Divergent Synthesis of Bioactive Dithiodiketopiperazine Natural Products Based on a Double C(sp3)−H Activation Strategy

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4605143
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Year 2020
Title Divergent Synthesis of Bioactive Dithiodiketopiperazine Natural Products Based on a Double C(sp3)−H Activation Strategy
Journal Chemistry - A European Journal
Volume 26
This article provides a detailed report of our efforts to synthesize the dithiodiketopiperazine (DTP) natural products (−)epicoccin G and (−)rostratin A using a double C(sp3)−H activation strategy. The strategy's viability was first established on a model system lacking the C8/C8' alcohols. Then, an efficient stereoselective route including an organocatalytic epoxidation was secured to access a key bistriflate substrate. This bistriflate served as the functional handles for the key transformation of the synthesis: a double C(sp3)−H activation. The successful double activation opened access to a common intermediate for both natural products in high overall yield and on a multigram scale. After several unsuccessful attempts, this intermediate was efficiently converted to (−)epicoccin G and to the more challenging (−)rostratin A via suitable oxidation/reduction and protecting group sequences, and via a final sulfuration that occurred in good yield and high diastereoselectivity. These efforts culminated in the synthesis of (−)epicoccin G and (−)rostratin A in high overall yields (19.6 % over 14 steps and 12.7 % over 17 steps, respectively), with the latter being obtained on a 500mg scale. Toxicity assessments of these natural products and several analogues (including the newly synthesized epicoccin K) in the leukemia cell line K562 confirmed the importance of the disulfide bridge for activity and identified dianhydrorostratin A as a 20x more potent analogue.
Publisher Wiley
ISSN/ISBN 0947-6539 ; 1521-3765
URL https://chemistry-europe.onlinelibrary.wiley.com/doi/epdf/10.1002/chem.2020 03683
edoc-URL https://edoc.unibas.ch/78909/
Full Text on edoc Restricted;
Digital Object Identifier DOI 10.1002/chem.202003683
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/32852800