

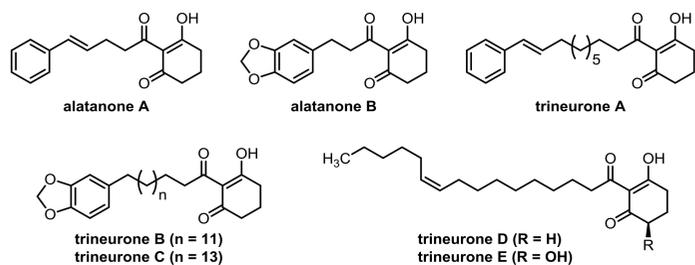
Introduction



Peperomia alata



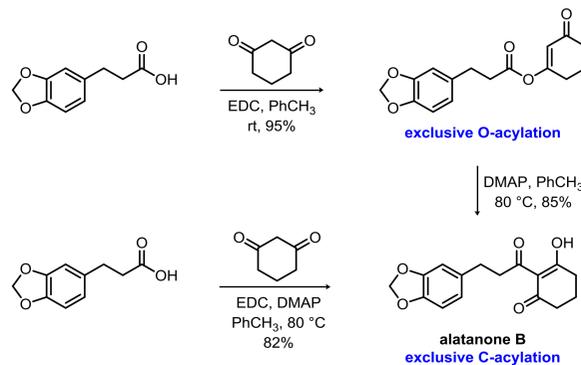
Peperomia trineura



- 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.

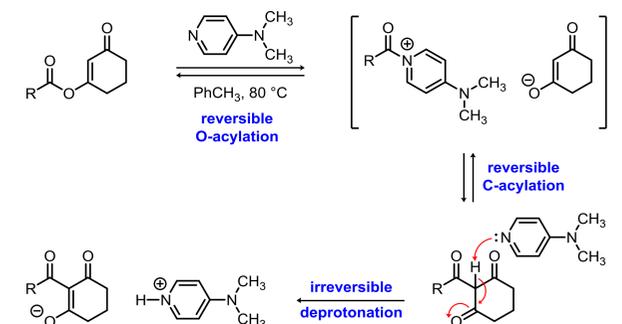
Development of a Selective C-Acylation



- 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.

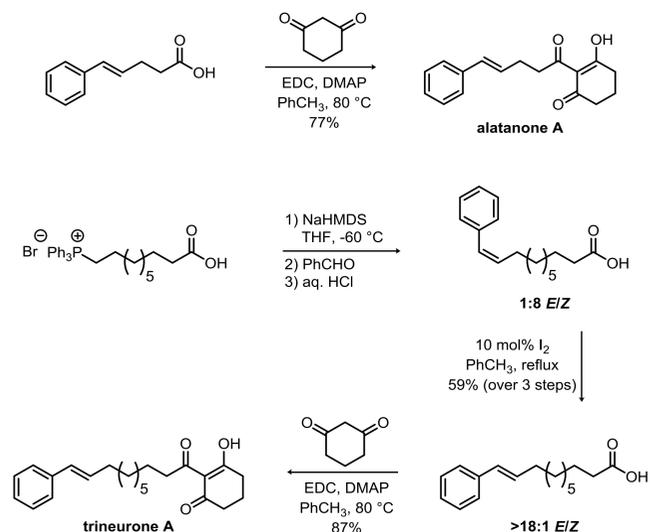
Mechanistic Rationale



- 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 ($pK_a = 9.8$ in DMSO) is irreversible, leading to isolation of the desired C-acylated product after workup.

pK_a data: Arnett, E., et al. *J. Am. Chem. Soc.* **1984**, *106*, 6759.

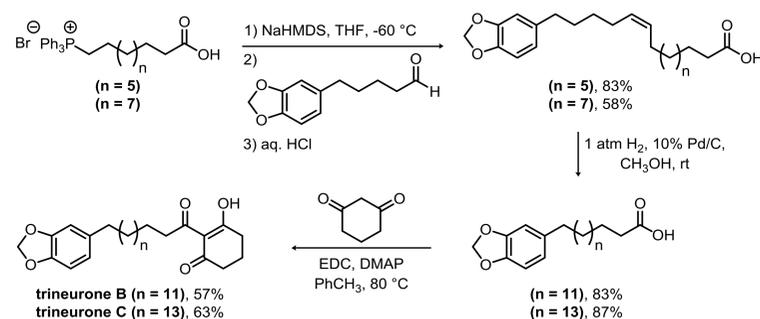
Synthesis of Alatanone and Trineurone A



- 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.

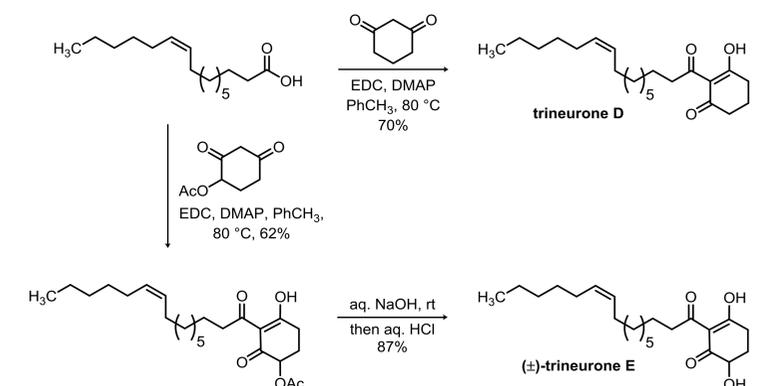
Synthesis of Trineurones B and C



- 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

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