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# Reversible Cyclopropane Ring-Cleavage Reactions within Etheno-Bridged [5.3.1]Propelladiene Frameworks Leading to Aza- and Oxa-[5.6.5.6]Fenestratetraenes

**Nora Heinrich, Anthony C. Willis, Ian A. Cade, Junming Ho, Michelle L. Coote, and Martin G. Banwell***[a]

In 2008 Takeya and co-workers reported[1] on the isolation and structural elucidation of the [5.3.1]propellane-containing and biologically active neoclerodane salvileucalin B (**1**, Figure 1). In connection with efforts to probe the origins of the cytotoxic effects of this natural product, we recently developed a synthesis of the key substructure **2**.[2] Part of the associated reaction sequence involved reduction of nitrile **3** to primary alcohol **4**. This proved to be an unexpectedly complex process because of the intervention of remarkable and reversible cyclopropane ring-cleavage processes leading to the formation (and disassembly) of aza- and oxa-[5.6.5.6]fenestratetraenes. These compounds represent unusual new examples of fenestranes that, as a class, continue to attract considerable attention because of the capacity they provide to examine the "plasticity" of the tetrahedral geometry normally imposed on sp$^3$-hybridized carbon atoms by virtue of the bonding in such systems.[3] Details are presented herein.

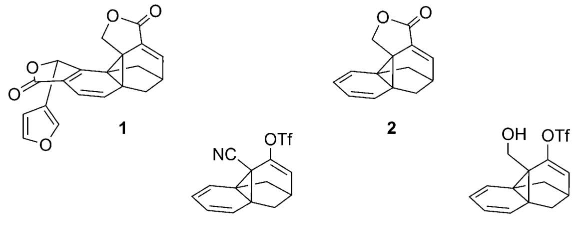

Figure 1. The natural product, salvileucalin B (**1**), and related substructures. Tf = trifluoromethanesulfonyl.

Our initial attempts to effect the conversion of **3** into **4** involved treating the first compound with DIBAl-H in dichloromethane ($CH_2Cl_2$) at −40 °C and then quenching the reaction mixture with Rochelle's salt. It was anticipated that this would provide the corresponding aldehyde. However, the only products of this reaction were the aza-[5.6.5.6]fenestratetrene **5** (15 %) and its oxa analogue **6** (variable yields), both of which proved to be rather unstable compounds (Figure 2). When the reaction mixture was quenched with aqueous HCl (rather than Rochelle's salt) then compound **6** (49 %) was the exclusive product of reaction. The structure of compound **5** was established by single-crystal X-ray analysis whereas that of congener **6** followed from the equivalent analysis of the readily obtained 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[4] adduct **7** (53 %), itself a bridged fenestrane.[5]

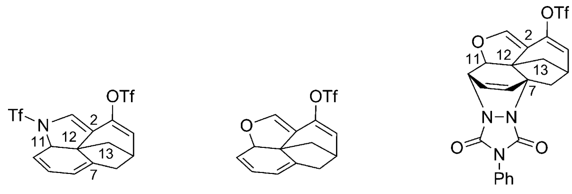

Figure 2. Fenestranes **5**, **6**, and **7**.

The bond angles, as determined by the above-mentioned X-ray analyses, about the central carbon atoms (C12 in each case) of compounds **5** and **7** are shown in Table 1. These data reveal that in each case there is some significant[3] deviation from tetrahedral geometry imposed on the central carbon atom by the surrounding framework, both in terms of angle compression (down to 100°) and angle widening

Table 1. Bond angles, as determined by X-ray analysis, about the central carbon atoms (C12) of fenestranes **5** and **7**.

| Compound 5 | | Compound 7 | |
|---|---|---|---|
| Atom array | Bond angle [°] | Atom array | Bond angle [°] |
| C2-C12-C7 | 112.7(2) | C2-C12-C7 | 113.5(2) |
| C2-C12-C11 | 102.60(19) | C2-C12-C11 | 101.5(2) |
| C2-C12-C13 | 104.61(19) | C2-C12-C13 | 107.2(2) |
| C7-C12-C11 | 115.1(2) | C7-C12-C11 | 109.4(2) |
| C7-C12-C13 | 100.5(2) | C7-C12-C13 | 100.1(2) |
| C11-C12-C13 | 121.2(2) | C11-C12-C13 | 126.0(2) |

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[a] N. Heinrich, Dr. A. C. Willis, Dr. I. A. Cade, Dr. J. Ho,
Prof. M. L. Coote, Prof. M. G. Banwell
Research School of Chemistry
The Australian National University
Canberra, ACT 0200 (Australia)
E-mail: mgb@rsc.anu.edu.au

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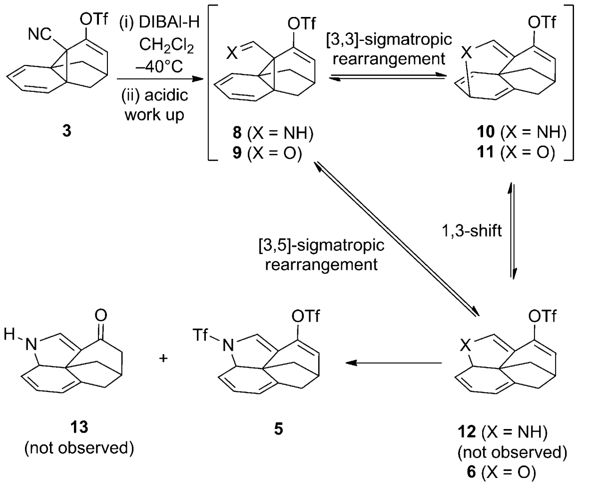
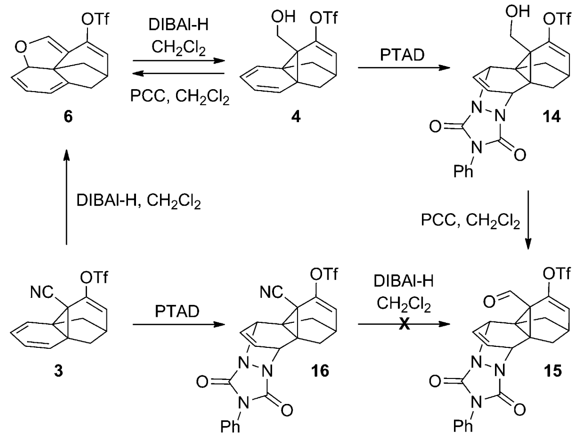


Scheme 1. Possible pathways to fenestratetraenes **5** and **6** from nitrile **3**.

(up to 126°) and thus further emphasizing the "plasticity" in the spatial arrangements of groups attached to an $sp^3$-hybridized carbon atom.

Two possible pathways to fenestratetraenes **5** and **6** are outlined in Scheme 1. Thus, either the initially formed imine **8** or the corresponding aldehyde **9** could engage in a [3,3]-sigmatropic rearrangement to deliver the cyclopropane-ring-cleavage products **10** and **11**, respectively. These could, in turn, participate in either a nonconcerted 1,3-nitrogen or a nonconcerted 1,3-oxygen shift (allylic rearrangement) to give compounds **12** and **6**, respectively. Compound **12** was not isolated because of the intervention of a Tf-group transfer reaction leading to the observed product (**5**) and (presumably) the vinylogous lactam **13**, a compound we have not been able to isolate from the reaction mixture. Another possible pathway to compounds **5** and **6** involves the direct [3,5]-sigmatropic rearrangement of imine **8** and aldehyde **9** to give tetraenes **12** and **6**, respectively. Theoretical studies by Houk and co-workers[6] on the [3,5]-sigmatropic reaction of the parent all-carbon system suggest that diradical intermediates are likely to be involved. Studies by Kohmoto et al.[7] also indicate that this type of reaction can occur within the norcaradiene framework. Our own calculations (see below) suggest that a [3,5]-sigmatropic process is probably operating during the course of the transformations described herein.

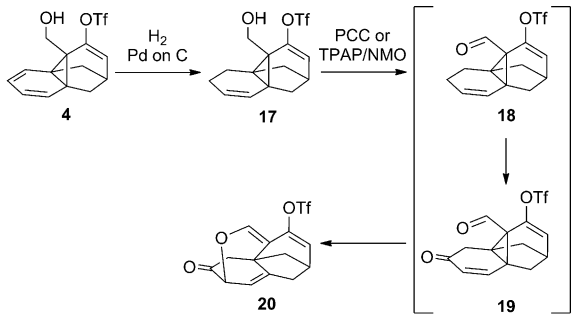
Interestingly, the conversion of **9** into **6** proposed above seems to occur in a reversible manner. Thus, when a pure sample of compound **6** was resubjected to reaction with DIBAl-H in $CH_2Cl_2$ at −40 °C (Scheme 2) and the reaction mixture quenched with aqueous HCl, then alcohol **4** was obtained in 66 % yield. Similarly, oxidation of compound **4** with pyridinium chlorochromate (PCC)[8] in $CH_2Cl_2$ at 18 °C for 2 hours regenerated, presumably via the initially formed aldehyde **9**, the fenestratetraene **6** in 76 % yield (based on recovered starting material). In contrast, when the readily obtained PTAD adduct, **14** (76 % yield), of alcohol **4** was oxidized with PCC then the stable aldehyde **15** was obtained



Scheme 2. The interconversion of compounds **4** and **6**.

in 88 % yield. Attempts to effect the DIBAl-H-mediated reduction of the readily obtained PTAD adduct, **16** (87 % yield), of nitrile **3** failed, presumably because of competing reactions involving the carbonyl-containing residues within the former compound.

In a further attempt to probe the nature of the conversion of **9** into **6**, the dihydro form of the former compound was sought on the basis that it could undergo a [3,3]- but not a [3,5]-sigmatropic rearrangement reaction. To these ends, compound **4** was subjected to reaction with dihydrogen in the presence of palladium on carbon (Scheme 3) and the desired diene **17** thereby obtained, albeit in low yield (14 %) because of the competing formation of over-reduced and isomeric materials.[2] Upon treatment of compound **17** with PCC or the Ley–Griffith reagent—tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[9]—a product containing a newly incorporated oxygen atom (in the form of a ketone) was obtained. On the basis of the spectroscopic data, we believe alcohol **17** is initially converted into aldehyde **18** (the sought-after dihydro form of aldehyde **9**) and that this itself undergoes an allylic oxidation to give enone **19**.[10] Finally, compound **19** engages in a [3,3]-sigmatropic rearrangement to give the observed product **20** (61 %), which itself is a fenestrane.



Scheme 3. The synthesis and oxidative rearrangement of [5.3.1]propellenol **17**.

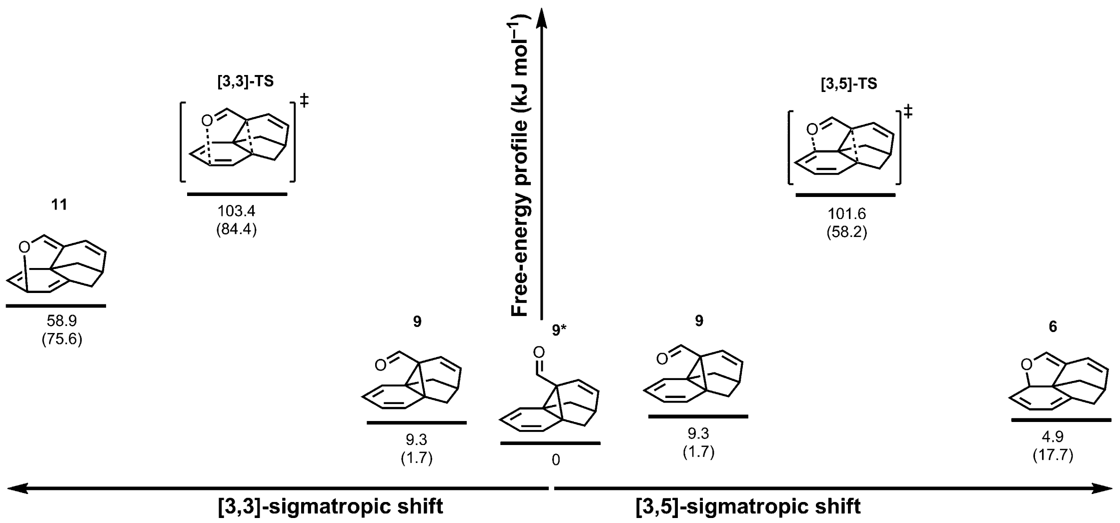


Figure 3. Gibbs-free-energy profiles for the [3,5]- and [3,3]-sigmatropic rearrangements of [5.3.1]propelladiene **9** in which the OTf group is replaced with a hydrogen atom (the values in parentheses refer to $Me_2HAl$-complexed analogues whereas * denotes the lowest energy conformer of **9**).

Because the above-mentioned experiments failed to differentiate between the two possible reaction pathways shown in Scheme 1, namely between a direct [3,5]-sigmatropic rearrangement and a [3,3]-sigmatropic rearrangement followed by a 1,3-migration process, computational assessments of the energetics of the interconversion of aldehyde **9** and fenestratetraene **6** were carried. These were conducted at a high level of theory [G3(MP2)RAD(+) and under "conditions" reflecting the experimental ones][11] albeit on compounds in which the OTf group was replaced by a hydrogen atom. These computations (Figure 3) revealed that the ground state energies of the two compounds were comparable (9.3 kJ mol$^{-1}$ versus 4.9 kJ mol$^{-1}$) whereas that of compound **11** was considerably higher (58.9 kJ mol$^{-1}$). A qualitatively similar situation was observed for the $Me_2HAl$-complexed forms of compounds **6** and **11**, namely the complex of **11** was also of higher energy than that of aldehyde **9**. It should be stressed that while the calculations presented here indicate that the equilibrium lies in favor of compound **9** (with **6** being 4.9 kJ mol$^{-1}$ higher in energy), this is entirely due to the model chosen where the OTf group was replaced with a hydrogen atom to reduce the computational cost. Qualitative assessment at a lower level of theory [B3LYP/6-31+G(d)] revealed that inclusion of the OTf group leads to compound **6** being the predominant (thermodynamically more stable) product, an outcome that is consistent with the experimental findings.

The transition states for the conversion of **9** into **6** and the conversion of **9** into **11** were calculated to be of similar energies (101.6 kJ mol$^{-1}$ versus 103.4 kJ mol$^{-1}$) but very significant differences were encountered for the corresponding $Me_2HAl$-complexed compounds (58.2 kJ mol$^{-1}$ versus 84.4 kJ mol$^{-1}$). The calculated natural-bond-order (NBO) atomic charges and solvation free energies indicate a significantly more polarized transition state in which, for example, the atomic charge on the carbonyl oxygen is 0.024 *e* more negative. These characteristics might account for the different stabilities of the $Me_2HAl$-complexed transition states.

The transition states detected were all closed-shell singlets and various attempts to locate either singlet biradical transition states or intermediates were unsuccessful. This result is unexpected because the [3,5]-sigmatropic rearrangement is thermally disallowed and when it does occur, it is thought to proceed through a stepwise pathway involving biradical intermediates.[6] Inspection of the frontier molecular orbitals (Figure 4) appears to provide an explanation in that the molecular geometry facilitates overlap between the HOMO (the π orbital of the diene) and the π* orbital of the carbonyl group (CO π*). This overlap results in an activation barrier of approximately 100 kJ mol$^{-1}$. This is relatively low in comparison to the values that are typical for thermally allowed hydrocarbon-based pericyclic reactions, which have activation barriers of approximately 140 kJ mol$^{-1}$.[6]

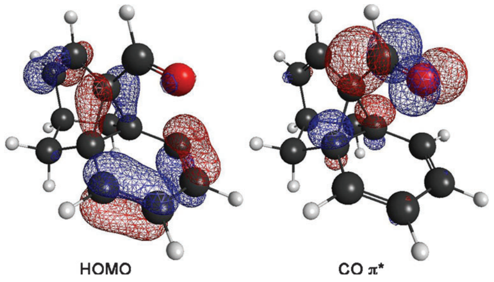


Figure 4. Frontier molecular orbitals of intermediate **9** (see Scheme 1) obtained at the B3LYP/6-31G(d) level of theory.

Under the "reaction conditions" used in the computational work (−40 °C), the calculated barriers associated with direct conversion of both **9** into **6** and **9** into **11** translate into half-lives of greater than 260 years. By comparison, the corresponding barriers associated with the $Me_2HAl$-complexed compounds confer half-lives that are consistent with the time-scale of the actual experiments. On this basis, acid-catalyzed [3,5]-sigmatropic rearrangements are believed to be operative in the conversions of **3** into **6**, **4** into **6**,[12] and **6** into **4**.

The above-mentioned transformations represent new and unconventional means of generating fenestranes and suggest that oxa- and aza-based variants of the [3,5]-sigmatropic rearrangement could be used for assembling complex heterocyclic frameworks. In light of these results, it is conceivable that the "retro-Claisen" rearrangement product observed during the course of the recently reported total synthesis of salvileucalin B (**1**) [13] may result from the operation of a [3,5]-sigmatropic rather than a [3,3]-sigmatropic process.

## Acknowledgements

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**Keywords:** cleavage reactions • fenestratetraenes • norcaradienes • salvileucalin B • sigmatropic rearrangement

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[3] For useful points of entry into the literature on fenestranes, see: a) M. Charpenay, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem.* **2012**, *124*, 4455; *Angew. Chem. Int. Ed.* **2012**, *51*, 4379, and references cited therein; b) S. E. Denmark, J. I. Montgomery, L. A. Kramps, *J. Am. Chem. Soc.* **2006**, *128*, 11620, and references cited therein; c) R. Keese, *Chem. Rev.* **2006**, *106*, 4787; d) H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 88–94.

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[5] Crystallographic data for compound **5**: $C_{15}H_{11}F_6NO_5S_2$, $M=463.38$, $T=200$ K, triclinic, space group $P\bar{1}$, $Z=2$, $a=6.8778(2)$, $b=10.8844(4)$, $c=12.8790(4)$ Å, $\alpha=99.1558(19)°$, $\beta=102.708(2)°$, $\gamma=104.325(2)°$; $V=887.71(5)$ Å$^3$, $D_x=1.733$ g cm$^{-3}$, 4063 unique data ($2\theta_{max}=55.2°$), $R=0.051$ [for 3003 reflections with $I>2.0\sigma(I)$]; $Rw=0.132$ (all data), $S=0.95$. Crystallographic data for compound **7**: $C_{22}H_{16}F_3N_3O_6S$, $M=507.45$, $T=200$ K, triclinic, space group $P\bar{1}$, $Z=2$, $a=6.6517(2)$, $b=11.4024(6)$, $c=14.7561(8)$ Å, $\alpha=79.894(2)°$, $\beta=83.096(3)°$, $\gamma=78.323(3)°$; $V=1074.84(9)$ Å$^3$, $D_x=1.568$ g cm$^{-3}$, 4921 unique data ($2\theta_{max}=55°$), $R=0.060$ [for 3027 reflections with $I>2.0\sigma(I)$]; $Rw=0.153$ (all data), $S=0.97$. CCDC-891377 (**5**) and 891378 (**7**) contain 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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[10] The possibility that the allylic oxidation step takes place first cannot be discounted.

[11] Gas phase Gibbs free energies were calculated with G3(MP2)-RAD(+)//B3LYP/6-31+G[d]. Solvation free energies were calculated using the SMD model at the M06–2X/6-31+G(d,p) level of theory in $CH_2Cl_2$ on solution-phase optimized geometry; the solvation contribution to the reaction energies (at 233 K) was approximated from those obtained at 298 K.

[12] In the case of this rearrangement, we assume the acidic nature of the reaction medium resulting from the presence of PCC facilitates the conversion of aldehyde **9** into oxa-[5.6.5.6]fenestratetraene **6**.

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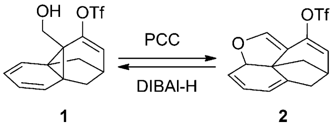
**Opening and closing a chemical window**: Oxidation of the etheno-bridged [5.3.1]propelladienol **1** with pyridinium chlorochromate (PCC) affords oxa-[5.6.5.6]fenestratetraene **2**. The reduction of **6** with diisobutylaluminum hydride (DIBAl-H) leads to the regeneration of its precursor (**1**; see scheme). These transformations most likely involve a [3,5]-sigmatropic rearrangement process.



**Sigmatropic Rearrangements**

*N. Heinrich, A. C. Willis, I. A. Cade, J. Ho, M. L. Coote, M. G. Banwell** …………… ▮▮▮▮–▮▮▮▮

**Reversible Cyclopropane Ring-Cleavage Reactions within Etheno-Bridged [5.3.1]Propelladiene Frameworks Leading to Aza- and Oxa-[5.6.5.6]Fenestratetraenes**