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[6] Complex **4** could not be isolated pure, but rather contained small amounts of dimer **2a**, even when a large excess of PCy_3 was used in the synthesis. ^{31}P NMR spectroscopy the confirmed *cis* disposition of P donors ($^2J_{PP} = 40$ Hz).

[7] Fu and co-workers have recently reported that highly sterically hindered tri*aryl*phosphanes can catalyze couplings of electronically deactivated aryl chlorides (see ref. [2b]), indicating that more subtle effects than brute donor-strength can play an important role.

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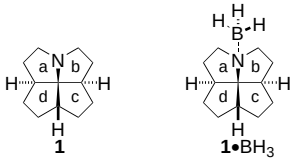
[9] We are assuming that the catalytic cycle proceeds by a Pd^0/Pd^{II} pathway. This assumption is made on the basis of studies into the activation of palladacyclic precatalysts in Suzuki coupling reactions. See reference [2c] for leading references.

Synthesis of *cis,cis,cis,cis*-[5.5.5.5]-1-Azafenestrane**

Scott E. Denmark,* Laurenz A. Kramps, and Justin I. Montgomery

The structural theory of organic chemistry is one of the most highly evolved constructs in natural science. The ability to explain and correctly predict the detailed molecular structure of millions of compounds naturally inspires research to test the limits of the theory. One important subset of this field of investigation probes the extent to which a tetracoordinate carbon atom (bearing all carbon substituents) can deviate from the van't Hoff/Le Bel tetrahedral geometry. The interesting family of compounds called fenestranes[1] comprises molecules with planarizing distortion of the central carbon atom. The magnitude of the distortion is dependent on the size and configuration of the fused rings. Because the parent, unsubstituted fenestranes are low molecular weight hydrocarbons, they are not amenable to X-ray crystallographic analysis. The few X-ray structures on record are of substituted and functionalized derivatives.[2]

We were intrigued by the possibility of replacing one of the ring-fusion carbon atoms with a nitrogen atom to facilitate salt formation and provide an opportunity for X-ray analysis of an unsubstituted fenestrane. In addition to establishing the full molecular structure and the extent of the central carbon planarization, the pyramidal distortion of the nitrogen atom would also be of interest; to our knowledge, no monoazafenestranes have been prepared. An unusual tetraamino [5.5.5.5]fenestrane is known and it exists as an equilibrium mixture of (degenerate) open and closed forms when protonated.[3] We describe herein the first synthesis of an unsubstituted 1-azafenestrane **1** along with the synthesis and X-ray crystallographic analysis of the borane adduct **1**·BH_3.



Analysis of the tetracyclic ring structure of **1** reveals that it contains an embedded pyrrolizidine unit fused to a bicyclo[3.3.0]octane system. In recent years, a large number of pyrrolizidine-based alkaloid natural products in the necine, alexine and australine families have been synthesized in these laboratories.[4] The key strategic operation in all of these syntheses is the tandem [4+2]/[3+2] cycloaddition of nitroalkenes.[5] This process allows for the facile and stereocontrolled construction of highly functionalized nitroso acetals that serve as precursors for pyrrolizidines upon catalytic hydrogenolysis.

The application of the tandem cycloaddition strategy to the synthesis of **1** is outlined in Scheme 1. Constructing the core of **1** requires the creation of one of the four rings in the tandem [4+2]/[3+2] process by cycloaddition of a C_2 dienophile (butyl vinyl ether (**3**)) with a cyclopentenyl nitro diene **2** (ring C) bearing the suitable dipolarophilic tether. The tetracyclic nitroso acetal **4** is then poised for hydrogenolytic unmasking to a tricyclic pyrrolizidine (third ring, c) which should undergo spontaneous lactam formation (→**5**; fourth ring, d) from the appended carboxylic ester. Thus, three of the four rings of [5.5.5.5]-1-azafenestrane can be assembled in two chemical manipulations. Two-stage reduction of the α-hydroxy lactam **5** leads to the target azafenestrane **1**. This approach allows for a modular synthesis of fenestranes containing rings of different size at various positions. With regard to the configuration at the ring fusions, only one relationship was expected to be variable. In the [4+2] process, the approach of the dienophile can take place on the two diastereotopic faces of the nitroalkene to create *cis* and *trans* isomers. The [3+2] process is formally in the spiro mode family[6] and thus is expected to

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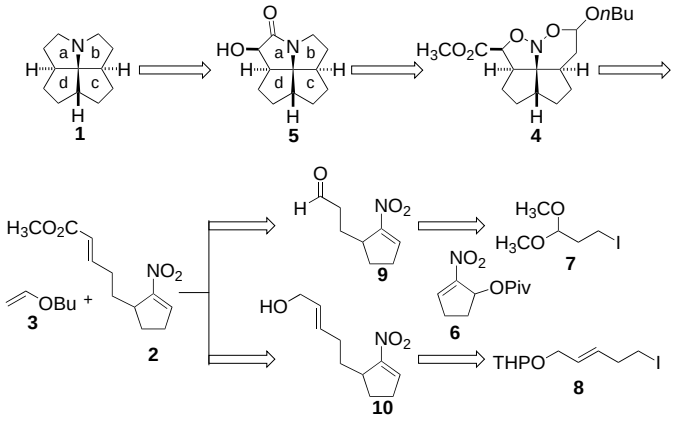
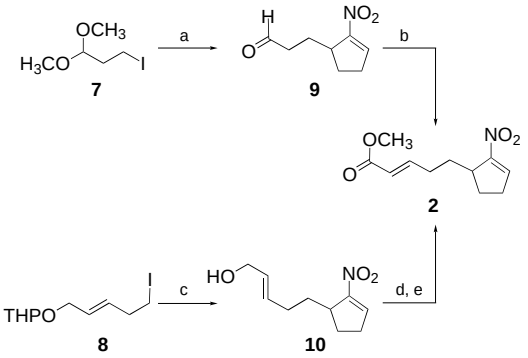


Scheme 1. Retrosynthetic strategy for the construction of azafenestrane **1** by tandem [4+2]/[3+2] cycloaddition. Piv = pivaloyl, THP = tetrahydropyranyl.

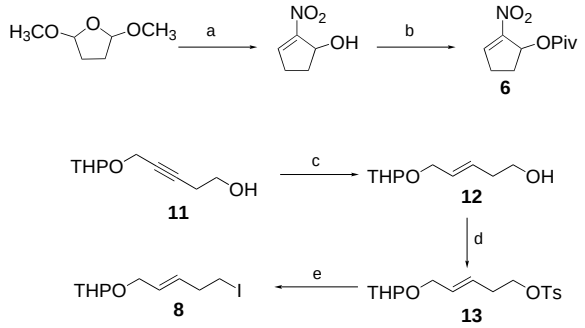


Scheme 3. a) 1. *t*BuLi, THF/hexane/Et_2O, −100 °C, 2. **6**, −50 °C, TsOH, aq. acetone, 61 %; b) trimethylphosphonoacetate, *n*BuLi, THF, −70 °C, 22 %; c) 1. *t*BuLi, THF/hexane/Et_2O, −100 °C, 2. **6**, −50 °C, TsOH, MeOH, 67 %; d) Dess–Martin reagent, CH_2Cl_2, 89 %; e) 1. [$(H_2bipy)Cl_5CrO$], CH_2Cl_2, 2. MeOH, 3. CH_2N_2, 36 % (three steps).

proceed via an *exo*-mode pathway to create a *cis* ring fusion independent of the tether length.

The side chain of nitroalkene **2** (that creates ring d) could be introduced by nucleophilic addition to the nitro allylation reagent **6**.[7] The required nucleophiles (alkyllithium reagents) could be obtained by halogen–metal exchange from the corresponding iodides **7** and **8**. Each side chain precursor requires a different sequence to complete the construction of the desired α,β-unsaturated ester: 1) Horner-Wadsworth-Emmons (HWE) or Wittig reaction with aldehyde **9** and 2) oxidation of an allyl alcohol **10** to the acid followed by esterification. Both approaches were pursued in view of the unknown sensitivity of the nitroalkene to these agents.

The synthesis began by preparation of the key subunits (Scheme 2). Pivalate **6** was prepared by modification of procedures for the synthesis of the analogous cyclohexene



Scheme 2. a) 1. HCl, 80 °C, 2. NaOH, $MeNO_2$, H_2O, MeOH, RT, 3. Al_2O_3, 40 °C; b) pivalic anhydride, H_2SO_4, 9 % (four steps); c) $LiAlH_4$, Et_2O, reflux, 70 %; d) TsCl, Et_3N, CH_2Cl_2 0 °C, 90 %; e) NaI, acetone, reflux, 99 %. Ts = tosyl.

derivative.[7] Unfortunately, the cyclopentenyl case could not be optimized above 9 %, but the reactions could be scaled up by using inexpensive starting materials. The iodo acetal **7**[8] and THP-protected iodide **8**[9] were prepared directly and by adaptation of literature procedures, respectively.

The nitro allylating agent **6** behaved similarly toward the two organolithium nucleophiles derived from **7** and **8** by iodine–lithium exchange with *tert*-butyl lithium[10] (Scheme 3).

Both the aldehyde **9** and the primary alcohol **10** were obtained in comparable, synthetically viable yields after hydrolysis of the protective groups. Homologation of **9** by using either methyl (triphenylphosphoranylidene)acetate or trimethylphosphonoacetate (with *n*BuLi) afforded low (15–22 %) yields of **2**. The oxidation of alcohol **10** could be effected with the Jones reagent, but low yields were obtained and the purification of the product proved to be difficult. Better results were obtained when [$(H_2bipy)Cl_5CrO$][11] in CH_2Cl_2 was used. This chromium(v) complex afforded a mixture of acid and acid chloride, which could be converted to the desired ester **2** simply by treatment with MeOH. The remaining carboxylic acid could be converted to **2** with diazomethane.

The [4+2] cycloaddition of nitroalkene **2** and butyl vinyl ether (**3**) afforded two diastereomers of nitronate **13**. Only one of these diastereomers underwent spontaneous [3+2] cycloaddition to give nitroso acetal **4a** (Scheme 4). Nuclear Overhauser NMR spectroscopic investigations of **4a** confirmed the relative configuration of this compound (Scheme 5).

The reaction has not been optimized to control the diastereoselectivity by the use of different Lewis-acids. Increasing the selectivity of the reaction would improve the yield of nitroso acetal **13a**. Nitronate **13b** is also a useful compound and the separation from the nitroso acetal **4a** was easy because of the high polarity of **13b** compared to that of **4a**. Preliminary investigations indicated that the nitronate **13b** can undergo [4+2] cycloaddition at elevated temperature ($NaHCO_3$, toluene, 97 °C) to give the diastereomeric nitroso acetal **4b**, which can potentially be transformed to diastereomeric fenestrane **1b** (Scheme 4).

Hydrogenation of nitroso acetal **4a** afforded hydroxy 1-azafenestranone **5** in 72 % yield. The yield of **5** from nitroalkene **2** is 48 %—remarkable for the formation of a fenestrane skeleton. Completion of the synthesis required two deoxygenation steps (Scheme 6). First, the hydroxy group was removed by conversion to the phenyl thionocarbonate **12**, which was reduced with nBu_3SnH/AIBN by a method originally described by Barton and McCombie.[12] The resulting lactam **13** was reduced with $LiAlH_4$ to give the target *cis*,*cis*,*cis*,*cis*-[5.5.5.5]-1-azafenestrane (**1**).

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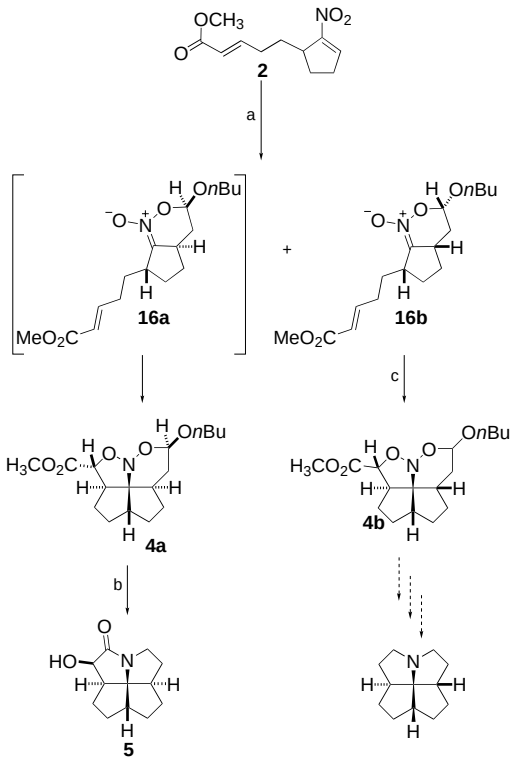
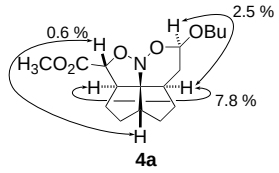
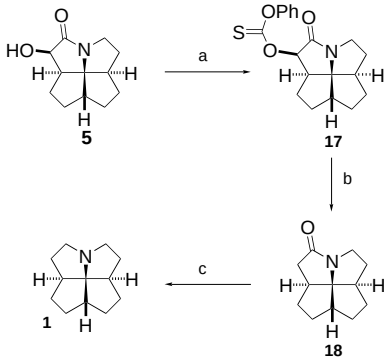


Scheme 4. a) **3**, Me_3Al, toluene, −70 °C, **4a** (67 %) and **16b** (27 %); b) Raney nickel, H_2 (1100 kPa, 160 psi), MeOH 72 %; c) benzene, K_2CO_3, 80 °C, 70 %.



Scheme 5. nOe analysis of nitroso acetal **4a**.



Scheme 6. a) Phenyl thionochloroformate, pyridine, DMAP, 77 %, b) nBu_3SnH, AIBN, benzene, reflux, 98 %; c) $LiAlH_4$, THF, reflux, 83 %.

The spectroscopic data for **1** clearly support the structure and C_h symmetry of the molecule (seven ^{13}C NMR signals).[13] To secure the detailed molecular structure, we surveyed the formation of crystalline salts and found that treatment of **1** with a solution of borane in THF formed an adduct (as judged by ^1H NMR analysis) which could be recrystallized from diethyl ether to afford **1**·BH_3 as colorless needles. X-ray crystallographic analysis[14] of **1**·BH_3 (Figure 1) confirms the gross molecular structure but also reveals that the compound

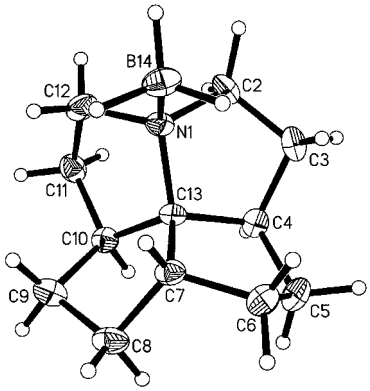


Figure 1. SHELXTL plot of **1**·BH_3 from X-ray analysis (35 % thermal ellipsoids).

crystallizes in a chiral space group ($P2_1$) because of the twist of the five-membered rings (dihedral angle B-N(1)-C(13)-C(7) = 11.6°).[15] The planarization of the central carbon atom (C(13)) is only modest as defined by the two orthogonal bond angles: N-C(13)-C(7) = 116.1° and C(4)-C(13)-C(10) = 116.6°. This was not unexpected as these angles in the *all-cis* stereoisomer of the parent [5.5.5.5]fenestrane hydrocarbon are calculated to be 113°.[1]

In summary, we have demonstrated the feasibility of a tandem cycloaddition approach to 1-azafenestranes and the ability to obtain crystalline adducts suitable for X-ray analysis. The preparation of more strained and flattened congeners is underway and will be reported in due course.

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[13] Data for **1**: b.p.: 40 °C (0.1 Torr); ^{1}H NMR (500 MHz, $CHCl_3$, TMS): $\delta = 1.33$ (m, 4H, HC(5), HC(4)), 1.46 (m, 2H; HC(2)), 1.78 (m, 4H; HC(5), HC(4)), 1.89 (m, 2H; HC(2)), 2.02 (m, 1H; HC(6)), 2.18 (m, 2H; HC(3)), 2.70 (dt, $J = 10.5$, 6.2 Hz, 2H; HC(1)), 2.92 ppm (dt, $J = 10.5$, 6.4 Hz, 2H; HC(1)); ^{13}C NMR (126 MHz, $CHCl_3$): $\delta = 29.6$, 30.3, 30.5 (C(2), C(4), C(5)), 50.9 (C(3)), 51.9 (C(6)), 52.4 (C(1)), 93.1 ppm (C(7)); IR (CH_2Cl_2): $\tilde{\nu} = 2945$ (s), 2864 (m), 1454 (w), 1269 (vw), 1209 (vw), 1173 (vw), 1119 (vw); MS (FAB): m/z (%): 178 ($M^+ + 1$, 100); TLC ($CHCl_3$/MeOH 20:1, Al_2O_3): $R_f = 0.64$; C,H,N analysis (%): calcd for $C_{12}H_{19}N$: C 81.30, H 10.80, N 7.90; found: C 81.02, H 10.95, N 7.97.

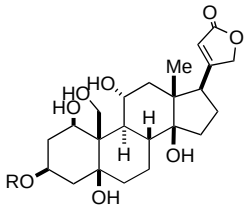
[14] X-ray crystal structure analysis of **1**·BH_3. A single crystal deposited from Et_2O solution at −25 °C: formula $C_{12}H_{22}BN$. $M_r = 191.12$, crystal size $0.2 \times 0.2 \times 0.02$ mm^3, $a = 6.2685(13)$ Å, $b = 12.773(3)$ Å, $c = 7.5043(15)$ Å, $\beta = 111.517(4)°$, $V = 558.93(19)$ Å^3, $\rho_{calcd} = 1.136$ g cm^{-3}, $\mu = 0.064$ mm^{-1}, absorption correction by integration, $Z = 2$, monoclinic space group $P2_1$, Siemens 3-circle platform diffractomer with a molybdenum ($K_\alpha = 0.71073$ Å) X-ray source and CCD area detector, $T = 193(2)$ K, 5835 measured reflections ($\pm h$, $\pm k$, $\pm l$), 1074 independent and 722 observed reflections with $I > 2\sigma(I)$, $R = 0.0423$, $wR = 0.0494$ (against $|F^2|$), residual electron density 0.12 e Å^3; programs used: SHELXTL V6. CCDC-189803 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[15] A similar twist has been established by electron diffraction (12.4°) in the parent hydrocarbon that gives rise to an overall D_2 symmetry: J. Brunvoll, R. Guidetti-Grept, I. Hargittai, R. Keese, *Helv. Chim. Acta* **1993**, *76*, 2838.

Efficient Synthesis of a Tricyclic BCD Analogue of Ouabain: Lewis Acid Catalyzed Diels–Alder Reactions of Sterically Hindered Systems**

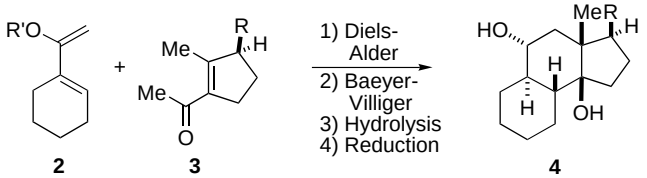
Michael E. Jung* and Pablo Davidov

The naturally occurring cardenolide ouabain (**1a**) and its aglycone ouabagenin (**1b**) are members of a class of highly oxygenated cardiotonic steroids (digitalis glycosides) used in the treatment of congestive heart failure.[1] Ouabain has been synthesized starting from other natural steroids,[2] however, no total synthesis[3] has been reported to date although an excellent synthetic route has been described.[4] We have reported some preliminary results on an approach to the bicyclic CD ring system of ouabain in which we attempted to use an anionic [1,3] sigmatropic shift of a 7-alkenylbicyclo[3.2.1]heptane-1,7-diol, which afforded products from an unusual anion-accelerated retroene reaction.[5] We report here a completely different route that allowed us to prepare a tricyclic BCD ring system analogue of ouabain in a very efficient manner. In this route we have developed a novel Diels–Alder reaction of sterically hindered enones and dienes to afford heavily substituted cyclohexene systems extremely easily.



1a R = L-rhamnose
1b R = H

Initially, we decided to investigate a possible Diels–Alder approach for the synthesis of the CD ring system of ouabain. Cycloaddition of a 1-(alkoxyvinyl)cyclohexene **2** with the enone **3** followed by conversion of the ketone to an acetate by a Baeyer–Villiger oxidation and final hydrolysis and reduction of the cyclic ketone would give the diol **4**, which has the required five contiguous asymmetric centers of the BCD ring system of ouabain (Scheme 1). The anticipated difficulty of carrying out a Diels–Alder reaction with a hindered dienophile such as **3** made us first investigate a simpler model system. All attempts at effecting the cycloaddition of 2-trimethylsilyloxybutadiene (**5**) with the known dienophile **6**



2 **3** **4**

Scheme 1. Diels–Alder approach to the diol **4**, which contains the BCD ring system of ouabain (**1a**).

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