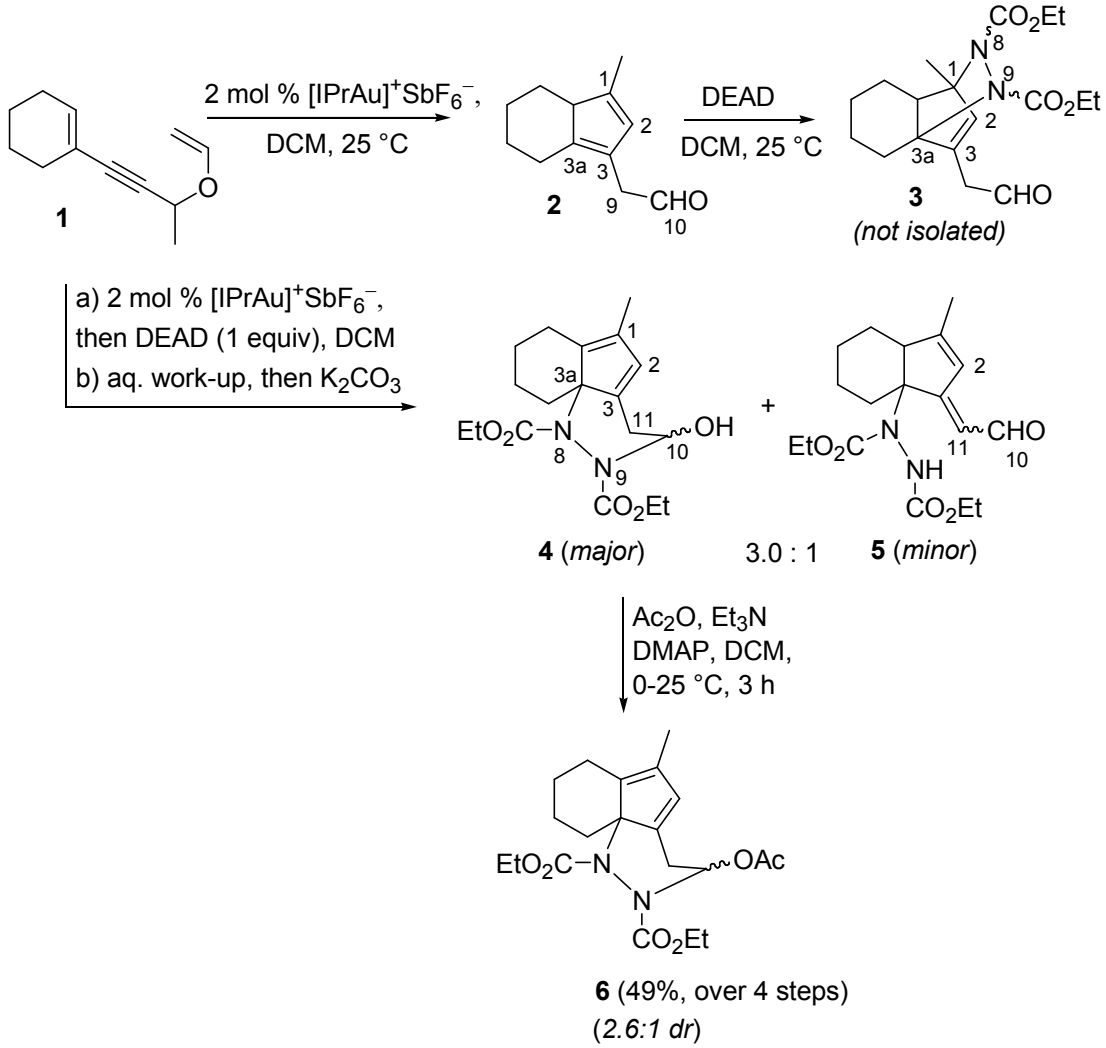
entry	Catalyst (2 mol %)	Reaction time (min)[b]	drying agent[c]	time (h)	**4**:**5**[d]
1	IPrAuCl/$AgSbF_6$	30	K_2CO_3 (n. m.)[e]	18	3.0:1
2	IPrAuCl/$AgSbF_6$	30	K_2CO_3 (100)	22	3.1:1
3	$Ph_3PAuCl/AgSbF_6$	30	K_2CO_3 (50)	16	3.1:1
4	$IPrAuNTf_2$	30	K_2CO_3 (50)	22	3.2:1
5[f]	$IPrAuNTf_2$	30	K_2CO_3 (50)	16	3.0:1
6[g]	$IPrAuNTf_2$	30	K_2CO_3 (50)	16	3.1:1

[a]Reactions carried out on 0.2 mmol of **1** with 1 equiv. of DEAD. [b]Time before aqueous work-up. [c]mmol of K_2CO_3 per mmol of **1**. [d]Measured by ^1H NMR of the crude reaction mixture. [e]Not measured. [f]Carried out by adding DEAD and then substrate **1** to the preformed catalyst. [g]Carried out in DCM distilled over CaH_2; aqueous-work-up with $NaHCO_3$(satd).

Results and Discussion

We carried out our first reaction on propargyl vinyl ether **1** in dichloromethane (from bottle) by adding 1 equiv of DEAD after the cycloisomerization of the substrate to **2**, promoted by 2 mol % of IPrAuCl/$AgSbF_6$ catalytic system,[11] was complete (by TLC, in about 15 min) (Scheme 2).

Scheme 2. Cycloisomerization and hetero Diels-Alder reaction on model substrate **1** with DEAD as heterodienophile.



Diene **2** was quickly consumed upon the addition of the heterodienophile and after about 30 min we carried out an aqueous work-up and left the organic solution to dry over K_2CO_3 overnight (Table 1, entries 1-2). To our surprise, we could not detect any signal corresponding to cycloadduct **3** in the ^1H NMR of the crude reaction mixture. Instead, two major products were present in an approximately 3:1 ratio, i.e., compound **4** (as a 2.2:1 mixture of epimers at the hemiaminal position) and α,β-unsaturated aldehyde **5**, plus some unidentified minor products. Similar results were obtained by using $Ph_3PAuCl/AgSbF_6$ and commercial $IPrAuNTf_2$ as catalysts (entries 3 and 4,

respectively), as well as when premixing substrate **1** and DEAD in DCM and adding this solution to a solution of the catalyst (entry 5). No appreciable differences were observed when carrying out the reaction in anhydrous DCM freshly distilled from CaH_2 (entry 6). Despite many attempts, the chromatographic separation of these two products was not optimal but we were able to obtain major compound **4** in pure form (as the epimeric mixture) by trituration and in a sufficient amount for a full spectroscopic analysis. We also managed to obtain crystals suitable for X-ray analysis, which were those of the major epimer, only (Figure 1) and which confirmed the structure of **4** assigned by NMR analysis.[18] To quantitatively separate **4** from **5**, we instead treated the crude reaction mixture with acetic anhydride to convert the former into the corresponding acetate **6** (Scheme 2),[18] which was obtained in 49% yield over the four steps forming the cascade reaction from **1**, and this was the procedure which we applied later in the evaluation of the scope of this reaction.

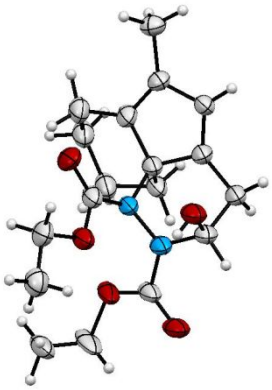
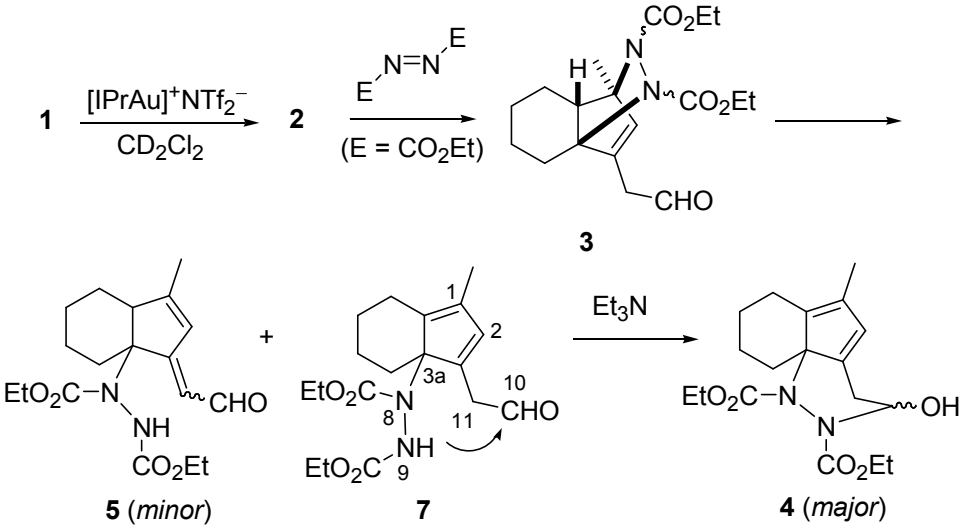


Figure 1. ORTEP diagram of compound **4** (thermal ellipsoids are shown at 50% probability level).

Based on its structure, compound **4** (and aldehyde **5**, as well) must derive from a highly regioselective cleavage of the C1-N8 bond in the cycloadduct **3** to form an intermediate aldehyde with appendages suitably positioned to undergo cyclization, upon treatment with K_2CO_3, by addition of the distal N atom of the diaza functionality at C3a to the carbonyl group. To have more insights into the mechanism, the reaction was directly monitored by ^1H NMR in CD_2Cl_2 (Scheme 3). The addition of the catalyst (2 mol % $[IPrAu]^+NTf_2^-$) to the solution of **1** in the deuterated solvent triggered a quick cycloisomerization of **1** to aldehyde **2**.[19] When the signals of the substrate almost disappeared (about 20 min), we added 1 equiv of DEAD. After 1 min from the addition, we recorded a very clean spectrum (see Supporting Information) in which there were no signals of aldehyde **2** but instead those of what we assumed to be cycloadduct **3**, as a single diastereomer,[20]

and signals of a minor product which we attributed to compound **7**.[21] The ratio between the signals of **7** and **3** increased while monitoring the reaction until those of **3** completely disappeared in 180 min (Figure 2).

Scheme 3. Experiment carried out on model substrate **1** with DEAD in CD_2Cl_2 for direct monitoring by ^1H NMR.



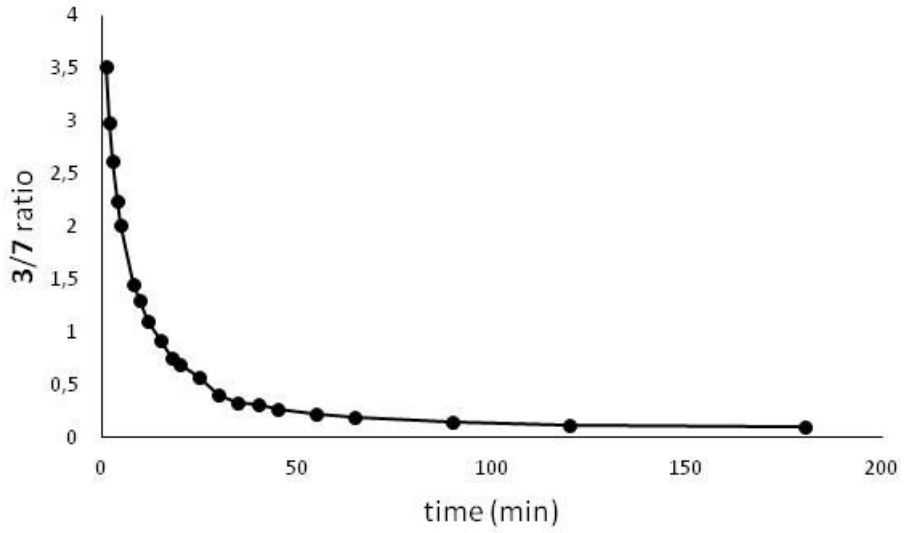
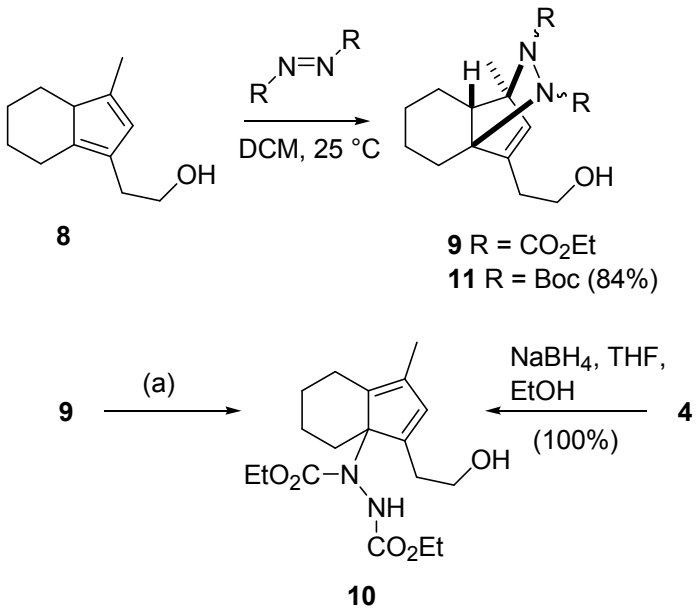


Figure 2. Plot showing the ratio of compounds **3**/**7** *versus* time. The cleavage of the C1-N8 bond in compound **3** was complete in 3 hours.

The transformation of **3** into **7** in the NMR tube was slower than in a flask under stirring, as under the latter conditions it was complete in 30 min. A third product, with the signals of α,β-unsaturated aldehyde **5**, was also detected in the ^1H NMR spectra, in a ratio with **7** practically

constant (about 1:3) during the whole experiment. Under these conditions (NMR tube), the addition of solid K_2CO_3 (50 equiv) was not very efficacious in promoting the expected cyclization of **7** to **4**, as we observed the appearance of the first traces of the typical signals of **4** only after 45 min. Instead, upon addition of Et_3N (1 equiv) compound **7** was completely converted into **4** in 180 min.

Scheme 4. Stepwise synthesis of compound **10**. Reaction conditions corresponding to (a): DCM (from bottle) 17 h (100% conv., 76%), or *p*-TsOH 5 min (100% conv.), or IPrAuNTf$_2$ 30 min (100% conv.).

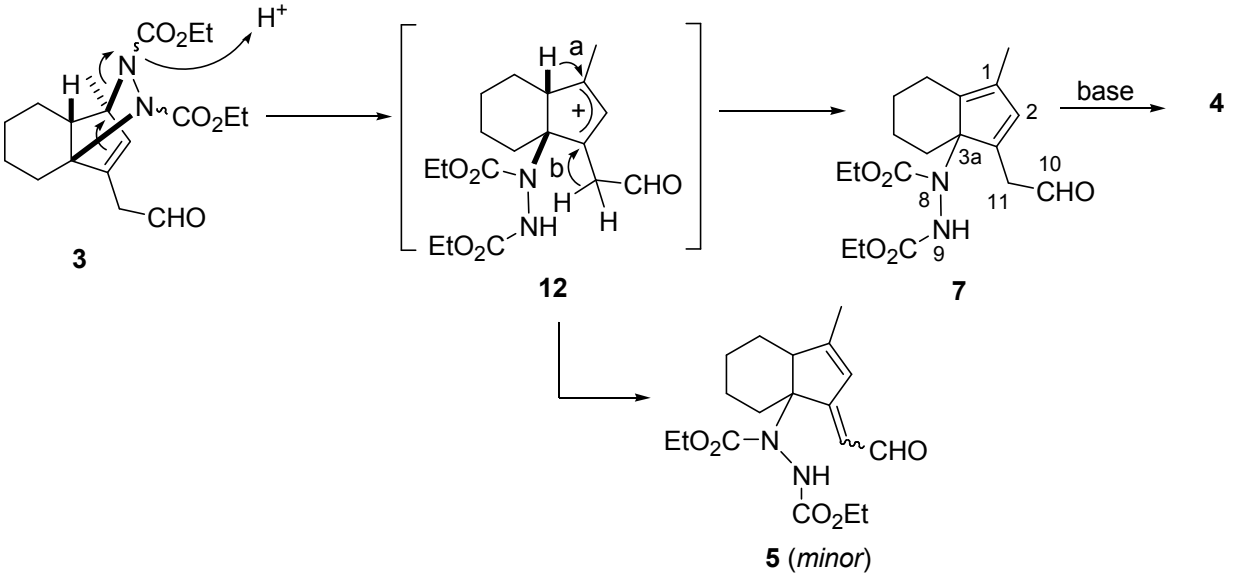


Because of the quick double bond isomerization we had observed occurring on aldehyde **2** during its isolation and purification,[11] in order to evaluate the role of Lewis [Au(I), Ag(I)] or protic acids in the ring opening process leading to **7**, we opted to carry out a few experiments with the corresponding alcohol **8** (Scheme 4)**,** prepared as previously reported.[11] In the first experiment, we added 1 equiv of DEAD to the diene **8** and left under stirring in DCM (from bottle) for 17 h. The only product we observed was **10**, deriving from the HDA reaction and the next slow, regioselective, C1-N8 ring cleavage, and whose structure was demonstrated by reducing **4** with $NaBH_4$ in THF/EtOH.[22] In another experiment carried out under the same conditions, monitoring the reaction by ^{1}H NMR after 30 min from the addition of DEAD we observed only the signals of another product which we could assign to cycloadduct **9** (see Supporting Information).[23,24] By adding a very small amount of *p*-TsOH·H_2O (0.4 mol %) to the reaction mixture, the conversion of **9** into **10** was complete in 5 min. In a parallel experiment, IPrAuNTf$_2$ (2 mol %) was added to the

reaction mixture 2 min after the formation of cycloadduct **9** and in this case the C-N cleavage occurred almost completely in 30 min to give **10**. We also carried out a cycloaddition using DBAD (R = Boc) as the heterodienophile. In this case, stopping the reaction after 30 min we managed to isolate and purify cycloadduct **11**, which was fully characterized, including X-ray analysis (see Supporting Information), thus eventually demonstrating the structure of our cycloaddition products.[24]

Taken together, all these results show that the C-N cleavage in cycloadduct **9** is promoted, or noticeably accelerated, by the presence of both protic acids (e.g., traces of *p*-TsOH) and the IPrAu(I)NTf_2 complex. Even the possible traces of HCl present in commercial CH_2Cl_2 are sufficient to catalyze a slow C-N cleavage (17 h) in **9**. As for cycloadduct **3** generated by adding DEAD after the gold(I)-catalyzed cycloisomerization of **1** (Schemes 2 and 3), it must be the Au(I) catalyst (or the conjugated acid of its counterion) used for the generation of intermediate **2** that promotes the ring opening to **7**, as the reaction well occurs in CH_2Cl_2 distilled over CaH_2.

Scheme 5. Proposed mechanism for the acid-catalyzed C1-N8 bond cleavage.

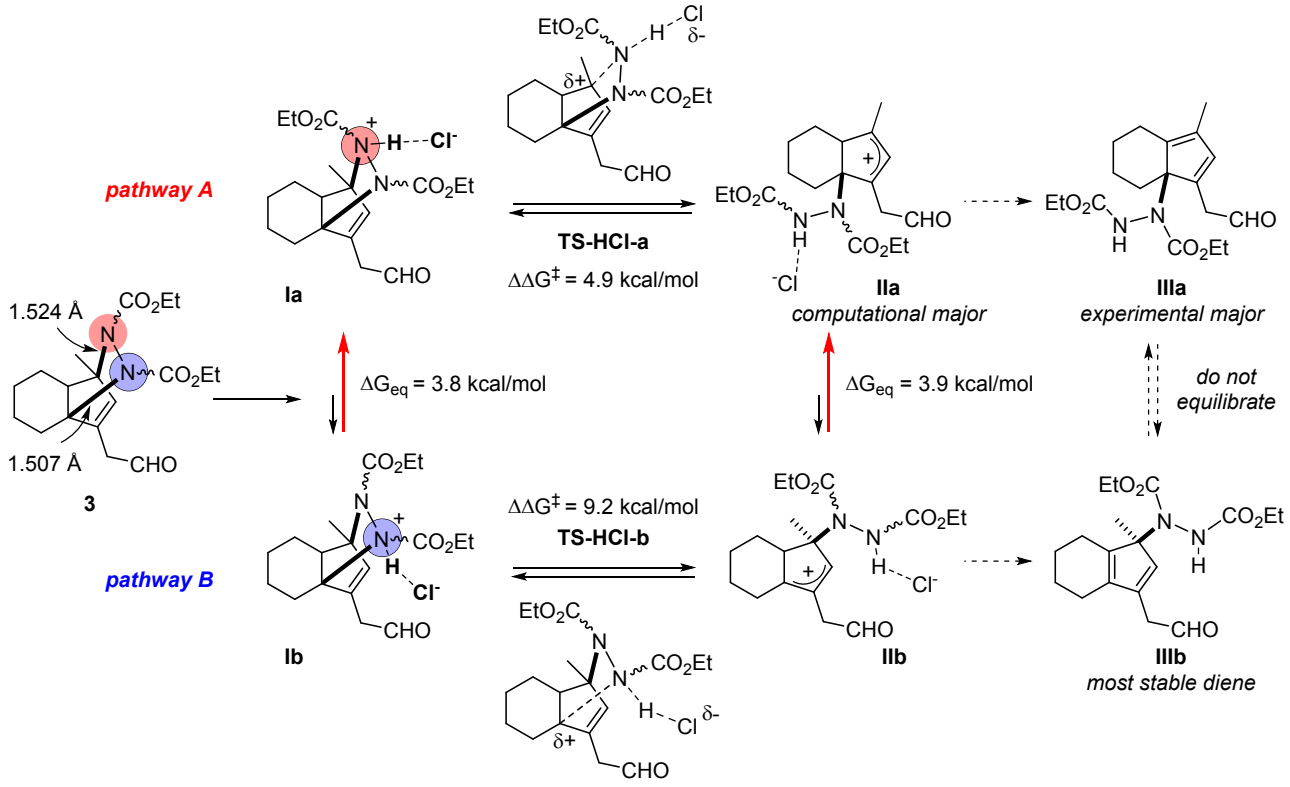


Concerning the reaction mechanism, it appears that the hetero Diels-Alder step occurs at a very fast rate and with high facial selectivity. In analogy to the results we have previously obtained reacting **2** with other dienophiles,[13] we may assume that the cycloaddition involves the less hindered face of **2**, i.e., the one on the same side of the bridgehead 7a-H atom. Then, once the cycloadduct is formed, the Lewis- or protic acid-catalyzed C-N bond cleavage in **3** (Scheme 5) starts immediately and with high regioselectivity, involving the C1-N8 bond, only. The high

regioselectivity could be due to the formation of an allyl cation intermediate (**12**) in which delocalization does not involve any of the junction C atom and thus to a less strained bicyclic system. From this, elimination of the C7a proton leads to **7**, whereas the concomitant formation of α,β-unsaturated aldehyde **5**, in a constant ratio with **7** as the reaction progresses, could be due to a competing H^+ elimination from the acidic β-position of aldehyde **12**. As for the regioselective C-N cleavage, we performed DFT calculations at the M06-2X level to validate our mechanistic hypothesis, focusing on two different crucial aspects.[25] First, we wanted to ascertain the feasibility of the uncatalyzed and catalyzed C-N ruptures, and about the conditions in which they would be energetically affordable; and second, we wanted to determine the reasons for the regioselectivity, since two different C-N bonds exist in the cyclic intermediate **3** (Scheme 6). At this point, it is interesting to note that the C-N bonds in **3** present quite different lengths, indicating a weaker bond (1.524 Å) for N marked in red (C1-N8) than for the blue one (1.507 Å). Initially, our computational efforts were directed to study the uncatalyzed cleavage of each C-N bond in **3**, but after extensive efforts, placing the C---N atoms at different distances, the transitions states could not be located. The stabilization of the positive and negative fragments that are forming is not efficient enough, even in implicit solvent models, and they always collapsed back during the optimization to form the C-N bond. Meanwhile, the introduction of a H-Cl molecule protonates either N in **3** to form structures **Ia** (pathway A) and **Ib** (pathway B), with energies favoring the former by a moderate 3.8 kcal/mol difference. Furthermore, HCl was found to promote an extremely easy cleavage of the C-N bond from both intermediates, showing activation energies of 4.9 and 9.2 kcal/mol respectively (again lower for pathway A). Intermediates **IIa** and **IIb** are formed after the cleavage, where the pairs of intermediates **Ia**/**IIa** and **Ib**/**IIb** are almost isoenergetic. This fact and the low energy of the transition states make the cleavage step reversible, while the whole process (**Ia**/**Ib**/**IIa**/**IIb**) occurs in thermodynamic conditions. Thus, we believe that the regioselectivity is dictated by the lowest energy of **IIa**, 3.9 kcal/mol below **IIb**, explaining the exclusive formation of experimental product **7** (Scheme 5). The fact that every structure in pathway A is lower in energy than its counterpart in pathway B reinforces the idea that the C-N (red) bond is the weakest and easiest to break, due to the greater stability of the allyl cation that is forming.[26] Finally, intermediates **IIa** and **IIb** would lead to products **IIIa** (**7**) and **IIIb** upon easy deprotonation/diene formation, which was not calculated. Importantly, and in contrast with the previous trend, **IIIb** is 6.0 kcal/mol more stable than **IIIa** owing to its less strained double bond disposition. This observation means that (a) **IIIa** and **IIIb** do not equilibrate in the reaction

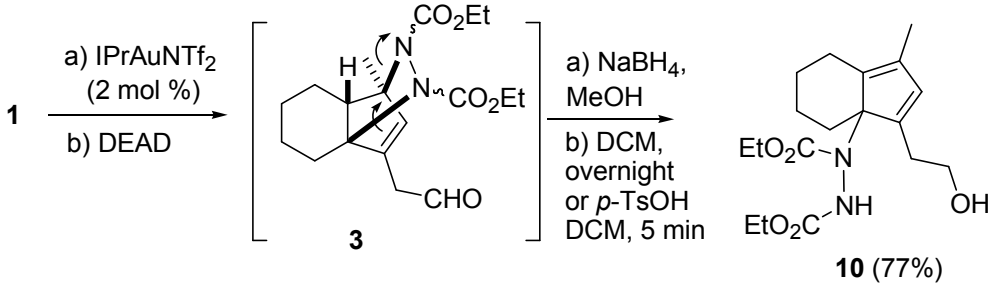
conditions, and (b) their stability does not determine the regioselectivity of the process, as otherwise the major isomer would be the opposite.

Scheme 6. Free energy diagram for the protic acid-catalyzed cleavage of the C-N bond in compound **3** with HCl. Both C1-N8 (pathway A, red) and C3a-N9 (pathway B, blue) bond cleavages are shown. Energies in kcal/mol.



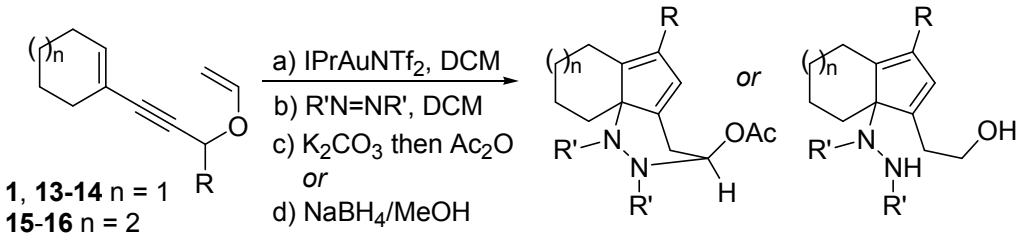
Based on the results above discussed, as formation of aldehyde **5** limits the conversion of the cycloadduct **3** into intermediate **7** (and thus into **4**), we decided to reduce *in situ* cycloadduct **3** just after its formation from **1** and let it undergo ring opening, as shown in Scheme 7.

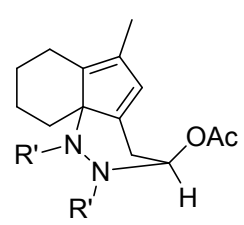
Scheme 7. Synthesis of **10** by cycloisomerization/hetero Diels-Alder/ring opening cascade reaction and *in situ* reduction.



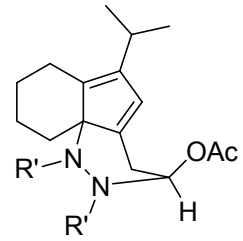
We hoped that reduction of the carbonyl group by $NaBH_4$ should be fast enough to outcompete the C-N bond cleavage in **3** ensuring therefore the formation of **10** from **1**. So, after adding DEAD, the solution was diluted with MeOH and added with $NaBH_4$. Gratifyingly, after aqueous work-up and leaving the organic solution overnight to dry over Na_2SO_4, cyclopentadiene derivative **10** was obtained in 77% yield after chromatographic purification.

Table 2. Substrate scope of the optimized processes.

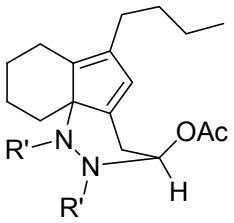




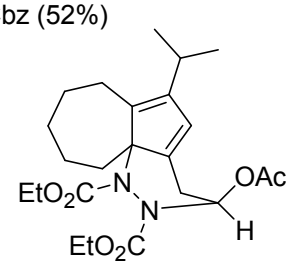
6, R' = Et (49%)[a]
17, R' = *i*-Pr (45%)
18, R' = Cbz (52%)



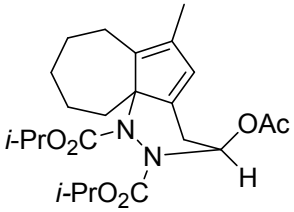
19, R' = Et (48%)
20, R' = Cbz (43%)



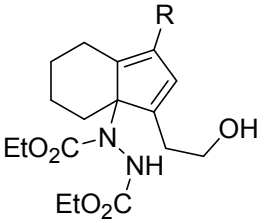
21, R' = i-Pr (49%)
22, R' = Cbz (52%)



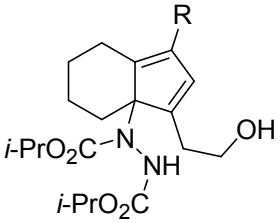
23 (52%)



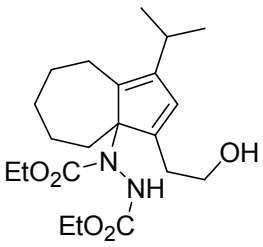
24 (43%)



10, R = Me (82%)[b]
25, R = *n*-Bu (77%)
26, R = *i*-Pr (72%)



27, R = i-Pr (82%)[b]
28, R = Me (72%)



29 (66%)

[a] $IPrAuSbF_6$ was used; [b] 1 mol % catalyst employed.

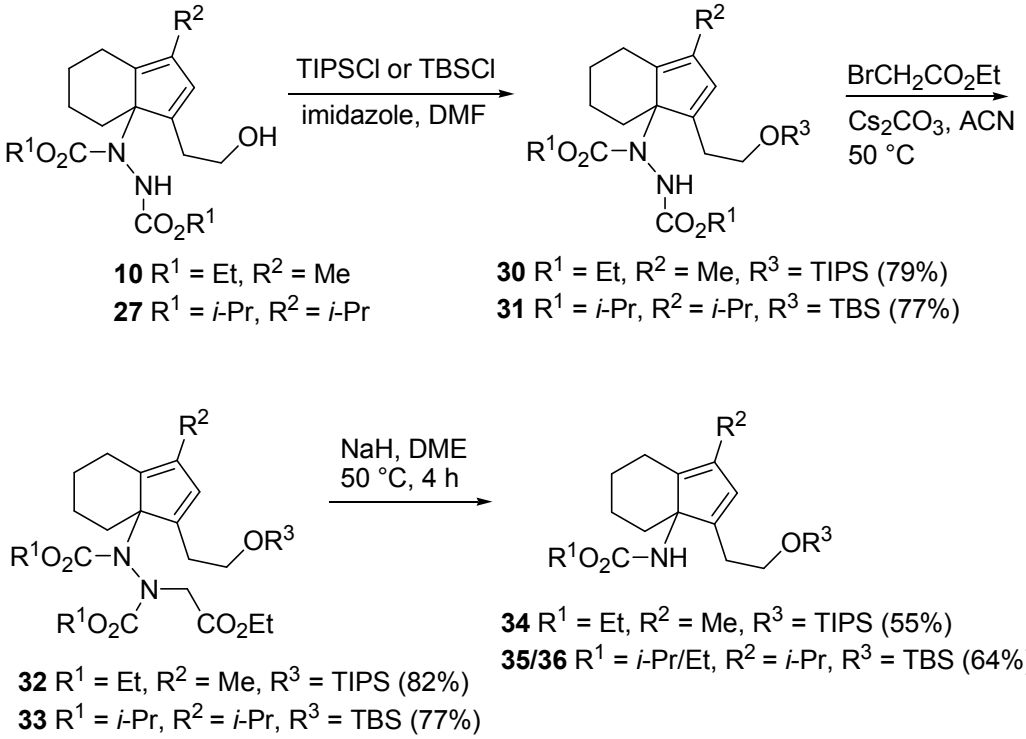
We also could accelerate the C1-N8 bond cleavage by addition of *p*-TsOH (0.4 mol % was sufficient to provide **10** in less than 5 min) and applied this procedure, in the evaluation of the scope of this reaction, when the cleavage was not complete after an overnight stirring in DCM. Both protocols, i.e., without and with *in situ* reduction, were thus exploited to assess the scope of the reaction, as in one case ring-fused cyclopentadienes like **6**, bearing an aldehyde group (protected as cyclic hemiaminal), are obtained, and the corresponding alcohols like **10** in the other. We screened four different heterodienophiles (DEAD, DIAD, dibenzyl azodicarboxylate and DBAD) and different substrates and the results are reported in Table 2.

The cycloaddition step, carried out after the cycloisomerization of the propargyl vinyl ether was complete, occurred with all azodicarboxylates and substrates, as we observed the quick disappearance of the intermediate dienes by TLC upon addition of the heterodienophile. With all of the heterodienophiles we used,[27] the regioselective C-N bond cleavage occurred and provided, after leaving overnight over K_2CO_3, products **6**, **17**-**22** and **23**-**24** (these latter with the cyclopentadiene moiety fused to a seven-membered ring) in 43-52% yields. Alcohols **10** and **25**-**29** were all obtained in good yield (66-82%) according to the above-described procedure by diluting the reaction mixture with MeOH and adding $NaBH_4$, this approximately 8-10 minutes after the cycloaddition step. With two substrates (**1**, R = Me, and **13**, R = *i*-Pr) this sequence was repeated on a mmol scale and with 1 mol % of the gold (I) catalyst, which provided compounds **10** and **27** both in 82% yield, after chromatography. Compounds **25**-**29**, analogously to compound **10**, were all obtained as mixtures of two rotamers at the NMR analysis.[22] In the same reaction carried out with DBAD as the dienophile, the C-N cleavage occurred only partially when leaving overnight after the reduction step, with the loss of a *t*-butyl group (see Supporting Information for a further discussion on this example).

To demonstrate that it was possible to obtain amino-functionalized cyclopentadienes by the cleavage of the N-N bonds, we used both the procedures reported by Magnus,[28] which we envisioned would leave the double bond system unaltered. Accordingly (Scheme 8), after protection of **10** and **27**, chosen as model compounds, as silyl ethers **30** and **31**, respectively, treatment with ethyl bromoacetate in acetonitrile at 50 °C gave alkylated compounds **32** and **33** (isolated and characterized) in 82 and 77% yield, respectively. A solution of compound **32** in acetonitrile was then refluxed in the presence of 3 equiv. of Cs_2CO_3[28a] for three days to give amino-cyclopentadienes **34** in 44% yield after chromatography. Gladly, shorter reaction times (4 h) and higher yield (55%) were attained by the other procedure, i.e., with NaH as a base[28b] in DME

(instead of diglyme as originally reported). The N-N cleavage in compound **33** with the *N*-CO_2*i*-Pr protected hydrazine moiety required longer reaction times by using Cs_2CO_3 in refluxing acetonitrile and did not reach completion even after 4 days. Aware of the possible "transesterification" which had been observed by Magnus,[28b] we carried out the same reaction with NaH in DME, by which the N-N bond cleavage was complete in 4 h but providing the final product as a 2:1 mixture of isopropyl (**35**) and ethyl (**36**) carbamates (in 64% yield) which we could not separate by chromatography. In any case, as the final fate of both the N- and O-protection is their removal, this transesterification should not represent a synthetic problem. Instead, we were especially pleased to see that both *O*-silyl protections, and the conjugated diene system as well, resisted under the above conditions, thus providing suitably protected amino-substituted cyclopentadienes ready for further synthetic elaborations.

Scheme 8. Synthesis of *N*- and *O*-protected aminoalcohols **34**-**36**.



Conclusions

With this work, we have demonstrated the synthetic usefulness of the Au(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization cascade reaction of propargyl vinyl ethers by the synthesis of complex, amino-functionalized cyclopentadienes via the spontaneous ring opening of the hetero-Diels-Alder cycloadducts obtained by *in situ* addition of dialkylazodicarboxylates. A

highly regioselective cleavage of one of two C-N bonds in the cycloadducts generates six- and seven-membered ring-fused cyclopentadienes with pendant hydrazine and aldehyde moieties which intramolecularly react to form hemiaminals when the crude reaction mixtures are left over K_2CO_3 in a DCM solution. The overall yields of these products are in the 40-50% range (after OH protection) because of a side reaction forming the corresponding α,β-unsaturated aldehydes. On the other hand, reducing *in situ* the aldehyde group just after addition of the heterodienophile allows one to overcome this problem and the regioselective C-N bond cleavage now generates the corresponding cyclopentadienes bearing the hydrazine and the alcohol appendages in excellent yields (66-82%) over the four steps entailed in the cascade process. Two examples from this class of compounds were also converted into six-membered ring-fused, functionalized cyclopentadienes, bearing a protected amino group, by the selective N-N cleavage of the hydrazine moiety.

EXPERIMENTAL SECTION

General experimental methods. Anhydrous solvents were prepared according 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 ($CDCl_3$), 3.31 and 49.00 (CD_3OD) in ^{1}H and ^{13}C NMR spectra, respectively. Mass spectra were carried out 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. IR spectra were recorded on Shimadzu IRAffinity-1S spectrometer using the sample either neat or as a solution in $CHCl_3$. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer. Compounds **1**, **8**, **13**-**16** are known.[11,13]

General Procedure for the propargyl Claisen rearrangement/Nazarov cyclization/[4+2] hetero-Diels-Alder reaction: The solution of propargyl vinyl ether **1**, **13**-**16** in *n*-hexane was concentrated and dried under *vacuum* just prior use. Commercially available gold(I) complex IPrAuNTf$_2$ was

generally used, whereas gold(I) complex $IPrAuSbF_6$ was generated *in situ* by mixing equimolar quantities of both IPrAuCl and $AgSbF_6$ and leaving the mixture stirring for 5 minutes at 25 °C before adding the substrates. The dienophile was added pure (DEAD or DIAD) or as a 1.1 M solution in DCM (dibenzyl azodicarboxylate).

Procedure A. To a solution of gold(I) complex LAuX (2-3 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 starting material (TLC monitoring, 10-20 minutes). The dienophile (0.3 mmol) was then added, and the stirring continued for 30 minutes. Water was added (6 mL) and, after separation of the phases, the product was further extracted with DCM (2 x 6 mL). The combined organic extracts were dried under stirring over anhydrous K_2CO_3 (15 mmol) for 18-20 hours. After filtration and evaporation of the solvent, the oily residue was dissolved into anhydrous DCM (3 mL) and cooled to 0 °C (ice bath). Triethylamine (0.9 mmol), a catalytic amount of DMAP (5 mol %) and acetic anhydride (0.6 mmol) were added and after 10 minutes the ice bath was removed and the mixture left to stir for 5 hours at room temperature. A satd solution of $NaHCO_3$ was added (5 mL) and the mixture vigorously stirred for 5 minutes. After separation of the phases, the product was extracted with DCM (2 x 5 mL) and the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude oil was purified by flash chromatography to afford the corresponding acetate.

Procedure B. To a solution of gold(I) complex LAuX (1-2 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 starting material (TLC monitoring, 10-20 minutes). The dienophile (0.3 mmol) was then added and, after 8-10 minutes, the mixture was diluted with MeOH (12 mL) and $NaBH_4$ (12 mg, 0.3 mmol) immediately added. After 10 minutes the reduction was complete. The solvent was then evaporated, methanol (2 mL) was added to the residue and evaporated again; this operation was repeated three times. Water was then 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.

*3-Hydroxy-6-methyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid diethyl ester (**4**).* Prepared following Procedure A, without the acetylation step, starting from **1** (72 mg, 0.41 mmol), DEAD (1 equiv.) and using $IPrAuSbF_6$ (3 mol %) as the catalyst. The crude oil was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 4 + 1% Et_3N; R_f = 0.18) affording the final product **4** in mixture with by-products, among which it was possible to identify the α,β–unsaturated aldehyde **5** in a 1:3 ratio with **4**. The trituration of this sample, with a mixture of EtOAc and *n*-hexane in 1 : 4 ratio, afforded pure compound **4**, in a sufficient amount (26 mg, 18%) for a full spectroscopic characterization. The crystals suitable for X-ray structure determination were obtained by slow evaporation of a solution of **4** in diethyl ether. White solid: m.p. 124.5 – 126.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (2.2 : 1 mixture of diastereoisomers): δ 6.09 – 6.06 (m, 1 H), 5.97 (d, *J* = 2.0 Hz, 1 H), 4.33 – 4.15 (m, 2 H), 4.10 – 3.97 (m, 2 H), 2.73 – 2.67 (m, 2 H), 2.66 – 2.58 (m, 1 H + OH), 2.44 – 2.36 (m, 1 H), 2.20 – 2.13 (m, 1 H), 1.95 – 1.87 (m, 1 H), 1.83 (s, 3 H), 1.76 – 1.67 (m, 1 H), 1.61 – 1.51 (m, 1 H), 1.33 (t, *J* = 7.2 Hz, 3 H, minor), 1.29 (t, *J* = 7.2 Hz, 3 H, major), 1.16 (t, *J* = 7.2 Hz, 3 H), 1.15 – 1.07 (m, 1 H), 0.69 (td, *J* = 13.6, 3.2 Hz, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 156.4, 155.2, 141.6 and 141.2, 140.43 and 140.36, 130.2 and 130.1, 129.5 and 129.4, 76.2 and 74.9, 72.6 and 72.5, 62.6 and 62.2, 62.5 and 62.1, 35.3 and 35.2, 31.4 and 31.1, 29.0 and 28.9, 25.9 and 25.8, 21.8, 14.5, 14.3 and 14.1, 12.32 and 12.28; MS (ESI) *m/z* (%): 727 ([2M + Na]$^+$, 59), 375 ([M + Na]$^+$, 100); IR (neat): 3420, 1727, 1673 cm^{-1}; Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 61.68; H, 8.34; N, 7.19.

*3-Acetoxy-6-methyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid diethyl ester (**6**).* Prepared following Procedure A, starting from **1** (62 mg, 0.35 mmol), DEAD (1 equiv.) and using $IPrAuSbF_6$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 4 + 1% Et_3N; R_f = 0.21), affording acetate **6** (67 mg, 49%) as a white solid: m.p. = 126.0 – 127.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (2.2 : 1 mixture of diastereoisomers): δ 6.94 (dd, *J* = 4.4, 1.6 Hz, 1 H, major), 6.82 (dd, *J* = 4.4, 1.2 Hz, 1 H, minor), 5.93 (s, 1 H), 4.37 – 4.31 (m, 1 H, minor), 4.31 – 4.17 (m, 1 H + 1 H major), 4.15 – 4.03 (m, 1 H), 3.91 – 3.82 (m, 1 H), 2.80 – 2.64 (m, 3 H), 2.46 – 2.38 (m, 1 H), 2.17 – 2.09 (m, 1 H), 1.94 (s, 3 H, minor), 1.93 (s, 3 H, major), 1.91 – 1.87 (m, 1 H), 1.85 (s, 3 H), 1.74 – 1.66 (m, 1 H), 1.60 – 1.51 (m, 1 H), 1.34 (t, *J* = 7.2 Hz, 3 H, minor), 1.28 (t, *J* = 7.2 Hz, 3 H, major), 1.15 (t, *J* = 7.2 Hz, 3 H), 1.12 – 1.05 (m, 1 H), 0.68 (td, *J* = 13.6, 3.2 Hz, 1 H, major), 0.66 (td, *J* = 13.6, 3.2 Hz, 1 H, minor); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.3 and 168.9, 155.0 and 154.3, 153.3, 142.1 and 141.6, 139.4, 129.9 and

129.5, 129.2 and 129.1, 74.9 and 74.0, 72.1 and 72.0, 62.9 and 62.4, 62.0 and 61.8, 35.4 and 35.3, 29.9 and 29.7, 29.0 and 28.9, 25.9 and 25.8, 21.82 and 21.77, 20.74 and 20.71, 14.5 and 14.4, 14.2 and 14.0, 12.39 and 12.36; MS (ESI) *m/z* (%): 807 ($[2M + Na]^+$, 100), 415 ($[M + Na]^+$, 52); IR (neat): 1749, 1733, 1714 cm^{-1}; Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.02; H, 7.28; N, 6.81.

*2-[7a-(N,N'-diethoxycarbonyl)hydrazino-3-methyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethanol (**10**).* *Method A*. Prepared following Procedure B, starting from **1** (193 mg, 1.1 mmol), DEAD (1 equiv.) and using $IPrAuNTf_2$ (1 mol %) as the catalyst. The reaction was complete in 15 minutes. After this time, the mixture was diluted with MeOH (44 mL), $NaBH_4$ (42 mg, 1.1 mmol) was added and the reaction stopped after 10 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1:1; R_f = 0.22) afforded pure compound **10** (313 mg, 82%) as a white foam: ^1H NMR (400 MHz, CD_3OD) (1.4 : 1 mixture of rotamers): δ 5.89 (t, J = 1.6 Hz, 1 H, minor), 5.81 (t, J = 1.6 Hz, 1 H, major), 4.18 – 4.03 (m, 4 H), 3.79 – 3.71 (m, 2 H), 3.19 – 3.01 (m, 1 H), 2.62 – 2.43 (m, 3 H), 2.14 – 2.05 (m, 1 H), 1.93 – 1.84 (m, 1 H), 1.76 (s, 3 H), 1.74 – 1.67 (m, 1 H), 1.59 – 1.44 (m, 2 H), 1.26 – 1.17 (m, 6 H), 1.13 – 1.02 (m, 1 H), 0.88 – 0.76 (m, 1 H); $^{13}C\{^1H\}$ NMR (100.4 MHz, CD_3OD) (mixture of rotamers): δ 159.0, 157.8, 149.8 and 149.6, 142.8 and 142.5, 130.8 and 129.7, 130.3, 78.4 and 78.1, 63.1 and 63.0, 62.5 and 62.4, 61.8, 37.6 and 37.3, 31.2 and 30.8, 30.2 and 30.1, 24.8 and 24.5, 23.0 and 22.4, 14.91 and 14.89, 14.72 and 14.68, 12.31 and 12.29; MS (ESI) *m/z* (%): 272 ($[2M + Na]^+$, 59), 375 ($[M + Na]^+$, 100); IR ($CHCl_3$): 3398, 1745, 1711 cm^{-1}; Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.34; H, 8.01; N, 7.95. Found: C, 61.02; H, 8.25; N, 7.73.

Method B. Compound **4** (64 mg, 0.18 mmol), obtained by trituration as described above, was dissolved in a 1 : 1 mixture of THF and absolute EtOH (7.2 mL) and the resulting solution cooled to 0 °C (ice bath). $NaBH_4$ (7 mg, 0.18 mmol) was added in one portion and the ice bath removed after 10 minutes. The mixture was left under stirring at room temperature for 3 hours. After this time, the solvent was removed under *vacuum* and the residue suspended in satd NH_4Cl solution (10 mL); the product was extracted with DCM (2 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude alcohol was purified by flash chromatography (see conditions above) to afford pure alcohol **10** (63 mg, quantitative) as a white foam.

Method C. DEAD (70 µL, 0.45 mmol) was dropwise added to a solution of alcohol **8** (80 mg, 0.45 mmol) in DCM (8.9 mL) and the mixture was left under stirring at 25 °C. After 17 h the solvent was

removed under *vacuum* and the oily residue purified by flash chromatography (see conditions above) to afford pure alcohol **10** (120 mg, 76%) as a white foam.

*10-(2-Hydroxyethyl)-7-methyl-8,9-diazatricyclo[5.2.2.0^{1,6}]undec-10-ene-8,9-dicarboxylic acid di-tert-butyl ester (**11**).* A 1.0 M solution of DBAD in DCM was prepared and this was dropwise added (450 µL, 0.45 mmol) to a solution of alcohol **8** (80 mg, 0.45 mmol) in DCM (8.9 mL). The mixture was left under stirring at 25 °C and, after 30 minutes, the solvent was removed under *vacuum* and the oily residue purified by flash chromatography (EtOAc/*n*-hexane, 1 : 4 + 1% Et_3N; R_f = 0.13) to afford pure alcohol **11** (154 mg, 84%) as a white solid. The crystals suitable for X-ray structure determination were obtained by slow evaporation of a solution of **11** in a 5 : 1 mixture of diethyl ether and dichloromethane: m.p. = 155.6 – 156.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (s, 1 H), 3.80 – 3.73 (m, 1 H), 3.63 – 3.53 (m, 1 H), 3.21 (br s, 1 H), 2.56 (br d, *J* = 12.4 Hz, 1 H), 2.43 – 2.33 (m, 2 H), 2.00 – 1.93 (m, 1 H), 1.83 – 1.74 (m, 1 H), 1.72 – 1.60 (m, 2 H), 1.66 (s, 3 H), 1.59 – 1.51 (m, 1 H), 1.46 (s, 9 H), 1.44 (s, 9 H), 1.16 – 0.94 (m, 3 H); ^{1}H NMR (400 MHz, CD_3OD): δ 5.75 (br s, 1 H), 3.72 – 3.62 (m, 2 H), 2.67 – 2.61 (m, 1 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 1.98 – 1.86 (m, 1 H), 1.86 – 1.78 (m, 1 H), 1.69 – 1.56 (m, 3 H), 1.66 (s, 3 H), 1.47 (s, 18 H), 1.23 – 1.12 (m, 2 H), 1.06 – 0.97 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 160.0, 152.9, 143.5, 133.0, 82.0, 80.9 (2 C), 76.5, 61.7, 60.1, 31.9, 28.3 (3 C), 28.0 (3 C), 27.3, 23.4 (2 C), 23.1, 16.0; MS (ESI) *m/z* (%): 839 ([2M +Na]$^+$, 100), 431 ([M + Na]$^+$, 69); IR (neat): 3464, 1726, 1701, 1662 cm^{-1}; Anal. Calcd for $C_{22}H_{36}N_2O_5$: C, 64.68; H, 8.88; N, 6.86. Found: C, 64.72; H, 8.91; N, 6.86.

*3-Acetoxy-6-methyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid diisopropyl ester (**17**).* Prepared following Procedure A, starting from **1** (50 mg, 0.28 mmol), DIAD (1 equiv.) and using $IPrAuNTf_2$ (3 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.08), affording pure **17** (53 mg, 45%) as a thick colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (4.5 : 1 mixture of diastereoisomers): δ 6.95 (dd, *J* = 4.0, 2.0 Hz, 1 H, major), 6.83 (dd, *J* = 4.4, 1.2 Hz, 1 H, minor), 5.92 (s, 1 H), 5.05 (sept, *J* = 6.4 Hz, 1 H), 4.76 (sept, *J* = 6.4 Hz, 1 H), 2.78 – 2.68 (m, 3 H), 2.47 – 2.39 (m, 1 H), 2.14 – 2.09 (m, 1 H), 1.97 (s, 3 H), 1.95 – 1.87 (m, 1 H), 1.85 (s, 3 H), 1.74 – 1.67 (m, 1 H), 1.56 – 1.52 (m, 1 H), 1.29 (d, *J* = 6.4 Hz, 3 H), 1.28 (d, *J* = 6.4 Hz, 3 H), 1.16 (d, *J* = 6.4 Hz, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.12 – 1.05 (m, 1 H), 0.67 (td, *J* = 13.6, 3.2 Hz, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.3 and 169.1, 153.9, 142.1, 141.7, 139.6 and 139.5, 129.8, 129.1, 74.9 and 74.4, 72.3 and 71.9,

70.7 and 70.2, 69.6 and 69.5, 35.4 and 35.3, 30.0 and 29.9, 29.1 and 29.0, 26.1 and 26.0, 22.2, 22.1, 22.0, 21.94, 21.85, 21.1, 12.4; MS (ESI) *m/z* (%): 863 ([2M + Na]$^+$, 36), 443 ([M + Na]$^+$, 100); IR ($CHCl_3$): 1708 cm^{-1}; Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66. Found: C, 62.63; H, 7.88; N, 6.48.

*3-Acetoxy-6-methyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid dibenzyl ester (**18**).* Prepared following Procedure A, starting from **1** (50 mg, 0.28 mmol), dibenzyl azodicarboxylate (1 equiv.) and using IPrAuNTf$_2$ (3 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.08), affording pure **18** (75 mg, 52%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (2 : 1 mixture of diastereoisomers): δ 7.48 – 7.44 (m, 2 H, minor), 7.40 – 7.32 (m, 2 H, major), 7.31 – 7.24 (m, 6 H), 7.21 – 7.14 (m, 2 H), 7.00 (dd, *J* = 4.4, 1.6 Hz, 1 H, major), 6.91 (dd, *J* = 4.8, 1.2 Hz, 1 H, minor), 5.95 (s, 1 H), 5.33 – 5.21 (m, 1 H), 5.13 – 5.02 (m, 2 H), 4.96 – 4.93 (m, 1 H, minor), 4.91 – 4.87 (m, 1 H, major), 2.81 – 2.62 (m, 3 H), 2.46 – 2.27 (m, 1 H), 2.17 – 2.07 (m, 1 H), 1.91 – 1.80 (m, 1 H), 1.85 (s, 3 H), 1.69 (s, 3 H, major), 1.63 (s, 1 H, minor), 1.58 – 1.47 (m, 1 H), 1.37 – 1.28 (m, 1 H), 1.14 – 0.97 (m, 1 H), 0.72 – 0.60 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.2 and 169.0, 154.9 and 154.3, 153.4, 142.0 and 141.5, 139.4, 135.9 and 135.8, 135.7 and 135.6, 130.1 and 129.9, 129.3 and 129.2, 128.51 and 128.49, 128.4, 128.3, 128.2 and 128.1, 127.9 and 127.8, 127.4 and 127.2, 74.7 and 74.1, 72.3, 68.6 and 68.3, 67.6 and 67.5, 35.4 and 35.3, 29.9 and 29.7, 29.0 and 28.9, 25.9 and 25.8, 21.8 and 21.7, 20.4 and 20.3, 12.4; MS (ESI) *m/z* (%): 539 ([M + Na]$^+$, 100); IR ($CHCl_3$): 1716 cm^{-1}; Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42. Found: C, 69.68; H, 6.35; N,5.29.

*3-Acetoxy-6-isopropyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid diethyl ester (**19**).* Prepared following Procedure A, starting from **13** (47 mg, 0.23 mmol), DEAD (1 equiv.) and using IPrAuNTf$_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.08), affording pure **19** (46 mg, 48%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (2.2 : 1 mixture of diastereoisomers): δ 6.94 (d, *J* = 4.4 Hz, 1 H; major), 6.83 (d, *J* = 4.4 Hz, 1 H, minor), 6.08 (d, *J* = 2.0 Hz, 1 H), 4.32 – 4.16 (m, 2 H), 4.14 – 4.02 (m, 1 H), 3.91 – 3.83 (m, 1 H), 2.82 (sept, *J* = 6.4 Hz, 1 H), 2.77 – 2.65 (m, 3 H), 2.43 – 2.34 (m, 1 H), 2.14 (d, *J* = 14.0 Hz, 1 H), 1.95 (s, 3 H), 1.96 – 1.86 (m, 1 H), 1.77 – 1.66 (m, 1 H), 1.59 – 1.50 (m, 1 H), 1.34 (t, *J* = 7.2 Hz, 3 H, minor), 1.28 (t, *J* = 7.2 Hz, 3 H, major), 1.15 (d, *J* = 7.2 Hz, 3 H), 1.13

(d, *J* = 7.2 Hz, 3 H), 1.11 – 1.04 (m, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.69 – 0.60 (m, 1 H); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.3 and 169.0, 155.0 and 154.4, 153.4, 140.3, 140.1 and 139.9, 139.5, 124.7 and 124.6, 74.8 and 73.9, 72.2 and 72.1, 62.8 and 61.9, 62.4 and 61.8, 35.8 and 35.7, 30.0 and 29.8, 29.5 and 29.4, 25.9 and 25.8, 25.6, 22.8, 22.1 and 22.0, 21.53 and 21.48, 20.79 and 20.76, 14.5 and 14.4, 14.2 and 14.1; MS (ESI) *m/z* (%): 863 ($[2M + Na]^+$, 52), 443 ($[M + Na]^+$, 100); IR ($CHCl_3$): 1712 cm^{-1}; Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66. Found: C, 62.65; H, 7.99; N, 6.40.

*3-Acetoxy-6-isopropyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid dibenzyl ester (**20**).* Prepared following Procedure A, starting from **13** (65 mg, 0.32 mmol), dibenzyl azodicarboxylate (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.07), affording pure **20** (75 mg, 43%) as a thick pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) (1.9 : 1): δ 7.49 – 7.43 (m, 1 H, minor), 7.41 – 7.32 (m, 1 H, major), 7.31 – 7.22 (m, 6 H), 7.21 – 7.15 (m, 2 H), 6.11 (t, *J* = 2.4 Hz, 1 H), 6.99 (dd, *J* = 4.4, 1.6 Hz, 1 H, major), 6.89 (dd, *J* = 4.4, 1.2 Hz, 1 H, minor), 5.32 – 5.23 (m, 1 H), 5.19 – 5.02 (m, 2 H), 4.95 – 4.87 (m, 1 H), 2.86 – 2.65 (m, 4 H), 2.44 – 2.26 (1 H), 2.21 – 2.07 (m, 1 H), 1.98 – 1.78 (m, 1 H), 1.68 (s, 3 H, major), 1.61 (s, 3 H, minor), 1.59 – 1.48 (m, 1 H), 1.34 – 1.26 (m, 1 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.10 – 1.03 (m, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H, minor), 0.99 (d, *J* = 6.8 Hz, 3 H, major), 0.70 – 0.58 (m, 1 H); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.3 and 169.1, 155.0, 154.4 and 153.5, 140.6 and 140.4, 139.9, 139.5, 136.1 and 136.0, 135.71 and 135.69, 128.49 and 128.48, 128.38 and 128.36, 128.24, 128.22 and 128.1, 127.9 and 127.7, 127.3 and 127.2, 124.8 and 124.7, 74.7 and 74.1, 72.5, 68.6 and 68.3, 67.5 and 67.4, 35.9 and 35.7, 30.0 and 29.9, 29.5 and 29.4, 25.9 and 25.8, 25.6, 22.82 and 22.79, 22.1 and 22.0, 21.4, 20.4 and 20.3; MS (ESI) *m/z* (%): 1111 ($[2M + Na]^+$, 21), 567 ($[M + Na]^+$, 100); IR ($CHCl_3$): 1717 cm^{-1}; Anal. Calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.36; H, 6.89; N, 5.01.

*3-Acetoxy-6-butyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid diisopropyl ester (**21**).* Prepared following Procedure A, starting from **14** (48 mg, 0.22 mmol), DIAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.09), affording pure **21** (50 mg, 49%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) (3 : 1 mixture of diastereoisomers): δ 6.96 – 6.94 (m, 1 H,

major), 6.84 – 6.82 (m, 1 H, minor), 5.97 (s, 1 H), 5.08 – 5.00 (m, 1 H), 4.79 – 4.73 (m, 1 H), 2.79 – 2.65 (m, 3 H), 2.43 (td, *J* = 13.2, 4.8 Hz, 1 H), 2.35 – 2.18 (m, 2 H), 2.17 – 2.10 (m, 1 H), 1.96 (s, 3 H), 1.97 – 1.89 (m, 1 H), 1.79 – 1.68 (m, 1 H), 1.60 – 1.50 (m, 1 H), 1.47 – 1.35 (m, 2 H), 1.33 (d, *J* = 6.0 Hz, 6 H, minor), 1.28 (d, *J* = 6.0 Hz, 3 H major), 1.27 (d, *J* = 6.0 Hz, 3 H major), 1.28 – 1.23 (m, 2 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H), 1.15 – 1.05 (m, 1 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.66 (td, *J* = 13.6, 3.2 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): *δ* 169.3 and 169.0, 154.6 and 153.9, 152.9, 141.9 and 141.5, 139.7, 134.7 and 134.6, 127.7 and 127.4, 74.8 and 74.4, 72.2 and 72.0, 70.6 and 70.2, 69.6 and 69.4, 35.8 and 35.5, 31.3, 30.1 and 29.9, 29.4, 26.5, 26.1 and 26.0, 22.4, 22.3, 22.0, 21.9, 21.86, 21.84 and 21.75, 21.0, 13.9; MS (ESI) *m/z* (%): 947 ($[2M + Na]^+$, 100), 485 ($[M + Na]^+$, 72); IR ($CHCl_3$): 1707 cm^{-1}; Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.85; H, 8.34; N, 6.02.

*3-Acetoxy-6-butyl-3,4,7,8,9,10-hexahydro-1,2-diazabenzo[c]indene-1,2-dicarboxylic acid dibenzyl ester (**22**).* Prepared following Procedure A, starting from **14** (52 mg, 0.24 mmol), dibenzyl azodicarboxylate (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.05), affording pure **22** (70 mg, 52%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (1.8 : 1 mixture of diastereoisomers): *δ* 7.48 – 7.44 (m, 2 H, minor), 7.40 – 7.31 (m, 2 H, major), 7.31 – 7.23 (m, 6 H), 7.20 – 7.15 (m, 2 H), 7.00 (dd, *J* = 4.4, 1.6 Hz, 1 H, major), 6.90 (dd, *J* = 4.4, 1.2 Hz, 1 H, minor), 6.00 (s, 1 H), 5.33 – 5.23 (m, 1 H), 5.14 – 5.03 (m, 2 H), 4.97 – 4.86 (m, 1 H), 2.82 – 2.64 (m, 3 H), 2.44 – 2.17 (m, 3 H), 2.16 – 2.06 (m, 1 H), 1.97 – 1.79 (m, 1 H), 1.68 (s, 3 H, major), 1.61 (s, 3 H, minor), 1.59 – 1.49 (m, 1 H), 1.45 – 1.20 (m, 5 H), 1.14 – 0.97 (m, 1 H), 0.89 (t, *J* = 7.2 Hz, 3 H, minor), 0.88 (t, *J* = 7.2 Hz, 3 H, major), 0.71 – 0.59 (m, 1 H); $^{13}C\{^{1}H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): *δ* 169.03 and 169.01, 154.9, 154.3 and 153.4, 141.8 and 141.4, 139.5, 136.0 and 135.9, 135.7 and 135.6, 135.0 and 134.8, 128.50 and 128.47, 128.4, 128.3, 128.1 and 128.0, 127.9 and 127.8, 127.7, 127.4 and 127.2, 74.7 and 74.1, 72.4, 68.6 and 68.3, 67.6 and 67.4, 35.8 and 35.6, 31.3 and 31.2, 30.0 and 29.8, 29.3 and 29.2, 26.5, 25.9 and 25.8, 22.42 and 22.39, 21.93 and 21.86, 20.4 and 20.3, 14.0; MS (ESI) *m/z* (%): 581 ($[M + Na]^+$, 100); IR ($CHCl_3$): 1717 cm^{-1}; Anal. Calcd for $C_{33}H_{38}N_2O_6$: C, 70.95; H, 6.86; N, 5.01. Found: C, 70.78; H, 6.93; N, 4.99.

*4-Acetoxy-8-isopropyl-2,3-diaza-tricyclo[7.5.0.0^{1,6}]tetradeca-6,8-diene-2,3-dicarboxylic acid diethyl ester (**23**).* Prepared following Procedure A, starting from **16** (53 mg, 0.24 mmol), DEAD (1 equiv.)

and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.07), affording pure **23** (54 mg, 52%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (1.5 : 1 mixture of diastereoisomers): δ 6.91 (dd, *J* = 4.0, 1.6 Hz, 1 H, major), 6.79 (d, *J* = 4.0 Hz, 1 H, minor), 6.06 (s, 1 H), 4.37 – 4.29 (m, 1 H, minor), 4.29 – 4.17 (m, 1 H + 1 H major), 4.13 – 4.06 (m, 1 H), 3.94 – 3.87 (m, 1 H), 2.80 (sept, *J* = 6.8 Hz, 1 H), 2.74 – 2.61 (m, 3 H), 2.52 – 2.43 (m, 1 H), 1.98 – 1.87 (m, 1 H), 1.94 (s, 3 H), 1.82 – 1.61 (m, 3 H), 1.61 – 1.44 (m, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H, minor), 1.28 (t, *J* = 7.2 Hz, 3 H, major), 1.15 (t, *J* = 7.2 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.96 – 0.80 (m, 1 H); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.4 and 169.0, 154.4 and 154.3, 153.3, 144.0 and 143.8, 141.6 and 141.2, 138.2 and 138.0, 125.8, 76.0 and 75.9, 74.5 and 73.8, 62.8 and 62.4, 61.9 and 61.7, 32.8 and 32.7, 30.6 and 30.5, 29.8 and 29.6, 28.7 and 28.5, 28.1 and 28.0, 25.8, 23.5 and 23.3, 21.75 and 21.72, 21.38 and 21.37, 20.80 and 20.76, 14.5 and 14.4, 14.3 and 14.2; MS (ESI) *m/z* (%): 891 ($[2M + Na]^+$, 100), 457 ($[M + Na]^+$, 41); IR ($CHCl_3$): 1712 cm^{-1}; Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.57; H, 7.89; N, 6.45. Found: C, 63.64; H, 7.99; N, 6.37.

*4-Acetoxy-8-methyl-2,3-diaza-tricyclo[7.5.0.0^{1,6}]tetradeca-6,8-diene-2,3-dicarboxylic acid diisopropyl ester (**24**).* Prepared following Procedure A, starting from **15** (47 mg, 0.25 mmol), DIAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The crude acetate was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10 + 1% Et_3N; R_f = 0.08), affording pure **24** (47 mg, 43%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (1.7 : 1 mixture of diastereoisomers): δ 6.92 (t, *J* = 2.8 Hz, 1 H, major), 6.79 (d, *J* = 4.0 Hz, 1 H, minor), 5.89 (s, 1 H), 5.02 (m, 1 H, major), 5.00 (m, 1 H, minor), 4.79 (m, 1 H), 2.73 – 2.63 (m, 2 H), 2.57 – 2.46 (m, 1 H), 1.96 (s, 3 H), 1.94 – 1.87 (m, 1 H), 1.84 (s, 3 H), 1.79 – 1.70 (m, 2 H), 1.65 – 1.61 (m, 1 H), 1.57 – 1.46 (m, 3 H), 1.45 – 1.38 (m, 1 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 1.30 – 1.27 (m, 3 H), 1.17 – 1.14 (m, 6 H), 0.90 – 0.80 (m, 1 H); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 169.4 and 169.1, 154.0 and 153.8, 152.7, 144.0 and 143.8, 137.8, 133.7 and 133.6, 130.2, 75.7 and 75.6, 74.5 and 74.1, 70.7 and 70.4, 69.4 and 69.3, 32.6 and 32.5, 30.6, 29.8 and 29.6, 28.8 and 28.6, 28.0 and 27.7, 23.6 and 23.5, 22.1, 22.0, 21.95 and 21.91, 21.8, 21.04 and 21.02, 12.8; MS (ESI) *m/z* (%): 891 ($[2M + Na]^+$, 100), 457 ($[M + Na]^+$, 54); IR ($CHCl_3$): 1729, 1705 cm^{-1}; Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.57; H, 7.89; N, 6.45. Found: C, 63.39; H, 8.02; N, 6.28.

2-[7a-(N,N'-diethoxycarbonyl)hydrazino-3-butyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethanol (***25***). Prepared following Procedure B, starting from **14** (57 mg, 0.26 mmol), DEAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The reaction was complete in 13 minutes. After this time, the mixture was diluted with MeOH (10.4 mL), $NaBH_4$ (10 mg, 0.26 mmol) was added and the reaction stopped after 20 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1 : 2; R_f = 0.19) afforded pure **25** (79 mg, 77%) as a colourless oil: ^{1}H NMR (400 MHz, CD_3OD) (1.2 : 1 mixture of rotamers): δ 5.96 (s, 1 H, minor), 5.86 (s, 1 H, major), 4.17 – 4.05 (m, 4 H), 3.79 – 3.73 (m, 2 H), 3.19 (br s, 1 H), 2.60 – 2.48 (m, 3 H), 2.19 (t, *J* = 7.2 Hz, 2 H), 2.13 – 2.02 (m, 1 H), 1.95 – 1.85 (m, 1 H), 1.84 – 1.69 (m, 1 H, major), 1.61 – 1.45 (m, 1 H and 1 H minor), 1.46 – 1.38 (m, 2 H), 1.31 – 1.19 (m, 8 H), 1.13 – 1.00 (m, 1 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.86 – 0.76 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, CD_3OD) (mixture of rotamers): δ 158.8, 158.0, 150.0 and 149.5, 143.2 and 142.4, 134.6, 129.6 and 128.9, 78.8 and 78.3, 63.1 and 63.0, 62.4 and 62.3, 61.8 and 61.7, 37.5 and 37.1, 32.2, 31.3 and 30.8, 30.4 and 30.3, 27.2, 24.8 and 24.6, 23.2 and 23.1, 22.5, 14.9, 14.8 and 14.7, 14.3; MS (ESI) *m/z* (%): 811 ([2M + Na]$^+$, 63), 417 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3502, 3420, 1745, 1711 cm^{-1}; Anal. Calcd for $C_{21}H_{34}N_2O_5$: C, 63.93; H, 8.69; N, 7.10. Found: C, 63.80; H, 8.95; N, 6.98.

2-[7a-(N,N'-diethoxycarbonyl)hydrazino-3-isopropyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethanol (***26***). Prepared following Procedure B, starting from **13** (53 mg, 0.26 mmol), DEAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The reaction was complete in 11 minutes. After this time, the mixture was diluted with MeOH (10.4 mL), $NaBH_4$ (10 mg, 0.26 mmol) was added and the reaction stopped after 20 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1 : 2; R_f = 0.22) afforded pure **26** (71 mg, 72%) as a colourless oil: ^{1}H NMR (400 MHz, CD_3OD) (1.4 : 1 mixture of rotamers): δ 6.08 (s, 1 H, minor), 5.99 (s, 1 H, major), 4.14 – 4.06 (m, 4 H), 3.79 – 3.73 (m, 2 H), 3.13 (br s, 1 H), 2.80 – 2.69 (m, 1 H), 2.67 – 2.43 (m, 3 H), 2.17 – 2.02 (m, 1 H), 1.96 – 1.85 (m, 1 H), 1.81 – 1.71 (m, 1 H, minor), 1.61 – 1.43 (m, 1 H + 1 H major), 1.27 – 1.15 (m, 6 H), 1.10 – 1.05 (m, 1 H), 1.08 (d, *J* = 6.8 Hz, 3 H, minor), 1.07 (d, *J* = 6.8 Hz, 3 H, major), 1.02 (d, *J* = 6.8 Hz, 3 H, minor), 1.01 (d, *J* = 6.8 Hz, 3 H, major), 0.89 – 0.76 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, CD_3OD) (mixture of rotamers): δ 158.8, 157.9, 150.3, 141.0 and 140.5, 126.4, 125.7, 78.2, 63.1 and 63.0, 62.4, 61.8, 37.4, 31.4 and 31.0, 30.8 and 30.6, 26.9, 24.8 and 24.6, 23.3, 22.9, 22.6, 21.9, 15.0 and 14.8; MS (ESI) *m/z* (%): 783 ([2M + Na]$^+$, 100), 403 ([M + Na]$^+$, 79); IR ($CHCl_3$): 3422, 1747, 1708 cm^{-1}; Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.13; H, 8.48; N, 7.36. Found: C, 62.98; H, 8.59; N, 7.21.

*2-[7a-(N,N'-diisopropoxycarbonyl)hydrazino-3-isopropyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethanol (**27**).* Prepared following Procedure B, starting from **13** (231 mg, 1.13 mmol), DIAD (1 equiv.) and using $IPrAuNTf_2$ (1 mol %) as the catalyst. The reaction was complete in 28 minutes. After this time, the mixture was diluted with MeOH (45 mL), $NaBH_4$ (43 mg, 1.13 mmol) was added and the reaction stopped after 30 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1 : 2; R_f = 0.20), afforded pure **27** (380 mg, 82%) as a pale yellow foam: ^{1}H NMR (400 MHz, CD_3OD) (1.7 : 1 mixture of rotamers): δ 6.07 (s, 1 H, minor), 5.98 (s, 1 H, major), 4.93 – 4.74 (m, 2 H), 3.81 – 3.72 (m, 2 H), 3.13 (br m, 1 H), 2.79 – 2.69 (m, 1 H), 2.66 – 2.57 (m, 1 H), 2.57 – 2.42 (m, 2 H), 2.19 – 2.03 (m, 1 H), 1.96 – 1.85 (m, 1 H), 1.83 – 1.68 (m, 1 H, minor), 1.60 – 1.44 (m, 1 H + 1 H major), 1.27 – 1.16 (m, 12 H + 2 H), 1.09 (d, *J* = 6.8 Hz, 3 H, minor), 1.08 (d, *J* = 6.8 Hz, 3 H, major), 1.10 – 1.04 (m, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H, minor), 1.01 (d, *J* = 6.8 Hz, 3 H, major), 0.87 – 0.75 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 156.1, 155.9, 148.5 and 147.9, 138.9, 126.7 and 126.0, 125.3, 69.7, 69.5, 69.3, 61.3 and 60.5, 36.1, 30.3 and 29.9, 29.4 and 29.3, 25.5, 24.3 and 23.7, 22.5, 22.0 and 21.9, 21.8, 21.77, 21.4 and 21.3; MS (ESI) *m/z* (%): 431 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3420, 1739, 1704 cm^{-1}; Anal. Calcd for $C_{22}H_{36}N_2O_5$: C, 64.68; H, 8.88; N, 6.86. Found: C, 64.56; H, 9.00; N, 6.95.

*2-[7a-(N,N'-diisopropoxycarbonyl)hydrazino-3-methyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethanol (**28**).* Prepared following Procedure B, starting from **1** (63 mg, 0.36 mmol), DEAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The reaction was complete in 4 minutes. After this time, the mixture was diluted with MeOH (14.2 mL), $NaBH_4$ (13 mg, 0.36 mmol) was added and the reaction stopped after 13 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1 : 2; R_f = 0.11) afforded pure **28** (99 mg, 72%) as a colourless oil; ^{1}H NMR (400 MHz, CD_3OD) (1.2 : 1 mixture of rotamers): δ 5.87 (s, 1 H, minor), 5.80 (s, 1 H, major), 4.89 – 4.70 (m, 2 H), 3.83 – 3.68 (m, 2 H), 3.14 – 2.95 (m, 1 H), 2.63 – 2.42 (m, 3 H), 2.18 – 2.03 (m, 1 H), 1.94 – 1.83 (m, 1 H), 1.76 (s, 3 H), 1.59 – 1.42 (m, 2 H), 1.28 – 1.14 (m, 12 H), 1.12 – 1.03 (m, 1 H), 0.88 – 0.75 (m, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of diastereoisomers): δ 156.3 (2 C), 148.0 and 147.5, 141.9, 130.8, 130.0, 69.7, 69.6, 69.5, 61.4 and 60.7, 36.3 and 35.6, 30.1 and 29.8, 28.9 and 28.8, 24.4 and 23.8, 22.01, 21.96, 21.9, 21.8, 21.2, 12.2; MS (ESI) *m/z* (%): 783 ([2M + Na]$^+$, 24), 403 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3502, 3415, 1742, 1704 cm^{-1}; Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.13; H, 8.48; N, 7.36. Found: C, 63.05; H, 8.62; N, 7.19.

*2-[8a-(N,N'-diethoxycarbonyl)hydrazino-3-isopropyl-4,5,6,7,8,8a-hexahydroazulen-1-yl]-ethanol (**29**).* Prepared following Procedure B, starting from **16** (70 mg, 0.32 mmol), DEAD (1 equiv.) and using $IPrAuNTf_2$ (2 mol %) as the catalyst. The reaction was complete in 15 minutes. After this time, the mixture was diluted with MeOH (12.8 mL), $NaBH_4$ (12 mg, 0.32 mmol) was added and the reaction stopped after 20 minutes. Purification by flash chromatography (EtOAc/*n*-hexane, 1 : 2; R_f = 0.14) afforded pure **29** (83 mg, 66%) as a colourless oil: ^{1}H NMR (400 MHz, CD_3OD) (1.3 : 1 mixture of rotamers): δ 5.98 (s, 1 H, minor), 5.92 (s, 1 H, major), 4.15 – 4.01 (m, 4 H), 3.81 – 3.71 (m, 2 H), 2.78 – 2.69 (m, 1 H), 2.55 – 2.36 (m, 4 H), 2.33 – 2.27 (m, 1 H + 1 H minor), 2.22 – 2.15 (m, 1 H, major), 1.74 – 1.47 (m, 5 H), 1.27 – 1.17 (m, 7 H), 1.07 – 1.03 (m, 6 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 156.4 (2 C), 147.3, 144.4 and 144.0, 139.9 and 139.3, 125.8, 81.5 and 81.1, 62.1 and 61.6, 61.8 and 61.4, 60.6, 34.2, 30.5, 29.9 and 29.7, 27.8, 25.9 and 25.8, 24.8 and 24.7, 24.1, 22.1 and 21.7, 21.3 and 21.2, 14.50 and 14.46, 14.43 and 14.39; MS (ESI) *m/z* (%): 811 ([2M + Na]$^+$, 40), 417 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3421, 1745, 1710 cm^{-1}; Anal. Calcd for $C_{21}H_{34}N_2O_5$: C, 63.93; H, 8.69; N, 7.10. Found: C, 64.02; H, 8.56; N, 7.05.

*Triisopropyl-{2-[7a-(N,N'-diethoxycarbonyl)hydrazino-3-methyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethoxy}-silane (**30**).* Compound **10** (313 mg, 0.89 mmol) was dissolved into anhydrous DMF (3.0 mL) and to this solution imidazole (181 mg, 2.66 mmol) and TIPS chloride (380 µL, 1.78 mmol) were added. The mixture was heated at 45 °C (external) and left under stirring for 18 h. After cooling at room temperature, water (30 mL) was added and the product extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 5; R_f = 0.30), affording pure compound **30** (358 mg, 79%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (1.25 : 1 mixture of rotamers): δ 6.65 (br s, 1 H, NH major), 6.44 (br s, 1 H, NH minor), 5.89 (s, 1 H, minor), 5.79 (s, 1 H, major), 4.21 – 3.99 (m, 4 H), 3.88 – 3.78 (m, 2 H), 3.25 (br m, 1 H, major), 2.98 (br m, 1 H, minor), 2.61 – 2.38 (m, 3 H), 2.34 – 2.24 (m, 1 H major), 2.05 – 1.79 (m, 2 H), 1.75 (s, 3 H, minor), 1.73 (s, 3 H, major), 1.65 – 1.39 (m, 2 H), 1.27 – 1.13 (m, 6 H), 1.11 – 1.00 (m, 22 H), 0.91 – 0.73 (m, 1 H and 1 H minor); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 156.7 and 156.3, 155.7, 147.9 and 146.8, 142.6 and 141.5, 131.9 and 129.6, 78.0 and 76.3, 62.5 and 62.1, 61.9, 61.6 and 61.0, 36.3 and 35.6, 30.9 and 30.0, 29.0 and 28.8, 24.1 and 23.7, 22.2 and 21.1, 18.0 and 17.9 (6 C), 14.4 and 14.2 (2 C), 12.22

and 12.18, 11.93 and 11.88 (3 C); MS (ESI) *m/z* (%): 531 ([M + Na]$^+$, 100); Anal. Calcd for $C_{27}H_{48}N_2O_5Si$: C, 63.74; H, 9.51; N, 5.51. Found: C, 63.59; H, 10.00; N, 5.72.

*tert-Butyldimethylsilyl-{2-[7a-(N,N'-diisopropoxycarbonyl)hydrazino-3-isopropyl-5,6,7,7a-tetrahydro-4H-inden-1-yl]-ethoxy}-silane (**31**).* Prepared as reported for compound **30**, starting from **27** (162 mg, 0.40 mmol) and TBS chloride (120 mg, 0.80 mmol), heating at 35 °C (external). Purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1 : 10; R_f = 0.20) afforded pure **31** (161 mg, 77%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (1.5 : 1 mixture of rotamers): δ 6.71 (br s, 1 H, NH, major), 6.24 (br s, 1 H, NH, minor), 6.06 (s, 1 H, major), 5.95 (s, 1 H, minor), 4.98 – 4.79 (m, 2 H), 3.85 – 3.73 (m, 2 H), 3.43 – 2.90 (m, 1 H), 2.77 – 2.67 (m, 1 H), 2.66 – 2.59 (m, 1 H, major), 2.54 – 2.30 (m, 3 H), 1.96 – 1.84 (m, 1 H), 1.82 – 1.69 (m, 1 H, minor), 1.67 – 1.57 (m, 1 H), 1.57 – 1.42 (m, 1 H), 1.29 – 1.11 (m, 12 H), 1.09 – 0.95 (m, 7 H), 0.89 (s, 9 H), 0.85 – 0.69 (m, 1 H), 0.07 (s, 6 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 156.5 and 155.9, 155.2, 148.5 and 146.7, 141.0 and 139.2, 127.7 and 125.1, 69.8 and 69.5, 69.4 and 69.1, 68.2, 62.4 and 61.9, 36.7 and 35.3, 30.9 and 29.9, 29.5 and 29.3, 26.0 (3 C), 25.6 and 25.5, 24.0 and 23.6, 22.8 and 22.4, 22.0 and 21.9, 21.9 and 21.6, 21.4 and 21.2, 18.37 and 18.32, -5.27 and -5.31, -5.34 and -5.39; MS (ESI) *m/z* (%): 545 ([M + Na]$^+$, 100); IR ($CHCl_3$): 1742, 1705 cm^{-1}; Anal. Calcd for $C_{28}H_{50}N_2O_5Si$: C, 64.33; H, 9.64; N, 5.36. Found: C, 64.52; H, 9.85; N, 5.22.

*{N,N'-diethoxycarbonyl-N'-[1-methyl-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydroinden-3a-yl]-hydrazino}-acetic acid ethyl ester (**32**).* A solution of compound **30** (138 mg, 0.27 mmol) in anhydrous ACN (1.4 mL) was prepared in a screw-cap vial under nitrogen atmosphere and to this solution ethyl bromoacetate (60 µL, 0.54 mmol) and anhydrous Cs_2CO_3 (221 mg, 0.68 mmol) were added. The vial was sealed and the mixture was heated at 50 °C (external) and left under vigorous stirring for 22 h. After cooling at room temperature, the reaction was stopped by adding satd NH_4Cl solution (5 mL). The product was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 8; R_f = 0.30), affording pure compound **32** (131 mg, 82%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (2 : 1 mixture of rotamers): δ 5.90 (s, 1 H, minor), 5.81 (s, 1 H, major), 4.26 – 3.99 (m, 7 H), 3.92 – 3.83 (m, 2 H), 3.75 (d, *J* = 16.8 Hz, 1 H, minor), 3.59 – 3.49 (m, 1 H, major), 3.40 (d, *J* = 16.4 Hz, 1 H, major), 2.91 – 2.83 (m, 1 H, minor), 2.65 – 2.40 (m, 3 H), 2.39 – 2.22 (m, 1 H), 2.20 – 2.08 (m, 1 H, major), 1.96 –

1.81 (m, 1 H and 1 H minor), 1.81 – 1.67 (m, 1 H major), 1.70 (s, 3 H), 1.60 – 1.51 (m, 1 H), 1.29 – 1.18 (m, 6 H), 1.08 – 1.03 (m, 22 H), 0.90 – 0.84 (m, 1 H, minor), 0.81 – 0.71 (m, 1 H, major); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 167.7, 167.2, 156.4, 149.0, 141.1, 130.6, 77.5, 62.9 and 62.2, 61.92, 61.89, 61.0 and 60.5, 53.3 and 52.6, 36.2 and 35.8, 31.4 and 31.2, 28.8 and 28.5, 23.9 and 23.8, 21.0 and 20.9, 17.99 and 17.96 (6 C), 14.42 and 14.39, 14.34 and 14.30, 14.11 and 14.07, 12.3, 12.0 and 11.9 (3 C); MS (ESI) *m/z* (%): 1211 ([2M + Na]$^+$, 47), 617 ([M + Na]$^+$, 100); Anal. Calcd for $C_{31}H_{54}N_2O_7Si$: C, 62.59; H, 9.15; N, 4.71. Found: C, 62.38; H, 9.39; N, 4.70.

*{N,N'-diisopropoxycarbonyl-N'-[1-isopropyl-3-(2-tert-butyldimethylsilanyloxyethyl)-4,5,6,7-tetrahydroinden-3a-yl]-hydrazino}-acetic acid ethyl ester (**33**).* Prepared as reported for **32**, starting from **31** (134 mg, 0.26 mmol). Purification of the crude by flash chromatography (EtOAc/*n*-hexane, 1 : 10; R_f = 0.25) afforded pure compound **33** (122 mg, 77%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) (6 : 1 mixture of rotamers): δ 5.98 (s, 1 H, major), 5.97 (s, 1 H, minor), 4.96 – 4.85 (m, 2 H), 4.09 – 4.03 (m, 3 H), 3.85 – 3.77 (m, 2 H), 3.64 – 3.51 (m, 1 H), 3.37 (d, *J* = 16.8 Hz, 1 H, minor), 3.36 (d, *J* = 16.4 Hz, 1 H, major), 2.77 – 2.67 (m, 1 H), 2.62 – 2.52 (m, 2 H), 2.50 – 2.39 (m, 1 H), 2.33 – 2.15 (m, 1 H), 1.97 – 1.78 (m, 2 H), 1.60 – 1.52 (m, 1 H), 1.32 – 1.16 (m, 15 H), 1.14 – 1.06 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.76 – 0.65 (m, 1 H), 0.07 (s, 6 H, minor), 0.05 (s, 6 H, major); $^{13}C\{^1H\}$ NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers): δ 167.6 and 167.1, 155.9 and 155.8, 155.53 and 155.47, 149.7, 140.2 and 140.0, 139.5 and 139.3, 126.0 and 125.8, 77.66 and 77.63, 70.1, 69.8, 61.4 and 61.0, 60.43 and 60.35, 52.8 and 52.1, 37.0 and 36.8, 31.6 and 31.5, 29.5 and 29.1, 25.8 (3 C), 25.4, 23.8 and 23.7, 23.0 and 22.8, 22.2, 22.0, 21.9 and 21.87, 21.4, 20.9, 20.7 and 20.6, 18.1, 14.1 and 14.0, -5.33, -5.36; MS (ESI) *m/z* (%): 631 ([M + Na]$^+$, 100); IR ($CHCl_3$): 1755, 1706 cm^{-1}; Anal. Calcd for $C_{32}H_{56}N_2O_7Si$: C, 63.12; H, 9.27; N, 4.60. Found: C, 62.89; H, 9.56; N, 4.41.

*[1-Methyl-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydroinden-3a-yl]-carbamic acid ethyl ester (**34**). Method A*. A solution of compound **32** (131 mg, 0.22 mmol) in anhydrous ACN (880 µL) was prepared in a screw-cap vial under nitrogen atmosphere and anhydrous Cs_2CO_3 (216 mg, 0.66 mmol) was added. The vial was sealed and the mixture was heated at 100 °C (external) and left under vigorous stirring until the complete consumption of **32** (TLC monitoring; 40 h). After cooling at room temperature, the reaction was stopped by adding satd NH_4Cl solution (5 mL). The product was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over anhydrous

Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10; R_f = 0.34), affording pure compound **34** (51 mg, 55%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1 H), 4.65 (s, 1 H), 4.02 – 3.94 (m, 2 H), 3.90 – 3.80 (m, 2 H), 2.60 – 2.55 (m, 1 H), 2.48 – 2.39 (m, 2 H), 2.28 – 2.21 (m, 1 H), 1.99 – 1.83 (m, 2 H), 1.80 (s, 3 H), 1.61 – 1.42 (m, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 1.13 – 1.01 (m, 22 H), 0.89 (td, *J* = 13.2, 4.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100.4 MHz, $CDCl_3$): δ 148.3, 140.0, 129.0, 128.62, 128.60, 67.7, 62.5, 60.3, 37.7, 30.2, 28.8, 23.5, 21.2, 18.0 (6 C), 14.5, 12.4, 12.0 (3 C); MS (ESI) *m/z* (%): 444 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3440, 1720 cm^{-1}; Anal. Calcd for $C_{24}H_{43}NO_3Si$: C, 68.36; H, 10.28; N, 3.32. Found: C, 68.11; H, 10.42; N, 3.25.

Method B. A solution of compound **32** (67 mg, 0.11 mmol) in anhydrous DME (225 µL) was prepared in a screw-cap vial under nitrogen atmosphere and NaH (9 mg, 0.23 mmol) was added in one portion. The vial was sealed and the mixture was heated at 50 °C (external) and left under stirring for 4.5 h. After cooling at 0 °C (ice bath), the reaction was stopped by adding satd NH_4Cl solution (5 mL). The isolation and purification of the product were carried out as reported above in Method A. Pure compound **34** (30 mg, 64%) was so obtained as a colourless oil.

*[3-(2-tert-Butyldimethylsilanyloxyethyl)-1-isopropyl-4,5,6,7-tetrahydroinden-3a-yl]-carbamic acid isopropyl ester (**35**) and [3-(2-tert-butyldimethylsilanyloxyethyl)-1-isopropyl-4,5,6,7-tetrahydroinden-3a-yl]-carbamic acid ethyl ester (**36**). Method A*. Prepared as reported for **34**, starting from **33** (68 mg, 0.11 mmol) and affording, after purification by flash chromatography (EtOAc/*n*-hexane, 1 : 12; R_f = 0.25), pure compound **35** (11 mg, 24%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (s, 1 H), 4.83 – 4.77 (m, 1 H), 4.55 (s, 1 H), 3.82 – 3.77 (m, 2 H), 2.79 – 2.72 (m, 1 H), 2.64 – 2.56 (m, 1 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 2.36 – 2.22 (m, 1 H), 1.98 – 1.84 (m, 2 H), 1.62 – 1.44 (m, 3 H), 1.20 – 1.11 (m, 6 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.86 – 0.81 (m, 1 H), 0.06 (s, 6 H); MS (ESI) *m/z* (%): 444 ([M + Na]$^+$, 100); IR ($CHCl_3$): 3441, 1715 cm^{-1}.

Method B. Prepared as reported for **34**, starting from **33** (79 mg, 0.13 mmol). The crude oil was purified by flash chromatography (EtOAc/*n*-hexane, 1 : 12; R_f = 0.25), affording the inseparable mixture of **35** and **36** in 2 : 1 ratio (35 mg, 64% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) (2 : 1 mixture of **35** and **36**) diagnostic signals: δ 4.83 – 4.77 (m, 1 H, **35**), 4.64 (s, 1 H, **36**), 4.55 (s, 1 H, **35**), 4.04 – 3.95 (m, 2 H, **36**).

Supporting information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/...

^{1}H NMR and ^{13}C{^{1}H} NMR spectra; X-ray crystallographic data (Tables S1-S2 and Figures S1-S3); calculation data (Table S3 and Figures S4-S5), calculations coordinates

Accession Codes

CCDC 2144694 and 2144695 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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(18) In the ^{1}H NMR spectrum, the diagnostic signal of **4** (and of all analogous compounds, in general) is that of the hemiaminal proton 10-H which resonates at 6.09 (major epimer) and 5.96 ppm (minor epimer) as a doublet of doublet, and which is downfield shifted to 6.94 and 6.83 ppm, respectively, in the corresponding acetate **6**, allowing for the correct determination of the epimeric ratio (in **4** the signal at 5.96 ppm is almost isochronous with the olefin proton 2-H signal at 5.98 ppm). In the ^{13}C NMR spectrum, the signal of the only quaternary C atom (C3a) of the bicyclic skeleton bearing a N atom resonates at 72.4 (major) and 72.5 ppm (minor) and that of the

hemiaminal C atom at 74.9 ppm (major) and 76.2 ppm (minor). Diagnostic signals in the ^{1}H NMR spectrum of the α,β-unsaturated aldehyde **5** are a doublet at 9.93 ppm for the aldehydic CHO proton, a singlet at 6.82 ppm and a doublet at 5.51 ppm for the two olefinic protons at position 2 and 11, respectively. See Supporting Information for the full spectroscopic characterization.

(19) Diagnostic ^{1}H NMR signal of **2** are a broad singlet at 9.58 ppm (CHO), a singlet at 5.90 (2-H) and an apparent singlet (actually an AB system) at 3.29 ppm (two protons, 9-H). The methyl group resonates at 1.93 ppm.

(20) Diagnostic ^{1}H NMR signal of **3** are a triplet at 9.55 (CHO), a singlet at 5.90 (2-H), the multiplet at 4.18–4.04 ppm (N-CO_2Et), a singlet (actually an AB system) at 3.20 ppm (11-H), two triplets at 1.27–1.20 ppm (N-CO_2Et). The methyl group resonates at 1.70 ppm as a singlet.

(21) In compound **7**, the CHO signal is at 9.58 ppm, 2-H resonates at 6.00 ppm and the AB system associated to 11-H protons is found at 3.42 ppm. The methyl group resonates at 1.79 and 1.80 ppm (two rotamers).

(22) Compound **10**, as well as all compounds of the same series, is a mixture of two rotamers in an approximately 1.7:1 ratio. Diagnostic signals are the NH broad singlets between 6 and 7 ppm (in $CDCl_3$), the *CH_2*OH protons resonating as a multiplet at 3.8 ppm and the methyl group at 1.76 ppm. The olefinic proton resonates at 5.94 and 5.90 ppm.

(23) The isolation and purification of crude cycloadduct **9** failed because of its degradation during the chromatographic purification on silica gel.

(24) Compounds **9** and **11** are characterized by the presence of only one singlet for the olefinic proton (no rotamers) at around 5.8 ppm and by the *CH_2*OH protons being quite clearly differentiated as two multiplets at 3.75 and 3.60 ppm in $CDCl_3$ because of an H-bond between the OH group and the closest N atom, as demonstrated by the fact that by recording the spectrum in CD_3OD the two multiplets collapse into a simple triplet. Diagnostically, the methyl group is now shielded compared to compound **10** and resonates just below 1.70 ppm (see Supporting Information).

(25) The calculations were performed with the Gaussian 16 set of programs, at the M06-2X/6-311^{++}G(d,p) with the implicit IEF-PCM solvent model, in dichloromethane. For more details, see the Supporting Information.

(26) This mechanistic proposal is independent of the proton source used in the calculations. We confirmed computationally that a similar energy profile is operative when the nitrogen atoms are protonated with just a H^+ instead of HCl. See Supporting Information for complete data.

(27) Commercial CbzN=NCbz is not sufficiently pure and requires a quick filtration through silica gel before usage.

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Graphical abstract.