

# Total Synthesis of Limonin

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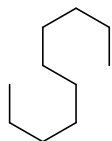
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## I. Introduction

- Limonin
  - Linomin was first isolated from citrus fruit in 1841<sup>1</sup>
  - The precise structure of limonin was determined in 1960<sup>2</sup>
  - Several related compounds have been synthesized
  - This report describes the first total synthesis of ( )-limonin
- triterpenes known as limonoids

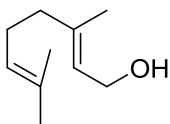
## II. Retrosynthetic Analysis



1) Bernays, *Justus Liebigs Ann. Chem.* **1841**, *40*, 317-318; 2) Arigoni, D. *et al. Experientia* **1960**, *16*, 41-49.

# Total Synthesis of (±)-Limonin

## III. Synthesis



geraniol  
100g /

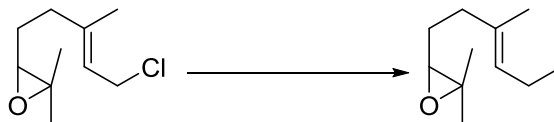
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- $\text{PCl}_3$  chlorination:



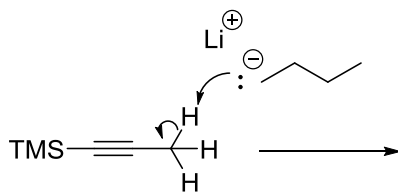
- 
- mCPBA oxidation:
- |

# Total Synthesis of (±)-Limonin

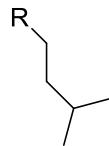
## III. Synthesis



- Formation of **S1**:<sup>3</sup>



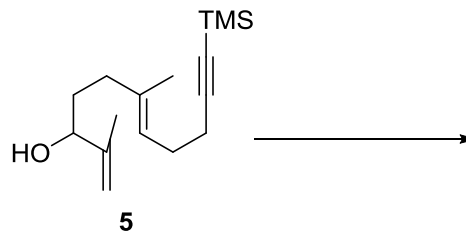
- Allylic alcohol formation:<sup>4</sup>



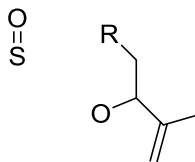
3) a) Lipshutz, B. H. *et al. J. Am. Chem. Soc.* **1999**,

# Total Synthesis of (±)-Limonin

## III. Synthesis



- $\text{SOCl}_2$  chlorination/  
isomerization

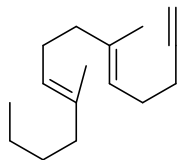


## III. Synthesis

- Dianion formation and SN2:<sup>5</sup>

# Total Synthesis of (±)-Limonin

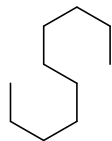
## III. Synthesis



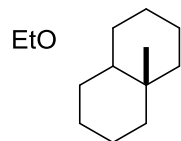


# Total Synthesis of (±)-Limonin

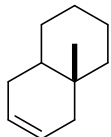
## III. Synthesis



- Dimethylation:<sup>7</sup>



- Reduction:

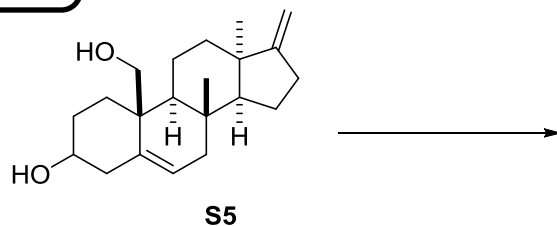


<sup>7</sup>) Kato, M. *et al. Tetrahedron* **1987**, *43*, 711-722.

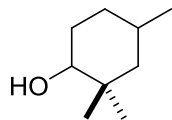


# Total Synthesis of (±)-Limonin

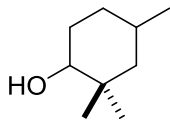
## III. Synthesis



- TBS protection:



- O-acylation:



# Total Synthesis of ( $\pm$ )-

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# Total Synthesis of (±)

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# Total Synthesis of (±)-Limonin

## III. Synthesis

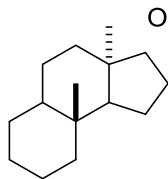
- TBAF deprotection (slide 5) followed by cyclization:



- Chemoselective reduction of the C7 ketone was achieved through the use of a single equivalent of a bulky aluminum alkoxide reducing agent (see slide 8)

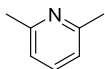
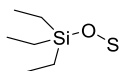
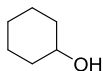
# Total Synthesis of (±)-Limonin

## III. Synthesis

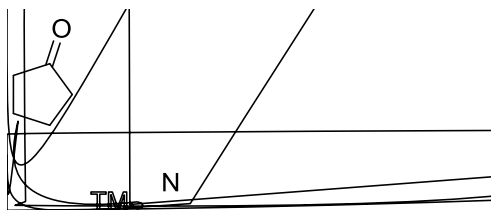


pre-15

- TES protection of alcohols at C3 and C7 resulted in a 4.6:1 mixture of diastereomers at C7 favoring the sterically less hindered substrate:



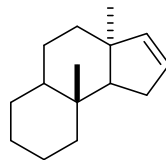
- Enolate formation:



- Silyl enol ether formation (slide 9)

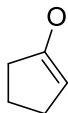
# Total Synthesis of (±)-Limonin

## III. Synthesis



15'

- Ito-Saegusa oxidation:<sup>11</sup>

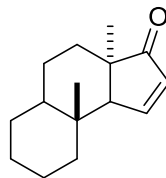


11) Ito, Y. *et al. J. Org. Chem.* **1978**, *43*, 1011-1013.



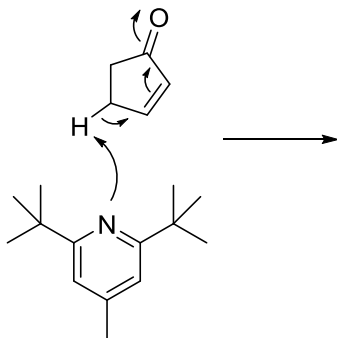
# Total Synthesis of (±)-Limonin

## III. Synthesis



16

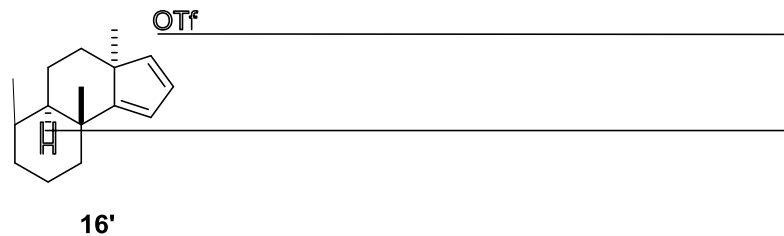
- Vinylogous enol triflate formation:<sup>12</sup>



12) Stang, P. J. *et al. Synthesis*, **1979**, 438-440.

# Total Synthesis of (±)-Limonin

## III. Synthesis



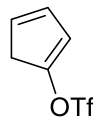
- Synthesis of 17:<sup>13</sup>

13) Hollingworth

# Total Synthesis of (±)-Limonin

## III. Synthesis

- Stille Coupling:<sup>14</sup>



14) Han, X. *et al. J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

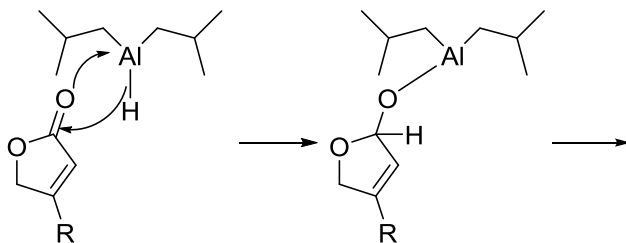


# Total Synthesis of (±)-Limonin

## III. Synthesis

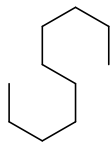
|  
|

- DIBAL reduction, acylation with DMAP (slide 9), deacylation to yield furan ring:



# Total Synthesis of (±)-Limonin

## III. Synthesis



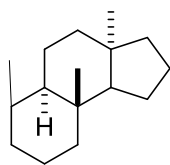
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- Ruthenium  
catalized  
endope



# Total Synthesis of (±)-Limonin

## III. Synthesis



21 $\beta$

- Baeyer-Villiger oxidation and subsequent silane

deprotection  $\rho$ 6 321.91 T41ET $\rho$ 512 450 856 307.51 T3sS( 6321.7):6 307.51 Tm[ $\rho$ 6 321.943(n21 0 0 1 101.86 307.51 Tm/F5 12 T

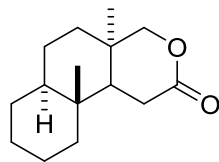


# Total Synthesis of ( $\pm$ )

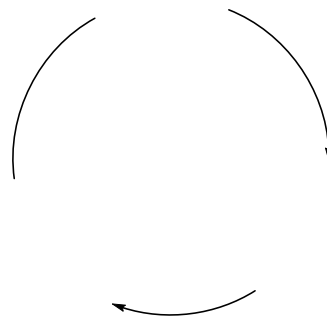
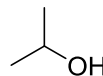
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# Total Synthesis of (±)-Limonin

## III. Synthesis



- Silane deprotection (slide 5) and Ley oxidation:<sup>18</sup>



18) Ley, S. V. *et al. Synthesis* **1994**, 639-666.

## IV. Summary

- The first total synthesis of racemic limonin has been achieved in 35 steps from geraniol
- **Key synthetic features:**
  - 1) Efficient construction of the limonoid androstane framework with C13 conformation through radical cyclization
  - 2) Ketone formation from the *exo* methylene group through epoxidation and nitrile-promoted rearrangement
  - 3) Singlet-oxygen cycloaddition to install the epoxylactone moiety
- 
- The synthetic strategy developed should be amenable to synthesizing other related limonoids