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Divergent Total Syntheses of Isobatzellines A/B and Batzelline A

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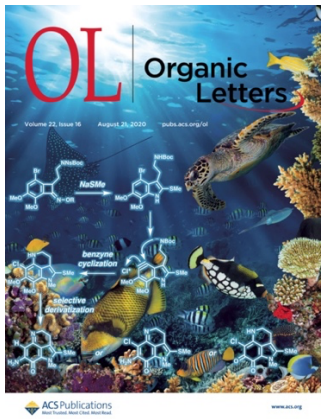
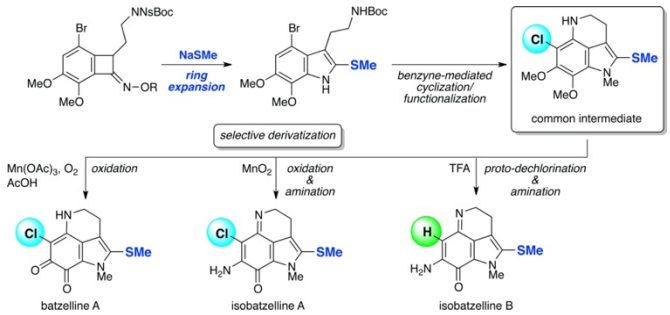
Org. Lett. **2020**, *22*, 6239–6243. **DOI:** 10.1021/acs.orglett.0c01894



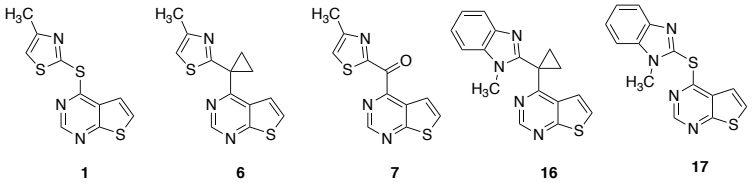


Abstract: Divergent total syntheses of isobatzellines A/B and batzelline A were accomplished. A highly substituted pyrrolidine-fused common indole intermediate bearing C-2 methylthio and C-5 chloro groups was rapidly constructed via ring expansion of benzocyclobutenone oxime sulfonate with NaSMe and a benzyne-mediated cyclization/functionalization protocol as the key steps. The total synthesis of isobatzelline B was achieved via iminoquinone formation by the redox-neutral TFA-promoted C-5 proto-dechlorination of the common intermediate. Selective derivatization to isobatzelline A and batzelline A were completed in a divergent manner via manganese-oxidant-dependent oxidation of piperidine-fused 2-methylthioindole to the benzoquinone or iminoquinone derivative.

Evaluation of 1,1-Cyclopropylidene as a Thioether Isostere in the 4-Thio-thienopyrimidine (TTP) Series of Antimalarials

Robert D. Barrows, Jared T. Hammill, Michael C. Tran, Mofolusho O. Falade, Amy L. Rice, Christopher W. Davis, Thomas J. Emge, Paul R. Rablen, R. Kiplin Guy, Spencer Knapp*
(spencer.knapp@rutgers.edu)

Bioorg. & Med. Chem. **2020**, *28*, 115758 (1–8). **DOI:** 10.1016/j.bmc.2020.115758



Abstract: The 4-(heteroarylthio)thieno[2,3-*d*]pyrimidine (TTP) series of antimalarials, represented by **1** and **17**, potently inhibit proliferation of the 3D7 strain of *P. falciparum* (EC_{50} 70–100 nM), but suffer from oxidative metabolism. The 1,1-cyclopropylidene isosteres **6** and **16** were designed to obviate this drawback. They were prepared by a short route that features a combined Peterson methylenation/cyclopropanation transformation of, e.g., ketone **7**. Isosteres **6** and **16** possess significantly attenuated antimalarial potency relative to parents **1** and **17**. This outcome can be rationalized based on the increased out-of-plane steric demands of the latter two. In support of this hypothesis, the relatively flat ketone **7** retains some of the potency of **1**, even though it appears to be a comparatively inferior mimic with respect to electronics and bond lengths and angles. We also demonstrate crystallographically and computationally an apparent increase in the strength of the intramolecular sulfur hole interaction of **1** upon protonation.

Total Synthesis of (–)-Sigillin A: A Polychlorinated and Polyoxygenated Natural Product

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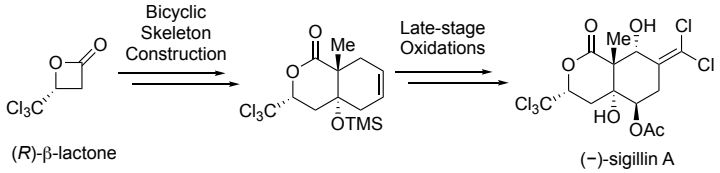
Org. Lett. **2020**, *22*, 7721–7724. **DOI:** 10.1021/acs.orglett.0c02930



Abstract: The total synthesis of (–)-sigillin A, a highly chlorinated and oxygenated octahydroisocoumarin, is described herein. A hexahydroisocoumarin skeleton was constructed from (R)-4-(trichloromethyl)oxetan-2-one in seven steps. Its unique manganese oxidation provided an enone as the key intermediate of sigillin A. Stereoselective installation of two hydroxy groups and formation of *gem*-dichloroalkene from the corresponding ketone led to the total synthesis of (–)- sigillin A in a total of 16 steps.

New Syntheses of Haloketo Acid Methyl Esters and Their Transformation to Halolactones by Reductive Cyclization

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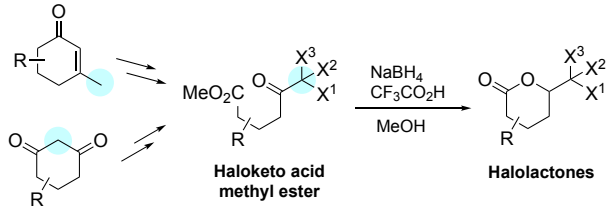
Russ. Chem. Bull., Int. Ed. **2020**, *69*, 1804–1810. **DOI:** 10.1007/s11172-020-2965-6



Abstract: A new method for haloketo acid methyl ester synthesis is reported on the basis of the ring-opening of cyclic α,β-unsaturated ketones followed by halogenation under mild conditions. Di- and tri-haloketo acid methyl esters are conveniently synthesized via the hydrolytic ring-opening reaction through this method. Halolactones can be readily obtained from these haloketo acid methyl esters by reductive cyclization employing $NaBH_4$ and trifluoroacetic acid. Derivatizations of this obtained halolactone utilizing the exo-halomethylene moiety were also demonstrated.

Pd-Catalyzed Cyanoselenylation of Internal Alkynes: Access to Tetrasubstituted Selenoenol Ethers

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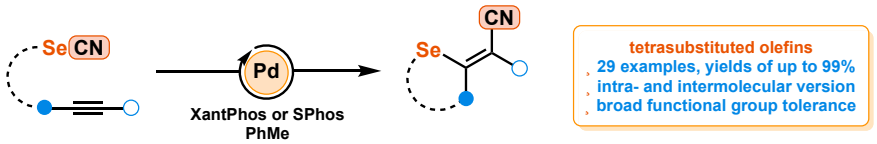
(d.werz@tu-braunschweig.de)

Org. Lett. **2020**, *22*, 5025–5029. **DOI:** 10.1021/acs.orglett.0c01582



Abstract: The intra- and intermolecular synthesis of selenium-substituted acyclic and heterocyclic acrylonitrile derivatives is presented. The 1,2-difunctionalization of several internal alkynes substituted not only by aliphatic and aromatic residues but also by heteroelements is realized by the Pd-catalyzed activation of aromatic and aliphatic selenocyanates. A high functional group tolerance allows straightforward access to a broad scope of tetrasubstituted olefins. X-ray studies of some products reveal noncovalent chalcogen–chalcogen interactions between oxygen and selenium

Electron-Rich Phenothiazine Congeners and Beyond: Synthesis and Electronic Properties of Isomeric Dithieno[1,4]thiazines

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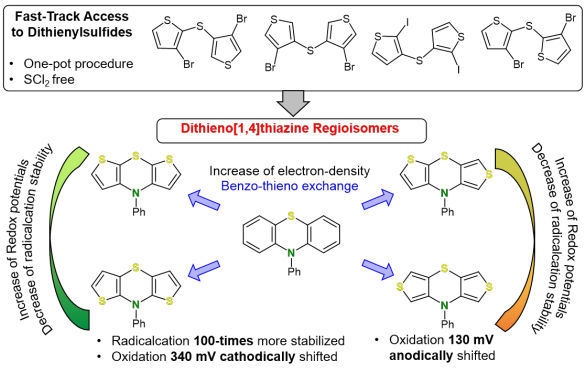
Chem. Eur. J. **2020**, *26*, 12111–12118. **DOI:** 10.1002/chem.202000137



Abstract: A series of isomeric dithieno[1,4]thiazines is accessible via intermolecular-intramolecular Buchwald–Hartwig amination starting from dihalodithienyl sulfides. The electronic properties of dithieno[1,4]thiazine isomers differ conspicuously over a broad range depending on the thiophene- thiazine anellation: a large cathodic (340 mV) or an anodic shift (130 mV) of the redox potentials relative to corresponding phenothiazines is possible. Structure-property relationships of the dithieno[1,4]thiazine constitution derived from DFT-calculations and cyclic voltammetry not only reveal increased electron density but also different delocalization of the radical cations that determines the electrochemical properties significantly. In addition, photophysical properties (absorption and emission) qualify dithieno[1,4]thiazines as promising substitutes of phenothiazine and beyond due to increased tunable electron richness.

Widely Electronically Tunable 2,6-Disubstituted Dithieno[1,4]thiazines–Electron-Rich Fluorophores Up to Intense NIR Emission

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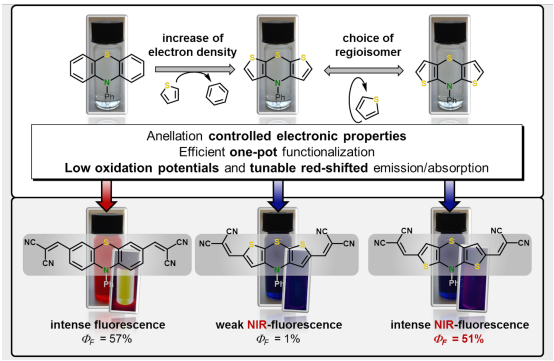
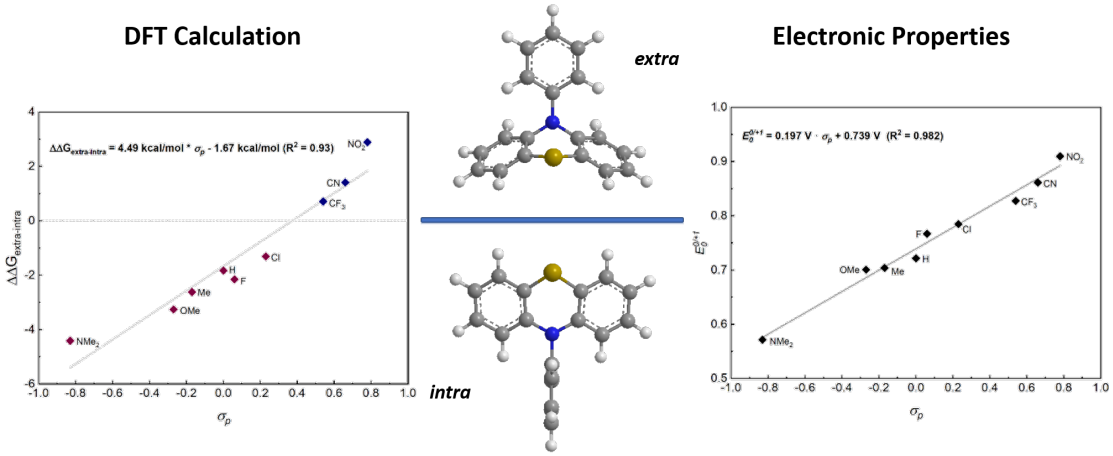
Chem. Eur. J. **2020**, *26*, 12978–12986. **DOI:** 10.1002/chem.202000859



Abstract: 2,6-Difunctionalized dithieno[1,4]thiazines were efficiently synthesized by (pseudo)five- or (pseudo)three-component one-pot processes based on lithiation-electrophilic trapping sequences. As supported by structure-property relationships, the thiophene anellation mode predominantly controls the photophysical and electrochemical properties and the electronic structures (as obtained by DFT calculations). From molecular geometries and redox potentials to fluorescence quantum yields in solution, the interaction of the dithieno[1,4]thiazine-core with the substituents causes striking differences within the series of regioisomers. Most interestingly, strong acceptors introduced in *anti-anti* dithieno[1,4]thiazines nearly induce a planarization of the ground-state geometry and a highly intense NIR fluorescence (F_F = 0.52), whereas an equally substituted *syn-syn* dithieno[1,4]thiazine exhibits a much stronger folded molecular structure and fluoresces poorly (F_F = 0.01). In essence, electrochemical and photophysical properties of dithieno[1,4]thiazines can be tuned widely and outscore the compared phenothiazine with cathodically shifted oxidation potentials and redshifted and more intense absorption bands.

The Interplay of Conformations and Electronic Properties in *N*-Aryl Phenothiazines

Laura Mayer, Lars May, and Thomas J. J. Müller* (thomasjj.mueller@hhu.de)
Org. Chem. Front. **2020**, *7*, 1206–1217. **DOI:** 10.1039/d0qo00182a



Abstract: A broad series of electronically diverse *N*-aryl substituted phenothiazines was readily synthesized by Buchwald–Hartwig amination of 10*H*-phenothiazine and aryl bromides with variable electronic nature in moderate to excellent yields (61–97%). This library of *N*-aryl phenothiazines was studied with respect to their electronic properties by absorption and emission spectroscopy, cyclic voltammetry, and quantum chemical calculations to elucidate the electronic structure. Furthermore, DFT calculations allow assigning substituent dependent dominance of *intra* or *extra* conformations by virtue of the electronic nature of the remote *N*-aryl substituent. Electron releasing substituents favor *intra* and electron withdrawing substituents favor *extra* conformations in the electronic ground state. The experimentally determined oxidation potentials as well as the calculated molecular geometries strongly correlate with Hammett σ_p parameters of the remote *para*-substituents. Therefore, transmission of the substituent effect operates by both resonance and inductive mechanisms. This linear correlation equation can be applied to assign new sigma parameters σ_p for several substituents on the basis of the experimentally determined oxidation potentials.

Synthesis of Novel Chiral Spiroisoxazolidine-β-Lactams from 6-Alkylidenepenicillanates: A 1,3-Dipolar Cycloaddition Approach

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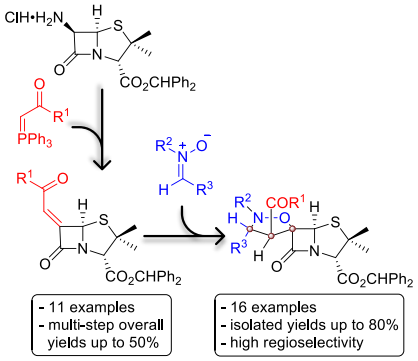
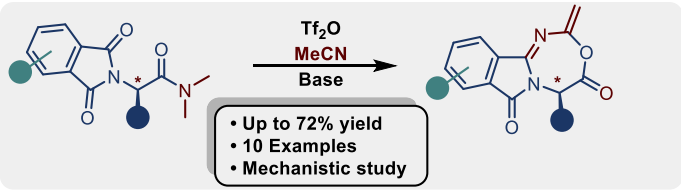
Eur. J. Org. Chem. **2020**, 6259–6269. **DOI:** 10.1002/ejoc.202001085



Abstract: The synthesis of a library of 6-alkylidene-β-lactams, derived from 6-aminopenicillanic acid is reported. The 1,3-dipolar cycloaddition of these 6-alkylidenepenicillanates with nitrones was explored as an approach to synthesize novel chiral spiroisoxazolidine-β-lactams. Quantum chemical calculations, at the DFT level of theory, were carried out to elucidate the 3D structure of the synthesized compounds. The reported methodology, which involves the generation of three new consecutive stereogenic centers, proved to be regio- and stereoselective, leading to novel chiral spiroisoxazolidine-penicillanates efficiently.

A Novel Class of 7-Membered Heterocyclic Compounds

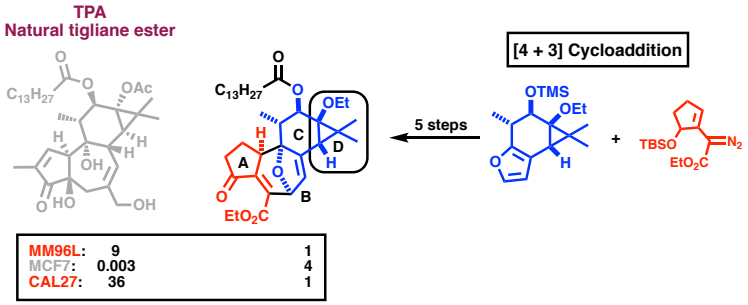
Adriano Bauer, Eszter Borsos, and Nuno Maulide* (nuno.maulide@univie.ac.at)
Eur. J. Org. Chem. **2020**, 3971–3974. **DOI:** 10.1002.ejoc.202000363



Abstract: This work describes the serendipitously discovered synthesis of a formerly inaccessible class of heterocyclic compounds. The reaction relies on α-phtalimido-amides, which are readily prepared from amino acids in 2 simple reaction steps. Under amide activation conditions in which classical keteniminium ions are not formed, the nitrile solvent is incorporated into the new fused 7-membered ring system. Due to the absence of a keteniminium intermediate, the stereogenic information in the α-position is fully retained.

Synthetic Tigliane Intermediates Engage Thiols to Induce Potent Cell Line Selective Anti-Cancer Activity

Sharon Chow, Tanja Krainz, Christian J. Bettencourt, Natasa Broit, Blake Ferguson, Mingzhao Zhu, Kenneth G. Hull, Gregory K. Pierens, Paul V. Bernhardt, Peter G. Parsons, Daniel Romo, Glen M. Boyle, and Craig M. Williams* (c.williams3@uq.edu.au)
Chem. Eur. J. **2020**, *26*, 13372–13377. **DOI:** 10.1002/chem.202003221



Abstract: The tigliane ring system (e.g. phorbol and TPA) is widely known to display numerous potent biological activity profiles, and thus is utilized as a mainstream biochemical tool. Historically, these systems are regarded as tumor promotors through PKC activation, although in more recent times newly reported natural derivatives have demonstrated anti-tumorigenesis. Given the limited number of synthetic investigations toward skeletal modification for these complex and bioactive natural products, it seemed useful that non-natural systems be constructed for a better understanding of the tigliane pharmacophore. Presented herein is the concise *de novo* construction of a number of highly functionalized non-natural D-ring inverted phorbol esters, which were evaluated using a range of cancer cell lines. The biological results reinforce the theory that subtle changes in structure can have dramatic effects on potency. Interestingly, the non-natural derivatives outperformed natural phorbols in the MM96L and CAL27 cancer cell lines, but not MCF7 (PKC sensitive cell line). This observation strongly suggested an alternate mode of action involving thiol addition, supported via glutathione addition, and NF-κB reporter activity.