

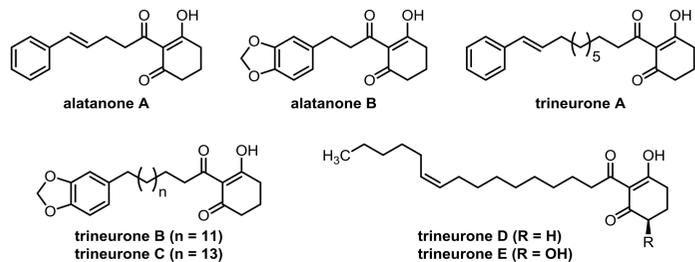
## Introduction



*Peperomia alata*



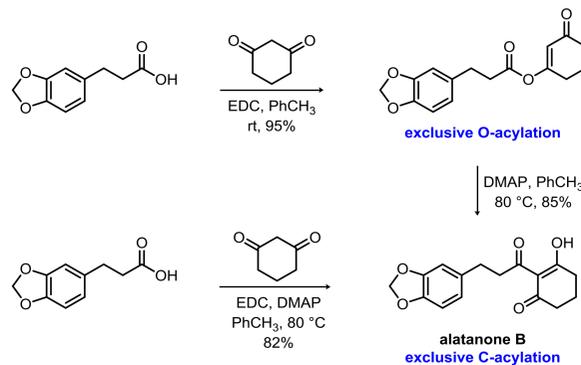
*Peperomia trineura*



- The alatanones and trineurones are a family of polyketides isolated from perennial herbs of the genus *Peperomia* by Kato and coworkers in 2014.
- These natural products exhibit antifungal activity against several species of *Cladosporium* and cytotoxicity against selected leukemia cell lines.

Isolation: Kato, M., et. al. *J. Nat. Prod.* **2014**, *77*, 1377.

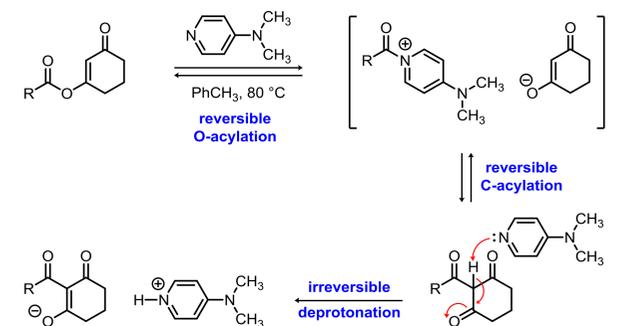
## Development of a Selective C-Acylation



- Direct coupling of 1,3-cyclohexanedione with the carboxylic acid substrate in the presence of the carbodiimide EDC forms exclusively the O-acylated product.
- This O-acylated product could be cleanly isomerized to the desired C-acylated product alatanone B in the presence of 4-(dimethylamino)pyridine (DMAP).
- Direct C-acylation could be achieved by adding DMAP to the carbodiimide-mediated coupling reaction and heating to 80 °C.

DMAP isomerization: Ichihara, A., et. al. *Synlett* **1993**, 651.

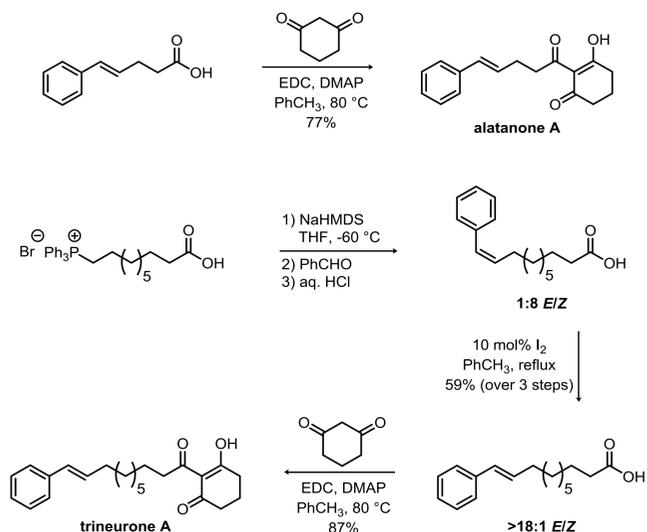
## Mechanistic Rationale



- Under the reaction conditions, the O-acylated product is formed initially (i.e. there is a kinetic preference for O-acylation with a “hard” electrophile).
- DMAP can then reversibly react with the O-acylated compound to form an acylpyridinium / enolate ion pair that can undergo reversible C-acylation.
- Deprotonation of the resulting tricarbonylmethane group (pK<sub>a</sub> = 9.8 in DMSO) is irreversible, leading to isolation of the desired C-acylated product after workup.

pK<sub>a</sub> data: Arnett, E., et. al. *J. Am. Chem. Soc.* **1984**, *106*, 6759.

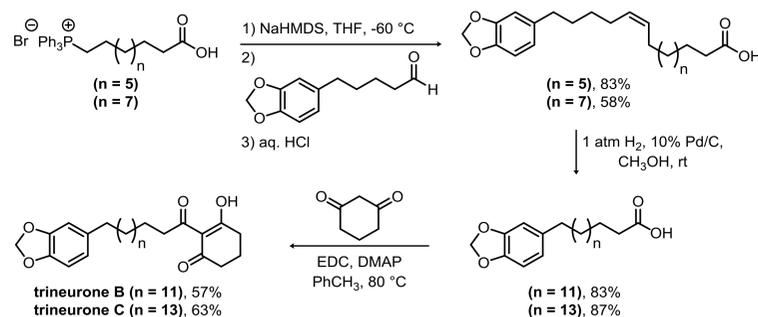
## Synthesis of Alatanone and Trineurone A



- The Wittig reaction favored formation of the (Z)-alkene, which was isomerized to the thermodynamically favored (E)-alkene upon heating with iodine.

Synthesis: Reber, K. and Lewis, A. *Tetrahedron Lett.* **2016**, *57*, 1083.

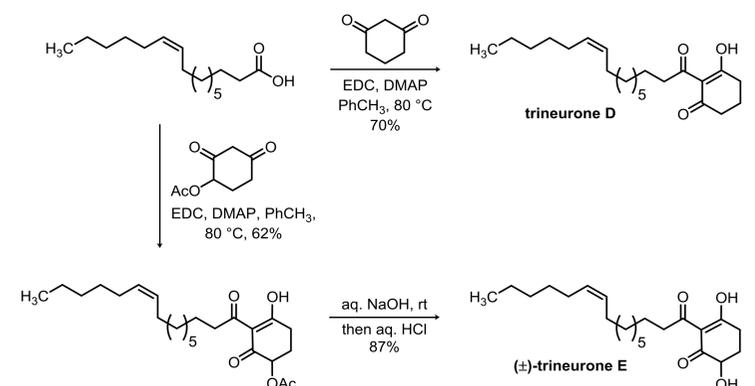
## Synthesis of Trineurones B and C



- A Wittig reaction between the phosphonium acids and the known methylenedioxy-substituted aldehyde afforded exclusively the (Z)-alkenes.
- Hydrogenation of the disubstituted alkenes under standard conditions gave the corresponding long-chain saturated carboxylic acids in high yield.
- Coupling of the acids with 1,3-cyclohexanedione occurred under our standard conditions to give trineurones B and C.

Aldehyde: Lu, W., et. al. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4844.

## Synthesis of Trineurones D and E



- The synthesis of trineurone E required the use of an acetoxy-substituted 1,3-cyclohexanedione, which was prepared in racemic form.
- After the standard coupling reaction, basic hydrolysis of the acetate afforded racemic trineurone E.
- All natural products synthesized in this study and several unnatural analogs are currently being screened for biological activity through Eli Lilly's Open Innovation Drug Discovery (OIDD) program.

Synthesis: Reber, K. and Lewis, A. *Tetrahedron Lett.* **2016**, *57*, 1083.

## Acknowledgements

We gratefully acknowledge Towson university for supporting this work through faculty start-up funding. We also thank Dr. John Eng (Princeton University) for assistance with HRMS analyses and Dr. István Pelczer (Princeton University) for helpful discussion related to NMR spectroscopy. Finally, we would like to acknowledge Eli Lilly's OIDD program for biological evaluation of samples.