Fluxional Molecules

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Synthesis of Barbaralones and Bullvalenes Made Easy by Gold Catalysis

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Abstract: *The gold(I)-catalyzed oxidative cyclization of 7-ethynyl-1,3,5-cycloheptatrienes gives 1-substituted barbaralones in a general manner, which simplifies the access to other fluxional molecules. As an example, we report the shortest syntheses of bullvalene, phenylbullvalene, and disubstituted bullvalenes, and a readily accessible route to complex cage-type structures by further gold(I)-catalyzed reactions.*

Fluxional molecules, such as barbaralone (**1a**), bullvalone (**2a**), and bullvalene (**3a**) have been central to the understanding of the phenomena of valence tautomerism (see Figure 1).[1,2] These molecules undergo low energy [3.3]-sigmatropic rearrangements, which in the case of bullvalene

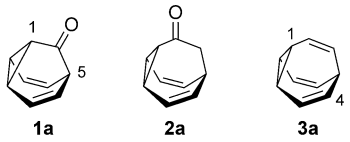

Figure 1. Barbaralone (**1a**), bullvalone (**2a**), and bullvalene (**3a**).

lead to 1209600 degenerate tautomers,[3–5] whereas a lower number of constitutional isomers are possible for substituted bullvalenes[6–8] and only two exist for barbaralone (**1a**).[9]

Syntheses of these fluxional molecules requires multistep procedures that proceed with low overall yield, often using explosive and toxic diazomethane. Thus, the optimized synthesis of barbaralone (**1a**), en route to bullvalene (**3a**),[10] starts with the Büchner reaction of ethyl diazoacetate with benzene to form **4**,[11,12] which is converted into **1a** in four steps via diazomethyl ketone **5** (Scheme 1).[10] Bullvalene (**3a**) can be prepared from **1a** in four additional steps by two different procedures by homologation of **1a** to bullvalone (**2a**) with diazomethane.[2,10] Barbaralone (**1a**) has also been prepared from (cyclooctatetraene)tricarbonyliron in two steps in approximately 36% yield.[13]

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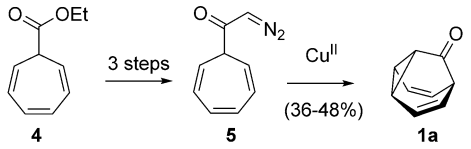


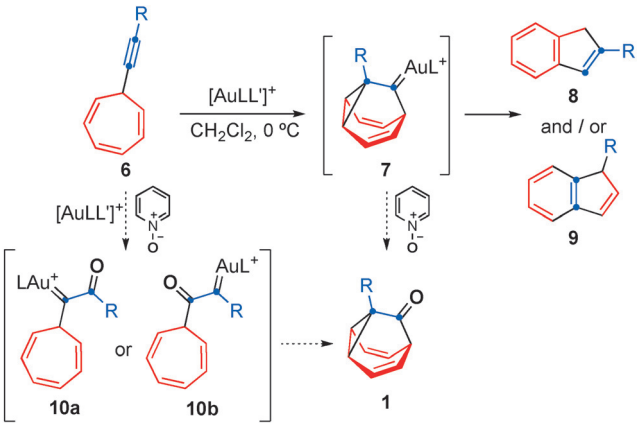
Scheme 1. Synthesis of barbaralone (**1a**) from ethyl cyclohepta-2,4,6-triene-1-carboxylate (**4**).

1-Methylbarbaralone (**1w**) was prepared by a procedure similar to that shown in Scheme 1 using ethyldiazomethane in the reaction with cycloheptatriene carbamoyl chloride to form the homologue of **5**.[9b] Although some ingenious syntheses of highly substituted bullvalenes have been designed,[8] most bullvalenes have been prepared from parent **3a**. Thus, for example, phenylbullvalene (**3b**) was obtained in three steps (26% yield) from **3a** by dibromination, dehydrobromination with KO*t*Bu, and reaction of the resulting bromobullvalene with Ph_2CuLi.[7d]

Current synthetic art does not allow preparation of substituted barbaralones in a general way,[14] which limits the access to fluxional homologues and other theoretically interesting molecules.[12,15] We have recently found that 7-aryl-1,3,5-cycloheptatrienes undergo a gold(I)-catalyzed retro-Büchner reaction to form highly reactive aryl gold(I) carbenes (a decarbenation reaction).[16] However, 7-ethynyl-1,3,5-cycloheptatrienes (**6**) react differently to form fluxional barbaralyl gold(I) intermediates **7**; after a series of complex rearrangements **7** finally leads to indenes **8** and/or **9**, depending on the gold catalyst (Scheme 2).[17] Since the gold-catalyzed oxidation of alkynes has been shown to take place readily with oxidants such as sulfoxides, or amine-*N*-oxides to form α-oxo gold(I) carbenes,[18,19] we envisioned that the oxidation of intermediates **7** could lead to 1-substituted barbaralones **1** (Scheme 2). However, if the oxidation takes place directly on 7-ethynyl-1,3,5-cycloheptatrienes (**6**), the two regioisomeric α-oxo gold(I) carbenes **10a** and **10b** would be formed,[18] of which only **10b** would lead to barbaralones **1** by intramolecular cyclopropanation.

Herein, we report a general and straightforward synthesis of 1-substituted barbaralones **1** from alkynes and commercially available tropylium tetrafluoroborate in just two steps by oxidative cyclization of 7-ethynyl-1,3,5-cycloheptatrienes.

We first studied the reaction of 7-(phenylethynyl)cyclohepta-1,3,5-triene (**6b**) with different gold(I) catalysts in the presence of diphenylsulfoxide ($\mathbf{Ox_1}$), and the *N*-oxides of pyridine ($\mathbf{Ox_2}$), 3,5-dichloropyridine ($\mathbf{Ox_3}$), or 8-methylquinoline ($\mathbf{Ox_4}$) as oxidants (Table 1). Using Johnphos gold(I) complex **A** in combination with $\mathbf{Ox_3}$, 1-phenylbarbaralone

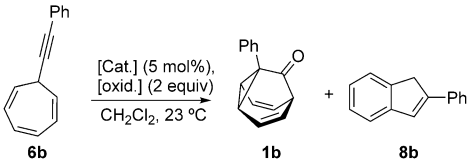


Scheme 2. Two different pathways for the formation of barbaralones **1** by gold(I)-catalyzed oxidative cyclization of 7-ethynyl-1,3,5-cycloheptatrienes (**6**).

(**1b**) was obtained in 50% yield, together with 2-phenyl-1*H*-indene (**8b**; Table 1, entry 3). Related gold(I) complexes **B** and **C** led to **1b** in lower yields in the presence of $\mathbf{Ox_3}$ (Table 1, entries 5 and 6). The best yields of **1b** were obtained using [IPrAu(MeCN)][SbF_6] (**D**) and either $\mathbf{Ox_1}$ or $\mathbf{Ox_3}$ (Table 1, respectively entries 7 and 9). Oxidants $\mathbf{Ox_2}$ and $\mathbf{Ox_4}$ led to very poor results (Table 1, respectively entries 8 and 10). Interestingly, whereas phosphite gold(I) complex **E** afforded low yields (Table 1, entries 11 and 12), pycolinate gold(III) complex provided **1b** in a similar yield in the presence of $\mathbf{Ox_3}$ (Table 1, entry 14). Reactions of alkynes with pyridine-*N*-oxides can also be performed with Brønsted acids[20] or Zn^{II} catalysts.[21] However, in our system, a complex reaction mixture was obtained in the presence of methanesulfonic acid (Table 1, entry 15) and starting material was recovered when $Zn(OTf)_2$ was used as the catalyst (Table 1, entry 16).

To assess the generality of this oxidative cyclization, various 7-ethynyl-1,3,5-cycloheptatrienes (**6a–v**) were prepared[17] and the combinations of catalyst and oxidant that provided the best results in the preliminary studies (conditions: A) cat. **D**, $\mathbf{Ox_1}$; B) cat. **D**, $\mathbf{Ox_3}$; C) cat. **A**, $\mathbf{Ox_3}$) were tested on these substrates (Table 2). The most simple substrate, 7-ethynyl-1,3,5-cycloheptatriene (**6a**), produced barbaralone (**1a**) in 97% yield. The reaction was compatible with 7-(arylethynyl)-1,3,5-cycloheptatrienes **6c–o** bearing different *o*-, *m*-, or *p*- substituents on the phenyl ring, such as methyl-, *tert*-butyl-, fluorine-, chlorine-, methoxy-, or trifluoromethyl-, affording the corresponding 1-substituted barbaralones (**1c–o**) in moderate to good yields. Substrates **6p–q**, possessing a naphthyl or a thiophenyl substituent, gave barbaralones **1p–q** in yields up to 88%. This catalytic procedure was extendible to alkynyl cycloheptatrienes with aliphatic or alkyl groups (**6s–v**), including *n*-butyl, *n*-hexyl, 2-phenylethyl, and cyclopropyl, giving the desired barbaralones **1s–v** in moderate to excellent yields. The reaction was also applicable to a substrate containing two alkynes (**6r**), affording dibarbaralone **1r** in 60% yield. The process was efficiently scalable, providing up to 850 mg of barbaralone (**1a**) in one run in 96% yield. Mechanistically, the formation of aryl substituted barbaralones **1b–r** strongly suggests that

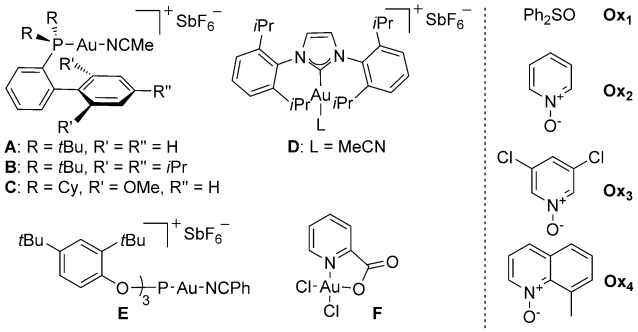
Table 1: Gold(I)-catalyzed oxidative reaction of **6b** to give 1-phenylbarbaralone (**1b**).



6b **1b** **8b**

Entry	[Cat.]	Oxid.	Time [h]	**1b** Yield [%][a]	**8b** Yield [%][a]
1	**A**	$\mathbf{Ox_1}$	2.5	12	58
2	**A**	$\mathbf{Ox_2}$	16	5	–
3	**A**	$\mathbf{Ox_3}$	2.5	50 (50)[b]	28
4	**A**	$\mathbf{Ox_4}$	16	23	–
5	**B**	$\mathbf{Ox_3}$	3	30	36
6	**C**	$\mathbf{Ox_3}$	3	32	42
7	**D**	$\mathbf{Ox_1}$	3	(83)[b]	–
8	**D**	$\mathbf{Ox_2}$	24	2	–
9	**D**	$\mathbf{Ox_3}$	3	64	–
10	**D**	$\mathbf{Ox_4}$	3	7	–
11	**E**	$\mathbf{Ox_1}$	2.5	20	–
12	**E**	$\mathbf{Ox_3}$	2.5	30	–
13	**F**	$\mathbf{Ox_1}$	5	14	61
14	**F**	$\mathbf{Ox_3}$	5	61	–
15	$MeSO_3H$[c]	$\mathbf{Ox_3}$	2.5	complex mixture	
16	$Zn(OTf)_2$[d]	$\mathbf{Ox_3}$	24	starting material	

[a] Yields determined by ^{1}H NMR using mesitylene as an internal standard. [b] Yield of isolated products. [c] 4 equiv [d] 10 mol%. Catalyst (cat.), oxidant (oxid.).

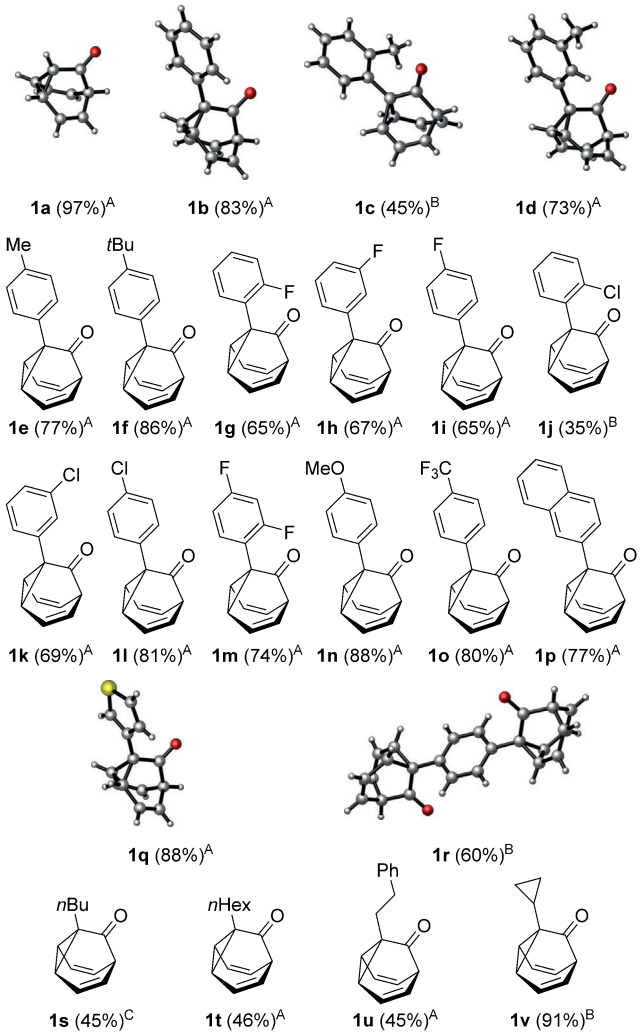


the oxidation takes place on barbaralyl gold(I) intermediates **7** (Scheme 2), rather than on the alkyne, which would favor formation of unproductive intermediate **10a** by benzylic oxidation.[18]

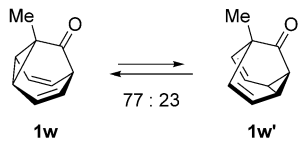
The introduction of a methyl substituent was found to shift the sigmatropic equilibrium toward the 1-substituted isomer (Scheme 3).[6c,9b] Our NMR data show that 1-substituted barbaralones are in all cases the most stable tautomers, as confirmed by the X-ray diffraction structures of **1a–d**, **1q**, and **1r** (Table 2).[22]

With the synthesis of barbaralones (**1**) in hand, and the preparation of bullvalenes (**3**) in mind, we examined the applicability of this oxidative cyclization for the synthesis of bullvalone (**2a**) using propargyl cycloheptatriene as substrate (**11**). Thus, the reaction of propargyl cycloheptatriene (**11**) with different gold(I) catalysts in the presence of the previously employed oxidants was investigated (Table 3). However, instead of the desired bullvalone, arising from a

Table 2: Gold(I)-catalyzed oxidative synthesis of barbaralones **1a–v**.



Conditions: A) cat. **D**, $\mathbf{Ox_1}$; B) cat. **D**, $\mathbf{Ox_3}$; C) cat. **A**, $\mathbf{Ox_3}$.

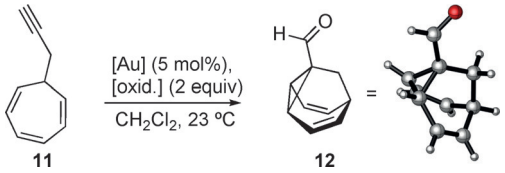


Scheme 3. Equilibrium between 1-methyl- and 5-methylbarbaralones.[9b]

5-*endo-dig* oxidative cyclization, in all cases we observed the recovered starting material or formation of 1-formylbarbaralane (**12**),[22] the product of a 5-*exo-dig* process. While Johnphos gold(I) complex **A** gave poor results regardless of the oxidant used (Table 3, entries 1–4), good yields were obtained with *t*BuXPhos gold(I) catalyst (**B′**) and [IPrAu(MeCN)]SbF_6 (**D**) with $\mathbf{Ox_1}$ (Table 3, entries 5 and 8). A better yield of aldehyde **12** was obtained using phosphite gold(I) complex **E′** and $\mathbf{Ox_1}$ (Table 3, entry 10).

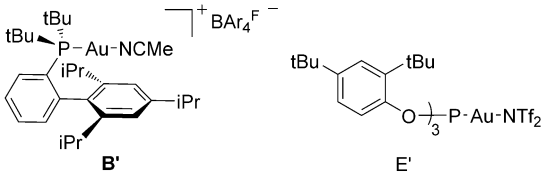
At this stage we considered accessing bullvalones (**2**) via barbaralones (**1**) en route to bullvalenes (**3**). Homologation of **1a** with diazomethane has been reported to give bullvalone

Table 3: Gold(I)-catalyzed oxidative reaction of propargyl cycloheptatriene (**11**) to give 1-formylbarbaralane (**12**).



Entry	[Au]	Oxid.	Time [h]	**12** Yield [%][a]
1	**A**	$\mathbf{Ox_1}$	18	27
2	**A**	$\mathbf{Ox_2}$	15	–
3	**A**	$\mathbf{Ox_3}$	18	5
4	**A**	$\mathbf{Ox_4}$	15	–
5	**B′**	$\mathbf{Ox_1}$	17	91 (87)[b]
6	**B′**	$\mathbf{Ox_3}$	17	7
8	**D**	$\mathbf{Ox_1}$	4	90 (87)[b]
9	**D**	$\mathbf{Ox_3}$	18	8
10	**E′**	$\mathbf{Ox_1}$	6	92
11	**E′**	$\mathbf{Ox_3}$	24	–

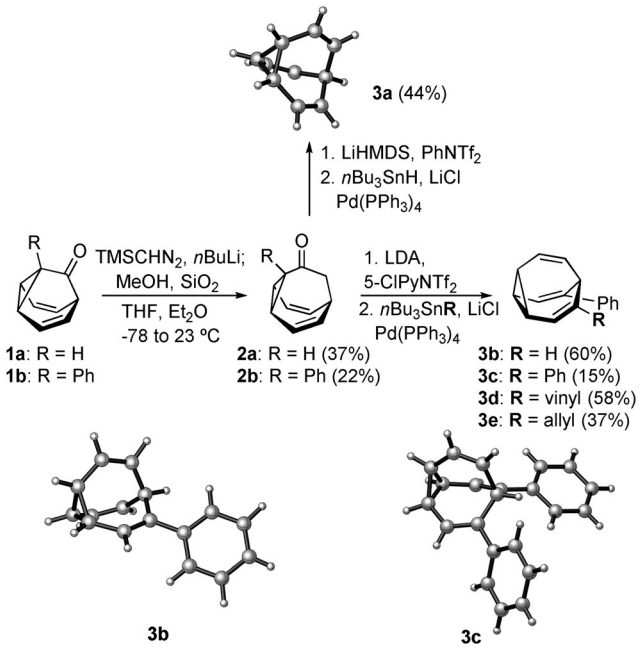
[a] Yields determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [b] Yield of isolated products.



(**2a**) in 24% yield along with an isomeric aldehyde (34%).[2,10] Reduction of **2a** followed by acetylation led to the corresponding acetate (40%, two steps), which was pyrolyzed at 345 °C to give a 1:1 ratio of bullvalene (**3a**) and *cis*-9,10-dihydronaphthalene.[2,23] An improved procedure was reported via bullvalone tosylhydrazone, providing bullvalene (**3a**) in approximately 5% yield from **2a** in four steps.[10,24]

In our new approach, bullvalene (**3a**) and phenylbullvalene (**3b**) were prepared from barbaralones **1a–b** by a three-step procedure. A homologation reaction of **1a** and **1b** with the lithium anion of (trimethylsilyl)diazomethane[25] gave bullvalones **2a** and **2b** in 37 and 22% yield, respectively (Scheme 4). Formation of the corresponding enol triflates using LDA and Comins' reagent, or LiHMDS and $PhNTf_2$ followed by immediate reduction with n-Bu_3SnH and $Pd(PPh_3)_4$ as catalyst,[26] afforded **3a** and **3b**[27] in 44% and 60% yield, respectively, whose structures were confirmed by X-ray diffraction.[22] This new synthesis of bullvalene (**3a**) is the most efficient to date as it requires a total of five steps (10% overall yield) from commercially available tropylium tetrafluoroborate and ethynyl magnesium bromide.

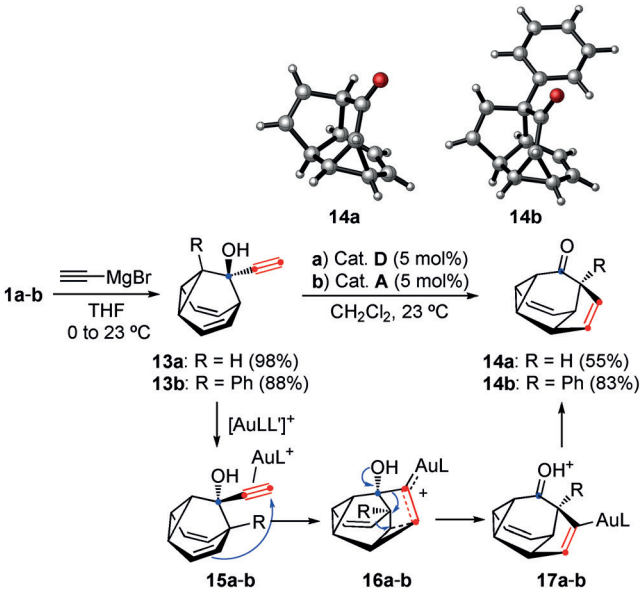
Various disubstituted bullvalenes **3c–e** were also prepared from phenyl bullvalone (**2b**) through sequential formation of the enol triflate followed by Stille couplings (Scheme 4).[28] The molecular structure of diphenyl bullvalene **3c** was determined by X-ray diffraction.[22] Bullvalenes **3c–e** were in equilibrium with the 3,6- and 3,7-disubstituted isomers at −40 °C; the observed ratios of the respective compounds was 7.6:5.7:1, 5.2:1.5:1, and 3.8:2.3:1.[7d]



Scheme 4. Synthesis of bullvalene (**3a**), phenylbullvalene (**3b**), and disubstituted bullvalenes **3c–e**.

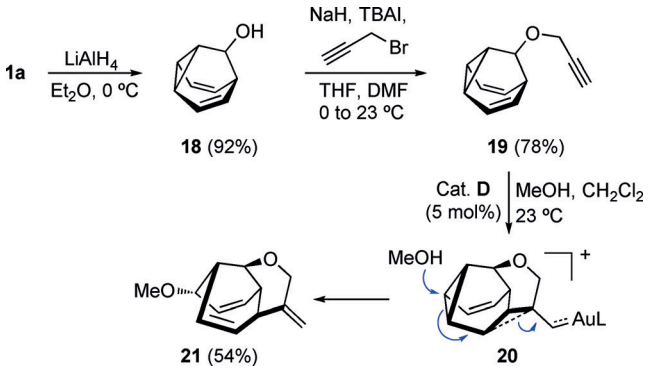
Barbaralones **1a** and **1b** were converted into **14a** and **14b** in two steps by the addition of ethynyl magnesium bromide and subsequent gold(I)-catalyzed reaction of the corresponding alcohols **13a** and **13b**, which proceeded by a new type of cyclization/rearrangement (Scheme 5). Structures **14a** and **14b** were confirmed by X-ray diffraction.[22]

Unprecedented tetracyclic cages **14a** and **14b** are probably formed by coordination of gold(I) of the alkyne of the minor tautomer of **13a** and **13b** to give **15a** and **15b**, followed by intramolecular attack of the alkene to form delocalized intermediates **16a** and **16b**[29,30] and semipinacol-type rearrangement to give **17a** and **17b** (Scheme 5). To the best of our knowledge, and despite the many different types of gold(I)-catalyzed cycloisomerizations,[30] this formation of a five-membered ring by cyclization-rearrangement is unprecedented.



Scheme 5. Preparation of highly fused tetracyclic molecules **14a** and **14b**.

Furthermore, alkylation of barbaralol **18**[22] with propargyl bromide gives 1,7-enyne **19**, which undergoes an *exo-dig* cyclization with gold(I) catalyst **D** to form intermediate **20**,[30] which then reacts with methanol as a nucleophile to form tricyclic system **21** (Scheme 6).



Scheme 6. Formation of tricyclic derivative **21** from barbaralol (**18**).

In summary, we have developed an efficient synthesis of 1-substituted barbaralones by gold(I)-catalyzed oxidative cyclization of 7-(substituted ethynyl)-1,3,5-cycloheptatrienes. This method has allowed accomplishment of the shortest syntheses of bullvalene and other substituted bullvalenes. Thus, parent bullvalene (**3a**) is obtained in five steps from commercially available starting materials in 10% overall yield, which compares favorably with previous procedures that require nine or more steps and proceeded with very low overall efficiency. The straightforward access to barbaralones opens a way to obtain complex cage systems with unprecedented molecular architectures.

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Keywords: barbaralones · bullvalenes · cyclization reactions · gold · valence tautomerism

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