Gold-Catalyzed Cycloisomerization of Functionalized 1,5-Enynes – An Entry to Polycyclic Framework

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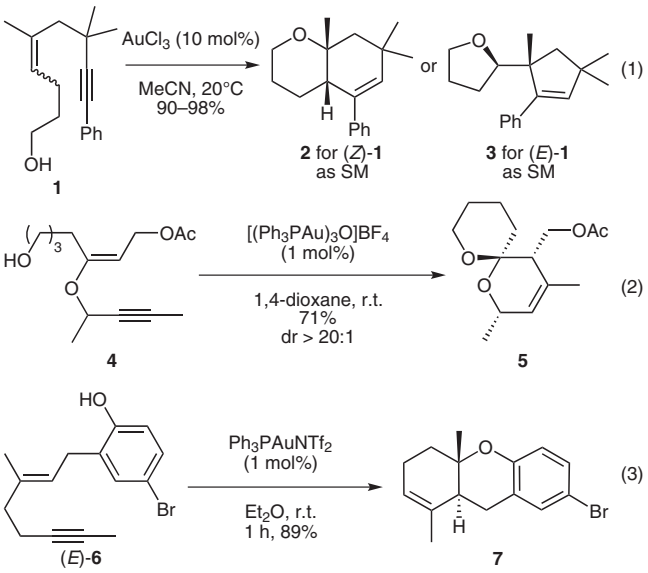
Abstract: The gold-catalyzed cycloisomerization reactions of variously functionalized 1,5-enynes are presented. The cyclization processes implying aryl- and 1,3-dicarbonyl-substituted skeletons are conducted under mild conditions and lead to cyclic structures obtained according to 6-*endo*-dig or 5-*endo*-dig mode depending on the involved nucleophilic partner. Some competitive pathways and trapping of carbocationic intermediates are highlighted.

Key words: gold catalyst, cycloisomerization, 1,5-enynes, atom economy, polycyclization

Gold-catalyzed cycloisomerization reactions of 1,n-enynes have emerged as conceptually and chemically fascinating processes as they offer the opportunity to develop new atom-economical reactions.[2,3] The recent emergence of interest associated with the polycyclization processes of enynes opened the way to the development of selective gold catalysts.[4,5] A wide variety of carbo- and heterocycles presenting a high degree of structural complexity were described using those new catalytic systems, which made these methodologies competitive to previous efficient reported catalytic systems for enynes.[6] The field of polycyclization of 1,5-enynes has received less attention.

The Kozmin group described the formation of bicyclic ethers upon cycloisomerization of 1,5-enynes possessing an internal hydroxyl or amine function in the presence of either Au(I) or Au(III) catalysts according to a 6-*endo* or 5-*endo* process, depending on the stereochemistry of the alkene **1** (Scheme 1, equation 1).[5e] Later on, Toste et al. developed a stereoselective efficient access to bicyclic spiroketal frameworks starting from propargyl vinyl ether **4** (Scheme 1, equation 2).[5f] Our group[5h] and Gagné's group[6d] have recently extended the polycyclization methodology to the intramolecular phenoxycyclization reactions on 1,5-enynes under mild conditions following the *6-endo* mode of cyclization (Scheme 1, equation 3).[5h] As part of our ongoing research program on the gold activation of alkynes towards a variety of nucleophiles[7] and on cycloisomerization of 1,6-enynes,[8,9] we decided to study the gold-catalyzed cycloisomerization of functionalized 1,5-enynes focusing on aryl- and 1,3-dicarbonyl-functionalized ones. In this paper, we describe their skeleton rearrangements leading to cyclic derivatives and highlighting various mechanistic pathways.



Scheme 1 Gold-catalyzed polycyclization of 1,5-enynes

At the outset of our investigations, we turned our attention to the known aryl-functionalized enynes **9** and **10**, prepared starting from allylic bromide **8** (Scheme 2). These derivatives have indeed been cycloisomerized according to an intramolecular domino Friedel–Crafts-type reaction–cyclization by Nishizawa and co-workers in the presence of $Hg(OTf)_2$ salt.[6a–6c] We also prepared two oxygen-tethered analogues **11**[6b] and **12** via classical alkylation reactions in the presence of 3,5-dimethoxyphenol and 4-methoxyphenol, respectively.

Anticipating the crucial importance of the substitution of the alkenyl moiety, we also envisaged synthesizing 1,5-enynes bearing a disubstituted *exo*-methylene moiety. For this purpose, starting from 1-trimethylsilylpropyne **13** and modifying the electrophilic partners compared to the literature,[5b] enynes **14**–**19** possessing an electron-rich and electron-neutral aromatic nucleophile were obtained in two to four steps. The alkenyl side chain was introduced after propargylic deprotonation on **13** followed by the addition of 2-methyl-3-bromoprop-1-ene in 83% yield.[5b] A similar reaction conducted in the presence of a bromobenzyl derivative allowed the preparation of the desired enynes **14** and **15** in 48% and 35% yield, respectively,

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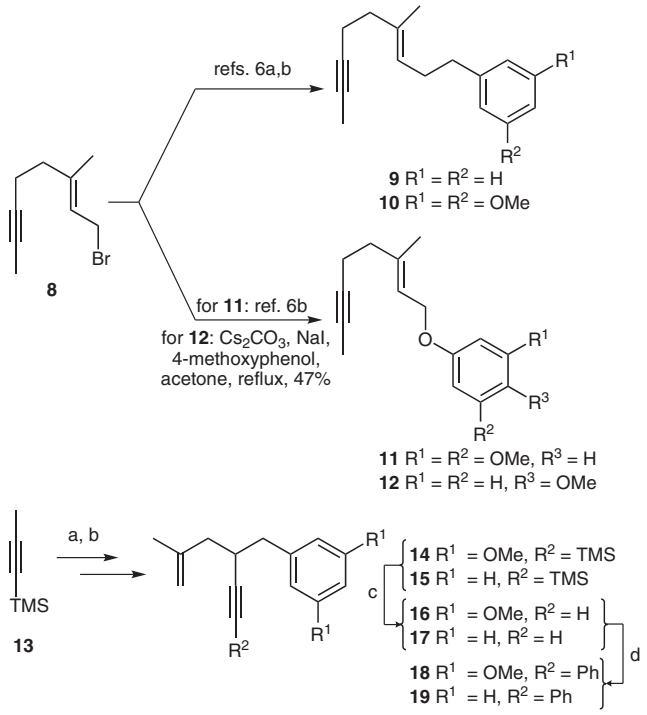


Scheme 2 Synthesis of 1,5-enynes. *Reagents and conditions*: a) *n*-BuLi, 3-bromo-2-methylprop-1-ene, THF, 0 °C; b) *n*-BuLi, 3,5-dimethoxybenzylbromide or benzylbromide, THF, 0 °C, 48% (**14**), 35% (**15**); c) TBAF, THF, 0 °C to r.t.; d) $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), Et_3N, PhI, 45 °C, 4 h, 61% (**18**), 42% (**19**).

over two steps. The silyl group could be deprotected, and further Sonogashira cross-coupling[10] in the presence of phenyl iodide led to the desired enynes **18** and **19**.

On the basis of our previous studies on intermolecular domino Fridel–Crafts-type addition–cyclization,[8b,e] we selected the $PPh_3AuCl/AgSbF_6$ system as the gold cationic and carbophilic system in diethyl ether as the solvent.[11] Results are presented in Table 1. Whereas the cycloisomerization of enyne **9** led to several unidentified byproducts (Table 1, entry 1), we were pleased to find that substrate **10** reacted smoothly under mild conditions (Table 1, entry 2) leading to the desired product in 92% yield. The hexahydrophenanthrene **21** was isolated as a single isomer, similarly as in the presence of $Hg(OTf)_2$. The cycloisomerization reactions of oxygen-tethered analogues **11** and **12** were surprisingly much less effective. As previously described with mercury salts,[6b] the *cis* isomer was formed as the major product in the presence of the commercially available Gagosz catalyst[12] PPh_3AuNTf_2, but several other unidentified byproducts were present: attempts to isolate some of them were unfortunately unsuccessful (Table 1, entry 3). The cyclization of the oxygen-tethered analogue **12** was sluggish, and after prolonged reaction time (24 h) it did not give the expected product. Pleasingly, the major product could be isolated this time, and ^1H–^{13}C COSY NMR spectroscopic experiments confirmed the structure of **23**[13] (Table 1, entry 4), resulting from an intermolecular hydroxycylization reaction, already observed for 1,5- and 1,6-enynes.[8,9,14]

Table 1 Gold-Catalyzed Cycloisomerization of 1,5-Enynes

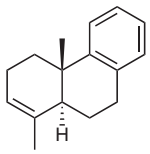
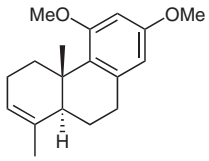
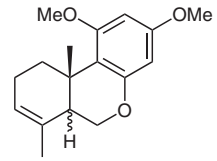
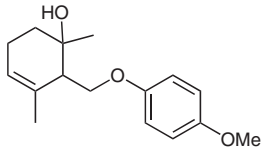
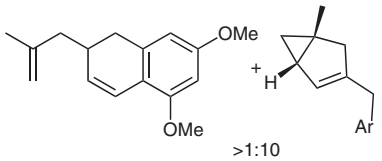
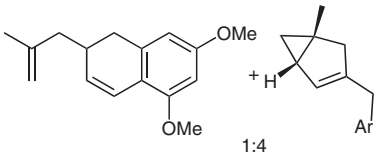
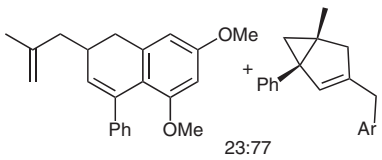
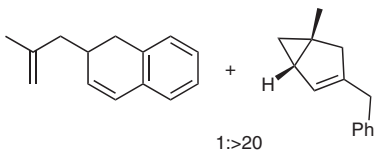
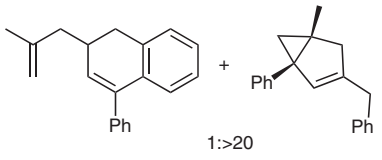
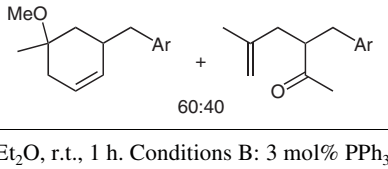
Entry	Starting material	Conditions[a]	Product		Yield (%)[b]
1	**9**	A		**20**	–
2	**10**	A		**21**	92
3	**11**	B[c]	 *cis*/*trans* = 80:20	**22**	71[d]
4[e]	**12**	B		**23**	40

Table 1 Gold-Catalyzed Cycloisomerization of 1,5-Enynes (continued)

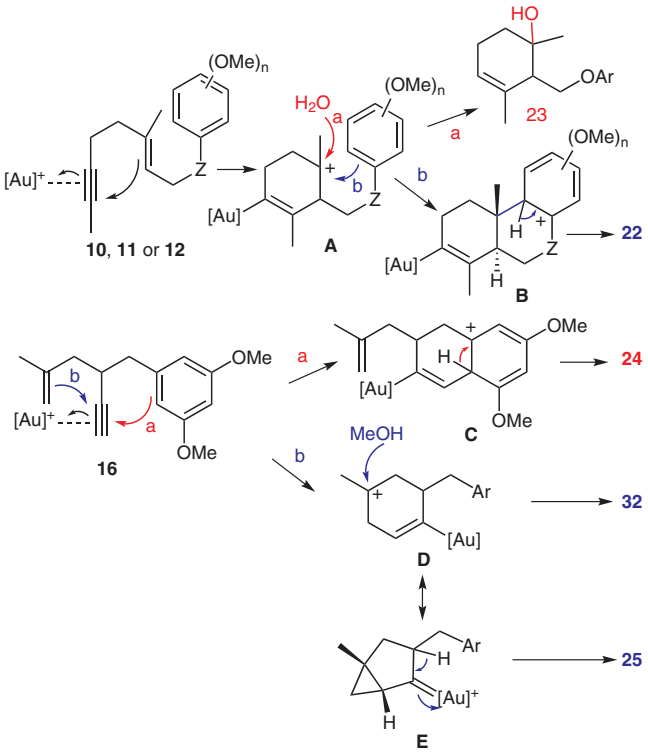
Entry	Starting material	Conditions[a]	Product		Yield (%)[b]
5	**14**	A	 >1:10	**24** **25**	82
6	**16**	A	 1:4	**24** **25**	90
7	**18**	A	 23:77	**26** **27**	92
8	**15**	A	 1:>20	**28** **29**	57
9	**19**	A	 1:>20	**30** **31**	65
10	**16**	A[f]	 60:40	**32** **33**	66

[a] Conditions A: 3 mol% PPh_3AuCl, 3 mol% $AgSbF_6$, Et_2O, r.t., 1 h. Conditions B: 3 mol% PPh_3AuNTf_2, Et_2O, r.t., 1 h.
[b] Isolated yields.
[c] CH_2Cl_2 was used in place of Et_2O.
[d] Mixture of *cis*/*trans* isomers.
[e] Reaction time: 24 h.
[f] MeOH was used in place of Et_2O. Isomeric ratio determined by ^1H NMR spectroscopy. Ar = 2,4-$(MeO)_2C_6H_3$.

We then tested the reactivity of substrates **14**–**19** in the presence of 3 mol% gold catalyst in diethyl ether for one hour, speculating that a similar Friedel–Crafts-type addition–cyclization would occur. Surprisingly, no product resulting from the domino process was formed in all cases (Table 1, entries 5–10). The formation of bicyclo[3.1.0]hexenyl adducts was the major competitive pathway, and bicyclic derivatives **25**, **27**, **29**, and **31** were detected without the intervention of the benzylic moiety. As minor products, the bicyclic derivatives **24**, **26**, **28**, and **30**, resulting from the gold-catalyzed hydroarylation of the alkynyl part,[15] were also formed. Several attempts to separate the respective mixtures were unfortunately unsuccessful.[16] In the case of enynes **14** and **15**, the TMS group was cleaved under these reaction conditions (Table 1, entries 5 and 8). This would presumably occur after the cycloisomerization or hydroarylation processes, considering the difference of the ratio for the products **24** and **25** during the reaction of **14** and **16** (Table 1, entry 5 vs. entry 6). It is noteworthy that free or substituted alkynes reacted in a similar manner (Table 1, entry 6 vs. entry 7, and entry 8 vs. entry 9). The competitive hydroarylation reaction of the alkyne is only observed for electron-rich aromatic substrates (**16** and **18**) whereas it is almost completely suppressed for benzyl-substituted alkynes such as **15** and **19**. We also envisaged challenging the hydroarylation and cycloisomerization pathways by conducting the reaction of **16** in the presence of an external nucleophile (Table 1, entry 10). When methanol was used as solvent instead of diethyl ether, the expected methoxycyclization reaction leading to cyclohexene **32** was observed, with no trace of product **24**. The competitive intermolecular Markovnikov addition of MeOH to the alkyne moiety[8c,7b,d,17] and hydrolysis furnished ketone **33**, the 60:40 mixture of **32** and **33** being isolated in 66% yield (Table 1, entry 10).

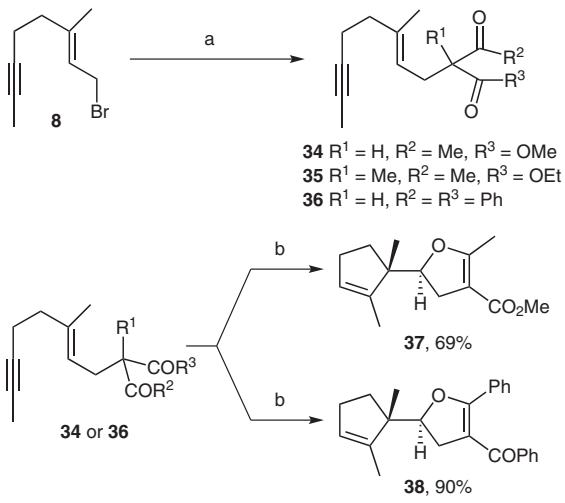
Mechanistically, the cycloisomerization reactions of the above-mentioned 1,5-enynes rely on an electrophilic carbon π-activation of the alkyne moiety in the presence of the cationic gold complex such as depicted in Scheme 3 for derivatives **10**, **11**, **12**, and **16**. Depending on the substitution pattern of the alkenyl chain, various scenarios may occur. In the case of enyne **10** and in line with Nishizawa's reports with mercury,[6a–c] a carbocationic-like cascade would lead to intermediates **A** and **B**, the latter resulting presumably from a concerted or stepwise addition of the aromatic ring to the alkenyl part and the cyclization process.[18] The trapping of carbocation **A** by water was evidenced in the case of **12**, leading to alcohol **23**. This may be explained by a nonfavored chair-like intermediate when Z is an oxygen atom instead of a CH_2 group. The tricyclic hexahydrophenanthrene **22** was therefore obtained via a 6-*endo*-dig process, after re-aromatization and protodemetalation steps. The cycloisomerization of 1,5-enyne **16** was particularly interesting as it highlighted two pathways depending on the 'active' nucleophile. The activation of the alkyne by the carbophilic gold complex would lead either to the cation **C** or intermediates **D/E**, depending on the relative nucleophilicity of the side chains (alkene vs. aromatic ring). The formation of **24** would be explained by the hydroarylation of the alkyne via intermediate **C**, which would evolve via re-aromatization and protodemetalation towards the dihydronaphthalene. The enyne **16** may react independently from the benzylic chain and would give the cationic/carbenoid intermediates **D/E**. The carbocation **D** could be trapped in the presence of MeOH and after protodemetalation would afford ether **32**. In the absence of MeOH, the more pronounced carbenic character of the Au(I) intermediate accounted for the formation of bicyclic derivative **25**, which is in full agreement with the previous report from Toste's group.[5c]

We finally envisaged studying the influence of the nucleophilic part on 1,5-enynes analogous to **10** and turned our attention to the 1,3-dicarbonyl derivatives. Whereas the Conia-ene reaction implying the addition of the enol form of the carbonyl nucleophile (ketones, 1,3-diketones, and β-keto esters) on the alkyne has been well documented in the presence of gold,[19] the implication of such nucleophiles has been scarcely studied on enynes.[20] The preparation of enynes **34**–**36** was straightforward starting from allylic bromide **8** and realizing nucleophilic substitution in the presence of methyl 3-oxobutanoate, ethyl 2-methyl-3-oxobutanoate, and 1,3-diphenylpropane-1,3-dione, respectively, as 1,3-dicarbonyl partners (Scheme 4). Anticipating a similar 6-*endo*-dig process as for analogue **11** implying the oxygen atom of the enol intermediate, we remarkably observed the clean and stereoselective (dr > 95%) formation of dihydrofurans **37** and **38** in the presence of 1 mol% of PPh_3AuNTf_2 catalyst in 69% and 90% isolated yields, respectively.[21] These examples constitute unique cases in addition with the one described by Kozmin and co-workers (Scheme 1, compound **3**),[5e] where the substitution of the enyne changes the course of the cyclization. The case of enyne **35** was particularly peculiar as no 'classic' enol form was possible: the cycloisomerization reaction unfortunately led to several unidentified byproducts.



Scheme 3 Mechanism rationale

In conclusion, we have extended the methodology for the use of a simple gold catalyst in cycloisomerization reactions of 1,5-enynes. The design of 1,5-enynes bearing an aromatic side chain highlighted various competitive mechanistic pathways related to carbocationic-type cyclizations. Depending on the arrangement and substitution of the alkenyl moiety, the formation of bicyclo[3.1.0]hex-



Scheme 4 Cyclosiomerization reactions of 1,3-dicarbonyl-functionalized 1,5-enynes. *Reagents and conditions*: a) NaH, THF, 0 °C to r.t., methyl 3-oxobutanoate, ethyl 2-methyl-3-oxobutanoate, or 1,3-diphenylpropane-1,3-dione 85% (**34**), 57% (**35**), 80% (**36**); b) PPh_3AuNTf_2 (1 mol%), Et_2O, r.t., 2.5 h.

enyl, dihydronaphtalenes, or phenanthrenes adducts were obtained. The polycyclization of (*E*)-1,3-dimethoxy-5-(4-methyl-3-nonen-7-ynyl)benzene smoothly afforded the corresponding hexahydrophenanthrene derivative in excellent yield. Modifying the carbon framework allowed either the trapping of carbocationic intermediates or quite remarkably the change of the course of the reaction. The 6-*endo*-dig process was not observed when 1,3-dicarbonyl substituents were introduced instead of the electron-rich aromatic ring. Such b-keto ester or b-diketone derivatives reacted according to a clean and stereoselective 5-*endo*-dig pathway. Further studies will be directed towards the applications and extensions of such methodologies.

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(1) These two authors contributed equally to this work.

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(11) **Typical Procedure for the Gold-Catalyzed Reactions of 1,5-Enynes**
PPh_3AuCl (3.3 mg, 0.0066 mmol) and $AgSbF_6$ (2.3 mg, 0.0066 mmol) were added to a flask under argon atmosphere. Then, anhyd Et_2O (0.44 mL) and **10** (60 mg, 0.22 mmol) were introduced, and the mixture was stirred for 1 h at r.t. After filtration of the reactant, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–EtOAc, 100:1) on silica gel to give **21** (55 mg, 92% yield) as a colorless oil.

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(13) **2-[(4-Methoxyphenoxy)methyl]-1,3-dimethylcyclohex-3-enol (23)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (6 H, m), 1.76–1.75 (4 H, m), 2.50 (1 H, m), 3.77 (3 H, s), 3.94–3.92 (1 H, dd, *J* = 5.8, 7.3 Hz), 4.12–4.08 (1 H, dd, *J* = 3.0, 7.3 Hz), 5.50 (1 H, t, *J* = 1.2 Hz), 6.87–6.77 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 23.0, 24.8, 33.7, 50.5, 55.8, 68.9, 71.6, 76.8, 77.1, 77.4, 114.7, 115.7, 123.7, 131.6, 152.7, 154.2. MS (CI): *m/z* = 245 $[M - H_2O + H]^+$, 262 $[M - H_2O + NH_4]^+$, 263 $[M + H]^+$, 280 $[M + NH_4]^+$.

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(16) **3-(3,5-Dimethoxybenzyl)-5-methylbicyclo[3.1.0]hex-2-ene (25) and 1,2-Dihydro-5,7-dimethoxy-2-(2-methylallyl)naphthalene (24)**
Compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (1 H, dd, *J* = 3.4, 2.4 Hz), 0.67 (1 H, dd, *J* = 7.2, 3.5 Hz), 1.24 (3 H, s), 1.41–1.44 (1 H, m), 2.25 (2 H, s), 3.22 (2 H, s), 3.78 (6 H, s), 5.60 (1 H, d, *J* = 1.7 Hz), 6.30 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 22.6, 24.1, 29.9, 37.9, 43.8, 55.2, 97.9, 106.8, 130.3, 141.4, 142.6, 160.7.
Compound **24**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (3 H, s), 1.70–1.84 (1 H, m), 2.10–2.15 (1 H, m), 2.50–2.70 (2 H, m), 2.75–2.80 (1 H, m), 3.80 (6 H, s), 4.72 (1 H, br s), 4.82 (1 H, br s), 5.75–5.85 (1 H, m), 6.30–6.36 (2 H, m), 6.70–6.77 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 31.3, 34.4, 42.5, 55.0, 55.5, 96.3, 105.1, 112.1, 115.6, 120.6, 129.4, 137.5, 143.5, 156.0, 159.0. MS (CI): *m/z* = 245 $[M + H]^+$.
3-(3,5-Dimethoxybenzyl)-5-methyl-1-phenylbicyclo-[3.1.0]hex-2-ene(27) and 1,2-Dihydro-5,7-dimethoxy-2-(2-methylallyl)-4-phenylnaphthalene (26)
Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.64 (1 H, d, *J* = 4.1 Hz), 0.96 (3 H, s), 1.35 (1 H, d, *J* = 4.1 Hz), 2.40 (2 H, s), 3.33 (2 H, s), 3.79 (6 H, s), 5.72 (1 H, s), 6.26–6.37 (3 H, m), 7.15–7.31 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 27.1, 30.4, 37.8, 43.0, 45.0, 55.2, 97.9, 106.8, 125.7, 128.0, 128.3, 133.4, 140.3, 141.3, 142.5, 160.8.
Compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (3 H, s), 1.70–1.84 (1 H, m), 2.20–2.28 (1 H, m), 2.50–2.70 (2 H, m), 2.75–2.80 (1 H, m), 3.74 (3 H, s), 3.79 (3 H, s), 4.72 (1 H, br s), 4.82 (1 H, br s), 5.83–5.85 (1 H, m), 6.25–6.37 (2 H, m), 7.15–7.31 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 32.1, 36.6, 42.2, 55.1, 55.2, 97.3, 101.0, 104.8, 112.1, 125.2, 125.8, 126.8, 132.4, 137.6, 141.0, 143.5, 157.5, 158.1, 159.6. MS (CI): *m/z* = 321 $[M + H]^+$.
3-Benzyl-5-methylbicyclo[3.1.0]hex-2-ene (29)
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (1 H, dd, *J* = 3.4, 3.3 Hz), 0.67 (1 H, dd, *J* = 7.3, 3.5 Hz), 1.24 (3 H, s), 1.41–1.43 (1 H, m), 2.25 (2 H, s), 3.28 (2 H, s), 5.56 (1 H, br s), 7.12–7.30 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 22.6, 24.2, 29.9, 37.6, 43.9, 125.8, 128.2, 128.7, 130.0, 139.0, 142.0. MS (CI): *m/z* = 184 $[M]^+$.
3-Benzyl-5-methyl-1-phenylbicyclo[3.1.0]hex-2-ene (31)
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.63 (1 H, d, *J* = 4.1 Hz), 0.95 (3 H, s), 1.34 (1 H, d, *J* = 4.1 Hz), 2.40 (2 H, s), 3.39 (2 H, s), 5.67 (1 H, s), 7.18–7.22 (6 H, m), 7.26–7.31 (4 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 27.2, 30.4, 37.4, 43.0, 45.1, 125.7, 125.9, 127.9, 128.3, 128.8, 133.2, 140.0, 140.4, 141.8. MS (CI): *m/z* = 260 $[M]^+$.

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(21) **Methyl 5-(1,2-dimethylcyclopent-2-en-1-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (37)**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (3 H, s), 1.60–1.67 (4 H, m), 1.87 (1 H, m), 2.16 (3 H, s), 2.16–2.25 (2 H, m), 2.65–2.81 (2 H, m), 3.71 (3 H, s), 4.59 (1 H, t, *J* = 10.2 Hz), 5.40 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.1, 21.5, 29.0, 31.7, 32.3, 50.6, 53.1, 86.6, 101.9, 126.1, 143.2, 166.7, 168.7. MS (CI): *m/z* = 237 $[M + H]^+$.
1,2-(Dimethylcyclopent-2-en-1-yl)-2-phenyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (38)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (3 H, s), 1.67 (1 H, m), 1.74 (3 H, s), 2.04 (1 H, m), 2.23–2.27 (2 H, m), 3.19, 3.14 (2 H, 2 dd, *J* = 15.0, 10.3 Hz), 4.83 (1 H, t, *J* = 10.3 Hz), 5.43 (1 H, br s), 6.99–7.20 (8 H, m), 7.39 (2 H, dd, *J* = 1.4, 8.4 Hz). ^{13}C NMR (75MHz, $CDCl_3$): δ = 13.3, 21.6, 29.1, 33.0, 34.8, 53.2, 86.8, 112.7, 126.3, 127.5, 127.6, 128.8, 129.3, 129.8, 130.3, 130.9, 139.3, 143.2, 166.7, 193.7. MS (CI): *m/z* = 345 $[M + H]^+$.