Strained Polycycles

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Synthesis of Bridged Oxafenestranes from Pleuromutilin**

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Abstract: *Fenestranes are an intriguing class of highly strained molecules possessing a quaternary carbon with bonds that deviate from the canonical tetrahedral geometry. Herein we report the discovery that the natural product pleuromutilin can be used as a structurally complex starting material for the synthesis of a series of bridged cis,cis,cis,cis-[4.5.5.5]- and cis,cis,cis,cis-[4.5.7.5]oxafenestranes through a carbocation rearrangement cascade. X-ray crystallographic analysis of several cis,cis,cis,cis-[4.5.5.5]oxafenestranes shows a significant planarization of the central tetracoordinate carbon atom and demonstrates the influence of bridgehead substituents and bridging rings on planarity.*

The tetrahedral four-coordinate carbon is one of the fundamental structural features of organic molecules,[1] thus compounds possessing such carbon atoms but with altered geometries have long been of interest.[2] Fenestranes are a class of compounds designed to deviate from the tetrahedral geometry by planarization of a four-coordinate carbon.[3] The fenestrane scaffold consists of four rings fused about a central quaternary carbon, whose planarization can be measured by two opposing bond angles, α and β (**1**, Figure 1). The magnitudes of α and β are dependent on the ring size and the relative configuration and substitution pattern of the bridgehead atoms.[3a] The potential for creating molecules with highly planarized tetracoordinate carbon atoms and the discovery of the fenestrane natural products laurenene **2**,[4] penifulvins A–E (e.g. **3**),[5] and asperaculin A **4**[6] have made fenestranes appealing synthetic targets. Thus, several noteworthy methods have been developed for the synthesis of fenestranes with a full-carbon scaffold[7] and fenestranes containing heteroatoms (oxafenestranes[8] and azafenestranes).[8c,d,9] However, the synthesis of chiral nonracemic fenestranes remains challenging, and only a few oxafenestranes have been synthesized as single enantiomers[8a,b,e] and no enantioselective methods for the synthesis of full-carbon fenestranes have been reported.[3a]

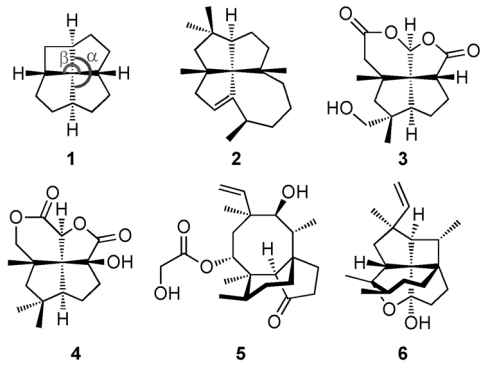

Figure 1. The structures of *cis*,*cis*,*cis*,*cis*-[4.5.5.5]fenestrane **1**, laurenene **2**, penifulvin B **3**, asperaculin A **4**, pleuromutilin **5**, and bridged *cis*,*cis*,*cis*,*cis*-[4.5.5.5]oxafenestrane **6**.

Natural products are abundant sources of molecular complexity and are attractive starting points for the synthesis of enantioenriched complex molecules. Medicinally important but low abundant natural products, including taxol,[10] doxorubicin,[11] and artemisinin,[12] are derived semisynthetically from more easily available natural product precursors. Semisynthesis is also used to access natural product derivatives with improved efficacy and pharmacokinetic competence (e.g. camptothecin to topotecan, erythromycin to azithromycin, and pleuromutilin to retapamulin).[13] Furthermore, readily available natural products have been employed as complex starting materials in the synthesis of numerous classes of natural products and commodity chemicals (adrenosterone to ouabagenin,[14] dehydroepiandrosterone to cyclopamine,[15] and sclareol to ambroxan).[16]

Complex natural products also provide a useful template for the synthesis of novel molecular scaffolds of biological and theoretical interest.[17] We have reported a strategy for creating structurally diverse collections of complex small molecules from readily available natural products, called complexity-to-diversity.[18] The key feature of our approach is the systematic utilization of ring distortion reactions (i.e. ring expansion, contraction, cleavage, and rearrangement) to dramatically alter natural product ring systems and create compounds that are structurally distinct from each other and the starting natural product. In addition to the utility of such molecules in drug discovery, the strategic application of ring distortion reactions to complex natural products can facilitate the creation of compounds to investigate unusual structural phenomena, such as the planarization of four-coordinate carbon atoms.

Pleuromutilin **5** (Figure 1) is a diterpene natural product, first isolated from *C. passeckerianus*, that exhibits potent antibacterial activity by binding to the bacterial 50S ribosome.[19] Due to its use as the starting material for the semisynthesis of the approved antibiotics retapamulin, tiamulin, and valnemulin,[20] large quantities of **5** are readily available from several commercial sources. The core ring system of **5** is composed of 5-, 6-, and 8- membered rings

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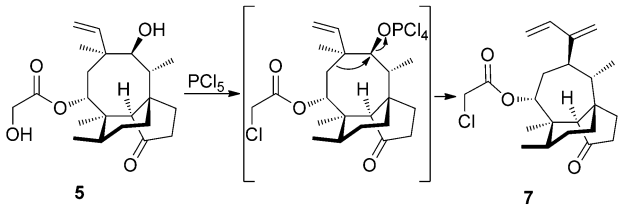
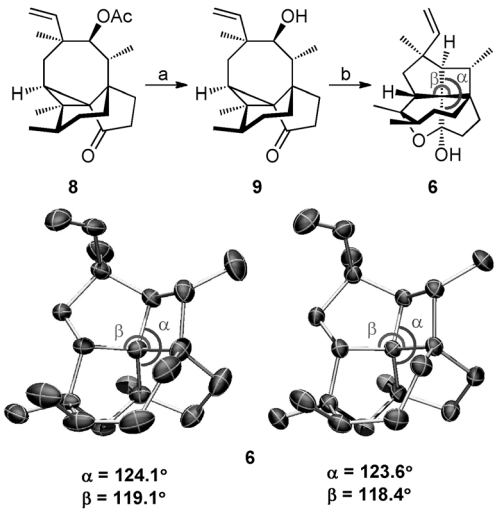
containing a common C–C bond and bears eight stereogenic centers (Figure 1). The advantageous arrangement of oxygen-containing functional groups (ketone, alcohol, and ester) on the congested core scaffold of **5** facilitates the creation of highly strained ring systems in short synthetic sequences through ring distortion. As part of our ongoing studies on **5**, we have developed a method for the preparation of a unique class of bridged *cis*,*cis*,*cis*,*cis*-[4.5.5.5]oxafenestranes that contain highly planarized four-coordinate carbon atoms (e.g. **6**, Figure 1).

Previous studies have shown that the treatment of **5** with phosphorus pentachloride results in a carbocation-mediated ring contraction of the 8-membered ring to form diene **7** (Scheme 1).[21] Inspired by this result, we investigated carbocation rearrangements as a late-stage ring distortion strategy for the modification of structurally diverse compounds originating from **5**. We identified cyclopropane **8** as an enticing potential scaffold for carbocation rearrangement due to the possibility of cyclopropane ring opening (Scheme 2). Cyclopropane **8** is readily accessible from **5** in three steps (41% overall yield) through modified literature procedures (see the Supporting Information).[21,22] Saponification of **8** with potassium hydroxide provides the desired rearrangement precursor, **9** (Scheme 2). Exposure of **9** to phosphorus pentachloride results in cyclopropane opening and rearrangement to the bridged *cis*,*cis*,*cis*,*cis*-[4.5.5.5]oxafenestrane **6** in 51% yield as a single diastereomer and single enantiomer. Fenestrane **6** is one of the few examples of a chiral non-racemic oxafenestrane that has been synthesized and suggests the potential of pleuromutilin as the starting point for the preparation of enantioenriched fenestranes.



Scheme 1. Ring contraction of pleuromutilin (**5**) developed by Birch et al.[21]



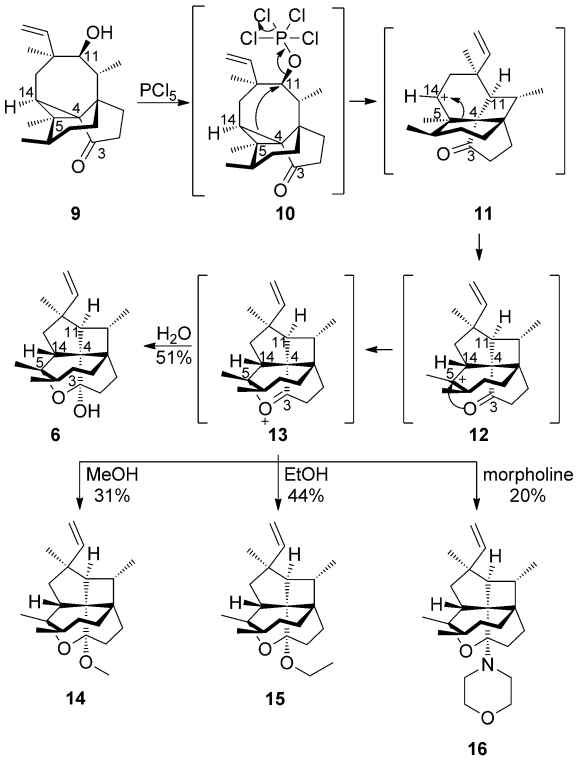
Scheme 2. Synthesis of bridged *cis*,*cis*,*cis*,*cis*-[4.5.5.5]oxafenestrane **6**: a) KOH, EtOH, reflux, 12 h (71%); b) PCl_5, CH_2Cl_2, 0°C to rt, 1 h (51%). The X-ray crystal structure shows that **6** exists as a hydrogen-bonded dimer in the solid state and exhibits central bond angles with significant planarization.

From the X-ray crystal structure of **6**, the degree of planarization about the central carbon was assessed based on the bond angles α and β (Scheme 2). Since **6** crystallized as a hydrogen-bonded dimer, the bond angles about the central carbon for each molecule of the dimer were measured. The observed bond angles of $\alpha = 124.1°$, $\beta = 119.1°$ and $\alpha = 123.6°$, $\beta = 118.4°$ show significant planarization of the central carbon and the values for α are larger than any previously reported for a *cis*,*cis*,*cis*,*cis*-[4.5.5.5]fenestrane.[3a] The large value for α is likely due to the presence of the bridging 7-membered ring, as bridged [4.6.4.6]- and [5.5.5.5]fenestranes exhibit similar increases in planarization for one bond angle.[7h,8c] However, the degree of planarization found in **6** is less than the planarization possible in fenestranes with *trans*-bridgehead substituents,[23] fenestranes with bridgehead olefins,[24] or fenestranes with smaller ring sizes.[7c]

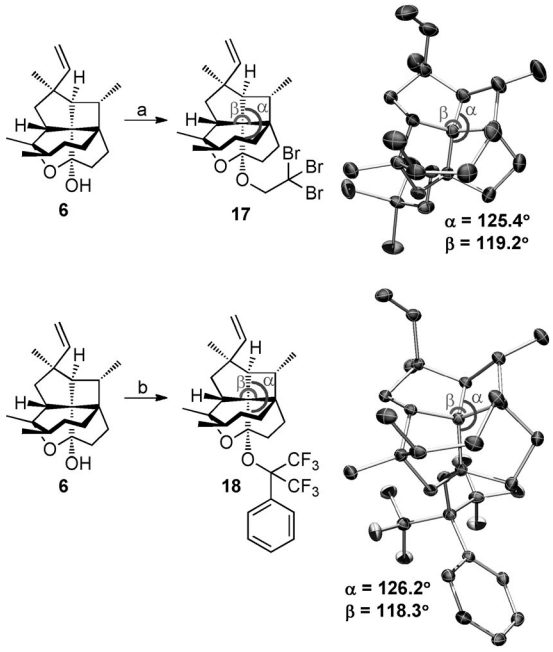
The crystal structure of **6** also provides insight into the possible mechanism of this reaction (Scheme 3), as an inversion of configuration occurs at carbon atoms C5, C11, and C14 during the course of the reaction. The inversion at C11 is indicative of a cyclopropyl bond migration to displace the activated alcohol (**10**). Due to the proximity of the C4–C14 bond to C11 and the inversion of configuration at C14, it is likely that migration of the C4–C14 bond occurs first to form a carbocation at C14 (**11**). The newly-formed six-membered ring then undergoes a ring flip to orient the empty C14 π-orbital so that the *Si* face overlaps with the C4–C5 bond, leading to the observed configuration at C14 upon migration of the C4–C5 bond to form a tertiary carbocation at C5 (**12**).

The C5 carbocation is geometrically constrained to only react with the ketone from the *Si* face to form oxocarbenium **13** (Scheme 3). Addition of water upon completion of the reaction results in the formation of the product hemiketal **6**. However, if the reaction mixture is quenched by addition of an alternative nucleophile such as methanol, ethanol, or even morpholine, the respective ketal or aminal is formed (**14**–**16**). This result provides strong evidence for the presence of a stable oxocarbenium under the reaction conditions.

The influence of substituents on the planarization of the central carbon atom was studied with crystalline derivatives of **6** (Scheme 4). Treatment of **6** with tribromoethanol and *p*-toluenesulfonic acid gives tribromoethyl ketal **17**. X-ray crystallographic analysis of **17** reveals central bond angles of $\alpha = 125.4°$ and $\beta = 119.2°$, demonstrating that ketal substituents have a substantial impact on the bond angle α and increase the planarization of the central carbon. Attempts to introduce bridgehead olefins through hemiketal dehydration were hindered by the tendency of **6** to undergo S_N1 reactions. For example, tertiary alcohols and hemiketals typically



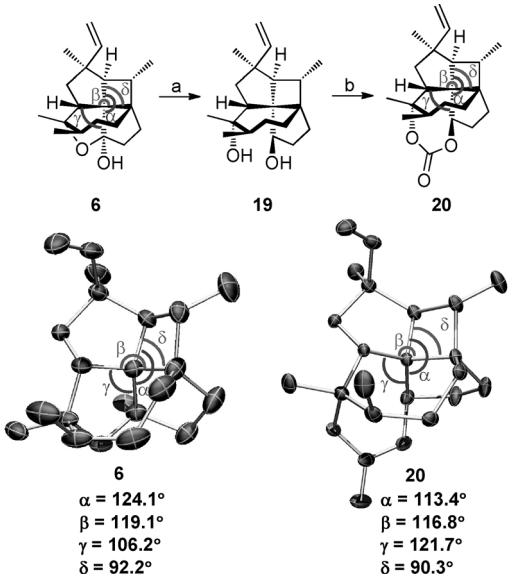
Scheme 3. Proposed mechanism for the formation of **6**: Alcohol activation and displacement affords the secondary carbocation **11**, which undergoes a 1,2-migration to form the tertiary carbocation **12**. The tertiary carbocation is trapped by the carbonyl group to form oxocarbenium **13**, which forms hemiketal **6** upon quenching with water. Quenching the reaction with methanol, ethanol, or morpholine leads to the corresponding ketal or aminal (**14**–**16**).



Scheme 4. Crystalline ketal derivatives of **6**: a) 2,2,2-tribromoethanol, *p*TsOH, DMF, 0°C to rt, 17 h (37%); b) Martin's sulfurane, CH_2Cl_2, 0°C to rt, 1 h (70%).

undergo E1 elimination upon exposure to Martin's sulfurane.[25] Treatment of **6** with Martin's sulfurane results in the formation of ketal **18**, in spite of the poor nucleophilicity of 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (Scheme 4). Ketal **18** is highly crystalline and provides insight into the effects of bulky ketal substituents on planarization of the central carbon. The crystal structure of **18** shows that significant steric bulk on one face of the molecule forces the fenestrane skeleton toward the opposite face, leading to a large increase in α and a modest decrease in β.

Further ring distortion of **6** was performed to assess the influence of ring size on planarization. Reduction of **6** with sodium borohydride provides the broken fenestrane **19** (Scheme 5). Exposure of **19** to triphosgene results in cyclic



Scheme 5. Synthesis of bridged *cis*,*cis*,*cis*,*cis*-[4.5.7.5]oxafenestrane **20** from **6**: a) $NaBH_4$, MeOH, THF, 0°C to rt, 6 h (87%); b) triphosgene, pyridine, CH_2Cl_2, 0°C to rt, 1 h (96%).

carbonate formation to provide bridged *cis*,*cis*,*cis*,*cis*-[4.5.7.5]dioxafenestrane **20**. To our knowledge, this is the first report of a [4.5.7.5]fenestrane. The X-ray crystal structure of **20** demonstrates the effects of increasing ring size on the geometry of the central carbon atom (Scheme 5). While [4.5.5.5]oxafenestranes, such as **6**, exhibit a high degree of planarization and large values of α and β, [4.5.7.5]dioxafenestrane **20** shows only modest planarization of the central carbon ($\alpha = 113.4°$ and $\beta = 116.8°$). Instead, the greater flexibility of the 7-membered ring enables **20** to exhibit scissor-type distortion,[9c] a type of distortion commonly found in molecules containing small rings characterized by one angle contracting from the tetrahedral geometry and the opposite angle enlarging to compensate (demonstrated by the large difference between angles γ and δ).

In conclusion, the ring distortion of natural products provides an advantageous method for the efficient preparation of molecules to investigate unusual structural phenomena. Synthetic modification of the readily available diterpene natural product pleuromutilin (**5**) enabled the synthesis of the

highly complex bridged *cis*,*cis*,*cis*,*cis*-[4.5.5.5]oxafenestrane **6** in five synthetic steps and 15% overall yield. The key step of this sequence was a phosphorus pentachloride-mediated carbocation rearrangement cascade to create the fenestrane scaffold. The X-ray crystal structure of **6** shows a high degree of planarization of the central four-coordinate carbon as evidenced by the large magnitude of the central bond angles α and β. The presence of the bridging 7-membered ring leads to a disproportionate increase in the value for one of the central bond angles (α). X-ray crystallographic analysis of ketal derivatives of **6** shows that increased steric bulk at the bridgehead positions results in further increases in the value of α but exceedingly bulky ketal substituents can decrease the magnitude of the opposite bond angle β. Ring expansion of the hemiketal of **6** to a cyclic carbonate enabled the synthesis of the bridged *cis*,*cis*,*cis*,*cis*-[4.5.7.5]dioxafenestrane **20**, which predominately exhibits scissor type distortion of the central four-coordinate carbon. Natural products continue to be a convenient source of structural complexity that can rapidly be converted to very diverse compounds.

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