Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

First ketene cycloaddition approach to (±)- junionone

Ihsan Erden,* and Samuel E. Watson

San Francisco State University, Department of Chemistry and Biochemistry, 1600 Holloway Avenue, San Francisco, CA 94132, USA

Leave this area blank for abstract info.

First ketene cycloaddition approach to (±)-junionone

Ihsan Erden,* and Samuel E. Watson

San Francisco State University, Department of Chemistry and Biochemistry, 1600 Holloway Avenue, San Francisco, CA 94132, USA

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

junionone

dimethylketene

cyclobutanone

Huang-Minlon reduction

Wacker-Tsuji oxidation

ABSTRACT

Junionone is the first monocyclic cyclobutane monoterpenoid isolated from a plant. Of the existing four syntheses of this compound, none employs a ketene cycloaddition to construct the four-membered ring. Herein, we report the first total synthesis of junionone that features a ketene cycloaddition for the synthesis of this compound, starting from the commercially available 1,5-hexadiene.

2009 Elsevier Ltd. All rights reserved.

1. Introduction

Cyclobutane monoterpenes originate from the degradation of pinenes. Most of them have been isolated from plants, some others from animal sources and occur as insect pheromones.¹ Well-known examples include junionone (**1**),² the first vegetable monocyclic monoterpenoid, isolated from fruits of the juniper tree *Juniperus communis* (Cupressaceae), and fragranol (**2**),³ found in the roots of *Artemisia fragrans* (Asteraceae). The diastereomer of **2**, grandisol (**3**),⁴ on the other hand, is the major constituent in the pheromone cocktail (grandlure) of the male boll weevil *Anthonomus grandis*, while planococcyll acetate **4** represents the male pheromone of the citrus flour beetle *Plenococcus citri*.⁵

Figure 1. Monocyclic cyclobutane monoterpenoids

The synthetic route to **1** by Gaoni takes advantage of a LiAlH_4 reduction of arylsulfonylbicyclobutanes and involves 7 steps with an overall yields of 3.5%.^{6a,b} Thomas' synthesis commences with caryophyllene and involves 6 steps; though no yields were reported for the first 5 steps, the introduction of the double bond from the saturated precursor proceeds in ca 4% yield.^{2,17} In Venkateswaran's route the four-membered ring is formed by a ring contraction from an α -diazoketone, and the synthesis requires 10 steps (including the three-step synthesis of 2,2-dimethyl cyclopentanone) to give **1** in 12.4% overall yield.^{6d}

* Corresponding author. Tel.: +0-415-338-1627; fax: +0-415-338-2384; ierden@sfsu.edu

Lovchik's synthesis features a Lewis acid catalyzed intramolecular nucleophilic substitution with allylic rearrangement (S_Ni') is enantioselective, however lengthy (9 steps) with an overall yield of 6%.^{6c} Though junionone contains a four-membered ring, it is surprising to note that none of the previous four syntheses employed a ketene cycloaddition for cyclobutane formation. It seemed that a shorter and more efficient total synthesis of junionone was warranted. We decided to take advantage of our past experience in ketene chemistry⁷ to devise a suitable synthesis for **1** featuring a [2+2] ketene cycloaddition as the key step. In this *Letter* we report on the details of our short synthesis of racemic junionone.

2. Results and Discussion

Our synthesis commences with commercially available and inexpensive (~30¢/mL) 1,5-hexadiene. We decided that it was advantageous to construct the cyclobutane ring early in the synthesis; the 2+2 cycloaddition with dimethylketene was tried first converting 2,2-dimethylmalonic acid thermally to dimethylketene acylal, followed by treatment of the latter with K_2CO_3 in the presence of 1,5-hexadiene **6** at 120 °C.⁸ Under these conditions only minute amounts of the desired cyclobutanone were formed. We next tried the cycloaddition by the dehydrochlorination of isobutyryl chloride with NEt_3 .⁹ We found that instead of stirring the mixture at room temperature, refluxing the alcohol-free chloroform solution overnight doubled the yield. Thus, cyclobutanone formation was achieved in 60% isolated yield after bulb-to-bulb distillation. In addition to the ^1H and ^{13}C NMR spectral data confirming the proposed structure,¹⁰ the presence of the $\nu_{\text{C=O}}$ stretch at 1778 cm^{-1} was diagnostic of the cyclobutanone in **7**. Moreover, the regioselectivity observed in the cycloaddition was consistent with the frontier orbital considerations¹¹ (Scheme 1).

Scheme 1. Cycloaddition of **5** onto dimethylketene, generated in situ from **6**

The next step in our synthetic plan was the ketone-methylene reduction before the terminal double bond was subjected to an oxidative transformation. Toward that end **7** was converted to its ethylene thioketal with 1,2-ethanedithiol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Though thioketalization proceeded smoothly in good yield, the subsequent reductive desulfurization step using freshly prepared Raney nickel (activity W-2) proved to be unsatisfactory. The Wolff-Kishner reduction (Huang-Minlon modification)¹² using 85% hydrazine hydrate with NaOH in diethylene glycol proved more successful; however the yield of the reduction (35%) was still not satisfactory. Finally, the Barton modification for sterically hindered ketones using anhydrous hydrazine under strictly anhydrous conditions proved to be the method of choice,¹³ furnishing **8** in 90% yield.¹⁴ Next, the terminal double bond was subjected to a Wacker-Tsuji oxidation using PdCl_2 , freshly prepared CuCl_2 in DMF under an oxygen atmosphere.¹⁵ Yields on the ketone **9** were consistently in the 80% range for this step (Scheme 2).¹⁶

Scheme 2. Reduction of **7** with 100% NH_2NH_2 , followed by Wacker-Tsuji oxidation of the vinyl group

Although the obtention of **9** completed formal synthesis of junionone, since **9** had been converted to **1** with HIO_4 , in albeit low yields,¹⁷ we decided to improve the dehydrogenation step by using *o*-iodoxybenzoic acid (IBX) using the method by Nicolaou et al.¹⁸ Under these conditions (IBX, 1.3 equiv. DMSO, 65°C), junionone **1** was obtained in a yield of 82%. The spectral data of **1** so obtained were identical in all respects to those previously reported.^{1, 6c}

3. Conclusions

We have developed an exceptionally simple and short synthesis (4 steps) of the monocyclic cyclobutane terpenoid junionone (**1**) starting from the commercially available 1,5-hexadiene, and employing the first ketene cycloaddition approach for the construction of the cyclobutane ring. The synthesis is short, straightforward and high yielding and is superior to the existing syntheses in terms of overall yield (24% over 4 steps) and brevity. We are in the process to implement a similar strategy for the synthesis of several other monocyclic cyclobutane monoterpenes.

Acknowledgments

We gratefully acknowledge financial support of this work by funds from the National Institutes of Health (Grant No. SC1 GM082340). We also thank the National Science Foundation (CHE-1228656) for the purchase of the QExactive mass spectrometer on which all HRMS data were collected.

References and notes

- Breitmaier E. Terpenes: Flavors, Fragrances, Pharmaca, Pheromones; Wiley-VCH, Weinheim, 2006; p 13.
- Thomas, A. F.; Ozainne, M. *Chem. Commun.* **1973**, 746.
- Bohlmann, F.; Zedor, C.; Faas, U. *Chem. Ber.* **1973**, *106*, 2904-2909.
- Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A. *Science*, **1969**, *166*, 1010-1012.
- Zada, A.; Dunkelblum, E.; Harel, M.; Assael, F.; Gross, S.; Mendel, Z. *J. Econ. Entomol.* **2004**, *97*, 361-368.
- (a) Gaoni, Y. *Tetrahedron Lett.* **1982**, *23*, 5219-5220; (b) Gaoni, Y.; Tomažič, A. *J. Org. Chem.* **1985**, *50*, 2948-2957; (c) Lovchik, M. A.; Fráter, G.; Goetze, A.; Hug, W. *Chem. Biodivers.* **2008**, *5*, 126-139; (d) Ghosh, A.; Banerjee, U. K.; Venkateswaran, R. V. *Tetrahedron*, **1990**, *46*, 3077-3088.
- (a) Erden, I.; Cao, W.; Price, M.; Colton, M. *Tetrahedron*, **2008**, *64*, 5497-5501; (b) Erden, I.; Sorensen, E. M. *Tetrahedron Lett.* **1983**, *24*, 2731-2732; (c) Erden, I.; de Meijere, A. *Tetrahedron Lett.*, **1983**, *24*, 3811-3814; (d) Erden, I. *Tetrahedron Lett.*, **1984**, *25*, 1535-1538; (e) Erden, I. *Tetrahedron Lett.* **1985**, *26*, 5635-5638.
- Bestian H.; Günther, D. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 608-613.
- Huber, U. A.; Dreiding, A. S. *Helv. Chim. Acta*, **1970**, *53*, 495-513.
- Compound **7**: ^1H NMR (300 MHz, CDCl_3) δ 5.82 (m, 1H); 4.95-5.1 (m, 2H); 3.1 (dd, $J = 17.4, 9.0$ Hz, 1H); 2.7 (dd, $J = 17.4, 7.5$ Hz, 1H); 2.15-2.0 (m, 3H); 1.7 (m, 1H); 1.5 (m, 1H); 1.17 (s, 3H); 1.09 (s, 3H); ^{13}C NMR (75 Hz, CDCl_3) δ 213.9; 137.6; 114.6; 60.2; 48.0; 35.6; 32.2; 29.7; 23.1; 16.6 ppm; FT-IR (neat): ν 3023, 2971, 2870, 1778, 1640, 1464, 1066, 1024, 758 cm^{-1} ; HRMS (ESI) calcd for m/z $\text{C}_{10}\text{H}_{16}\text{O}$: 152.1201. Found: 152.1203.
- Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*, Wiley, Chippendale, Wiltshire, 2010.
- Minlon, H. *J. Am. Chem. Soc.* **1946**, *68*, 2487-2488.
- Barton, D. H. R.; Ives, D. A. J.; Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.
- Compound **8**: ^1H NMR (300 MHz, CDCl_3) δ 5.8 (m, 1H); 4.95 (m, 1H); 4.85 (m, 1H); 1.92 (m, 5H); 1.45-1.62 (m, 4H); 1.04 (s, 3H); 0.99 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.1; 114.1; 44.2; 38.8; 32.7; 31.9; 30.6; 30.5; 22.6; 22.5 ppm; FT-IR (neat) ν 3078, 2955, 2950, 2925, 2862, 1641, 1464, 1456, 910 cm^{-1} ; HRMS (ESI) calcd for m/z $\text{C}_{10}\text{H}_{18}$: 138.1409. Found: 138.1408.
- Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854-3867.
- The spectral data of **9** were in all respects identical to those reported in ref. 17. However, a higher resolution ^1H NMR of **9** is listed here: (300 MHz, CDCl_3) δ 2.3 (m, 2H); 2.10 (s, 3H); 1.87 (m, 2H); 1.45-1.63 (m, 5H); 1.04 (s, 3H); 1.00 (s, 3H).
- Thomas, A. F. 1972, Swiss Patent No. CH-559517.
- Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596-7597.