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Synthesis of the sesquiterpenoid lactarane skeleton by a radical cyclobutylcarbinyl/cyclopropylcarbinyl fragmentation sequence

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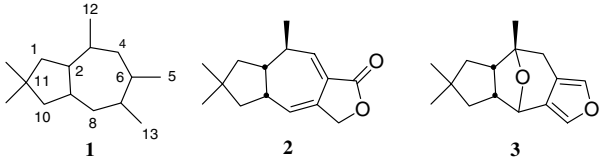
Abstract—A radical reaction of a tetracyclic iodide results in a tandem cyclobutylcarbinyl/cyclopropylcarbinyl fragmentation sequence to generate the framework of the sesquiterpenoid lactarane family.

Lactaranes are a class of sesquiterpenoids isolated from the Lactarius and Russulaceae species of mushrooms, which are believed to possess antifeedant, mutagenic and antimicrobial activities.[1,2] Lactaranes have non-isoprenoid carbon skeleton **1**[3], and vellerolactone **2** and furanether B **3** are representative members of this family of natural products. Total syntheses of **2**[4] and **3**[5,6] as well as a limited number of other lactaranes have been reported.[4,7,8]



1 **2** **3**

We previously employed radical fragmentation/reduction,[9,10] fragmentation/elimination[11–13] and fragmentation/cyclization sequences[14] in the synthesis of a variety of terpenoid systems. In this Letter we report the efficient synthesis of the lactarane carbon skeleton employing a novel cyclobutylcarbinyl/cyclopropylcarbinyl fragmentation sequence.

The substrate required for our tandem fragmentation/fragmentation methodology was synthesized as follows (Scheme 1). [2+2] Photoaddition of cyclopentene with enone **4** gave the known cis–anti–cis adduct **5** along with a small amount of the inseparable cis–syn–cis adduct.[15] Regioselective reaction of **5** with MeLi at low temperature gave carbinol **6**, which could be separated from the *syn*-carbinol by flash chromatography. Carefully controlled dehydration of **6** with $POCl_3$/pyridine gave a 3.5:1 mixture of unsaturated esters **7** and **8**. $LiAlH_4$ reduction of the ester mixture followed by separation of the minor isomer gave alcohol **9**, which upon stereoselective cyclopropanation with Et_2Zn/CH_2I_2[16] gave the novel strained adduct **10** containing fused cyclopropane, cyclobutane and two cyclopentane rings. Iodination of **10** employing our standard protocol[17] gave substrate **11**, the desired target for investigation of the tandem fragmentation sequence.

Treatment of iodide **11** with SmI_2 under typical radical conditions resulted in the formation in a reasonable yield of diene **12** with a fused 5/7 ring system. This transformation involved reductive loss of iodide ion from **11** to give the highly strained intermediate **A** (Scheme 2). Cyclobutylcarbinyl fragmentation of **A** yielded radical **B**, which upon cyclopropylcarbinyl fragmentation gave radical **C**, the precursor of product **12**. The breaking of the external rather than internal cyclopropyl bond in **B** suggests a more favorable alignment of that bond with the adjacent radical orbital. Product **12** possesses the same carbon skeleton as the non-isoprenoid lactarane family (e.g., **1**) with the exception of the *gem*-dimethyl groups. These methyls could readily be introduced by employing 4,4-dimethyl-1-cyclopentene rather than cyclopentene in the initial photoaddition step.[9]

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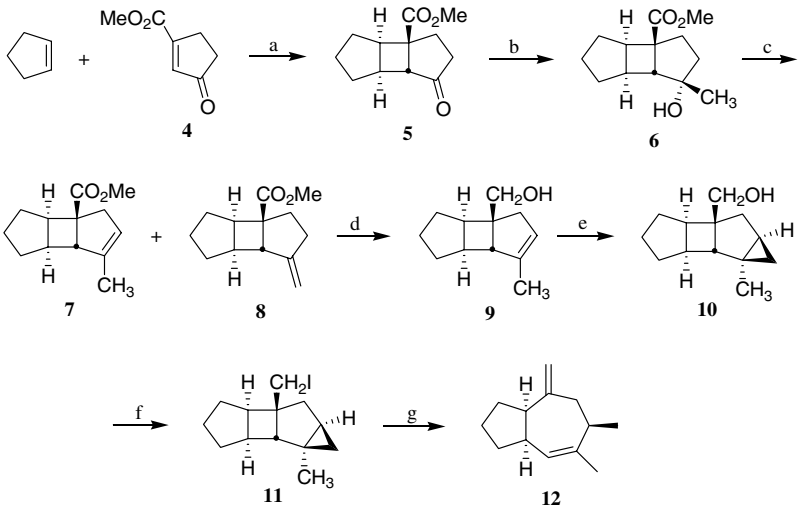
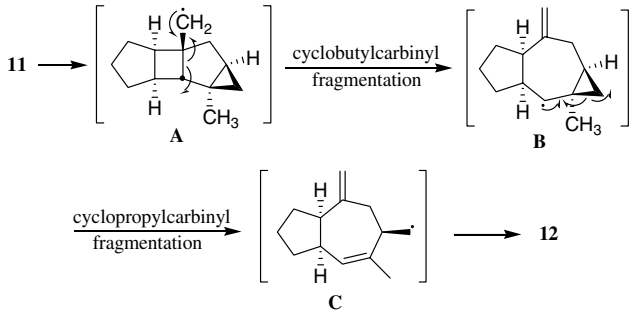
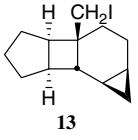


Scheme 1. Synthesis of a lactarane skeleton from a photoadduct via tandem radical fragmentations. Reagents and Conditions: (a) hν, CH_2Cl_2, 0 °C, 75%; (b) MeLi, ether, −78 °C, 61%; (c) $POCl_3$, pyr./CH_2Cl_2, 0 °C, 74%; (d) $LiAl_4$, ether, reflux, 75%; (e) Et_2Zn, CH_2Cl_2/ether, rt, 87% (f) PPh_3, imid., I_2, CH_2Cl_2, rt, 80%; (g) SmI_2, HMPA/THF, rt, 67%.

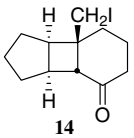


Scheme 2. Cyclobutylcarbinyl/cyclopropylcarbinyl fragmentations.

In related radical studies we found that attempted fragmentation of the less strained iodide **13** resulted only in reduction of the iodomethyl function leaving the polycyclic framework intact.[18] In contrast, our previous study showed that fragmentation of iodide **14** gave a reasonable yield of the expected 5/8 ring system.[9]



13



14

The present study describes a novel radical reaction in which fragmentation of tetracyclic iodide **11** results in the formation of the desired 5/7 ring system with regiospecific introduction of two double bonds and generation of a methyl group at the 6-position in the lactarane skeleton.[19]

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