

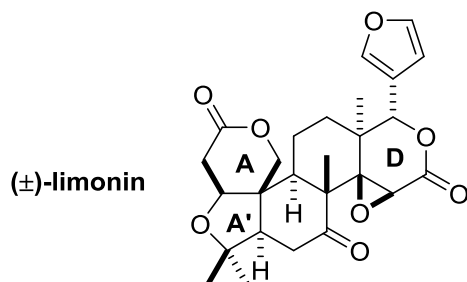
Total Synthesis of Limonin

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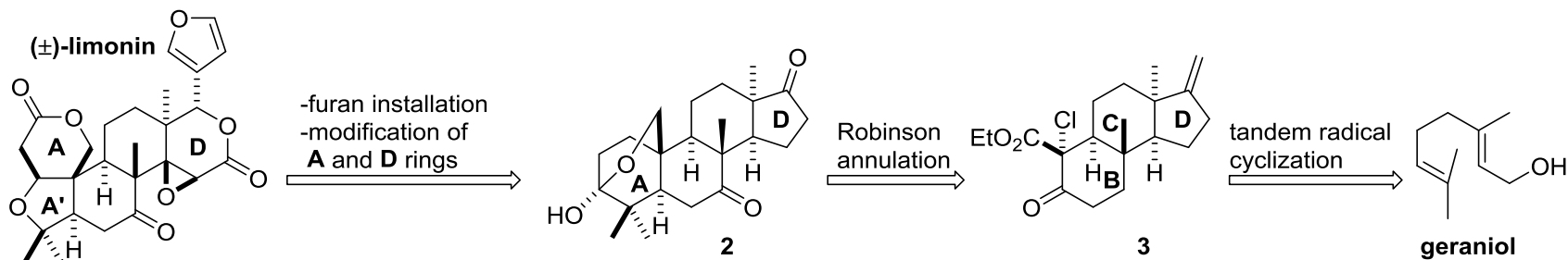
Early View, article first published online: 3 June 2015

I. Introduction



- Limonin is the “flagship” congener of the class of C_{13α}-triterpenes known as limonoids
- Limonin was first isolated from citrus fruit in 1841¹
- The precise structure of limonin was determined in 1960²
- Several related compounds have been synthesized
- This report describes the first total synthesis of (±)-limonin

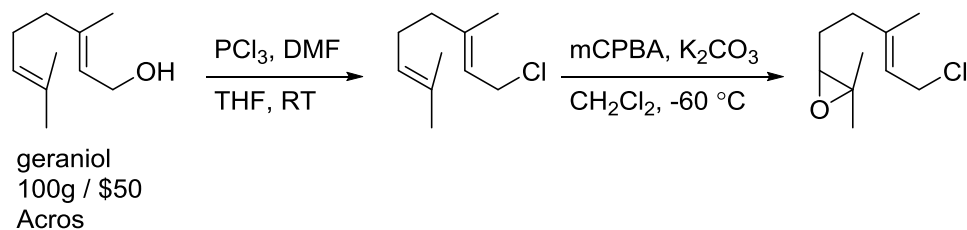
II. Retrosynthetic Analysis



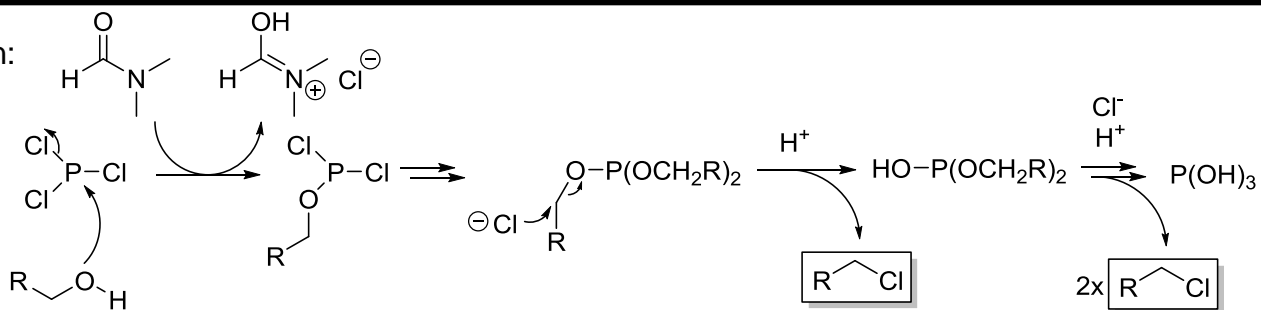
1) Bernays, *Justus Liebigs Ann. Chem.* **1841**, *40*, 317-318; 2) Arigoni, D. *et al. Experientia* **1960**, *16*, 41-49.

Total Synthesis of (±)-Limonin

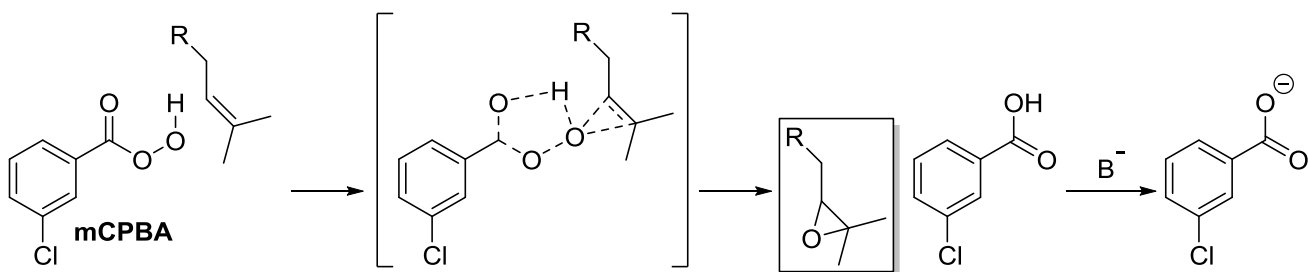
III. Synthesis



- PCl_3 chlorination:

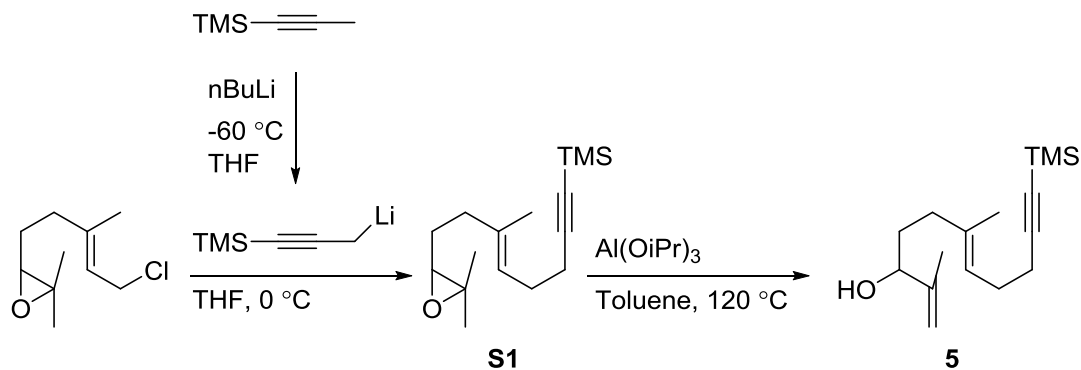


- mCPBA oxidation:

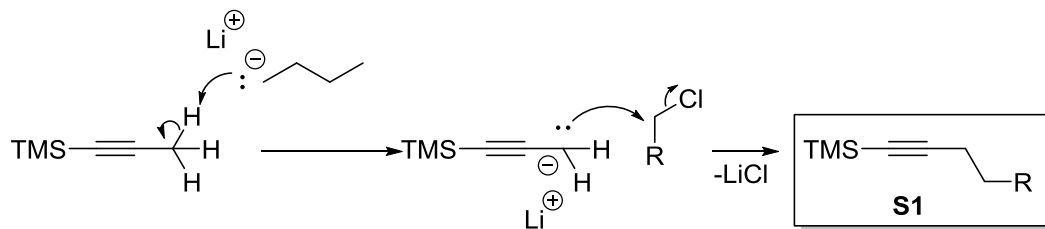


Total Synthesis of (±)-Limonin

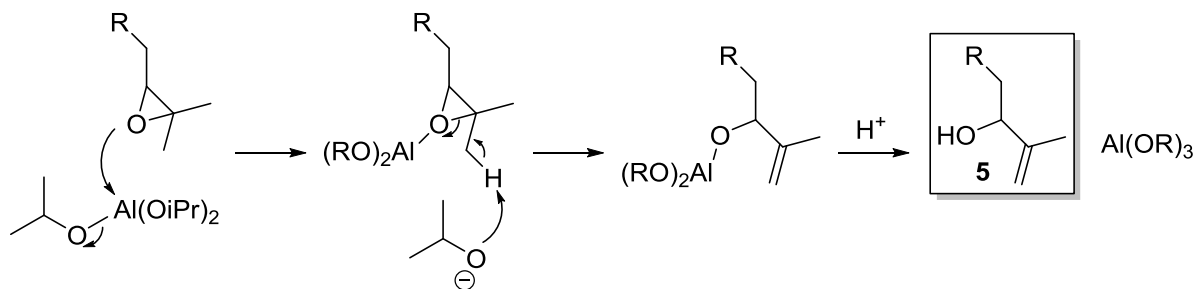
III. Synthesis



- Formation of **S1**:³



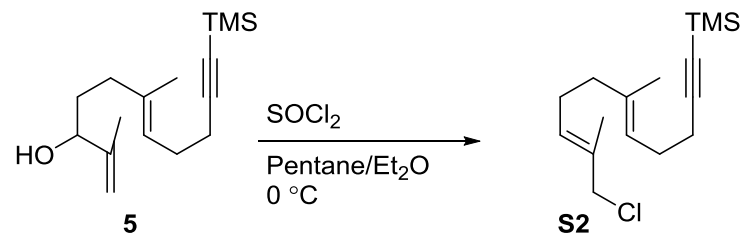
- Allylic alcohol formation:⁴



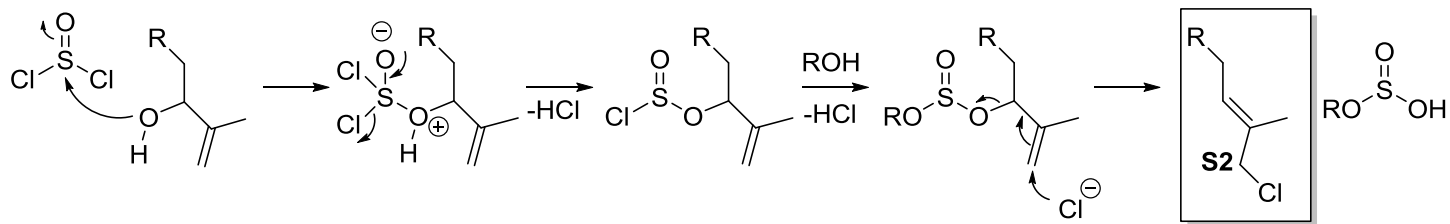
3) a) Lipshutz, B. H. *et al. J. Am. Chem. Soc.* **1999**, *121*, 11664-11673; Corey, E. J. *et al. Tetrahedron Lett.* **1982**, *23*, 719-722; 4) Doron, E. *et al. J. Am. Chem. Soc.* **1988**, *110*, 4356-4362.

Total Synthesis of (±)-Limonin

III. Synthesis

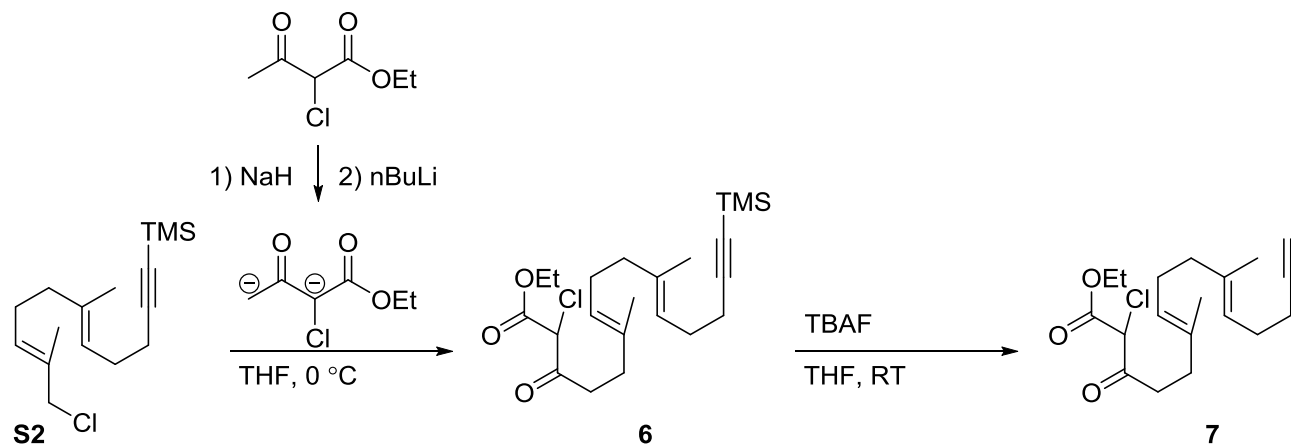


- SOCl_2 chlorination/
isomerization

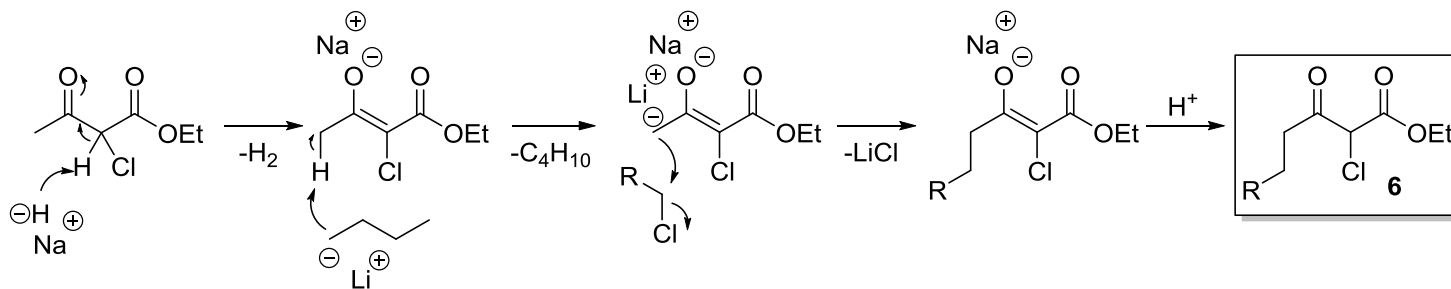


Total Synthesis of (±)-Limonin

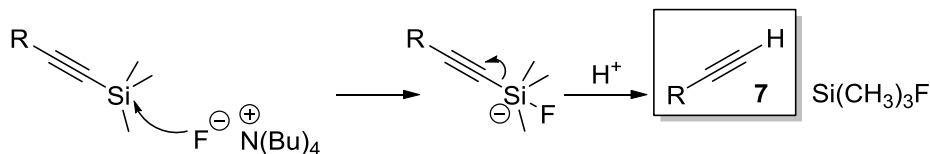
III. Synthesis



- Dianion formation and SN2:⁵



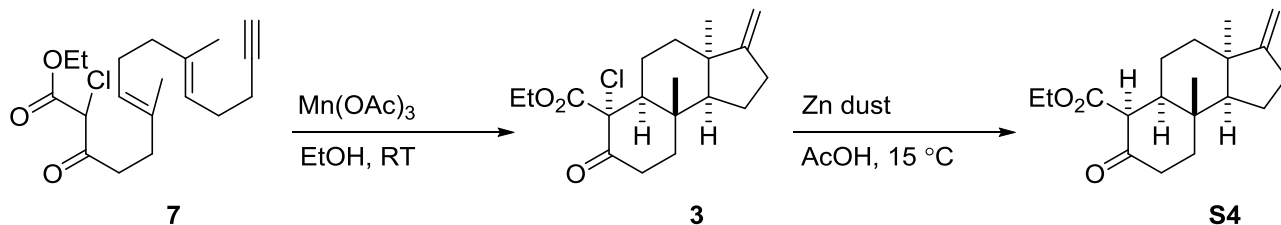
- TBAF deprotection:



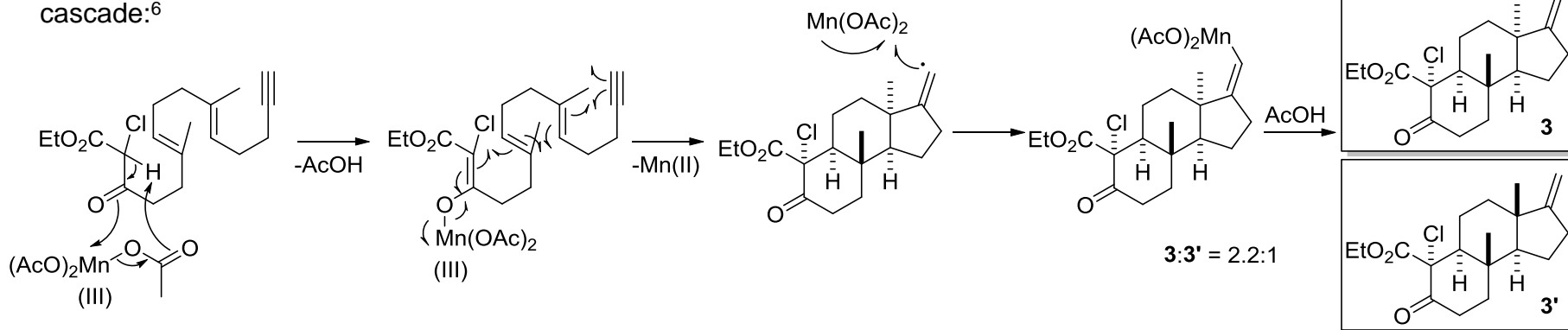
5) a) Huckin, S. N. *et al. J. Am. Chem. Soc.* **1974**, 96, 1082-1087; b) Brown, R. C. D. *et al. J. Org. Chem.* **2002**, 67, 8079-8085.

Total Synthesis of (±)-Limonin

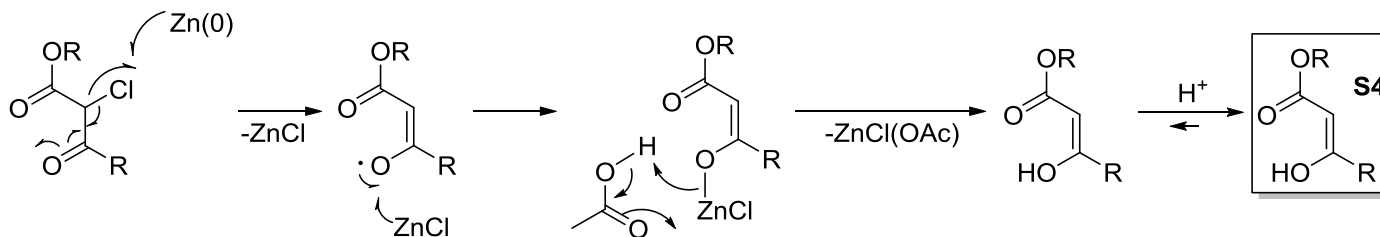
III. Synthesis



- Radical cyclization cascade:⁶



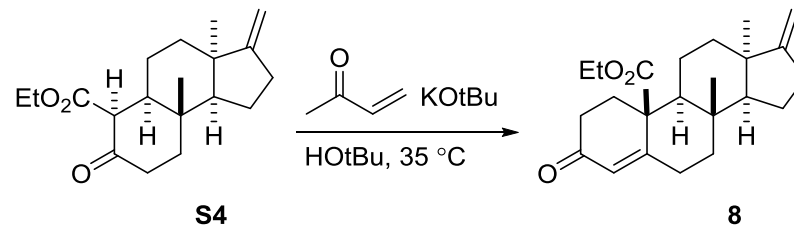
- Dechlorination:



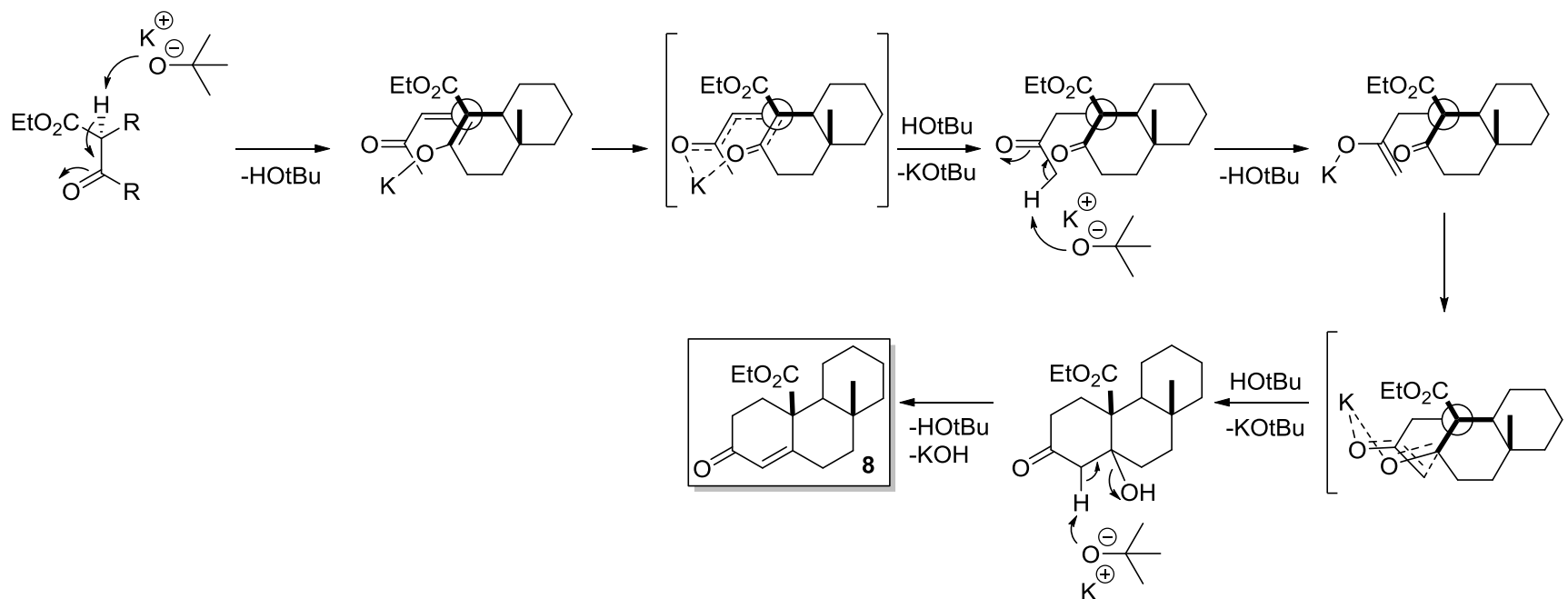
6) a) Snider, B. B. *et al. J. Org. Chem.* **1988**, 53, 2137-2143; b) Snider, B. B. *Chem. Rev.* **1996**, 96, 339-363.

Total Synthesis of (±)-Limonin

III. Synthesis

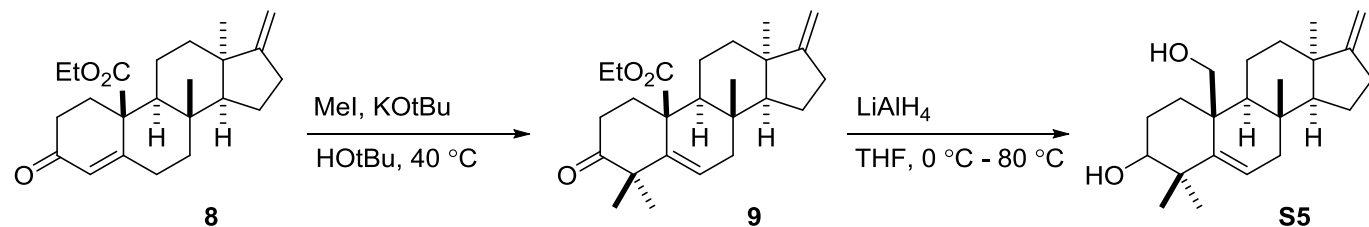


- Robinson
Annulation:

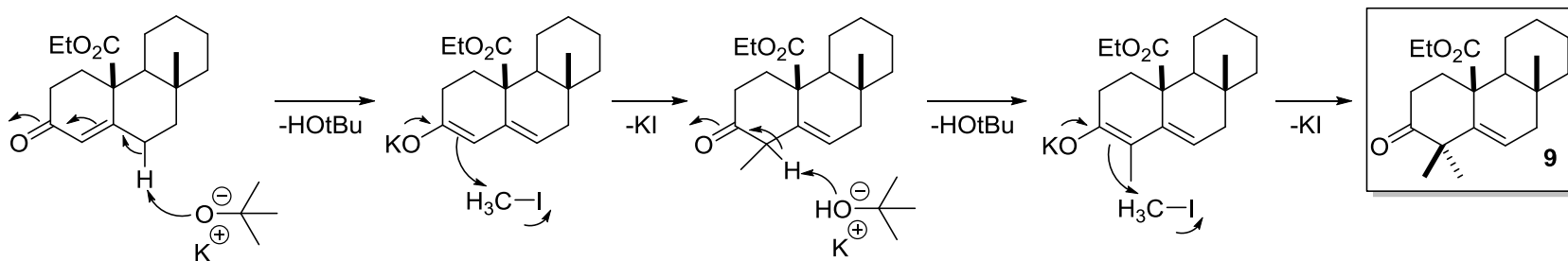


Total Synthesis of (±)-Limonin

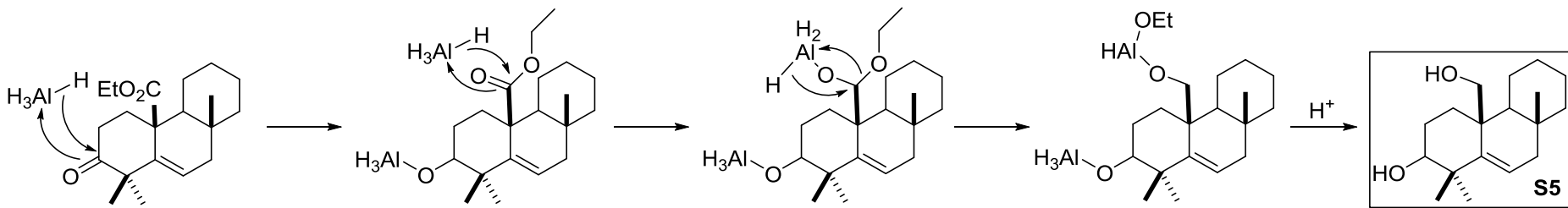
III. Synthesis



- Dimethylation:⁷



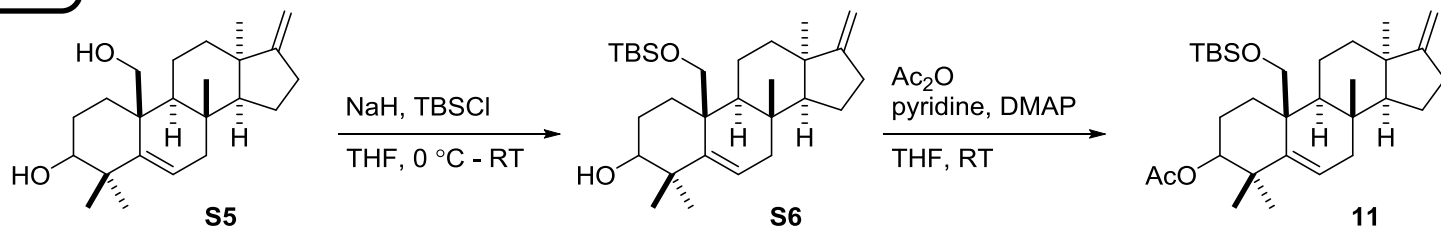
- Reduction:



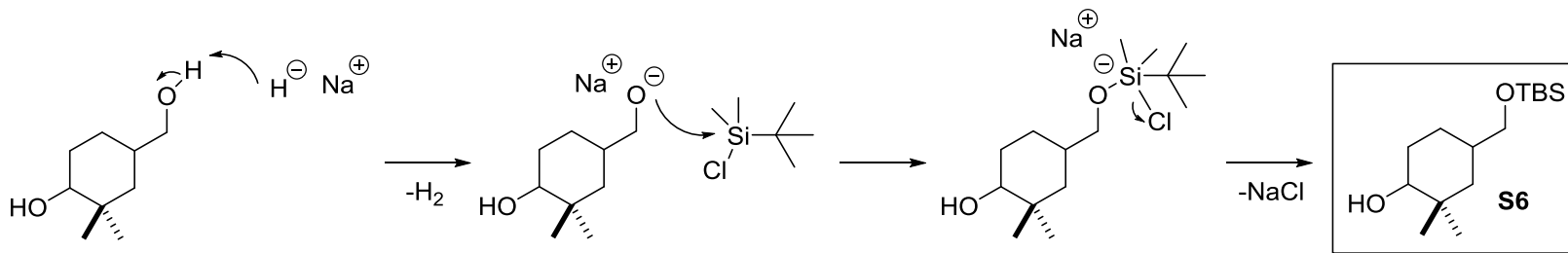
⁷) Kato, M. et al. *Tetrahedron* **1987**, *43*, 711-722.

Total Synthesis of (±)-Limonin

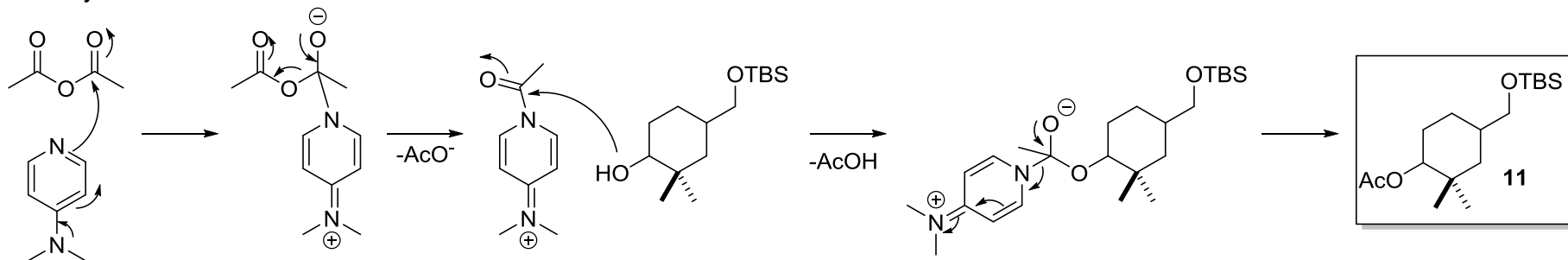
III. Synthesis



- TBS protection:

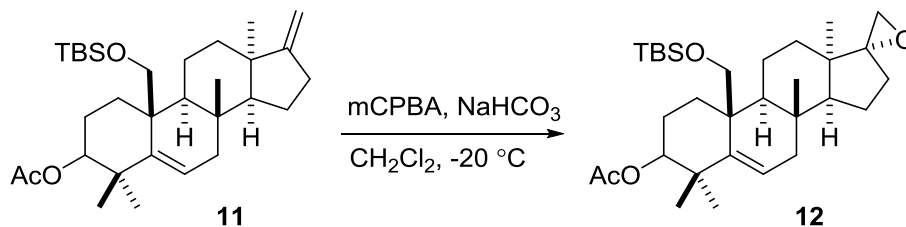


- O-acylation:



Total Synthesis of (±)-Limonin

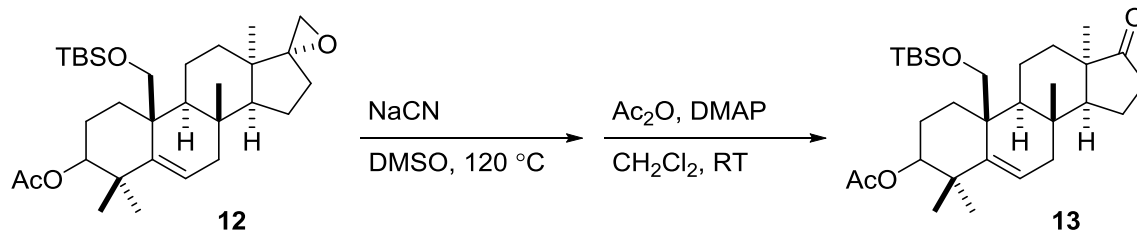
III. Synthesis



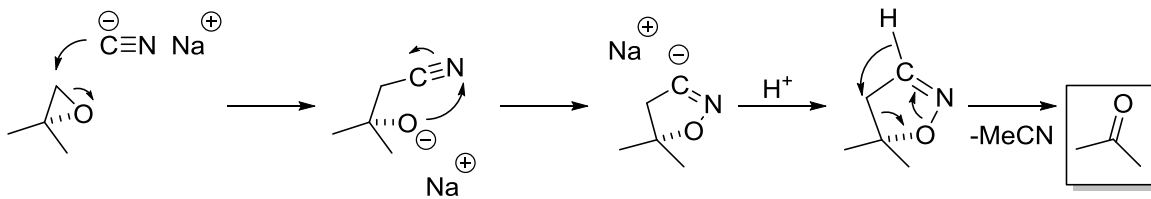
- Direct oxidative cleavage of the exo methylene group was unsuccessful (i.e., reaction with OsO₄ did not proceed)
- A stepwise route was designed starting with epoxidation
- mCPBA epoxidation from least hindered (re) face of olefin (mechanism on slide 2)

Total Synthesis of (±)-Limonin

III. Synthesis



- Epoxide ring opening and isomerization with cyanide anion:⁸

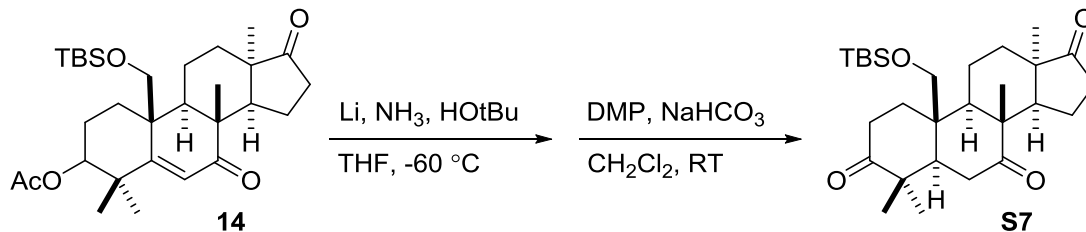


- Partial deacylation was observed under the reaction conditions, so the crude product of the cyanide reaction was re-acylated to obtain **13**

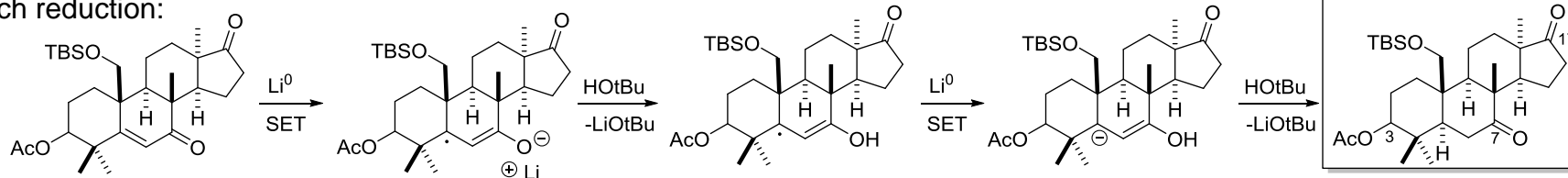
8) Wade, P. A. *et al. J. Org. Chem.* **1987**, *52*, 2973-2977.

Total Synthesis of (±)-Limonin

III. Synthesis

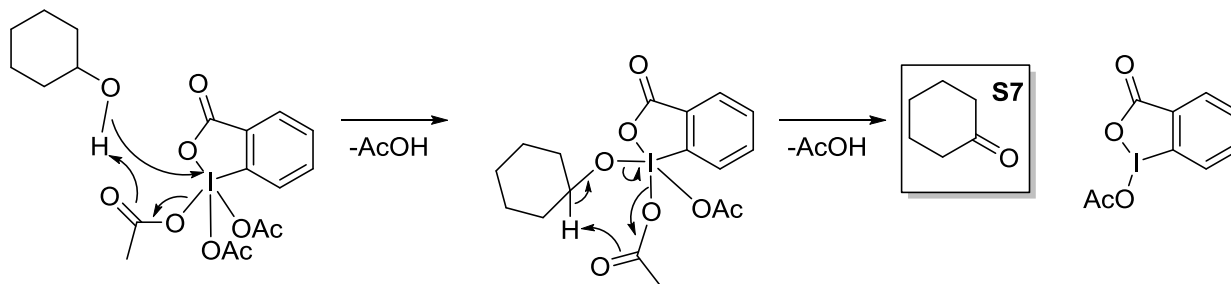


- Birch reduction:



- Complete deacylation at C3 was observed, and a mixture of C3, C7, and C17 alcohols was obtained. The crude mixture was globally oxidized in the following step:

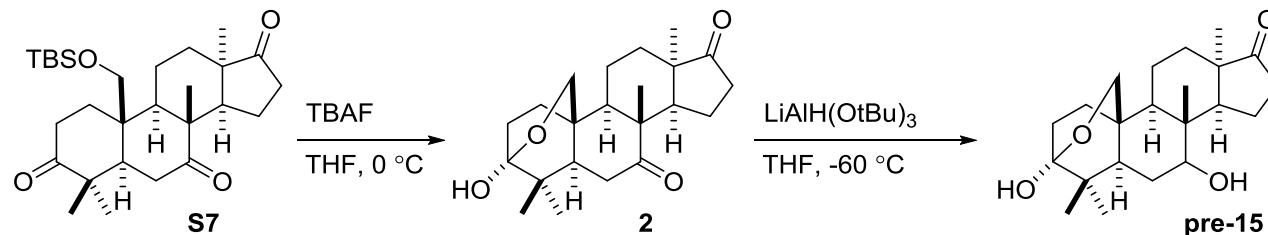
- DMP oxidation:



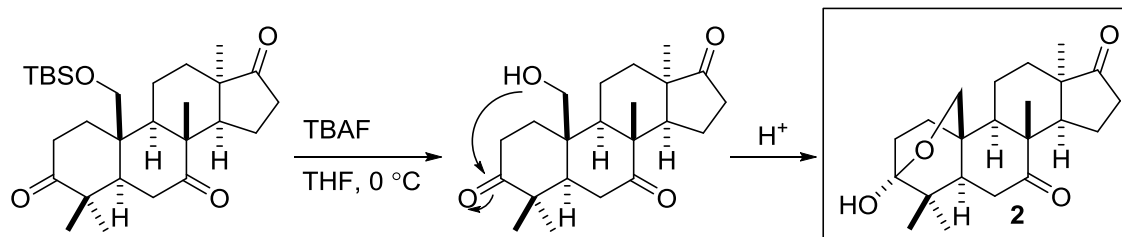
10) Dess, D. B. *et al. J. Org. Chem.* **1983**, *48*, 4155-4156.

Total Synthesis of (±)-Limonin

III. Synthesis



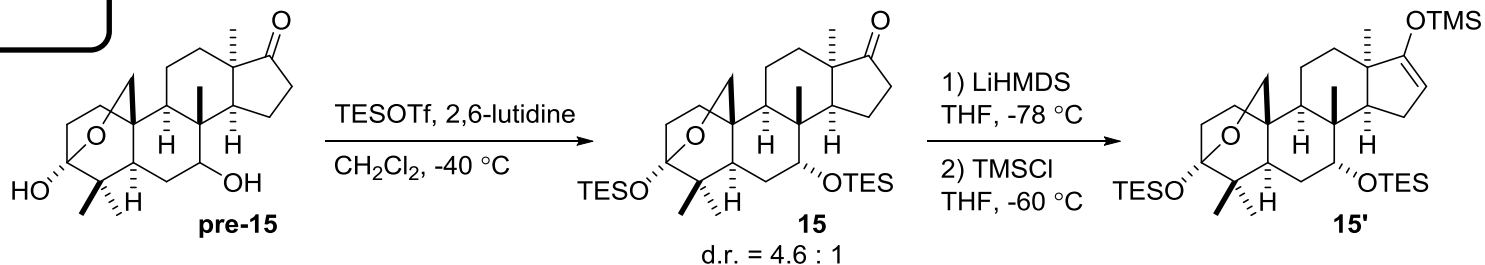
- TBAF deprotection (slide 5) followed by cyclization:



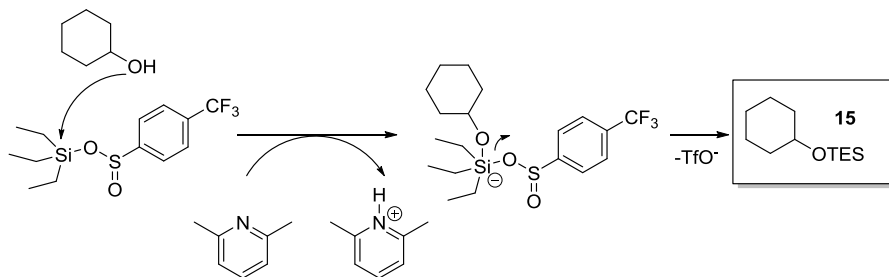
- Chemoselective reduction of the C7 ketone was achieved through the use of a single equivalent of a bulky aluminum alkoxide reducing agent (see slide 8)

Total Synthesis of (±)-Limonin

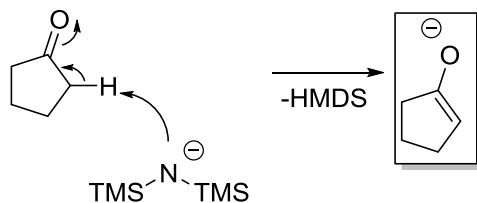
III. Synthesis



- 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:



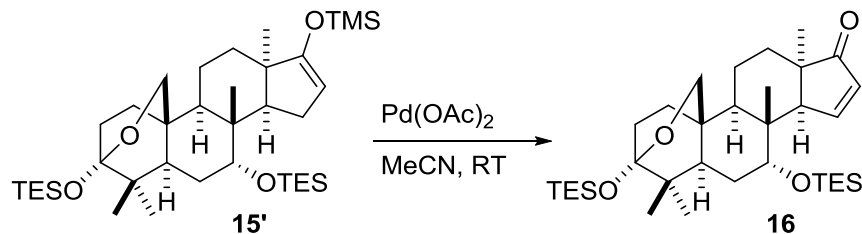
- Enolate formation:



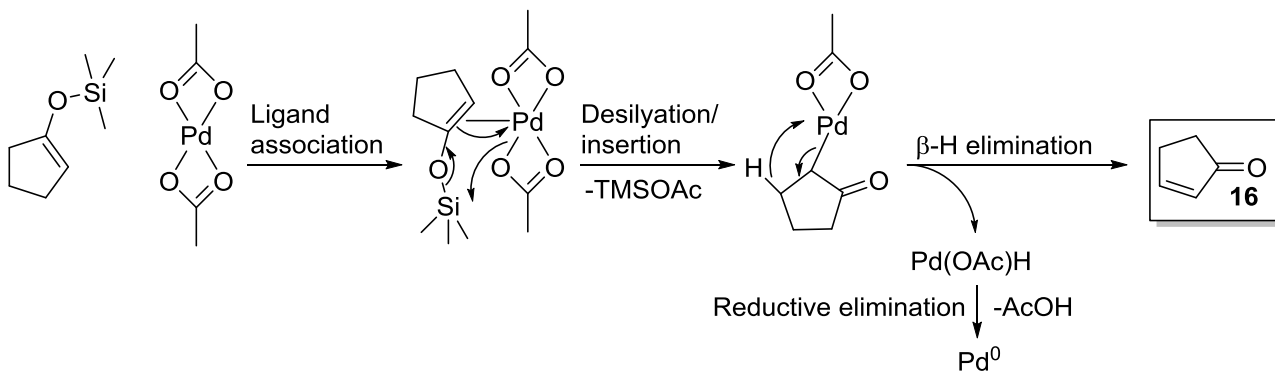
- Silyl enol ether formation (slide 9)

Total Synthesis of (±)-Limonin

III. Synthesis



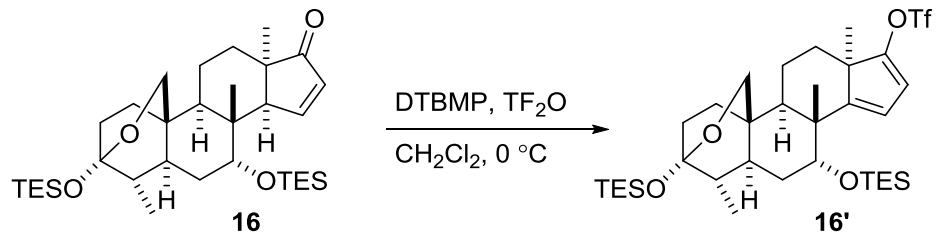
- Ito-Saegusa oxidation:¹¹



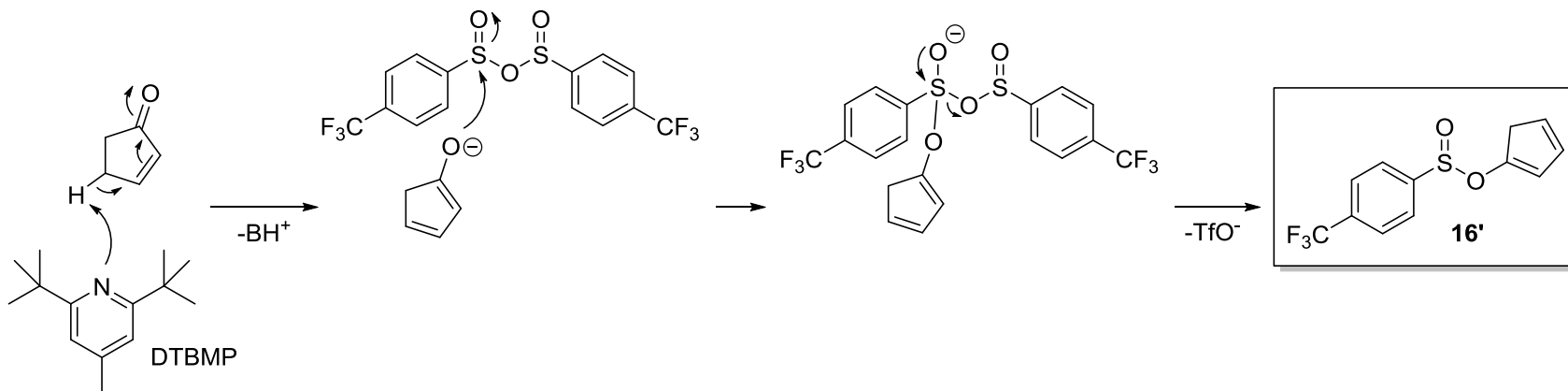
11) Ito, Y. *et al.* *J. Org. Chem.* **1978**, *43*, 1011-1013.

Total Synthesis of (±)-Limonin

III. Synthesis



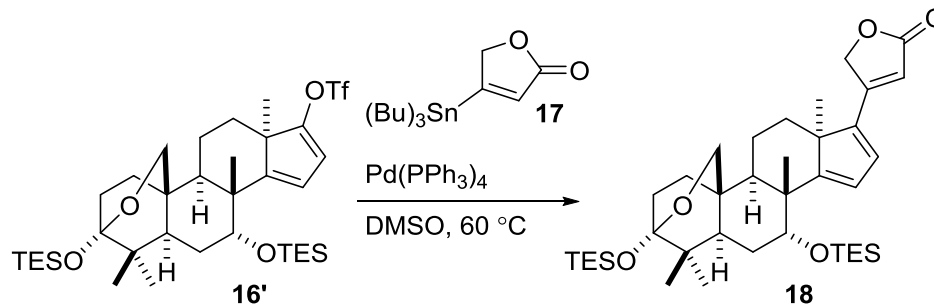
- Vinylogous enol triflate formation:¹²



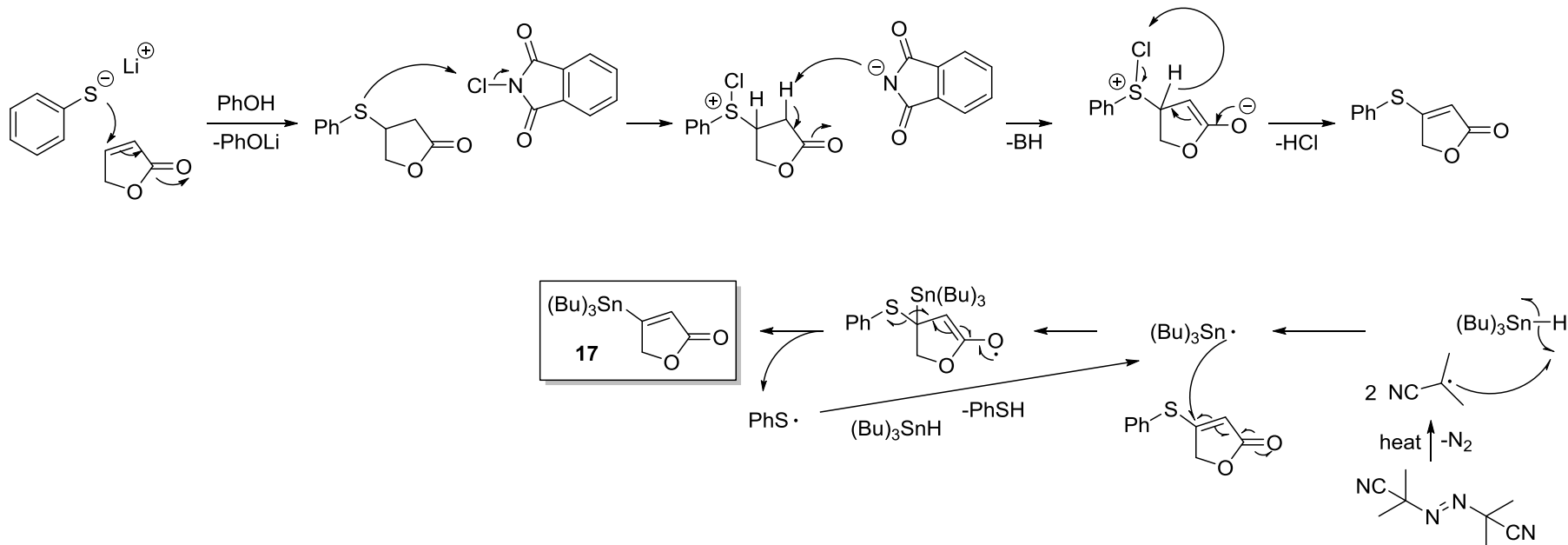
12) Stang, P. J. *et al. Synthesis*, **1979**, 438-440.

Total Synthesis of (±)-Limonin

III. Synthesis



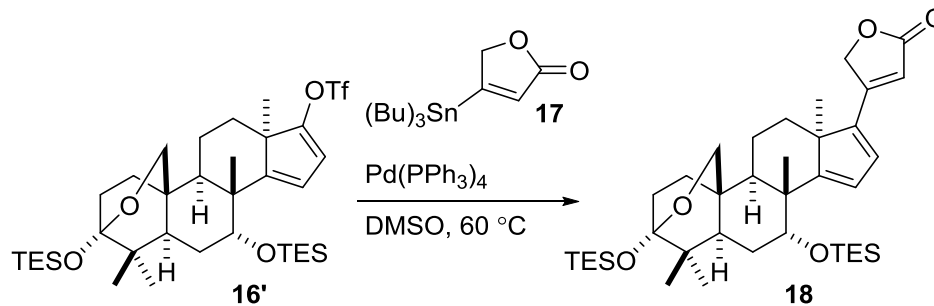
- Synthesis of **17**:¹³



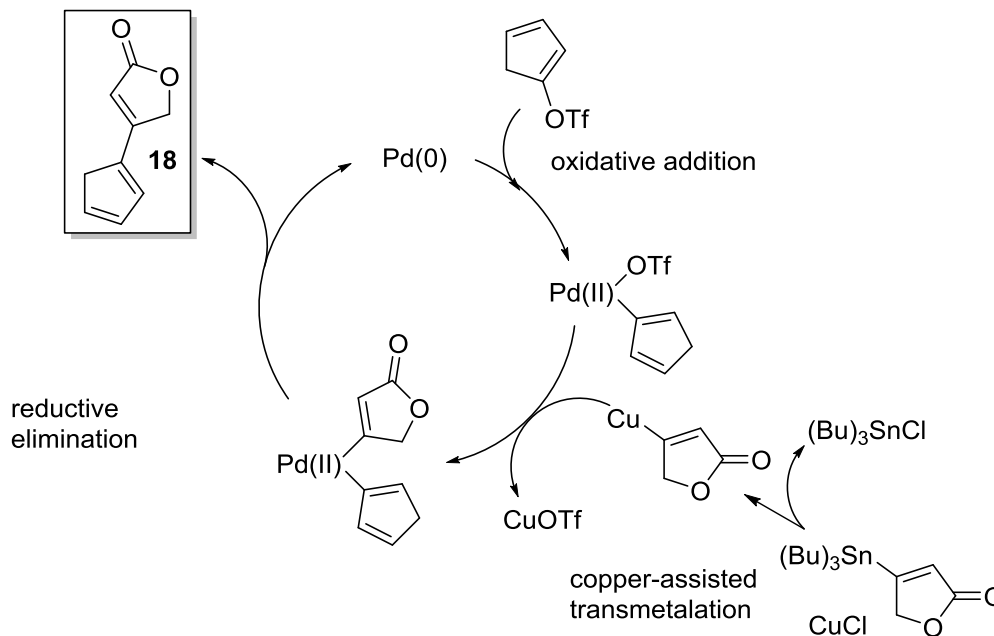
13) Hollingworth, G. J. *et al. J. Chem. Soc. Perkin Trans. 1* **1996**, 1913-1919.

Total Synthesis of (±)-Limonin

III. Synthesis



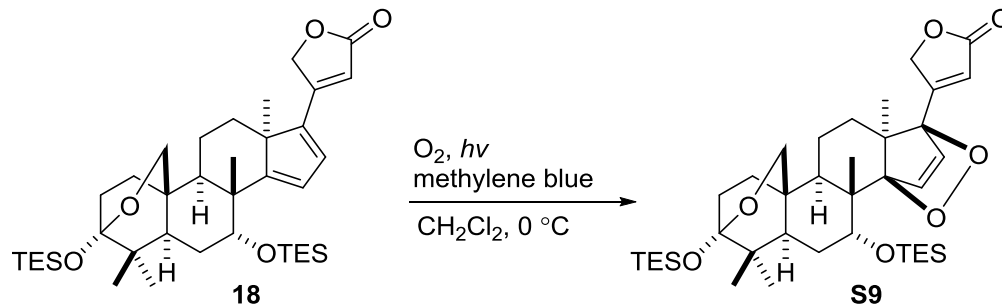
- Stille Coupling:¹⁴



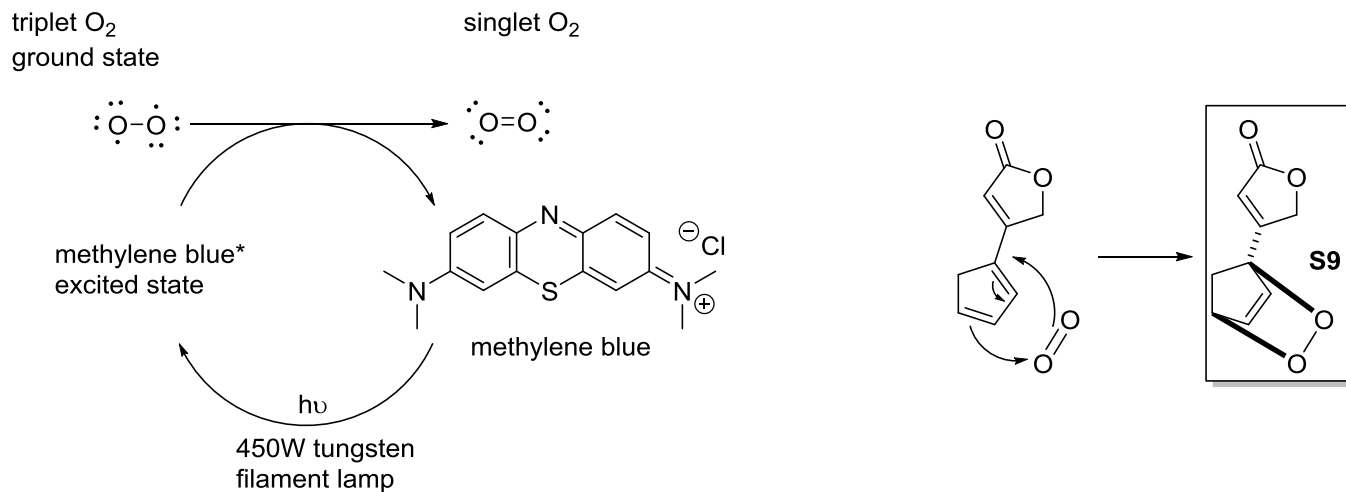
14) Han, X. *et al. J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

Total Synthesis of (±)-Limonin

III. Synthesis



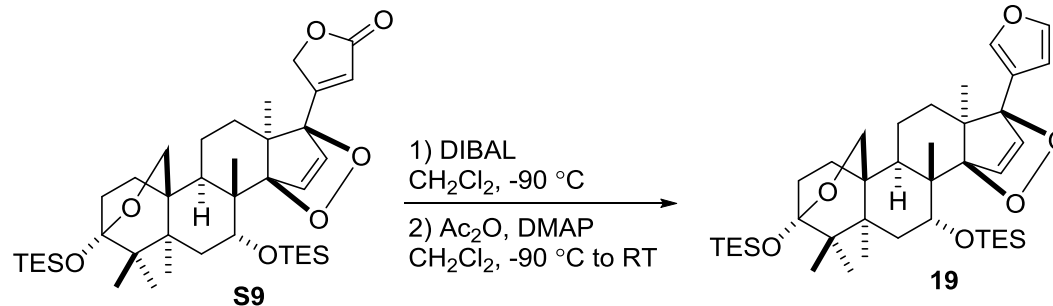
- Cycloaddition with singlet oxygen:¹⁵



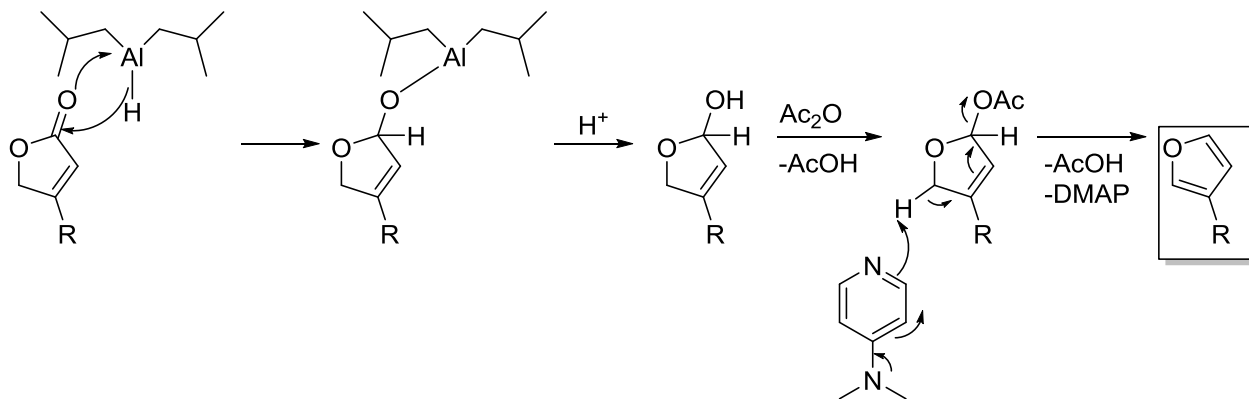
15) Li, W. *et al. Org. Lett.* **2003**, *5*, 2849-2852.

Total Synthesis of (±)-Limonin

III. Synthesis

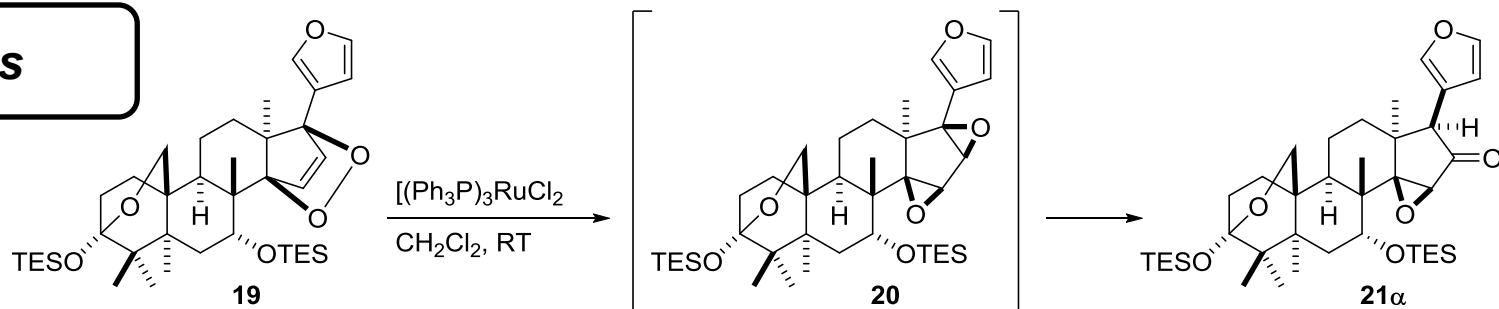


- DIBAL reduction, acylation with DMAP (slide 9), deacylation to yield furan ring:

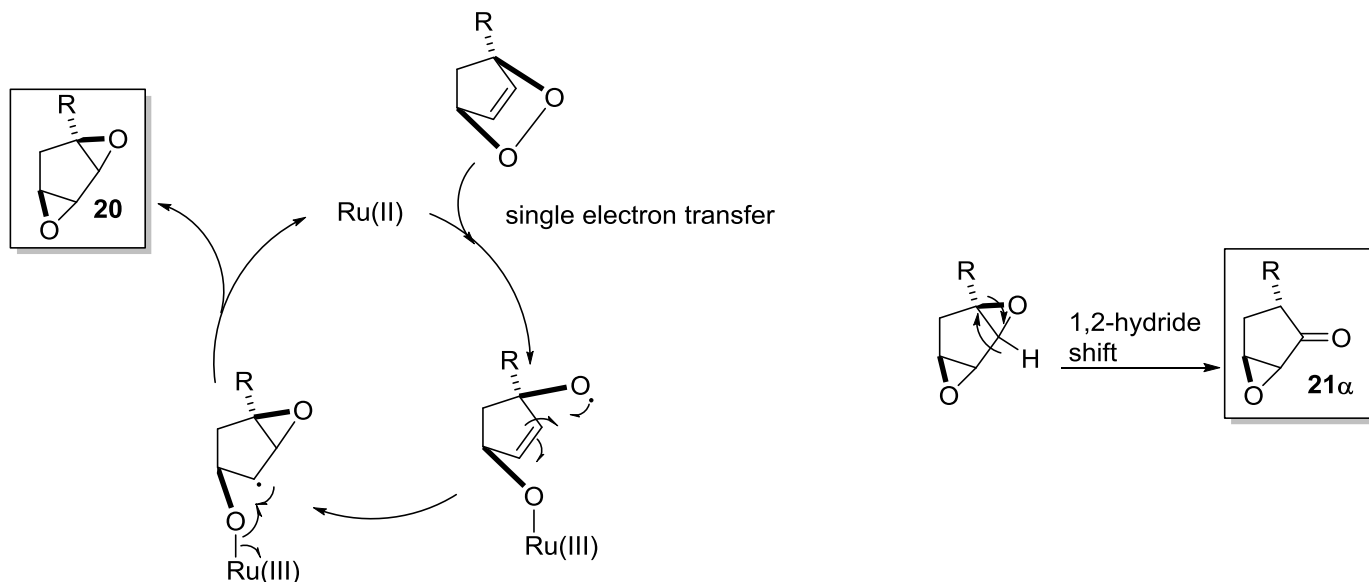


Total Synthesis of (±)-Limonin

III. Synthesis



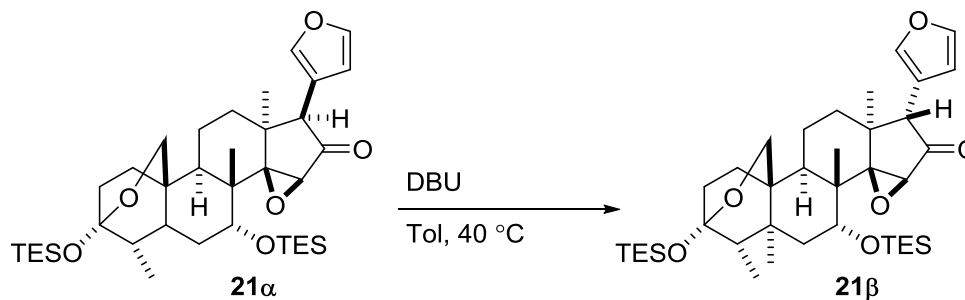
- Ruthenium catalyzed endoperoxide isomerization and rearrangement:¹⁶



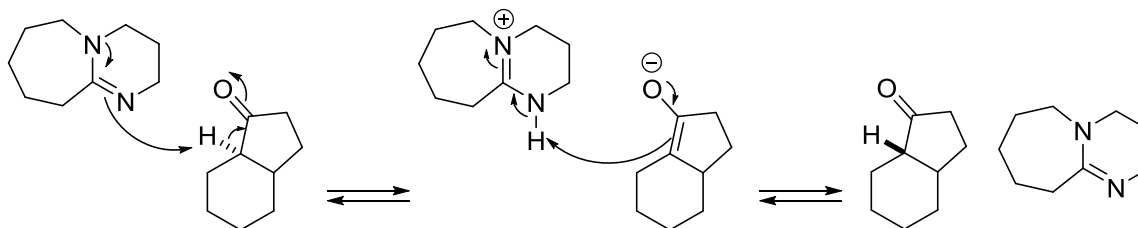
16) Suzuki, M. *et al. J. Org. Chem.* **1989**, *54*, 5292-5302.

Total Synthesis of (±)-Limonin

III. Synthesis

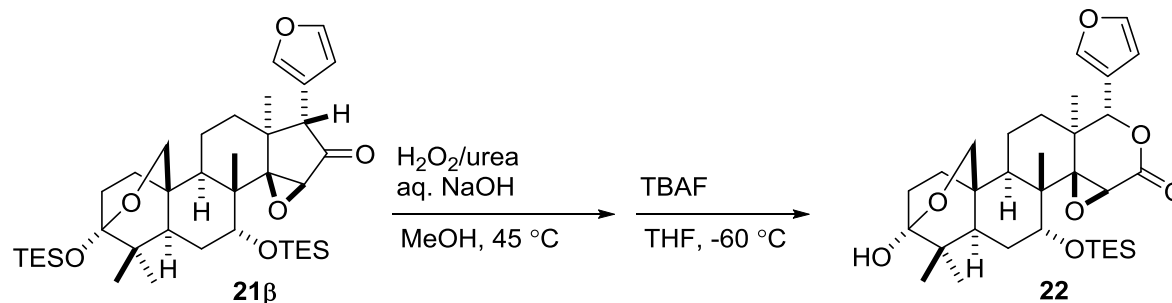


- Base-catalyzed epimerization:

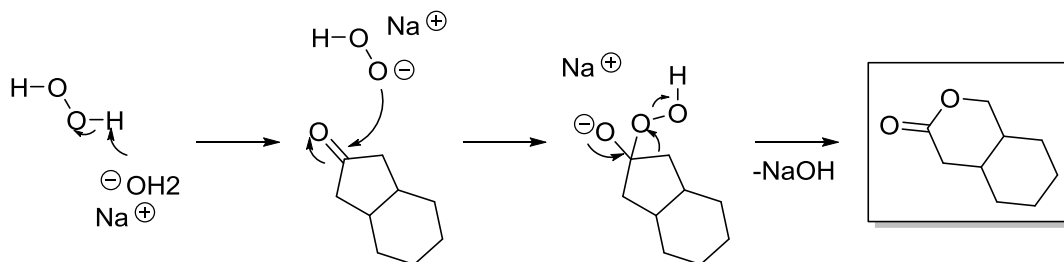


Total Synthesis of (±)-Limonin

III. Synthesis



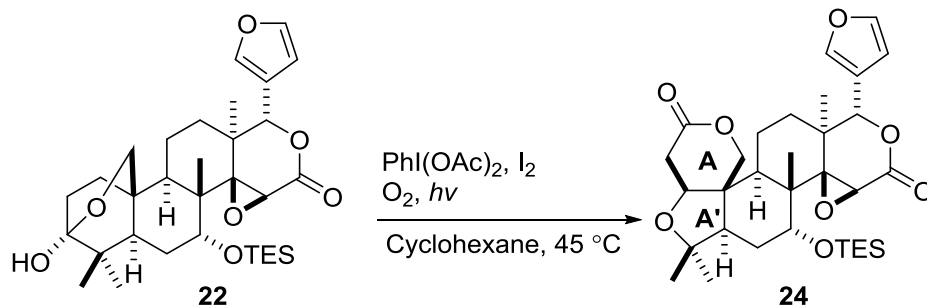
- Baeyer-Villiger oxidation and subsequent silane deprotection (slide 5):



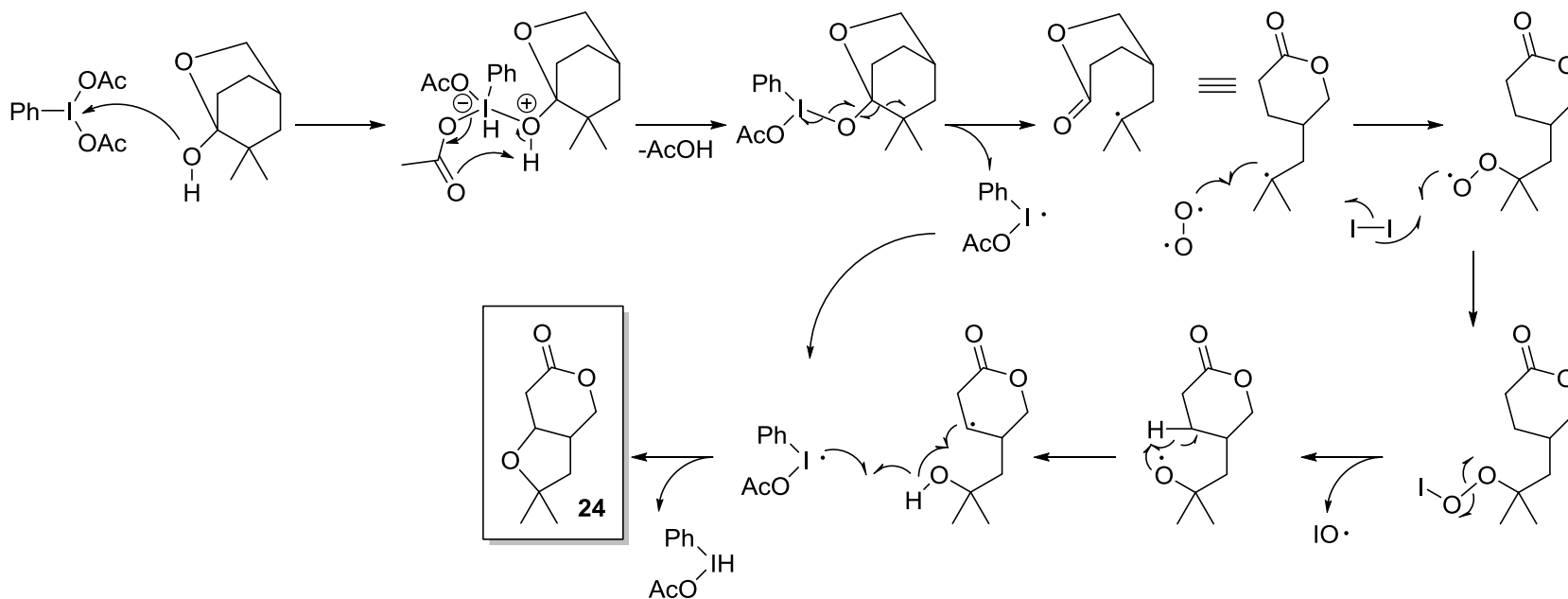
- In the case of unsymmetrical substrates, the group that can best bear a partial positive charge migrates preferentially

Total Synthesis of (±)-Limonin

III. Synthesis



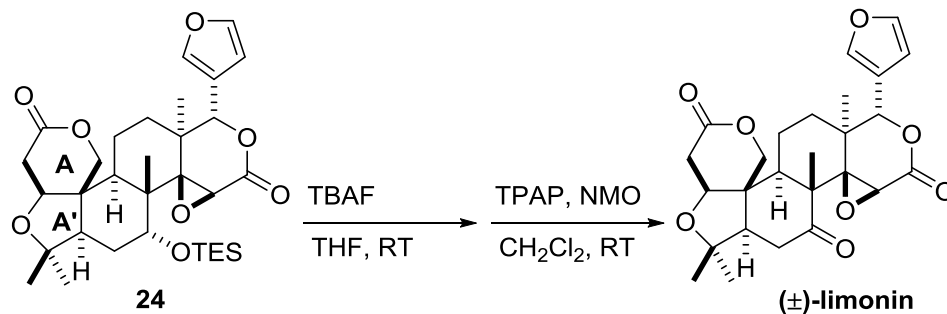
- Suárez reaction:¹⁷



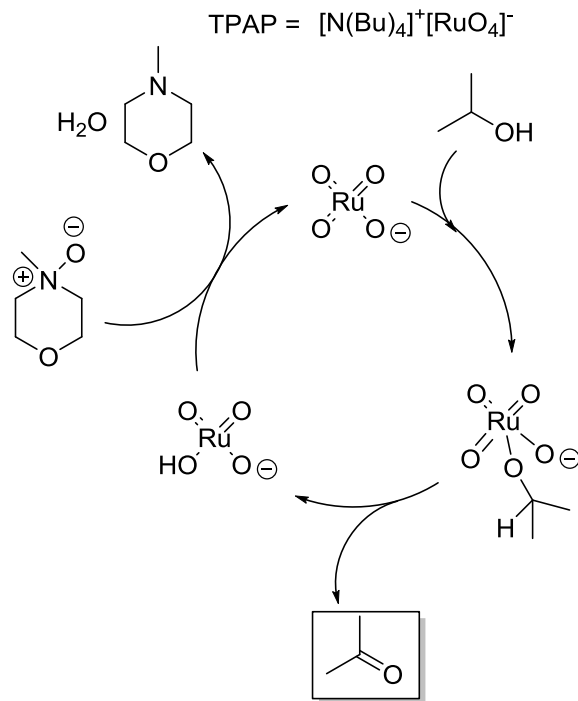
17) Boto, A. *et al. J. Org. Chem.* **1997**, *62*, 2975-2981.

Total Synthesis of (±)-Limonin

III. Synthesis



- Silane deprotection (slide 5) and Ley oxidation:¹⁸

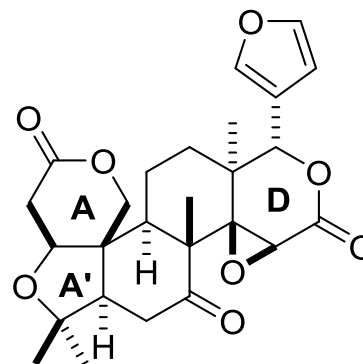


18) Ley, S. V. *et al. Synthesis* **1994**, 639-666.

Total Synthesis of (\pm)-Limonin

IV. Summary

(\pm)-limonin



- 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 α 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
 - 4) Suárez reaction to construct the AA' ring system
- The synthetic strategy developed should be amenable to synthesizing other related limonoids