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1: isocomene

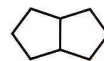# 14

M. C. Pirrung (1979)

Isocomene

14.1 Introduction

One of the constituents of the rayless golden rod, *Isocoma wrightii*, is the novel tricyclic sesquiterpene isocomene (**1**). Its structure was first revealed in 1977 by Zalkow and coworkers[1] and is distinguished by an angular fusion of three cyclopentane rings (angular triquinane). For a molecule that possesses only fifteen carbon atoms, isocomene is very interesting. Its compact molecular framework is the host of four contiguous stereogenic centers, and the situation is complicated further by the fact that three of these are fully substituted (i.e. quaternary). The expedient and elegant total synthesis of isocomene (**1**) by Michael C. Pirrung[2] demonstrates, in a dramatic way, the value of intramolecular [2+2] photocycloaddition[3] and cation-induced skeletal rearrangement processes for the synthesis of stereochemically and architecturally complex polycyclic molecules.

## 14.2 Retrosynthetic Analysis and Strategy

The key features of Pirrung's synthesis of isocomene are outlined retrosynthetically in Scheme 1. Working one step back from **1** gives the tertiary carbocation intermediate **2**. The intermediacy of **2** should be brief, for it should readily participate in an E_1-type reaction, in the forward sense, to give isocomene (**1**). Inspired by the observation that bicyclo[3.3.0] frameworks can be accessed from bicyclo[4.2.0] frameworks through cyclobutyl carbinyl cation rear-

bicyclo[3.3.0] system

bicyclo[4.2.0] system
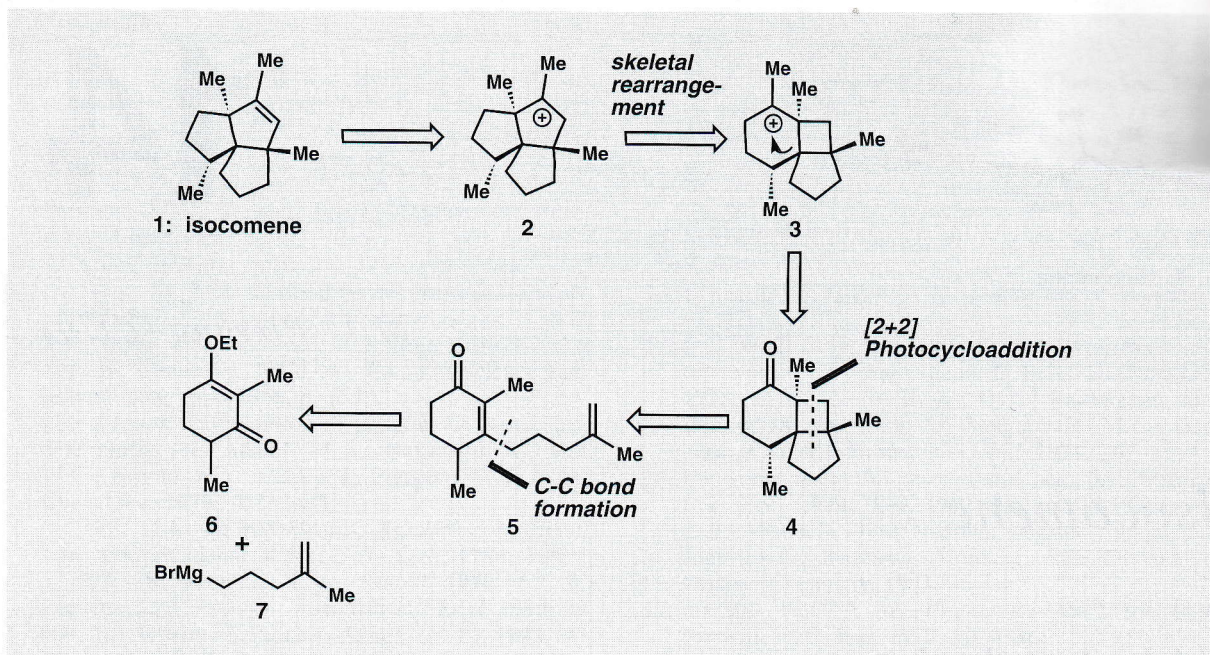
**Scheme 1.** Retrosynthetic analysis of isocomene (**1**).

rangements,[4] it was anticipated that intermediate cation **2** would form upon rearrangement of the isomeric tertiary cation, intermediate **3**. Like intermediate **2**, cation **3** is expected to be a transient species; once formed, its carbon skeleton could rearrange in the indicated way to give **2**. In the context of bicyclo[4.2.0] frameworks, the facility with which cyclobutyl carbinyl cations rearrange to isomeric bicyclo[3.3.0] frameworks was known.[4] This skeletal rearrangement benefits from the thermodynamic driving force provided by the relief of ring strain inherent in the cyclobutane system.

It was projected that intermediate **3** could be derived in a straightforward manner from ketone **4**. Retrosynthetic dissection of **4** by cleavage of the indicated carbon–carbon bonds leads to intermediate **5**. It is here, in this retrosynthetic step, that we witness significant structural simplification. In the synthetic direction, enone olefin **5** could participate in a photo-induced intramolecular enone–olefin [2+2] cycloaddition reaction to give intermediate **4**. If successful, this single transformation would create two new carbon–carbon bonds and three contiguous, quaternary stereogenic centers[5] and, from intermediate **4**, the completion of the synthesis would require only two operations. Cleavage of the indicated bond in **5** leads back to simple and readily available starting materials **6** and **7**.

14.3 *Total Synthesis*

The synthesis of key intermediate **4** is presented in Scheme 2. The synthesis commences with the C-methylation of vinylogous ester **8** to give intermediate **6**. In the presence of Grignard reagent **7**, derived from 5-bromo-2-methyl-1-pentene, the ketone carbonyl in **6** undergoes ready attack to give a labile tertiary alcohol. Enone **5** is obtained in a yield of 90 % when this alcohol is exposed to aqueous HCl. The preparation of intermediate **5** sets the stage for the crucial enone–olefin [2+2] photocycloaddition reaction. In the event, irradiation of a 0.01 M solution of **5** in hexane with light (350 nm) induces a regio- and stereospecific intramolecular [2+2] cycloaddition reaction to give key intermediate **4**. To avoid destabilizing steric interactions, the disubstituted, terminal olefin engages the enone diastereoface opposite to the secondary methyl substituent, and it is noteworthy that photo adduct **4** is produced in 77 % yield. This reaction creates, in one step, a tricyclo[6.3.0.0^{1,6}] undecanone framework and three contiguous stereocenters all of which are quaternary! Single-crystal X-ray analysis of a derivative of **4** established its relative stereochemistry.

It was predicted, *a priori*, that isocomene could be formed simply by treating **4** with methyllithium, followed by exposure of the resultant tertiary carbinol to acid.[2b] However, many attempts to effect the addition of a variety of nucleophilic methyl derivatives to ketone **4** were unsuccessful. It was revealed by deuterium quenching experiments that ketone **4** undergoes ready enolization in the presence of nucleophilic methyl derivatives. Despite its hindered nature, however, the ketone carbonyl in **4** reacts with methylenetri-
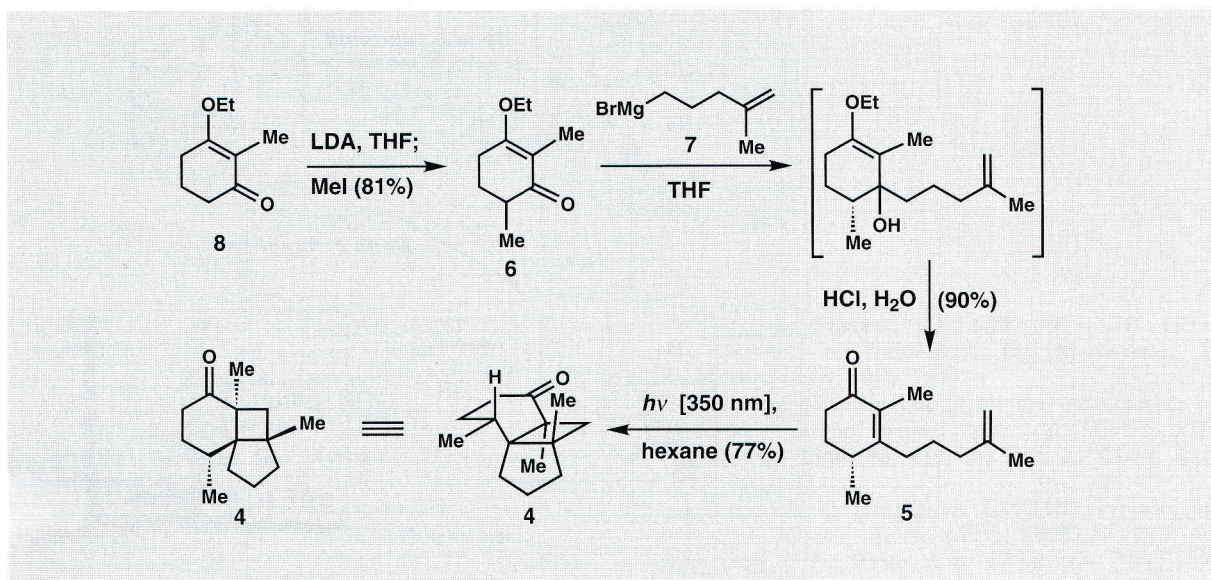
Scheme 2. Synthesis of intermediate **4**.

phenylphosphorane (see Scheme 3). In DMSO at 70 °C, **4** is converted to intermediate **9** through a Wittig reaction.[6] When **9** is dissolved in benzene and heated to reflux in the presence of *para*-toluenesulfonic acid, the newly formed exocyclic methylene is protonated to give the putative tertiary cation **3**. The carbocation in **3** could conceivably react in several different ways; however, by virtue of its spatial relationship to the cyclobutane ring, the prerequisites for a thermodynamically driven skeletal rearrangement are satisfied. If bond a migrates, the isomeric tertiary cation **2** is formed. Loss of a proton from **2** would then complete the synthesis of isocomene (**1**). If, on the other hand, bond b in intermediate **3** migrates, then bridged tertiary cation **10** is formed. Although the homology with isocomyl cation **2** is not obvious, intermediate **10** can be converted into **2** after a second bond migration. Thus, either or both rearrangement pathways can lead to the formation of isoco-
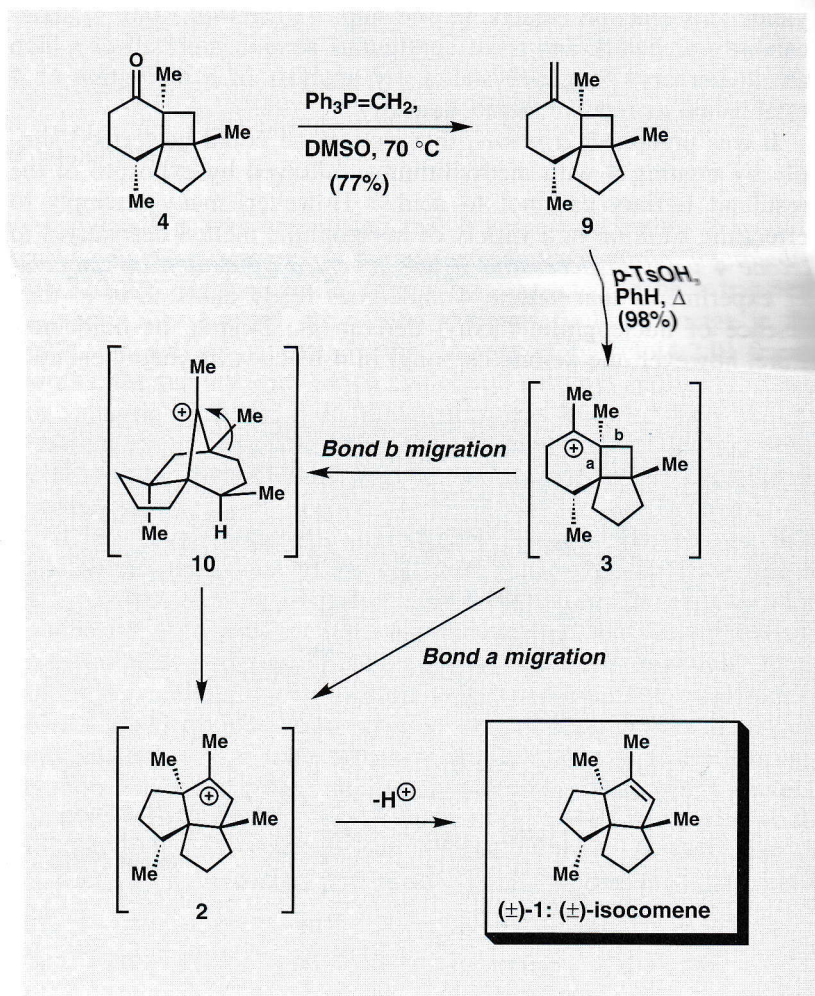
Scheme 3. Synthesis of (±)-isocomene [(±)-**1**].

myl cation **2** and thence isocomene. The action of *para*-toluenesul-fonic acid on intermediate **9** furnishes racemic isocomene [(±)-**1**] in a most elegant way and in a yield of 98 %!

14.4   Conclusion

In this synthesis, we have witnessed the dramatic productivity of the intramolecular enone–olefin [2+2] photocycloaddition reaction. This single reaction creates three contiguous and fully substituted stereocenters and a strained four-membered ring that eventually provides the driving force for a skeletal rearrangement to give iso-comene.

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