Total Synthesis of Pyrophen and Campyrones A, B and C

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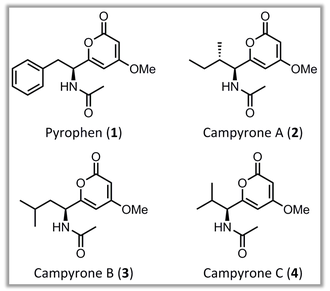
Introduction

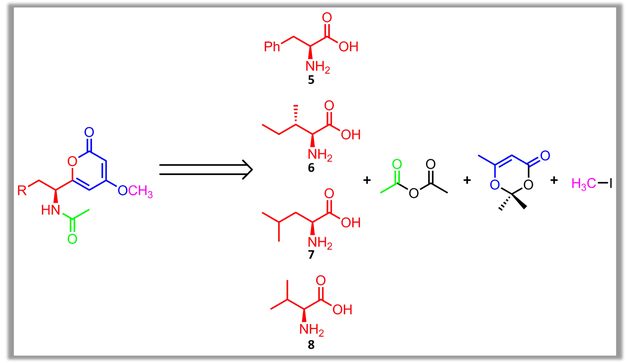


Pictured above: Four natural products from the fungus *A. niger* (left) and the fruiting bodies of the fungus itself (right).

Pyrophen was first isolated from the fungus *Aspergillus niger* in 1990, followed by the isolation of campyrones A, B and C from the same source in 2013. Pyrophen displayed promising antifungal activity when tested against *Candida albicans*, but is biologically scarce enough that further testing was impeded by the lack of available material. The goal of this project was to synthesize pyrophen and campyrones A-C, then submit them to Eli Lilly's Open Innovation Drug Discovery (OIDD) program for biological testing.

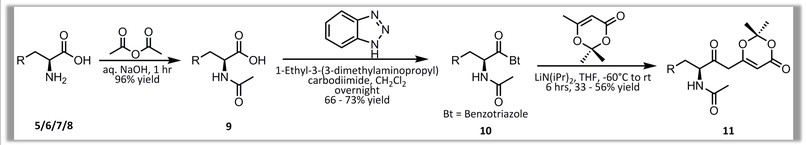
Barnes et. al. *Int. J. Peptide Protein Res*. **1990**, 36,292-296.
Laatsch et. al. *Tetrahedron*. **2013**, *69*, 7147-7151.

Retrosynthetic Analysis



Retrosynthesis aimed to follow a biomimetic approach, beginning from amino acid precursors **5-8** and coupling them *via* Claisen condensation to 2,2,6-trimethyl-1,3-dioxin-4-one, a synthon for the 1,3-diketone shown in blue, which it reveals when heated. Cyclization of the tricarbonyl produced from this sequence would provide the α-pyrone moiety, which would be methylated to give the natural products.

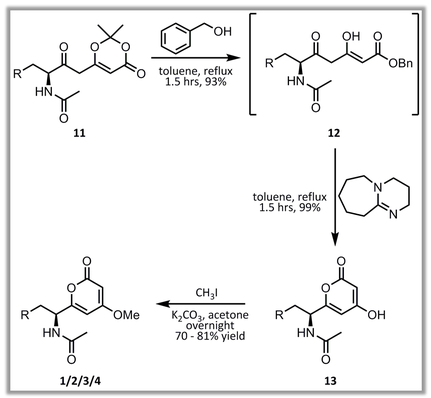
Key Fragment Union by Claisen Condensation



N-acetyl amino acids were formed in good yield as highly crystalline white solids, but are also available commercially. Carbodiimide coupling gave the *N*-acylbenzotriazoles, also as crystalline solids. The same method was also used to prepare phenyl esters, *para*-nitrophenyl esters, and pentafluorophenyl esters to be tested as substrates in the subsequent Claisen condensation. The best yields by far were achieved with the *N*-acylbenzotriazoles, producing the dioxinone derivatives as amorphous solids. This reaction could also be performed without warming, but required up to 9 hours at -78°C and would still only go to about 50% completion.

Katritzky, A.; Wang, Z.; Wang, M.; Hall, C.; Suzuki, K. *ChemInform*. **2005**, 36, 4854-4856.

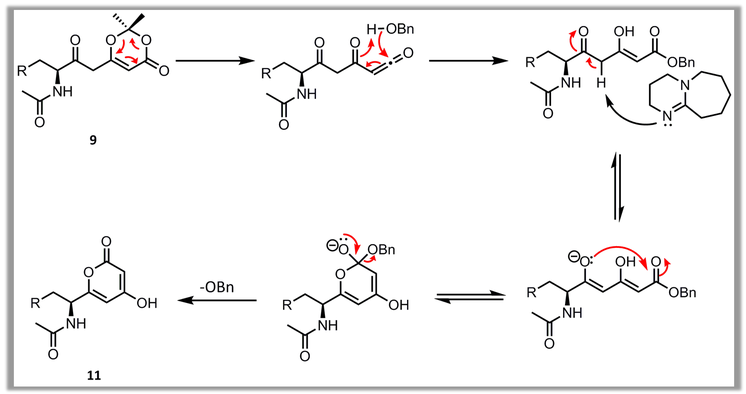
Cyclization and Methylation Yield Final Product



The dioxinone component of **11** could be opened under thermal conditions to give an acyl ketene, which was attacked by benzyl alcohol to give the tricarbonyl **12**. The addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to intramolecular cyclization. The tricarbonyl compounds could be isolated, but existed as a mixture of keto-enol tautomers. Transformation from **11** to **13** could also be carried out as a two-step, one-pot reaction with an overall yield of 83%. Subsequent methylation of the resulting α-pyrone led to the natural products without event.

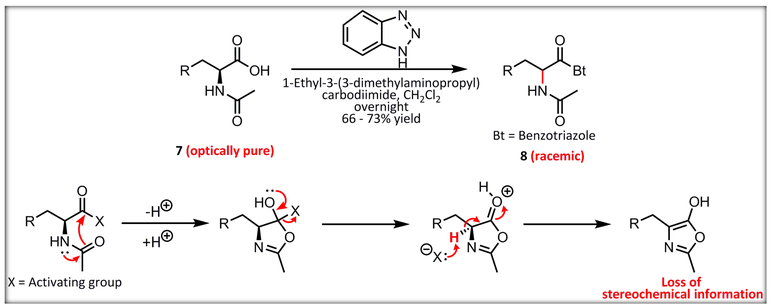
Reber, K.; Tilley, S.; Sorensen, E. *Chem. Soc. Rev*. **2009**, *38*, 3022-34.

Mechanism of Dioxinone Alcoholysis and Base-Mediated Cyclization



Reber, K.; Tilley, S.; Sorensen, E. *Chem. Soc. Rev*. **2009**, *38*, 3022-34.

Further Work: A Remedy for Epimerization



Upon synthesis of the natural products, their spectra and optical rotations were compared to those from the isolation paper. The NMR spectra matched those reported, but the optical rotations of the synthetic compounds were $[\alpha]_D$ 0 (as compared to the expected $[\alpha]_D$ −13, −39, −21, and −16 for **1**, **2**, **3**, and **4** respectively). Literature reports show that under coupling conditions, *N*-acetyl amino acids can cyclize to the corresponding azalactone, which can then tautomerize to erase any stereochemical integrity. Efforts are now focused on completing the synthesis *via* the same route, but starting with the *N*-Boc (*tert*-butyloxycarbonyl*)* amino acid and swapping the protecting group for an acetyl group at the final stage of the synthesis.

Du Vigneaud, V.; Meyer, C.E. *J. Biol. Chem*. **1932**, *99,* 143-151.

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