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Synthesis of [4.6.4.6]Fenestradienes and [4.6.4.6]Fenestrenes Based on an 8π−6π-Cyclization-Oxidation Cascade

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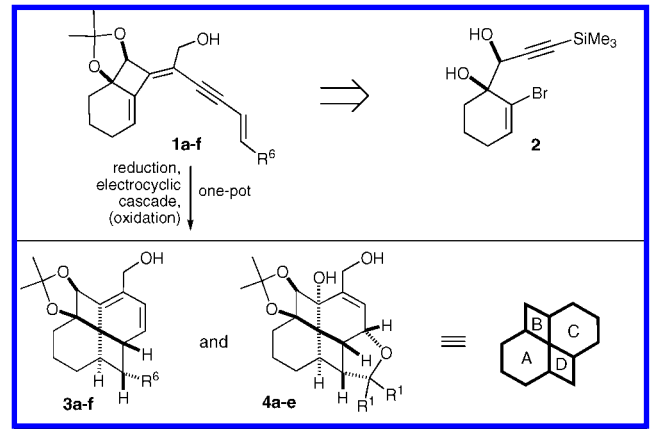
The fenestranes comprise a structurally and theoretically fascinating class of organic molecules in which a quaternary carbon is shared by four rings. Found in natural products such as laurenene and in a wide range of targets of theoretical interest, these polycyclic scaffolds have attracted much synthetic interest over the past 35 years.[1] These studies have focused mainly on the energetic consequences of forcing the tetravalent carbon common to the tetracyclic network toward a strained planar geometry. Several impressive syntheses of fenestranes with improved step economy and efficiency have been reported.[2]

Notwithstanding these advancements, the introduction of methods that access novel fenestranes is central to exploiting these polycycles as ligands for catalysis, materials, and drug discovery opportunities. An especially important attribute of smaller ring fenestranes is that they provide a scaffold for the display of pharmaceutically relevant functionalities in a unique, spatially and conformationally defined fashion. Toward this end, we describe herein a step-economical synthesis of a new family of substituted fenestradienes **3a**−**f** and fenestrenes **4a**−**e**. These novel systems **4a**−**e** are obtained directly, in a one-pot operation, through a remarkable cascade starting with the Ni-catalyzed semihydrogenation of trienynes **1a**−**f** readily prepared from diol **2** in six steps and in good overall yield (Scheme 1).[3]

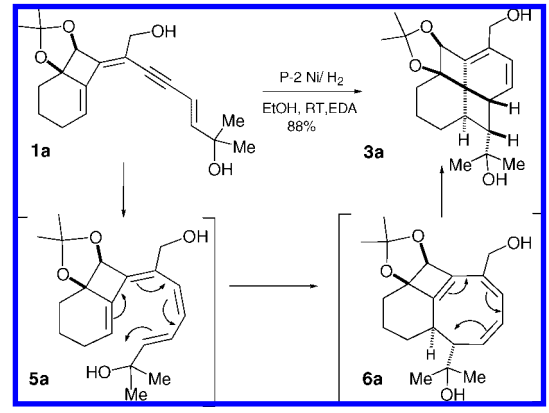
Several classical catalysts (Lindlar, Zn(0)/CuBr, $NiCl_2$/$NaBH_4$, $Ni(OAc)_2 \cdot 4H_2O$-BER),[4] well-known for their ability to partially hydrogenate a triple bond, were selected and tested on the model substrate **1a**. Unexpectedly, in all cases, only traces of compound **3a** were isolated. Gratifyingly, when P-2 Ni[5] ($Ni(OAc)_2 \cdot 4(H_2O)$, 1 equiv; $NaBH_4$, 1 equiv; EDA, 3.5 equiv; EtOH, H_2 1 atm, 16 h, room temp) was used, compound **1a** was almost completely consumed and a new cyclized product **3a** was formed in 88% yield. Scheme 2 illustrates the proposed mechanism for the remarkable conversion of **1a** to the observed [4.6.4.6]fenestradiene **3a**. Partial reduction of the alkyne functionality in **1a** generates tetraene **5a**, which can undergo an 8π-conrotatory electrocyclization to form cyclooctatriene **6a**. This intermediate then undergoes a 6π-disrotatory electrocyclic cyclization to provide **3a** as the sole product isolated in this reaction sequence. No traces of intermediates **5a** or **6a** were detected during the process. Of particular interest was the nature of the cyclized product. The reaction was stereoselective, and only one diastereomer of the [4.6.4.6]fenestradiene was obtained with the relative configuration shown in Scheme 2 as determined by NOESY experiments.

When compound **3a** was stored at −20 °C under air for several hours, it reacted slowly with O_2 to give a new product that possesses all characteristic data corresponding to the [4.6.4.6]fenestrene **4a** (Scheme 3). Exemplary of the novel chemistry of strained fenestranes, the transformation of **3a** into

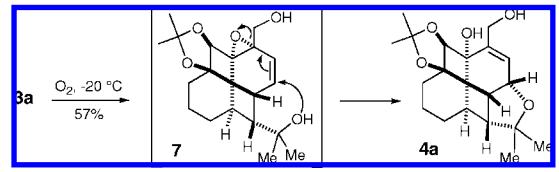
Scheme 1. Structure of [4.6.4.6]Fenestradienes **3a**−**f**, [4.6.4.6]Fenestrenes **4a**−**e** (For details see Table 1.)



Scheme 2. Proposed Mechanism for the Formation of **3a**



Scheme 3. Spontaneous Cyclization of **3a** to **4a** in the Presence of Air/O_2 or *m*-CPBA



4a can be explained by a spontaneous oxidation of the highly reactive [4.6.4.6]fenestradiene **3a** with molecular oxygen. To confirm the oxidation sequence, **3a** was submitted to 1 equiv of *m*-CPBA in CH_2Cl_2 at 0 °C; compound **4a** was isolated in pure form in 63% yield. These experiments suggest that epoxide **7** is generated as a nonisolable intermediate, which leads to **4a** by an $S_{N'}$ attack of the dimethylcarbinol on the double bond of

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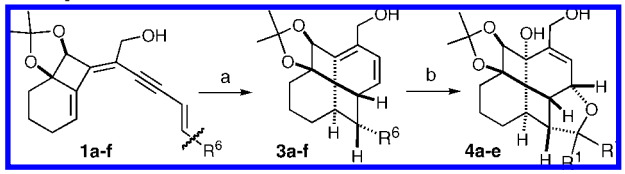
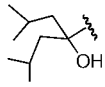
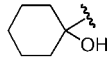
Figure 1. X-ray crystal structure of the 3,5-dinitrobenzoate derivative **8**. The majority of hydrogens are omitted for clarity.

Table 1. Synthesis of [4.6.4.6]Fenestradienes **3a**−**f** and [4.6.4.6]Fenestrenes **4a**−**e**



Entry	starting compound R^6	product	yield [%][c]	product	yield [%][c]
1	**1a** $C(CH_3)_2OH$	**3a**	88	**4a** R^1= Me	63, (57)[e]
2	**1b** 	**3b**	63[h]	**4b** R^1= *iso*-Bu	67
3	**1c** 	**3c**	86	**4c** R^1,R^1= $(CH_2)_5$	68
4	**1d** 	**3d**	93	**4d** R^1,R^1= $(CH_2)_4$	62
5	**1e** CH_2OH	**3e**	f	**4e** R^1,R^1= H	35[g]
6	**1f** $(CH_2)_5CH_3$	**3f**	90	–	–

[a] P-2 Ni, 1 equiv, EDA, EtOH, H_2, 1 atm. [b] *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 20 min−1 h. [c] Yield determined by ^{1}H-NMR on the crude. [d] Yield of isolated product after chromatography. [e] Neat, under air/O_2. [f] Not determined. [g] Yield for the two steps (a, b) from **1e**. [h] The product **3b** was contaminated by 30% of inseparable **1b**.

the epoxide **7** as shown in Scheme 3. The stereochemistry observed for this transformation is completely controlled by the shape of the three contiguous CBD ring and the intramolecular attack of the hydroxy group onto the double bond occurred from the less hindered face of the molecule. The resulting [4.6.4.6]fenestrene **4a** is stable and can be purified by classical silica gel chromatography. The structure of **4a** was elucidated by extensive ^{1}H and ^{13}C NMR analysis and high resolution mass spectrum analysis (MS−MS). Structural confirmation was obtained through X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative **8** (Figure 1). This X-ray structure shows significant distortion of the central quaternary carbon atom that is attributable to the size and configuration of the fused rings. The two important orthogonal bond angles α and β are respectively widened to 118° and 124°.

These high values can be compared to those of the corresponding angles, determined by X-ray analysis in several fenestranes, that are widened between 116° and 134.9° for the most representative ones.[6] To the best of our knowledge, this sequence represents the first reported $8\pi\rightarrow6\pi\rightarrow$[$O_2$-oxi] cyclization cascade to highly substituted fenestrenes of this type and complexity. The extension of this reaction sequence to other systems has also been investigated. In all cases the fenestradienes **3a**−**f** were obtained from **1a**−**f** in very good yields (63–93%) in view of the complexity of the reaction sequence. Only **3a** was stable enough to be purified by chromatography on silica gel treated with Et_3N. Due to the high purities of the crude reaction products and their sensitivity to silica gel, compounds **3b**−**d** were not purified by chromatography but directly engaged into the *m*-CPBA oxidation step producing **4b**−**d** in good yields (62–68%). Compound **4e** was obtained in 35% yield in two steps.

In conclusion, we have reported a means of preparing a new family of [4.6.4.6]fenestradienes, and [4.6.4.6]fenestrenes through a unique $8\pi\rightarrow6\pi\rightarrow$[$O_2$-oxi] cascade electrocyclization sequence. The high yields and the limited number of steps of the reaction sequence render this process very attractive for the synthesis of new fenestranes. Further extensions of this chemistry to the rapid and efficient syntheses of compounds of significant structural complexity are underway in our laboratory.

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Supporting Information Available: Full experimental details are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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