

Literature Report

Total Synthesis of Limonin

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Checker: Yue Ji

Date: 2015-07-07

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Angew. Chem. Int. Ed. **2015**, *54*, 8538–8541.

Contents

1 Introduction

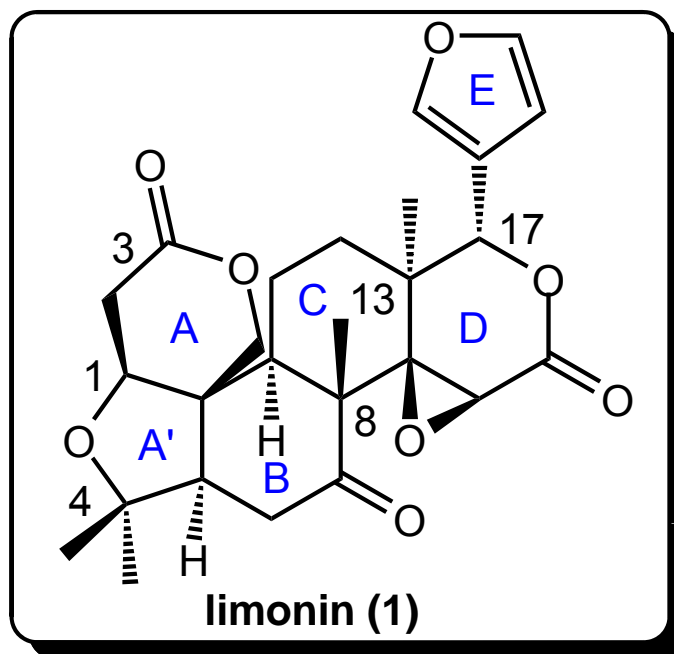
2 Brief retrosynthetic analysis of limonin (1)

3 Total synthesis of limonin (1)

4 Total synthesis of limonoid (2)

5 Summary

Introduction



- ◆ first isolated from citrus fruit in **1841**
- ◆ the structure of **1** remained unknown until **1960**
- ◆ first total synthesis of (±)-limonin **1** in **2015**
- ◆ 抗肿瘤、镇痛抗炎、防虫杀虫、抗氧化活性、抗菌性、抑制 HIV、降低胆固醇、明显的利尿作用、改善心脑血管循环及改善睡眠、抗病毒、调节细胞色素等

Introduction



柠檬苦素

【CAS号】1180-71-8

产品名称：柠檬苦素

英文名称：Limonate D-ring-lactone; Limonoic acid di-delta-lactone; Limonin

分子式：C₂₆H₃₀O₈ 分子量：470.52

性状：白色粉末 结构式：

含量：≥95%，≥98%，≥99%

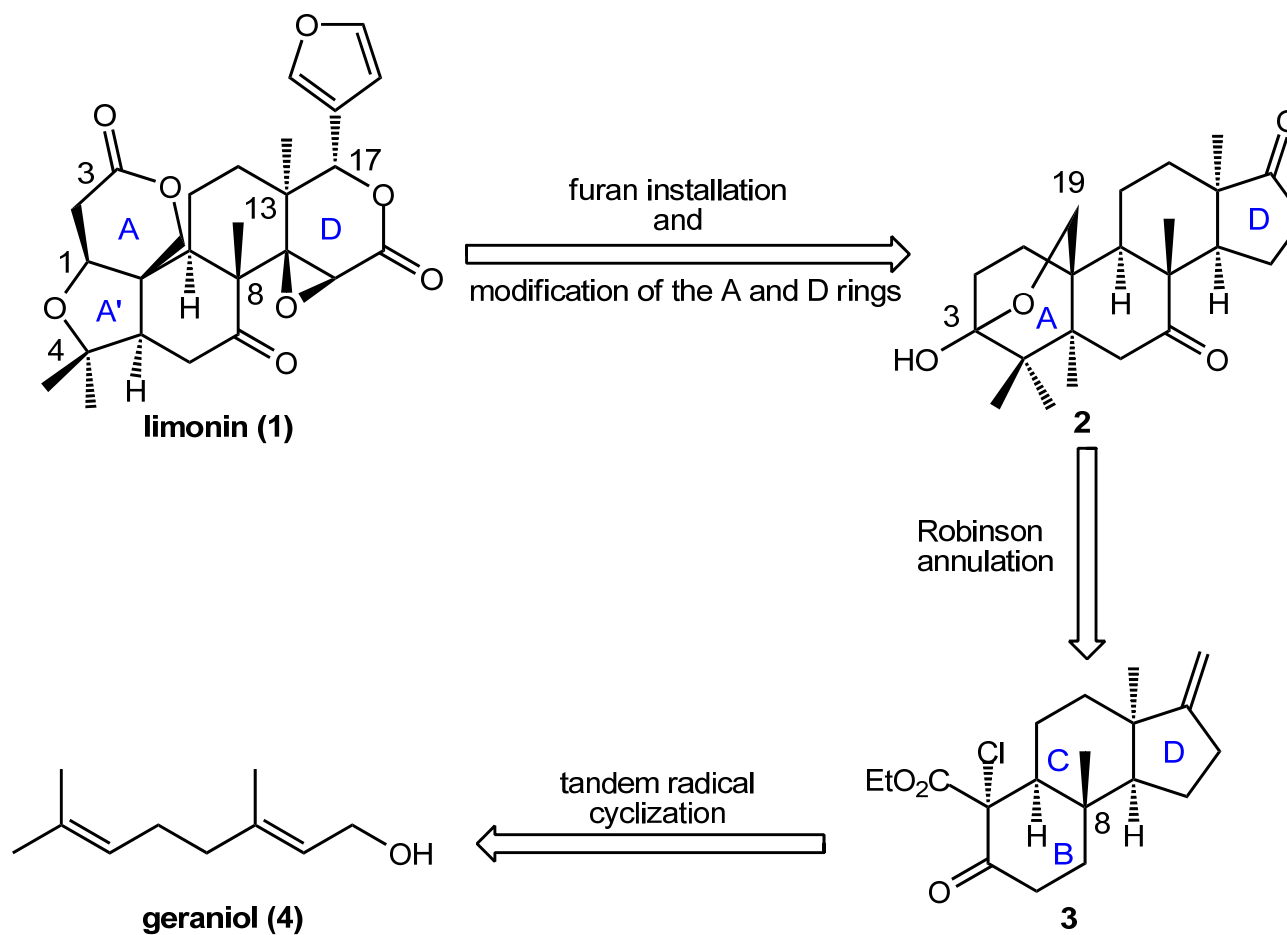
包装：1克-1千克外铝箔内衬双层塑料袋
5公斤、15公斤、25公斤外纸板筒内衬双层塑料袋。

理化性质：
易于溶脂性有机溶剂，难溶于水，在甲醇、乙醇中溶解度较大。熔点298℃[α]_D-128 (C 1.21, 丙酮)

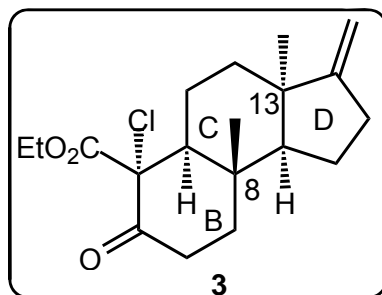
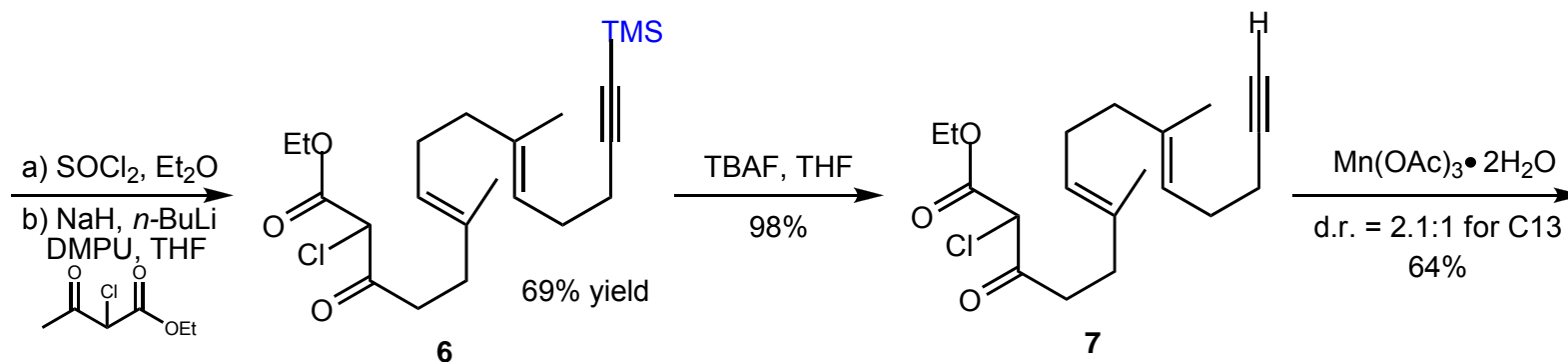
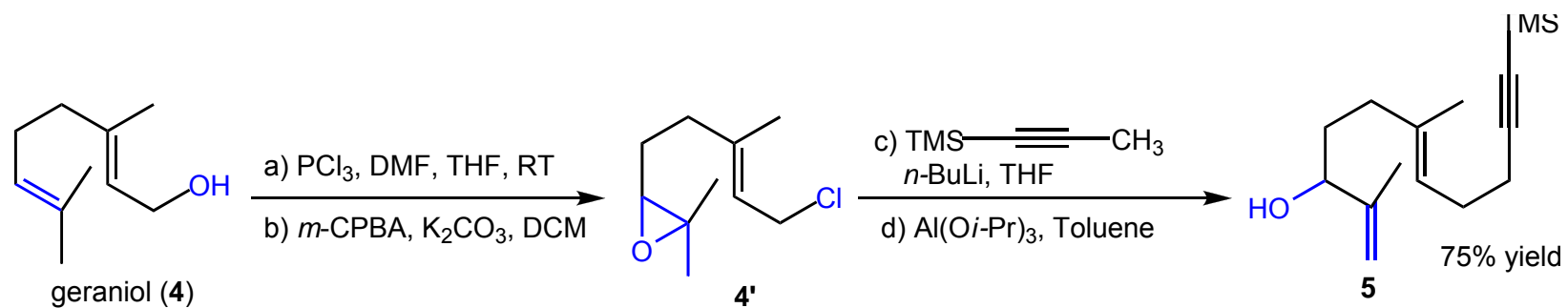
药理作用：
柠檬苦素类化合物主要存在于芸香科植物果实中，如枳实（脐橙、柑桔、香橙、柚）等中。从柑桔属植物中分离和鉴定的柠檬苦素类化合物约50多种，常见的有柠檬苦素（limonin）、诺米林（nomilin）、脱乙酰诺米林（deacetylnomilin）、黄柏酮（obacunone）、米林酸（nomilinic acid）等，它们都是具有呋喃环的三萜类化合物。

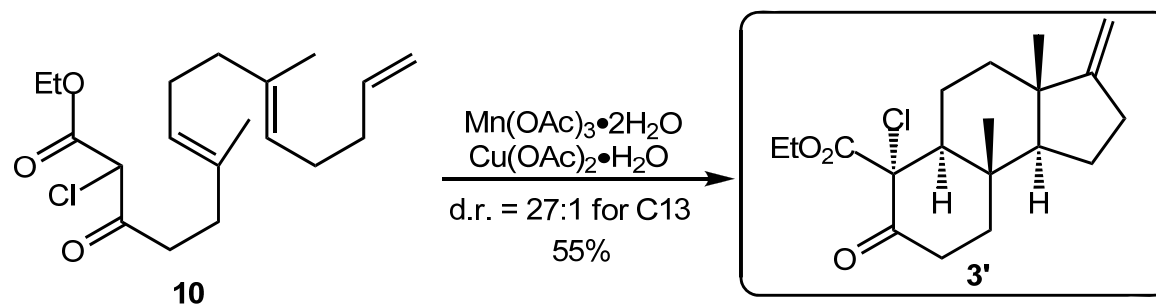
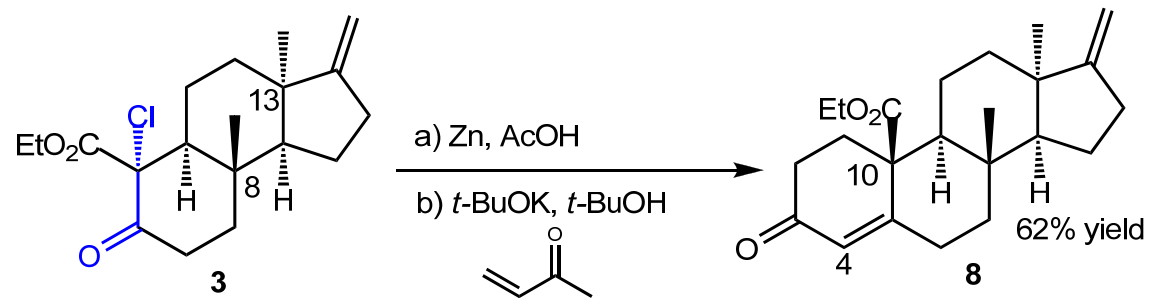
Baidu 百科

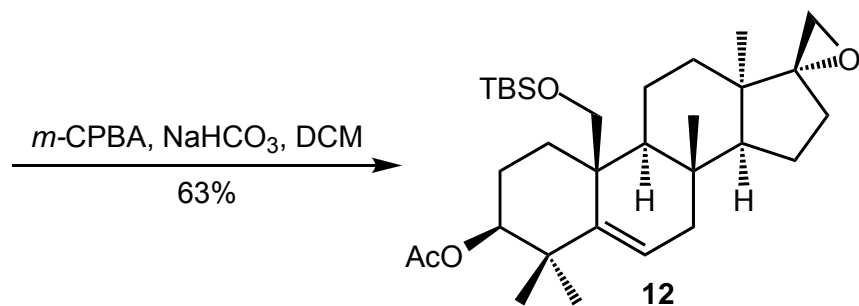
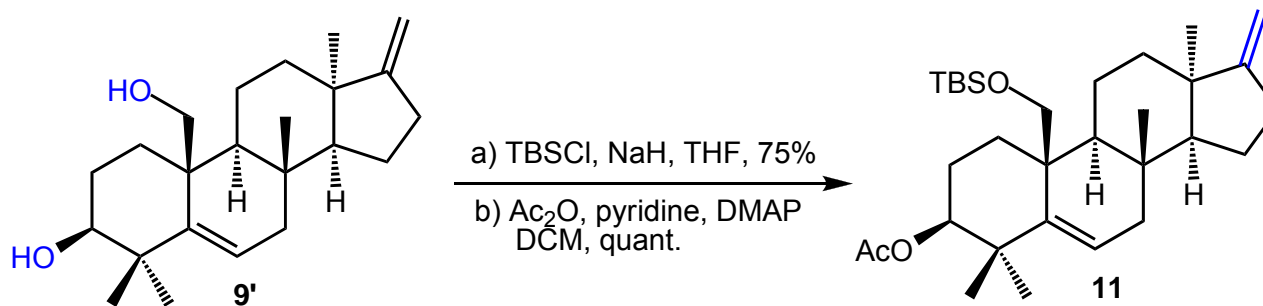
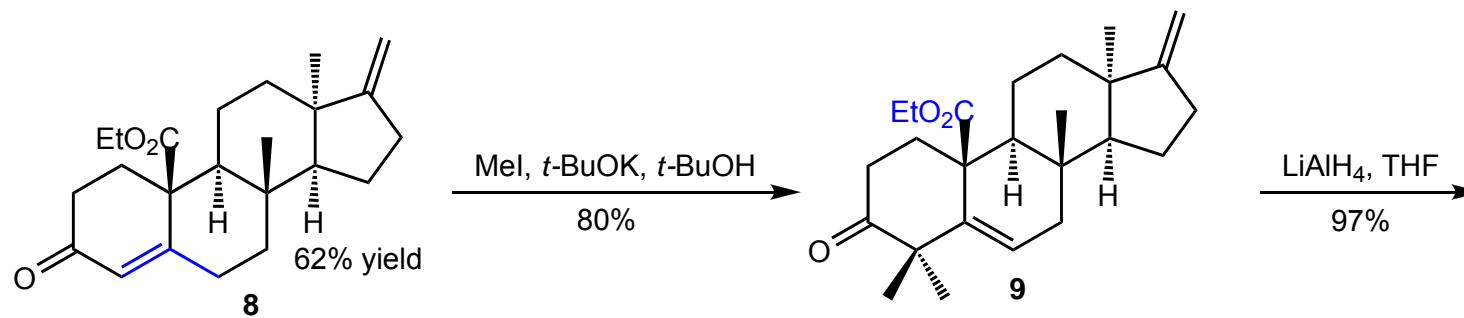
Brief retrosynthetic analysis of limonin (1)

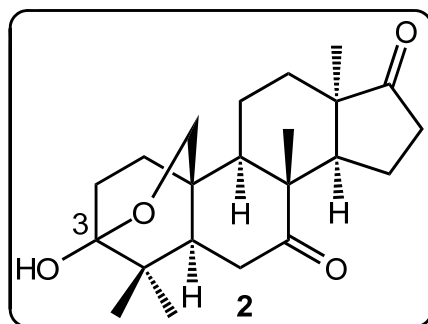
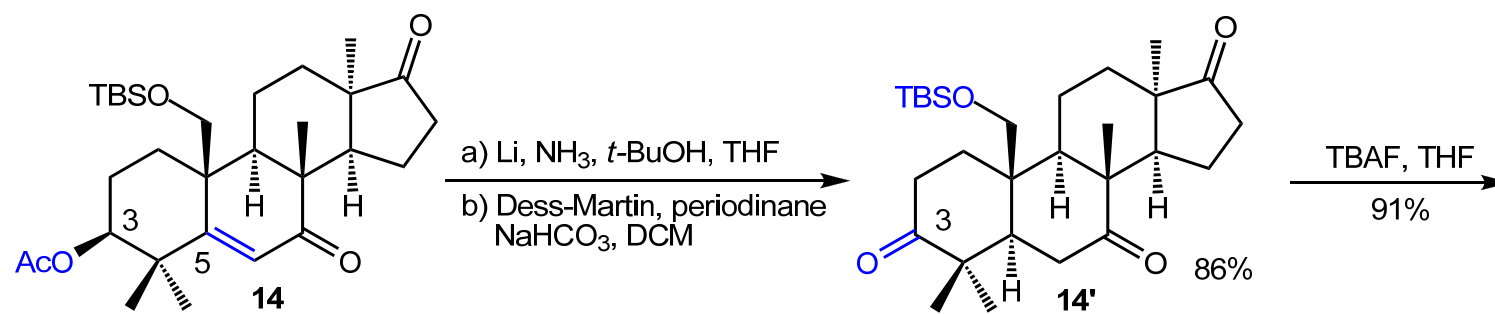


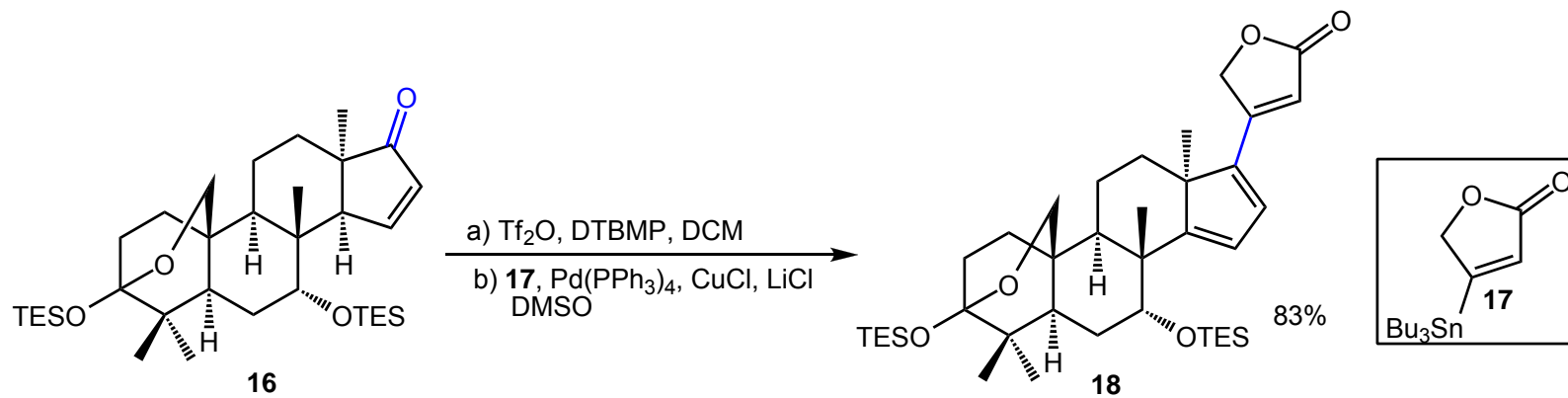
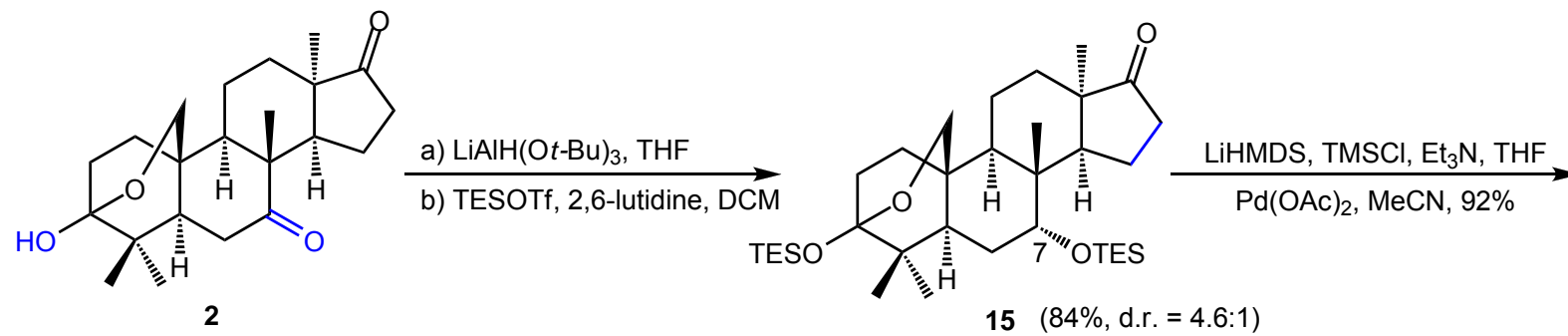
Construction of the limonoid framework

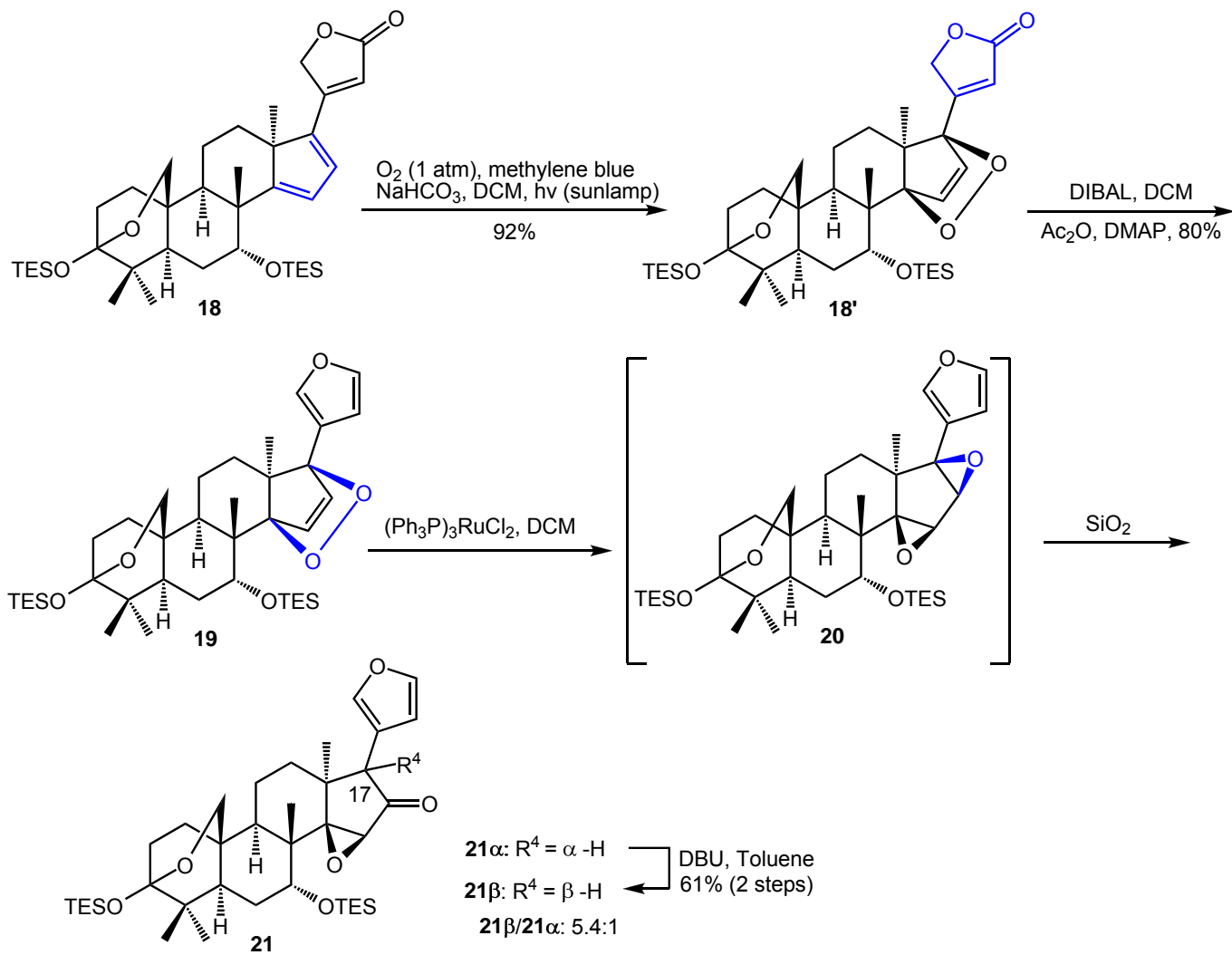


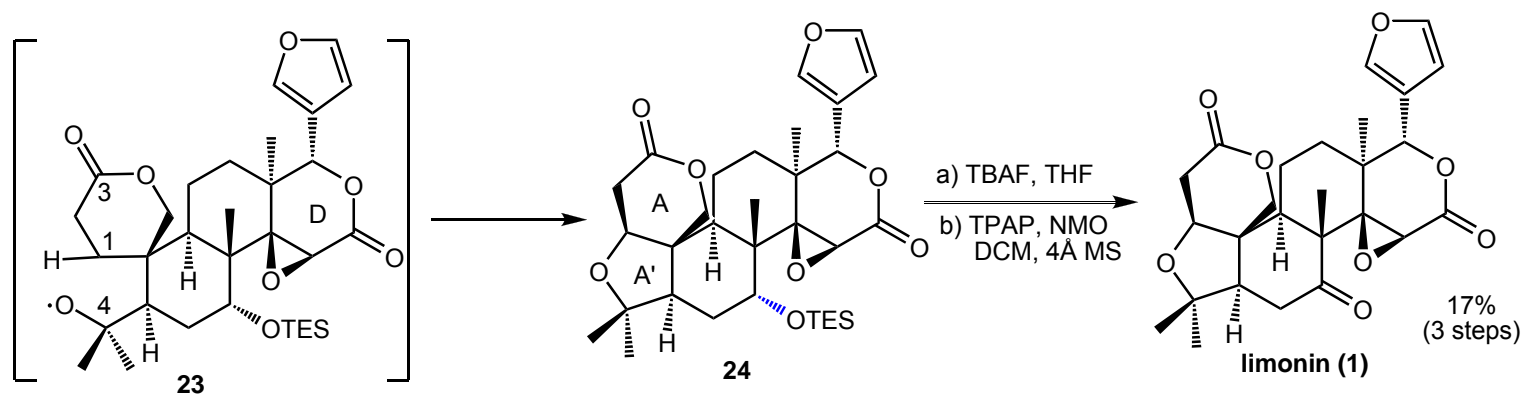
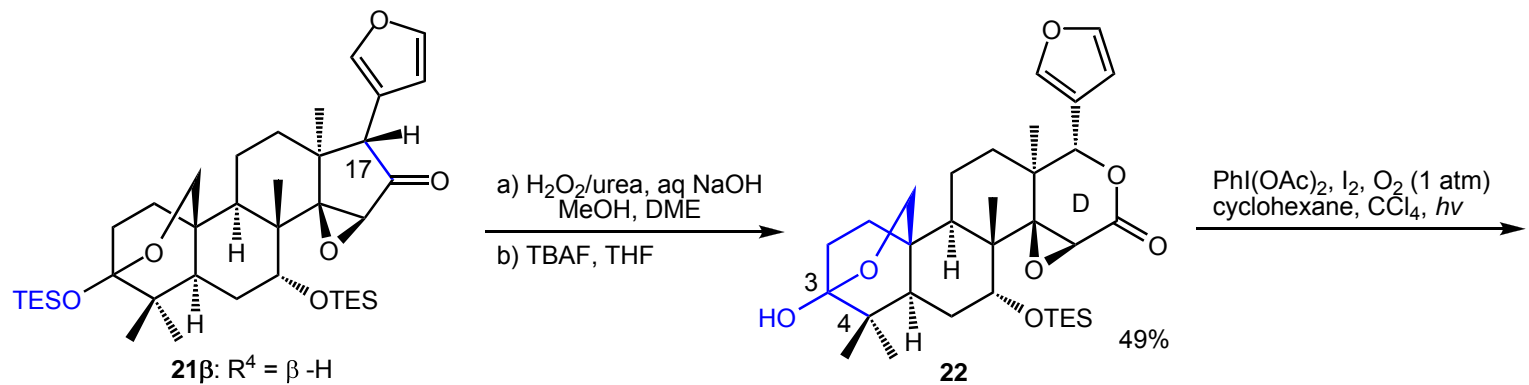




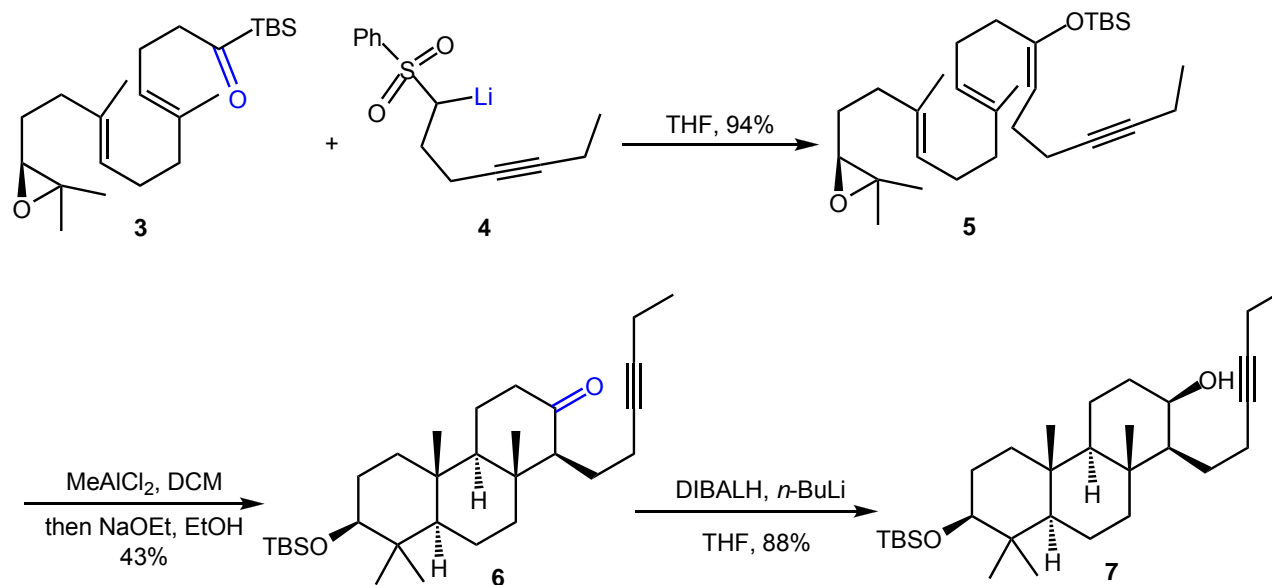


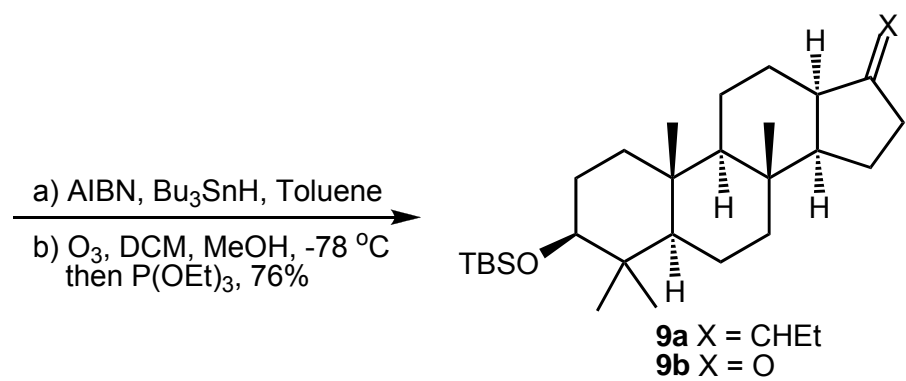
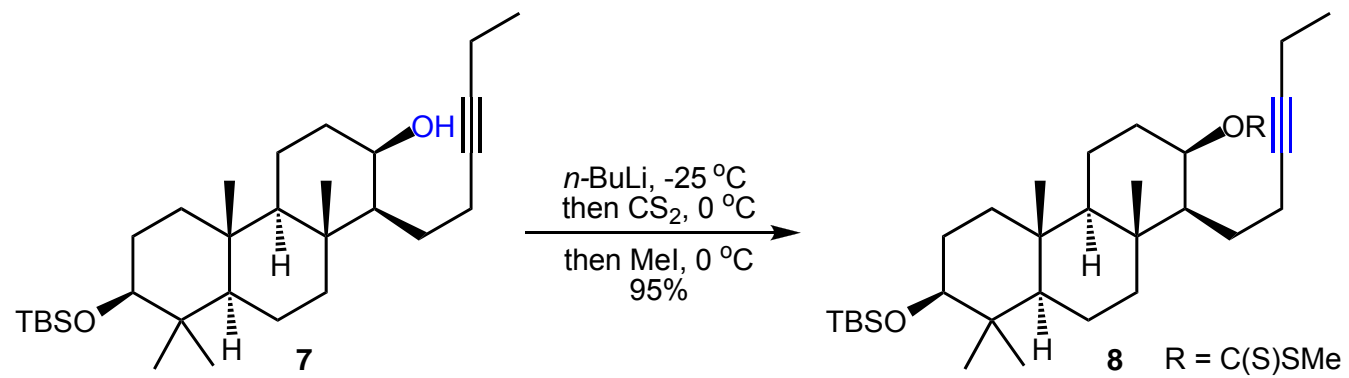


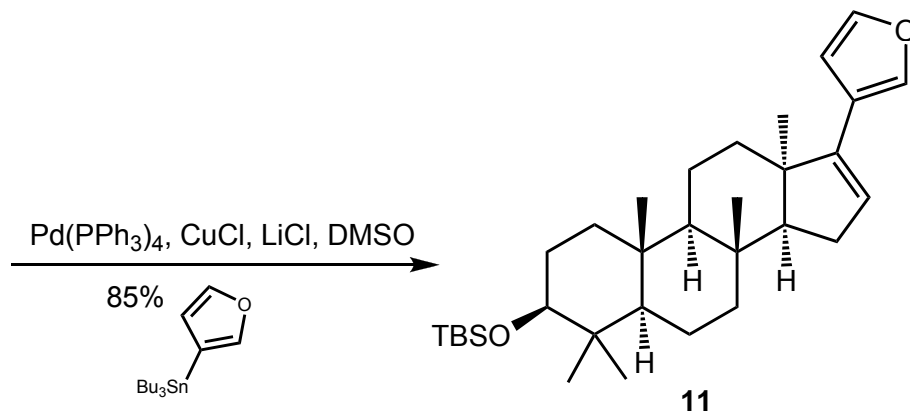
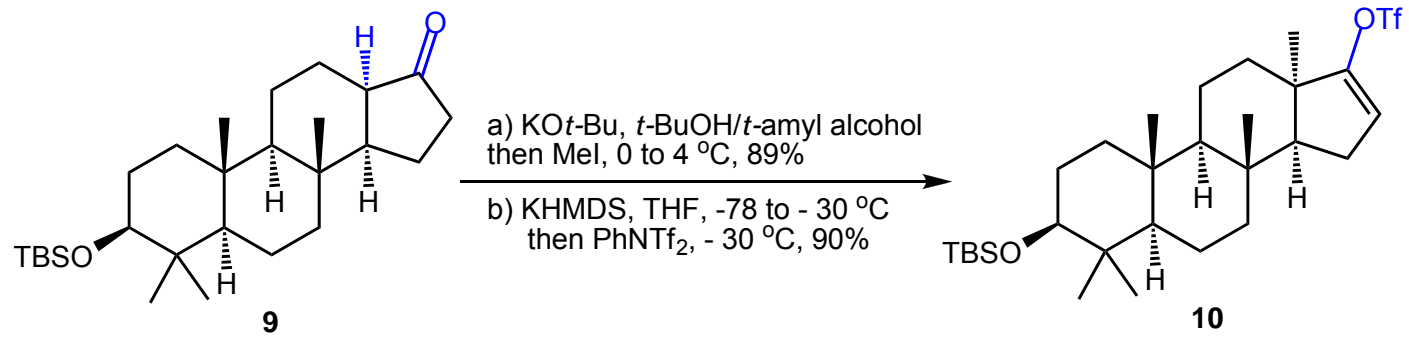


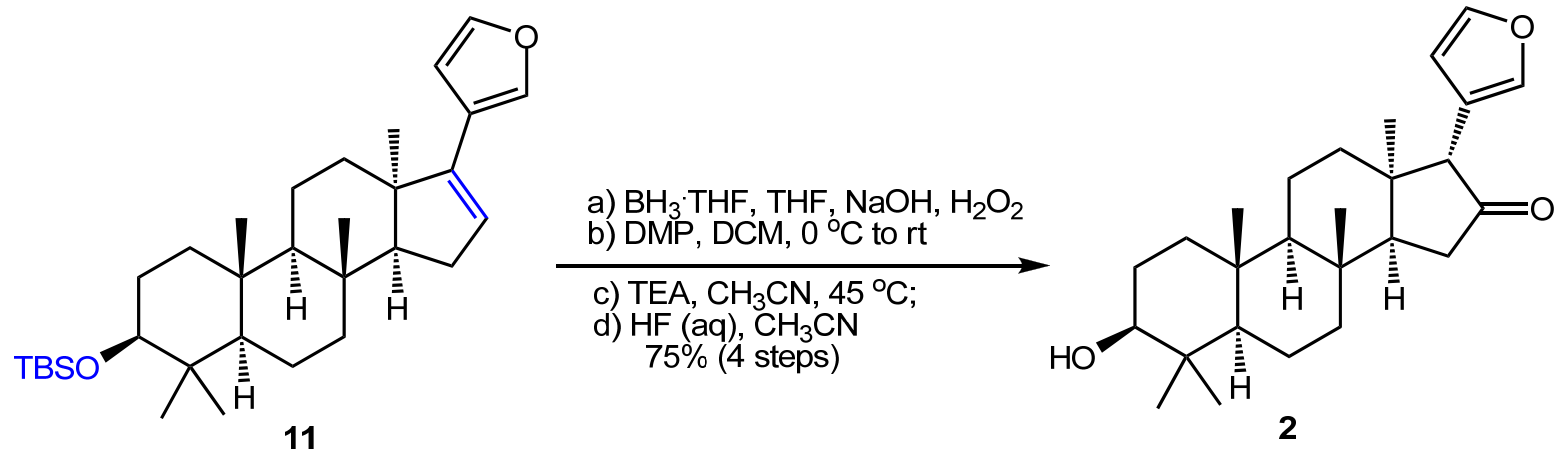


Simple enantioselective approach to synthetic limonoids

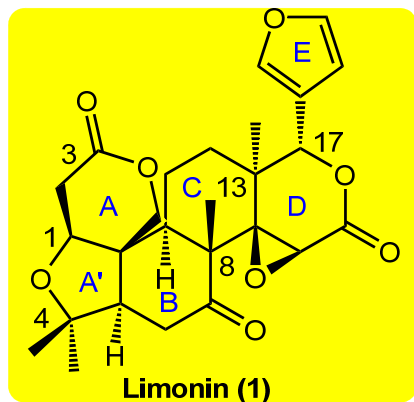






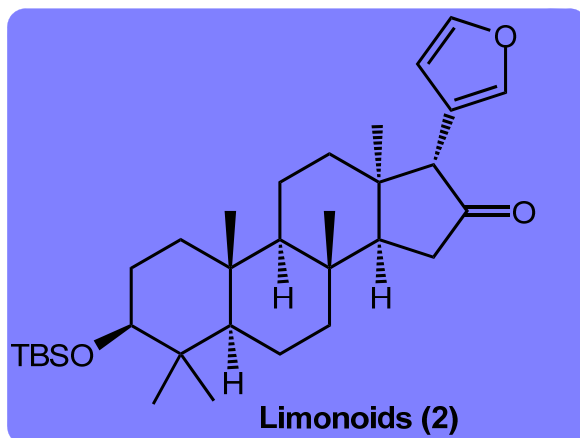


Summary



Yamashita's group: 35 steps

key steps: Tandem radical cyclization
Robinson annulation
Baeyer–Villiger oxidation
Suárez reaction



Corey's group: 13 steps

key steps: Tandem radical cyclization
Stille coupling

Limonin (**1**), the flagship congener of the limonoids, was first isolated in 1841 during studies on the bitter components of the citrus fruit. However, the structure of **1** remained unknown until 1960, when a historic collaboration between the Arigoni, Barton, Corey, Jeger, and Robertson groups led to the determination of the exact structure of **1** by chemical derivatization and X-ray diffraction methods. Since then, several hundred limonoids have been isolated. The intact limonoid framework is characterized by a 4,4,8-trimethyl-17-furyl-13 α -androstandane, but this family encompasses a diverse array of structural architectures as a result of oxidations and skeletal rearrangements. Not surprisingly, the unique architectures and the wide spectrum of biological properties of limonoids have attracted keen interest from the synthesis community, and for example, azadiradione, cipadonoid, mexicanolides, and azadirachtin have been synthesized. Herein, we describe the first total synthesis of (\pm)-limonin (**1**).

In summary, we have achieved the first total synthesis of (\pm)-limonin (**1**) in 35 steps from geraniol (**4**). Our synthesis features 1) the efficient construction of the limonoid androstane framework with C13 α configuration by a tandem radical cyclization and subsequent Robinson annulation (**7** \rightarrow **3** \rightarrow **9**), 2) a ketone formation from the hindered *exo* methylene group, possibly through epoxidation and nitrile addition followed by MeCN elimination (**11** \rightarrow **13**), 3) the installation of an epoxylactone moiety by singlet-oxygen cycloaddition, ruthenium-catalyzed bis(epoxide) formation, and Baeyer–Villiger oxidation (**18** \rightarrow **22**), and 4) a Suárez reaction to construct the unique AA' ring system from the hemiacetal (**22** \rightarrow **24**). We believe that the synthetic strategy developed here will allow for the synthesis of diverse limonoid architectures.