Synthetic Methods

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An Expeditious and Atom-Economical Synthesis of a New Generation of Substituted [4.6.4.6]Fenestradienes**

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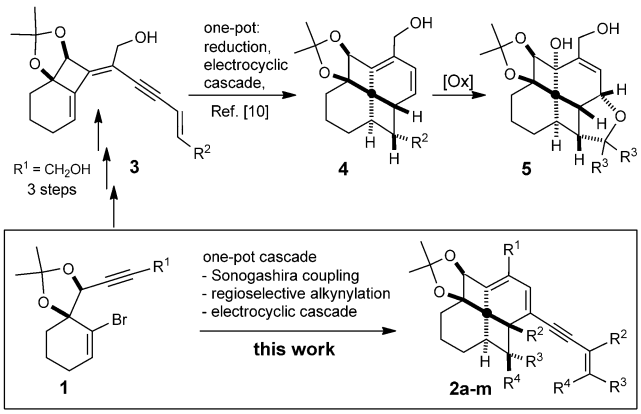
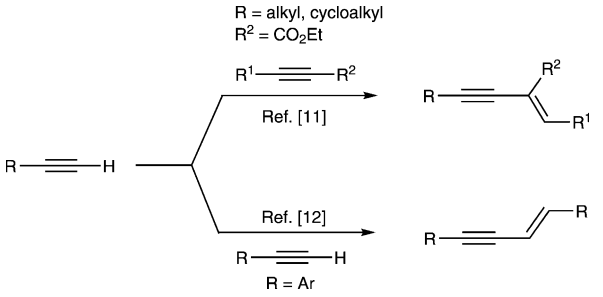
The development of step-economical reactions to access novel structures of biological, material, therapeutic, or theoretical interest is one of the most challenging areas of synthetic chemistry today.[1] In most bond-forming reactions only one or two bonds are formed at a time, but by triggering a cascade of reactions many bonds can be formed in one operation and thus simple starting materials can be efficiently converted into highly sophisticated complex structures. Achieving complexity with such brevity is indeed a key characteristic of the ideal and green synthesis.[2] Toward these ends, we have focused our attention on developing facile routes to unusual scaffolds to prepare structurally diverse materials of potential theoretical and biological value.[3]

Fenestranes have been examined by different research groups from both a theoretical and a synthetic perspective because of their unique structure and occurrence in nature, and their unexplored potential as molecular scaffolds, probes, and materials.[4] Several syntheses of fenestranes have been reported and since the appearance of the earliest contributions in this field, access to these compounds has improved in terms of the number of steps required and overall yield.[5] Intramolecular arene–olefin photo-cycloadditions,[6] photoinduced [2+2] cycloadditions,[7] transition-metal-induced cyclizations,[8] and cascade cyclizations[9] are some of the powerful methods that have been used to generate this class of compounds.

A new approach to the fenestranes was recently demonstrated by our group.[10] Although, fenestradienes **4** were obtained in excellent yields, the method required the use of tin compounds, a sensitive nickel(0) catalyst, and hydrogen, and the intermediate trienyne species **3** was prone to polymerization if not handled with special care (Scheme 1). We herein report a one-step procedure that overcomes these problems and provides facile access to substituted fenestradienes **2** directly from alkenyl bromides **1** (Scheme 1). Our approach was inspired by a method developed by Trost et al.[11] for the selective synthesis of head-to-tail enynes in the presence of $Pd(OAc)_2$ and tris(2,6-dimethoxyphenyl)phosphine (TDMPP), and a similar method developed by Gevorgyan and Rubina for the palladium-catalyzed head-to-head dimerization of aryl acetylenes (Scheme 2).[12] The high regio- and stereoselectivities of these reactions were attributed to the strong steric influence of the ester group R^2 and specific agostic interactions between the *ortho* proton of the aromatic ring and the palladium center, respectively.



Scheme 1. A one-pot synthesis of substituted [4.6.4.6]fenestradienes.



Scheme 2. Head-to-tail and head-to-head synthesis of enynes according to Trost et al.,[11] and Rubina and Gevorgyan.[12]

Our new method is based on a remarkable cascade reaction that involves a 4-*exo*-dig cyclocarbopalladation, a Sonogashira-type coupling, a regioselective alkynylation of a disubstituted triple bond, and $8\pi/6\pi$ electrocyclizations. In accordance with our previous results, an initial Sonogashira-type reaction of alkenyl bromide **1** should generate **7**,[13] which based on the work of the Trost[11] and Gevorgyan[12] groups, should be converted into **9** upon regioselective attack of an appropriate terminal alkyne. The highly unsaturated compound **9** could then collapse through a cascade rearrangement to give fenestradiene **10** (Scheme 3).

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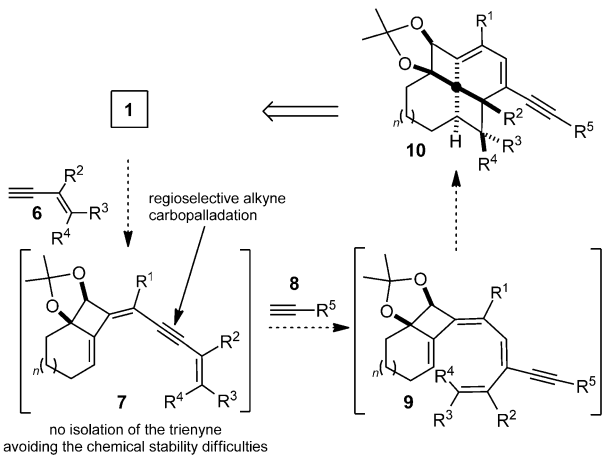
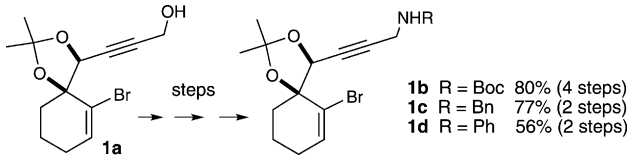


Scheme 3. Retrosynthetic approach to fenestradienes **10**.

We describe herein the preparation of new fenestradienes **2a–n** from the alkenyl bromides **1** using a one-pot cascade reaction of the type described above (Scheme 1). The highly substituted members of this new family of fenestradienes are reasonably stable at room temperature and do not oxidize and cyclize, as was the case for the first generation of fenestradienes (**5**), which were obtained through a reduction of trienyne **3** using a P2-Ni catalyst[17] (Scheme 1). They represent the first examples of fenestradienes **2** possessing a conjugated trienyne and variable substituents that can be used for further elaboration. Alkenyl bromide **1a** was chosen as a suitable model substrate for this study and was easily prepared from 2-bromocyclohexenone by a previously reported sequence of four steps in good overall yield.[14] The propargylic amine derivatives **1b**, **1c**, and **1d** were prepared in two or four steps from **1a** (Scheme 4).



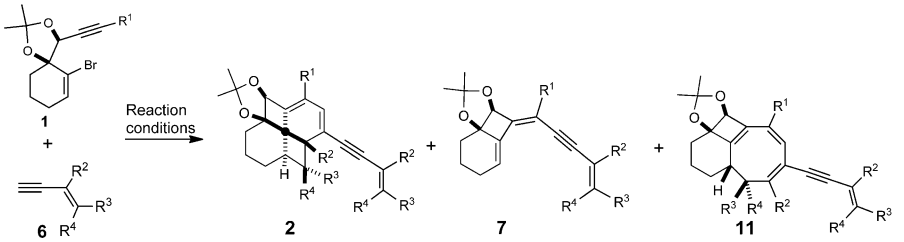
Scheme 4. Preparation of propargylic amines **1b–d.**

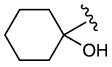
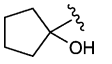
As summarized in Table 1, the alkenyl bromides **1a–d**, were treated with $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), and diisopropylamine and after heating (90–100°C) using a microwave, afforded, in a single five-step process, the stable and diastereomerically pure fenestradienes **2a–n**. The yields were strongly influenced by the structure of both starting materials. A variety of enynes **6** reacted with dioxolane **1a** to give [4.6.4.6]fenestradienes **2a–h** in moderate to good yields (entries 1–8). When amines **1b–d** were subjected to the same reaction conditions, the corresponding fenestradienes **2i–n**, including an allylic amine (entries 9–14) were obtained in good yields (40–80%).

Two side-products, the cyclooctatriene **11** and the trienyne **7**, were observed in variable amounts in several cases (Table 1), but could be easily separated from **2** by using silica gel flash chromatography. As well as fenestradiene **2**, in seven cases (entries 3, 4, 6, 7, 10, 13, and 14), trienynes **7c**, **7d**, **7f**, **7g**, **7j**, **7m**, and **7n** were also isolated and in nine cases (entries 1–4, 6, 8–10, and 13), cyclooctatrienes **11a**, **11b**, **11c**, **11d**, **11f**, **11h**, **11i**, **11j**, and **11m** were also isolated. Despite a screen of reaction conditions, the formation of these products could not be avoided, as they are formed in competition with the fenestradienes, which represent the kinetic products (see below).

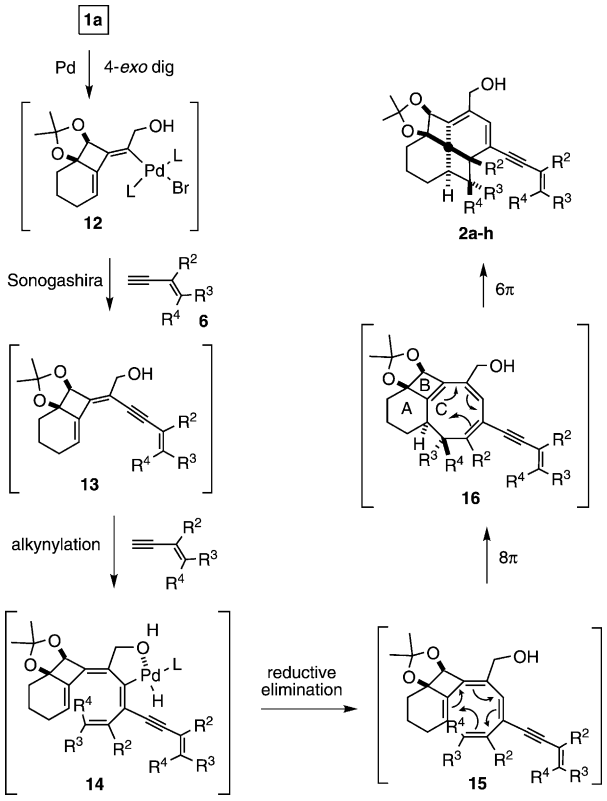
To rationalize the above results, we proposed the mechanistic pathway depicted in Scheme 5. After an initial 4-*exo*-dig cyclocarbopalladation of the alkenyl bromide **1a** to produce the palladium derivative **12**, a Sonogashira-type reaction could occur to form **13**. This highly unsaturated trienyne **13** could then react with a second equivalent of the enyne **6** to afford the hydrido palladium intermediate **14**, which could then undergo rapid reductive elimination to

Table 1: Synthesis of substituted fenestradienes **2**.[a]



Entry	1	R^2	R^3	R^4	2	Yield [%][b]	7	Yield [%][b]	11	Yield [%][b]
1	**1a**	H	CH_2NHBoc	H	**2a**	43	–	–	**11a**	25
2	**1a**	CH_3	H	H	**2b**	73	–	–	**11b**	15
3[c]	**1a**	H		H	**2c**	39	**7c**	47	**11c**	9
4	**1a**	H		H	**2d**	59	**7d**	25	**11d**	8
5	**1a**	CH_3	(*E*)-CH_2OH	H	**2e**	68	–	–	–	–
6	**1a**	CH_3	(*E*)-$CH_2OTBDMS$	H	**2f**	72	**7f**	8	**11f**	10
7[c]	**1a**	CH_3	H	(*Z*)-$CH_2OTBDMS$	**2g**	40	**7g**	30	–	–
8[d]	**1a**	H	CH_2CH_2Ph	H	**2h**	46	–	–	**11h**	36
9	**1d**	CH_3	H	H	**2i**	72	–	–	**11i**	15
10	**1d**	CH_3	(*E*)-$CH_2OTBDMS$	H	**2j**	40	**7j**	29	**11j**	22
11	**1c**	CH_3	H	H	**2k**	80	–	–	–	–
12	**1c**	CH_3	H	(*Z*)-$CH_2OTBDMS$	**2l**	59	–	–	–	–
13	**1b**	CH_3	H	H	**2m**	48	**7m**	20	**11m**	7
14	**1d**	CH_3	H	(*Z*)-$CH_2OTBDMS$	**2n**	45	**7n**	48	–	–

[a] Reaction Conditions: Enyne **6** (3 equiv), $Pd(OAc)_2$ (5 mol%), CuI (10 mol%), PPh_3 (10 mol%), iPr_2NH, MW, Δ, 60 min. [b] Yields of isolated products after chromatography. [c] Reaction time of 120 min was used. [d] Reaction time of 30 min was used.



Scheme 5. Mechanistic proposal for the regioselective preparation of substituted fenestradienes.

regenerate Pd^0. We believe that the high regioselectivity of the alkynylation is controlled by chelation of the metal to the proximate allylic alcohol or amine, which is in the α position to the triple bond; this chelation stabilizes intermediate **14**. Compound **15** cannot be isolated because it undergoes spontaneous and torquoselective conrotatory 8π electrocyclization to give cyclooctatriene **16**, the relative stereochemistry of which would be in accordance with our previous results.[10b] The postulated cyclooctatrienes **16**, would undergo further reaction in the form of a torquoselective disrotatory 6π electrocyclic process to generate the [4.6.4.6]fenestradienes **2a**–**h**.

Notably, the addition of one equivalent of enyne **6**, followed by microwave irradiation, then the addition of a second equivalent of **6** (or any other structurally different enyne) under the same reaction conditions, did not produce any of the corresponding fenestradiene. More importantly, when a trienyne of type **13** (obtained by the reaction of 1.2 equivalents of **6** with **1a**) was subjected to the reaction conditions with 1.2 equivalents of enyne **6**, fenestradiene **2** was not obtained; the starting material was fully recovered. The presence of at least 2.5 equivalents of enyne **6** at the beginning of the process is therefore essential for the reaction to proceed in the desired manner.

The [4.6.4.6]fenestradienes **2a**–**n** were isolated in diastereomerically pure form and were characterized using NMR spectroscopy, including the analysis of NOESY experiments, and mass spectrometry. Structural confirmation was obtained through X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative of **2d** (compound **17**, Figure 1).[15] This X-ray structure exhibited a significantly distorted central quaternary carbon atom that is attributable to the size and configuration of the fused rings. The associated orthogonal

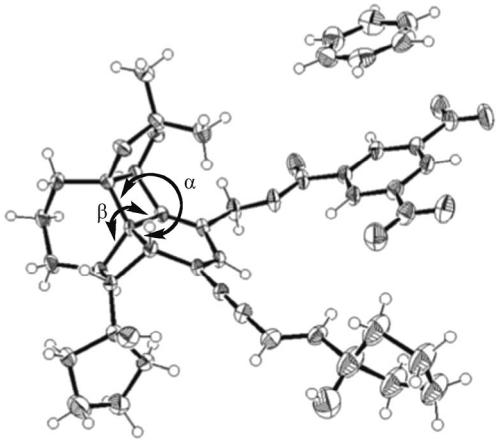
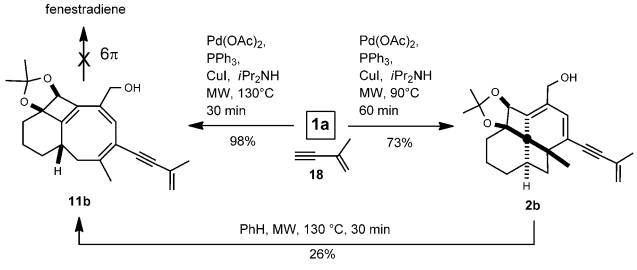


Figure 1. X-ray crystal analysis of the 3,5-dinitrobenzoate derivative **17**. Thermal ellipsoids are set at 50% probability and hydrogen atoms have been removed for clarity.

bonds angles, α and β, are 126° and 122°, respectively, thus making this compound one of the most distorted members of the fenestrane family to be reported in the literature.[16] DFT calculations, which were carried out on related compounds,[10b] imply that the relative configuration of the centers in 2a–n arises from a 6π electrocyclization that proceeds in a direction that is dictated by the shape of the three contiguous ABC rings of the cyclooctriene **16**.

When the reaction of compound **1a** was conducted at 130 °C in the presence of 3 equivalents of the enyne **18**, palladium acetate, PPh_3 and copper iodide, the cyclooctatriene **11b** was cleanly obtained in very good yield (98%) without any trace of the corresponding fenestradiene (Scheme 6). As anticipated by our previous studies, the inferred torquoselectivity of the 8π electrocyclization reaction that is required for the formation of **11b** is opposite to that required for the cascade reaction toward fenestradiene. Undoubtedly, the cyclooctatriene **11b** represents the thermodynamically more stable product in this reaction. The isolation of **11b**, albeit in only 26% yield, when the fenestradiene **2b** was heated to 130 °C using microwave



Scheme 6. Thermodynamic/kinetic control of the reaction.

irradiation for 30 minutes, supports this hypothesis. This low yield can be explained by the existence of other transformative pathways involving the fenestradiene **2b** at 130 °C. This behavior was found to be general for all other fenestradienes subjected to similar reaction conditions. The amino-substituted fenestradienes **2i**–**n** are more kinetically stable than the corresponding hydroxy derivatives **2a**–**h** as inferred by the higher temperatures that were required for the transformation of the former into their corresponding cyclooctatrienes **11**.

In conclusion, we have herein reported a new method for the preparation of [4.6.4.6]fenestradienes that involves, in a one pot reaction, an unprecedented 4-*exo*-dig C–C bond formation, a Sonogashira-type coupling, a regioselective alkynylation, and a 8π/6π electrocyclization cascade reaction. The exceptional efficiency of this process is highlighted by the limited number of steps that were required to synthesize these structurally complex products. These fenestranes are unusual as suggested in part by their highly strained bond angles. Further extension of this chemistry to the rapid and efficient synthesis of similar compounds, for example, those bearing five- or seven-membered rings or the use of cycloalkyl iodides, triflates or substituted cyclohexenyl bromide as substrates are underway. DFT calculations will also be carried out to understand more fully the observed regio- and torquoselectivity.

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[15] CCDC 827789 (**17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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