Strained Polycycles

Synthesis of *cis*,*cis*,*cis*,*cis*-[5.5.5.4]-1-Azafenestrane with Discovery of an Unexpected Dyotropic Rearrangement**

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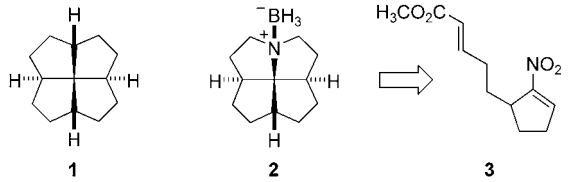
Fenestranes[1] [*fenestra* (Lat.), window] are a unique family of compounds with four fused carbocycles that share a central quaternary carbon atom which exhibits planarizing distortion (for example, **1**, Scheme 1).[2] By changing ring sizes and ring-



Scheme 1. *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-Fenestrane (**1**) and *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-1-azafenestrane·BH_3 (**2**).

fusion configurations, variable planarization of the central carbon atom results, thus giving chemists a tool with which to probe one of the cornerstone theories of organic chemistry.[3] Unfortunately, unsubstituted fenestranes are low-molecular-weight hydrocarbons, and therefore crystallization for single-crystal analysis and quantification of the distortions to the central carbon atom is difficult.[4] By substituting a nitrogen

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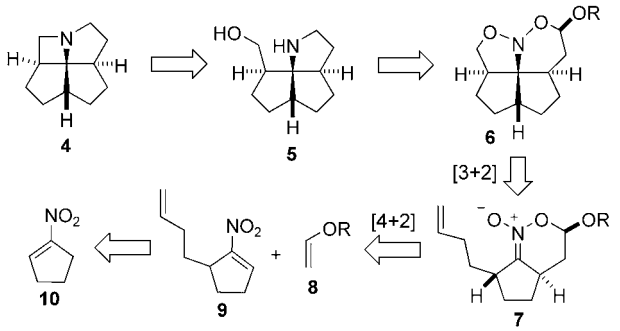
atom for one of the external bridgehead carbons, new opportunities for X-ray crystallographic analysis exist.

We recently reported the first synthesis of a 1-azafenestrane, *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-1-azafenestrane·BH_3 (**2**),[5] which featured the tandem [4+2]/[3+2] cycloaddition[6] of nitrocyclopentene **3** as the key step. Although the tandem cycloaddition allows for rapid and stereoselective formation of the required skeleton, problematic steps in the synthesis of nitroalkene **3** led to a poor overall yield of azafenestrane **2** (18 steps, 0.02% overall yield). Furthermore, azafenestrane **2** displayed only modest planarizing distortions to the central carbon atom.[7] Therefore, an efficient route to an even more strained azafenestrane was sought, and the successful realization of that goal is described herein.

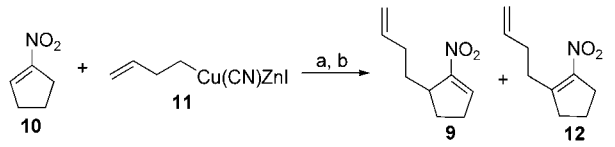
Contraction of one of the pyrrolizidine five-membered rings in azafenestrane **2** should lead to increased planarization of the central carbon atom.[8] Retrosynthetic analysis for *cis*,*cis*,*cis*,*cis*-[5.5.5.4]-1-azafenestrane (**4**) is presented in Scheme 2. The azetidine ring in **4** should be formed through



Scheme 2. Retrosynthetic analysis for *cis*,*cis*,*cis*,*cis*-[5.5.5.4]-1-azafenestrane (**4**).

an irreversible intramolecular displacement of an activated alcohol **5**, which is derived from nitroso acetal **6** through hydrogenolysis. This reduction involves two N–O-bond cleavages and a reductive amination to form the pyrrolidine ring in a single operation. Nitroso acetal **6** is the direct product of tandem inter-/intramolecular [4+2]/[3+2] cycloaddition of nitroalkene **9** and a suitable vinyl ether. Presumably, vinyl ether **8** would approach from the less hindered side of the nitroalkene (opposite the tethered olefin) to give an *anti* relationship between the hydrogen atoms at the ring-fusion sites in nitronate **7**. An *exo*-fold, [3+2] cycloaddition[9] with the unactivated dipolarophile[10] would then set the remaining two stereogenic centers (final ring fusion and central carbon atom) in the required sense for the all-*cis* azafenestrane skeleton. The required 5-butenyl-1-nitrocyclopentene **9** would be available from 1-nitrocyclopentene (**10**) through 1,4-addition followed by regeneration of the nitroalkene.

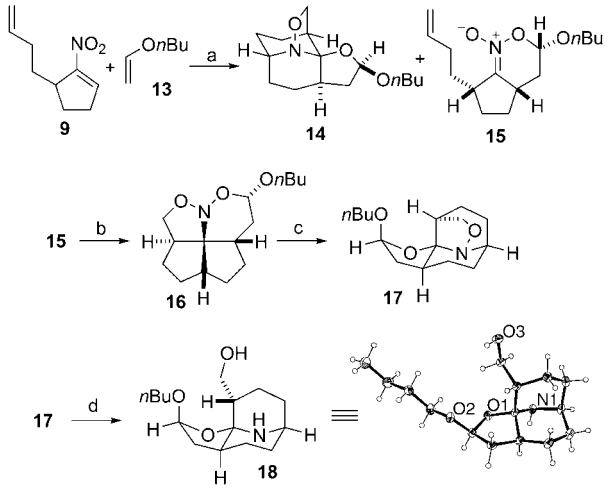
A route analogous to that reported for nitroalkene **3** involving nitroallylation[11] was first investigated for the synthesis of **9**. Although the desired target was obtained, a very poor overall yield for the sequence prompted the development of a more efficient synthesis (Scheme 3). Treatment of 1-nitrocyclopentene (**10**)[12] with 3-butenylcyanozinc cuprate **11**,[13] followed by trapping of the resulting nitro-



Scheme 3. a) THF, 0°C, 1 h, then PhSeBr, 0°C→RT, 1 h; b) H_2O_2, THF, 0°C→RT, 30 min (78% from **10**; **9**/**12** 2:1).

nate[14] with phenylselenyl bromide, provided a mixture of nitroselenides. Upon oxidation, *syn* selenoxide elimination gave the desired nitroalkene **9**, along with its double-bond isomer **12** (**9**/**12**, 2:1) in 78% combined yield from 1-nitrocyclopentene. All attempts at chromatographic separation of the two nitroalkenes were unsuccessful. Ultimately, the most efficient way to separate the two nitroalkenes was simply to carry out the next step of the azafenestrane synthesis with the mixture of compounds. Trimethylaluminum-promoted [4+2] cycloaddition of trisubstituted nitroalkene **9** with various vinyl ethers takes place in less than one hour at −78°C and leaves tetrasubstituted nitroalkene **12** unreacted.

Treatment of nitroalkene **9** (Scheme 4) with *n*-butyl vinyl ether in the presence of trimethylaluminum was expected to provide nitroso acetal **6** (Scheme 2, R = *n*-butyl), the product

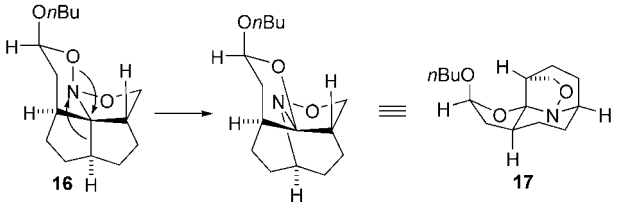


Scheme 4. a) $AlMe_3$, CH_2Cl_2, −78°C, 30 min (48% **14**, 36% **15**); b) K_2CO_3, toluene, reflux, 2 h; c) SiO_2, room temperature; d) H_2 (26 atm), Raney Ni, MeOH, 14 h (46% from **15**). ORTEP-3 plot of **18** (30% thermal ellipsoids).

of tandem [4+2]/[3+2] cycloaddition. However, the major product of the reaction was compound **14**, which contains an azabicyclononane ring system and two five-membered rings! The minor [4+2] cycloadduct **15** derived from *endo* approach of *n*-butyl vinyl ether from the same face as the tethered dipolarophile was also isolated. The structure of aminal **14** was established from studies carried out with the minor cycloadduct **15**: Thermal intramolecular [3+2] cycloaddition of nitronate **15** with its tethered dipolarophile in refluxing toluene gave nitroso acetal **16**. However, upon purification with silica gel, a new product, **17**, which is a diastereomer of aminal **14**, was formed. The structure of **17**, and by analogy

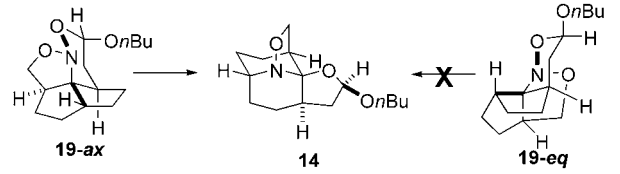
that of its diastereomer **14**, was confirmed by X-ray crystallographic analysis[15] of hydrogenation product **18**, in which the only N–O bond has been cleaved.

This novel rearrangement that converts nitroso acetal **16** into aminal **17** involves breaking both an N–O bond and a C–C bond with formation of a C–O bond and a C–N bond (Scheme 5). Analysis of the 3D structure of nitroso acetal **16** clearly shows the two breaking bonds in near-perfect antiperiplanar alignment. The ensuing transposition, known as a dyotropic rearrangement,[16] can take place readily to give the rearranged product **17**.[17]



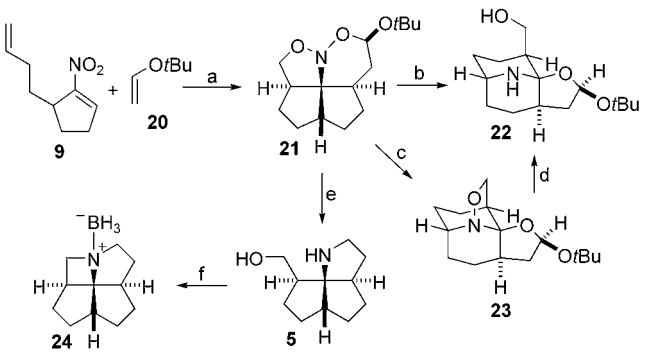
Scheme 5. Dyotropic rearrangement of nitroso acetal **16**.

Although this unexpected dyotropic rearrangement is mechanistically intriguing and potentially useful synthetically, its occurrence in the formation of the major product under the conditions employed for the tandem cycloaddition reaction precludes formation of the desired amino alcohol **5**. However, from conformational analysis of nitroso acetal **19** (the product of tandem [4+2]/[3+2] cycloaddition with approach of the dienophile from the opposite side to that occupied by the tethered dipolarophile, and the precursor to aminal **14**), a means to prevent the rearrangement became apparent (Scheme 6). The 1,2-oxazine ring in nitroso acetal **19-*ax*** adopts a chair conformation, which places the butyloxy group in an (anomerically stabilized) axial orientation. This conformation exhibits the required stereoelectronic alignment of the two migrating bonds (bold); thus the rearrangement takes place readily to give aminal **14**. However, in a second low-energy conformation, depicted in structure **19-*eq***, a chair flip has occurred, and the migrating bonds (bold) are no longer in alignment. By favoring this conformation, the rearrangement should be suppressed, and hydrogenolysis might provide the desired tricyclic amino alcohol **5**. Calculations[18] suggest that the two conformers are very close in energy. A nitroso acetal derived from a bulkier vinyl ether might favor the equatorial conformer and consequently deter or prevent the undesired dyotropic rearrangement.



Scheme 6. Conformations of nitroso acetal **19**.

In the event, tandem cycloaddition of *tert*-butyl vinyl ether with nitroalkene **9** promoted by trimethylaluminum (Scheme 7) led to formation of nitroso acetal **21** with no rearrangement under the reaction conditions, thus providing support for the proposed hypothesis. The crude reaction mixture contained, in a 2:1 ratio, nitroso acetal **21** (*endo* approach of the dienophile from the side opposite the tethered dipolarophile) and the minor nitronate (*endo* approach of the dienophile from the same side as the dipolarophile), which does not undergo spontaneous [3+2] cycloaddition. Purification of nitroso acetal **21** on silica gel did lead to partial rearrangement to aminal **23**; however, chromatography on basic alumina provided **21** in 67% yield.



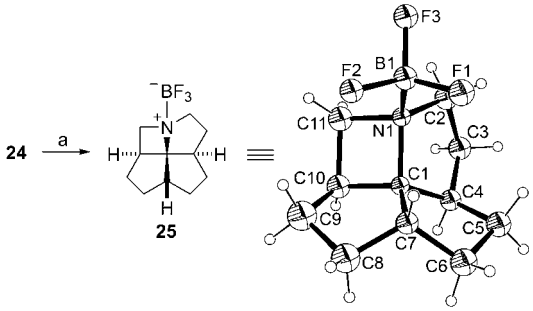
Scheme 7. a) $AlMe_3$, CH_2Cl_2, −78 °C, 1 h, purification on Al_2O_3 (67%); b) H_2 (1 atm), Raney Ni, MeOH, (94%); c) MeOH, 3 h, room temperature, (70%); d) H_2 (26 atm), Raney Ni, MeOH, room temperature, 15 h, (98%); e) H_2 (26 atm), Raney Ni, 10% H_2O-saturated EtOAc in EtOAc (0.25 M), 20 h, (85%); f) PPh_3, diisopropyl azodicarboxylate (DIAD), CH_2Cl_2, 0 °C, 40 min, then BH_3·THF, −78 °C→RT, 1 h (87%).

With nitroso acetal **21** in hand, we were poised to complete the synthesis in short order. Unfortunately, standard hydrogenolysis conditions (H_2, Raney Ni, MeOH) provided the reduced, rearranged product **22**, with no sign of the desired amino alcohol. An investigation of reaction conditions uncovered the fact that protic solvents induced the dyotropic rearrangement. In fact, simply stirring nitroso acetal **21** in methanol at room temperature provided aminal **23** in good yield. Consequently, new hydrogenation conditions had to be developed that would allow reduction of nitroso acetal **21** without promoting the rearrangement. Attempts to carry out the hydrogenation in nonprotic, dry solvents were unsuccessful; however, rearrangement did not take place under these conditions. In the end, it was discovered that by adding a controlled amount of water in the form of water-saturated ethyl acetate (10% in dry ethyl acetate) to the reaction mixture, the desired hydrogenolysis took place to give amino alcohol **5** while still suppressing the rearrangement.

At the outset of the synthesis, the formation of the azetidine ring from amino alcohol **5** was believed to be the most challenging step of the proposed route. However, simple treatment of **5** under Mitsunobu[19] coupling conditions led to formation of the desired azafenestrane, which was efficiently isolated as its borane complex *cis*,*cis*,*cis*,*cis*-[5.5.5.4]-1-azafenestrane·BH_3 (**24**) in 87% yield.[20] The availability of **24** from 5-butenyl-1-nitrocyclopentene **9** in only three steps and 50% overall yield demonstrates the power of the tandem

nitroalkene cycloaddition reaction for rapidly building molecular complexity.

To quantify the planarizing distortions at the central carbon atom in **24**, X-ray crystallographic analysis is required. Although the azafenestrane–borane adduct is a crystalline solid, crystals suitable for X-ray diffraction could not be obtained.[21] Fortunately, simple treatment of **24** with boron trifluoride etherate promoted an exchange to give the crystalline BF_3 adduct **25** (Scheme 8). Cooling of a warm, saturated solution of **25** in hexane to room temperature gave crystals of a quality suitable for X-ray crystallographic



Scheme 8. a) $BF_3{\cdot}OEt_2$, room temperature. ORTEP-3 plot of **25** (form 1, 30% thermal spheres).

analysis that formed in an unambiguous[22] space group $P2_1/n$.[23] The two most populated crystal forms in the disordered model exhibit similar planarization as defined by the angles around the central carbon atom; form 1: N1-C1-C7 119.8(7)° and C4-C1-C10 120.7(8)°, form 2: N1-C1-C7 119.2(8)° and C4-C1-C10 121.2(10)°. The degree of distortion agrees well with calculated values for the corresponding parent hydrocarbon.[2] Ab initio DFT calculations predict that the strain energy of azafenestrane **4** is 17.8-kcal mol^{-1} higher than that of the previously synthesized *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-1-azafenestrane.[24]

In conclusion, the synthesis of *cis*,*cis*,*cis*,*cis*-[5.5.5.4]-1-azafenestrane·BH_3 (**24**) was completed efficiently in five steps and 26% overall yield from 1-nitrocyclopentene by using a tandem [4+2]/[3+2] cycloaddition of a nitroalkene as the key step. Along the way, an unprecedented dyotropic rearrangement was discovered that converts nitroso acetals into tetracyclic aminals. The rearrangement is controlled by the conformation of the six-membered ring in the nitroso acetal precursors. By utilizing a bulky vinyl ether and developing new hydrogenation conditions, the rearrangement was suppressed, thus allowing the synthesis of the desired azafenestrane. The [5.5.5.4]-1-azafenestrane was analyzed by X-ray crystallography as its BF_3 adduct to quantify the planarizing distortion around the central carbon atom. Efforts toward even more strained azafenestranes, as well as investigations into the reported dyotropic rearrangement and its use in synthesis, are currently underway.

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[7] Central angles in **2**: N-C-C 116.1°, C-C-C 116.6°.
[8] Calculated central angles for **4**: N-C-C 117.9°, C-C-C 123.6° (DFT B88-LYP). All calculations were performed with CAChe WorkSystem Pro Version 6.1.10, Fujitsu Limited.
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[15] Monoclinic, $P2_1/c$, crystal ($0.64\times0.56\times0.10$ mm^3) from hexane: $a=11.087(4)$ Å, $b=14.064(5)$ Å, $c=9.473(4)$ Å, $\beta=96.733(7)°$, $V=1466.9(10)$ Å^3, $\rho=1.220$ Mg m^{-3}. Bruker SMART CCD data $2\theta_{max}=50.74°$, Mo radiation, $\lambda=0.71073$ Å, ω-scan profiles, 193(2) K, reflections (11547 measured, 2691 independent, $2020>2\sigma(I)$), limits ($-13\le h\le13$, $-16\le k\le16$, $-11\le l\le11$), corrected for L-p effects and absorption (integration, $\mu=0.084$ mm^{-1}, transmission $0.992>0.941$). Direct-methods solution (Bruker SHELXTL) and full-matrix least-squares refinement on F^2 (Bruker SHELXTL) by using 179 parameters against 2691 data points, observed $R1=0.040$, $wR2=0.094$, residual range 0.18 to -0.18 e Å^{-3}. CCDC 262117 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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[20] Full experimental details for **24** and all other compounds are available as Supporting Information.
[21] Adduct **24** was soluble in many organic solvents. Thin needles could be obtained from hexane at low temperature, but multiple attempts to collect X-ray diffraction data were unsuccessful. Crystals could be obtained from other nonpolar solvents (e.g. tetraalkyl silanes, fluorocarbons) at ambient temperature, but again, only weak diffraction patterns were observed.
[22] A detailed analysis of the unusual X-ray crystal structure of **25** is available in the Supporting Information.
[23] Monoclinic, $P2_1/n$, crystal ($0.60\times0.20\times0.04$ mm^3) from hexane: $a=6.257(3)$ Å, $b=14.424(6)$ Å, $c=12.596(5)$ Å, $\beta=91.932(8)°$, $V=1136.0(9)$ Å^3, $\rho=1.351$ Mg m^{-3}. Bruker SMART CCD data $2\theta_{max}=50.60°$, Mo radiation, $\lambda=0.71073$ Å, ω-scan profiles,

193(2) K, reflections (12439 measured, 2055 independent, 676 > $2\sigma(I)$), limits ($-7 \le h \le 7$, $-17 \le k \le 17$, $-15 \le l \le 15$), corrected for L-p effects and absorption (integration, $\mu = 0.112\ mm^{-1}$, transmission 0.995 > 0.946). Direct-methods solution (Bruker SHELXTL) and full-matrix least-squares refinement on F^2 (Bruker SHELXTL) by using 196 parameters and 237 restraints against 2050 data points, observed $R1 = 0.076$, $wR2 = 0.240$, residual range 0.28 to $-0.26\ e\ Å^{-3}$. CCDC 262116 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.

[24] This value represents the total energy difference between **4** and *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-1-azafenestrane (B88-LYP) with an adjustment for removal of a CH_2 group in **4** (energy of unstrained CH_2 determined by the average difference in total energy upon minimization of ethane, propane, and butane); see: a) T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450; b) R. D. Bach, O. Dmitrenko, *J. Org. Chem.* **2002**, *67*, 3884.

