International Society of Heterocyclic Chemistry
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Issue 9; February 2017

The ISHC Bulletin

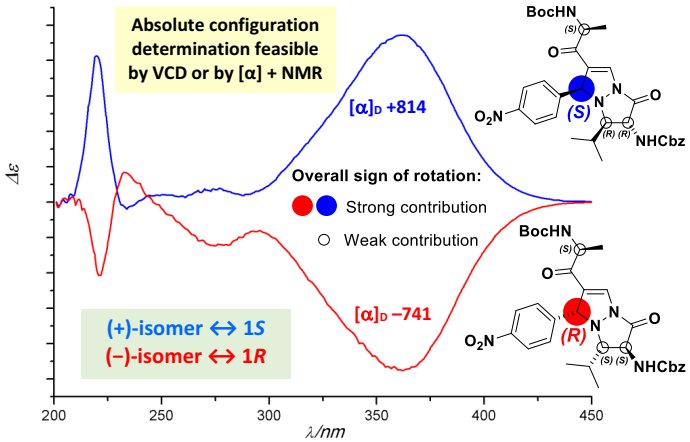
Recent Publications of ISHC Members

Issue 9; February 2017

Absolute Configuration Determination of 2,3-Dihydro-1*H*,5*H*-pyrazolo-[1,2-*a*]pyrazoles using Chiroptical Methods at Different Wavelengths.

Eva Pušavec Kirar, Uroš Grošelj, Amalija Golobič, Franc Požgan, Stefan Pusch, Carina Weber, Lars Andernach, Bogdan Štefane, Till Opatz, and Jurij Svete

J. Org. Chem. **2016**, *81*, 11802−11812. **DOI:** 10.1021/acs.joc.6b02270

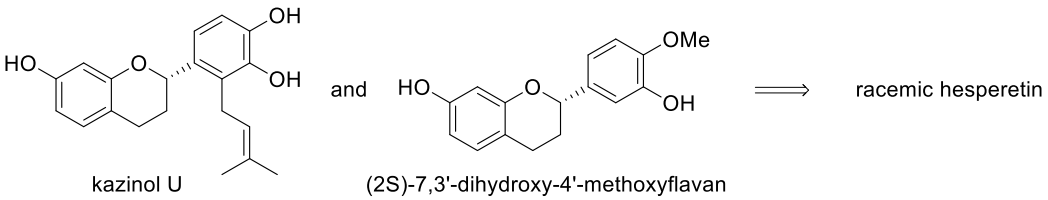


Abstract: A correlation between the absolute configuration and chiroptical properties of nonracemic 1,6,7-trisubstituted 2,3-dihydro-1H,5H-pyrazolo[1,2-*a*]pyrazoles was studied. A series of 16 novel representatives were prepared by Cu-catalyzed [3 + 2] cycloadditions of racemic (*Z*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ides to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate, and their structures were determined by NMR, VCD, ECD, and X-ray diffraction. A clear correlation between the sign of specific rotation and configuration at position C(1) allows for easy determination of the absolute configuration of 1,6,7-trisubstituted 2,3-dihydro-1H,5H-pyrazolo[1,2-*a*]pyrazoles by ECD and NMR. While VCD, requiring milligram quantities, allowed the determination of the correct relative and absolute configuration without additional information from other methods, the stereochemical analysis by ECD required knowledge of the relative configuration derived from NMR at a comparable computational level.

Enantioselective Synthesis of 2′- and 3′-Substituted Natural Flavans by Domino Asymmetric Transfer Hydrogenation/Deoxygenation

Anton Keßberg and Peter Metz

Org. Lett. **2016**, *18*, 6500–6503. **DOI:** 10.1021/acs.orglett.6b03459

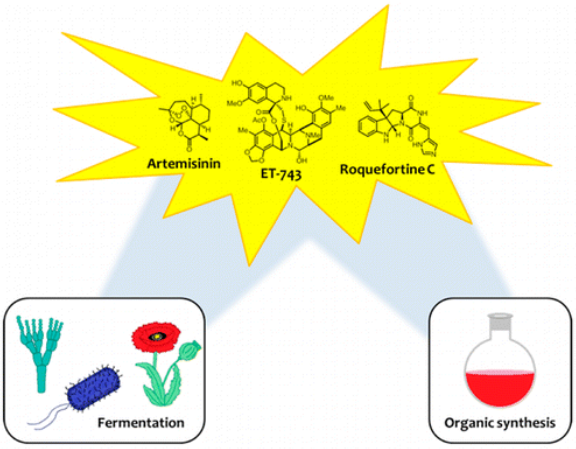


Abstract: A concise and highly enantioselective synthesis of the natural flavans kazinol U and (2*S*)-7,3′-dihydroxy-4′-methoxyflavan is reported for the first time. The key transformation is a single-step conversion of a racemic flavanone to a flavan by means of an asymmetric transfer hydrogenation / deoxygenation cascade with kinetic resolution.

Joining Forces: Fermentation and Organic Synthesis for the Production of Complex Heterocycles

Claire M. Gober and Madeleine M. Joullié*

J. Org. Chem. **2016**, *81*, 10136–10144. **DOI:** 10.1021/acs.joc.6b01308



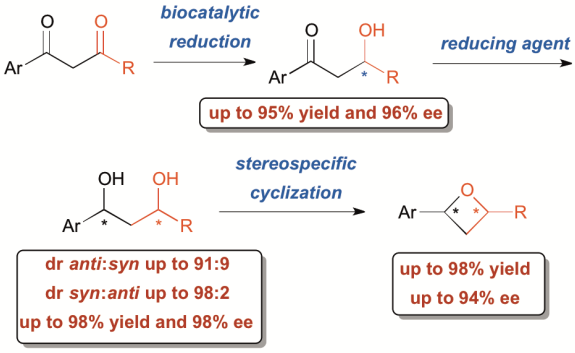
Abstract: Commercial application of many promising heterocyclic natural products is limited by their natural abundance. While organic synthesis provides access to many natural products, total synthesis of numerous complex molecules is not economically feasible. In recent years, the combination of fermentation and organic synthesis has provided a new route for the production of complex heterocycles that are inaccessible by typical synthetic methods. This JOCSynopsis will review examples of how this union of disciplines has overcome obstacles in both academia and industry.

**Special Issue dedicated to Heterocyclic Chemistry*

Asymmetric Chemoenzymatic Synthesis of 1,3-Diols and 2,4-Disubstituted Aryloxetanes by Using Whole Cell Biocatalysts

Paola Vitale, Filippo Maria Perna, Gennaro Agrimi, Antonio Scilimati, Antonio Salomone, Cosimo Cardellicchio and Vito Capriati

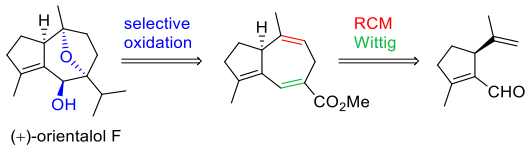
Org. Biomol. Chem. **2016**, *14*, 11438–11445. **DOI:** 10.1039/c6ob02320g



Abstract: Regio- and stereoselective reduction of substituted 1,3-aryldiketones, investigated in the presence of different whole cell microorganisms, was found to afford β-hydroxyketones or 1,3-diols in very good yields (up to 95%) and enantiomeric excesses (up to 96%). The enantiomerically enriched aldols, obtained with opposite stereo-preference by baker's yeast and *Lactobacillus reuteri* DSM 20016 bioreduction, could then be diastereoselectively transformed into optically active *syn*- or *anti*-1,3-diols by a careful choice of the chemical reducing agent (diastereomeric ratio up to 98:2). The latter, in turn, were stereospecifically cyclized into the corresponding oxetanes in 43–98% yields and in up to 94% ee, thereby giving a diverse selection of stereodefined 2,4-disubstituted aryloxetanes.

A Metathesis Route to (+)-Orientalol F, a Guaiane Sesquiterpene from *Alisma Orientalis*

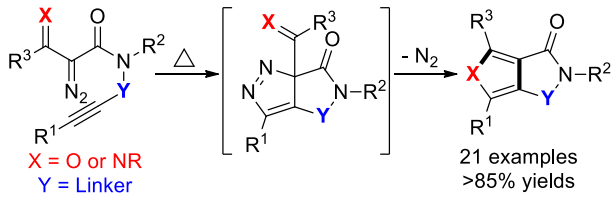
Martin Zahel, Yuzhou Wang, Anne Jäger, and Peter Metz
Eur. J. Org. Chem. **2016**, 5881–5886. **DOI:** 10.1002/ejoc.201601197



Abstract: The synthesis of (+)-orientalol F (**1**) started with aldehyde **6**, which is available from (*R*)-limonene in two steps. Wittig reaction of **6** with unsaturated ylide **7** to give a tetraene, and subsequent ring-closing metathesis yielded hydroazulene **4**, selective epoxidation of which gave epoxy ester **3**. After generation of the requisite isopropyl unit and regioselective reductive epoxide opening, the derived dienol **2** was used for the installation of the oxygen bridge through intramolecular oxymercuration followed by oxidative demercuration. The resulting allylic alcohol epimers **15** and **16** were readily converted into the target natural product **1** by oxidation/reduction sequences.

Thermally Induced [3 + 2] Cycloaddition of Alkynyl-Tethered Diazoamides: Synthetic and Mechanistic Insights

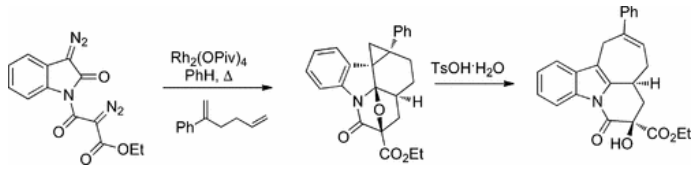
Cheng Zhang, Jingjing Huang, Lihua Qiu, and Xinfang Xu
Org. Lett. **2016**, *18*, 6208−6211. **DOI:** 10.1021/acs.orglett.6b03288



Abstract: A general and unpresented thermally induced formal [3+2]-cycloaddition has been developed, which provides a general access to the fused lactam derivatives in high to excellent yields with broad substrate scope. In comparison to the reported metal-catalyzed carbene/alkynyl metathesis, this is the only example in this area under catalyst-free conditions with excellent selectivity. Mechanistic study indicates that the 3*H*-pyrazole is the key intermediate in this cascade reaction, which is confirmed spectroscopically for the first time.

Polycyclic Ring Formation Using *Bis*-Diazolactams for Cascade Stitching

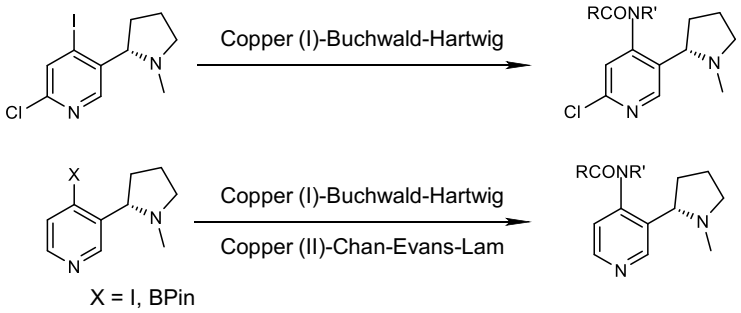
Sara A. Bonderoff and Albert Padwa
J. Org. Chem. **2017**, *82*, 642–651. **DOI:** 10.1021/acs.joc.6b02663



Abstract: The chemoselective reaction of donor/acceptor (D/A) and acceptor/acceptor (A/A) diazo moieties in the same molecule was examined using 3-diazo-1-(ethyl 2-diazomalonyl)indolin-2-one under rhodium(II) catalysis. The metallo carbenoid derived from the D/A diazo group is preferentially formed and undergoes selective CH, NH and OH insertion reactions, cyclopropanation, cyclopropenation, sulfur ylide formation/2,3-sigmatropic rearrangement, as well as nitrogen ylide formation followed by azetidine ring expansion. The initial reaction can be paired with a subsequent tandem cascade sequence involving dipole formation/cycloaddition in either an intra- or intermolecular sense to generate polycyclic *N*-heterocycles in one pot, with the formation up to three new rings in a single operation. Excellent diastereoselectivity was observed in the intramolecular cycloaddition reaction producing 5 to 7-membered rings.

Synthesis of C-4 Substituted Amido Nicotine Derivatives via Copper (I)- and (II)-Catalyzed Cross-Coupling Reactions

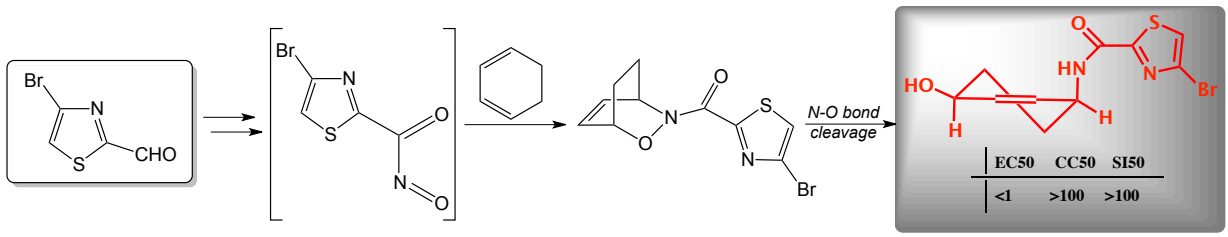
Jiancheng Zhu, Monica F. Enamorado and Daniel L. Comins
J. Org. Chem. **2016**, *81*, 11529-11534. **DOI:** 10.1021/acs.joc.6b02319



Abstract: The syntheses of seven novel amido nicotine derivatives from (*S*)-nicotine are presented. (*S*)-Nicotine and (*S*)-6-chloronicotine derivatives were cross-coupled with the corresponding amides at the C-4 position of the pyridine ring via copper (I)-mediated reactions. Derivatives were also obtained via copper(II)-mediated reactions from (*S*)-nicotine containing a C-4 boronic acid pinacol ester group. The optimization of reaction conditions for both routes provided a useful method for preparing C-4 amide-containing nicotine analogs.

Pericyclic Reactions for Antivirals: Synthesis of 4-Bromo-N-[(1R*,4S*)-4-hydroxy-2-cyclohexen-1-yl]-2-thiazolecarboxamide

Dalya Al-Saad, Misal G. Memeo and Paolo Quadrelli
Lett. Org. Chem. **2016**, *13*, 757–763. **DOI:** 10.2174/1570178614666161128150457



Abstract: Background: Nitrosocarbonyl intermediates are fleeting compounds obtainable from the periodate oxidation of hydroxamic acids and easily trapped with dienes and alkenes to give the products of hetero Diels-Alder and ene reactions in high yields.

Methods: A fleeting heterocyclic nitrosocarbonyl derived from the corresponding nitrile oxide is at work in a short-cut synthesis of 4-bromo-*N*-[(1R*,4S*)-4-hydroxy-2-cyclohexen-1-yl]-2-thiazolecarboxamide. The synthetic strategy is based on hetero Diels-Alder cycloaddition followed by mild reductive cleavage of the N-O bond.

Results: A new 2-thiazolecarboxamide derivative is obtained in good yields and the results of the in vitro a viral tests are briefly discussed. The product was found active against HPV virus and some structural evidences allow shining some light on future perspectives on the application of pericyclic reactions to the synthesis of biological active molecules.

Conclusion: The findings demonstrated that the synthetic methodology works well for the preparation of heterocyclic substituted novel compounds that displayed interesting and promising activity against viruses and in particular against the HPV.

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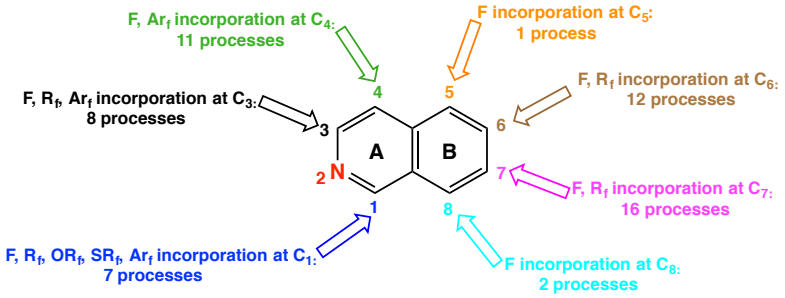
Advances in the Preparation of Fluorinated Isoquinolines: A Decade of Progress
(*Review Article)*

Joseph C. Sloop

Journal of Chemistry, **2017**, *2017*, Article ID 2860123, 15 pp. **DOI:** 10.1155/2017/2860123



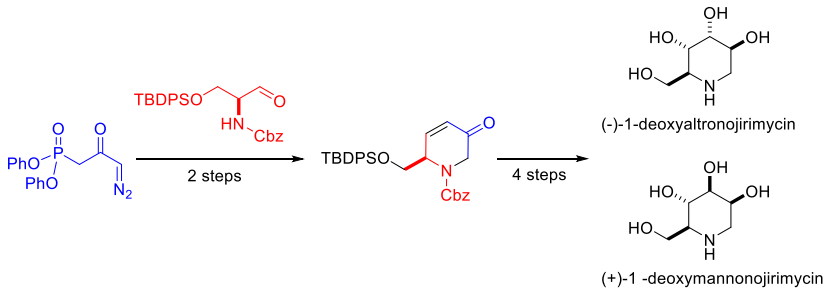
Isoquinoline fluorination, fluoroalkylation and fluoroarylation sites and processes

Abstract: Heterocyclic molecules incorporating fluorinated isoquinoline components are found in many medicinally and agriculturally important bioactive products as well as industrially impactful materials. Within the past decade, a variety of isoquinolinic ring assembly techniques has enabled the introduction of diverse fluorine-containing functionalities which can enhance potential bioactivity and industrial utility. This review examines recent noncatalyzed and transition metal catalyzed synthetic approaches to the assembly of isoquinoline derivatives that are ring-fluorinated and/or result in the incorporation of fluorine-containing functional groups. Specifically, efficient synthetic methods and regioselectivity in the incorporation of functional groups into isoquinoline ring systems are examined.

Six-Step Synthesis of (–)-1-deoxyaltronojirimycin and (+)-dexoymannonojirimycin from *N*-*Z*-O-TBDPS-L-serinal

Meire Y. Kawamura, Alexánder G. Talero, João V. Santiago, Edson Garambel-Vilca, Isac G. Rosset and Antonio C. B. Burtoloso

J. Org. Chem. **2016**, *81*, 10569–10575.* **DOI:** 10.1021/acs.joc.6b01575



Abstract: Highly stereoselective 6-step syntheses of (–)-1-altronojirimycin (*altro*-DNJ) and (+)-1-deoxymannojirimycin (*manno*-DNJ) from *N*-Cbz-O-TBDPS-L-serinal are described. Key transformations involve a two-step preparation of a functionalized dihydropyridin-3-one as a common intermediate followed by Luche reduction and dihydroxylation (for *altro*-DNJ). The same sequence employing an epoxidation/epoxide-opening in place of dihydroxylation furnishes deoxymannonojirimycin (*manno*-DNJ).

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