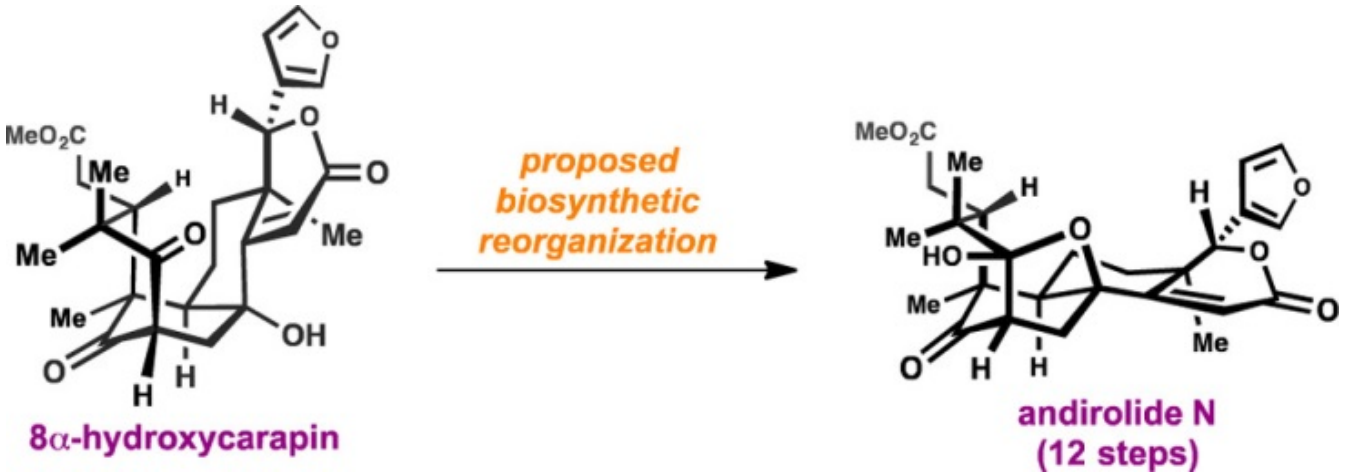
Assembly of the Limonoid Architecture by a Divergent Approach: Total Synthesis of (±)-Andirolide N via (±)-8α-Hydroxycarapin

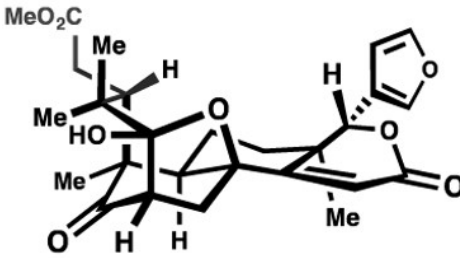
Alexander W. Schuppe and Timothy R. Newhouse*
J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268



Liming Cao
Wipf Group Current Literature
1/21/2017

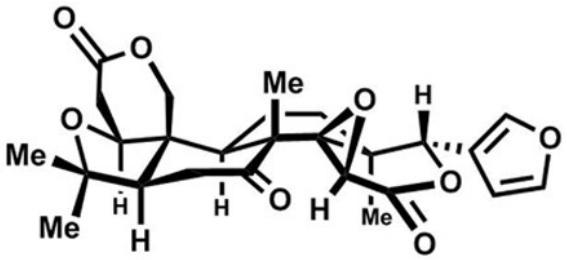
Andirolide N from *Carapa Guianensis*

- First isolated by Tanaka from the flowers of *Carapa Guianensis*-a mahogany tree in Amazonian rainforest
- The towering tree not only used as timber but also as herbal medicine: the oil collected from its flower used for the treatment of wounds, preventing skin diseases, and as an insect repellant
- The structure containing synthetically demanding bicyclo [3.3.1]nonane ring system with a bridging tetrahydrofuran ring
- Biological properties including antimalarial and cytotoxic activities

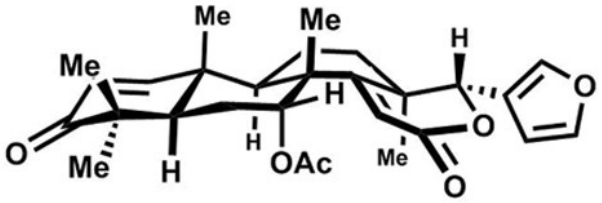


Tetrahedron **2012**, 68, 3669
J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268
http://www.tipdisease.com/2014/12/benefits-of-andiroba-carapa-guianensis.html
http://www.discoverlife.org/mp/20q?search=Carapa+guianensis (Smithsonian Tropical Research Institute, 2003-2006)

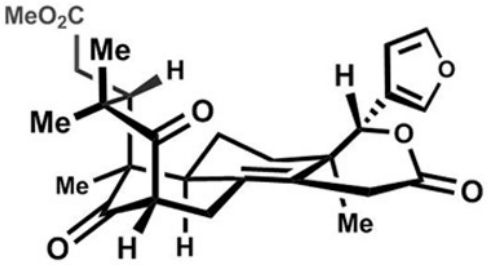
Limonoids Exemplifying Structural Diversity of the A-ring



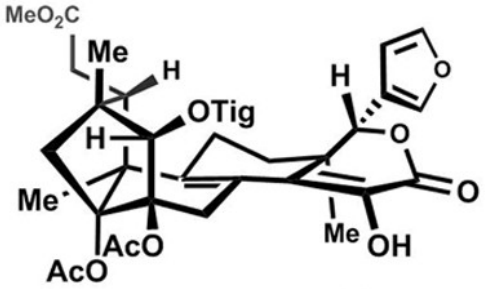
limonin (1)



deoxygedunin (2)

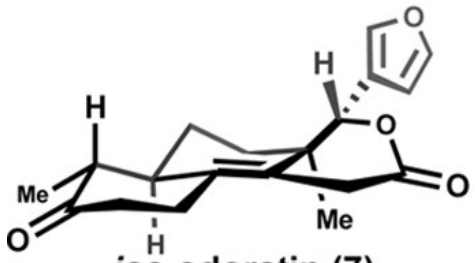


mexicanolide (3)



trichagmalin A (4)

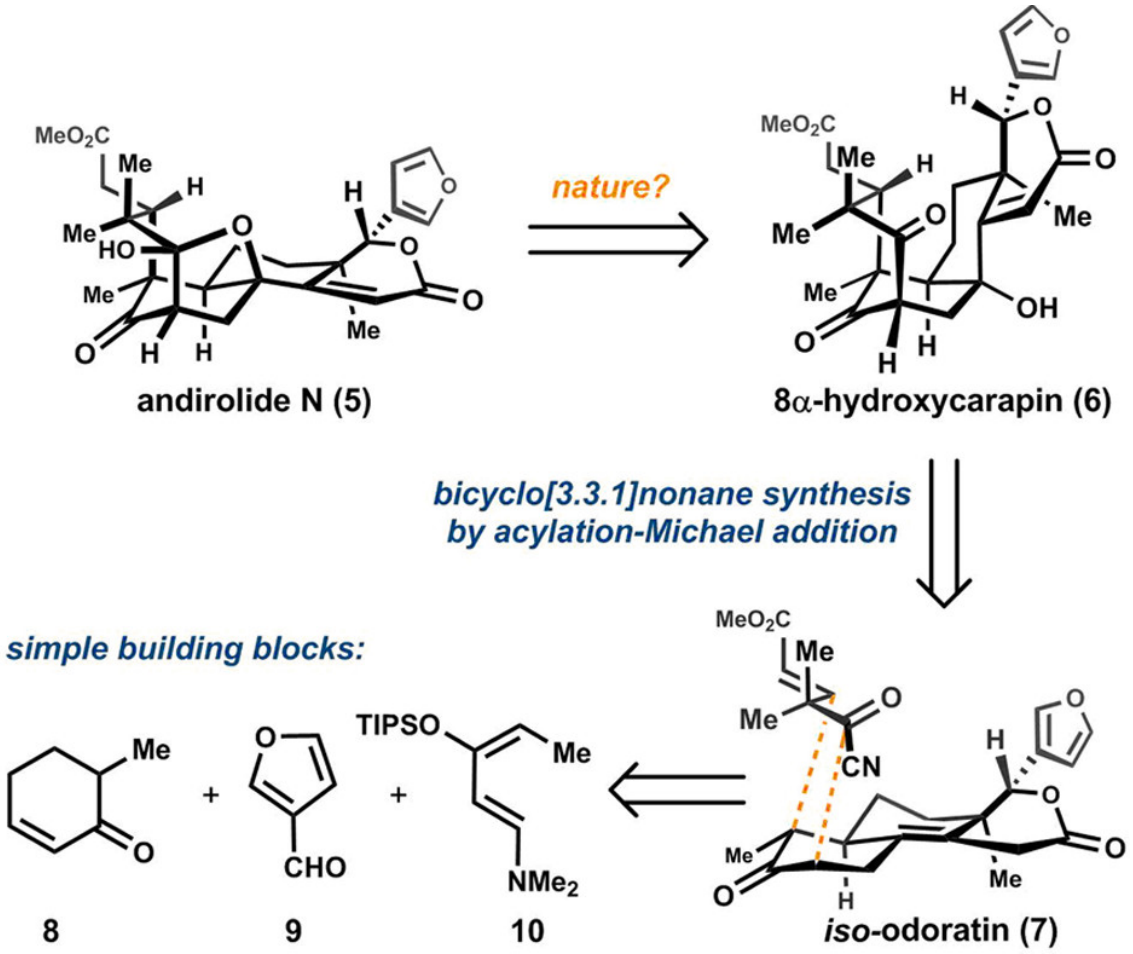
A general synthetic approach to access limonoids with different A ring structures:



iso-odoratin (7)

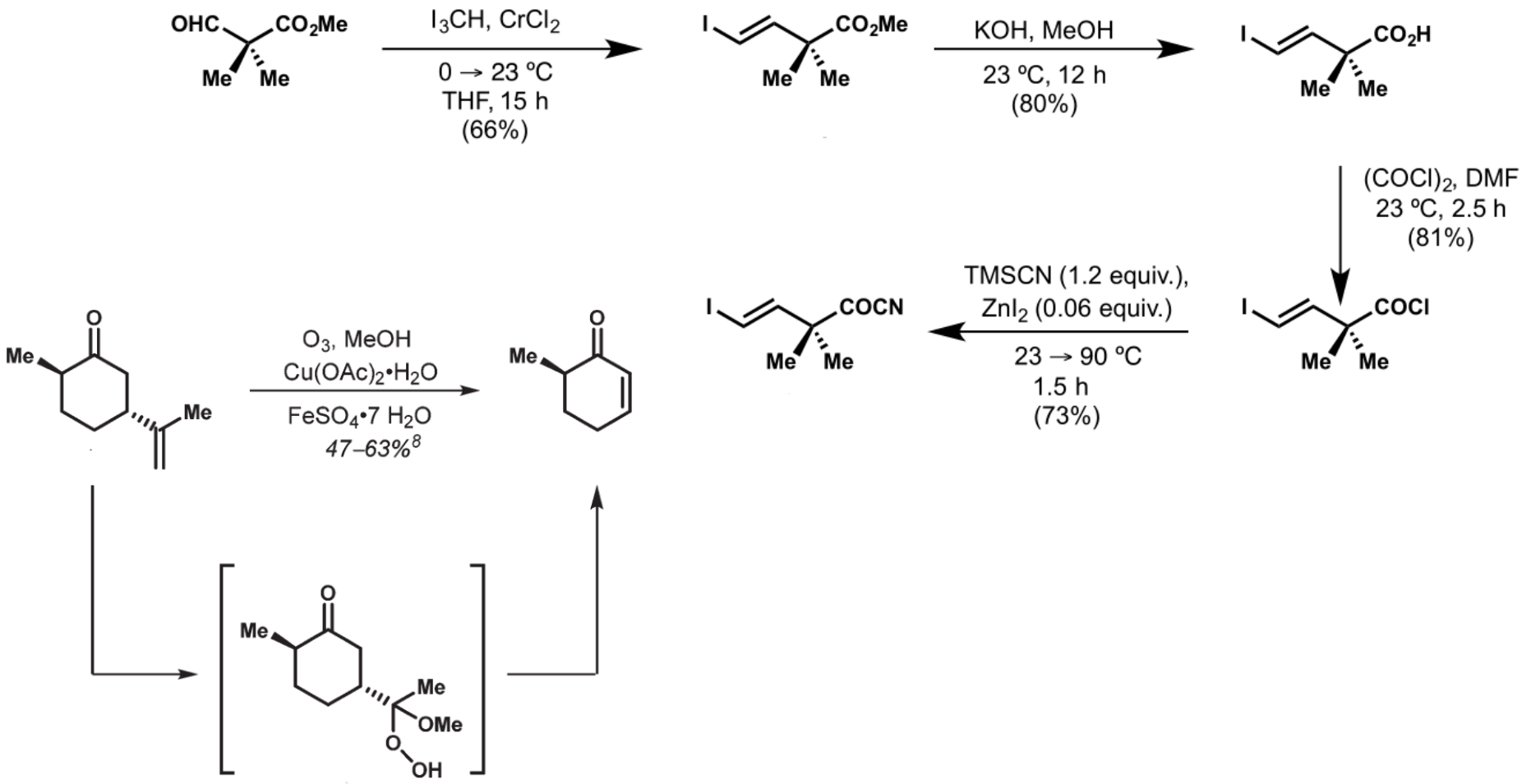
J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

Retrosynthetic Analysis



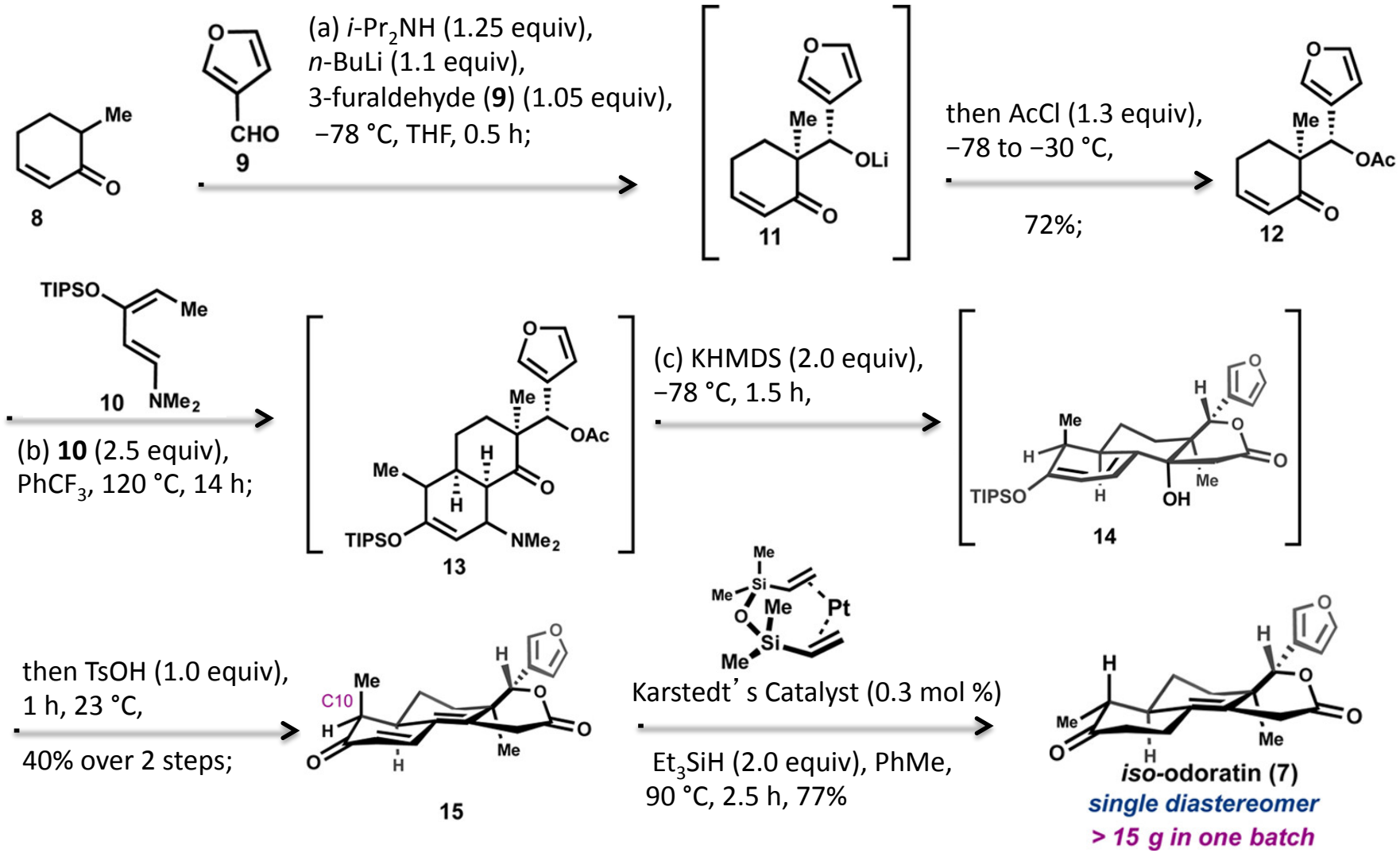
J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

Starting Material



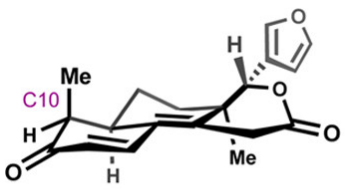
Org. Biomol. Chem. **2016**, 14, 6197
J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

Scalable Synthesis of *iso*-Odoratin (7)

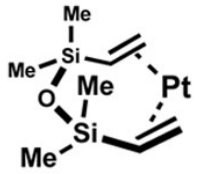


J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

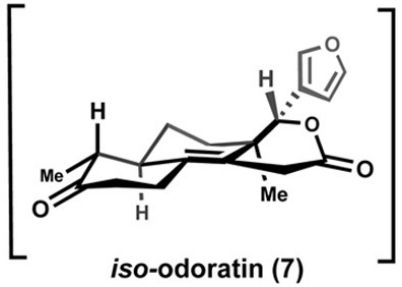
Total Synthesis of Andirolide N (5) via the Presumed Biosynthetic Precursor 8α-Hydroxycarapin (6)



15



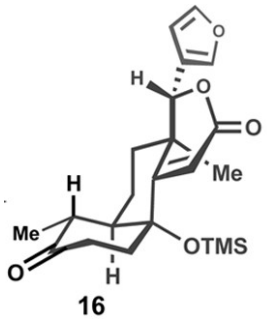
(a) Karstedt's Catalyst (0.3 mol %), Et_3SiH (2.0 equiv), PhMe, 90 °C, 2.5 h,



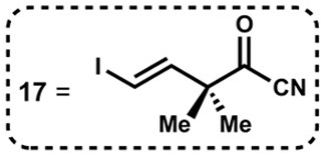
iso-odoratin (7)

then DBU (2.0 equiv), $P(OMe)_3$ (1.5 equiv), O_2 (1 atm), MeCN, 35 °C, 2 h, 52%

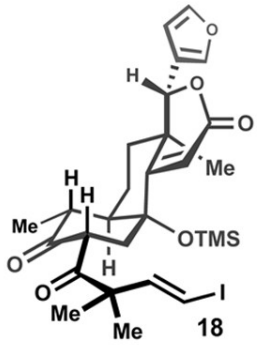
(b) TMSCl (1.5 equiv), imid. (3.5 equiv), CH_2Cl_2, 23 °C, 3 h, 60%;



16

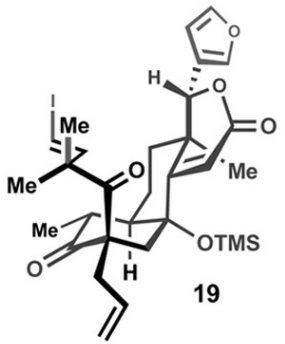


(c) LiHMDS (1.5 equiv), **17** (1.1 equiv), Et_2O–THF (4:1), −78 to 0 °C, 1 h, 76%;



18

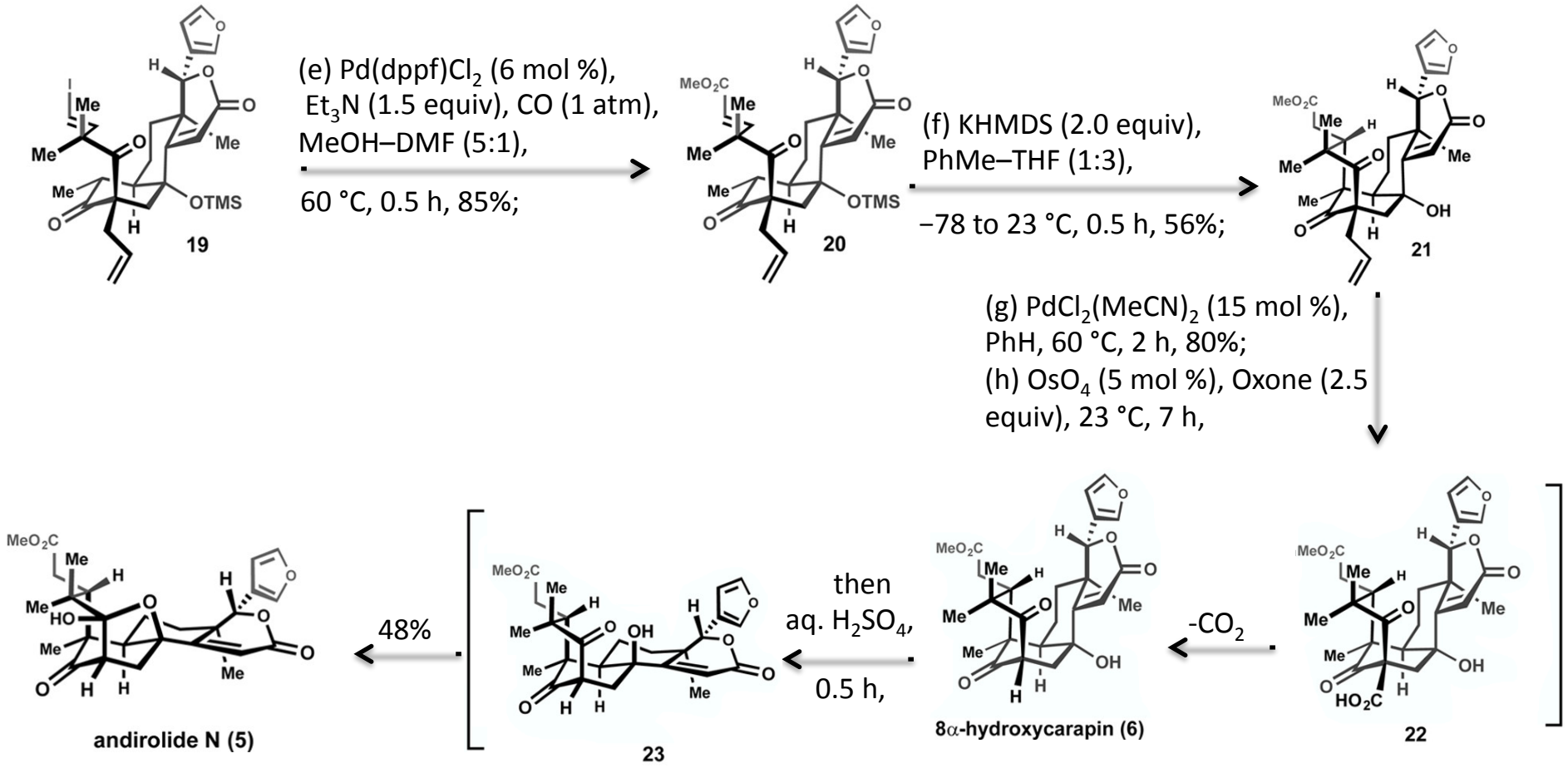
(d) Cs_2CO_3 (2.5 equiv), allyl iodide (1.7 equiv), acetone, 56 °C, 12 h, 86%;



19

J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

Total Synthesis of Andirolide N (5) via the Presumed Biosynthetic Precursor 8α-Hydroxycarapin (6)



J. Am. Chem. Soc., **DOI:** 10.1021/jacs.6b12268

Conclusion

- A 12-step synthesis of the limonoid andirolide N (**5**) have been from commercially available dihydrocarvone.

- An acylation-Michael strategy for bicyclo[3.3.1]nonane construction from the degraded limonoid *iso*-odoratin (**7**) was employed.

- The unique tetrahydrofuran appended to the bicyclic structure of the carbocyclic skeleton of andirolide N was installed via an acid-mediated reorganization of 8α-hydroxycarapin (**6**).

- While these studies demonstrate the chemical feasibility that 8α-hydroxycarapin could be the biosynthetic precursor to andirolide N, whether or not the polycyclic structure of andirolide N is formed in nature by this pathway remains unknown.