INTRODUCTION

Ring strain is a property possessed by small molecules and is recognized by chemists as an exceptionally efficient and practical tool for attaining challenging transformations. Organic chemistry has witnessed tremendous progress towards this end with the development of a plethora of methods that can harvest the high energy of a strained system and direct it into productive pathways. Thus, the transition-metal catalyzed activation of a C–C sigma bond, a long-standing challenge, has been achieved utilizing the strain of four-membered rings. The energy stored in norbornadiene has been exploited in its use as an acceptor for group transfer, a relay tool for selective C–H activation, and a ligand scaffold for efficient catalysis. The use of overbred intermediates (intermediates en route to cyclic structures that have one or more excess C-C bonds) for realizing difficult disconnections has been proven to be a fruitful strategy in total synthesis. Extreme cases of strained molecules include propellanes, quadricyclanes, and bicyclobutane. These molecules were synthesized in the mid-20th century and were the subjects of intensive studies due to their peculiar chemical and physical properties. Recently, renewed interest from the organic community has begun to unveil new reactivity and utility of these unique motifs.

OUTLINE

In the mid-70s Gassman and co-workers demonstrated that bicyclobutanes can be fragmented to produce a variety of different products. The outcome is highly sensitive towards the substitution pattern of the substrate, choice of catalyst, concentration, and temperature. Due to the unpredictable nature of the process, this pioneering work has more theoretical significance than practical. Not until 2008 was this intriguing reactivity revisited by Wipf and co-workers, who reported a rhodium-catalyzed cycloisomerization of the bicyclobutanes. This process selectively leads to 7,3- or 5,3-fused bicycles, depending on the ligand of choice (Scheme 1). Thus, fine tuning of the catalytic system results in controllable conversion of strain energy into polycyclic frameworks.

\[
\begin{align*}
&\text{Scheme 1. Cycloisomerization of bicyclobutanes.}
\end{align*}
\]
In 2004, Baran and co-workers completed the first total synthesis of sceptrin, a natural product with potent antiviral and antibacterial activities.³ Retrosynthetic analysis reveals cyclobutane 5 as a key intermediate (Scheme 2). Due to the dense substitution pattern, the precursor is inaccessible via standard protocols (i.e., intermolecular [2+2]-cycloaddition).

Inspired by the early work of Nelsen,⁴ the authors exploited an acid-mediated rearrangement of another type of the high-energy molecule, 3-oxoquadricyclane 4. Use of this transformation coupled with an elegant elaboration of intermediate 5 allowed them to accomplish the synthesis in only 12 steps and 24% overall yield.

[1.1.1]propellane is one of the most strained systems known to date.⁵ Myriad studies devoted to the physical and chemical characteristics of this structure pre-date the actual synthesis, which was achieved in 1982 by Wiberg and co-workers.⁶ For decades, [1.1.1]propellane did not find any practical application despite its unique properties. In 1996, bicyclo[1.1.1]pentane, the product of difunctionalization of the bridging C–C bond in propellane, was recognized as a non-classical bioisostere (Scheme 3).⁷ In 2012, Stepan at Pfizer showed that the bicyclo[1.1.1]pentane moiety increased solubility and permeability in a γ-secretase inhibitor, improving overall drug-candidate performance.⁸ Since then much effort has been put into the development of new methodologies aimed at diverse functionalization of [1.1.1]propellane.

REFERENCES