An Enantioselective Total Synthesis of (+)-Duocarmycin SA
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**Abstract:** An efficient, concise enantioselective total synthesis of the potent antitumor antibiotic (+)-duocarmycin SA is described. The invented route is based on a disconnection strategy that was devised to facilitate rapid and efficient synthesis of key core compounds to enable preclinical structure-activity relationship investigations. The key tricycle core was constructed with a highly enantioselective indole hydrogenation to set the stereochemistry and a vicarious nucleophilic substitution/cyclization sequence to effectively forge a final indole ring. Additionally, development of a new, stable, sulfonamide protecting group, capable of mild chemoselective cleavage greatly enhanced sequence yield and throughput. An understanding of key reaction parameters ensured a robust, reproducible sequence easily executable on decagram scales to this highly promising class of compounds.

Synthesis of Novel Aza-aromatic Curcuminoids with Improved Biological Activities towards Various Cancer Cell Lines
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**Abstract:** Curcumin, a natural compound extracted from the rhizomes of *Curcuma longa*, displays pronounced anticancer properties but lacks good bioavailability and stability. In a previous study, we initiated structure modification of the curcumin scaffold by imination of the labile β-diketone moiety to produce novel β-enaminone derivatives. These compounds showed promising properties for elaborate follow-up studies. In this work, we focused on another class of nitrogen-containing curcuminoids with a similar objective: to address the bioavailability and stability issues and to improve the biological activity of curcumin. This paper thus reports on the synthesis of new pyridine-, indole- and pyrrole-based curcumin analogues (aza-aromatic curcuminoids) and discusses their water solubility, antioxidant activity and anti-proliferative properties. In addition, multivariate statistics, including hierarchical clustering analysis and principal component analysis, was performed on a broad set of nitrogen-containing curcuminoids. Compared to their respective mother structures, i.e. curcumin and bisdemethoxycurcumin, all compounds, and especially the pyridin-3-yl β-enaminone analogues, showed a better water solubility profile. Interestingly, the pyridine-, indole- and pyrrole-based curcumin derivatives demonstrated improved biological effects in terms of mitochondrial activity impairment and protein content, in addition to a comparable or decreased antioxidant property. Overall, the biologically active *N*-alkyl β-enaminone aza-aromatic curcuminoids were shown to offer a desirable balance between good solubility and significant bioactivity.
Absolute Configuration and Pharmacology of the Poison Frog Alkaloid Phantasmidine
Richard W. Fitch, Barry B. Snider, Quan Zhou, Bruce M. Foxman, Anshul A. Pandya, Jerrel L. Yakel, Thao T. Olson, Nour Al-Muhtasib, Yingxian Xiao, Kevin D. Welch, Kip E. Panter

Abstract: Phantasmidine, a rigid congener of the well-known nicotinic acetylcholine receptor agonist epibatidine, is found in the same species of poison frog (*Epipedobates anthonyi*). Natural phantasmidine was found to be a 4:1 scalemic mixture, enriched in the (2aR,4aS,9aS) enantiomer by chiral-phase LC-MS comparison to the synthetic enantiomers whose absolute configurations were previously established by Mosher’s amide analysis. The major enantiomer has the opposite S configuration at the benzylic carbon to natural epibatidine, whose benzylic carbon is R. Pharmacological characterization of the synthetic racemate and separated enantiomers established that phantasmidine is ~10-fold less potent than epibatidine, but ~100-fold more potent than nicotine in most receptors tested. Unlike epibatidine, phantasmidine is sharply enantioselective in its activity and the major natural enantiomer whose benzylic carbon has the 4aS configuration is more active. The stereoselective pharmacology of phantasmidine is ascribed to its rigid and asymmetric shape as compared to the nearly symmetric conformations previously suggested for epibatidine enantiomers. While phantasmidine itself is too toxic for direct therapeutic use, we believe it is a useful platform for the development of potent and selective nicotinic agonists which may have value as pharmacological tools.

Total Synthesis of the Neoclerodane Diterpene Salvinorin A via an Intramolecular Diels–Alder Strategy
Yuzhou Wang and Peter Metz
*Org. Lett.* **2018**, *20*, 3418–3421. DOI: 10.1021/acs.orglett.8b01357

Abstract: A concise total synthesis of the neoclerodane diterpene salvinorin A from 3-furaldehyde is reported using two highly diastereoselective intramolecular Diels–Alder reactions (IMDA) as the key transformations.

Enantioselective Total Synthesis of Natural Isoflavans: Asymmetric Transfer Hydrogenation/Deoxygenation of Isoflavanones with Dynamic Kinetic Resolution
Anton Keßberg, Tilo Lübken, Peter Metz
*Org. Lett.* **2018**, *20*, 3006–3009. DOI: 10.1021/acs.orglett.8b01034

Abstract: A concise and highly enantioselective synthesis of structurally diverse isoflavans from a single chromone is described. The key transformation is a single-step conversion of racemic isoflavonones into virtually enantiopure isoflavans by domino asymmetric transfer hydrogenation/deoxygenation with dynamic kinetic resolution.
(Poly)cationic $\lambda^3$-Iodane-Mediated Oxidative Ring Expansion of Secondary Alcohols

Jennifer C. Walters, Anthony F. Tierno, Aimee H. Dubin, Sarah E. Wengryniuk  
DOI: 10.1002/ejoc.201800118

**Abstract:** Herein, a simplified approach to the synthesis of medium-ring ethers through the electrophilic activation of secondary alcohols with (poly)cationic $\lambda^3$-iodanes (N-HVIs) is reported. Excellent levels of selectivity are achieved for C–O bond migration over established $\alpha$-elimination pathways, enabled by the unique reactivity of a novel 2-OMe-pyridine-ligated N-HVI. The resulting hexafluoroisopropanol (HFIP) acetals are readily derivatized with a range of nucleophiles, providing a versatile functional handle for subsequent manipulations. The utility of this methodology for late-stage natural product derivatization was also demonstrated, providing a new tool for diversity-oriented synthesis and complexity-to-diversity (CTD) efforts. Preliminary mechanistic investigations reveal a strong effect of alcohol conformation on the reactive pathway, thus providing a predictive power in the application of this approach to complex molecule synthesis.

Photochemically Induced Intramolecular Radical Cyclization Reactions with Imines

Corentin Lefebvre, Clément Michelin, Thomas Martzel, Vaneck Djou’ou Mvondo, Véronique Bulach, Manabu Abe, Norbert Hoffmann  
DOI: 10.1021/acs.joc.7b02810

**Abstract:** The photochemically induced intramolecular hydrogen abstraction or hydrogen atom transfer in cyclic imines 8a,b followed by a cyclization is investigated. Two types of products are observed, one resulting from the formation of a C–C bond, the other from the formation of a C–N bond. A computational study reveals that hydrogen is exclusively transferred to the imine nitrogen leading to a triplet diradical intermediate. After intersystem crossing, the resulting zwitterionic intermediate undergoes cyclization leading to the final product.

Formal [4+2] Cycloaddition of Imines with Alkoxyisocoumarins

Claire L. Jarvis, Neyra M. Jemal, Spencer Knapp, Daniel Seidel  
DOI: 10.1039/C8OB01015C

**Abstract:** A new preparation of $\delta$-lactams is reported. In the presence of a Lewis acid promoter, alkoxyisocoumarins engage a range of $N$-aryl and $N$-alkyl imines to form $\delta$-lactams with a pendent carboalkoxy substituent. A sulfonamide-thiourea catalyst enables the synthesis of these products in moderate to good enantioselectivities.
Synthesis, Biological Investigation, and Structural Revision of Sielboldianin A
Renate Kristianslund, Marius Aursnes, Jørn E. Tungen, Carl H. Görbitz and Trond V. Hansen


Abstract: The total synthesis of the proposed structure of the tetrahydrofuran derived sesquiterpenoid (+)-sielboldianin A (1) has been reported. Moreover, revision of the absolute configuration of this natural product was performed based on X-ray analysis of the δ-lactone 2, specific rotation values and NOESY data of final product and intermediates. Biological studies revealed that the enantiomer of 1 exhibited potent antioxidant effects without any cytotoxic activity (IC₅₀ > 50 µM). The total synthesis was based on a recently reported organocatalyzed enantioselective bromolactonization protocol that yields synthetically useful heterocycles such as 2.

Palladium-Catalyzed Seven-Membered Silacycle Construction: 1,7-Enyne Hydroxycyclization To Give a Benzosilepine Skeleton

Kohei Takamoto, Shohei Yoshioka, Hiromichi Fujioka, Mitsuhiro Arisawa

*Org. Lett.* **2018**, *20*, 1773–1776. DOI: 10.1021/acs.orglett.8b00271

Abstract: A palladium-catalyzed hydroxycyclization reaction of 1,7-ynes to afford seven-membered silacycles (1H-benz[b]-silepine skeletons) is developed. This is the first example of both seven-membered ring construction from enynes using a palladium catalyst and hydroxycyclization of enynes to give seven-membered silacycles.

Photoswitching Behavior of 5-Phenylazopyrimidines: In Situ Irradiation NMR and Optical Spectroscopy Combined with Theoretical Methods

Lucie Čechová, Jonas Kind, Martin Dračinský, Juraj Filo, Zlatko Janeba, Christina M. Thiele, Marek Čigáň, Eliška Procházková


Abstract: The photoswitching behavior of 5-phenylazopyrimidines was investigated by optical methods and NMR spectroscopy with in situ irradiation sustained by mathematical modelling and DFT calculations. Irradiation of various compounds with electron donating groups on the pyrimidine ring and substituents with electron withdrawing as well as electron donating substituent in the para-position of the phenyl ring were examined. All compounds could successfully be converted to the cis isomer; this isomerization and the subsequent thermal fading was studied. Switching cycles can be repeated without signs of photodegradation for most of the compounds, which makes them adepts to molecular photoswitches. Interestingly, the chloro and cyano derivatives can be switched without UV light, which makes them Vis (π→π*)-Vis (n→π*) photoswitches. *Trans*-to-*cis* photoisomerization quantum yields for π→π* and n→π* excitation are surprisingly equal, which indicates the blocking of the inversion pathway following π→π* excitation. Contrary to the photosomerization mechanism, DFT computations suggest the inversion mechanism for the thermal *cis*-to-*trans* isomerization of 5-phenylazopyrimidines.