Synthesis of Antifungal Alatanone and Trineurone Polyketides
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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 Chaetomium and cytotoxicity against selected leukemia cell lines.


Synthesis of Alatanone and Trineurone A

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.


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 / molate 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.


Synthesis of Trineurones B and C

- A Wittig reaction between the phosphonium acids and the known methyleneedioxy-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.

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 acetoxy affording 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.

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Synthesis of Trineurones D and E