Tetrahedron 69 (2013) 7831–7839

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New cycloaddition/fragmentation strategies for preparing 5-7-5 and 5-7-6 fused tricyclic ring systems

Jing He, Marc L. Snapper *

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467, USA

ARTICLE INFO

Article history:
Received 29 April 2013
Received in revised form 25 May 2013
Accepted 28 May 2013
Available online 4 June 2013

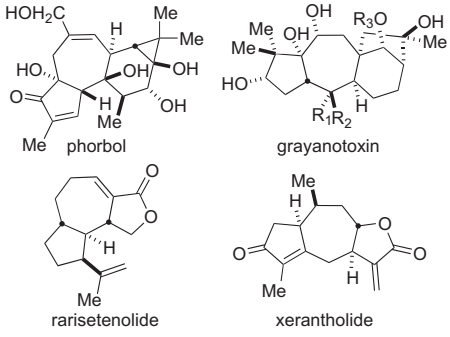
Keywords:
Cyclobutadiene
Cycloaddition
Intramolecular
Cyclopropanation
Fragmentation

ABSTRACT

Tethering additional functionality to cyclobutadienyl iron tricarbonyl complexes provides new opportunities for the rapid construction of medium-ring-containing polycyclic compounds. Specifically, an intramolecular cycloaddition between cyclobutadiene and a tethered olefin, followed by an intramolecular cyclopropanation of the resulting cyclobutene-containing adduct generates highly strained pentacyclic intermediates. These compounds can then be relaxed thermally to generate 5-7-5 and 5-7-6 fused tricyclic ring systems that are shared with numerous natural products.

1. Introduction

Medium-ring-containing, polycyclic natural products, such as phorbol, grayanotoxin, rarisetenolide, and xerantholide provide ample motivation for improved strategies toward 5-7-5 or 5-7-6 tricyclic ring systems. The construction of these tricyclic ring systems has been accomplished by various approaches.[1] Of the myriad ring forming strategies that are possible, only a handful has been used in total synthesis.



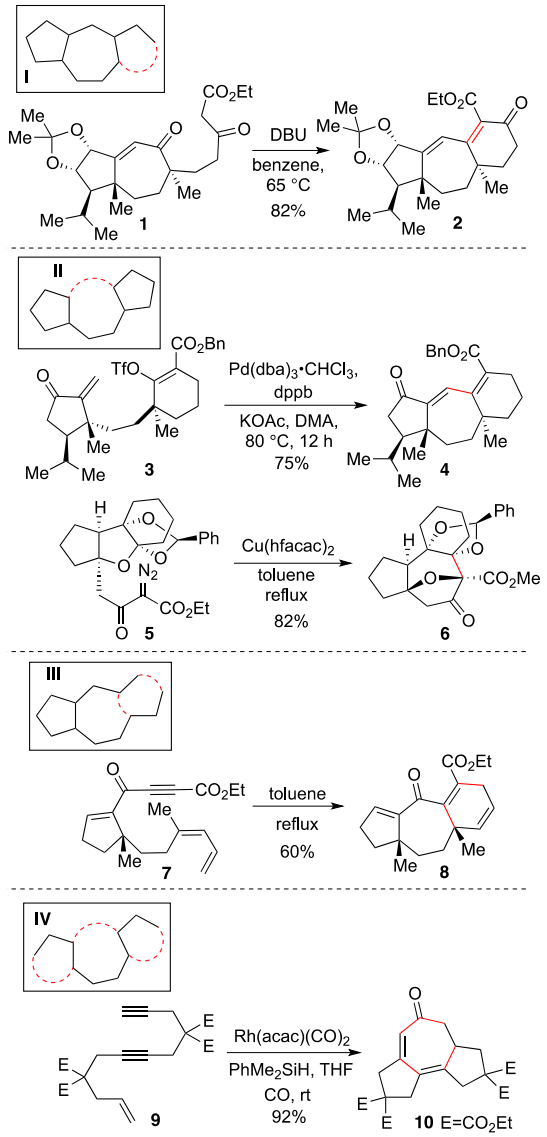
Some of the recent approaches are summarized in Scheme 1. The first example relies on annulation of a third ring onto a fused bicyclic ring precursor.[2] For example, a Knoevenagel condensation served as a key step to annulate the six-membered ring on a bicyclic hydroazulene precursor **1**→**2** in the study toward the synthesis of guanacastepene C.[3] The second strategy highlighted is an intramolecular ring closure between the two outer rings to generate the central seven-membered ring. A variety of general methods for synthesis of seven-membered ring are applied in this category. For example, the Overman group reported a convergent and enantioselective total synthesis of (+)-guanacastepene N featuring a regioselective 7-*endo* Heck cyclization as the key step to afford the tricyclic skeleton (**3**→**4**).[4] In a related disconnection, the West group used an oxonium ylide [1,2]-shift in their approach to the tigliane-daphnane skeleton (**5**→**6**).[5] Both high yield and selectivity were achieved in this transformation.

A third strategy is based on an intramolecular cycloaddition between two groups attached to a preexisting ring to generate two additional rings. In the total synthesis of C8-*epi*-guanacastepene O, the Yang team applied the intramolecular Diels–Alder reaction between an alkyne and diene to form the desired tricyclic systems with cis-annulated methyl groups in 60% yield.[6] Wender's successful syntheses of phorbol and related natural products also featured this general strategy.[1b,7] The fourth approach represents a particularly rapid means of generating complex ring systems from acyclic precursors. Transition-metal catalyzed cyclization plays a significant role in this category. The Ojima's group, for example, developed a rhodium catalyzed, silane-mediated [2+2+2+1] cycloaddition of enediynes in moderate to excellent yields to provide tricycle **10**.[8]

We have been interested in developing new methods of constructing medium-ring-containing compounds. In particular,

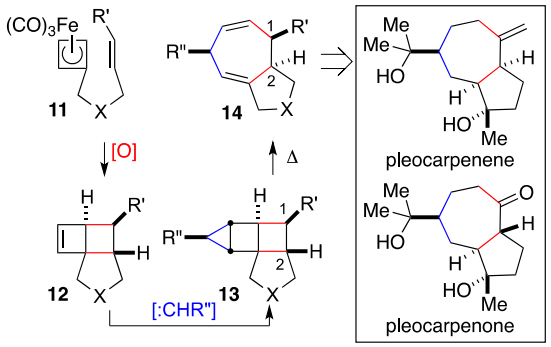
* Corresponding author. Tel.: +1 617 552 8096; fax: +1 617 552 1442; e-mail address: marc.snapper@BC.edu (M.L. Snapper).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.05.129



Scheme 1. Construction of 5-7-5(6) ring systems.

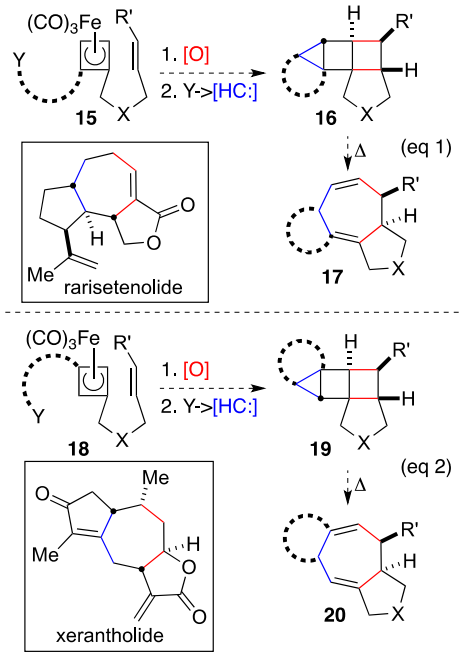
intramolecular cycloadditions of iron tricarbonyl cyclobutadienyl complexes have been shown to generate highly functionalized, strained cyclobutene adducts that can be used to access medium ring skeletons through subsequent fragmentations.[9] For example, as shown in Scheme 2, we have used this cycloaddition, followed by an intermolecular cyclopropanation and thermal fragmentation to



Scheme 2. 5-7 Ring systems through a cyclobutadiene cycloaddition/cyclopropanation/thermal fragmentation sequence.

prepare 5-7 ring systems. Interestingly, the stereochemistry at the C2 position becomes inverted during the thermal rearrangement step of this sequence. This synthetic strategy has been used in the total syntheses of (+)- and (−)-pleocarpenene and pleocarpenone.[10]

Given the prevalence of tricyclic ring systems among terpenoid natural products, we thought that an efficient approach toward these targets could be achieved by incorporating an *intramolecular* cyclopropanation[11] of the cyclobutene intermediate **12** in this reaction sequence. While generating the strained precursor to the central seven-membered ring, the intramolecular cyclopropanation would also establish an additional ring of the polycyclic target. Furthermore, as illustrated in Scheme 3, depending on the attachment point of the tethered carbenoid precursor (Y in **15** and **18**), two unique tricyclic ring systems **17** and **20** should be accessible through this approach (Eqs. 1 and 2). Described herein are our preliminary studies exploring the feasibility of this strategy for generating these medium-ring-containing tricyclic systems.



Scheme 3. Generation of tricyclic ring systems using an intramolecular cyclopropanation.

2. Results and discussion

The first challenge to be addressed in advancing this strategy was the introduction of the additional functionality on the cyclobutadienyl iron tricarbonyl complex. A solution is summarized in Scheme 4. DIBAL-H reduction of the iron methyl ester complex **21**, followed by formation of the MOM-ether **22** allowed for the directed *ortho* lithiation, which generates a mixture of 1,2- and 1,3-disubstituted iron complexes **23** and **24** in a 5:1 ratio. At this stage, the separation of these regioisomers through silica gel column chromatography was not readily feasible. Therefore, the two regioisomers, **23** and **24** were carried through the subsequent transformations together. Under acidic conditions, the MOM group was replaced by an allyl group. Treatment of the resulting ether with styrene in the presence of Hoveyda–Grubbs second catalyst (HG2) provided efficiently compounds **25** and **26**, which were then oxidized with CAN to form cyclobutenes **27** and **28**. These two regioisomeric cycloadducts were separable and each subjected independently to the following studies.