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An Arene-Alkene Photocycloaddition-Radical Cyclization Cascade: The First Syntheses of *cis,cis,cis,trans*-[5.5.5.5]-Fenestranes

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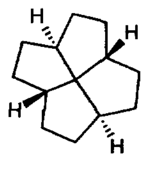
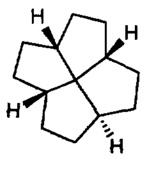
Abstract: The first *cis,cis,cis,trans*-[5.5.5.5]-fenestranes have been synthesized in three steps using a novel arene-alkene photocycloaddition-radical cyclization cascade, which creates overall 5 new rings and 8 stereogenic centers. A lead tetraacetate mediated ring expansion of a 5,5-fused ring system, discovered in the course of exploring the chemistry of these new materials, is also described.

A principal challenge of organic synthesis is the invention of reactions and strategies that allow for the facile conversion of simple compounds into complex materials, medicines, or molecules of theoretical interest.[2] With the capacity to produce up to 3 new rings and 6 new stereogenic centers in one step, the arene-alkene photocycloaddition reaction[3] provides a remarkably effective means of addressing this challenge. We now illustrate how a new version of this cycloaddition reaction, employing arene-*bis*-alkenes, can be coupled to a radical cascade process to produce *in 3 steps overall a product with 5 new rings and 8 stereocenters.* The sequence allows for the first syntheses of *cis,cis,cis,trans*-[5.5.5.5]-fenestranes,[4] compounds of theoretical interest with potential for use in materials and medicinal research.

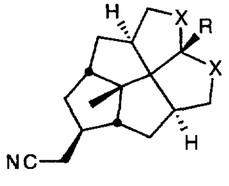
Fenestranes[5] (e.g., **1a**, **1b**) possess four rings sharing a central carbon atom. Like steroids, fenestranes are conformationally rigid and chemically robust, providing a surface which could serve[6] as a scaffold for molecular recognition elements,[7] novel catalysts,[8] chiral auxiliaries,[9] chemical libraries,[10] and mechanistic studies requiring spatially defined functionality.[11] Unlike steroids, fenestranes have been relatively unavailable.



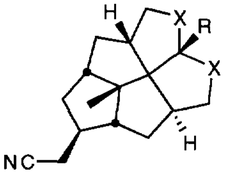
1a
a *cis,cis,cis,cis*-
[5.5.5.5]-fenestrane



1b
a *cis,cis,cis,trans*-
[5.5.5.5]-fenestrane



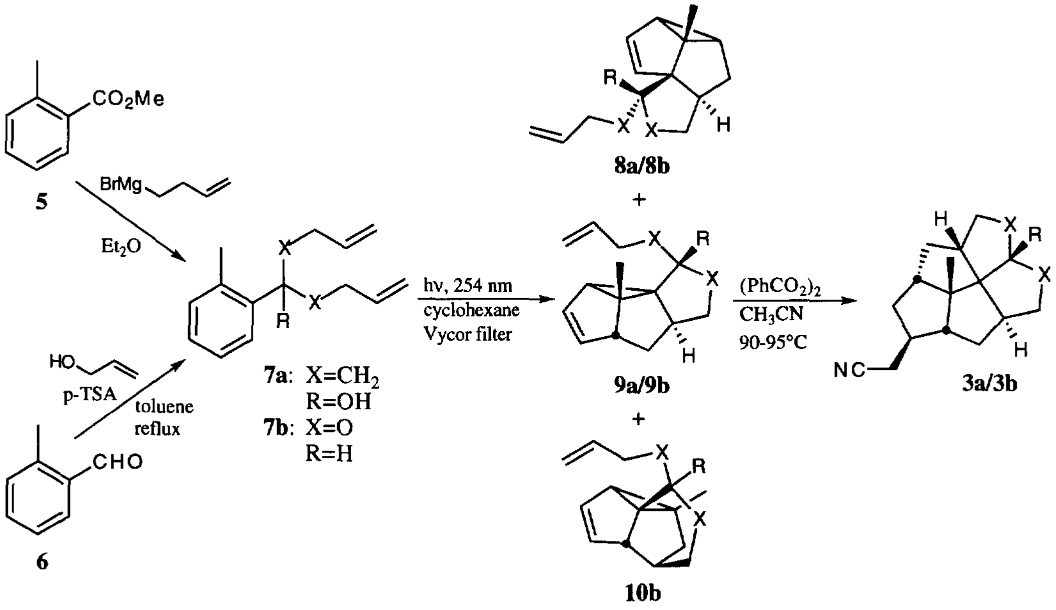
2a: R=OH, X=CH_2
2b: R=H, X=O
cis,cis,cis,cis



3a: R=OH, X=CH_2
3b: R=H, X=O
cis,cis,cis,trans

Starting from toluic acid derivatives, we have developed a three step synthesis of fenestrane derivatives **3a** and **3b**. Unlike previously synthesized fenestranes, **3a** and **3b** possess the higher energy *cis,cis,cis,trans*-[5.5.5.5]-fenestrane skeleton;[12] semi-empirical calculations (PM3/Spartan™) estimate **3a** to be approximately 11.2 kcal/mol higher in energy than **2a** and **3b** to be approximately 20.4 kcal/mol higher than **2b**.

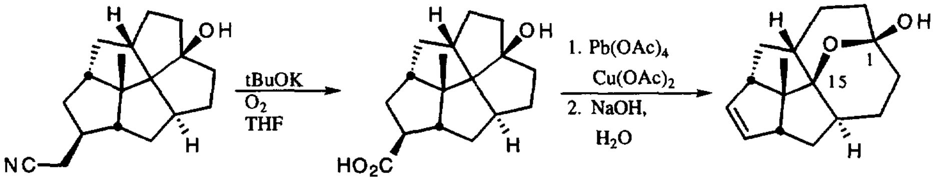
The syntheses are shown in Scheme 1. 5-(2'-Methylphenyl)-nona-1,8-dien-5-ol (**7a**) was prepared in 40% yield by treating *o*-toluate **5** with 2.5 equivalents of 3-butenyl-1-magnesium bromide. Irradiation (Hanovia 450 watt Hg lamp, Vycor filter) of the dienol **7a** (4.34mmol/30ml cyclohexane) produced two major photoadducts, the angular vinyl cyclopropane **8a** and the linear isomer **9a**, in a 37% isolated yield and in a 1:2 ratio after flash chromatography and MPLC (9:1 hexanes/Et_2O). In earlier studies,[13] we have shown that related vinyl cyclopropanes can be cleaved by free radical addition to the cyclopentene. We have now found that the intermediate free radical produced in this process can be trapped with a tethered alkene.[14] Thus, when exposed to acetonitrile radicals generated from benzoyl peroxide in refluxing acetonitrile, the linear adduct **9a** undergoes a remarkable cascade reaction producing the pentacyclic nitrile **3a** in 35% yield.



Scheme 1

Reacting *o*-tolualdehyde **6** with allylic alcohol and catalytic *p*-toluenesulfonic acid in refluxing toluene gave the allylic acetal **7b** in 84% yield after removal of excess reagents under reduced pressure. Irradiation of **7b** produced **8b** and **10b** (24%) and **9b** (22%) with recovery of starting material (22%) after flash chromatography and MPLC (5% EtOAc/hexanes). The linear adduct **9b** gave the fenestrane **3b** in 32% yield upon treatment with acetonitrile radicals in refluxing acetonitrile. A trace amount of addition to the terminal olefin was observed.

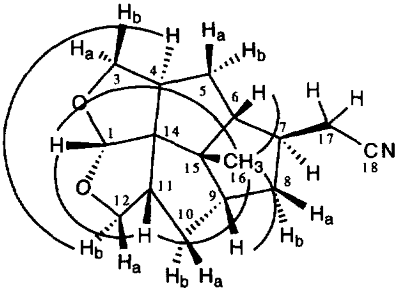
Since the signals in the NMR of **3a** are insufficiently dispersed for complete assignment, efforts were directed at producing a suitable derivative of **3a** for X-ray crystallography (Scheme 2). Oxidative cleavage[15] of **3a** using potassium *tert*-butoxide and molecular oxygen in THF gave the acid **11** which, when treated with lead tetraacetate followed by base hydrolysis, gave **12** as a crystalline solid (50% yield). X-ray crystallography[16] established the structure of **12**, and consequently that **3a** possesses the novel *cis,cis,cis,trans*-[5.5.5.5]-fenestrane subunit. This conclusion is further afforced by the lack of a symmetry plane in **12**, as revealed by ^{13}C NMR spectroscopy. The oxidation of **11** represents an example of a novel lead tetraacetate mediated ring expansion of a bicyclo[3.3.0]octane subunit,[17] a process which previews some of the interesting chemistry to be discovered in this new compound class. Presumably, this oxidation proceeds by fragmentation of the lead(IV) alkoxide to a C1 ketone and C15 tertiary radical. Copper(II)acetate oxidation of the latter to the cation, followed by transannular trapping by a C1 hemiketal would give the acetate, from which **12** is derived by hydrolysis.[18]



3a **11** **12**

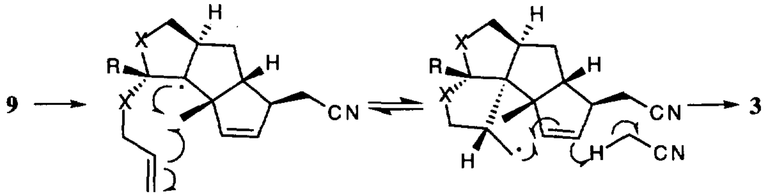
Scheme 2

Acetal **3b**, while also not crystalline, exhibited sufficient signal dispersion for structural characterization by COSY, NOESY, and HETCOR experiments and by analogy with **3a**. NOE data confirmed that **3b** was the higher energy *cis,cis,cis,trans*-[5.5.5.5]-fenestrane analog. Crosspeaks were observed for enhancements due to H16–H1, H1–H11, H11–H16, H16–H6, and H16–H9 interactions establishing that all of these protons were positioned on the top face of the fenestrane. No crosspeak was observed for H16–H4, but one for H12b–H4 was observed indicating that these protons were on the opposite side of the structure from H11.



3b

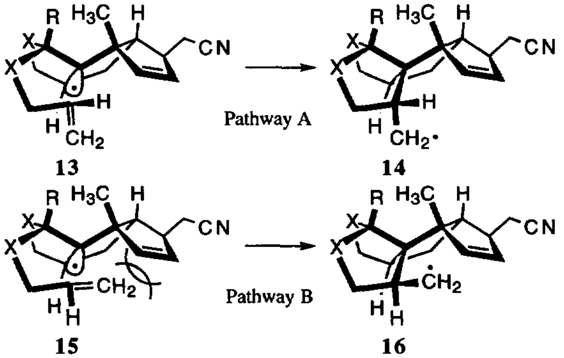
It is noteworthy that the above radical cascade reactions (**9a**/**9b** to **3a**/**3b**) produce the *higher* energy fenestranes (Scheme 3). The conversion of **13** to **14** determines the course of this reaction as well as the stereochemistry of the final product.[19] There are two trajectories for the addition of the tertiary radical to the tethered alkene in **13**. Steric interactions between the alkene and the cyclopentene ring disfavor pathway B (Scheme 4). In contrast, closure through pathway A is less sterically encumbered, leading to radical **14**. PM3/Spartan™ calculations indicate that **14** (X=O) and **14** ($X=CH_2$) are 8.5 and 3.9 kcal/mol lower in energy than **16** (X=O) and **16** ($X=CH_2$), respectively. Subsequent addition to the proximate alkene and abstraction of hydrogen from the solvent gives **3** and regenerates the acetonitrile radical.



13 **14**

Scheme 3

We have synthesized the first fenestrane isomers with an energetically unfavorable *trans* ring fusion. The sequence used is remarkably concise, producing in 3 steps 5 new carbon-carbon bonds, 8 new stereocenters, and 5 new rings. In addition, we have begun to investigate the chemistry of this strained ring system, illustrated by the novel oxidative ring expansion reaction of the bicyclo[3.3.0]octane subunit. Further studies on the synthesis and use of these new materials are in progress.



Scheme 4

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