Tetrahedron 69 (2013) 7810–7816

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

An asymmetric total synthesis of (+)-pentalenene

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ARTICLE INFO

Article history:
Received 23 April 2013
Received in revised form 16 May 2013
Accepted 20 May 2013
Available online 24 May 2013

Keywords:
Stereoselective
Total synthesis
Triquinane
Trimethylenemethane
Tandem cycloaddition

ABSTRACT

A stereoselective total synthesis of (+)-pentalenene was achieved through the tandem cycloaddition reaction of the allenyl diazo substrate prepared from (+)-citronellal. The initial intramolecular [2+3] cycloaddition reaction between the diazo functionality and the allenyl group produced the trimethylenemethane (TMM) intermediate after immediate loss of nitrogen molecule from the cycloaddition intermediate. Subsequent [2+3] cycloaddition of the TMM with olefin produced the angularly fused triquinane structure stereoselectively.

1. Introduction

Since the isolation of isocomene[1] from natural sources in 1977, angularly fused triquinanes have attracted synthetic chemistry community for their highly congested structural features with diverse substitution patterns (Fig. 1).[2] Various ingenious synthetic strategies have been developed for the construction of this tricyclic structure.[3] Variety of synthetic strategies of the skeleton became a tool for assessments of the complexity derived evaluation of synthetic strategies[4] and eventually became one of the test sets for various measures of ideal synthesis.[5]

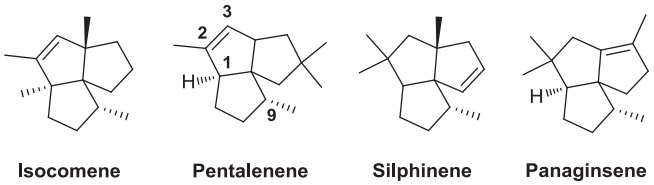
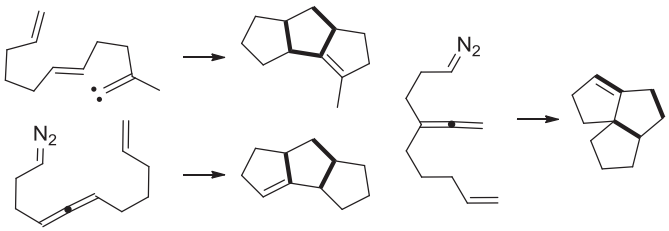


Fig. 1. Angularly fused triquinane natural products.

Pentalenene, a sesquiterpene with tricycle[6.3.0.0]undecane core structure was isolated from *Streptomyces griseochromogenes* by Seto and Yonehara in 1980.[6] A great attention has been drawn to this natural product since it is the representative angular triquinane natural product to test newly developed synthetic methodologies and is the biosynthetic precursor of pentalenolactone, an antibiotic metabolites, produced by several *Streptomyces* species.[7] There have been numerous synthetic efforts of the total and formal synthesis of pentalenene[8] that culminated several total syntheses of the natural product mostly in racemic form except two.[9,12]

Most synthetic approaches toward the linear and angularly fused triquinanes employed sequential annulations to construct the tricyclic ring system by adding one ring at a time. Only few strategies that assembled two or more rings in one-step were reported; thermolytic rearrangemnt,[8e] metal-catalyzed transformation,[8p] squarate ester cascade,[8q] tandem radical cyclization,[10] arene-olefin photocycloaddition,[11] and intramolecular Pauson–Khand reaction.[12]

Recently, we have developed synthetic strategies of constructing the triquinane structures directly from linear substrates through tandem cycloaddition reaction via trimethylenemethane (TMM) intermediates.[13] (Scheme 1) The tandem cycloaddition strategies have been applied to the total synthesis of linearly fused triquinane natural products.[13a,14]



Scheme 1. Tandem cycloaddition routes to triquinanes.

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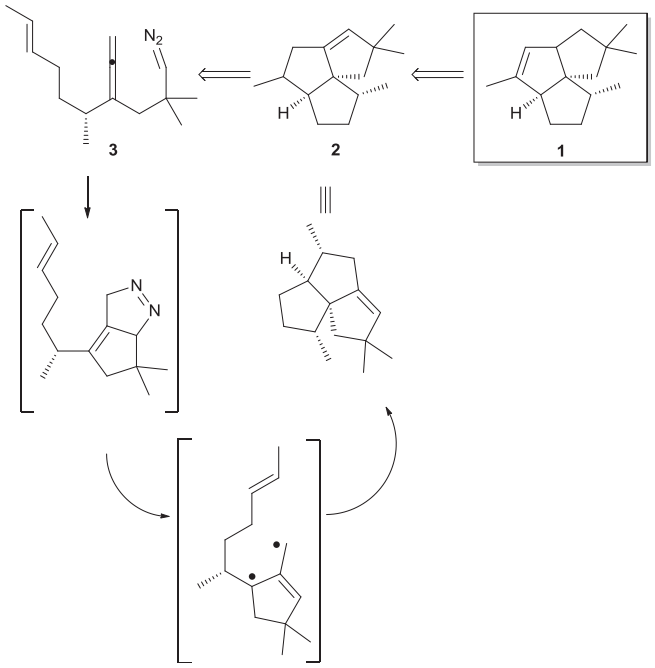
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.05.095

Herein, We report an application of the tandem cycloaddition strategy via TMM diyl [2+3] cycloaddition reaction[13b] to the total synthesis of (+)-pentalenene.

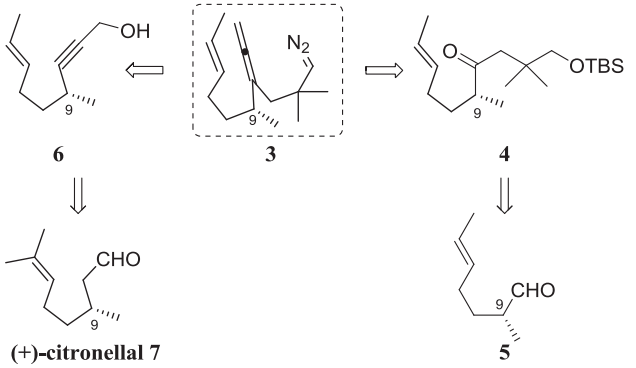
Pentalenene could be synthesized from the isomeric triquinane **2** that would be obtained from the linear precursor **3** through the tandem cycloaddition reaction. The cycloaddition reaction was expected to be stereoselective as the stereochemistry at the C-9 of the substrate was known to control the relative stereochemistry of the triquinane product[15] (Scheme 2).



Scheme 2. Synthetic analysis of pentalenene.

2. Result and discussion

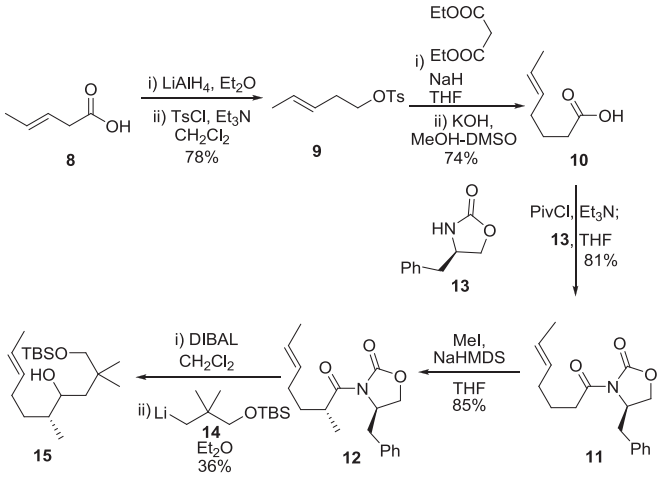
The enantioselective preparation of the cycloaddition precursor **3** was the key to the total synthesis of (+)-pentalenene (Scheme 3). The allenyl compound **3** could be obtained from the corresponding ketone **4** that should be readily synthesized from the aldehyde **5**. The aldehyde **5** would be obtained through an asymmetric alkylation of the corresponding carboxylic acid **8**.



Scheme 3. Synthetic routes to the key intermediate **3**.

Alternatively, the allenyl moiety of **3** could be synthesized from the propargyl alcohol **6** that can be obtained from (+)-citronellal **7** that possesses the desired absolute stereochemistry of the methyl group at C-9 of **7**. Based on our early experience with the racemic synthesis of pentalenene, we first explored the synthetic strategy that was based on the asymmetric alkylation process developed by Evans.[16]

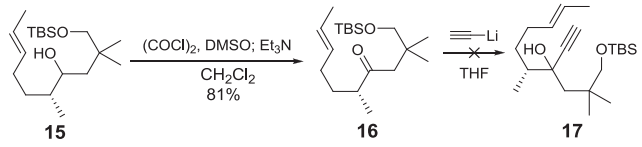
Preparation of the substrate to generate **3** for the tandem cycloaddition started from the synthesis of the carboxylic acid **10** and subsequent asymmetric methylation of the corresponding amide possessing Evans' chiral auxiliary **12** (Scheme 4).



Scheme 4. Preparation of the chiral alcohol **15**. Acronyms and abbreviations: TsCl, *p*-toluenesulphonyl chloride; DMSO, dimethylsulfoxide; PivCl, pivaloyl chloride; NaHMDS, sodium hexamethyldisilazide; THF, tetrahydrofuran; DIBAL, diisobutylaluminum hydride.

The carboxylic acid **10** was prepared from *trans*-2-pentenoic acid **8** through malonate ester synthesis for the two carbon extension. The carboxylic acid **8** was reduced to the alcohol and activated as the tosylate **9**. Diethyl malonate anion addition to the tosylate **9** followed by decarboxylative hydrolysis produced the desired carboxylic acid **10**. Following the Evans' protocol,[17] chiral amide **10** was prepared by amide formation with chiral oxazolidinone **13** via activation as the mixed anhydride using pivaloyl chloride. Methylation of the enolate of **11** produced the chiral center C-9 stereoselectively[18] and DIBAL reduction furnished the chiral aldehyde **5**. Treating known Li reagent **14**[13b] formed alcohol **15**.

After the Swern's oxidation to form ketone addition of lithiumacetylide to the ketone produced the alkynol **17** as a mixture of diastereomers in trace, and the reaction was sluggish even at room temperature. Due to the low reactivity of the ketone and the long reaction time to form **17**, the enantiomeric purity of the methyl group at the C-9 was lost completely as judged by the optical rotation of the product **17** and the recovered ketone **16** from the reaction (Scheme 5).



Scheme 5. Synthesis of **17**.

Several efforts to minimize the racemization at the C-9 stereocenter during the acetylide addition reaction were not fruitful. Thus the other synthetic route to **3** was explored starting from (+)-citronellal **7**. Synthesis of **6** from citronellal required the conversion of the aldehyde into the alkyne and deletion of one methyl group (Scheme 6).