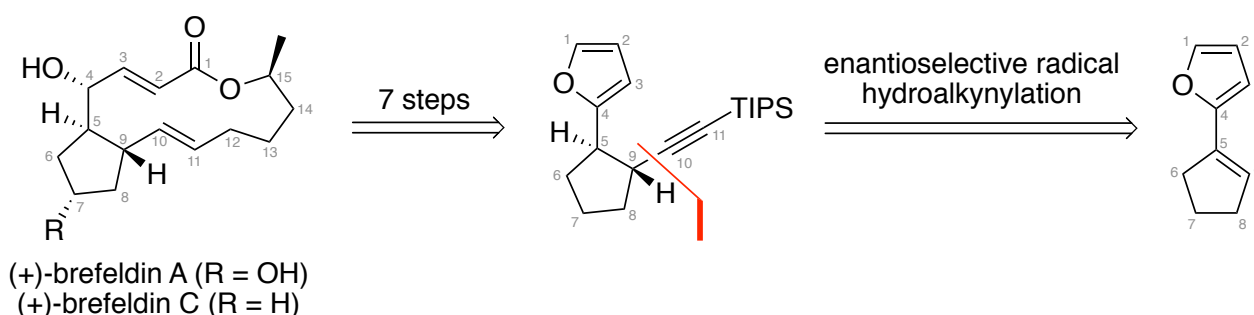


## A Short Synthesis of (+)-Brefeldin C via Enantioselective Radical Hydroalkynylation

Lars Gnägi, Severin Martz, Daniel Meyer, Robin Schärer, and Philippe Renaud\*  
 Department of Chemistry and Biochemistry, University of Bern, 3012 Bern, Switzerland  
 Lars.gnaegi@dcb.unibe.ch

Brefeldin C is a 13-membered macrocyclic natural product isolated and characterized in 1963. [1] Along with its analogue Brefeldin A, the two molecules have received much attention over the past decades due to their biological properties and served as lead structures for drug development. We herein report a very concise total synthesis of the lesser studied Brefeldin C applying a method for hydrofunctionalization of trisubstituted nonactivated alkenes recently reported from our group. [2]



This approach is based on an unprecedented enantioselective radical hydroalkynylation process to introduce the two cyclopentane stereocenters at C5 and C9 in a single step. The use of a furan substituent allows to achieve a high *trans* diastereoselectivity during the radical process and it contains the four carbon atoms C1–C4 of the natural product in an oxidation state closely related to the one of the target molecule. The eight step synthesis requires six product purifications and it provides (+)-brefeldin C in 18% overall yield.

- [1] Härrri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, C. *Helv. Chim. Acta* **1963**, *46* (4), 1235–1243  
 [2] Meyer, D.; Renaud, P. *Angew. Chem. Int. Ed.* **2017**, *56* (36), 10858–10861