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Expeditious cascade reactions: controlled syntheses of fenestradienes and cyclooctatrienes under palladium catalysis

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ABSTRACT

Palladium cyclization cascades represent an elegant way to access complex polycyclic scaffolds in a minimum amount of steps. Herein we provide a complete account on two new methodologies including these kind of cascades, each leading to two types of attractive compounds, cyclooctatrienes and [4.6.4.6]fenestradienes. The reader will first discover a strategy requiring three steps starting from alkenyl bromides, based on a first 4-*exo*-dig carbopalladation/Sonogashira coupling tandem reaction, and a subsequent P-2 Ni induced semi-hydrogenation. This leads to a first generation of cyclooctatrienes and [4.6.4.6]fenestradienes. Next, the second approach will be presented, in which the second generation of these compounds is accessed in a one-pot reaction including five steps, starting from the same alkenyl bromide compounds. These methods are appealing in terms of atom economy, the use of easy to handle conditions as well as the variability of its scope.

1. Introduction

The usefulness of strategies based on palladium cyclization cascades leading to polycyclic frameworks in a regio- and stereoselective manner has been demonstrated in the past.[1] Today, one of the challenges of modern synthetic method development is to form as many bonds as possible in the least number of steps, ideally in a single operation.[2] Significant recent studies in our laboratory are directed toward the development of synthetic methodologies to design highly strained scaffolds from simple starting materials using common reagents and mild reaction conditions. In this context, we report herein our investigations of cascade reactions involving a semi-hydrogenation of an alkyne moiety in first generation and in a second one a fascinating palladium catalyzed alkyne addition reaction. Both lead to two types of polycyclic structures, fenestradienes and cyclooctatrienes.

Eight-membered ring substructures are present in over 100 different natural products, many of, which demonstrate exceptional and broad-ranging biological activity. For example, Ophiobolin A[3] exhibits a broad spectrum of biological activity against nematodes, fungi, and bacteria,[4] as well as showing potent antitumor activity.[5] Aleurodiscal[6] is an antifungal and antibiotic, while one of the most notable examples is the diterpene paclitaxel (taxol), that is, a major anticancer agent used in clinics today.[7] Synthesis of eight-membered ring compounds has constantly been a challenging area due to high degree of ring strain, transannular interactions and unfavorable entropic and enthalpic factors. However, modern synthetic methods allow access toward a large variety of cyclooctanoids[8] (Fig. 1).

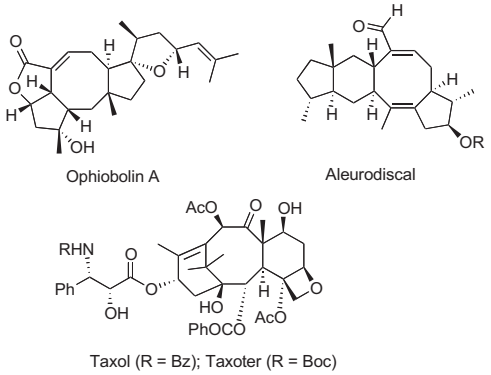

Fig. 1. Natural products containing an eight-membered ring.

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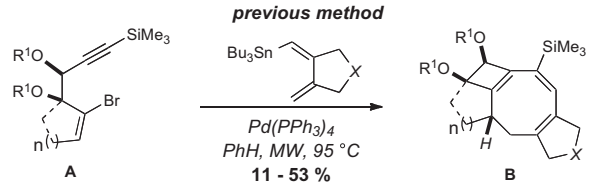
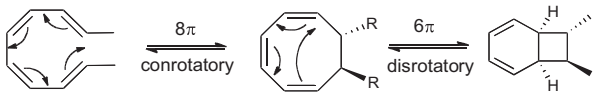
Sato et al. recently reported a Rh^{I}-catalyzed intermolecular cycloaddition of 4-allenals with alkynes to provide various monocyclic eight-membered rings in good to high yields in a stereoselective manner.[9] Another example by Snyder et al. displays a rapid access to diverse members of the lauroxocane family, natural products containing an oxocene core. This oxygen-containing eight-membered ring compound is designed by a novel diastereoselective ring-expanding bromoetherification reaction of tetrahydrofurans triggered by a unique bromonium source (BDSB, $Et_2SBr\cdot SbBrCl_5$). Strategically positioned and designed nucleophilic traps, afford diverse functionalities on the eight-membered ring backbone.[10] Despite diversity in strategy and in product structures, none of these approaches involve the direct formation of a 5-8-5 or 6-8-5 tricyclic skeleton.

We have previously reported a straightforward preparation of 5-8-5 or 6-8-5 condensed polycycles that employs an 8π electrocyclization reaction (Scheme 1).[11] Cyclooctatrienes **B** can be obtained in a one-step operation starting from simple alkenyl bromides **A**, using mild reaction conditions, and common palladium catalysts and solvents. The key step is a tandem reaction, namely a 4-*exo*-dig carbopalladation/Stille coupling. In some cases, the reaction suffered from low yields (<20%), but these were compensated for the complexity of the products formed in a one-step operation. To the best of our knowledge, this is the shortest reported route to functionalized polycyclic cyclooctanoid structures of this type and degree of complexity. Encouraged by these promising results, we investigated this methodology further in hope of developing a new versatile and efficient route to this type of cyclooctatriene derivatives in higher yields.



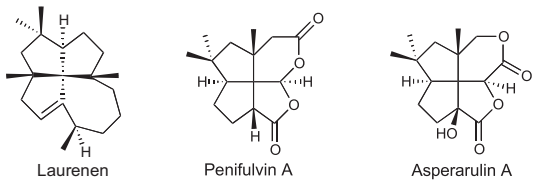
Scheme 1. Cyclooctatriene synthesis starting from alkenyl bromides **A**.

In general, few methodologies utilize the 8π electrocyclization reaction because of the formation of cyclohexadiene by a spontaneous 6π electrocyclization reaction, which leads to a 4-6 bicyclic skeleton (Scheme 2).[12] The equilibrium between the cyclooctatriene and the bicyclooctadiene depends on the reaction conditions used, and examples have been shown by several authors in total syntheses.[13] For this reason, the 1,3,5-cyclooctatriene moiety is not a common substructure and is very rarely encountered in natural products.[14] Therefore it appears to be of interest to develop new accesses to this type of structure, which can be the starting point of the synthesis of more complex natural or unnatural compounds.[15]



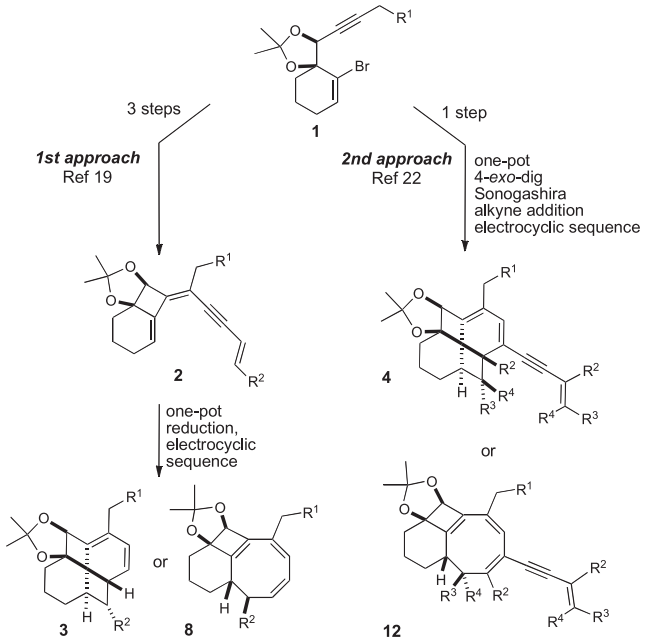
Scheme 2. Equilibrium between cyclooctatrienes and bicyclooctadienes.

During our initial investigations on the uses of the 8π electrocyclization for the synthesis of stable 1,3,5-cyclooctatrienes, we were pleased to discover that a subsequent 6π electrocyclization reaction took place at room temperature after the 8π process providing in excellent yields a new class of fenestranes: the [4,6,4,6] fenestradienes and fenestrenes. The fenestrane family represents structurally fascinating compounds, which contain four condensed cycles sharing the same central carbon atom (Scheme 3). Laurenen is the only all carbon fenestrane natural product known.[16] This compound does not present any significant biological activity. However, natural products of the fenestrane family, which contain various heteroatoms, such as the penifulvines and asperarulines, have been reported.[17] The fenestranes have attracted much synthetic interest over the past 40 years, because of the planar geometry of the central carbon atom.[18] For some examples, the bond angles around this central atom can be enlarged up to 130° instead the regular 109.5°.



Scheme 3. Some examples of natural product structurally related to the fenestrane family.

Our group has developed methodologies toward both cyclooctatrienes and new members of this family, the [4.6.4.6]fenestradienes (Scheme 4).[19] Herein we present for the first time a complete account on two different approaches: the earlier P-2 Ni strategy, leading to the first generation of polycycles, and the alkynylation strategy, leading to the second generation. In the first approach, fenestradienes **3** were obtained with excellent yields, from precursor trienynes **2** synthesized in three steps from alkenyl bromides **1**.[20] This sequence requires the use of stannanes for the 4-*exo*-dig carbopalladation/Stille coupling in the preparation of the precursors **2**, and then a sensitive nickel(0) catalyst and hydrogen gas. The stannanes could later be eliminated by the development of a new tandem reaction, 4-*exo*-dig carbopalladation/Sonogashira coupling.[21] In the second approach, a new type of fenestradienes **4** was directly prepared from alkenyl bromides **1**, thus shortening the synthesis drastically and avoiding dangerous hydrogenation.[22] We will describe the results for this one-pot synthesis of fenestradienes **4**, the limits of this method as well as the synthesis of a new series of 6-4-8, 7-4-8 or 4-8 fused systems.

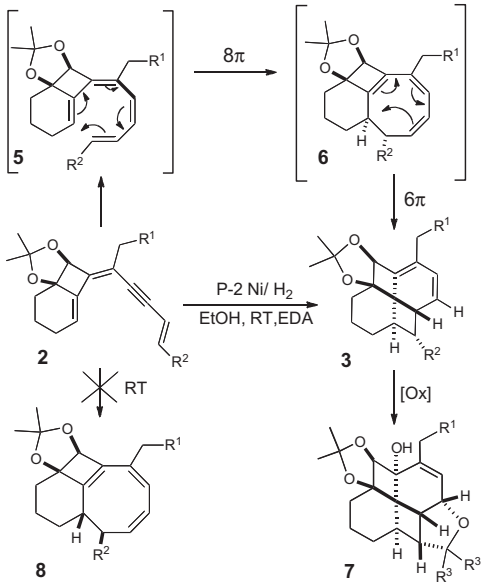


Scheme 4. Different pathways toward [4.6.4.6]fenestradienes **3** and **4** or cyclooctatrienes **8** and **12**.

2. Results and discussion

2.1. The first generation of fenestradienes and cyclooctatrienes

While applying a 4-*exo*-dig cyclocarbopalladion reaction toward efficient cascade processes, we discovered a step-economical synthesis of a new family of substituted fenestradienes **3** and cyclooctatrienes **8** (Scheme 4). These novel systems are obtained directly, in a one-pot operation, by a remarkable cascade reaction starting with the Ni-catalyzed semi-hydrogenation of trienynes **2**, readily prepared from alkenyl bromides **1** in three steps and in good overall yield. The partial reduction of the triple bond was successfully achieved using P-2 Ni ($Ni(OAc)_2 \cdot 4H_2O$, 1 equiv; $NaBH_4$, 1 equiv; EDA, 3.5 equiv; EtOH, H_2 1 atm, 16 h, room temperature). These conditions generate tetraene **5**, which can undergo a conrotatory 8π electrocyclization to form cyclooctatriene **6** (Scheme 5). This intermediate, then reacts further with a disrotatory 6π electrocyclization, to provide **3** as the sole product isolated in this reaction sequence. One can note that the reaction is totally torquoselective, none of the other diastereomer **8** is formed at room temperature. This behavior, explaining the unique formation of **3** in the cascade reaction, has been carefully studied by DFT calculations.[16b]

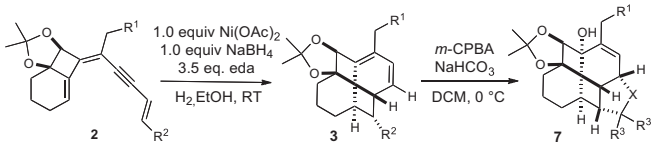


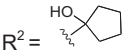
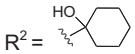
Scheme 5. Mechanism of formation of the fenestradiene **3** and fenestrene **7** of the first generation.

When compound **3** was stored at −20 °C under air for several days, it produces a new product that possesses all characteristic data corresponding to the [4.6.4.6]fenestrene **7** (Scheme 5). Exemplary of the novel chemistry of strained fenestranes, the transformation of **3** into **7** can be explained by a spontaneous oxidation of the highly reactive [4.6.4.6]fenestradiene **3** with molecular oxygen. Another oxidation conditions using *m*-CPBA in CH_2Cl_2 also lead to the same product in similar yields. All the results regarding this first generation of [4.6.4.6]fenestradienes and fenestrenes are summarized in Table 1. Numerous products containing either a hydroxy group (R^1=OH, entries 1–7) an amino group (R^1=NHPh, NHBn, NHBoc, entries 8–11), or a 1,2,3-triazole (entry 12) have been obtained in moderate to good yields (28–93%). One example with R^2 as an amino group (R^2=CH_2NHBoc, entry 7) also produced the oxidized fenestrene **7g** in 28% yield (two steps).

When the reaction conditions were slightly modified by increasing the temperature to 70 °C, none of the fenestradiene **3a** was obtained and we only observed a clean formation of the

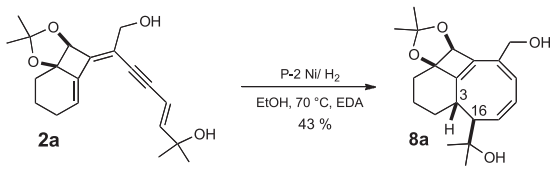
Table 1
Synthesis of first generation fenestradienes and fenestrenes



Entry	2	R^1, R^2	3	Yield (%)	7	R^3	Yield (%)[b]
1[h]	**2a**	R^1=OH R^2=$C(CH_3)_2OH$	**3a**	88[a]	**7a**	CH_3	63
2[h]	**2b**	R^1=OH R^2=$C(^i butyl)_2OH$	**3b**	63[a,c]	**7b**	^{i}Butyl	67
3[h]	**2c**	R^1=OH R^2= 	**3c**	93[a]	**7c**	$(CH_2)_4$	62
4[h]	**2d**	R^1=OH R^2= 	**3d**	86[a]	**7d**	$(CH_2)_5$	68
5[h]	**2e**	R^1=OH R^2=CH_2OH	**3e**	[d]	**7e**	H	35[e]
6[h]	**2f**	R^1=OH R^2=$(CH_2)_5CH_3$	**3f**	90[a]	—	—	—
7[h]	**2g**	R^1=OH R^2=CH_2NHBoc	**3g**	[d]	**7g**	H	28[e]
8	**2h**	R^1=NHPh R^2=$C(CH_3)_2OH$	**3h**	51[b]	—	—	—
9	**2i**	R^1=NHPh R^2=$C(^i butyl)_2OH$	**3i**	36[b]	—	—	—
10	**2j**	R^1=NHBn R^2=$C(^i butyl)_2OH$	**3j**	41[b]	—	—	—
11	**2k**[f]	R^1=NHBoc R^2=$C(^i butyl)_2OH$	**3k**	53[b]	—	—	—
12	**2l**	R^1=1,2,3-triazole-4-$(CH_2)_4OTBS$ R^2=$C(^i butyl)_2OH$	**3l**	28[g]	—	—	—

[a] Yield determined by ^{1}H NMR of the crude.
[b] Yield of isolated product after chromatography.
[c] The product **3b** was contaminated by 30% of inseparable **2b**.
[d] Not determined.
[e] Yield for the two steps (a, b) from **2g**.
[f] 11% of **2k** is recovered.
[g] The product **3l** was contaminated by 50% of inseparable **2l**.
[h] Previous results.[19]

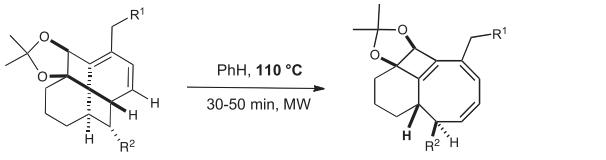
cyclooctatriene **8a**. It is important to note that the stereochemistry of the newly formed bond C3–C16 is opposite to that present in the fenestradiene **3a**. In other words, the torquoselectivity of the 8π electrocyclization is different when the reaction was conducted at room temperature or at 70 °C (Scheme 6).



Scheme 6. Direct access to cyclooctatriene **8a** from trienyne **2a**.

Furthermore when fenestradienes **3** were subjected to microwave irradiation at 110 °C for 30–50 min in benzene, stable cyclooctatrienes **8** were obtained in good yields (Scheme 7).

These polycyclic compounds represent the thermodynamic products, while the corresponding fenestradienes **3** are the kinetic compounds. It is worth mentioning that the first generation method did not give fenestradienes, but only cyclooctatrienes, when trienynes bearing no cycle or a seven-membered cycle were used in place



3a R^1 = OH, R^2 = $C(CH_3)_2OH$
3h R^1 = NHPh, R^2 = $C(CH_3)_2OH$
3j R^1 = NHBn, R^2 = C(*i*-butyl)$_2$OH

8a R^1 = OH, R^2 = $C(CH_3)_2OH$, 63%[a]
8h R^1 = NHPh, R^2 = $C(CH_3)_2OH$, 94%
8j R^1 = NHBn, R^2 = C(*i*-butyl)$_2$OH 60%
[a] previous result[19]

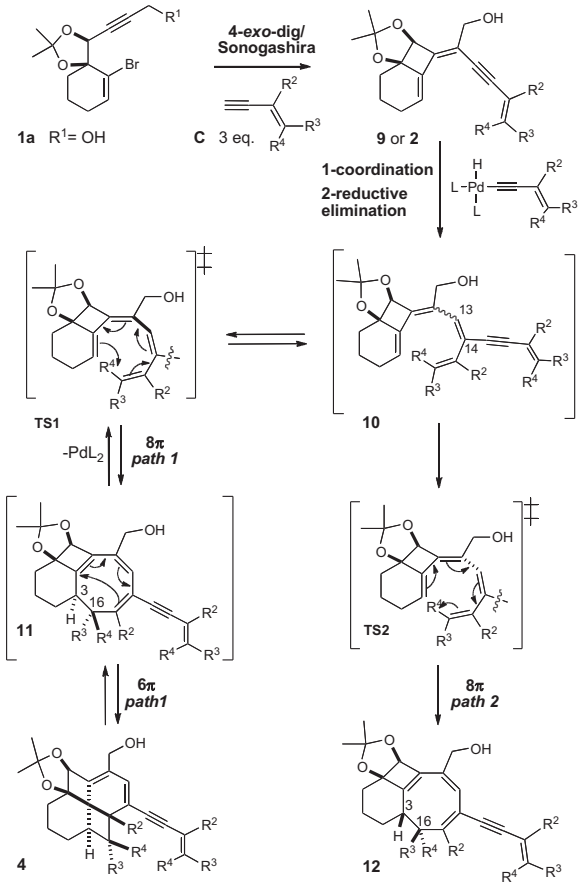
Scheme 7. Preparation of cyclooctatrienes **8** from fenestradienes **3**.

of the six-membered ring.[19b] However, this first generation methodology suffers from some inconveniences. First, the manipulation and purification of the sensitive polyenynes **2** are difficult, in some cases leading to partial degradation. Secondly, the reaction is conducted using a sensitive and toxic Ni(0) catalyst, which must be prepared in situ before the cascade reaction and, which is added in stoichiometric amount. Finally, the reduction of the triple bond involves the use of molecular hydrogen that needs some precautions, a special apparatus and room to be conducted under safe conditions. These inconveniences drove us to find an alternative route for the formation of related, but new classes of fenestradienes and cyclooctatrienes. In this regard, we recently proposed new shorter and safer syntheses of these types of compounds.

2.2. The second generation of fenestradienes and cyclooctatrienes

The second approach to fenestradienes of type **4** proceeds via a new cascade reaction of five steps, forming five new carbon−carbon bonds starting from the alkenyl bromide compounds **1** previously used. This was the first described cascade reaction with five non-identical steps. In the meantime, another complex cascade reaction has been reported in the literature.[23] The key reaction is an alkyne addition reaction, which is totally regioselective and avoids the inclusion of dihydrogen and sensitive P-2 Ni catalyst. Two recent contributions to this field inspired this new route: the first was developed by Gevorgyan et al.,[24] who managed to dimerize terminal alkynes to obtain mainly head-to-head regioisomer enynes, while Trost et al. developed conditions to add terminal donor alkynes on internal triple bonds substituted by an electron-withdrawing group, affording head-to-tail regioisomer enynes.[25] Another contribution by Tsukada, Inoue et al.[26] proposed a regioselective addition of terminal silylated alkynes onto non-activated internal asymmetric acetylenes. Our strategy is based on employing an excess of enyne **C** to induce the regioselective addition of the terminal triple bond onto the internal alkyne function of the intermediate trienyne **9** or **2** (Scheme 8). In the first approach, the corresponding compounds **2** were easily obtained in pure form in one-step starting from alkenyl bromide **1**, employing a 4-*exo*-dig carbopalladation/Sonogashira cascade reaction following our previous results,[21] but here they directly reacted further without isolation.

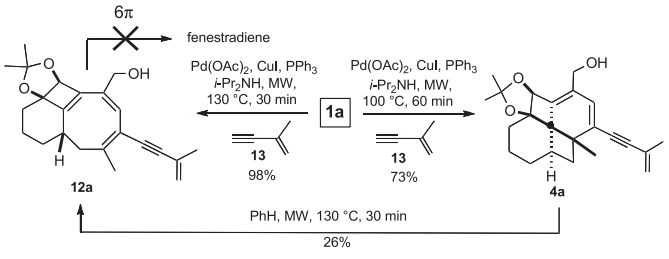
The regioselective addition of enyne **C** onto the triple bond of **9** or **2** furnished a highly unsaturated intermediate tetraene **10** with the enyne moiety at carbon 14. This intermediate, never isolated, was prone to spontaneously undergo an 8π, followed by a 6π electrocyclization leading to the [4.6.4.6]fenestradiene **4**. According to this result and previous calculations made in the field,[27] we propose the following mechanism. The conrotatory 8π electrocyclization of the intermediate tetraene **10** takes place via Möbius aromatic transition structures of helical conformations TS1 and TS2, which present opposite *M*- and *P*-helical topologies. At lower reaction temperatures, the transition state TS1 of the 8π electrocylization present a *M*-helical topology, and the cyclooctatriene **11** obtained includes a proton at carbon 3 and R^3 substituent at carbon 16 on the opposite face of the polycycle compared to the acetonide



Scheme 8. Proposed cascade reaction mechanism.

moiety. This eight-membered ring derivative **11** undergoes spontaneously the 6π electrocylization leading to the expected fenestradiene **4**. If the temperature of the reaction is increased, the transition state TS2, with opposite helical topology of a higher energy, can be reached, leading to the cyclooctatriene **12**, which does not undergo the 6π electrocyclization. This polycycle presents a proton at carbon 3 and R^3 substituent at carbon 16 on the same face of the polycycle compared to the acetonide moiety. The 8π electrocyclization via *pathway 2* presents an opposite torquoselectivity than for the reaction via *pathway 1*, shown by the structures of the transition states TS1 and TS2 (Scheme 8).

The 8π electrocyclizations are stereospecific, fenestradienes **4** and cyclooctatrienes **12** are obtained with complete diastereoselectivity. When the reaction was performed at higher temperature (e.g., 130 °C), the cyclooctatriene **12a**, was obtained as the sole product in a very high yield of 98% (Scheme 9).



Scheme 9. Two different products obtained from **1a**.

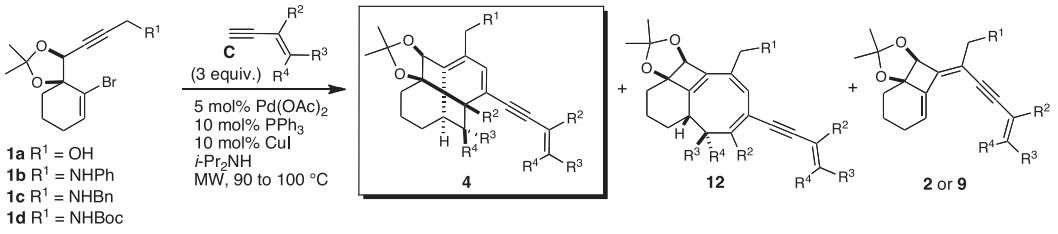
More interestingly, the electrocyclic reactions *via pathway 1* are reversible and this hypothesis was confirmed by experimentation. When fenestradiene **4a** is subjected to microwave irradiation in

benzene for 30 min at 130 °C, only one product is obtained, the cyclooctatriene **12a**, in a modest 26% yield. This low yield can be explained by the weak stability of highly tense polycycle **4a** at 130 °C. Considering all these observations and accordingly to our previous results for the first generation of fenestradienes **3**, in addition to DFT calculations, we propose that cyclooctatrienes **12** are the thermodynamic products as well, while the fenestradienes **4** are the kinetic products. This rearrangement of kinetic into thermodynamic products implies the following sequence: a retro 6π, retro 8π, and then 8π electrocyclization among *pathway 2*. In summary, we have performed a straightforward synthesis of substituted fenestradienes and cyclooctatrienes by simply adjusting the microwave irradiation time and temperature.

2.2.1. Scope of the step-economical synthesis of [4.6.4.6]fenestradienes. In order to define the scope and limitations of this cascade reaction, several differently substituted dioxolanes **1** and enynes (**13**–**28**) were tested. The alkenyl bromide **1a** was easily prepared from 2-bromocyclohexenone in a sequence of four steps in good overall yield, as previously reported[20] and was first chosen as a suitable model for this study. Then, a series of amine derivatives **1b**–**d** were synthesized in 2–4 steps.[21]

These starting materials were then treated with $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and CuI (10 mol %) as catalysts in the presence of 3 equiv of enyne **C** in diisopropylamine under microwave irradiation (90–100 °C), affording in a single process the stable fenestradienes **4**. The results obtained are summarized in Table 2. Isolated yields are moderate to high in regards to the highly strained structures obtained in only one-step: 13–80 %. Several enynes **13**–**28** bearing different chemical functions appeared to be effective in this cascade reaction: aliphatic enynes **13**–**17** (entries 1–5), aromatic enyne **18** (entry 6), free or methylated primary alcohols **19** and **24** (entries 7, 12), tertiary alcohols **20**–**23** (entries 8–11), silylated ethers **25**–**27** (entries 13–15), and a protected amine **28** (Entry 16). As for the starting material substituted by a propargylic alcohol **1a**, we were surprised to observe that a linear conjugated enyne such as **14** and **15** (entries 2 and 3) appeared to be less effective than those bearing a methyl group in α position to the triple bond such as **13**, **19**, and **25**, which could appear more sterically hindered (entries 1, 7, 13). Moreover, a congested environment around the oxygen in allylic position of enynes **25**–**26** does not prevent the cascade to occur (entries 7, 13 and 14). However, a disfavoring parameter would be the steric hindrance of alkyl groups in allylic position. Indeed the fenestradiene **4h** is isolated with a 59% yield when alkyl groups are cyclopentanol in allylic position and it drops to 39% when the enyne **21** employed bears a cyclohexanol group (entries 8 and 9). As expected, a sterically hindered (*Z*)-enyne **26** presents lowered effectiveness compared to the (*E*)-enyne **25** (entries 13 and 14). And yet, the results of the cascade reaction using starting material **1b**–**d** substituted by a propargylic amine were slightly divergent. The cascade reaction was also effective using enyne **13** when protected amine functionalities were used (entries 1, 17, 20). The yield drops from 72–80% to 48% when the carbamate **1d** is engaged (entry 23). We were also surprised to observe that when the amine function was protected with a phenyl group (**1b**), the results of the cascade reaction using substituted enynes with silylated ethers **25**–**26** (entries

Table 2
One pot synthesis of fenestradienes 4



Entry	1	Enyne	Time (min)	4	Yield (%)	12	Yield (%)	2 or 9	Yield (%)
1[k]	**1a**	**13** R^2=Me, R^3=R^4=H	60	**4a**	73	**12a**[a]	15	**9a**[a]	—
2[k]	**1a**	**14** R^2=R^4=H, R^3=CH_2CH_2Ph	30	**4b**	46	**12b**	36	**9b**	—
3	**1a**[b]	**15** R^2=R^4=H, R^3=$(CH_2)_5CH_3$	60	**4c**	Traces	**12c**	47	**2f**	—
4	**1a**[c]	**16** R^4=H, R^2–R^3=$(CH_2)_4$	60	**4d**	—	**12d**	11	**9d**	59[c]
5	**1a**[d]	**17** R^2=H, R^3–R^4=$(CH_2)_3$	60	**4e**	—	**12e**	—	**9e**	Traces
6	**1a**[e]	**18** R^2=R^4=H, R^3=Ph	60	**4f**	—	**12f**	44[e]	**9f**	—
7[k]	**1a**	**19** R^2=Me, R^3=CH_2OH, R^4=H	60	**4g**	68	**12g**	—	**9g**	—
8[k]	**1a**	**20** R^2=R^4=H, R^3= 	60	**4h**	59	**12h**	8	**2c**	25
9[k]	**1a**	**21** R^2=R^4=H, R^3= 	120	**4i**	39	**12i**	9	**2d**	47
10	**1a**	**22** R^2=R^4=H, R^3=$C(Me)_2OH$	60	**4j**	32	**12j**	34	**2a**	32
11	**1a**	**23** R^2=R^4=H, R^3=$C(^tbutyl)_2OH$	60	**4k**	—	**12k**	6	**2b**	94
12	**1a**[f]	**24** R^2=Me, R^3=CH_2OMe, R^4=H	60	**4l**	32	**12l**	—	**9l**	57
13[k]	**1a**	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	60	**4m**	72	**12m**	10	**9m**	8
14[k]	**1a**	**26** R^2=Me, R^3=H, R^4=CH_2OTBS	120	**4n**	40	**12n**	—	**9n**	30
15	**1a**[g]	**27** R^2=CH_2OTBS, R^3=R^4=H	60	**4o**	18	**12o**	14	**9o**	—
16[k]	**1a**[h]	**28** R^2=R^4=H, R^3=NHBoc	60	**4p**	43	**12p**	25	**2g**	—
17[k]	**1b**	**13** R^2=Me, R^3=R^4=H	60	**4q**	72	**12q**	15	**9q**	—
18[k]	**1b**	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	60	**4r**	40	**12r**	22	**9r**	29
19[k]	**1b**	**26** R^2=Me, R^3=H, R^4=CH_2OTBS	60	**4s**	45	**12s**	—	**9s**	48
20[k]	**1c**	**13** R^2=Me, R^3=R^4=H	60	**4t**	80	**12t**	—	**9t**	—
21	**1c**	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	60	**4u**	[i]	**12u**	[i]	**9u**	—
22[k]	**1c**	**26** R^2=Me, R^3=H, R^4=CH_2OTBS	60	**4v**	59	**12v**	—	**9v**	—
23[k]	**1d**[j]	**13** R^2=Me, R^3=R^4=H	60	**4w**	48	**12w**	7	**9w**	20

Table 2 (*continued*)

Entry	1	Enyne	Time (min)	4	Yield (%)	12	Yield (%)	2 or 9	Yield (%)
24	**1d**	**20** R^2=R^4=H, R^3 = 	60	**4x**	14	**12x**	—	**9x**	45
25	**1d**	**21** R^2=R^4=H, R^3 = 	60	**4y**	13	**12y**	7	**9y**	38
26	**1d**	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	60	**4z**	13	**12z**	—	**9z**	45

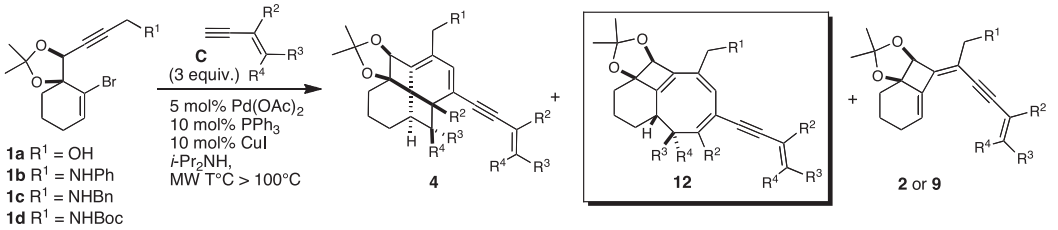
[a] Inseparable mixture with 11% of starting material **1a**.
[b] 39% of **1a** is recovered.
[c] Inseparable mixture of 19% of **1a** and 59% of **9d**.
[d] 33% of **1a** is recovered.
[e] Inseparable mixture of 38% of **1a** and 44% of **12f**.
[f] 20% of **1a** is recovered.
[g] 23% of **1a** is recovered.
[h] 29% of **1a** is recovered.
[i] 77% of a mixture of **4u** and **12u** (2:1).
[j] 6% of **1d** is recovered.
[k] Previous result.[22]

18–19) are lower to those using as a starting material propargylic alcohol **1a** (entries 13–14). Pleasingly, we observed that (*Z*)-enyne **26** with **1c** allowed to isolate up to 59% of the corresponding fenestradiene **4v** (entry 22). In this study, alternative products formation could not be avoided and trienynes **2a**–**d**, **9d**, **9l**–**n**, **9r**–**s**, and **9w**–**z**, were isolated between 8 and 94% yield, while cyclooctatrienes **12a**–**d**, **12f**, **12h**–**k**, **12m**, **12o**–**r**, **12w**, and **12y** were obtained in 6–47% yield. Both product types can be separated by column chromatography.

2.2.2. Scope of the step-economical synthesis of cyclooctatrienes. Our second objective was to determine the best reaction conditions in order to selectively prepare the substituted cyclooctatriene derivative **12** directly from the protected alkenyl bromide **1**. Toward this goal, we tested several microwave irradiation times and temperatures. As it was described above (Scheme 8), this direct transformation of **1** into **12** is the result of a thermodynamic control of the cascade reaction leading to the more stable polycycle.

In this particular case, DFT calculations have clearly shown in the first generation of cyclooctatrienes **8** that these types of compounds are more stable than the corresponding fenestradienes **3**. The optimized reaction conditions for this transformation were a compromise between irradiation time and temperature to force consumption of the starting compound **1** and avoid decomposition: 100–130 °C, 30 min to 3 h, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CuI (10 mol %) in pure $^iPr_2NH$ in the presence of 3 equiv of the enyne **C**. We were pleased to isolate, after silica gel chromatography, the cyclooctatriene **12** in acceptable to very good yield when considering the complexity of these cascade events (Table 3). The propargylic alcohol **1a** gave the best result with the formation of **12a** (entry 1) in 98% yield after only 30 min of microwave irradiation. The presence of R^3 group as an alkyl group (entries 2–4) or as a phenyl substituent (entry 5) usually conducted to a good yield of the expected cyclooctatrienes, respectively **12b**–**d** and **12f**. Depending on the enyne used, we observed, in some cases, the formation of a non-negligible amount of the kinetic product, for instance the fenestradienes **4m** and **4q** (entries 9 and 11). Despite applying a longer reaction time, it was not possible to increase the yields of the corresponding cyclooctatrienes **12m** and **12q**. When the enyne bearing a free primary alcohol **19** was used under standard irradiation conditions, only the cyclooctatriene **12g** was obtained in good yield (80%) (entry 6). Employing the protected allylic alcohol **25** dramatically reduced the formation of product **12m** to 15% (entry 9). Aside **12m**, the trienyne **9m** was isolated in 55% yield and fenestradiene **4m** in 16% yield. In

Table 3
One-pot synthesis of cyclooctatrienes **12**



Entry	1	Enyne	MW conditions	4	Yield (%)	12	Yield (%)	2 or 9	Yield (%)
1	**1a**	13 R^2=Me, R^3=R^4=H	30 min, 130 °C	**4a**	—	**12a**	98	**9a**	—
2	**1a**	14 R^2=R^4=H, R^3=CH_2CH_2Ph	1 h, 110 °C	**4b**	—	**12b**	59	**9b**	—
3	**1a**	15 R^2=R^4=H, R^3=$(CH_2)_5CH_3$	3 h, 100 °C	**4c**	Traces	**12c**	72	**2f**	—
4	**1a**	16 R^4=H, R^2–R^3=$(CH_2)_4$	2 h, 100 °C	**4d**	—	**12d**	77	**9d**	20
5	**1a**	18 R^2=R^4=H, R^3=Ph	3 h, 100 °C	**4f**	—	**12f**	68	**9f**	—
6	**1a**	19 R^2=Me, R^3=CH_2OH, R^4=H	2 h, 130 °C	**4g**	—	**12g**	80	**9g**	—
7	**1a**	20 R^2=R^4=H, R^3 = 	1 h, 130 °C	**4h**	Traces	**12h**	81	**2c**	Traces
8	**1a**	21 R^2=R^4=H, R^3 = 	3 h, 100 °C	**4i**	Traces	**12i**	51	**2d**	30
9	**1a**	25 R^2=Me, R^3=CH_2OTBS, R^4=H	1 h, 130 °C	**4m**	16	**12m**	15	**9m**	55

(*continued on next page*)

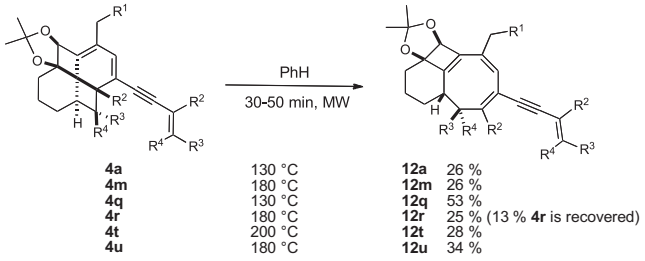
Table 3 (*continued*)

Entry	1	Enyne	MW conditions	4	Yield (%)	12	Yield (%)	2 or 9	Yield (%)
10	**1a**	28 R^2=H, R^3=CH_2NHBoc, R^4=H	1 h, 130 °C	**4p**	—	**12p**	41	**9p**	—
11	**1b**	13 R^2=Me, R^3=R^4=H	1 h, 130 °C	**4q**	23	**12q**	65	**9q**	—
12	**1c**	13 R^2=Me, R^3=R^4=H	1 h, 130 °C	**4t**	—	**12t**	66	**9t**	—
13	**1c**	25 R^2=Me, R^3=CH_2OTBS, R^4=H	1 h, 130 °C	**4u**	[a]	**12u**	[a]	**9u**	—
14	**1d**	13 R^2=Me, R^3=R^4=H	1 h, 130 °C	**4w**	—	**12w**	62	**9w**	—

[a] 26% of an inseparable mixture of **4u** and **12u** (1:3).

spite of applying a longer reaction time both products did not rearrange to **12m**. Similarly, the protected propargylic amine **1c** gave a low yield (26%) of an inseparable mixture (1:3) of **4u** and **12u** (entry 13). The sterically congested tetraene **10u** (see Scheme 8) probably requires much higher activation energy to eventually form the favorable *P*-helical topologies affording the final cyclooctatriene **12u**. This behavior can also be observed when the enyne is switched from **20** (cyclopentanol substitution) to **21** (cyclohexanol substitution) (entries 7 and 8). These results support the fact that the full cascade process is quite sensitive to the steric hindrance in the allylic position of the enyne moiety. The presence of a protected amine in the starting alkenyl bromides **1b**–**d** as well as in the allylic position of the enyne **28** did not affect the cascade leading to the cyclooctatrienes **12p**–**q**, **12t**, and **12w** in acceptable yield (41–66%, entries 10–12 and 14).

The direct transformation of some fenestradienes **4** into cyclooctatrienes **12** has been accomplished by simply heating **4** under microwave irradiation at temperatures up to 130 °C. The sequence retro 6π–8π than 8π cyclization afforded low yields (25–53%) of the corresponding cyclooctatriene **12** with an opposite torquoselectivity compared to **4** (Scheme 10).



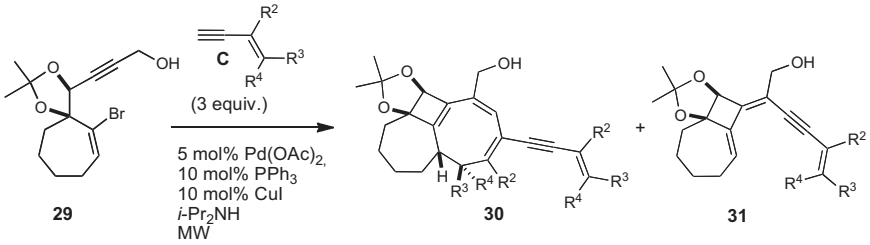
Scheme 10. Direct transformation of fenestradienes **4** into cyclooctatrienes **12**.

Another substrate of interest was the starting material bearing a cycloheptene moiety **29**.[20] When applying our classical reaction conditions used for the six-membered compounds **1a**–**d**, not surprisingly, no trace of the [4.6.4.7]fenestradiene was isolated. This observation was in accordance to our previous results obtained by the semi-hydrogenation procedure using P-2 Ni for the synthesis of cyclooctatrienes **8** (first generation). [4.6.4.7]fenestradienes present a high energy level and cannot be isolated.[19b]

Similarly to previous examples, diverse irradiation conditions were used, the best results are summarized in Table 4. When the enyne **13** was engaged in optimized conditions using the seven-membered ring starting material **29**, the expected cyclooctatriene **30a** was isolated in 86% yield (entry 1). A 3 h irradiation time was required to isolate the condensed 7-4-8 polycycle **30b** in high yield (89%) as sole product when the enyne **14** was used (entry 2). When using enyne **20**, the yield of the reaction dropped to 45% for **30g** while no cyclooctatriene **30h** was formed when enyne **21** was reacted with **29** (entries 7 and 8). Only the trienyne **31h** was isolated in 95% yield in this case. Utilizing higher irradiation temperature only resulted in degradation of the trienyne **31h**. In the majority of cases, the tricycle **30** was accompanied by the corresponding trienyne **31** formed after the monoaddition of the enyne moiety on **29** (entries 3–9). With enyne **16** and **21,** the non-expected products **31d** and **31h** became the major ones (entries 4 and 8). Using the enyne substituted with an aliphatic chain **15**–**16**, irradiating the reaction mixture longer only resulted in degradation (entries 3 and 4). Again the alkynylation step on the triple bond of **29** was totally regioselective and no formation of the other regioisomer was detected after completion of the reaction.

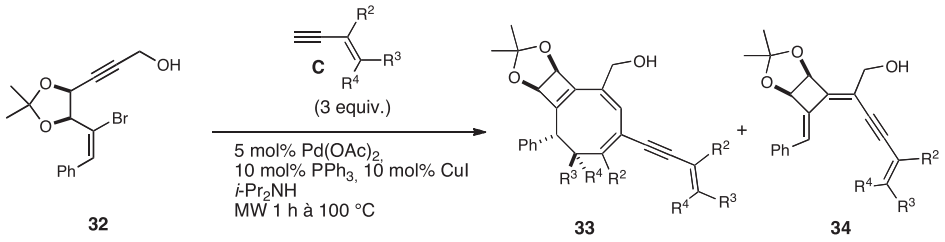
Considering all the above results, the effectiveness of the cascade reaction does not depend on the enyne structure indeed. We

Table 4
One-pot synthesis of cyclooctatrienes **30**



Entry	Enyne	MW conditions	30	Yield (%)	31	Yield (%)
1	**13** R^2=Me, R^3=R^4=H	30 min, 130 °C	**30a**	86	**31a**	—
2	**14** R^2=R^4=H, R^3=CH_2CH_2Ph	3 h, 100 °C	**30b**	89	**31b**	—
3	**15** R^2=R^4=H, R^3=$(CH_2)_5CH_3$	1 h, 100 °C	**30c**	58	**31c**	20
4	**16** R^4=H, R^2-R^3=$(CH_2)_4$	3 h, 100 °C	**30d**	32	**31d**	68
5	**18** R^2=R^4=H, R^3=Ph	1 h, 130 °C	**30e**	50	**31e**	45
6	**19** R^2=Me, R^3=CH_2OH, R^4=H	3 h, 100 °C	**30f**	60	**31f**	35
7	**20** R^2=R^4=H, R^3= 	3 h, 100 °C	**30g**	45	**31g**	40
8	**21** R^2=R^4=H, R^3= 	1 h, 100 °C	**30h**	—	**31h**	95
9	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	1 h, 100 °C	**30i**	64	**31i**	29

Table 5
One-pot synthesis of cyclooctatrienes **33**



Entry	Enyne	MW conditions	33	Yield (%)	34	Yield (%)
1	**13** R^2=Me, R^3=R^4=H	1 h, 100 °C	**33a**	Degradation	**34a**	Degradation
2	**14** R^2=R^4=H, R^3=CH_2CH_2Ph	1 h, 100 °C	**33b**	Degradation	**34b**	Degradation
3	**16** R^4=H, R^2–R^3=$(CH_2)_4$	1 h, 100 °C	**33c**	—	**34c**	75
4	**16** R^4=H, R^2–R^3=$(CH_2)_4$	5 min, 100 °C	**33c**	—	**34c**	100
5	**25** R^2=Me, R^3=CH_2OTBS, R^4=H	1 h, 100 °C	**33d**	Degradation	**34d**	Degradation

can suggest that the activation energy of the 8π electrocyclization leading to cyclooctatrienes **12** and **30** appears to be particularly high for some compounds (**12m**, **12p** and **30d**, **30e**, **30g**, **30h**), resulting in a medium to high yields for the intermediate trienynes.

Next, we were interested in examining the reactivity of an acyclic starting material **32** in the conditions of the cascade reaction (Table 5).[20] When aliphatic enynes **13**–**14** and silylated enyne **25** were used, a complex mixture of inseparable products was obtained, and the expected cyclooctatriene **33** and trienyne **34** were not observed (entries 1–2, 5). When ethynylcyclohexene **16** was engaged in the same conditions, the trienyne **34c** was isolated in 75% yield (entry 3). In fact, the reaction was already quantitative in only 5 min (entry 4). The 4-8 condensed polycycle **33a**,**b** and **33d** and the cyclobutane containing compound **34a**,**b** and **34d** appeared to be sensitive toward microwave irradiation. Moreover, the trienyne **34** does not seem to be a good substrate toward alkyne addition reaction, probably due to the high degree of liberty of the structure. The enynes used in this study have proven to be effective with cyclic starting materials **1a**–**d** and **29**, thus cannot be the problematic component here. These examples demonstrate a limit of the scope of this cascade reaction.

3. Conclusion

In summary we have given a complete account of the new methods for the synthesis of cyclooctatrienes, fenestradienes, and fenestrenes developed in our group. The first strategy allows for the access to a first generation of cyclooctatrienes **8**, fenestradienes **3**, and fenestrenes **7**. This method can be applied to a series of precursor trienynes **2** bearing a hydroxy group or amino groups in homopropargylic position, obtained in three steps from alkenyl bromides **1**. In the second strategy, a new generation of polycycles was directly prepared from alkenyl bromides **1**. The cascade reaction involves five steps, which is the first of its kind and renders the synthesis even more efficient and shorter. Twenty-one new fenestradienes **4** were obtained bearing a hydroxy group or amino groups in homopropargylic position in modest to very good yields, and using a variety of enynes (aliphatic and aromatic enynes, as well as enynes bearing a protected amine, a free primary alcohol, tertiary alcohols, and silylated ethers). Changing only the microwave irradiation conditions selectively give access to 20 new cyclooctatrienes **12**. Using the different precursors bearing not a six- but seven-membered cycle, the isolation of eight new cyclooctatrienes **30** was equally achieved. Thus, especially this second new approach reveals to be appealing in terms of atom and step economy, the use of easy to handle conditions, as well as the variability of its scope. Furthermore, the alkynylation reaction on the attacked triple bond is totally regioselective leading to only one diastereomer. This is the first alkyne addition reaction of a simple enyne onto a non-activated internal triple bond, using the very common catalytic system $Pd(OAc)_2/PPh_3$. It proved efficient with different functions on the alkyne donor: alkyl groups but also inductive electron-withdrawing groups as alcohols. Investigations explaining the high regioselectivity are being undertaken.

4. Experimental section

4.1. General

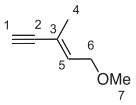
Microwave irradiations were performed using a BIOTAGE Smith Creator apparatus. The crude products were purified by flash column chromatography on Merck silica gel Si 60 (40–63 μm). For some compounds, with 5% Et_3N in Et_2O treated silica gel was used to avoid decomposition due to the acidity of the not treated silica gel. Analytical thin layer chromatography (TLC) was carried out on Merck aluminum sheets silica gel 60 F254. TLC spots were examined under UV light and revealed by sulfuric acid/anisaldehyde. NMR spectra were recorded in $CDCl_3$ on a Bruker 500 MHz, Ultrashield+, Avance III BBFO+ probe spectrometer, a Bruker Avance III 400 MHz BBFO+ probe spectrometer for ^1H and 100 MHz for ^{13}C, and a Bruker Avance 300 MHz dual probe spectrometer for 1H. Proton chemical shifts are reported in parts per million (δ), relatively to residual $CHCl_3$ (δ 7.26 ppm). Carbon chemical shifts are reported in ppm (δ), relatively to the internal standard ($CDCl_3$, δ 77.16 ppm). ^1H and ^{13}C NMR signals were assigned mostly on the basis of DEPT and 2D-NMR (COSY, HMBC, HMQC) experiments, and using increment tables.[28] Chemical ionization (CI) mass spectra were recorded on a Thermo Trace GC/DSQ II GC/MS mass spectrometer. High Resolution Mass Spectral analysis (HRMS) was performed using an Agilent 1200 RRLC HPLC chain and an Agilent 6520 Accurate mass QToF. Infrared spectra (IR) were recorded on an FT IR Thermo Nicollet ATR 380, Diamant Spectrometer.

4.2. Experimental data for the starting materials

The syntheses of the following starting materials were described in earlier publications: **1a**,[20] **1b**–**e**,[21] seven-membered ring **29**[20] and acyclic **32**,[20] (*E*)-hex-3-en-5-yn-1-ylbenzene **14**,[22] (*E*)-1-(but-1-en-3-yn-1-yl)cyclopentanol **20**,[22] (*E*)-1-(but-1-en-3-yn-1-yl) cyclohexanol, **21**[22] (*E*)-*tert*-butyldimethyl((3-methylpent-2-en-4-yn-1-yl)oxy)silane **25**,[22] (*Z*)-*tert*-butyldimethyl((3-methylpent-2-en-4-yn-1-yl)oxy)silane **26**,[21] (*E*)-*tert*-butylpent-2-en-4-yn-1-ylcarba-mate **28**,[22] (*E*)-4-*iso*butyl-2-methyloct-5-en-7-yn-4-ol **23**,[21] prop-2-yn-1-ylidenecyclobutane **17**.[29]

The following enynes are commercially available: 2-methyl-1-buten-3-yne **13**, ethynylcyclohexene **16**, 2-bromo-2-propen-1-ol, and (*E*)-3-methyl-2-penten-4-yn-1-ol **19**, which was distilled prior to use.

*4.2.1. (E)-5-Methoxy-3-methylpent-3-en-1-yne (**24**).*

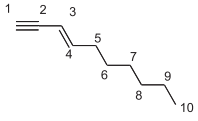


To a solution of NaH (60% dispersion in mineral oil, 272 mg, 6.81 mmol, 1.5 equiv) in anhydrous THF (21 mL, 0.3 M) was added dropwise, at 0 °C, a solution of (*E*)-3-methylpent-2-en-4-yn-1-ol (436 mg, 4.54 mmol, 1 equiv) in anhydrous THF (40 mL, 0.1 M). Then MeI (848 μL, 13.6 mmol, 3 equiv) was added at 0 °C. The reaction mixture was stirred for 1 h at room temperature and quenched with a saturated solution of NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O (2×). The combined organic phase was washed with water, brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product is unstable on silica gel, even treated with Et_3N (5%), so the crude product is purified by a treatment with activated carbon and filtrated over Celite to afford 300 mg of **24** (60%) as orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (td, ^3J=8.0 Hz, ^4J=1.2 Hz, 1H, H-5), 4.00 (d, ^3J=8.0 Hz, 2H, H-6), 3.33 (s, 3H, H-7), 2.83 (s, 1H, H-1), 1.84 (s, 3H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2 (C-5), 120.5 (C-3), 86.0 (C-2), 75.2 (C-1), 68.6 (C-6), 58.3 (C-7), 17.7 (C-4).

4.3. General procedure I for enynes 15, 18, 22

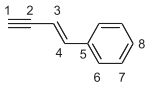
To a solution of TMS–acetylene (1 equiv) in anhydrous THF (0.13 M) was added at 0 °C a solution of vinyl iodide (1 equiv), $Pd(PPh_3)_2Cl_2$ (0.03 equiv), and CuI (0.1 equiv) in anhydrous THF (0.80 M). Then diisopropylamine (12 equiv) was added. The reaction mixture was stirred 5 min at 0 °C and then 1 h at room temperature. The reaction was quenched with NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water, brine, dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was then purified by flash chromatography over silica gel to afford the silylated enyne, which was then deprotected according to the following procedure: the enyne was dissolved in MeOH (0.20 M) and K_2CO_3 was added (1 equiv). The reaction mixture was stirred for 1 h at room temperature, quenched with NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water, brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure before purification.

*4.3.1. (E)-Dec-3-en-1-yne (**15**).*



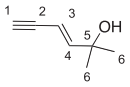
The enyne **15** was prepared following the **general procedure I** starting from a solution of TMS–acetylene (110 μL, 0.80 mmol, 1 equiv) in anhydrous THF (6.2 mL, 0.13 M), a solution of (*E*)-1-iodo-1-octene (190 mg, 0.80 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (17 mg, 0.02 mmol, 0.03 equiv), CuI (15 mg, 0.08 mmol, 0.1 equiv) in THF (1.0 mL, 0.8 M), and diisopropylamine (1.35 mL, 9.6 mmol, 12 equiv). The crude product was then directly deprotected with K_2CO_3 (111 mg, 0.80 mmol, 1 equiv) in MeOH (4.9 mL, 0.20 M). The crude product was purified by flash chromatography over silica gel (elution: pentane), to afford 100 mg of **15** (92% over two steps) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dt, ^3J=15.8 Hz, ^3J=6.9 Hz, 1H, H-4), 5.45 (dt, ^3J=15.8 Hz, ^4J=2.0 Hz, 1H, H-3), 2.77 (dd, ^4J=2.0 Hz, ^5J=0.4 Hz, 1H, H-1), 2.17–2.08 (m, 2H, H-5), 1.43–1.24 (m, 8H, H-6, H-7, H-8, H-9), 0.88 (t, ^3J=7.0 Hz, 3H, H-10). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1 (C-4), 143.5 (C-3), 108.6 (C-2), 82.8 (C-1), 75.6 (C-5), 33.2 (CH_2, non assig.), 33.1 (CH_2, non assig.), 28.9 (CH_2, non assig.), 28.7 (CH_2, non assig.), 14.2 (C-10). IR (neat) ν (cm^{-1})=3315, 2926, 2856, 2360, 1733, 1458, 1250, 954, 850, 635.

*4.3.2. (E)-but-1-en-3-yn-1-ylbenzene (**18**).*



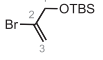
The enyne **18** was prepared following the **general procedure I** starting from a solution of TMS–acetylene (470 μL, 3.33 mmol, 1 equiv) in anhydrous THF (26 mL, 0.13 M), a solution of (*E*)-(4-iodobut-1-en-3-yn-1-yl)benzene[30] (766 mg, 3.33 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (70 mg, 0.10 mmol, 0.03 equiv), CuI (63 mg, 0.33 mmol, 0.1 equiv) in THF (4.2 mL, 0.80 M), and diisopropylamine (5.7 mL, 40 mmol, 12 equiv). The crude product was then directly deprotected in MeOH (17 mL, 0.20 M) with K_2CO_3 (460 mg, 3.33 mmol, 1 equiv). The crude product was then purified by flash chromatography over 10 cm of silica gel (elution: pentane) to afford 367 mg (86% over two steps) of **18** as a yellow oil; R_f=0.76 (hexane/EtOAc=95:05). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–6.91 (m, 5H, H-6, H-7, H-8), 6.93 (dd, ^3J=16.2 Hz, ^4J=1.2 Hz, 1H, H-3), 6.01 (ddd, ^3J=16.2 Hz, ^4J=2.2 Hz, ^4J=2.2 Hz, 1H, H-4), 2.94 (dd, ^4J=1.2 Hz, ^5J=2.2 Hz, 1H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C-3), 136.0 (C-5), 129.0 (C-8), 128.8 (C-7), 126.5 (C-6), 107.2 (C-4), 83.0 (C-2), 79.4 (C-1). IR (neat) ν (cm^{-1}) 3289, 3031, 2098, 1491, 1447, 953, 746, 687, 604, 518, 477.

*4.3.3. (E)-2-Methylhex-3-en-5-yn-2-ol (**22**).*



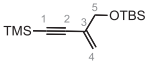
The enyne **22** was prepared following the **general procedure I** starting from a solution of TMS–acetylene (200 μL, 1.41 mmol, 1 equiv) in anhydrous THF (11.0 mL, 0.13 M), a solution of (*E*)-4-iodo-2-methylbut-3-en-2-ol[19a] (300 mg, 1.41 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol, 0.03 equiv), CuI (27 mg, 0.14 mmol, 0.1 equiv) in THF (2.0 mL, 0.80 M), and diisopropylamine (2.4 mL, 17.0 mmol, 12 equiv). The crude product was then directly deprotected with K_2CO_3 (195 mg, 1.41 mmol, 1 equiv) in MeOH (7.1 mL, 0.20 M). The product is unstable on silica gel, even treated with Et_3N (5%), so the crude product is purified by a treatment with activated carbon and filtrated over Celite to afford 101 mg of **22** (65% in two steps) as orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, ^3J=16.4 Hz, 1H, H-4), 5.65 (dd, ^3J=16.4 Hz, ^4J=2.3 Hz, 1H, H-3), 2.84 (d, ^4J=2.3 Hz, 1H, H-1), 1.27 (s, 6H, H-6), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (C-4), 105.7 (C-3), 82.0 (C-2), 77.7 (C-1), 70.8 (C-5), 29.2 (2C, C-6). IR (neat) ν (cm^{-1})=(3393, 2967, 2927, 2856, 2360, 2342, 1717, 1459, 1363, 1262, 1121, 956, 907, 729, 647, 541.). GC–MS (CI-NH_4, positive ion): 220.05 [$2M^{+\bullet}$].

*4.3.4. tert-Butyl(dimethyl)[(2-methylenebut-3-yn-1-yl)oxy]silane (**27**).*

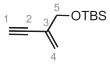


To a solution of alcohol 2-bromo-2-propen-1-ol (885 mg, 6.50 mmol, 1.0 equiv) in dry CH_2Cl_2 (21 mL) at 0 °C was added imidazole (665 mg, 9.76 mmol, 1.50 equiv), DMAP (79.4 mg, 0.65 mmol, 0.10 equiv), and TBSCl (1.47 g, 9.76 mmol, 1.5 equiv). The transparent solution turned into a white suspension, and the reaction mixture was stirred first at 0 °C and then for 5 h at room temperature. The reaction was quenched with H_2O, the phases

were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel (elution: pentane/Et_2O=95:5) to afford 1.63 g (100%) as colorless oil. R_f=0.38 (pentane/Et_2O=95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, ^2J=1.6 Hz, 1H, H-3a), 5.53 (d, ^2J=1.6 Hz, 1H, H-3b), 4.20 (br s, 2H, H-1), 0.92 (s, 9H, TBS), 0.10 (s, 6H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0 (C-2), 114.8 (C-3), 67.6 (C-1), 25.9 (TBS), 18.5 (TBS), −5.2 (TBS). GC–MS (positive ion, 70 eV): 251.10 and 253.13 [M+H$^+$•].



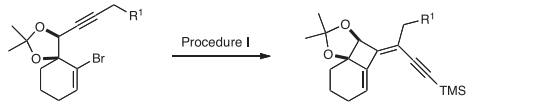
A solution of the previous compound (1.63 g, 6.50 mmol, 1.0 equiv) in MeCN and Et_3N (c=0.10 M, MeCN/Et_3N=8:2, 52.0 mL MeCN, 13.0 mL Et_3N) was degassed under vacuum and put under argon. At room temperature was then added TMS–acetylene (1.0 mL, 7.15 mmol, 1.10 equiv), $Pd(PPh_3)_4$ (230 mg, 0.20 mmol, 0.05 equiv), and CuI (186 mg, 0.96 mmol, 0.15 equiv). The yellow solution turned brown-red. After 1 h stirring at room temperature, ethanolamine (10 equiv/CuI) was added; the solution was stirred for another 2 h and then quenched with H_2O. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel (elution: pentane) yielding 1.78 g (100%) of the TMS–enyne as gray oil. R_f=0.37 (pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, ^2J=1.6 Hz, 1H, H-4a), 5.49 (d, ^2J=1.6 Hz, 1H, H-4b), 4.13 (br s, 2H, H-5), 0.92 (s, 9H, TBS), 0.18 (s, 9H, TMS), 0.08 (s, 6H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1 (C-3), 120.6 (C-4), 103.3 (C-2), 95.4 (C-1), 65.2 (C-5), 26.0 (TBS), 18.5 (TBS), 0.08 (TMS), −5.2 (TBS). GC–MS (positive ion, 70 eV): 269.24 [M+H$^+$•].



The TMS–enyne (350 mg, 1.30 mmol, 1.0 equiv) was then deprotected in MeOH (8.70 mL) and with K_2CO_3 (180 mg, 1.30 mmol, 1.0 equiv). The crude product was purified by flash chromatography over silica gel (elution: pentane/Et_2O=98:2 to pentane/Et_2O=95:5) to afford 196 mg (77%) of **27** as a yellow oil, with traces of a byproduct. R_f=0.37 (pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (m, 1H, H-4a), 5.54 (m, 1H, H-4b), 4.16 (br s, 2H, H-5), 2.91 (s, 1H, H-1), 0.92 (s, 9H, TBS), 0.09 (s, 6H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.2 (C-3), 121.2 (C-4), 82.0 (C-2), 78.2 (C-1), 65.0 (C-5), 26.0 (TBS), 18.5 (TBS), −5.2 (TBS). GC–MS (positive ion, 70 eV): 214.19 [M + NH_4^+•].

4.4. General procedure I for the tandem reaction 4-*exo*-dig/Sonogashira coupling

The syntheses of the following starting materials were described in an earlier publication: **1b**, **1c**, and **1d**.[21]

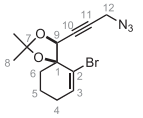


1b R^1 = NHPh
1c R^1 = NHBn
1d R^1 = NHBoc
1e R^1 = 1,2,3-triazole-4-$(CH_2)_4$OTBDMS

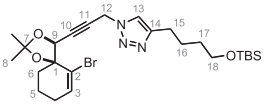
35 R^1 = NHPh
36 R^1 = NHBn
37 R^1 = NHBoc
38 R^1 = 1,2,3-triazole-4-$(CH_2)_4$OTBDMS

In a 2–5 mL microwave vial were added the propargylic amine (1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), copper iodide (0.10 equiv), and triphenylphosphine (0.10 equiv). The vial was sealed with a Teflon cap and the reaction mixture was then dissolved in diisopropylamine (c=0.05 M). The reaction mixture was degassed with two freeze–pump–thaw cycles. Then, the TMS–acetylene (1.5 equiv) was added to the reaction mixture. The vial was irradiated in the microwave for 20 min at 100 °C. The reaction mixture was then filtered through Celite to eliminate the metal traces and then concentrated under vacuum. The crude product was purified by flash column chromatography.

4.4.1. 1-{3-[(4S,5S*)-6-Bromo-2,2-dimethyl-1,3-dioxaspiro[4.5]dec-6-en-4-yl]prop-2-yn-1-yl}-4-(4-{[tert-butyl(dimethyl)silyl]oxy}butyl)-1H-1,2,3-triazole (**1e**).*



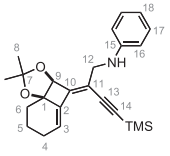
The (4S*,5S*)-6-bromo-4-(3-bromoprop-1-ynyl) 2,2-dimethyl-1,3-dioxaspiro[4.5]dec-6-ene[20] (731 mg, 2.01 mmol, 1.0 equiv) was diluted in DMF (20.0 mL) in a microwave tube. Sodium azide (1.04 g, 16.1 mmol, 8 equiv) was added and the tube was sealed. The mixture was irradiated 10 min at 80 °C in the microwave and then quenched with H_2O distilled. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residual yellow oil was purified by flash chromatography over silica gel (elution: pentane/Et_2O=9:1) yielding 622 mg (95%) of the azide as a yellow oil. R_f=0.33 (pentane/Et_2O=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (t, ^3J=4.4 Hz, 1H, H-3), 4.77 (s, 1H, H-9), 3.98 (s, 2H, H-12), 2.21–1.69 (m, 6H, H-4, H-5, and H-6), 1.69 (s, 3H, H-8), 1.41 (s, 3H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (C-3), 124.2 (C-2), 110.8 (C-7), 84.0 (C-1), 81.9 (C-11), 81.5 (C-10), 75.6 (C-9), 40.2 (C-12), 38.4 (C-6), 27.6 (C-4), 26.5 (C-8), 26.5 (C-8), 19.9 (C-5). IR (neat) ν (cm^{-1})=2985, 2939, 2865, 2096, 1634, 1456, 1378, 1248, 1209, 1165, 1079, 1066, 1038, 989, 907, 891, 850, 709, 631, 521. HRMS (ESI, 120 eV) calculated for $C_{13}H_{16}BrN_3O$ [M$^+$•] 325.04259, found 325.04291 (Diff: 0.98 ppm).



The azide (169 mg, 0.52 mmol, 1.0 equiv) was diluted in t-BuOH (10.0 mL), H_2O (2.0 mL) and H_2O (2.0 mL). TBS protected hexynol (110 mg, 0.52 mmol, 1.0 equiv) was added followed by aqueous solutions of $CuSO_4$ (0.50 mL, 1 M, 1.0 equiv) and sodium ascorbate (0.50 mL, 1 M, 1.0 equiv). The mixture was stirred for 10 min at room temperature and quenched with brine. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude yellow residue was purified by flash chromatography over silica gel (elution: DCM/MeOH=9:1) to afford 269 mg (96%) of the triazole **1e** as colorless oil. R_f=0.63 (DCM/MeOH=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)=7.63 (s, 1H, H-13), 6.28 (t, ^3J=3.8 Hz, 1H, H-3), 5.23 (dd, ^2J=17.8 Hz, ^5J=1.8 Hz, 1H, H-12), 5.17 (dd, ^2J=17.8 Hz, ^5J=1.8 Hz, 1H, H-12), 4.73 (t, ^5J=1.8 Hz, 1H, H-9), 3.63 (t, ^3J=6.4 Hz, 2H, H-15 or H-18), 2.74 (t, ^3J=7.6 Hz, 2H, H-15 or H-18), 2.19–1.53 (m, 10H, H-4, H-5, H-6, H-16, and H-17), 1.68 (s, 3H, H-8), 1.40 (s, 3H, H-8), 0.88 (s, 9H, TBS), 0.03 (s, 6H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)=148.7 (C-14), 135.4 (C-3), 124.3 (C-2),

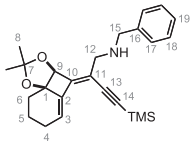
120.8 (C-13), 111.0 (C-7), 83.8 (C-1), 81.8 (C-10), 80.9 (C-11), 75.5 (C-9), 62.9 (C-18), 40.1 (C-12), 38.4 (C-6), 32.5 (C-15), 27.6 (C-4), 26.4 (C-8), 26.4 (C-8), 26.1 (TBS), 25.9 (C-16 or C-17), 25.6 (C-16 or C-17), 19.7 (C-5), 18.5 (TBS), −5.2 (TBS). IR (neat) ν (cm^{-1})=2933, 2857, 1734, 1634, 1550, 1461, 1379, 1252, 1210, 1100, 1066, 10,339, 903, 834, 774. HRMS (ESI, 120 eV) calculated for $C_{25}H_{40}BrN_3O_3Si$ [$M^{+\bullet}$] 537.20223, found 537.20220 (Diff: 0.06 ppm).

4.4.2. [(2Z)-2-[(3aS,8aR*)-2,2-Dimethyl-7,8-dihydro-3aH-benzo [1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-(trimethylsilyl)but-3-yn-1-yl] phenylamine (**35**).*



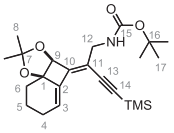
The **general procedure I** was followed using: phenylamine **1b** (240 mg, 0.64 mmol, 1.0 equiv), diisopropylamine (14 mL), $Pd(OAc)_2$ (7.20 mg, 0.03 mmol, 0.05 equiv), CuI (12.2 mg, 0.06 mmol, 0.10 equiv), PPh_3 (16.8 mg, 0.06 mmol, 0.10 equiv), and TMS−acetylene (140 μL, 0.96 mmol, 1.5 equiv). The crude brown residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=8:2 to pentane/Et_2O=6:4) to afford 206 mg (83%) of the desired product **35** as a yellow oil. R_f=0.90 (pentane/Et_2O=8:2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 and 6.70 (m, 5H, H_{arom}), 6.25 (t, ^3J=3.8 Hz, 1H, H-3), 4.83 (s, 1H, H-9), 4.28 (br s, 1H, NH), 3.93 (d, ^2J=6.1 Hz, 2H, H-12), 2.42 (m, 1H, H-4), 1.99 (m, 4H, H-4, H-5, and H-6), 1.55 (m, 1H, H-6), 1.53 (s, 3H, H-8), 1.44 (s, 3H, H-8), 0.20 (s, 9H, TMS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5 (C-10), 148.0 (C-2), 137.9 (C-15), 129.3 (C-17 or C-16), 125.7 (C-3), 117.7 (C-18), 117.5 (C-11), 114.4 (C-7), 113.3 (C-17 or C-16), 103.1 (C-13 or C-14), 102.6 (C-13 or C-14), 86.6 (C-1), 81.7 (C-9), 45.2 (C-12), 29.5 (C-6), 28.9 (C-8), 28.5 (C-8), 25.8 (C-4), 19.2 (C-5), 0.1 (TMS). GC−MS (CI-NH_4, positive ion): 394.4 [$MH^{+\bullet}$].

4.4.3. Benzyl[(2Z)-2-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-(trimethylsilyl)but-3-yn-1-yl]amine (**36**).*



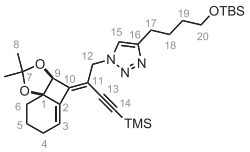
Benzylamine **1c** (110 mg, 0.28 mmol, 1.0 equiv), diisopropylamine (6 mL), $Pd(OAc)_2$ (3.2 mg, 0.01 mmol, 0.05 equiv), CuI (5.4 mg, 0.03 mmol, 0.10 equiv), PPh_3 (7.40 mg, 0.03 mmol, 0.10 equiv), and TMS−acetylene (60 μL, 0.42 mmol, 1.5 equiv). The crude brown residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=8:2 to pentane/Et_2O=6:4) to afford 106 mg (92%) of the desired product **36** as a yellow oil. R_f=0.55 (pentane/Et_2O=8:2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, H_{arom}), 6.28 (t, ^3J=3.8 Hz, 1H, H-3), 4.86 (s, 1H, H-9), 3.79 (s, 2H, H-15), 3.45 (d, ^2J=14.0 Hz, 1H, H-12), 3.39 (d, ^2J=14.0 Hz, 1H, H-12), 2.46−1.40 (m, 7H, H-4, H-5, H-6, and NH), 1.49 (s, 3H, H-8), 1.41 (s, 3H, H-8), 0.21 (s, 9H, TMS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0 (C-10), 140.6 (C-16), 138.1 (C-2), 128.5 (C-18 or C-17), 128.4 (C-18 or C-17), 127.0 (C-19), 125.6 (C-3), 117.1 (C-11), 114.3 (C-7), 103.6 (C-13 or C-14), 102.3 (C-13 or C-14), 86.4 (C-1), 81.6 (C-9), 52.8 (C-12), 49.6 (C-15), 29.6 (C-6), 28.9 (C-8), 28.4 (C-8), 25.8 (C-4), 19.2 (C-5), 0.2 (TMS). IR (neat) ν (cm^{-1})=3028, 2938, 2360, 2342, 2132, 1654, 1495, 1454, 1378, 1368, 1249, 1193, 1147, 1092, 1038, 999, 840, 758, 733, 697, 635. HRMS (ESI, 120 eV): calculated for $C_{25}H_{33}NO_2Si$ [$M^{+\bullet}$] 407.22806, found 407.22948 (Diff.: 3.49 ppm).

4.4.4. tert-Butyl [(2Z)-2-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-(trimethylsilyl)but-3-yn-1-yl]carbamate (**37**).*



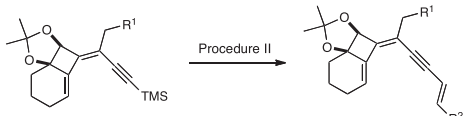
The **general procedure I** was followed, but 30 min irradiation at 110 °C were necessary for total conversion: Boc-protected amine **1d** (100 mg, 0.25 mmol, 1.0 equiv), diisopropylamine (5 mL), $Pd(OAc)_2$ (2.80 mg, 0.01 mmol, 0.05 equiv), CuI (6.60 mg, 0.03 mmol, 0.10 equiv), PPh_3 (4.80 mg, 0.03 mmol, 0.10 equiv), and TMS−acetylene (53 μL, 0.38 mmol, 1.5 equiv). The crude brown residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=9:1 to pentane/Et_2O=8:2) to afford 98 mg (94%) **37** as a yellow oil. R_f=0.34 (pentane/Et_2O=8:2). ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (t, ^3J=4.0 Hz, 1H, H-3), 4.97 (br s, 1H, NH), 4.90 (s, 1H, H-9), 3.88 (m, 2H, H-12), 2.45−1.39 (m, 6H, H-4, H-5, and H-6), 1.48 (s, 3H, H-8), 1.44 (s, 9H, H-17), 1.39 (s, 3H, H-8), 0.18 (s, 9H, TMS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (C-15), 150.7 (C-10), 137.8 (C-2), 125.9 (C-3), 114.7 (C-11), 114.3 (C-7), 102.7 (C-13 or C-14), 102.1 (C-13 or C-14), 86.4 (C-1), 81.4 (C-9), 79.3 (C-16), 41.7 (C-12), 29.4 (C-6), 28.7 (C-8), 28.4 (C-17), 28.3 (C-8), 25.8 (C-4), 19.1 (C-5), 0.0 (TMS). IR (neat) ν (cm^{-1})=3364, 2936, 2362, 2133, 1901, 1717, 1503, 1366, 1247, 1038, 839, 759. HRMS (ESI, 120 eV): calculated for $C_{23}H_{35}NO_4Si$ [$M^{+\bullet}$] 417.23354, found 417.23380 (Diff.: 0.64 ppm).

4.4.5. 4-(4-{[tert-Butyl(dimethyl)silyl]oxy}butyl)-1-[(2Z)-2-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-(trimethylsilyl)but-3-yn-1-yl]-1H-1,2,3-triazole (**38**).*



The **general procedure I** was followed using: triazole **1e** (161 mg, 0.30 mmol, 1.0 equiv), diisopropylamine (5 mL), $Pd(OAc)_2$ (3.40 mg, 0.02 mmol, 0.05 equiv), CuI (5.70 mg, 0.03 mmol, 0.10 equiv), PPh_3 (7.86 mg, 0.03 mmol, 0.10 equiv), and TMS−acetylene (63 μL, 0.45 mmol, 1.5 equiv). The crude brown residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=7:3 to pentane/Et_2O=5:5) to afford 100 mg (62%) of **38** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H, H-15), 6.33 (t, ^3J=4.0 Hz, 1H, H-3), 4.99 (d, ^2J=13.8 Hz, 1H, H-12), 4.91 (d, ^2J=13.8 Hz, 1H, H-12), 4.79 (s, 1H, H-9), 3.63 (t, ^3J=6.4 Hz, 2H, H-17 or H-20), 2.73 (t, ^3J=7.60 Hz, 2H, H-17 or H-20), 2.45−1.40 (m, 10H, H-4, H-5, H-6, H-18, and H-19), 1.51 (s, 3H, H-8), 1.43 (s, 3H, H-8), 0.89 (s, 9H, H-OTBS), 0.14 (s, 9H, TMS), 0.03 (s, 6H, H-OTBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (C-10), 148.3 (C-11), 137.5 (C-2), 128.2 (C-3), 121.0 (C-15), 114.9 (C-7), 110.8 (C-16), 103.5 (C-13 or C-14), 101.7 (C-13 or C-14), 86.4 (C-1), 81.3 (C-9), 63.0 (C-20), 50.6 (C-12), 32.5 (C-17, C-18 or C-19), 29.5 (C-6), 28.8 (C-8), 28.3 (C-8), 26.1 (C-OTBS), 26.0 (C-17, C-18 or C-19), 25.9 (C-17, C-18 or C-19), 25.7 (C-4), 19.1 (C-5), 18.5 (C-OTBS), −0.1 (TMS), −5.1 (C-OTBS).

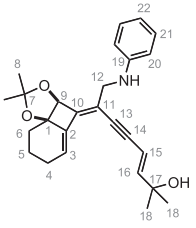
4.5. General procedure II for the synthesis of trienynes 2h–l



35 R^1 = NHPh
36 R^1 = NHBn
37 R^1 = NHBoc
38 R^1 = 1,2,3-triazole-4-$(CH_2)_4$OTBDMS

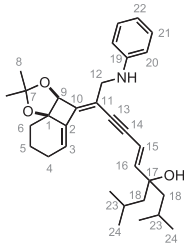
To a solution of acetylene (1.0 equiv) in MeOH (c=0.15 M) was added K_2CO_3 (1.0 equiv) at room temperature. The reaction mixture was stirred for 30 min and quenched with an aqueous, saturated solution of NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The intermediate product risks polymerization if dried completely. In order to keep the compound in solution, the solvent of the second step, MeCN (c=0.10 M) was added before the evaporation of the Et_2O was completed. The residual Et_2O was then evaporated and the remaining solution put in a Schlenk flask for the Sonogashira coupling. To the solution was added—under argon and at room temperature—the vinyl iodide (1.20 equiv), $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.15 equiv), and Et_3N (c=0.39 M, MeCN/Et_3N=8:2). The yellow solution turned to brown-red. After 10 min, ethanolamine (10 equiv/CuI) was added; the solution was stirred for additional 2 h and then quenched with an aqueous, saturated solution of $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N.

4.5.1. (3E,7Z)-8-Anilino-7-[(3aS,8aR*)-2,2-di-methyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-2-methyloct-3-en-5-yn-2-ol (**2h**).*



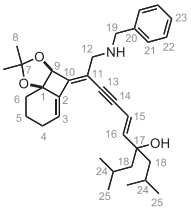
The **general procedure II** was followed using: dienyne **35** (100 mg, 0.25 mmol, 1.0 equiv), K_2CO_3 (35.1 mg, 0.25 mmol, 1.0 equiv), (*E*)-4-iodo-2-methylbut-3-en-2-ol[31] (64.6 mg, 0.31 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (14.7 mg, 0.01 mmol, 0.05 equiv), and CuI (7.20 mg, 0.04 mmol, 0.15 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=8:2 to pentane/Et_2O=4:6) and 73.8 mg (70%) of the desired product **2h** were isolated as an orange oil. R_f=0.22 (pentane/Et_2O=7:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (m, 2H, H_{arom}), 6.69 (m, 3H, H_{arom}), 6.22 (m, 2H, H-3 and H-16), 5.89 (d, ^3J=15.7 Hz, 1H, H-15), 4.86 (s, 1H, H-9), 4.26 (br s, 1H, NH), 3.95 (s, 2H, H-12), 2.41 (m, 1H, H-4a), 2.15 (m, 1H, H-4b), 2.51 (m, 4H, H-5 and H-6), 1.53 (s, 3H, H-8), 1.44 (s, 3H, H-8), 1.33 (s, 6H, H-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0 (C-16), 149.4 (C-10), 147.9 (C-19), 138.1 (C-2), 129.3 (C-20), 125.2 (C-3), 117.7 (C-22), 115.6 (C-11), 114.3 (C-7), 113.3 (C-21), 107.0 (C-15), 95.0 (C-14), 88.4 (C-13), 86.4 (C-1), 81.6 (C-9), 71.1 (C-17), 45.4 (C-12), 31.2 (2× C-18), 29.6 (C-6), 28.9 (C-8), 28.5 (C-8), 25.8 (C-4), 19.0 (C-5). GC–MS (CI-NH_4, positive ion): 406.4 [M+H^+•].

4.5.2. (5E,9Z)-10-Anilino-9-[(3aS,8aR*)-2,2-di-methyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-isobutyl-2-methyl-dec-5-en-7-yn-4-ol (**2i**).*



The **general procedure II** was followed using: dienyne **35** (102 mg, 0.26 mmol, 1.0 equiv), K_2CO_3 (36.0 mg, 0.26 mmol, 1.0 equiv), 4-[(*E*)-2-iodovinyl]-2,6-dimethylheptan-4-ol[19a] (92.0 mg, 0.31 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (15.0 mg, 0.01 mmol, 0.05 equiv), and CuI (7.40 mg, 0.04 mmol, 0.15 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=85:15 to pentane/Et_2O=7:3) and 86 mg (68%) of the desired product **2i** were isolated as an orange oil. R_f=0.23 (pentane/Et_2O=8:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 2H, H_{arom}), 6.70 (m, 3H, H_{arom}), 6.21 (br t, 1H, H-3), 6.09 (d, ^3J=16.0 Hz, 1H, H-16), 5.92 (d, ^3J=16.0 Hz, 1H, H-15), 4.86 (s, 1H, H-9), 4.27 (br s, 1H, NH), 3.96 (s, 2H, H-12), 2.41 (m, 1H, H-4a), 2.12 (m, 1H, H-4b), 1.72 (m, 6H, H-23, H-5, and H-6), 1.54 (s, 3H, H-8), 1.46 (s, 2H, H-18), 1.44 (s, 5H, H-8 and H-18), 0.96–0.90 (4s, 12H, H-24). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2 (C-16), 149.1 (C-10), 148.0 (C-19), 138.1 (C-2), 129.3 (C-20), 125.2 (C-3), 117.7 (C-22), 115.9 (C-11), 114.3 (C-7), 113.3 (C-21), 107.8 (C-15), 95.7 (C-14), 88.1 (C-13), 86.5 (C-1), 81.7 (C-9), 77.0 (C-17), 51.1 (2× C-18), 45.4 (C-12), 29.5 (C-6), 29.0 (C-8), 28.5 (C-8), 25.8 (C-4), 24.8–24.6 (4× C-24), 24.5 (C-23), 24.1 (C-23), 19.1 (C-5). IR (neat) ν (cm^{-1})=3541, 3396, 2951, 2867, 2360, 2241, 1602, 1505, 1466, 1380, 1368, 1254, 1191, 1147, 1062, 1037, 994, 961, 908, 862, 730, 691, 507. HRMS (ESI, 120 eV): calculated for $C_{32}H_{44}NO_3$ [M+H^+•] 489.32429, found 489.32517 (Diff.: 1.78 ppm).

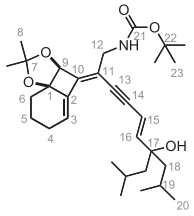
4.5.3. (5E,9Z)-10-(Benzylamino)-9-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta [1,2-d][1,3]dioxol-4(6H)-ylidene]-4-isobutyl-2-methyldec-5-en-7-yn-4-ol (**2j**).*



The **general procedure II** was followed using: dienyne **36** (130 mg, 0.32 mmol, 1.0 equiv), K_2CO_3 (44.0 mg, 0.32 mmol, 1.0 equiv), 4-[(*E*)-2-iodovinyl]-2,6-dimethylheptan-4-ol[19a] (114 mg, 0.38 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (18.0 mg, 0.02 mmol, 0.05 equiv), and CuI (9.10 mg, 0.05 mmol, 0.15 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/EtOAc=9:1 to pentane/EtOAc=7:3) and 117 mg (72%) of the desired product **2j** were isolated as an orange oil. R_f=0.28 (pentane/EtOAc=7:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H, H_{arom}), 6.23 (br t, 1H, H-3), 6.11 (d, ^3J=16.0 Hz, 1H, H-16), 5.93 (d, ^3J=16.0 Hz, 1H, H-15), 4.88 (s, 1H, H-9), 3.82 (s, 2H, H-12), 3.46 (AB system, 2H, J_{AB}=13.7 Hz, $\Delta\nu$=18.7 Hz, H-19), 2.43 (m, 1H, H-4a), 2.13 (m, 1H, H-4b), 1.72 (m, 7H, H-24, H-6, H-5, and NH), 1.50 (s, 3H, H-8), 1.47 (s, 2H, H-18), 1.45 (s, 2H, H-18), 1.41 (s, 3H, H-8), 0.96–0.91 (4s, 12H, H-25). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (C-16), 149.7 (C-10), 140.7 (C-20), 138.5 (C-2), 128.5 (C-22/C-21), 128.4 (C-

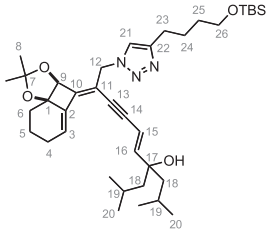
22/C-21), 127.0 (C-23), 124.9 (C-3), 117.5 (C-11), 114.3 (C-7), 107.9 (C-15), 95.5 (C-14), 88.5 (C-13), 86.3 (C-1), 81.6 (C-9), 77.1 (C-17), 53.0 (C-12), 51.3 (C-18), 51.2 (C-18), 49.9 (C-19), 29.6 (C-6), 29.0 (C-8), 28.6 (C-8), 25.8 (C-4), 24.8–24.6 (4× C-25), 24.1 (2× C-24), 19.2 (C-5). IR (neat) ν (cm^{-1})=3488, 3305, 3028, 2950, 2867, 2360, 2341, 1653, 149, 1455, 1379, 1368, 1254, 1193, 1147, 1091, 1037, 997, 962, 862, 744, 699, 529. HRMS (ESI, 120 eV): calculated for $C_{33}H_{46}NO_3$ [M+H$^+$•] 503.33994, found 503.34096 (Diff.: 2.01 ppm).

*4.5.4. (2Z,5Z)-2-((3aS,8aR)-2,2-Dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3] dioxol-4(6H)-ylidene)-7-isobutyl-9-methyldec-5-en-3-yne-1,7-diol (**2k**).*



The **general procedure II** was followed using: dienyne **37** (193 mg, 0.46 mmol, 1.0 equiv), K_2CO_3 (64.0 mg, 0.46 mmol, 1.0 equiv), 4-[(*E*)-2-iodovinyl]-2,6-dimethylheptan-4-ol[19a] (164 mg, 0.55 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (27.0 mg, 0.02 mmol, 0.05 equiv), and CuI (13.0 mg, 0.07 mmol, 0.15 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=85:15 to pentane/Et_2O=7:3) and 171 mg (72%) of the desired product **2k** were isolated as a yellow oil. R_f=0.31 (pentane/Et_2O=8:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (br s, 1H, H-3), 6.10 (d, ^3J=15.6 Hz, 1H, H-16), 5.90 (d, ^3J=15.6 Hz, 1H, H-15), 4.98 (br s, 1H, NH), 4.93 (s, 1H, H-9), 3.91 (m, 2H, H-12), 2.41 (m, 1H, H-4a), 2.11 (m, 1H, H-4b), 2.03–1.15 (m, 11H, OH, H-5, H-6, H-18, and H-19), 1.50 (s, 3H, H-8), 1.46 (s, 9H, H-23), 1.41 (s, 3H, H-8), 0.94–0.88 (4s, 12H, H-20). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C-21), 150.1 (C-16), 149.4 (C-10), 138.1 (C-2), 125.4 (C-3), 115.2 (C-11), 114.3 (C-7), 107.8 (C-15), 95.4 (C-14), 87.7 (C-13), 86.4 (C-1), 81.5 (C-9), 79.3 (C-22), 77.0 (C-17), 51.2 (2× C-18), 41.1 (C-12), 29.5 (C-6), 28.9 (C-8), 28.6 (C-23), 28.5 (C-8), 25.8 (C-4), 24.8–24.6 (4× C-20), 24.1 (2× C-19), 19.2 (C-5).

4.5.5. (5E,9Z)-10-[4-(4-{[tert-Butyl(dimethyl) silyl]oxy}butyl)-1H-1,2,3-triazol-1-yl]-9-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4] cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]-4-iso-butyl-2-methyldec-5-en-7-yn-4-ol (**2l**).*



The **general procedure II** was followed using: Dienyne **38** (100 mg, 0.19 mmol, 1.0 equiv), K_2CO_3 (26.0 mg, 0.19 mmol, 1.0 equiv), 4-[(*E*)-2-iodovinyl]-2,6-dimethylheptan-4-ol[19a] (66.0 mg, 0.22 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (11.0 mg, 0.01 mmol, 0.05 equiv), and CuI (5.30 mg, 0.03 mmol, 0.15 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O 6:4 to pentane/Et_2O=4:6) and 80.0 mg (66%) of the desired product **2l** were isolated as a yellow oil. R_f=0.24 (pentane/Et_2O=6:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H, H-21), 6.28 (t, ^3J=3.60 Hz, 1H, H-3), 6.03 (d, ^3J=16.0 Hz, 1H, H-16), 5.82 (d, ^3J=16.0 Hz, 1H, H-15), 5.14 (d, ^3J=14.4 Hz, 1H, H-12a), 4.99 (s, 1H, H-9), 4.90 (d, ^3J=14.4 Hz, 1H, H-12b), 3.60 (t, 2H, ^3J=6.40 Hz, H-26), 2.70 (t, 2H, ^3J=7.60 Hz, H-23), 2.40 (m, 1H, H-4a), 2.15 (m, 1H, H-4b), 2.05–1.35 (m, 15H, OH, H-5, H-6, H-18, H-19, H-24, and H-25), 1.49 (s, 3H, H-8), 1.41 (s, 3H, H-8), 0.90–0.85 (4s, 12H, H-20), 0.85 (s, 9H, TBS), 0.01 (s, 6H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (C-10), 150.9 (C-16), 148.3 (C-11), 137.6 (C-2), 127.6 (C-3), 120.8 (C-21), 114.8 (C-22), 111.2 (C-7), 107.3 (C-15), 96.2 (C-14), 86.6 (C-13), 86.2 (C-1), 81.2 (C-9), 76.9 (C-17), 63.0 (C-12), 51.0 (C-23), 50.6 (C-26), 32.4 (C-6), 29.4 (C-4), 28.8 (C-8), 28.2 (C-8), 26.1 (TBS), 25.9 (C-18/C-24/C-25), 25.8 (C-18/C-24/C-25), 25.6 (C-18/C-24/C-25), 24.7–24.6 (4× C-20), 24.0 (2× C-19), 19.0 (C-5), 18.4 (TBS), −5.2 (TBS). IR (neat) ν (cm^{-1})=3370, 2950, 2865, 2182, 1657, 1552, 1462, 1380, 1254, 1098, 1038, 963, 835, 775, 731, 661, 528.

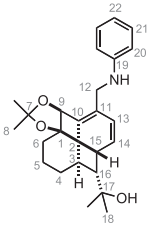
4.6. Experimental data for the first generation of compounds: fenestradienes 3, fenestranes 7, and cyclooctatrienes 8

The syntheses of the following starting materials and obtained products were described in earlier publications: **2a**–**g**, **3a**–**g**, **7a**–**g**, and **8a**.[19]

4.7. General procedure III for the synthesis of fenestradienes 3

To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (1.0 equiv) in EtOH (c=0.40 M)—at room temperature and under argon—was added a solution of $NaBH_4$ (1.0 equiv) in EtOH (c=1.22 M). The turquoise solution turned black and the formation of a gas was observed. In order to create the catalytic species in situ, the mixture was stirred for 1 h under H_2. A solution of the trienyne (1.0 equiv) and ethylenediamine (3.5 equiv) in EtOH (c=0.48 M) was then added. After the appropriate reaction time while stirring under H_2, the reaction mixture was filtered through a patch of Celite and the solvent was removed under reduced pressure. In some cases, the crude product was purified by flash chromatography over with 5% of Et_3N treated silica gel.

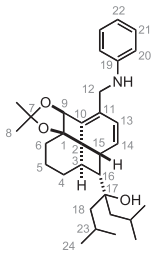
4.7.1. 2-[(1R,4aR*,7aS*,12R*)-8-(Anilinomethyl)-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-methanodibenzo[1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-12-yl]propan-2-olol (**3h**).*



The **general procedure III** was followed using: $Ni(OAc)_2.4H_2O$ (39.9 mg, 0.16 mmol, 1.0 equiv), $NaBH_4$ (6.0 mg, 0.16 mmol, 1.0 equiv), trienyne **2h** (65.0 mg, 0.16 mmol, 1.0 equiv), and ethylenediamine (0.06 mL, 0.56 mmol, 3.50 equiv). The reaction was repeated two times in order to achieve a complete conversion of the starting material. The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=8:2). 23.1 mg (51%) of the desired product **3h** were isolated as colorless oil, next to some traces of the starting material and the corresponding cyclooctatriene. R_f=0.13 (pentane/Et_2O=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 2H, H_{arom}), 6.70 (m, 3H, H_{arom}), 6.02 (m, 2H, H-14 and H-13), 5.05 (s, 1H, H-9), 4.42 (br s, 1H, NH), 3.89 (d, ^2J=16.1 Hz, 2H, H-12), 3.29 (m, 1H, H-15), 3.02 (m, 1H, H-3), 2.60 (t, ^3J=9.58 Hz, 1H, H-16), 2.00–1.76 (m, 4H, H-6, H-5a, and H-4a), 1.46 (s, 3H, H-8), 1.39 (s, 3H, H-18), 1.28 (s, 3H, H-8), 1.25 (m, 2H, H-5b and H-4b), 1.09 (s, 3H, H-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4 (C-19), 135.8 (C-10), 129.7 (C-14), 129.3 (C-20), 127.6 (C-11), 126.7 (C-13), 117.5 (C-22), 115.5 (C-7), 113.1 (C-21), 89.7 (C-1),

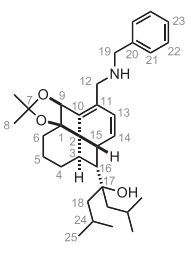
84.1 (C-9), 72.5 (C-17), 62.3 (C-16), 45.4 (C-12), 43.5 (C-2), 39.2 (C-3), 35.1 (C-15), 33.1 (C-6), 30.7 (C-4), 29.9 (C-8), 29.3 (C-8), 28.4 (C-18), 28.3 (C-18), 22.2 (C-5). IR (neat) ν (cm^{-1})=3382, 2971, 2932, 2861, 2361, 1689, 1602, 1508, 1443, 1379, 1351, 1202, 1076, 1015, 870, 770, 693, 509. HRMS (ESI, 120 eV): calculated for $C_{26}H_{33}NO_3$ [$M^{+\bullet}$] 407.24604, found 407.24715 (Diff.: 2.73 ppm).

4.7.2. 4-[(1R,4aR*,7aS*,12R*)-8-(Anilinomethyl)-6,6-dimethyl-1,2,3,4,7a,11-hexa-hydro-1,11-metha-nodibenzo[1,4:3,4]cyclobuta [1,2-d][1,3]dioxol-12-yl]-2,6-dimethylheptan-4-ol (**3i**).*



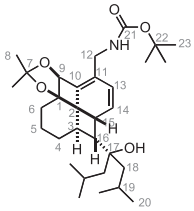
The **general procedure III** was followed using: $Ni(OAc)_2.4H_2O$ (38.1 mg, 0.15 mmol, 1.0 equiv), $NaBH_4$ (5.80 mg, 0.15 mmol, 1.0 equiv), trienyne **2i** (75.0 mg, 0.15 mmol, 1.0 equiv), and ethylenediamine (0.36 mL, 0.54 mmol, 3.50 equiv). The reaction was stirred for 3 d in order to achieve a complete conversion of the starting material. The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=9:1 to pentane/Et_2O=8:2) and 27.1 mg (36%) of the desired product **3i** were isolated as colorless oil. A fraction with ~7.5 mg (10%) of the corresponding cyclooctatriene mixed with impurities was also isolated. R_f=0.36 (pentane/Et_2O=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 2H, H_{arom}), 6.64 (m, 3H, H_{arom}), 6.02 (m, 2H, H-14 and H-13), 5.04 (s, 1H, H-9), 4.39 (br s, 1H, NH), 3.87 (d, ^2J=15.8 Hz, 1H, H-12), 3.71 (d, ^2J=16.1 Hz, 1H, H-12), 3.27 (m, 1H, H-15), 3.06 (m, 1H, H-3), 2.72 (t, ^3J=9.30 Hz, 1H, H-16), 2.05–1.58 (m, 8H, H-23, H-18a, H-6, H-5a, and H-4a), 1.46 (s, 3H, H-8), 1.37 (s, 3H, H-8), 1.47–1.08 (m, 5H, OH, H-18a, H-5b, and H-4b), 0.94 (m, 12H, H-24). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4 (C-19), 136.0 (C-10), 129.8 (C-14), 129.3 (C-20), 127.5 (C-11), 126.6 (C-13), 117.5 (C-22), 115.5 (C-7), 113.1 (C-21), 89.8 (C-1), 84.1 (C-9), 77.9 (C-17), 61.1 (C-16), 47.7 (C-18), 45.9 (C-12), 45.4 (C-18), 43.6 (C-2), 39.1 (C-3), 35.7 (C-15), 33.1 (C-6), 31.1 (C-4), 30.0 (C-8), 28.4 (C-8), 25.4 (C-23/C-24), 25.2 (C-23/C-24), 24.8 (C-23/C-24), 24.7 (C-23/C-24), 24.3 (C-23/C-24), 24.1 (C-23/C-24), 22.3 (C-5). IR (neat) ν (cm^{-1})=3566, 3375, 29,360, 2866, 2356, 1602, 1505, 1456, 1367, 1314, 1235, 1200, 1136, 1099, 1076, 908, 853, 730, 691, 506. HRMS (ESI, 120 eV): not stable, degradation.

4.7.3. 4-{(1R,4aR*,7aS*,12R*)-8-[(Benzylamino) methyl]-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-methanodibenzo[1,4:3,4]cyclobuta[1,2-d][1,3]di-oxol-12-yl}-2,6-dimethylheptan-4-ol (**3j**).*



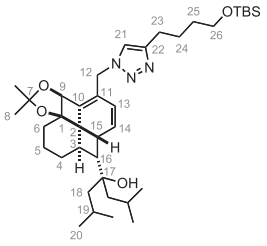
The **general procedure III** was followed using: $Ni(OAc)_2.4H_2O$ (23.8 mg, 0.10 mmol, 1.0 equiv), $NaBH_4$ (3.60 mg, 0.10 mmol, 1.0 equiv), trienyne **2j** (48.0 mg, 0.10 mmol, 1.0 equiv), and ethylenediamine (0.05 mL, 0.19 mmol, 3.50 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/EtOAc=9:1 to pentane/EtOAc=7:3) and 19.7 mg (41%) of the desired product **3j** were isolated as colorless oil, next to some traces of the corresponding cyclooctatriene. R_f=0.20 (pentane/EtOAc=7:3). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H, H_{arom}), 5.98 (m, 2H, H-14 and H-13), 5.16 (s, 1H, H-9), 3.82 (AB system, 2H, J_{AB}=13.3 Hz, $\Delta\nu$=28.8 Hz, H-12), 3.27 (AB system, 2H, J_{AB}=15.3 Hz, $\Delta\nu$=48.4 Hz, H-19), 3.26 (m, 1H, H-15), 3.08 (m, 1H, H-3), 2.60 (t, ^3J=9.40 Hz, 1H, H-16), 2.02–1.63 (m, 8H, H-24, H-18, H-6, H-5a, and H-4a), 1.42 (s, 3H, H-8), 1.30 (s, 3H, H-8), 1.24 (m, 4H, H-18, H-5b and H-4b), 0.98–0.86 (m, 12H, H-25). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5 (C-20), 135.8 (C-10), 129.1 (C-14), 128.8 (C-11), 128.5 (C-22/C-21), 128.2 (C-22/C-21), 127.5 (C-13), 127.0 (C-23), 115.4 (C-7), 89.9 (C-1), 84.3 (C-9), 77.3 (C-17), 61.1 (C-16), 53.7 (C-19/C-12), 50.2 (C-19/C-12), 47.7 (C-18), 45.8 (C-18), 43.7 (C-2), 39.2 (C-3), 35.7 (C-15), 33.2 (C-6), 31.3 (C-4), 30.0 (C-8), 28.4 (C-8), 25.4–24.1 (6C, C-25 and C-24), 22.2 (C-5). IR (neat) ν (cm^{-1})= 3548, 2950, 2865, 2363, 1665, 1453, 1367, 1234, 1200, 1135, 1099, 1078, 1047, 1028, 1001, 854, 735, 698. HRMS (ESI, 120 eV): calculated for $C_{33}H_{48}NO_3$ [$M+H^{+\bullet}$] 505.35559, found 505.35773 (Diff.: 4.23 ppm).

*4.7.4. tert-Butyl{[(1R,4aR,7aS,11R,12R)-12-(1-hydroxy-1-isobutyl-3-methylbutyl)-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-methanodibenzo [1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-8-yl]methyl} carbamate (**3k**).*



The **general procedure III** was followed using: $Ni(OAc)_2.4H_2O$ (100 mg, 0.40 mmol, 3.0 equiv), $NaBH_4$ (15.2 mg, 0.40 mmol, 3.0 equiv), trienyne **2k** (69.0 mg, 0.13 mmol, 1.0 equiv), and ethylenediamine (0.09 mL, 1.37 mmol, 10.5 equiv). The reaction was stirred for 16 h. The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=9:1 to pentane/Et_2O=8:2) and 36.7 mg (53%) of the desired product **3k** were isolated as colorless oil. A fraction with ~7.5 mg (11%) of the starting material was also isolated. R_f=0.42 (pentane/Et_2O=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 2H, H-14, H-13), 5.06 (s, 1H, H-9), 5.04 (br s, 1H, NH), 3.90 (m, 1H, H-12a), 3.56 (m, 1H, H-12b), 3.18 (m, 1H, H-15), 3.00 (m, 1H, H-3), 2.64 (t, ^3J=9.60 Hz, 1H, H-16), 2.00–1.54 (m, 7H, OH, H-19, H-6, H-5a, H-4a), 1.38 (s, 9H, H-23), 1.37 (s, 3H, H-8), 1.27 (s, 3H, H-8), 1.47–1.05 (m, 6H, H-18, H-5a, H-4a), 0.90–0.81 (m, 12H, H-20). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (C-21), 135.9 (C-10), 130.0 (C-14), 127.7 (C-11), 126.3 (C-13), 115.7 (C-7), 89.9 (C-1), 83.9 (C-9), 79.3 (C-17), 77.8 (C-22), 61.2 (C-16), 47.7 (C-18), 46.2 (C-18), 45.9 (C-12), 43.6 (C-2), 39.1 (C-3), 35.6 (C-15), 33.2 (C-6), 31.3 (C-4), 29.9 (C-8), 28.5 (C-23), 28.4 (C-8), 25.4–24.0 (C-20 and C-19), 22.4 (C-5). IR (neat) ν (cm^{-1})=3565, 3367, 2930, 2360, 1704, 1506, 1456, 1366, 1237, 1165, 1099, 1078, 1042, 919, 854, 733, 647, 510. HRMS (ESI, 120 eV): calculated for $C_{31}H_{49}NO_5$ [$M^{+\bullet}$] 515.36107, found 515.36022 (Diff.: 1.65 ppm).

4.7.5. 4-((1R,4aR*,7aS*,12R*)-8-{[4-(4-{[tert-Butyl(dimethyl)silyl] oxy}butyl)-1H-1,2,3-triazol-1-yl]methyl}-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-methanodibenzo-[1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-12-yl)-2,6-dimethylheptan-4-ol (**3l**).*

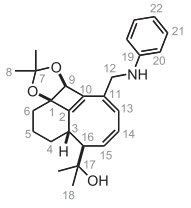


The **general procedure III** was followed using: $Ni(OAc)_2 \cdot 4H_2O$ (30.2 mg, 0.12 mmol, 1.0 equiv), $NaBH_4$ (4.60 mg, 0.12 mmol, 1.0 equiv), trienyne **2l** (79.0 mg, 0.12 mmol, 1.0 equiv), and ethylenediamine (0.28 mL, 0.42 mmol, 3.50 equiv). The reaction was stirred for 72 h. The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=6:4 to pentane/Et_2O=2:8). 21.8 mg (28%) of the desired product **3l** and 37.9 mg (50%) of the starting material **2l** were isolated. The two products were not separable, significant peaks could however be identified in the ^1H NMR spectrum. R_f=0.22 (pentane/Et_2O=6:4). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H, H-21), 6.03 (m, 1H, H-14 or H-13), 5.84 (m, 1H, H-14 or H-13), 5.12 (m, 1H, H-12a), 4.98 (s, 1H, H-9), 3.87 (m, 1H, H-12b), 3.62 (t, 2H, H-26), 3.23 (m, 1H, H-15), 3.10 (m, 1H, H-3), 2.72 (m, 3H, H-23, H-16), 2.05–1.58 (m, 17H, OH, H-25, H-24, H-19, H-18, H-6, H-5 and H-4), 1.43 (s, 3H, H-8), 1.33 (s, 3H, H-8), 0.95–0.90 (4s, 12H, H-20), 0.87 (s, 9H, TBS), 0.03 (s, 6H, TBS). HRMS (ESI, 120 eV): calculated for $C_{28}H_{63}N_3O_4Si$ [$M^{+\bullet}$] 653.4588, found 653.46042 (Diff.: 2.50 ppm).

4.8. General procedure IV for the transformation of fenestradienes 3h and 3j to access cyclooctatrienes 8

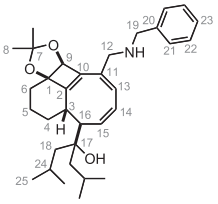
The fenestradienes **3** were dissolved in benzene (c=0.042 M) in an appropriate microwave vial. The vial was sealed with a Teflon cap and degassed with two freeze–pump–thaw cycles. Then, the vial was irradiated in the microwave for 50 min at 110 °C. The reaction mixture was then filtered through Celite and then concentrated under vacuum. The crude product was purified by flash column chromatography.

4.8.1. 2-[(3aR,4S*,5R*,9bS*)-9-(Anilinomethyl)-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propanocyclo-octa[3,4]cyclobuta[1,2-d][1,3]dioxol-5-yl]propan-2-ol (**8h**).*



The **general procedure IV** was followed using: fenestradiene **3h** (23.0 mg, 0.06 mmol, 1.0 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=8:2 to pentane/Et_2O=6:4) and 21.7 mg (94%) of the desired product **8h** were isolated as a yellow oil. R_f=0.24 (pentane/EtOAc=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 2H, H_{arom}), 6.68 (m, 3H, H_{arom}), 6.05 (d, ^3J=4.50 Hz, 1H, H-13), 5.95 (dd, ^3J=11.2 Hz, ^3J=4.50 Hz, 1H, H-14), 5.85 (m, 1H, H-15), 4.88 (s, 1H, H-9), 3.92 (AB system, 2H, J_{AB}=14.3 Hz, $\Delta\nu$=49.1 Hz, H-12), 3.86 (br s, 1H, NH), 2.62 (m, 1H, H-3), 2.40 (t, ^3J=10.1 Hz, 1H, H-16), 2.05 (m, 2H, H-6a and H-4a), 1.67 (m, 3H, H-6b and H-5), 1.40 (s, 3H, H-8), 1.38 (s, 3H, H-8), 1.25 (s, 3H, H-18), 1.11 (s, 3H, H-18), 1.08 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (C-2), 148.0 (C-19), 140.4 (C-15), 137.4 (C-10), 132.2 (C-11), 129.3 (C-20), 127.8 (C-13), 127.3 (C-14), 117.8 (C-22), 114.8 (C-7), 113.9 (C-21), 85.2 (C-1), 84.1 (C-9), 72.8 (C-17), 52.0 (C-16), 48.6 (C-12), 41.1 (C-3), 34.1 (C-4), 33.5 (C-6), 30.9 (C-18), 29.8 (C-8), 28.8 (C-8), 24.2 (C-18), 23.9 (C-5). HRMS (ESI, 120 eV): calculated for $C_{26}H_{33}NO_3$ [$M]^{+\bullet}$ 407.24765, found 407.24604 (Diff.: 3.95 ppm).

4.8.2. 4-{(3aR,4S*,5R*,9bS*)-9-[(Benzylamino) methyl]-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propa-nocycloocta[3,4]cyclobuta [1,2-d][1,3]dioxol-5-yl}-2,6-dimethylheptan-4-ol (**8j**).*



The **general procedure IV** was followed using: fenestradiene **3j** (20.0 mg, 0.04 mmol, 1.0 equiv). The crude product was purified by flash chromatography over silica gel, treated with 5% of Et_3N (elution: pentane/Et_2O=9:1 to pentane/Et_2O=7:3), and 13.0 mg (60%) of the desired product **8j** were isolated as a yellow oil. R_f=0.43 (pentane/EtOAc=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H, H_{arom}), 5.97 (m, 2H, H-14 and H-13), 5.63 (t, ^3J=9.70 Hz, 1H, H-15), 4.94 (s, 1H, H-9), 3.79 (AB system, 2H, J_{AB}=13.5 Hz, $\Delta\nu$=19.7 Hz, H-12), 3.44 (AB system, 2H, J_{AB}=13.5 Hz, $\Delta\nu$=69.9 Hz, H-19), 2.81 (t, ^3J=9.70 Hz, 1H, H-16), 2.70 (m, 1H, H-3), 1.51 (m, 8H, H-24, H-6, H-5, and H-4), 1.39 (s, 3H, H-8), 1.36 (s, 3H, H-8), 0.98 (s, 2H, H-18), 0.96–0.94 (m, 12H, H-25), 0.84 (s, 2H, H-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3 (C-2), 140.6 (C-20), 140.0 (C-15), 138.1 (C-10), 134.0 (C-11), 128.4 (C-22/C-21), 128.3 (C-22/C-21), 127.6 (C-13), 127.5 (C-14), 127 (C-23), 114.6 (C-7), 85.2 (C-1), 84.1 (C-9), 77.9 (C-17), 53.0 (C-12), 52.6 (C-12), 49.2 (C-19), 47.7 (C-18), 43.9 (C-18), 40.7 (C-3), 34.1 (C-6), 33.5 (C-4), 29.8 (C-8), 28.8 (C-8), 25.6 (C-24), 25.5 (C-24), 25.0–23.1 (4× C-25), 24.0 (C-5). IR (neat) ν (cm^{-1})=2928, 2866, 2359, 1726, 1435, 1366, 1259, 1232, 1203, 1184, 1142, 1028, 870, 840, 735, 698, 653. HRMS (ESI, 120 eV): calculated for $C_{33}H_{47}NO_3$ [$M^{+\bullet}$] 505.3559, found 505.35447 (Diff.: 2.23 ppm).

4.9. Experimental data for fenestradienes 4 (cyclooctatrienes 12 and trienynes 2 as a byproducts)

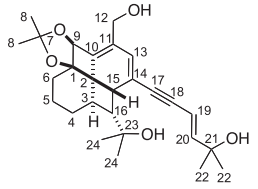
The syntheses of the fenestradienes **4a–b**, **4g–i**, **4m–n**, **4p–t**, **4v–w**, cyclooctatrienes **12a–b**, **12g–i**, **12m–n**, **12p–t** and **12v–w**, trienynes **2a–d** and **9m–n, 9r–s** and **9w** were described in earlier publications.[19,21,22]

4.10. General procedure V for fenestradienes 4 and cyclooctatrienes 12

In a 2–5 mL microwave vial were added the corresponding compound **1** (50 mg, 1 equiv), $Pd(OAc)_2$ (0.05 equiv), copper iodide (0.1 equiv), and PPh_3 (0.1 equiv). The vial was sealed with a Teflon cap and the reaction mixture was then dissolved in diisopropylamine (0.05 M). The reaction mixture was placed under argon, frozen in liquid nitrogen and put under vacuum. The O_2 liberation proceeds when the temperature rises back to rt. The operation was repeated three times. Then, the enyne (3.0 equiv) was added to the reaction mixture. The vial was irradiated in the microwave (MW), the time and temperature of each example being indicated in the following procedures. The reaction mixture was then filtered

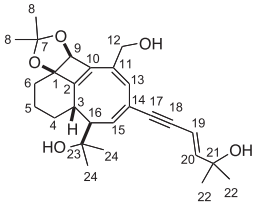
through Celite to eliminate the metal traces and then concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel.

4.10.1. (3E)-6-[(1R,4aR*,7aS*,11S*,12R*)-8-(Hydroxymethyl)-12-(1-hydroxy-1-methylethyl)-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-methano dibenzo[1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-10-yl]-2-methylhex-3-en-5-yn-2-ol (**4j**).*



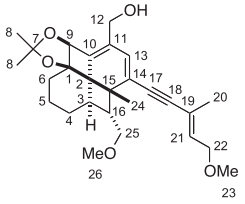
The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diisopropyl-amine (3.1 mL), and enyne **22** (55 mg, 0.50 mmol, 3 equiv) After a microwave irradiation of 1 h at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/AcOEt=9:1 to 5:5) and the desired product **4j** was isolated (23 mg, 32%, estimated yield) with inseparable, non-identified products, along with a second fraction with the corresponding cyclooctatriene **12j** (25 mg, 34%) and a third fraction with the trienyne **9j** (18 mg, 32%) as orange oils; R_f=0.12 (pentane/AcOEt=6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, ^3J=16.0 Hz, 1H, H-20), 6.22 (s, 1H, H-13), 5.86 (d, ^3J=16.0 Hz, 1H, H-19), 4.22 (s, 1H, H-9), 4.29–4.15 (m, 2H, H-12), 3.43 (d, ^3J=10.8 Hz, 1H, H-15), 2.82 (dd, ^3J=15.6 Hz, ^3J=10.8 Hz, 1H, H-3), 2.71 (dd, ^3J=10.8 Hz, ^3J=10.8 Hz, 1H, H-16), 2.00–1.78 (m, 5H, CH_2), 1.42 (s, 3H, H-8), 1.35 (s, 3H, H-8), 1.25 (s, 6H, H-22), 1.21 (s, 6H, H-24), 0.89–0.81 (m, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3 (C-20), 137.3 (C-10), 132.6 (C-11), 131.2 (C-13), 122.1 (C-14), 116.3 (C-7), 106.4 (C-19), 92.9 (C-18), 91.7 (C-1), 90.3 (C-17), 83.8 (C-9), 72.8 (C-21 or 23), 71.2 (C-21 or 23), 63.1 (C-12), 63.0 (C-3), 44.5 (C-2), 41.1 (C-22), 38.8 (C-24), 32.7 (C-6), 30.8 (C-4), 29.8 (C-8), 29.2 (C-8), 28.1 (C-22), 26.5 (C-24), 22.1 (C-5). IR ($CDCl_3$) ν (cm^{-1})=2929, 2251, 1670, 1452, 1371, 1223, 1141, 1075, 905, 725, 648.

4.10.2. (3E)-6-[(3aR,4S*,5R*,9bS*)-9-(Hydroxy-methyl)-5-(1-hydroxy-1-methylethyl)-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclo-buta[1,2-d][1,3]dioxol-7-yl]-2-methylhex-3-en-5-yn-2-ol (**12j**).*



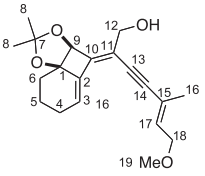
R_f=0.05 (pentane/AcOEt=6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (d, ^3J=16.0 Hz, 1H, H-20), 6.02 (s, 1H, H-13), 5.98 (d, ^3J=9.5 Hz, 1H, H-15), 5.80 (d, ^3J=16.0 Hz, 1H, H-19), 4.92 (s, 1H, H-9), 4.29 (AB system, J_{AB}=16.0 Hz, $\Delta\nu$=12.0 Hz, 2H, H-12), 2.64–2.63 (m, 2H, H-3, H-16), 2.23–2.20 (m, 1H, H-6a), 2.10–2.07 (m, 1H, H-4a), 1.79–1.66 (m, 3H, H-4b, H-5), 1.40 (s, 3H, H-8), 1.32 (s, 3H, H-8), 1.32–1.17 (m, 1H, H-6b), 1.27 (s, 6H, H-22), 1.16 (s, 6H, H-24). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (C-2), 150.3 (C-20), 145.6 (C-15), 136.9 (C-14), 135.6 (C-10), 126.3 (C-13), 121.9 (C-11), 115.1 (C-7), 106.9 (C-19), 89.9 (C-18), 86.3 (C-17), 85.3 (C-1), 84.1 (C-9), 73.0 (C-23), 71.2 (C-21), 65.0 (C-12), 52.3 (C-16), 41.0 (C-3), 34.0 (C-6), 33.4 (C-4), 31.2 (C-22), 29.82 (C-8), 28.82 (C-8), 24.32 (C-24), 23.8 (C-5). IR ($CDCl_3$) ν (cm^{-1})=3383, 2929, 2856, 2359, 2246, 1461, 1370, 1143, 1019, 905, 728, 648. HRMS (ESI, 120 eV) calculated $C_{27}H_{36}O_5$ $[M]^+$ 440.25627, found 440.25613 (Diff.: 0.33 ppm).

4.10.3. {(1R,4aR*,7aS*,11S*,12R*)-12-(Methoxy-methyl)-10-[(3E)-5-methoxy-3-methylpent-3-en-1yn-1-yl]-6,6,11-trimethyl-1,2,3,4,7a,11-hexahydro-1,11-methanodibenzo[1,4:3,4]cyclobuta[1,2-d][1,3] dioxol-8-yl}methanol (**4l**).*



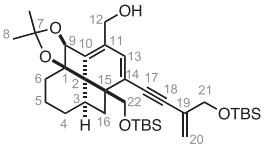
The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diisopropylamine (3.1 mL), and enyne **24** (55 mg, 0.5 mmol, 3 equiv). After 1 h of microwave irradiation at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/EtOAc=9:1) and the desired product **4l** was isolated as an orange oil (23 mg, 32%) along with a second fraction with the corresponding trienyne **9l** (31 mg, 57%, NMR estimated yield) as an orange oil and 20% (NMR estimated yield) of the starting material **1a**; R_f=0.27 (pentane/Et_2O=6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H, H-13), 5.92 (td, ^3J=8.8 Hz, ^4J=1.2 Hz, 1H, H-21), 5.14 (s, 1H, H-9), 4.23 (sl, 2H, H-12), 4.01 (d, ^3J=8.8 Hz, 2H, H-22), 3.83 (d, ^2J=10.7 Hz, 1H, H-25a), 3.68–3.64 (m, 1H, H-25b), 3.37–3.31 (m, 1H, H-16), 3.36 (s, 3H, H-23 or H-26), 3.31 (s, 3H, H-23 or H-26), 3.12–3.02 (m, 1H, H-16), 2.40–0.88 (m, 6H, H-4, H-5, H-6), 1.84 (s, 3H, H-20), 1.51 (s, 3H, H-24), 1.41 (s, 3H, H-8), 1.39 (s, 3H, H-8).

4.10.4. (2Z,5E)-2-((3aS,8aR*)-2,2-Dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene)-7-methoxy-5-methylhept-5-en-3-yn-1-ol (**9l**).*



R_f=0.18 (pentane/Et_2O=6:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, ^3J=3.3 Hz, 1H, H-3), 5.96 (td, ^3J=6.3 Hz, ^4J=1.6 Hz, 1H, H-17), 4.99 (s, 1H, H-9), 4.27 (d, ^3J=4.4 Hz, 2H, H-12), 4.26 (d, ^3J=6.3 Hz, 2H, H-18), 3.33 (s, 3H, H-19), 2.45–2.38 (m, 1H, H-4a), 2.22–2.09 (m, 1H, H-4b), 2.01–1.95 (m, 1H, H-6a), 1.96–1.86 (m, 2H, H-5), 1.86 (d, ^4J=1.6 Hz, 3H, H-16), 1.64–1.58 (m, 1H, H-6b), 1.52 (s, 3H, H-8), 1.41 (s, 3H, H-8).

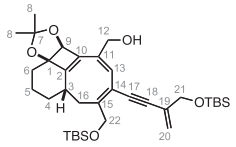
4.10.5. {(1R,4aR*,7aS*,11R*)-11-({[tert-Butyl (di-methyl)silyl]oxy}methyl)-10-[3-({[tert-butyl (dimethyl)silyl]oxy}methyl)but-3-en-1-yn-1-yl]-6,6-dimethyl-1,2,3,4,7a,11-hexahydro-1,11-metha-nodibenzo[1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-8-yl}methanol (**4o**).*



The **general procedure V** was followed using: propargylic alcohol **1a** (53.0 mg, 0.18 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.0 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4.70 mg, 0.02 mmol, 0.10 equiv), CuI (3.40 mg, 0.02 mmol, 0.10 equiv), and enyne **27** (106 mg, 0.54 mmol, 3.0 equiv). The mixture was irradiated in the microwave

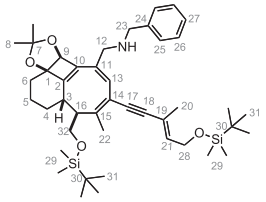
for 60 min at 100 °C. The crude residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=7:3 to pentane/Et_2O=5:5) to afford 12.4 mg (23%) of **1a**, 19.7 mg (18%) of the desired fenestradiene **4o** and 15.2 mg (14%) of the cyclooctatriene **12o** as impure yellow oils. However, the significant signals could be identified in the ^1H NMR spectra. R_f=0.33 (pentane/Et_2O=7:3). ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H, H-13), 5.57 (br s, 1H, H-20a), 5.37 (br s, 1H, H-20b), 5.09 (s, 1H, H-9), 4.16 (m, 6H, H-22, H-21, H-12), 2.55 (m, 1H, H-3), 2.25 (m, 2H, H-16), 2.21–1.15 (m, OH, H-4, H-5, and H-6), 1.38 (s, 3H, H-8), 1.37 (s, 3H, H-8), 0.95 (s, TBS), 0.90 (s, TBS), 0.10 (s, TBS), 0.07 (s, TBS).

4.10.6. {(3aR,4S*,9bS*)-6-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)but-3-en-1-yn-1-yl]-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl}methanol (**12o**).*



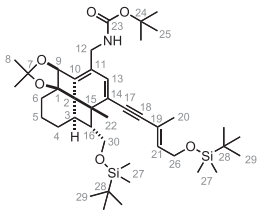
R_f=0.27 (pentane/Et_2O=7:3). ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H, H-13), 5.57 (br s, 1H, H-20a), 5.41 (br s, 1H, H-20b), 5.00 (s, 1H, H-9), 4.78 (d, J=12.2 Hz, 1H, H-22, H-21 or H-12), 4.53 (d, J=12.2 Hz, 1H, H-22, H-21 or H-12), 4.29 (s, 2H, H-22, H-21 or H-12), 4.15 (s, 2H, H-22, H-21 or H-12), 2.65 (m, 1H, H-3), 2.45 (m, 1H, H-16a), 2.11 (m, 2H, H-4a and H-16b), 1.87 (m, 1H, OH, H-4b, H-5 or H-6), 1.72 (m, 4H, OH, H-4b, H-5 or H-6), 1.40 (s, 3H, H-8), 1.34 (s, 3H, H-8), 1.05 (m, 1H, OH, H-4b, H-5 or H-6), 0.91 (s, 18H, TBS), 0.09 (s, 12H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (C-2), 151.9 (C-15), 136.9 (C-10), 133.1 (C-11), 131.1 (C-14), 127.1 (C-13), 118.9 (C-20), 116.9 (C-19), 115.1 (C-7), 91.9 (C-18), 88.5 (C-17), 84.7 (C-1), 84.5 (C-9), 66.1 (C-12/C-21/C-22), 65.5 (C-12/C-21/C-22), 65.1 (C-12/C-21/C-22), 38.6 (C-3), 34.1 (C-16/C-4/C-6), 33.4 (C-16/C-4/C-6), 33.1 (C-16/C-4/C-6), 29.6 (C-8), 29.0 (C-8), 26.0 (2× TBS), 23.3 (C-5), 18.5 (2× TBS), −5.2 (2× TBS). IR (neat) ν (cm^{-1})=3455, 2929, 2856, 2360, 1619, 1462, 1378, 1253, 1205, 1146, 1074, 1035, 939, 902, 834, 774, 738, 669, 515. HRMS (ESI, 120 eV): calculated for $C_{35}H_{56}O_5Si_2$ $[M]^+$ 612.36663, found 612.36541 (Diff.: 1.98 ppm).

4.10.7. Benzyl{[(3aR,4S*,5S*,9bS*)-5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-7-((3E)-5-{[tert-butyl(dimethyl)silyl]oxy}-3-methylpent-3-en-1-yn-1-yl)-2,2,6-trimethyl-4,9b-dihydro-5H-3a,4-propano-cycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl] methyl}amine (**12u**).*



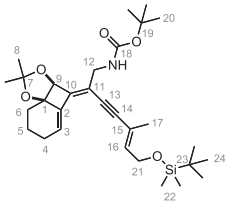
The **general procedure V** was followed using: benzylamine **1c** (40.0 mg, 0.10 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.15 mg, 0.005 mmol, 0.05 equiv), PPh_3 (3.0 mg, 0.01 mmol, 0.10 equiv), CuI (2.0 mg, 0.01 mmol, 0.10 equiv), and enyne **25** (65.0 mg, 0.31 mmol, 3.0 equiv). The mixture was irradiated in the microwave for 60 min at 100 °C. The crude residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=8:2 to pentane/Et_2O=6:4). A mixture of 58.0 mg (77%) containing both the desired fenestradiene **4u** and the corresponding cyclooctatriene **12u** was isolated as a yellow oil. Those two products could not be separated (**4u**/**12u** ~ 2:1), however, cyclooctatriene **12u** can be described. R_f=0.45 (pentane/EtOAc=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H, H_{arom}), 5.96 (s, 1H, H-13), 5.87 (t, ^3J=6.20 Hz, 1H, H-21), 4.99 (s, 1H, H-9), 4.24 (d, ^3J=6.20 Hz, 2H, H-28), 3.78 (m, 2H, H-23), 3.63 (s, 2H, H-32), 3.45 (m, 2H, H-12), 2.69 (m, 1H, H-3), 2.49 (m, 1H, H-16), 2.12 (m, 1H, H-6a), 1.99 (s, 3H, H-22), 1.83 (m, 1H, H-4a), 1.79 (s, 3H, H-20), 1.69 (m, 3H, H-6b and H-5), 1.39 (s, 3H, H-8), 1.32 (s, 3H, H-8), 1.05 (m, 1H, H-4b), 0.90 (s, 9H, H-31), 0.85 (s, 9H, H-31), 0.07 (s, 6H, H-29), 0.02 (s, 6H, H-29). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (C-2), 152.0 (C-15), 140.6 (C-10), 138.0 (C-24), 135.7 (C-21), 132.0 (C-11), 128.5 (C-26/C-25), 128.4 (C-26/C-25), 128.3 (C-13), 127.0 (C-27), 119.5 (C-14), 118.4 (C-19), 114.7 (C-7), 95.5 (C-18), 86.9 (C-1), 84.5 (C-17), 84.3 (C-9), 62.0 (C-32), 60.2 (C-28), 53.3 (C-12), 52.7 (C-23), 46.4 (C-3), 39.3 (C-16), 33.5 (C-6), 31.8 (C-4), 29.7 (C-8), 28.6 (C-8), 26.1 (6× C-31), 23.5 (C-5), 18.5 (C-30), 18.2 (C-30), 18.0 (C-22), 17.7 (C-20), −5.25 (4× C-29). HRMS (ESI, 120 eV): calculated for $C_{44}H_{67}NO_4Si_2$ $[M]^{+\bullet}$ 729.46086, found 729.46279 (Diff.: 2.65 ppm).

4.10.8. tert-butyl {[(1R,4aR*,7aS*,11S*,12R*)-12-({[tert-butyl(dimethyl)silyl]oxy}methyl)-10-((3E)-5-{[tert-butyl(dimethyl)silyl]oxy}-3-methylpent-3-en-1-yn-1-yl)-6,6,11-trimethyl-1,2,3,4,7a,11-hexa-hydro-1,11-methanodibenzo[1,4:3,4]cyclobuta[1,2-d][1,3]dioxol-8-yl]methyl} carbamate (**4z**).*



The **general procedure V** was followed using: Boc-protected amine **1d** (52.0 mg, 0.13 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.5 mg, 0.01 mmol, 0.05 equiv), PPh_3 (3.40 mg, 0.01 mmol, 0.10 equiv), CuI (2.50 mg, 0.01 mmol, 0.10 equiv), and enyne **25** (82 mg, 0.39 mmol, 3.0 equiv). The mixture was irradiated in the microwave for 60 min at 100 °C. The crude residue was purified by flash chromatography over silica gel (elution: pentane/EtOAc=9:1 to pentane/EtOAc=8:2). The following products were isolated: an impure mixture of the trienyne with another product, probably the cyclooctatriene (14 mg), 30.9 mg (45%) of the trienyne **9z** as a yellow oil and 13.2 mg (13%) of the fenestradiene **4z** mixed with impurities. R_f=0.54 (pentane/Et_2O=8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H, H-13), 5.87 (t, ^3J=4.80 Hz, 1H, H-21), 5.26 (br s, 1H, NH), 5.06 (s, 1H, H-9), 4.25 (d, ^3J=6.0 Hz, 2H, H-26), 3.98 (m, 2H, H-30a and H-12a), 3.67 (m, 1H, H-12b), 3.52 (m, 1H, H-30b), 2.25 (m, 2H, H-16 and H-3), 2.01–1.15 (m, 6H, H-6, H-5, and H-4), 1.80 (s, 3H, H-20), 1.46 (s, 9H, H-25), 1.43 (s, 3H, H-22), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-8), 0.90 (s, 9H, H-29), 0.86 (s, 9H, H-29), 0.07 (s, 6H, H-27), 0.01 (s, 6H, H-27).

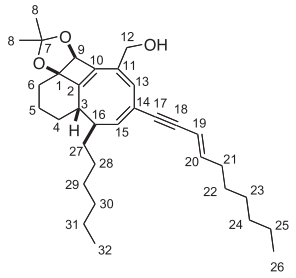
4.10.9. tert-butyl{(2Z,5E)-7-{[tert-Butyl(dimethyl)silyl]oxy}-2-[(3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta[1,2-d][1,3]dioxol-4(6H)-ylidene]hept-5-en-3-yn-1-yl}carbamate (**9z**).*



R_f=0.46 (pentane/Et_2O=82). ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (t, ^3J=3.70 Hz, 1H, H-3), 5.93 (t, ^3J=6.10 Hz, 1H, H-16), 4.96 (br s, 1H, NH), 4.92 (s, 1H, H-9), 4.26 (d, ^3J=6.10 Hz, 2H, H-21), 3.92 (m, 2H, H-

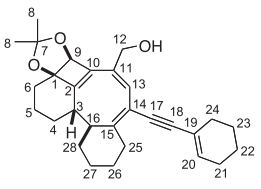
12), 2.41 (m, 1H, H-4a), 2.14 (m, 1H, H-4b), 2.02–1.73 (m, 3H, H-6a and H-5), 1.81 (s, 3H, H-17), 1.58 (m, 1H, H-6b), 1.49 (s, 3H, H-8), 1.45 (s, 9H, H-20), 1.41 (s, 3H, H-8), 0.90 (s, 9H, H-24), 0.07 (s, 6H, H-22). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C-18), 149.4 (C-10), 138.1 (C-2), 137.8 (C-16), 125.4 (C-3), 118.9 (C-15), 115.0 (C-11), 114.3 (C-7), 99.1 (C-14), 86.5 (C-1), 85.1 (C-19), 81.5 (C-9), 79.4 (C-13), 60.2 (C-21), 41.8 (C-12), 29.5 (C-6), 2 8.9 (C-8), 28.6 (C-20), 28.5 (C-8), 26.1 (C-24), 25.8 (C-4), 19.2 (C-5), 18.5 (C-23), 17.7 (C-17), −5.00 (C-22). IR (neat) ν (cm^{-1})=3367, 2930, 2857, 1718, 1502, 1456, 1367, 1247, 1168, 1092, 1062, 833, 775, 666, 527. HRMS (ESI, 120 eV): calculated for $C_{30}H_{47}NO_5Si$ $[M]^{+\bullet}$ 529.3224, found 529.3235 (Diff.: 2.16 ppm).

4.10.10. {(3aR,4S*,5R*,9bS*)-7-[(3E)-Dec-3-en-1-yn-1-yl]-5-hexyl-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclobuta [1,2-d][1,3] dioxol-9-yl}methanol (**12c**).*



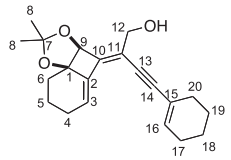
The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diiso-propylamine (3.1 mL), and enyne **15** (68 mg, 0.50 mmol, 3 equiv). After a microwave irradiation of 3 h at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/AcOEt=9:1) and the cyclooctatriene **12c** was isolated as orange oil (59 mg, 72%); R_f=0.34 (pentane/Et_2O=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14–6.07 (m, 1H, H-20), 5.99 (s, 1H, H-13), 5.98 (d, ^3J=8.8 Hz, 1H, H-15), 5.55 (dt, ^3J=16.0 Hz, ^4J=1.6 Hz, 1H, H-19), 4.93 (s, 1H, H-9), 4.31 (AB system, ^2J=13.1 Hz, $\Delta\nu$=15.6 Hz, 2H, H-12), 2.39–2.36 (m, 2H, H-16, H-3), 2.13–2.10 (m, 3H, H-21, H-6a), 2.09 (m, 1H, H-4a), 2.07–1.13 (m, 25H, H-5, H-6b, 8× CH_2 non assign., H-32, H-26), 1.42 (s, 3H, H-8), 1.10 (s, 3H, H-8), 0.92–0.85 (m, 3H, H-4b, H-27). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C-2), 149.6 (C-15), 144.8 (C-20), 137.1 (C-10), 134.3 (C-11), 127.1 (C-13), 121.6 (C-14), 115.0 (C-7), 109.6 (C-19), 88.3 (C-18), 86.4 (C-17), 85.0 (C-1), 84.3 (C-9), 65.6 (C-12), 42.4 (C-3), 42.3 (C-16), 33.4 (C-6), 33.3 (C-21), 31.9 (CH_2, non assig.), 31.8 (CH_2, non assig.), 31.4 (CH_2, non assig.), 29.7 (CH_2, non assig.), 29.6 (CH_2, non assig.), 29.0 (CH_2, non assig.), 28.9 (CH_2, non assig.), 28.9 (CH_2, non assig.), 28.9 (CH_2, non assig.), 27.3 (CH_2, non assig.), 23.4 (C-5), 22.8 (CH_2, non assig.), 14.2 (2C, C-26, C-32). IR ($CDCl_3$) ν (cm^{-1}) 2927, 1855, 2246, 1722, 1460, 1379, 1258, 1143, 1024, 906, 728. HRMS (ESI, 120 eV) calculated $C_{33}H_{48}O_3$ $[M]^+$ 492.36035, found 492.36104 (Diff.: 1.4 ppm).

4.10.11. [(7bS,10aR*,11S*,11aS*)-5-(Cyclohex-1-en-1-ylethynyl)-9,9-dimethyl-1,3,4,7b,11,11a-hexa-hydro-2H-10a,11-propanobenzo[4′,5′] cycloocta[1′,2′:3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl] methanol (**12d**).*



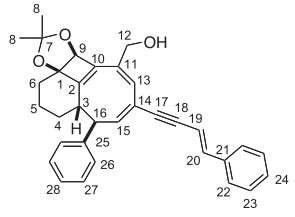
The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$, (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diisopropylamine (3.1 mL), and enyne **16** (59 μL, 0.50 mmol, 3 equiv). The vial was irradiated in the microwave for 2 h at 100 °C and the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=6:4). The cyclooctatriene **12d** was isolated (55 mg, 77%), along with a second fraction with the corresponding trienyne **9d** (11 mg, 20%), both as orange oils. R_f=0.15 (pentane/Et_2O=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H, H-13), 6.05–6.03 (m, 1H, H-20), 5.00 (s, 1H, H-9), 4.22 (AB system, J_{AB}=12.4 Hz, $\Delta\nu$=26.4 Hz, 2H, H-12), 2.65 (ddd, ^3J=10.6 Hz, ^3J=10.6 Hz, ^3J=5.4 Hz, 1H, H-3), 2.55–2.51 (m, 1H, H-16), 2.13–1.24 (m, 21H, CH_2 non assign., H-5, H-6, H-4a), 1.37 (s, 3H, H-8), 1.28 (s, 3H, H-8), 0.92–0.87 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7 (C-2), 155.5 (C-15), 136.9 (C-10), 134.0 (C-20), 132.5 (C-11), 128.2 (C-13), 121.2 (C-14), 115.3 (C-7), 114.7 (C-19), 94.9 (C-18), 85.9 (C-1), 84.7 (C-17), 84.5 (C-9), 65.9 (C-12), 40.2 (C-16), 38.5 (C-3), 33.4 (C-6), 31.5 (C-4), 30.4 (CH_2, non assign.), 29.6 (C-8), 29.5 (CH_2, non assign.), 28.7 (C-8), 26.5 (CH_2, non assign.), 26.4 (CH_2, non assign.), 25.8 (CH_2, non assign.), 23.4 (C-5), 22.5 (CH_2, non assign.), 21.7 (CH_2, non assign.), 20.6 (CH_2, non assign.). IR (neat) ν (cm^{-1}) 3335, 2972, 2931, 1659, 1446, 1379, 1186, 1143, 1087, 1045, 879, 629. HRMS (ESI, 120 eV) calculated $C_{29}H_{36}O_3$ $[M]^+$ 432.26645, found 432.26537 (Diff.: 2.49 ppm).

4.10.12. (Z)-4-(Cyclohex-1-en-1-yl)-2-((3aS,8aR*)-2,2-dimethyl-7,8-dihydro-3aH-benzo[1,4]cyclobuta [1,2-d][1,3]dioxol-4(6H)-ylidene)but-3-yn-1-ol (**9d**).*



R_f=0.42 (pentane/Et_2O=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (t, ^3J=3.6 Hz, 1H, H-3), 6.13 (m, 1H, H-16), 4.99 (s, 1H, H-9), 4.27 (sl, 2H, H-12), 2.45–2.39 (m, 1H, H-4a), 2.17–2.10 (m, 5H, H-4b, CH_2, non assign.), 2.00–1.86 (m, 3H, H-5, H-6a), 1.68–1.56 (m, 5H, H-6b, CH_2, non assign.), 1.52 (s, 3H, H-8), 1.42 (s, 3H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2 (C-10), 137.9 (C-2), 136.0 (C-16), 125.1 (C-3), 120.9 (C-15), 117.7 (C-11), 114.5 (C-7), 98.9 (C-14), 86.6 (C-1), 84.3 (C-13), 81.6 (C-9), 63.4 (C-12), 29.5 (C-17), 29.3 (C-6), 28.9 (C-8), 28.9 (C-8), 25.9 (CH_2, non assign.), 25.9 (CH_2, non assign.), 22.4 (CH_2, non assign.), 21.6 (CH_2, non assign.), 19.1 (C-5). IR (neat) ν (cm^{-1}) 3392, 2976, 2933, 2861, 2360, 2341, 1724, 1438, 1381, 1266, 1193, 1149, 1116, 1073, 1038, 844, 735, 542. HRMS (ESI, 120 eV) calculated for $C_{21}H_{26}O_3$ $[M]^+$ 326.07316 found 326.07093 (Diff.: 6.84 ppm).

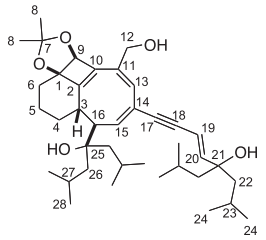
4.10.13. {(3aR,4S*,5R*,9bS*)-2,2-Dimethyl-5-phenyl-7-[(3E)-4-phenylbut-3-en-1-yn-1-yl]-4,9b-dihydro-5H-3a,4-propanocycloocta [3,4]cyclobuta [1,2-d][1,3]dioxol-9-yl}methanol (**12f**).*



The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$, (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diiso-propylamine (3.1 mL), and enyne **18** (64 mg, 0.50 mmol, 3 equiv). The vial was irradiated in the

microwave for 3 h at 100 °C the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=6:4). The cyclooctatriene **12f** was isolated as an orange oil (54 mg, 68%); R_f=0.13 (pentane/Et_2O=7:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.22 (m, 8H, H_{arom}), 7.18 (d, ^3J=7.0 Hz, 2H, H-26), 6.88 (d, ^3J=16.0 Hz, 1H, H-20), 6.46 (d, ^3J=9.5 Hz, 1H, H-15), 6.22 (d, ^3J=16.0 Hz, 1H, H-19), 6.11 (s, 1H, H-13), 5.02 (s, 1H, H-9), 4.38 (sl, 2H, H-12), 3.54 (dd, ^3J=10.5 Hz, ^3J=10.5 Hz, 1H, H-16), 2.91 (td, ^3J=10.5 Hz, ^3J=4.7 Hz, 1H, H-3), 2.12–2.10 (m, 1H, H-6a), 1.70–1.61 (m, 3H, H-6b, H-5), 1.50 (s, 3H, H-8), 1.44 (s, 3H, H-8), 1.33–1.30 (m, 1H, H-4a), 0.76–0.74 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C-2), 148.5 (C-15), 141.5 (C-25), 141.1 (C-20), 137.0 (C-10). 137.5 (C-11), 134.9 (C-21), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 127.9 (C_{arom}), 126.9 (C_{arom}), 126.4 (C_{arom}), 126.4 (C-13), 120.9 (C-14), 115.4 (C-7), 108.2 (C-19), 92.1 (C-18), 87.5 (C-17), 85.1 (C-1), 84.5 (C-9), 65.6 (C-12), 50.0 (C-16), 43.9 (C-3), 33.5 (C-6), 32.8 (C-4), 29.7 (C-8), 29.3 (C-8), 23.3 (C-5). IR (neat) ν (cm^{-1})=3435, 2937, 2856, 2358, 1727, 1600, 1493, 1449, 1380, 1368, 1348, 1314, 1284, 1258, 1229, 1207, 1184, 1143, 1125, 1078, 1026, 950, 763, 750, 704, 691. HRMS (ESI, 120 eV) calculated $C_{33}H_{32}O_3$ $[M]^+$ 476.23514, found 476.23637 (Diff.: 2.57 ppm).

4.10.14. (5E)-8-[(3aR,4S*,5R*,9bS*)-5-(1-Hydroxy-1-isobutyl-3-methylbutyl)-9-(hydroxymethyl)-2,2-dimethyl-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl]-4-isobutyl-2-methyloct-5-en-7-yn-4-ol (**12k**).*

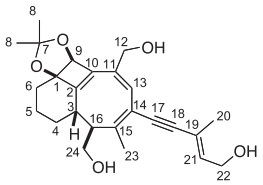


The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$, (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diisopropyl-amine (3.1 mL), and enyne **23** (97 mg, 0.50 mmol, 3 equiv). The vial was irradiated in the microwave for 1 h at 100 °C and the crude product was purified by flash column chromatography over silica gel (elution: pentane/AcOEt=8:2 to 5:5). The trienyne **2k** was isolated (65 mg, 94%), along with a second fraction with the corresponding cyclooctatriene **12k** (6 mg, 6%), both as orange oils; R_f=0.11 (pentane/Et_2O=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, ^3J=16.0 Hz, 1H, H-20), 6.02 (s, 1H, H-13), 5.97 (d, ^3J=10.4 Hz, 1H, H-15), 5.80 (d, ^3J=16.0 Hz, 1H, H-19), 4.91 (s, 1H, H-9), 4.30 (s, 2H, H-12), 2.83 (dd, ^3J=10.2 Hz, ^3J=10.2 Hz, 1H, H-16), 2.39 (ddd, ^3J=10.5 Hz, ^3J=10.5 Hz, ^3J=4.9 Hz, 1H, H-3), 2.17–0.82 (m, 18H, H-4, H-5, H-6, H-22, H-23, H-26, H-27), 1.39 (s, 6H, H-8), 0.89 (s, 3H, H-24 or H-28), 0.88 (s, 3H, H-24 or H-28), 0.88 (s, 3H, H-24 or H-28), 0.87 (s, 3H, H-24 or H-28).

4.11. Experimental data for cyclooctatrienes 12 (fenestradienes 4 and trienynes 2 as byproducts)

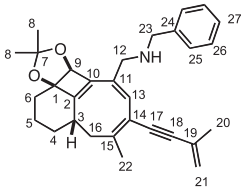
The used procedure is the same than for the fenestradienes **4** (**general procedure V**), only irradiation times and temperatures differ. Thus cyclooctatrienes already described before are not mentioned here again: cyclooctatrienes **12a**–**f**, **12h**–**q**, and **12u**–**w**.

4.11.1. (2E)-5-[(3aR,4S*,5S*,9bS*)-5,9-Bis (hydroxymethyl)-2,2,6-trimethyl-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl]-3-methylpent-2-en-4-yn-1-ol (**12g**).*



The **general procedure V** was followed using alcohol **1a**, $Pd(OAc)_2$, (2 mg, 0.01 mmol, 0.05 equiv), PPh_3 (4 mg, 0.02 mmol), CuI (3 mg, 0.02 mmol, 0.1 equiv) in diisopropyl-amine (3.1 mL), and enyne **19** (51 μL, 0.5 mmol, 3 equiv). After 2 h of irradiation at 130 °C, the crude product was purified by automatic flash column chromatography. (Run: 140 min, elution: CH_2Cl_2/MeOH=100:0 to 97:3 for 120 min and then CH_2Cl_2/MeOH=97:3 for 20 min) and the desired product **12g** was isolated as an orange oil (55 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.0 (s, 1H, H-13), 5.92 (t, ^3J=12.4 Hz, 1H, H-21), 4.97 (s, 1H, H-9), 4.32–4.18 (m, 4H, H-12, H-22), 3.69 (dd, ^2J=10.4 Hz, ^3J=5.2 Hz, 1H, H-24a), 3.62 (dd, ^2J=10.4 Hz, ^3J=10.4 Hz, 1H, H-24b), 3.46 (ddd, ^3J=10.4 Hz, ^3J=5.2 Hz, ^3J=5.2 Hz, 1H, H-16), 2.82 (td, ^3J=5.2 Hz, ^3J=10.4 Hz, 1H, H-3), 2.15–2.11 (m, 1H, H-6a), 1.81 (s, 3H, H-20), 1.79–1.65 (m, 4H, H-6b, H-4a, H-5), 1.49 (d, ^4J=6.4 Hz, 3H, H-23), 1.36 (s, 3H, H-8), 1.28 (s, 3H, H-8), 1.12–1.03 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (C-2), 151.2 (C-15), 137.2 (C-10), 134.9 (C-21), 133.5 (C-11), 127.5 (C-13), 121.1 (C-19), 119.5 (C-15), 114.9 (C-7), 95.7 (C-18), 87.0 (C-17), 84.6 (C-1), 84.3 (C-9), 65.2 (C-12), 61.5 (C-24), 59.1 (C-22), 48.0 (C-16), 46.6 (C-3), 33.3 (C-6), 31.6 (C-4), 29.6 (C-8), 28.6 (C-8), 23.3 (C-5), 19.3 (C-23), 17.8 (C-20). IR ($CDCl_3$) ν (cm^{-1})= 2937, 2360, 2253, 1381, 1025, 904, 723, 647. HRMS (ESI, 120 eV) calculated $C_{25}H_{32}O_5$ $[M]^+$ 412.225, found 412.2257 (Diff.: −1.86 ppm).

4.11.2. Benzyl{[(3aR,4S*,9bS*)-2,2,6-trimethyl-7-(3-methylbut-3-en-1-yn-1-yl)-4,9b-dihydro-5H-3a,4-propanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl]methyl}amine(**12t**).*



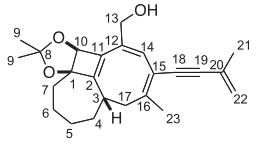
The **general procedure V** was followed using: benzylamine **1c** (57.0 mg, 0.15 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.60 mg, 7.30 mmol, 0.05 equiv), PPh_3 (3.90 mg, 15.0 mmol, 0.10 equiv), CuI (2.90 mg, 15.0 mmol, 0.10 equiv), and enyne **13** (43.0 μL, 0.45 mmol, 3.0 equiv). The crude residue was purified by flash chromatography over silica gel (elution: pentane/Et_2O=7:3 to pentane/Et_2O=6:4) to afford 43.5 mg (66%) of the desired cyclooctatriene **12t** as a yellow oil. R_f=0.46 (pentane/EtOAc=6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H, H_{arom}), 5.93 (s, 1H, H-13), 5.22 (d, 2H, ^2J=27.0 Hz, H-21), 5.03 (s, 1H, H-9), 3.78 (s, 2H, H-23), 3.45 (m, 2H, H-12), 2.53 (m, 1H, H-3), 2.28 (t, ^3J=11.4 Hz, 1H, H-16a), 2.13 (m, 1H, H-4a), 2.03 (s, 3H, H-22), 1.92 (s, 3H, H-20), 1.73 (m, 5H, H-16b, H-6a, H-5, and H-4b), 1.40 (s, 3H, H-8), 1.35 (s, 3H, H-8), 1.02 (m, 1H, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 (C-2), 149.7 (C-15), 140.6 (C-10), 138.2 (C-24), 131.2 (C-11), 128.5 (C-26/C-25), 128.4 (C-26/C-25), 128.2 (C-13), 127.4 (C-19), 127.0 (C-27), 120.8 (C-21), 117.4 (C-14), 114.8 (C-7), 93.6 (C-18), 88.5 (C-1), 84.6 (C-9), 84.2 (C-17), 53.7 (C-12), 52.6 (C-23), 38.9 (C-16), 38.1 (C-3), 34.2 (C-6), 33.4 (C-4), 29.5 (C-8), 28.9 (C-8), 23.8 (C-22), 23.4 (C-5), 23.3 (C-20). IR (neat) ν (cm^{-1})=3350, 2927, 2854,

2359, 1605, 1452, 1378, 1308, 1257, 1199, 1142, 1074, 1033, 891, 873, 841, 737, 698, 518. HRMS (ESI, 120 eV): calculated for $C_{30}H_{35}NO_2$ $[M]^{+\bullet}$ 441.26678, found 441.26543 (Diff.: 3.06 ppm).

4.12. General procedure VI for cyclooctatrienes 30

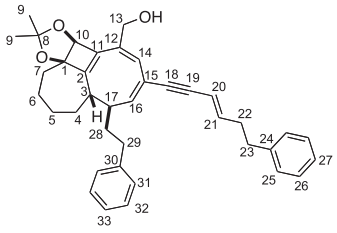
In a 2–5 mL microwave vial were added the compound **29** (50 mg, 0.159 mmol, 1 equiv), $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), copper iodide (3 mg, 0.02 mmol, 0.1 equiv), and PPh_3 (4 mg, 0.02 mmol, 0.1 equiv). The vial was sealed with a Teflon cap and the reaction mixture was then dissolved in diisopropylamine (3.2 mL, 0.05 M). The reaction mixture was placed under argon, frozen in liquid nitrogen and put under vacuum. The O_2 liberation proceeds when the temperature rises back to rt. The operation was repeated three times. Then, the enyne (3.0 equiv) was added to the reaction mixture. The vial was irradiated in the microwave, the time and temperature of each example being indicated in the following paragraphs. The reaction mixture was then filtered through Celite to eliminate the metal traces and then concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel.

4.12.1. [(3aR,4S*,9bS*)-2,2,6-Trimethyl-7-(3-methylbut-3-en-1-yn-1-yl)-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl]methanol (**30a**).*



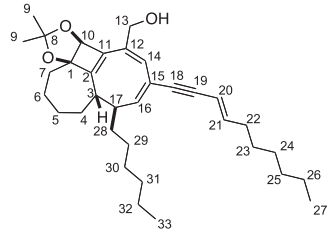
The **general procedure VI** was followed using enyne **13** (45 μL, 0.48 mmol, 3 equiv). After 30 min of irradiation at 130 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=6:4) and the cyclooctatriene **30a** was isolated as an orange oil (50 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H, H-14), 5.21 (m, 1H, H-22a), 5.17–5.15 (m, 1H, H-22b), 4.86 (s, 1H, H-10), 4.29 (AB system, J_{AB}=12.8 Hz, $\Delta\nu$=14.3 Hz, 2H, H-13), 2.57 (dd, ^3J=11.5 Hz, ^2J=11.5 Hz, 2H, H-17a), 2.47 (m, 1H, H-3), 2.19–2.13 (m, 1H, H-4a), 2.03 (s, 3H, H-23), 1.98–1.92 (m, 2H, H-17b, CH_2), 1.88 (s, 3H, H-21), 1.85–1.73 (m, 4H, H-4b, CH_2), 1.37 (s, 3H, H-9), 1.40–1.33 (m, 1H, CH_2), 1.31 (s, 3H, H-9), 1.20–1.08 (m, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (C-2), 149.4 (C-16), 141.8 (C-12), 135.0 (C-11), 127.6 (C-14), 127.3 (C-20), 120.8 (C-22), 117.9 (C-15), 114.2 (C-8), 94.3 (C-19), 90.7 (C-1), 87.5 (C-18), 82.7 (C-10), 65.5 (C-13), 40.1 (C-17), 38.8 (C-7), 37.4 (C-3), 35.2 (C-4), 30.1 (C-9), 29.7 (C-6), 28.4 (C-9), 25.1 (C-5), 23.8 (C-21), 22.5 (C-23). IR ($CDCl_3$) ν (cm^{-1})=3436, 2923, 2850, 2247, 1724, 1611, 1435, 1369, 1317, 1279, 1208, 1099, 1025, 906, 855, 728, 694, 518. HRMS (EI+) calculated $C_{24}H_{30}O_3$ $[M]^+$ 366.21949, found 366.21927 (Diff.: 0.62 ppm).

4.12.2. {(3aR,4S*,9bS*)-2,2-Dimethyl-5-(2-phenyl ethyl)-7-[(3E)-6-phenylhex-3-en-1-yn-1-yl]-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl}methanol (**30b**).*



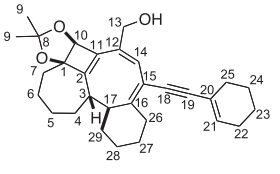
The **general procedure VI** was followed using enyne **14** (75 mg, 0.48 mmol, 3 equiv). After 3 h of irradiation at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=6:4) and the cyclooctatriene **30b** was isolated as an orange oil (77 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 6H, H-26, H-27, H-31, H-32, H-33), 7.21–712 (m, 4H, H-25, H-31), 6.14 (d, ^3J=9.3 Hz, 1H, H-16), 6.16–6.09 (m, 1H, H-21), 6.04 (s, 1H, H-14), 5.60 (d, ^3J=15.9 Hz, 1H, H-20), 4.83 (s, 1H, H-10), 4.27 (AB system, J_{AB}=13.0 Hz, $\Delta\nu$=13.1 Hz, 2H, H-13), 2.73–2.65 (m, 3H, H-27a, H-23), 2.49–2.36 (m, 4H, H-17, H-22, H-27b), 2.23–1.19 (m, 9H, H-3, H-4a, H-5, H-6, H-7a, H-28), 1.39 (s, 6H, H-9), 1.11–1.01 (m, 1H, H-4b), 0.90–0.81 (m, 1H, H-7b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (C-2), 147.3 (C-16), 143.3 (C-21), 142.3 (C-30), 141.8 (C-24), 141.3 (C-11), 137.2 (C-12), 128.5 (4C, C_{arom}), 128.4 (2C, C_{arom}), 126.6 (C-14), 126.1 (C_{arom}), 125.9 (C_{arom}), 122.9 (C-16), 114.6 (C-8), 110.4 (C-20), 91.0 (C-19), 88.1 (C-1), 87.2 (C-18), 82.1 (C-10), 65.8 (C-13), 42.9 (C-17), 42.2 (C-3), 36.5 (C-7), 35.3 (CH_2, non assig.), 35.3 (CH_2, non assig.), 35.2 (CH_2, non assig.), 35.0 (CH_2, non assig.), 33.4 (CH_2, non assig.), 30.2 (C-9), 29.8 (CH_2, non assig.), 28.8 (C-9), 25.0 (C-5). IR ($CDCl_3$) ν (cm^{-1})=3443, 3025, 2924, 2851, 2360, 2341, 1603, 1496, 1453, 1378, 1368, 1032, 908, 729, 698. GC–MS (ESI, 120 eV) calculated $C_{38}H_{42}O_3$ $[M]^+$ 546,3134, found 546.29846.

4.12.3. {(3aR,4S*,5R*,9bS*)-7-[(3E)-Dec-3-en-1-yn-1-yl]-5-hexyl-2,2-dimethyl-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]di-oxol-9-yl}methanol (**30c**).*



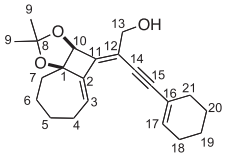
The **general procedure VI** was followed using enyne **15** (65 mg, 0.48 mmol, 3 equiv). After 3 h of irradiation at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: pentane/AcOEt=9:1) and the cyclooctatriene **30c** was isolated as an orange oil (47 mg, 58%), along with a second fraction with the corresponding trienyne **31c** in mixture with an unknown product; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10–6.03 (m, 3H, H-21, H-14, H-16), 5.53 (d, ^3J=15.9 Hz, ^4J=1.2 Hz, 1H, H-20), 4.83 (s, 1H, H-10), 4.30 (AB system, J_{AB}=13.2 Hz,=13.9 Hz, 2H, H-13), 2.41 (AB system, J_{Ax}=2.8 Hz, J_{Bx}=3.0 Hz, $\Delta\nu$=30.2 Hz, 2H, H-17, H-3), 2.17–1.96 (m, 6H, CH_2, non assig.), 1.81–1.51 (m, 7H, CH_2, non assig.), 1.38 (s, 6H, H-9), 1.33–1.06 (m, 15H, CH_2, non assig.), 0.89–0.85 (m, 6H, H-27, H-33). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (C-2), 147.8 (C-16), 144.6 (C-21), 141.7 (C-11), 136.9 (C-12), 127.0 (C-14), 122.3 (C-15), 114.8 (C-8), 109.7 (C-20), 91.0 (C-18), 87.8 (C-19), 87.2 (C-1), 82.2 (C-10), 65.1 (C-13), 43.3 (C-17), 42.3 (C-3), 36.7 (CH_2, non assig.), 35.4 (CH_2, non assig.), 33.3 (CH_2, non assig.), 31.9 (CH_2, non assig.), 31.8 (CH_2, non assig.), 30.2 (C-9), 30.0 (CH_2, non assig.), 29.5 (CH_2, non assig.), 28.9 (3C, CH_2, non assig.), 28.8 (C-9), 26.9 (CH2, non assig.), 25.1 (CH_2, non assig.), 22.8 (CH_2, non assig.), 22.7 (CH_2, non assig.), 14.2 (2C, C-27, C-33). IR ($CDCl_3$) ν (cm^{-1})=3458, 2922, 2853, 1446, 1372, 1346, 1206, 1142, 1031, 955, 854, 825, 776, 544. HRMS (EI+) calculated $C_{34}H_{50}O_3$ $[M]^+$ 506.37599, found 506.37710 (Diff.: 1.10 ppm).

4.12.4. [(7bS,10aR*,11S*,11aS*)-5-(Cyclohex-1-en-1-ylethynyl)-9,9-dimethyl-1,3,4,7b,11,11a-hexa-hydro-2H-10a,11-butanobenzo[4′,5′]cycloocta [1′,2′:3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl] methanol (**30d**).*



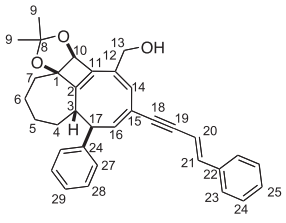
The **general procedure VI** was followed using enyne **16** (56 μL, 0.48 mmol, 3 equiv). The vial was irradiated in the microwave for 3 h at 100 °C and the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=6:4). The desired cyclooctatriene **30d** (23 mg, 32%) was isolated as an orange oil along with a second fraction with the corresponding trienyne **31d** (37 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H, H-14), 6.02–6.00 (m, 1H, H-21), 4.85 (s, 1H, H-10), 4.35–4.24 (AB system, J_{AB}=12.8 Hz, $\Delta\nu$=29.8 Hz, 2H, H-13), 2.79–2.75 (m, 1H, H-17), 2.54 (ddd, ^3J=11.0 Hz, ^3J=11.0 Hz, ^3J=4.0 Hz, 1H, H-3), 2.20–1.27 (m, 22H, CH_2, non assig.), 2.11–2.00 (m, 1H, H-4a), 1.25 (s, 6H, H-9), 0.92–0.86 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8 (C-2), 155.4 (C-16), 142.1 (C-12), 135.1 (C-11), 133.8 (C-21), 128.1 (C-14), 121.3 (C-20), 115.6 (C-15), 114.4 (C-8), 95.3 (C-19), 90.9 (C-1), 85.3 (C-18), 82.4 (C-10), 65.3 (C-13), 42.1 (C-17), 37.5 (C-3), 36.3 (CH_2, non assig.), 35.6 (C-4), 30.2 (CH_2, non assig.), 29.9 (C-9), 29.8 (C-9), 29.6 (CH_2, non assig.), 28.3 (CH_2, non assig.), 28.2 (CH_2, non assig.), 26.9 (CH_2, non assig.), 25.8 (CH_2, non assig.), 25.3 (CH_2, non assig.), 22.5 (CH_2, non assig.), 21.7 (CH_2, non assig.), 20.2 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3336, 2971, 2926, 2859, 2359, 1717, 1448, 1378, 1278, 1237, 1208, 1144, 1087, 1045, 880. HRMS (ESI, 120 eV) calculated $C_{30}H_{38}O_3$ $[M]^+$ 446.2821, found 446.28133 (Diff.: 1.71 ppm).

4.12.5. (Z)-4-(Cyclohex-1-en-1-yl)-2-((3aS,9aR*)-2,2-dimethyl-6,7,8,9-tetrahydrocyclohepta[1,4]cyclobuta[1,2-d][1,3]dioxol-4(3aH)-ylidene)but-3-yn-1-ol (**31d**).*



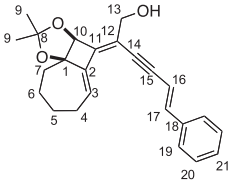
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, ^3J=7.7 Hz, ^3J=4.4 Hz, 1H, H-3), 6.16 (m, 1H, H-17), 4.86 (s, 1H, H-10), 4.32–4.21 (m, 2H, H-13), 2.47–2.40 (m, 1H, H-4a), 2.30–2.23 (m, 1H, H-4b), 2.19–2.11 (m, 4H, CH_2, non assig.), 1.97–1.87 (m, 4H, H-7a, CH_2), 1.78–1.71 (m, 1H, H-7b), 1.68–1.56 (m, 5H, CH_2, non assig.), 1.47 (s, 3H, H-9), 1.42 (s, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C-11), 144.8 (C-2), 136.3 (C-17), 130.3 (C-3), 120.0 (C-16), 117.8 (C-12), 114.6 (C-8), 100.6 (C-15), 90.2 (C-1), 85.0 (C-14), 81.9 (C-10), 63.4 (C-13), 34.7 (C-7), 34.7 (C-4), 29.7 (CH_2, non assig.), 29.3 (CH_2, non assig.), 29.0 (C-9), 28.9 (C-9), 27.9 (CH_2, non assig.), 26.9 (CH_2, non assig.), 26.0 (CH_2, non assig.), 22.4 (CH_2, non assig.), 21.6 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3419, 2927, 2857, 2177, 1715, 1651, 1435, 1379, 1369, 1260, 1191, 1147, 1093, 1052, 1006, 918, 842, 734, 539. HRMS (ESI, 120 eV) calculated $C_{22}H_{28}O_3$ $[M]^+$ 340.20384, found 340.20312 (Diff.: 2.14 ppm).

4.12.6. {(3aR,4S*,5R*,9bS*)-2,2-Dimethyl-5-phenyl-7-[(3E)-4-phenylbut-3-en-1-yn-1-yl]-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3] dioxol-9-yl}methanol (**30e**).*



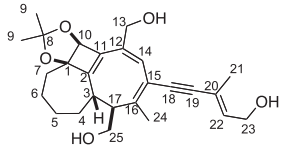
The **general procedure VI** was followed using enyne **18** (61 mg, 0.48 mmol, 3 equiv). The vial was irradiated in the microwave for 1 h at 130 °C and the crude product was purified by flash column chromatography over silica gel (elution: pentane/Et_2O=7:3). The desired cyclooctatriene **30e** (39 mg, 50%) was isolated as an orange oil along with a second fraction with the corresponding trienyne **31e** (26 mg, 45%); R_f=0.31 (pentane/Et_2O 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.21 (m, 8H, H_{arom}), 7.18–7.16 (m, 2H, H_{arom}), 6.84 (d, ^3J=16.4 Hz, 1H, H-21), 6.43 (d, ^3J=9.8 Hz, 1H, H-16), 6.19 (d, ^3J=16.4 Hz, 1H, H-20), 6.15 (s, 1H, H-14), 4.92 (s, 1H, H-10), 4.41 (AB system, J_{AB}=13.3 Hz, $\Delta\nu$=15.2 Hz, 2H, H-13), 3.66 (dd, ^3J=10.6 Hz, ^3J=10.6 Hz, 1H, H-17), 2.70 (td, ^3J=10.6 Hz, ^3J=3.6 Hz, 1H, H-3), 2.22–2.17 (m, 1H, H-7a), 1.83–1.74 (m, 3H, H-7b, H-6a, H-5a), 1.49–1.43 (m, 1H, H-4a), 1.46 (s, 3H, H-9), 1.42 (s, 3H, H-9), 1.17–1.03 (m, 2H, H-5b, H-6b), 0.94–0.81 (m, 1H, H-4b). ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.3 (C-2), 147.2 (C-16), 143.2 (C-26), 142.1 (C-22), 141.0 (C-21). 137.5 (C-11), 136.5 (C-12), 129.1 (C_{arom}), 128.8 (C_{arom}), 128.6 (C_{arom}), 127.9 (C_{arom}), 126.9 (C_{arom}), 126.4 (C_{arom}), 126.4 (C-14), 121.7 (C-15), 114.9 (C-8), 108.2 (C-20), 91.5 (C-19), 91.3 (C-1), 98.3 (C-18), 82.2 (C-10), 65.0 (C-13), 51.5 (C-17), 43.4 (C-3), 37.8 (C-7), 35.4 (C-4), 30.2 (C-9), 29.8 (C-6), 28.9 (C-9), 25.2 (C-5). HRMS (ESI, 120 eV) calculated $C_{34}H_{34}O_3$ $[M]^+$ 490.25079, found 490.25141 (Diff.: 1.25 ppm).

4.12.7. (2Z,5E)-2-((3aS,9aR*)-2,2-Dimethyl-6,7,8,9-tetra-hydrocyclohepta[1,4]cyclobuta[1,2-d][1,3]dioxol-4(3aH)-ylidene)-6-phenylhex-5-en-3-yn-1-ol (**31e**).*



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H, H_{arom}), 6.97 (d, ^3J=16.2 Hz, 1H, H-17), 6.68 Hz (d, ^3J=8.0 Hz, ^3J=4.5 Hz, 1H, H-3), 6.38 (d, ^3J=16.2 Hz, 1H, H-16), 4.89 (s, 1H, H-10), 4.38–4.26 (m, 2H, H-13), 2.51–2.44 (m, 1H, H-4a), 2.35–2.28 (m, 1H, H-4b), 2.00–1.89 (m, 5H, H-7a, H-5, H-6), 1.81–1.74 (m, 1H, H-7b), 1.50 (s, 3H, H-9), 1.44 (s, 3H, H-9). ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.1 (C-11), 144.7 (C-2), 141.9 (C-17), 136.3 (C-18), 131.1 (C-3), 129.0 (C_{arom}), 128.9 (C_{arom}), 127.0 (C_{arom}), 117.4 (C-12), 114.8 (C-8), 108.1 (C-16), 98.0 (C-15), 90.2 (C-1), 90.0 (C-14), 81.9 (C-10), 63.4 (C-13), 34.8 (C-7), 29.8 (C-4), 29.0 (C-9), 29.0 (C-9), 27.9 (C-6), 26.9 (C-5). HRMS (ESI, 120 eV) calculated $C_{24}H_{26}O_3$ $[M]^+$ 362.18819, found 362.18631 (Diff.: 5.21 ppm).

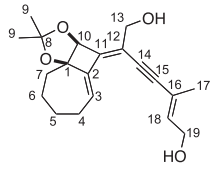
4.12.8. (2E)-5-[(3aR,4S*,5S*,9bS*)-5,9-Bis(hydroxymethyl)-2,2,6-trimethyl-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl]-3-methylpent-2-en-4-yn-1-ol (**30f**).*



The **general procedure VI** was followed using enyne **19** (49 μL, 0.48 mmol, 3 equiv). After 3 h of irradiation at 100 °C, the crude product was purified by automatic flash column chromatography (Run: 60 min, elution: CH_2Cl_2/MeOH=99:1 to 95:5) and the desired product **30f** was isolated (41 mg, 60%), along with a second fraction with the corresponding trienyne **31f** (19 mg, 35%) as an orange oils; R_f=0.18 (CH_2Cl_2/MeOH=97:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 1H, H-14), 5.89 (td, ^3J=6.8 Hz, ^4J=0.7 Hz, 1H, H-22), 4.84 (s, 1H, H-10), 4.28 (AB system, J_{AB}=13.2 Hz, $\Delta\nu$=24.3 Hz, 2H, H-13), 4.19 (d, ^3J=6.8 Hz, 2H, H-23), 3.72 (dd, ^2J=10.8 Hz, ^3J=4.8 Hz, 1H, H-25a), 3.57 (dd, ^2J=10.8 Hz, ^3J=10 Hz,

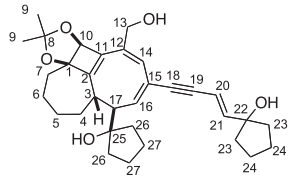
1H, H-25b), 3.01 (td, ^3J=4.8 Hz, ^3J=4.4 Hz, 1H, H-17), 2.30 (td, ^3J=4.4 Hz, ^3J=10.8 Hz, 1H, H-3), 2.18–1.66 (m, 7H, H-4a, H-5, H-6, H-7), 1.99 (s, 3H, H-21), 1.79 (s, 3H, H-24), 1.34 (s, 3H, H-9), 1.25 (s, 3H, H-9), 1.08–0.98 (m, 1H, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (C-2), 150.7 (C-16), 142.6 (C-11), 136.3 (C-12), 134.8 (C-22), 127.4 (C-14), 121.1 (C-20), 120.2 (C-15), 114.6 (C-8), 96.4 (C-19), 91.1 (C-1), 86.4 (C-18), 82.2 (C-10), 64.7 (C-13), 62.7 (C-25), 59.2 (C-23), 48.1 (C-17), 38.8 (C-3), 36.1 (C-7), 35.5 (C-4), 30.2 (C-6), 30.2 (C-9), 28.2 (C-9), 25.2 (C-5), 17.8 (C-24), 16.6 (C-21). IR ($CDCl_3$) ν (cm^{-1})=3385, 2929, 2361, 2250, 1448, 1380, 1317, 1279, 1239, 1208, 1140, 1022, 905, 725, 648. HRMS (ESI, 120 eV) calculated $C_{26}H_{34}O_5$ $[M]^+$ 426.24062, found 426.24066 (Diff.: 0.08 ppm).

4.12.9. (2E,6Z)-6-((3aS,9aR*)-2,2-Dimethyl-6,7,8,9-tetrahydrocyclohepta[1,4]cyclobuta[1,2-d][1,3]dioxol-4(3aH)-ylidene)-3-methylhept-2-en-4-yne-1,7-diol (**31f**).*



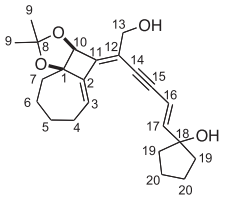
R_f=0.19 (Et_2O/pentane=7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, ^3J=7.6 Hz, ^3J=4.4 Hz, 1H, H-3), 6.03 (td, ^3J=6.8 Hz, ^4J=1.2 Hz, 1H, H-18), 4.87 (s, 1H, H-10), 4.33–4.22 (m, 4H, H-19, H-13), 2.50–1.60 (m, 8H, H-4, H-5, H-6, H-7), 1.88 (s, 3H, H-17), 1.48 (s, 3H, H-9), 1.43 (s, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0 (C-11), 144.7 (C-2), 136.5 (C-18), 130.9 (C-3), 120.9 (C-16), 117.3 (C-12), 114.7 (C-8), 100.4 (C-15), 90.2 (C-1), 85.9 (C-14), 81.8 (C-10), 63.4 (C-13), 59.4 (C-19), 34.7 (C-7), 29.7 (C-4), 29.0 (C-9), 27.9 (C-6), 26.8 (C-5), 17.7 (C-17). IR ($CDCl_3$) ν (cm^{-1})=3392, 2925, 3854, 2247, 1717, 1650, 1438, 1370, 1191, 1054, 1006, 909, 728, 541. HRMS (ESI, 120 eV) calculated $C_{20}H_{26}O_4$ $[M]^+$ 330.18311, found 330.18283 (Diff.: 0.85 ppm).

4.12.10. (2E)-5-[(3aR,4S*,5S*,9bS*)-5,9-Bis(hydroxymethyl)-2,2,6-trimethyl-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-7-yl]-3-methylpent-2-en-4-yn-1-ol (**30g**).*



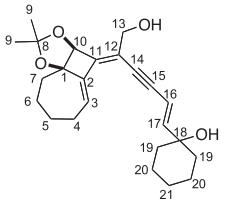
The **general procedure VI** was followed using enyne **20** (65 mg, 0.48 mmol, 3 equiv). After 3 h of irradiation at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: CH_2Cl_2/MeOH=99:1 to CH_2Cl_2/MeOH=95:5) and the cyclooctatriene **30g** was isolated as an orange oil (36 mg, 45%), along with a second fraction with the corresponding trienyne **31g** (24 mg, 40%) as an orange foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (s, 1H, H-16), 6.19 (d, ^3J=15.8 Hz, 1H, H-21), 6.06 (s, 1H, H-14), 5.84 (d, ^3J=15.8 Hz, 1H, H-20), 4.81 (s, 1H, H-10), 4.29 (AB system, J_{AB}=13.2 Hz, $\Delta\nu$=15.0 Hz, 2H, H-13), 2.67 (dd, ^2J=10.4 Hz, ^3J=10.4 Hz, 1H, H-17), 2.61 (ddd, ^3J=10.4 Hz, ^3J=10.4 Hz, ^3J=3.4 Hz, 1H, H-3), 2.39–2.36 (m, 1H, H-7a), 2.13–0.98 (m, 23H, H-7b, CH_2, non assig.), 1.36 (s, 3H, H-9), 1.35 (s, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C-2), 148.8 (C-21), 145.1 (C-16), 141.3 (C-11), 137.4 (C-12), 126.4 (C-14), 121.4 (C-15), 115.2 (C-8), 107.2 (C-20), 91.2 (C-1), 89.7 (C-19), 87.0 (C-22), 84.2 (C-25), 82.2 (C-18), 82.1 (C-10), 64.6 (C-13), 52.2 (C-17), 41.9 (CH_2, non assig.), 40.9 (C-3), 40.7 (CH_2, non assig.), 39.2 (CH_2, non assig.), 36.8 (CH_2, non assig.), 35.2 (CH2, non assig.), 30.3 (C-9), 28.8 (C-9), 24.8 (CH_2, non assig.), 24.4 (CH_2, non assig.), 23.0 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3353, 2917, 2850, 1738, 1448, 1379, 1179, 1027, 990, 956, 910, 851, 828, 730. HRMS (ESI, 120 eV) calculated $C_{32}H_{42}O_5$ $[M]^+$ 506.30322, found 506.30213 (Diff.: 2.16 ppm).

4.12.11. 1-((1E,5Z)-5-((3aS,9aR*)-2,2-Dimethyl-6,7,8,9-tetrahydrocyclohepta[1,4]cyclobuta[1,2-d][1,3]dioxol-4(3aH)-ylidene)-6-hydroxyhex-1-en-3-yn-1-yl)cyclopentanol (**31g**).*



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, ^3J=7.8 Hz, 4.3 Hz, 1H, H-3), 6.32 (d, ^3J=15.8 Hz, 1H, H-17), 6.02 (d, ^3J=15.8 Hz, 1H, H-16), 4.86 (s, 1H, H-10), 4.27 (AB system, J_{AB}=13.6 Hz, $\Delta\nu$=28.8 Hz, 2H, H-13), 2.48–2.40 (m, 1H, H-4a), 2.31–2.24 (m, 1H, H-4b), 1.97–1.85 (m, 6H, H-7a, CH_2, non assig.), 1.78–1.66 (m, 8H, H-7b, CH_2, non assig.), 1.47 (s, 3H, H-9), 1.42 (s, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1 (C-17), 145.7 (C-11), 144.6 (C-2), 130.8 (C-3), 117.4 (C-12), 114.7 (C-8), 107.2 (C-16), 96.8 (C-14), 90.2 (C-1), 88.0 (C-15), 82.3 (C-18), 81.8 (C-10), 63.3 (C-13), 40.8 (C-4), 34.7 (C-7), 29.7 (CH_2, non assig.), 29.0 (C-9), 28.9 (C-9), 27.9 (CH_2, non assig.), 26.8 (CH_2, non assig.), 23.9 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3290, 2922, 2852, 2184, 1730, 1639, 1616, 1449, 1368, 1258, 1193, 1147, 1051, 1004, 958, 844, 729, 687, 645, 537. IR ($CDCl_3$) ν (cm^{-1})=3290, 2922, 2852, 2184, 1730, 1639, 1616, 1449, 1368, 1193, 1087, 1004, 958, 844, 729, 534. HRMS (ESI, 120 eV) calculated $C_{23}H_{30}O_4$ $[M]^+$ 370.21441, found 370.21424 (Diff.: 0.45 ppm).

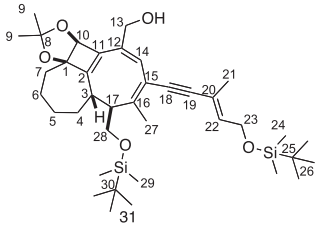
4.12.12. 1-((1E,5Z)-5-((3aS,9aR*)-2,2-Dimethyl-6,7,8,9-tetrahydrocyclohepta[1,4]cyclobuta[1,2-d][1,3]dioxol-4(3aH)-ylidene)-6-hydroxyhex-1-en-3-yn-1-yl)cyclohexanol (**31h**).*



The **general procedure VI** was followed using enyne **21** (72 mg, 0.48 mmol, 3 equiv). After 1 h of irradiation at 100 °C, the crude product was purified by flash column chromatography over silica gel (elution: CH_2Cl_2/MeOH=99:1 to CH_2Cl_2/MeOH=98:2) and the trienyne **31h** was isolated as an orange oil (58 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, ^3J=7.8 Hz, ^3J=4.3 Hz, 1H, H-3), 6.28 (d, ^3J=15.9 Hz, 1H, H-17), 5.97 (d, ^3J=15.9 Hz, 1H, H-16), 4.85 (s, 1H, H-10), 4.20 (AB system, J_{AB}=13.2 Hz, $\Delta\nu$=22.9 Hz, 2H, H-13), 2.46–2.39 (m, 1H, H-4a), 2.30–2.22 (m, 1H, H-4b), 1.97–1.86 (m, 4H, H-7a, CH_2, non assig.), 1.77–1.70 (m, 1H, H-7b), 1.65–1.39 (m, 10H, H-5a, CH_2, non assig.), 1.46 (s, 3H, H-9), 1.41 (s, 3H, H-9), 1.31–1.25 (m, 3H, H-5b, CH_2, non assig.). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3 (C-17), 145.7 (C-11), 144.6 (C-2), 130.8 (C-3), 117.4 (C-12), 114.6 (C-8), 107.4 (C-16), 96.9 (C-15), 90.1 (C-1), 88.1 (C-14), 81.8 (C-10), 72.1 (C-18), 63.2 (C-13), 37.6 (C-4), 34.7 (C-7), 29.6 (CH_2, non assig.), 28.9 (C-9), 28.9 (C-9), 27.9 (CH_2, non assig.), 26.8 (CH_2, non assig.), 25.4 (C-5),

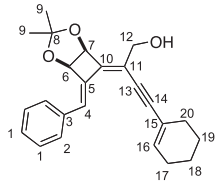
21.9 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3391, 2930, 2854, 1713, 1651, 1447, 1370, 1191, 1149, 1053, 1005, 957, 908, 845, 729, 541. HRMS (ESI, 120 eV) calculated $C_{24}H_{32}O_4$ $[M]^+$ 384.23006, found 384.23046 (Diff.: 1.04 ppm).

4.12.13. [(3aR,4S*,5S*,9bS*)-5-({[tert-Butyl(di-methyl)silyl]oxy} methyl)-7-((3E)-5-{[tert-butyl (dimethyl)silyl]oxy}-3-methylpent-3-en-1-yn-1-yl)-2,2,6-trimethyl-4,9b-dihydro-5H-3a,4-butanocycloocta[3,4]cyclobuta[1,2-d][1,3]dioxol-9-yl] methanol (**30i**).*



The **general procedure VI** was followed using enyne **25** (100 mg, 0.48 mmol, 3 equiv). After 1 h of irradiation at 100 °C, the crude product was purified by flash column chromatography (elution: pentane/Et_2O=7:3) and the desired product **30i** was isolated (67 mg, 64%, **NMR** determined yield) in an inseparable mixture with trienyne **31i** (21 mg, 29%, **NMR** determined yield), both as orange oils; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H, H-14), 5.82 (td, ^3J=6.3 Hz, ^4J=1.3 Hz, 1H, H-22), 4.86 (s, 1H, H-10), 4.30 (AB system, J_{AB}=12.3 Hz, $\Delta\nu$=26.9 Hz, 2H, H-13), 4.23 (dd, ^3J=6.3 Hz, ^5J=0.6 Hz, 2H, H-23), 3.61–3.60 (m, 2H, H-28), 2.89–2.84 (m, 1H, H-17), 2.46 (ddd, ^3J=11.1 Hz, ^3J=11.1 Hz, ^3J=4.0 Hz, 1H, H-3), 2.19–2.14 (m, 1H, H-7a), 2.01 (d, ^4J=1.1 Hz, 3H, H-27), 2.01–1.94 (m, 1H, H-4a), 1.84–1.65 (m, 5H, H-7b, H-6, H-5), 1.77 (d, ^4J=1.3 Hz, 3H, H-21), 1.36 (s, 3H, H-9), 1.25 (s, 3H, H-9), 1.11–1.01 (m, 1H, H-4b), 0.89 (s, 9H, H-26), 0.86 (s, 9H, H-31), 0.06 (s, 6H, H-24), 0.00 (d, ^4J=4.9 Hz, 6H, H-29). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (C-2), 152.8 (C-16), 142.4 (C-11), 135.8 (C-12), 135.7 (C-22), 127.9 (C-14), 119.4 (C-20), 118.5 (C-15), 114.5 (C-8), 96.1 (C-19), 91.1 (C-18), 86.0 (C-1), 82.2 (C-10), 65.2 (C-13), 62.7 (C-28), 60.2 (C-23), 47.6 (C-17), 37.9 (C-3), 36.3 (C-7), 35.5 (C-4), 30.2 (C-9), 28.8 (C-6), 28.2 (C-9), 26.1 (C-26), 25.9 (C-31), 25.4 (C-5), 18.7 (C-25), 18.2 (C-30), 17.9 (C-21), 17.4 (C-27), −5.04 (C-24), −5.4 (C-24), −5.6 (C-29). HRMS (ESI, 120 eV) calculated $C_{38}H_{62}O_5Si_2$ $[M]^+$ 654.41358, found 654.41323 (Diff.: 0.54 ppm).

4.12.14. (Z)-2-((1R,5S*,Z)-7-Benzylidene-3,3-di-methyl-2,4-dioxabicyclo[3.2.0]heptan-6-ylidene)-4-(cyclohex-1-en-1-yl)but-3-yn-1-ol (**34c**).*



In a 2–5 mL microwave vial were added the compound **32** (50 mg, 0.148 mmol, 1 equiv), $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), copper iodide (3 mg, 0.02 mmol, 0.1 equiv), and PPh_3 (4 mg, 0.02 mmol, 0.1 equiv). The vial was sealed with a Teflon cap and the reaction mixture was then dissolved in diisopropylamine (3.0 mL, 0.05 M). The reaction mixture was placed under argon, frozen in liquid nitrogen and put under vacuum. The O_2 liberation proceeds when the temperature rises back to rt. The operation was repeated three times. Then, the enyne **16** (52 μL, 0.44 mmol, 3 equiv) was added to the reaction mixture. The vial was irradiated in the microwave for 5 min at 100 °C. The reaction mixture was then filtered through Celite to eliminate the metal traces and then concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (elution: pentane/AcOEt=8:2) and the trienyne **34c** was isolated (54 mg, quantitative yield) as an orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, ^4J=2.0 Hz, 2H, H-2), 7.40–7.27 (m, 4H, H-1, H-4), 6.28–6.26 (m, 1H, H-16), 5.35–5.32 (m, 2H, H-6, H-7), 4.37–4.32 (m, 2H, H-12), 2.29–2.16 (m, 4H, CH_2, non assig.), 1.74–1.60 (m, 4H, CH_2, non assig.), 1.54 (s, 3H, H-9), 1.48 (s, 3H, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5 (C-10), 140.1 (C-5), 136.7 (C-16), 136.2 (C-3), 128.9 (C-4), 128.8 (3C, C-1, C-2), 128.3 (2C, C-2), 120.9 (C-15), 118.6 (C-11), 115.1 (C-8), 102.2 (C-14), 85.5 (C-13), 79.8 (C-6 or C-7), 78.8 (C-6 or C-7), 63.4 (C-12), 29.1 (C-17), 28.6 (C-9), 27.8 (C-9), 26.0 (CH_2, non assig.), 22.3 (CH_2, non assig.), 21.4 (CH_2, non assig.). IR ($CDCl_3$) ν (cm^{-1})=3428, 2933, 2248, 2177, 1605, 1381, 1371, 1253, 1206, 1144, 1078, 907, 727, 693. HRMS (ESI, 120 eV) calculated $C_{24}H_{26}O_3$ [M]+ 362.18819, found 362.18861 (Diff.: 1.16 ppm).

Acknowledgements

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