Bead-based screening in chemical biology and drug discovery

High-throughput screening is an important component of the drug discovery process. The screening of libraries containing hundreds of thousands of compounds requires assays amenable to miniaturisation and automation. Combinatorial chemistry holds a unique promise to deliver structural diverse libraries for early drug discovery. Among the various library forms, the one-bead-one-compound (OBOC) library, where each bead carries many copies of a single compound, holds the greatest potential for the rapid identification of novel hits against emerging drug targets. However, this potential has not yet been fully realized due to a number of technical obstacles. In this feature article, we review the progress that has been made towards bead-based library screening and applications to the discovery of bioactive compounds. We identify the key challenges of this approach and highlight key steps needed for making a greater impact in the field.
Oxidative Modification of Tryptophan-Containing Peptides

We herein present a broadly useful method for the chemoselective modification of a wide range of tryptophan-containing peptides. Exposing a tryptophan-containing peptide to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in a selective cyclodehydration between the peptide backbone and the indole side chain of tryptophan to form a fully conjugated indolyl-oxazole moiety. The modified peptides show a characteristic and significant emission maximum at 425 nm, thus making the method a useful strategy for fluorescence labeling.
Authors: Petersen, J. (Intern), Christensen, P. K. (Forskerdatabase), Nielsen, M. T. (Ekstern), Mortensen, K. T. (Intern), Komnatnyy, V. V. (Intern), Nielsen, T. E. (Intern), Qvortrup, K. (Intern)

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.16 SJR 1.03 SNIP 0.971
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.003 SNIP 0.954 CiteScore 3.13
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.021 SNIP 0.906 CiteScore 2.97
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.37 SNIP 1.298 CiteScore 3.38
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.74 SNIP 1.342 CiteScore 3.46
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.403 SNIP 1.025
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.015 SNIP 0.933
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.267 SNIP 0.996
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.975 SNIP 0.871
Scopus rating (2007): SJR 1.125 SNIP 0.978
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.106 SNIP 1.004
Scopus rating (2005): SJR 1.138 SNIP 1.076
Scopus rating (2004): SJR 1.382 SNIP 1.189
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.571 SNIP 1.169
Scopus rating (2002): SJR 3.244 SNIP 1.08
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 1.726 SNIP 1.059
Scopus rating (2000): SJR 2.141 SNIP 0.971
Web of Science (2000): Indexed yes

Original language: English
Fluorescent labeling, Site-selective protein modification, Solid-phase peptide synthesis, Tryptophan
Petasis/Diels-Alder/Cyclization Cascade Reactions for the Generation of Scaffolds with Multiple Stereogenic Centers and Orthogonal Handles for Library Production

A new effective strategy for the synthesis of sp3-rich small molecules for library production is presented. The key steps to generate complexity highlight Petasis 3-component reaction followed by an intramolecular Diels-Alder and cyclization to generate a densely enriched tricyclic or tetracyclic scaffolds with 3-4 stereocenters with 3 handles for decoration. The strategy was used for the production of 143 molecules for the European Lead Factory.

General information
State: Accepted/In press
Organisations: Department of Chemistry, Organic Chemistry, EDELRIS
Authors: Flagstad, T. (Intern), Azevedo, C. M. G. (Intern), Min, G. (Intern), Willaume, A. (Ekstern), Morgentin, R. (Ekstern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Number of pages: 8
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BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.643 SJR 1.037 CiteScore 2.65
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.74 SJR 1.177 SNIP 0.679
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.225 SNIP 0.776 CiteScore 2.88
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.23 SNIP 0.799 CiteScore 2.96
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.336 SNIP 0.827 CiteScore 2.96
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.54 SNIP 0.852 CiteScore 2.93
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.576 SNIP 0.868 CiteScore 3.2
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.615 SNIP 0.812
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.562 SNIP 0.823
Photolabile Linkers for Solid-Phase Synthesis

Photolabile linkers are the subjects of intense research, because they allow the release of the target molecule simply by irradiation. Photochemical substrate release is often facilitated without additional reagents under mild reaction conditions, which may even be environmentally friendly and appealing in the context of greener chemistry. The mild conditions may, furthermore, become attractive for applications of released crude material in subsequent biological screening experiments, where contamination with cleavage reagents would be detrimental. This review pays attention to the increasing number of photolabile linkers developed for solid-phase synthesis and release. It covers (i) o-nitrobenzoxo linkers, (ii) o-nitrobenzylamino linkers, (iii) α-substituted o-nitrobenzyl linkers, (iv) o-nitroveratryl linkers, (v) phenacyl linkers, (vi) p-alkoxyphenacyl linkers, (vii) benzoin linkers, (viii) pivaloyl linkers, (ix) other photolabile linkers.

General information
State: Accepted/In press
Organisations: Department of Chemistry, Organic Chemistry, Department of Organic Chemistry, Technical University of Denmark
Authors: Mikkelsen, R. J. T. (Intern), Grier, K. E. (Ekstern), Mortensen, K. T. (Intern), Nielsen, T. .. (Intern), Qvortrup, K. (Intern)
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Web of Science (2018): Indexed yes
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Scopus rating (2017): CiteScore 3.17 SJR 1.049 SNIP 0.907
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.16 SJR 1.03 SNIP 0.971
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.003 SNIP 0.954 CiteScore 3.13
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.021 SNIP 0.906 CiteScore 2.97

Photolabile Linkers for Solid-Phase Synthesis
Photolabile linkers are the subjects of intense research, because they allow the release of the target molecule simply by irradiation. Photochemical substrate release is often facilitated without additional reagents under mild reaction conditions, which may even be environmentally friendly and appealing in the context of greener chemistry. The mild conditions may, furthermore, become attractive for applications of released crude material in subsequent biological screening experiments, where contamination with cleavage reagents would be detrimental. This review pays attention to the increasing number of photolabile linkers developed for solid-phase synthesis and release. It covers (i) o-nitrobenzoxo linkers, (ii) o-nitrobenzylamino linkers, (iii) α-substituted o-nitrobenzyl linkers, (iv) o-nitroveratryl linkers, (v) phenacyl linkers, (vi) p-alkoxyphenacyl linkers, (vii) benzoin linkers, (viii) pivaloyl linkers, (ix) other photolabile linkers.

General information
State: Accepted/In press
Organisations: Department of Chemistry, Organic Chemistry, Department of Organic Chemistry, Technical University of Denmark
Authors: Mikkelsen, R. J. T. (Intern), Grier, K. E. (Ekstern), Mortensen, K. T. (Intern), Nielsen, T. .. (Intern), Qvortrup, K. (Intern)
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Scopus rating (2017): CiteScore 3.17 SJR 1.049 SNIP 0.907
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.16 SJR 1.03 SNIP 0.971
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.003 SNIP 0.954 CiteScore 3.13
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.021 SNIP 0.906 CiteScore 2.97
A broad range quorum sensing inhibitor working through sRNA inhibition

For the last decade, chemical control of bacterial virulence has received considerable attention. Ajoene, a sulfur-rich molecule from garlic has been shown to reduce expression of key quorum sensing regulated virulence factors in the opportunistic pathogen *Pseudomonas aeruginosa*. Here we show that the repressing effect of ajoene on quorum sensing occurs by inhibition of small regulatory RNAs (sRNA) in *P. aeruginosa* as well as in *Staphylococcus aureus*, another important human pathogen that employs quorum sensing to control virulence gene expression. Using various reporter constructs, we found that ajoene lowered expression of the sRNAs RsmY and RsmZ in *P. aeruginosa* and the small dual-function regulatory RNA, RNAIII in *S. aureus* that controls expression of key virulence factors. We confirmed the modulation of RNAIII by RNA sequencing and found that the expression of many QS regulated genes encoding virulence factors such as hemolysins and proteases were lowered in the presence of ajoene in *S. aureus*. Importantly, our findings show that sRNAs across bacterial species potentially may qualify as targets of anti-virulence therapy and that ajoene could be a lead structure in search of broad-spectrum compounds transcending the Gram negative-positive borderline.

**General information**

State: Published

Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen, Imperial College London, Statens Serum Institut

Authors: Jakobsen, T. H. (Ekstern), Warming, A. N. (Ekstern), Vejborg, R. M. (Ekstern), Moscoso, J. A. (Ekstern), Stegger, M. (Ekstern), Lorenzen, F. (Ekstern), Rybtke, M. T. (Ekstern), Andersen, J. B. (Ekstern), Petersen, R. (Intern), Andersen, P. S. (Ekstern), Nielsen, T. E. (Intern), Tolker-Nielsen, T. (Ekstern), Filloux, A. (Ekstern), Ingmer, H. (Ekstern),
The European Lead Factory is an EU-based initiative (part of the Innovative Medicines Initiative), which has been set to foster drug discovery in Europe. Among the objectives, a 200,000-compound collection is being generated. Lactams represent a large class of valuable scaffolds for medicinal chemistry and remain a wide and interesting area of study. In this context, 2 libraries based on a 1,4,5 γ-lactam core have been designed and produced using cascade reactions involving an aldehyde moiety, an amine and a nucleophilic partner as the key reaction. One library is focused on a 3-MCR on oxo-esters, while the other is based on a Ritter-type cascade. On several occasions these multi-component and one-pot processes have been used directly as the production step, thus allowing very fast and diverse library syntheses, whereas in other cases, the choice of partners bearing other anchoring groups permitted further functionalization and the production of even more diverse members of the libraries. The > 1,000 compounds based on these scaffolds have been delivered for HTS at the European Screening Center where they are currently being tested.
A Linker for the Solid-Phase Synthesis of Hydroxamic Acids and Identification of HDAC6 Inhibitors

We herein present broadly useful, readily available and nonintegral hydroxylamine linkers for the routine solid-phase synthesis of hydroxamic acids. The developed protocols enable the efficient synthesis and release of a wide range of hydroxamic acids from various resins, relying on high control and flexibility with respect to reagents and synthetic processes. A trityl-based hydroxylamine linker was used to synthesize a library of peptide hydroxamic acids. The inhibitory effects of the compounds were examined for seven HDAC enzyme subtypes using a chemiluminescence-based assay.

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Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen, Nanyang Technological University
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.16 SJR 1.03 SNIP 0.971
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.003 SNIP 0.954 CiteScore 3.13
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.021 SNIP 0.906 CiteScore 2.97
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.37 SNIP 1.298 CiteScore 3.38
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.74 SNIP 1.342 CiteScore 3.46
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.403 SNIP 1.025
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.015 SNIP 0.933
Development of a UV-Cleavable Protecting Group for Hydroxylamines, Synthesis of a Structurally Wide Variety of Hydroxamic Acids, and Identification of Histone Deacetylase Inhibitors

Photo-cleavable protecting groups are highly applicable for the synthesis of structural complex and sensitive compounds, including biological important molecules. Herein, we present the development of a novel O-hydroxylamine photo-cleavable protecting group, based on the methyl-6-nitroveratryl moiety. We demonstrate the application of the protected hydroxylamine derivative for the synthesis of N-alkylated hydroxamic acids. We have shown that the construct is stable toward a diverse set of reaction conditions, as well as orthogonal with conventional protection groups. The O-protected hydroxylamine derivative was applied to synthesize a small collection of N-alkylated hydroxamic acids as inhibitors of the histone deacetylase enzymes, an important class of enzymes for the treatment of a range of diseases, most importantly cancer. During my external stay at Nanyang Technological University, Singapore, I worked on a project with the aim of synthesizing compounds that target the quorum sensing network in Pseudomonas aeruginosa, important for the treatment of bacterial infections. The structure was based on a recent found hit compound, by our collaborators in Singapore, showing high activity.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Mortensen, K. T. (Intern), Qvortrup, K. (Intern), Nielsen, T. E. (Intern)
Number of pages: 271
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Original language: English
Main Research Area: Technical/natural sciences
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Development of a UV-Cleavable Protecting Group for Hydroxylamines, Synthesis of a Structurally Wide Variety of Hydroxamic Acids, and Identification of Histone Deacetylase Inhibitors
Publication: Research › Ph.D. thesis – Annual report year: 2017
Diastereoselective Synthesis of Novel Heterocyclic Scaffolds through Tandem Petasis 3-Component/Intramolecular Diels-Alder and ROM-RCM Reactions

A high-yielding, stereoselective and extraordinarily complexity generating Petasis 3-component/intramolecular Diels-Alder reaction has been developed. In combination with ROM-RCM, rapid access to complex sp3-rich heterocyclic scaffolds amenable to subsequent functionalization and library synthesis is provided.
Scaffold Diversity from N-Acyliminium Ions

N-Acyliminium ions are powerful reactive species for the formation of carbon-carbon and carbon-heteroatom bonds. Strategies relying on intramolecular reactions of N-acyliminium intermediates, also referred to as N-acyliminium ion cyclization reactions, have been employed for the construction of structurally diverse scaffolds, ranging from simple bicyclic skeletons to complex polycyclic systems and natural-product-like compounds. This review aims to provide an overview of cyclization reactions of N-acyliminium ions derived from various precursors for the assembly of structurally diverse scaffolds, covering the literature over the past 12 years (from 2004 to 2015).

General information
State: Published
Organisations: Department of Chemistry
Authors: Wu, P. (Intern), Nielsen, T. E. (Intern)
Number of pages: 46
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Publication date: 2017
Main Research Area: Technical/natural sciences

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Journal: Chemical Reviews
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ISSN (Print): 0009-2665
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 11.97 SJR 23.414 CiteScore 51.08
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 42.79 SJR 19.51 SNIP 10.358
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 18.035 SNIP 11.285 CiteScore 45.92
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Solvent-Controlled Chemoselectivity in the Photolytic Release of Hydroxamic Acids and Carboxamides from Solid Support

The synthetic utility and theoretical basis of a photolabile hydroxylamine-linker are presented. The developed protocols enable the efficient synthesis and chemoselective photolytic release of either hydroxamates or carboxamides from solid support. The bidetachable mode of the linker unit is uniquely dependent on the solvent. Hydroxamic acids are obtained by performing photolysis in protic solvents, whereas photolysis in aprotic solvents enables the selective release of carboxamides.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Technical University of Denmark
Authors: Qvortrup, K. (Intern), Petersen, R. G. (Intern), Dohn, A. O. (Intern), Møller, K. B. (Intern), Nielsen, T. E. (Intern)
Number of pages: 4
Pages: 3263-3266
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.197 SJR 2.853 CiteScore 6.16
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.32 SJR 2.985 SNIP 1.216
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.005 SNIP 1.324 CiteScore 6.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.964 SNIP 1.324 CiteScore 6.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.157 SNIP 1.322 CiteScore 6.12
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.338 SNIP 1.355 CiteScore 5.7
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.267 SNIP 1.356 CiteScore 5.81
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.014 SNIP 1.304
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.061 SNIP 1.37
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 3.319 SNIP 1.299
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 3.207 SNIP 1.284
Scopus rating (2006): SJR 2.975 SNIP 1.342
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 2.598 SNIP 1.318
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 2.53 SNIP 1.251
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 2.518 SNIP 1.313
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 4.43 SNIP 1.296
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 2.267 SNIP 1.392
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 1.893 SNIP 1.161
Web of Science (2000): Indexed yes
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Synthesis and biological evaluation of dihydropyrano-[2,3-c]pyrazoles as a new class of PPARγ partial agonists

Perxisome proliferator-activated receptor γ (PPARγ) is a well-known target for thiazolidinedione antidiabetic drugs. In this paper, we present the synthesis and biological evaluation of a series of dihydropyrano[2,3-c]pyrazole derivatives as a novel family of PPARγ partial agonists. Two analogues were found to display high affinity for PPARγ with potencies in the micro molar range. Both of these hits were selective against PPARγ, since no activity was measured when tested against PPARα, PPARδ and RXRa. In addition, a novel modelling approach based on multiple individual flexible alignments was developed for the identification of ligand binding interactions in PPARγ. In combination with cell-based transactivation experiments, the flexible alignment model provides an excellent analytical tool to evaluate and visualize the effect of ligand chemical structure with respect to receptor binding mode and biological activity.

General information

State: Published
Organisations: Department of Chemistry, Organic Chemistry, Department of Organic Chemistry, Department of Systems Biology, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Integrative Systems Biology, Technical University of Denmark, University of Copenhagen
Authors: Qvortrup, K. (Intern), Jensen, J. F. (Intern), Sørensen, M. S. (Ekstern), Kouskoumvekaki, E. (Intern), Petersen, R. K. (Ekstern), Taboureau, O. (Intern), Kristiansen, K. (Ekstern), Nielsen, T. E. (Intern)
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.01 SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.425 SNIP 1.233 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
Accessing Tri-substituted γ-Lactam Scaffolds Via Cascade Reactions: What Opportunities For Libraries!

The European Lead Factory is an EU-based initiative (part of the Innovative Medicines Initiative), which has been set to foster drug discovery in Europe. Among the objectives, a 200,000-compound collection is being generated. Lactams represent a large class of valuable scaffolds for medicinal chemistry and remain a wide and interesting area of study. In this context, 2 libraries based on a 1,4,5 γ-lactam core have been designed and produced using cascade reactions involving an aldehyde moiety, an amine and a nucleophilic partner as the key reaction. One library is focused on a 3-MCR on oxo-esters, while the other is based on a Ritter-type cascade. On several occasions these multi-component and one-pot processes have been used directly as the production step, thus allowing very fast and diverse library syntheses, whereas in other cases, the choice of partners bearing other anchoring groups permitted further functionalization and the production of even more diverse members of the libraries. The > 1,000 compounds based on these scaffolds have been delivered for HTS at the European Screening Center where they are currently being tested.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Department of Organic Chemistry, EDELRIS
Authors: Bonnet, K. (Ekstern), Clausen, M. H. (Intern), Fleury-Brégeot, N. (Ekstern), Lardy, C. (Ekstern), Morgentin, R. (Ekstern), Nielsen, T. E. (Intern), Petersen, M. A. (Intern), Rasmussen, M. O. (Ekstern), Roche, D. (Ekstern), Wu, P. (Intern)
Publication date: 2016
Event: Abstract from Experimental biology 2016, San Diego, United States.
Main Research Area: Technical/natural sciences
Links:
http://www.fasebj.org/content/30/1_Supplement/lb473.abstract
Source: FindIt
Source-ID: 2388939920
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

A metal-catalyzed enyne-cyclization step for the synthesis of bi- and tricyclic scaffolds amenable to molecular library production

A facile metal-catalyzed diversification step for the synthesis of novel bi- and tricyclic scaffolds from enyne substrates is reported in this study. From a single starting material, topologically diverse scaffolds for library synthesis can be generated and decorated in a few steps. The methodology was used to produce a library of 490 compounds within the European Lead Factory (ELF) Consortium.

General information
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Organisations: Organic Chemistry, Department of Chemistry, EDELRIS
Catalytic Enantioselective Synthesis of Tetrahydocarbazoles and Exocyclic Pictet-Spengler-Type Reactions

A synthetic strategy for the synthesis of chiral tetrahydocarbazoles (THCAs) has been developed. The strategy relies on two types of 6-exo-trig cyclization of 3-substituted indole substrates. Enantioselective domino Friedel-Crafts-type reactions leading to THCAs can be catalyzed by chiral phosphoric acid derivatives (with up to >99% ee), and the first examples of exocyclic Pictet-Spengler reactions to form THCAs are reported.

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Pages: 5990-5993
Publication date: 2016
Main Research Area: Technical/natural sciences

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Volume: 18
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ISSN (Print): 1523-7060
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.197 SJR 2.853 CiteScore 6.16
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.32 SJR 2.985 SNIP 1.216
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.005 SNIP 1.324 CiteScore 6.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.964 SNIP 1.324 CiteScore 6.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.157 SNIP 1.322 CiteScore 6.12
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.338 SNIP 1.355 CiteScore 5.7
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
A one bead–one compound screening format is presented. Following solid-phase synthesis on a photolabile linker, library compounds were readily released and screened inside polymer beads. The release of screening compounds was readily controlled by varying photolysis time and light intensity. Dose-response experiments were carried out to effectively distinguish high- and low-affinity ligands. A library containing 55,800 compounds was synthesized and screened in a fluorometric assay, thereby identifying potent HDAC inhibitors with IC$_{50}$ values in the nanomolar range.

**General information**

**State:** Published  
**Organisations:** Department of Chemistry, Organic Chemistry  
**Authors:** Qvortrup, K. (Intern), Nielsen, T. E. (Intern)  
**Number of pages:** 4  
**Pages:** 4548-4551  
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**Main Research Area:** Technical/natural sciences

**Publication information**

**Journal:** Angewandte Chemie  
**Volume:** 128  
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**Ratings:**  
BFI (2018): BFI-level 1  
BFI (2017): BFI-level 1

**In-Bead Screening of Hydroxamic Acids for the Identification of HDAC Inhibitors**

A one bead–one compound screening format is presented. Following solid-phase synthesis on a photolabile linker, library compounds were readily released and screened inside polymer beads. The release of screening compounds was readily controlled by varying photolysis time and light intensity. Dose-response experiments were carried out to effectively distinguish high- and low-affinity ligands. A library containing 55,800 compounds was synthesized and screened in a fluorometric assay, thereby identifying potent HDAC inhibitors with IC$_{50}$ values in the nanomolar range.

**General information**

**State:** Published  
**Organisations:** Department of Chemistry, Organic Chemistry  
**Authors:** Qvortrup, K. (Intern), Nielsen, T. E. (Intern)  
**Number of pages:** 4  
**Pages:** 4548-4551  
**Publication date:** 2016  
**Main Research Area:** Technical/natural sciences

**Publication information**

**Journal:** Angewandte Chemie  
**Volume:** 128  
**Issue number:** 14  
**ISSN (Print):** 0044-8249  
**Ratings:**  
BFI (2018): BFI-level 1  
BFI (2017): BFI-level 1
In-Bead Screening of Hydroxamic Acids for the Identification of HDAC Inhibitors

A one bead–one compound screening format is presented. Following solid-phase synthesis on a photolabile linker, library compounds were readily released and screened inside polymer beads. The release of screening compounds was readily controlled by varying photolysis time and light intensity. Dose-response experiments were carried out to effectively distinguish high- and low-affinity ligands. A library containing 55 800 compounds was synthesized and screened in a fluorometric assay, thereby identifying potent HDAC inhibitors with IC_{50} values in the nanomolar range.

**General information**

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Organisations: Department of Chemistry, Organic Chemistry
Authors: Qvortrup, K. (Intern), Nielsen, T. E. (Intern)
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Pages: 4472-4475
Publication date: 2016
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Issue number: 14
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes

BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes

BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Web of Science (2016): Indexed yes

BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.888 SNIP 2.225 CiteScore 11.13
Web of Science (2015): Indexed yes
Combinatorial libraries, HDAC inhibitors, In-bead screening, Photolabile linker

Small-molecule kinase inhibitors: an analysis of FDA-approved drugs

Small-molecule kinase inhibitors (SMKIs), 28 of which are approved by the US Food and Drug Administration (FDA), have been actively pursued as promising targeted therapeutics. Here, we assess the key structural and physicochemical properties, target selectivity and mechanism of function, and therapeutic indications of these approved inhibitors. Our analysis showed that >30% of approved SMKIs have a molecule weight (MW) exceeding 500 and all have a total ring count of between three and five. The assumption that type II inhibitors tend to be more selective than type I inhibitors has been proved to be unreliable. Although previous SMKI research was concentrated on tyrosine kinase inhibitors for cancer treatment, recent progress indicates diversification of SMKI research in terms of new targets, mechanistic types, and therapeutic indications.
Synthesis of sp3-rich scaffolds for molecular libraries through complexity-generating cascade reactions
An efficient strategy for the synthesis of complex small molecules from simple building blocks is presented. Key steps of the strategy include tandem Petasis and Diels–Alder reactions, and divergent complexity-generating cyclization cascades from a key dialdehyde intermediate. The methodology is validated through the synthesis of a representative compound set, which has been used in the production of 1617 molecules for the European Lead Factory.
Tandem Mannich/Diels–Alder reactions for the synthesis of indole compound libraries
A tandem Mannich/Diels–Alder sequence for the synthesis of small-molecule libraries with an indolyl-octahydro-3a,6-epoxy-isoidole core structure is demonstrated in this study. Representative diversification examples based on this scaffold were performed, and a library is being produced within the European Lead Factory (ELF) Consortium.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, EDELRIS
Authors: Wu, P. (Intern), Petersen, M. Å. (Intern), Petersen, R. (Intern), Flagstad, T. (Intern), Guilleux, R. (Ekstern), Ohsten Rasmussen, M. (Ekstern), Morgentin, R. (Ekstern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Pages: 46654-46657
Publication date: 2016
Main Research Area: Technical/natural sciences

Publication information
Journal: RSC Advances
Volume: 2016
Issue number: 6
ISSN (Print): 2046-2069
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.01 SJR 0.863 SNIP 0.736
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.06 SJR 0.889 SNIP 0.757
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.947 SNIP 0.834 CiteScore 3.42
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.113 SNIP 0.962 CiteScore 3.87
Web of Science (2014): Indexed yes
A Four-Component Reaction for the Synthesis of Dioxadiazaborocines

A four-component reaction for the synthesis of heterocyclic boronates is reported. Readily available hydrazides, α-hydroxy aldehydes, and two orthogonally reactive boronic acids are combined in a single step to give structurally distinct bicyclic boronates, termed dioxadiazaborocines (DODA borocines). In this remarkable process, one boronic acid reacts as a carbon nucleophile and the other as a boron electrophile to provide enantio- and diastereomerically pure heterocyclic boronates with multiple stereocenters in high yields.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Flagstad, T. (Intern), Petersen, M. T. (Intern), Nielsen, T. E. (Intern)
Number of pages: 3
Pages: 8395-8397
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information
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Ratings:
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.888 SNIP 2.225 CiteScore 11.13
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.811 SNIP 2.307 CiteScore 10.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.702 SNIP 2.198 CiteScore 10.7
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
A Four-Component Reaction for the Synthesis of Dioxadiazaborocines

A four-component reaction for the synthesis of heterocyclic boronates is reported. Readily available hydrazides, α-hydroxy aldehydes, and two orthogonally reactive boronic acids are combined in a single step to give structurally distinct bicyclic boronates, termed dioxadiazaborocines (DODA borocines). In this remarkable process, one boronic acid reacts as a carbon nucleophile and the other as a boron electrophile to provide enantio- and diastereomerically pure heterocyclic boronates with multiple stereocenters in high yields.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Flagstad, T. (Intern), Petersen, M. T. (Intern), Nielsen, T. E. (Intern)
Number of pages: 3
Pages: 8515-8517
Publication date: 2015
Main Research Area: Technical/natural sciences

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DOI: 10.1002/anie.201502989
Source: FindIt
Source-ID: 275500477
Publication: Research - peer-review » Journal article – Annual report year: 2015
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
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Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.888 SNIP 2.225 CiteScore 11.13
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.811 SNIP 2.307 CiteScore 10.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.702 SNIP 2.198 CiteScore 10.7
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 6.407 SNIP 2.329 CiteScore 10.55
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 6.063 SNIP 2.361 CiteScore 10.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.921 SNIP 2.303
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.571 SNIP 2.246
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 5.589 SNIP 2.153
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 4.528 SNIP 1.888
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 4.868 SNIP 2.165
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.797 SNIP 2.279
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 4.247 SNIP 2.198
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 3.559 SNIP 2.117
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 4.012 SNIP 2.142
Scopus rating (2001): SJR 3.788 SNIP 2.069
Scopus rating (2000): SJR 3.447 SNIP 2.1
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 3.529 SNIP 2.046
Cyclic N-acyliminium ions for the diversity-oriented synthesis of functionalized γ-lactams

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Wu, P. (Intern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Number of pages: 1
Publication date: 2015
Event: Abstract from 250th American Chemical Society National Meeting & Exposition, Boston, United States.
Main Research Area: Technical/natural sciences
Source: PublicationPreSubmission
Source-ID: 115058791
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2015

Multiple diguanylate cyclase-coordinated regulation of pyoverdine synthesis in Pseudomonas aeruginosa

The nucleotide signalling molecule bis-(3′-5′)-cyclic dimeric guanosine monophosphate (c-di-GMP) plays an essential role in regulating microbial virulence and biofilm formation. C-di-GMP is synthesized by diguanylate cyclase (DGC) enzymes and degraded by phosphodiesterase (PDE) enzymes. One intrinsic feature of c-di-GMP signalling is the abundance of DGCs and PDEs encoded by many bacterial species. It is unclear whether the different DGCs or PDEs coordinate the c-di-GMP regulation or function independently of each other. Here, we provide evidence that multiple DGCs are involved in regulation of c-di-GMP on synthesis of the major iron siderophore pyoverdine in Pseudomonas aeruginosa. Constitutive expression of the WspG or YedQ DGC in P. aeruginosa is able to induce its pyoverdine synthesis. Induction of pyoverdine synthesis by high intracellular c-di-GMP depends on the synthesis of exopolysaccharides and another two DGCs, SiaD and SadC. SiaD was found to boost the c-di-GMP synthesis together with constitutively expressing YedQ. The exopolysaccharides and the SiaD DGC were found to modulate the expression of the RsmY/RsmZ ncRNAs. Induction of the RsmY/RsmZ ncRNAs might enhance the pyoverdine synthesis through SadC. Our study sheds light on a novel multiple DGC-coordinated c-di-GMP regulatory mechanism of bacteria.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Nanyang Technological University, University of Copenhagen
Authors: Chen, Y. (Ekstern), Yuan, M. (Ekstern), Mohanty, A. (Ekstern), Yam, J. K. H. (Ekstern), Liu, Y. (Ekstern), Chua, S. L. (Ekstern), Nielsen, T. E. (Intern), Tolker-Nielsen, T. (Ekstern), Givskov, M. (Ekstern), Cao, B. (Ekstern), Yang, L. (Ekstern)
Number of pages: 10
Pages: 498-507
Publication date: 2015
Main Research Area: Technical/natural sciences
Publication information
Journal: Environmental Microbiology Reports
Volume: 7
Issue number: 3
ISSN (Print): 1758-2229
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.876 SJR 1.299 CiteScore 2.98
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.47 SJR 1.504 SNIP 0.935
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.646 SNIP 0.979 CiteScore 3.39
Reductive Cyclization and Petasis-Like Reaction for the Synthesis of Functionalized γ-Lactams

An efficient reductive cyclization strategy was employed for the synthesis of N-substituted β,γ-dihydroxy-γ-lactams. A subsequent Petasis-like reaction (PLR) through nucleophilic additions of boronic acids to intermediate N-acyliminium ions produced substituted γ-lactams. Overall, the application of this protocol provides β,γ-dihydroxy-γ-lactams and functionalized γ-lactams with potential interest for synthetic and bioorganic chemistry.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Center for Nanomedicine and Theranostics
Authors: Wu, P. (Intern), Petersen, M. Å. (Intern), Cohrt, A. E. (Intern), Petersen, R. (Intern), Clausen, M. H. (Intern), Nielsen, T. E. (Intern)
Number of pages: 5
Publication date: 2015
Main Research Area: Technical/natural sciences
Ritter-Hydrolysis Cascade Strategy for the Synthesis of Substituted gamma-Lactams

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Wu, P. (Intern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Number of pages: 1
Publication date: 2015
Event: Abstract from 98th Canadian Chemistry Conference and Exhibition, Ottawa, Canada.
Main Research Area: Technical/natural sciences
Electronic versions:
CSC98_Ottawa_2015_Peng_Wu.pdf
Links:
Synthesis of 1,4,5 trisubstituted γ-lactams via a 3-component cascade reaction

A three component one-pot cascade reaction was developed for the synthesis of 1,4,5-trisubstituted γ-lactams. The resulting scaffold can be modified independently at three positions, two of which are conveniently accessed by changing the components of the one-pot reaction. The phases of building block generation, scaffold synthesis and subsequent appendage modification were adapted to library production, which resulted in a screening library of 500 compounds.

General information

State: Published
Organisations: Department of Chemistry, Organic Chemistry, EDELRIS
Authors: Petersen, M. Å. (Intern), Mortensen, M. A. (Intern), Cohrt, A. E. (Intern), Petersen, R. (Intern), Wu, P. (Intern), Fleury-Brégeot, N. (Ekstern), Morgentin, R. (Ekstern), Lardy, C. (Ekstern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Number of pages: 4
Pages: 2695-2698
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information

Journal: Bioorganic & Medicinal Chemistry
Volume: 23
Issue number: 11
ISSN (Print): 0968-0896
Ratings:
  BFI (2018): BFI-level 1
  Web of Science (2018): Indexed yes
  BFI (2017): BFI-level 1
  Scopus rating (2017): SNIP 0.956 SJR 0.871 CiteScore 2.9
  Web of Science (2017): Indexed Yes
  BFI (2016): BFI-level 1
  Scopus rating (2016): SJR 0.984 SNIP 0.975 CiteScore 2.96
  BFI (2015): BFI-level 1
  Scopus rating (2015): SJR 1.03 SNIP 1.052 CiteScore 3
  Web of Science (2015): Indexed yes
  BFI (2014): BFI-level 1
  Scopus rating (2014): SJR 1.01 SNIP 1.095 CiteScore 2.87
  Web of Science (2014): Indexed yes
  BFI (2013): BFI-level 1
  Scopus rating (2013): SJR 1.064 SNIP 1.198 CiteScore 3.08
  ISI indexed (2013): ISI indexed yes
  Web of Science (2013): Indexed yes
  BFI (2012): BFI-level 1
  Scopus rating (2012): SJR 1.204 SNIP 1.307 CiteScore 3.12
  ISI indexed (2012): ISI indexed yes
  Web of Science (2012): Indexed yes
  BFI (2011): BFI-level 1
  Scopus rating (2011): SJR 1.137 SNIP 1.257 CiteScore 3.09
  ISI indexed (2011): ISI indexed yes
  Web of Science (2011): Indexed yes
  BFI (2010): BFI-level 1
  Scopus rating (2010): SJR 1.083 SNIP 1.29
The Ritter-type reaction of aryl nitriles and N-acyliminium ions generated in situ from dihydroxy-γ-lactams gave tetrahydropyrrolo[2,3-d]oxazol-5-ones in excellent yields. A subsequent acidic hydrolysis in EtOH/H2O/TFA (trifluoroacetic acid) yielded new (arylamido)pyrrolidinones with excellent cis diastereoselectivity. A combined one-step Ritter–hydrolysis procedure proved to be of equal efficiency. This versatile method, which was successfully used for the construction of a screening library containing 706 molecules within the European Lead Factory consortium, provides a simple way to access new compounds incorporating an arylamido and a pyrrolidinone moiety, both of which are widely found in marketed drugs and in biologically active molecules.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, EDELRIS
Authors: Wu, P. (Intern), Petersen, M. Å. (Intern), Petersen, R. (Intern), Ohsten Rasmussen, M. (Ekstern), Bonnet, K. (Ekstern), Nielsen, T. E. (Intern), Clausen, M. H. (Intern)
Number of pages: 8
Pages: 5633-5639
Publication date: 2015
Main Research Area: Technical/natural sciences

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Issue number: 25
ISSN (Print): 1434-193X
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.643 SJR 1.037 CiteScore 2.65
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.74 SJR 1.177 SNIP 0.679

Molecular libraries of natural product-like and structurally diverse compounds are attractive in early drug discovery campaigns. In here, we present synthetic methodology for library production of hexahydropyrrolo[2,1-a]isoquinoline (HPIQ) compounds. Two advanced HPIQ intermediates, both incorporating two handles for diversification, were synthesized through an oxidative cleavage/Pictet–Spengler reaction sequence in high overall yields. A subsequent metal-
A catalyzed cross coupling/amidation protocol was developed and its utility in library synthesis was validated by construction of a 20-membered natural product-like molecular library in good overall yields.

**General information**
- **State**: Published
- **Organisations**: Department of Chemistry, Organic Chemistry
- **Authors**: Petersen, R. (Intern), Cohrt, A. E. (Intern), Petersen, M. Å. (Intern), Wu, P. (Intern), Clausen, M. H. (Intern), Nielsen, T. E. (Intern)
- **Number of pages**: 4
- **Publication date**: 2015
- **Main Research Area**: Technical/natural sciences

**Publication information**
- **Journal**: Bioorganic & Medicinal Chemistry
- **Volume**: 23
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- **Ratings**:
  - BFI (2018): BFI-level 1
  - Web of Science (2018): Indexed yes
  - BFI (2017): BFI-level 1
  - Web of Science (2017): Indexed Yes
  - BFI (2016): BFI-level 1
  - Web of Science (2016): Indexed yes
  - Scopus rating (2016): SJR 0.984 SNIP 0.975 CiteScore 2.96
  - BFI (2015): BFI-level 1
  - Web of Science (2015): Indexed yes
  - Scopus rating (2015): SJR 1.03 SNIP 1.052 CiteScore 3
  - BFI (2014): BFI-level 1
  - Web of Science (2014): Indexed yes
  - Scopus rating (2014): SJR 1.01 SNIP 1.095 CiteScore 2.87
  - BFI (2013): BFI-level 1
  - Web of Science (2013): Indexed yes
  - Scopus rating (2013): SJR 1.064 SNIP 1.198 CiteScore 3.08
  - ISI indexed (2013): ISI indexed yes
  - Web of Science (2012): Indexed yes
  - Scopus rating (2012): SJR 1.204 SNIP 1.307 CiteScore 3.12
  - ISI indexed (2012): ISI indexed yes
  - Web of Science (2011): Indexed yes
  - Scopus rating (2011): SJR 1.137 SNIP 1.257 CiteScore 3.09
  - ISI indexed (2011): ISI indexed yes
  - Web of Science (2010): Indexed yes
  - Scopus rating (2010): SJR 1.083 SNIP 1.29
  - Web of Science (2010): Indexed yes
  - BFI (2009): BFI-level 1
  - Scopus rating (2009): SJR 1.13 SNIP 1.349
  - Web of Science (2009): Indexed yes
  - BFI (2008): BFI-level 1
  - Scopus rating (2008): SJR 1.206 SNIP 1.284
  - Web of Science (2008): Indexed yes
  - Scopus rating (2007): SJR 1.062 SNIP 1.229
  - Web of Science (2007): Indexed yes
  - Scopus rating (2006): SJR 0.928 SNIP 1.163
  - Web of Science (2006): Indexed yes
  - Scopus rating (2005): SJR 0.894 SNIP 0.992
  - Web of Science (2005): Indexed yes
Synthesis of Substituted γ- and δ-Lactams through Mannich-Type Reactions of Solid-Supported N-Acyliminium Ions

We report the results of our recent investigations into the reactivity of cyclic solid-supported N-acyliminium ions. An intermolecular Mannich-type transformation of these intermediates was used to generate libraries of substituted lactams. Masked aldehyde building blocks were readily prepared and coupled to peptides immobilized on PEGA800 (polyethylene glycol dimethyl acrylamide) resin through an HMBA [4-(hydroxymethyl)benzoic acid] linker. When treated with acid, the aldehyde was cleanly released and condensed with the amide backbone to form a hydroxylactam/N-acyliminium ion, which underwent intermolecular reactions with a series of nucleophilic heterocycles, such as substituted indoles, thiophenes, furans, and electron-rich benzenes. The resulting lactams were formed within a few minutes and in high purities (typically >85 %).

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen, Nanyang Technological University
Authors: Komnatnyy, V. V. (Intern), Taveras, K. M. (Intern), Nandurkar, N. S. (Intern), Le Quement, S. T. (Intern), Givskov, M. C. (Ekstern), Nielsen, T. E. (Intern)
Number of pages: 7
Pages: 3524-3530
Publication date: 2015
Main Research Area: Technical/natural sciences

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ISSN (Print): 1434-193X
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.643 SJR 1.037 CiteScore 2.65
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.74 SJR 1.177 SNIP 0.679
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.225 SNIP 0.776 CiteScore 2.88
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.23 SNIP 0.799 CiteScore 2.96
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.336 SNIP 0.827 CiteScore 2.96
Triazole-containing N-acyl homoserine lactones targeting the quorum sensing system in *Pseudomonas aeruginosa*

In an attempt to devise new antimicrobial treatments for biofilm infections, the bacterial cell-cell communication system termed quorum sensing has emerged as an attractive target. It has proven possible to intercept the communication system by synthetic non-native ligands and thereby lower the pathogenesis and antibiotic tolerance of a bacterial biofilm. To identify the structural elements important for antagonistic or agonistic activity against the *Pseudomonas aeruginosa* LasR protein, we report the synthesis and screening of new triazole-containing mimics of natural N-acyl homoserine lactones. A series of azide- and alkyne-containing homoserine lactone building blocks was used to prepare an expanded set of 123 homoserine lactone analogues through a combination of solution- and solid-phase synthesis methods. The resulting compounds were subjected to cell-based quorum sensing screening assays, thereby revealing several bioactive compounds, including 13 compounds with antagonistic activity and 9 compounds with agonistic activity. (C) 2015 Elsevier Ltd. All rights reserved.

**General information**

State: Published

Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen


**Solid-phase synthesis, Nitrogen heterocycles, Lactams, N-Acyliminium ions, Aromatic substitution**

**DOIs:**

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Source: FindIt

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Publication: Research - peer-review › Journal article – Annual report year: 2015
Nielsen, T. E. (Intern)

Number of pages: 13
Pages: 1638-1650
Publication date: 2015
Main Research Area: Technical/natural sciences

Publication information
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Volume: 23
Issue number: 7
ISSN (Print): 0968-0896

Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.956 SJR 0.871 CiteScore 2.9
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.984 SNIP 0.975 CiteScore 2.96
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.03 SNIP 1.052 CiteScore 3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.01 SNIP 1.095 CiteScore 2.87
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.064 SNIP 1.198 CiteScore 3.08
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.204 SNIP 1.307 CiteScore 3.12
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.137 SNIP 1.257 CiteScore 3.09
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.083 SNIP 1.29
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.13 SNIP 1.349
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.206 SNIP 1.284
Scopus rating (2007): SJR 1.062 SNIP 1.229
Scopus rating (2006): SJR 0.928 SNIP 1.163
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.894 SNIP 0.992
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.811 SNIP 1.008
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.883 SNIP 1.001
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.971 SNIP 0.927
An Improved Protocol for the Synthesis of 1-(Mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT)

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, R. (Intern), Jensen, J. F. (Intern), Nielsen, T. E. (Intern)
Pages: 267-271
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Organic Preparations and Procedures International
Volume: 46
Issue number: 3
ISSN (Print): 0030-4948
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.502 SJR 0.413 CiteScore 1.49
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.492 SNIP 0.577 CiteScore 1.57
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.417 SNIP 0.641 CiteScore 1.6
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.422 SNIP 0.632 CiteScore 1.14
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.524 SNIP 0.521 CiteScore 1.23
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.735 SNIP 0.692 CiteScore 1.62
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.529 SNIP 0.61 CiteScore 1.1
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.425 SNIP 0.354
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.458 SNIP 0.466
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.364 SNIP 0.462
Scopus rating (2007): SJR 0.415 SNIP 0.492
Scopus rating (2006): SJR 0.202 SNIP 0.414
Scopus rating (2005): SJR 0.27 SNIP 0.412

Scopus rating (2001): SJR 0.771 SNIP 0.795
Scopus rating (2000): SJR 0.777 SNIP 0.776
Scopus rating (1999): SJR 0.864 SNIP 0.754
Original language: English
Quorum sensing, Antibiotics, 1,2,3-Triazole, Homoserine lactone, Pseudomonas aeruginosa
DOIs:
10.1016/j.bmc.2015.01.038
Source: FindIt
Source-ID: 274548532
Publication: Research - peer-review › Journal article – Annual report year: 2015
A Photolabile Linker for the Solid-Phase Synthesis of Peptide Hydrazides and Heterocycles

A photolabile hydrazine linker for the solid-phase synthesis of peptide hydrazides and hydrazine-derived heterocycles is presented. The developed protocols enable the efficient synthesis of structurally diverse peptide hydrazides derived from the standard amino acids, including those with side-chain protected residues at the C-terminal of the resulting peptide hydrazide, and are useful for the synthesis of dihydropyrano[2,3-c]pyrazoles. The linker is compatible with most commonly used coupling reagents and protecting groups for solid-phase peptide synthesis.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Nanyang Technological University
Authors: Qvortrup, K. (Intern), Komnatnyy, V. V. (Intern), Nielsen, T. E. (Intern)
Pages: 4782-4785
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Organic Letters
Volume: 16
Issue number: 18
ISSN (Print): 1523-7060
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.197 SJR 2.853 CiteScore 6.16
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.32 SJR 2.985 SNIP 1.216
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.005 SNIP 1.324 CiteScore 6.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.964 SNIP 1.324 CiteScore 6.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.157 SNIP 1.322 CiteScore 6.12
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.338 SNIP 1.355 CiteScore 5.7
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.267 SNIP 1.356 CiteScore 5.81
Bacteria-Triggered Release of Antimicrobial Agents

Medical devices employed in healthcare practice are often susceptible to microbial contamination. Pathogenic bacteria may attach themselves to device surfaces of catheters or implants by formation of chemically complex biofilms, which may be the direct cause of device failure. Extracellular bacterial lipases are particularly abundant at sites of infection. Herein it is shown how active or proactive compounds attached to polymeric surfaces using lipase-sensitive linkages, such as fatty acid esters or anhydrides, may be released in response to infection. Proof-of-concept of the responsive material is demonstrated by the bacteria-triggered release of antibiotics to control bacterial populations and signaling molecules to modulate quorum sensing. The self-regulating system provides the basis for the development of device-relevant polymeric materials, which only release antibiotics in dependency of the titer of bacteria surrounding the medical device.
Bacteria-Triggered Release of Antimicrobial Agents

Medical devices employed in healthcare practice are often susceptible to microbial contamination. Pathogenic bacteria may attach themselves to device surfaces of catheters or implants by formation of chemically complex biofilms, which may be the direct cause of device failure. Extracellular bacterial lipases are particularly abundant at sites of infection. Herein it is shown how active or proactive compounds attached to polymeric surfaces using lipase-sensitive linkages, such as fatty acid esters or anhydrides, may be released in response to infection. Proof-of-concept of the responsive material is demonstrated by the bacteria-triggered release of antibiotics to control bacterial populations and signaling molecules to modulate quorum sensing. The self-regulating system provides the basis for the development of device-relevant polymeric materials, which only release antibiotics in dependency of the titer of bacteria surrounding the medical device.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Singapore Centre on Environmental Life Sciences Engineering, University of Copenhagen
Authors: Komnatnyy, V. V. (Intern), Chiang, W. (Ekstern), Tolker-Nielsen, T. (Ekstern), Givskov, M. C. (Ekstern), Nielsen, T. E. (Intern)
Pages: 439-441
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication Information
Volume: 53
Issue number: 2
ISSN (Print): 1433-7851
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Combining Organometallic Catalysis and Organocatalysis for the Synthesis of Heterocyclic Scaffolds

The main work presented in this thesis describes the development of efficient and novel methodologies for the synthesis of pharmaceutically interesting indolecontaining alkaloids, i.e., the 1,2,3,4-tetrahydro-β-carboline and the 1,2,3,4-tetrahydrocarbazole scaffolds. The synthesis of 1,2,3,4-tetrahydro-β-carbolines was based on a transition metal/Bønsted acid-catalyzed tandem isomerization/N-acyliminium ion cyclization of N-acylated allylic tryptamines. First, the reaction conditions for the tandem reaction were optimized to high efficiency, culminating in the use of the ruthenium hydride...
catalyst RuHCl(CO)(PPh3)3 combined with diphenyl phosphate at elevated temperature (refluxing toluene). The optimized reaction conditions were, in most cases, successfully applied to a broad range of Nacylated allyltryptamines, and the desired products were obtained in good yields (68–96%). With highly electron-withdrawing substituents, the reaction resulted in the formation of the corresponding enamides. When substituents capable of coordinating the catalyst were used, no conversions of the starting materials were observed. In an enantioselective version of the reaction, the substituent α to the nitrogen in the allylic system proved to be highly important for the enantioselectivity. Enantiomeric excesses up to 57% was obtained.

The synthesis of 1,2,3,4-tetrahydrocarbazole relied on novel Brønsted acidcatalyzed Friedel-Crafts-type reactions. Three different kinds of 1,2,3,4-tetrahydrocarbazole could be synthesized from one common carbonyl starting material. Type 1 reactions involved direct intramolecular cyclization from an indole moiety to an aldehyde resulting in the corresponding alcohols. The reaction was limited to electron-rich nucleophiles. Type 2 reactions deal with addition of nucleophiles, either to the cyclized alcohol obtained from type 1 reactions or directly to the carbonyl followed by cyclization. The reaction conditions were dependent on whether the addition of the nucleophile occurred before or after cyclization. An enantioselective version of the reaction was highly dependent on the substitution pattern, as enantiomeric excesses between 6 and >99% were obtained in 35–94% isolated yield. Type 3 reactions aimed for addition of organometallic reagents to the carbonyl with subsequently cyclization. No one-pot reaction directly from the carbonyl species to the 1,2,3,4-tetrahydrocarbazole was developed. A two-step synthetic route, via the alcohols, was investigated and found to be highly dependent on the presence of carbocation stabilizing groups around the alcohol; therefore only three final type 3 products were synthesized in good yields (64–95%).

A small project, which attempted to take advantage of the above described to be use as a novel cleavage strategy for solid support linkers, is also presented here. Unfortunately, no successful conditions were developed.

Comparative Systems Biology Analysis To Study the Mode of Action of the Isothiocyanate Compound Iberin on Pseudomonas aeruginosa

Food is now recognized as a natural resource of novel antimicrobial agents, including those that target the virulence mechanisms of bacterial pathogens. Iberin, an isothiocyanate compound from horseradish, was recently identified as a quorum-sensing inhibitor (QSI) of the bacterial pathogen Pseudomonas aeruginosa. In this study, we used a comparative systems biology approach to unravel the molecular mechanisms of the effects of iberin on QS and virulence factor expression of P. aeruginosa. Our study shows that the two systems biology methods used (i.e., RNA sequencing and proteomics) complement each other and provide a thorough overview of the impact of iberin on P. aeruginosa. RNA sequencing-based transcriptomics showed that iberin inhibits the expression of the GacA-dependent small regulatory RNAs RsmY and RsmZ; this was verified by using gfp-based transcriptional reporter fusions with the rsmY or rsmZ promoter regions. Isobaric tags for relative and absolute quantitation (iTRAQ) proteomics showed that iberin reduces the abundance of the LadS protein, an activator of GacS. Taken together, the findings suggest that the mode of QS inhibition in iberin is through downregulation of the Gac/Rsm QS network, which in turn leads to the repression of QS-regulated virulence factors, such as pyoverdine, chitinase, and protease IV. Lastly, as expected from the observed repression of small regulatory RNA synthesis, we also show that iberin effectively reduces biofilm formation. This suggests that small regulatory RNAs might serve as potential targets in the future development of therapies against pathogens that use QS for controlling virulence factor expression and assume the biofilm mode of growth in the process of causing disease.
Metal-catalyzed variations on the Pictet-Spengler theme

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Hansen, C. L. (Intern), Ascic, E. (Intern), Le Quement, S. T. (Intern), Nielsen, T. E. (Intern)
Publication date: 2014
Conference: 245th National Spring Meeting of the American-Chemical-Society, New Orleans, LA, United States, 07/04/2013 - 07/04/2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Abstracts of Papers of the American Chemical Society
Volume: 245
Article number: 831-ORGN
ISSN (Print): 0065-7727
Ratings:
Web of Science (2018): Indexed yes
Web of Science (2017): Indexed Yes
Scopus rating (2014): SJR 0.101 SNIP 0.013
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 0.101 SNIP 0.003
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 0.1 SNIP 0
Scopus rating (2011): SJR 0.101 SNIP 0
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 0.102 SNIP 0
Scopus rating (2009): SJR 0.102 SNIP 0
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.102 SNIP 0
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.102 SNIP 0
Scopus rating (2006): SJR 0.102
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.104
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.104 SNIP 0.028
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.123 SNIP 0.013
Scopus rating (2002): SJR 0.141 SNIP 0.096
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.112 SNIP 0.037
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 0.111
Original language: English
Publication: Research - peer-review › Conference abstract in journal – Annual report year: 2014
Novel 4-component reaction for the synthesis of boron heterocyclic scaffolds

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, M. T. (Intern), Flagstad, T. (Intern), Nielsen, T. E. (Intern)
Publication date: 2014
Event: Abstract from 14th Belgian Organic Synthesis Symposium, Louvain-La-Neuve, Belgium.
Main Research Area: Technical/natural sciences
Electronic versions:
BOSS_Book_of_abstracts_V2_cutepdf.pdf
Source: PublicationPreSubmission
Source-ID: 98865873
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2014

Petasis-type reactions for the synthesis of substituted pyrrolidin-2-ones
Pyrrolidin-2-ones are important heterocyclic motifs found in natural products and biologically active synthetic molecules. Addition of nucleophiles, including allylsilanes, isonitriles and organometallics, to N-acyliminium ions represents one of the most commonly used approaches for the formation of substituted pyrrolidin-2-ones. Only few studies on the nucleophilic addition of organoboronic acids to N-acyliminium ions have been reported. Herein, we disclose our recent efforts for the synthesis of substituted pyrrolidin-2-ones through Lewis-acid-mediated Petasis-type reactions. By implementing a reductive cyclization reaction, linear L-malic acid derivatives were rapidly converted into cyclic N-acyliminium ions. Under the optimized conditions, entailing the use of HFIP as solvent, both electron-rich and electron-deficient boronic acids were successfully added to a range of cyclic N-acyliminium ions, typically with excellent diastereoselectivity with electron-deficient boronic acids.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Wu, P. (Intern), Clausen, M. H. (Intern), Nielsen, T. E. (Intern)
Publication date: 2014
Conference: 248th National Fall Meeting of the American Chemical Society, San Francisco, CA, United States, 10/08/2014 - 10/08/2014
Main Research Area: Technical/natural sciences
Publication information
Journal: Abstracts of Papers of the American Chemical Society
ISSN (Print): 0065-7727
Ratings:
Web of Science (2018): Indexed yes
Web of Science (2017): Indexed Yes
Scopus rating (2014): SJR 0.101 SNIP 0.013
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 0.101 SNIP 0.003
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 0.1 SNIP 0
Scopus rating (2011): SJR 0.101 SNIP 0
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 0.102 SNIP 0
Scopus rating (2009): SJR 0.102 SNIP 0
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.102 SNIP 0
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.102 SNIP 0
Scopus rating (2006): SJR 0.102
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.104
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.104 SNIP 0.028
Web of Science (2004): Indexed yes
Solid-Phase Synthesis and Biological Evaluation of N-Dipeptido L-Homoserine Lactones as Quorum Sensing Activators

Bacteria use small signaling molecules to communicate in a process termed "quorum sensing" (QS), which enables the coordination of survival strategies, such as production of virulence factors and biofilm formation. In Gram-negative bacteria, these signaling molecules are a series of N-acylated L-homoserine lactones. With the goal of identifying non-native compounds capable of modulating bacterial QS, a virtual library of N-dipeptido L-homoserine lactones was screened in silico with two different crystal structures of LasR. The 30 most promising hits were synthesized on HMBA-functionalized PEGA resin and released through an efficient acid-mediated cyclative release mechanism. Subsequent screening for modulation of QS in Pseudomonas aeruginosa and E. coli identified six moderately strong activators. A follow-up library designed from the preliminary derived structure–activity relationships was synthesized and evaluated for their ability to activate the QS system in this bacterium. This resulted in the identification of another six QS activators (two with low micromolar activity) thus illuminating structural features required for QS modulation.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, University of Copenhagen
Pages: 460-465
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: ChemBioChem
Volume: 15
Issue number: 3
ISSN (Print): 1439-4227
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.721 SJR 1.407 CiteScore 2.64
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.64 SJR 1.283 SNIP 0.735
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.268 SNIP 0.749 CiteScore 2.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.392 SNIP 0.85 CiteScore 2.88
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.634 SNIP 0.847 CiteScore 3.15
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Solid-phase synthesis of NH-1,2,3-triazoles using 4,4′-bismethoxybenzhydryl azide

Readily available 4,4′-bismethoxybenzhydryl azide was found to be a useful building block for the synthesis of NH-1,2,3-triazoles through copper(I)-catalyzed cycloaddition reactions with solid-supported terminal alkynes, followed by acid-mediated deprotection. Peptide-containing NH-1,2,3-triazoles were obtained in good yield and excellent purity (typically >95%).
Solid-phase synthesis of peptide thioureas and thiazole-containing macrocycles through ru-catalyzed ring-closing metathesis

N-Terminally modified α-thiourea peptides can selectively be synthesized on solid support under mild reaction conditions using N,N'-di-Boc-thiourea and Mukaiyama's reagent (2-chloro-1-methyl-pyridinium iodide). This N-terminal modification applies to the 20 proteinogenic amino acid residues on three commonly used resins for solid-phase synthesis. Complementary methods for the synthesis of α-guanidino peptides have also been developed. The thiourea products underwent quantitative reactions with α-halo ketones to form thiazoles in excellent purities and yields. When strategically installed between two alkene moieties, said thiazole core was conveniently embedded in peptide macrocycles via Ru-catalyzed ring-closing metathesis reactions. Various 15-17 membered macrocycles were easily accessible in all diastereomeric forms using this methodology. The developed "build/couple/pair" strategy is well suited for the generation of larger and stereochemically complete screening libraries of thiazole-containing peptide macrocycles.
Synthesis of 4-Halogenated 3-Fluoro-6-methoxyquinolines: Key Building Blocks for the Synthesis of Antibiotics

A practical and scalable 4-step route is presented for the synthesis of 4-bromo-3-fluoro-6-methoxyquinoline and 3-fluoro-4-iodo-6-methoxyquinoline from readily available 2,4-dichloro-3-fluoroquinoline with an overall yield of 81-85%. Halogenated quinoline building blocks have found much use in antimicrobial drug discovery, and the method reported here would be useful for the synthesis of these compounds. © Georg Thieme Verlag.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen
Authors: Flagstad, T. (Intern), Petersen, M. T. (Intern), Hinnerfeldt, D. M. (Intern), Givskov, M. C. (Ekstern), Nielsen, T. E. (Intern)
Pages: 3263–3267
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Synthesis
Volume: 46
Issue number: 26
ISSN (Print): 0039-7881
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.577 SJR 0.974 CiteScore 2.31
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.067 SNIP 0.572 CiteScore 2.34
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.061 SNIP 0.666 CiteScore 2.39
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.066 SNIP 0.677 CiteScore 2.43
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.123 SNIP 0.668 CiteScore 2.37
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.176 SNIP 0.681 CiteScore 2.2
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.21 SNIP 0.695 CiteScore 2.36
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.2 SNIP 0.709
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.224 SNIP 0.769
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Synthesis of a Natural Product-Like Compound Collection through Oxidative Cleavage and Cyclization of Linear Peptides

Massive efforts in molecular library synthesis have strived for the development of synthesis methodology which systematically delivers natural product-like compounds of high spatial complexity. Herein, we present a conceptually simple approach that builds on the power of solid-phase peptide synthesis to assemble precursor peptides (oligomers) designed to undergo oxidative cascade reactions. By harnessing the structural side-chain diversity and inherent stereochemical features offered by readily available amino acids (monomers), a proof-of-concept collection of 54 skeletally and stereochemically diverse compounds was generated, and selected compounds were elaborated into isoform-selective metalloprotease inhibitors.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, R. (Intern), Le Quement, S. T. (Intern), Nielsen, T. E. (Intern)
Pages: 11778-11782
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Volume: 53
ISSN (Print): 1433-7851
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.888 SNIP 2.225 CiteScore 11.13
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.811 SNIP 2.307 CiteScore 10.84
Web of Science (2014): Indexed yes
Synthesis of a Natural Product-Like Compound Collection through Oxidative Cleavage and Cyclization of Linear Peptides.

Massive efforts in molecular library synthesis have strived for the development of synthesis methodology which systematically delivers natural product-like compounds of high spatial complexity. Herein, we present a conceptually simple approach that builds on the power of solid-phase peptide synthesis to assemble precursor peptides (oligomers) designed to undergo oxidative cascade reactions. By harnessing the structural side-chain diversity and inherent stereochemical features offered by readily available amino acids (monomers), a proof-of-concept collection of 54 skeletally and stereochemically diverse compounds was generated, and selected compounds were elaborated into isoform-selective metalloprotease inhibitors.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, R. (Intern), Le Quement, S. T. (Intern), Nielsen, T. E. (Intern)
Synthesis of heterocycles through transition-metal-catalyzed isomerization reactions

Metal-catalyzed isomerization of N- and O-allylic systems is emerging as an effective method to form synthetically useful iminium and oxocarbenium intermediates. In the presence of tethered nucleophiles, several recent examples illuminate this approach as a powerful strategy for the synthesis of structurally complex and diverse heterocycles. In this Concept article, we attempt to cover this area of research through a selection of recent versatile examples. A sea of opportunities!

Transition-metal-catalyzed isomerization of N- and O-allylic compounds provides a mild, selective and synthetically versatile method to form iminium and oxocarbenium ions. Given the number of reactions involving these highly electrophilic intermediates, this concept provides a sea of opportunities for heterocycle synthesis, (see scheme; \( \text{Nu} = \text{nucleophile} \)). © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Ishøy, M. (Intern), Nielsen, T. E. (Intern)
Pages: 8832-8840
Publication date: 2014
Main Research Area: Technical/natural sciences
Synthesis of Oxacyclic Scaffolds via Dual Ruthenium Hydride/Brønsted Acid-Catalyzed Isomerization/Cyclization of Allylic Ethers

A ruthenium hydride/Brønsted acid-catalyzed tandem sequence is reported for the synthesis of 1,3,4,9-tetrahydropyrano[3,4-b]indoles (THPIs) and related oxacyclic scaffolds. The process was designed on the premise that readily available allylic ethers would undergo sequential isomerization, first to enol ethers (Ru catalysis), then to oxocarbenium ions (Brønsted acid catalysis) amenable to endo cyclization with tethered nucleophiles. This methodology provides not only an attractive alternative to the traditional oxa-Pictet–Spengler reaction for the synthesis of THPIs, but also convenient access to THPI congeners and other important oxacycles such as acetals.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Pages: 3297-3300
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: Chemistry: A European Journal
Volume: 20
Issue number: 12
ISSN (Print): 0947-6539
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.02 SJR 2.265 CiteScore 4.9
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.03 SJR 2.352 SNIP 1.068
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.461 SNIP 1.195 CiteScore 4.99
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.526 SNIP 1.222 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.643 SNIP 1.239 CiteScore 5.68
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.935 SNIP 1.291 CiteScore 5.55
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.902 SNIP 1.319 CiteScore 5.46
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.791 SNIP 1.295
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Synthesis of substituted gamma-lactams through petasis-type addition of boronic acids to N-acyliminium ions

Substituted γ-lactams are important heterocyclic motifs found in various biologically active compounds and marketed drugs, such as glimepiride, doxapram, and levetiracetam. Among available methods for the synthesis of substituted γ-lactams, the addition of nucleophiles to N-acyliminium ions remains the most widely utilized approach. Even though hydroxylactams are important precursors of cyclic N-acyliminium ions, few approaches for their synthesis have been reported so far. By implementing a reductive cyclization reaction, linear L-malic acid derivatives were rapidly converted into cyclic N-acyliminium ions. Under the optimized conditions, entailing the use of HFIP as solvent, both electron-rich and electron-deficient boronic acids were successfully added to a range of cyclic N-acyliminium ions, thereby obtaining a collection of pharmaceutically relevant substituted γ-lactams.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Wu, P. (Intern), Clausen, M. H. (Intern), Nielsen, T. E. (Intern)
Publication date: 2014
Main Research Area: Technical/natural sciences

Publication information
Journal: ChemMedChem
ISSN (Print): 1860-7179
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.805 SJR 1.137 CiteScore 2.91
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.156 SNIP 0.904 CiteScore 3.11
Web of Science (2016): Indexed yes
Clearance of Pseudomonas aeruginosa Foreign-Body Biofilm Infections through Reduction of the Cyclic Di-GMP Level in the Bacteria

Opportunistic pathogenic bacteria can engage in biofilm-based infections that evade immune responses and develop into chronic conditions. Because conventional antimicrobials cannot efficiently eradicate biofilms, there is an urgent need to develop alternative measures to combat biofilm infections. It has recently been established that the secondary messenger cyclic diguanosine monophosphate (c-di-GMP) functions as a positive regulator of biofilm formation in several different bacteria. In the present study we investigated whether manipulation of the c-di-GMP level in bacteria potentially can be used for biofilm control in vivo. We constructed a Pseudomonas aeruginosa strain in which a reduction in the c-di-GMP level can be achieved via induction of the Escherichia coli YhjH c-di-GMP phosphodiesterase. Initial experiments showed that induction of yhjH expression led to dispersal of the majority of the bacteria in in vitro-grown P. aeruginosa biofilms. Subsequently, we demonstrated that P. aeruginosa biofilms growing on silicone implants, located in the peritoneal cavity of mice, dispersed after induction of the YhjH protein. Bacteria accumulated temporarily in the spleen after induction of biofilm dispersal, but the mice tolerated the dispersed bacteria well. The present work provides proof of the concept that modulation of the c-di-GMP level in bacteria is a viable strategy for biofilm control.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen
Design, Synthesis and Biological Evaluation of Quorum Sensing Modulators

Pseudomonas aeruginosa is an opportunistic pathogen associated with the majority of hospital-acquired infections and lung infections in cystic fibrosis. P. aeruginosa uses an intercellular communication process termed quorum sensing to control formation of a drug-resistant biofilm and generation of virulence factors. The system is driven by small signaling molecules, usually N-acylated homoserine lactones (AHLs). In the search for new treatment methods for biofilm infections the quorum sensing system has emerged as an attractive target. Recent advances in this area have proved that it is possible to intercept the communication system by synthetic non-native ligands and thereby lower the pathogenesis and antibiotic tolerance of a bacterial biofilm. To identify new ligands with quorum sensing modulating activities, three types of AHL analogs were synthesized using different synthetic strategies. The effect of replacing the acyl chain of the natural AHL ligand with a dipeptide was investigated. An in silico screening of N-dipeptido homoserine lactones against the protein responsible for the control of quorum sensing in P. aeruginosa identified a number of hits. The best hits were synthesized using a solid-phase strategy. Another library in which the amide bond was replaced with a triazole unit was synthesized by means of the copper- and ruthenium-catalyzed azide-alkyne cycloadditions. Finally, the synthesis of compounds with biaryl functionalities in the position of the acyl chain was carried out. Overall, 17 compounds were identified as quorum sensing activators with EC50 values in the low micromolar range. Two build/couple/pair strategies for the synthesis of structurally diverse small molecules are presented. In the first strategy, the Petasis 3-component reaction (Petasis 3-CR) of hydrazides is applied in the coupling of functionalized building blocks. Diversification by functional group pairing was envisioned to provide a diverse range of cyclized products. Triphosgene mediated carbonylative stiching of the 1,2-hydrazido alcohol from the Petasis 3-CR afforded a mixture of oxazolidinone and oxadiazolone products. Optimization afforded a method for the selective synthesis of either oxazolidinones or oxadiazolones and a small compound library was synthesized. Ring-closing metathesis of appropriately situated alkene moieties incorporated in the Petasis 3-CR products yielded five different cyclized products. In the second strategy, a number of alkylene- and azidecontaing amino acid-derivatives were coupled and macrocyclic peptidomimetics were obtained after intramolecular ruthenium-catalyzed azide-alkyne cycloadditions.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Hansen, M. R. (Intern), Nielsen, T. E. (Intern)
Number of pages: 183
Publication date: 2013

Publication information
Publisher: Technical University of Denmark, Department of Chemical Engineering
Original language: English
Main Research Area: Technical/natural sciences
Source: dtu
Source-ID: u::8670
Publication: Research › Ph.D. thesis – Annual report year: 2013

Discovery of a novel selective PPARγ ligand with partial agonist binding properties by integrated in silico / in vitro work flow

Full agonists to the peroxisome proliferator-activated receptor (PPARγ), such as Rosiglitazone, have been associated with a series of undesired side effects, such as weight gain, fluid retention, cardiac hypertrophy, and hepatotoxicity. Nevertheless, PPARγ is involved in the expression of genes that control glucose and lipid metabolism and is an important target for drugs against type 2 diabetes, dyslipidemia, atherosclerosis, and cardiovascular disease. In an effort to identify novel PPARγ ligands with an improved pharmacological profile, emphasis has shifted to selective ligands with partial agonist binding properties. Toward this end we applied an integrated in silico/in vitro workflow, based on pharmacophore- and structure-based virtual screening of the ZINC library, coupled with competitive binding and transactivation assays, and adipocyte differentiation and gene expression studies. Hit compound 9 was identified as the most potent ligand (IC50 = 0.3 μM) and a relatively poor inducer of adipocyte differentiation. The binding mode of compound 9 was confirmed by
molecular dynamics simulation, and the calculated free energy of binding was -8.4 kcal/mol. A novel functional group, the carbonitrile group, was identified to be a key substituent in the ligand-protein interactions. Further studies on the transcriptional regulation properties of compound 9 revealed a gene regulatory profile that was to a large extent unique, however functionally closer to that of a partial agonist. © 2013 American Chemical Society.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Chemistry, Organic Chemistry, National Food Institute, Division of Toxicology and Risk Assessment, University of Copenhagen
Authors: Kouskoumvekaki, I. (Intern), Petersen, R. K. (Ekstern), Fratev, F. F. (Intern), Taboureau, O. (Intern), Nielsen, T. E. (Intern), Oprea, T. (Intern), Sonne, S. B. (Forskerdatabase), Flindt, E. N. (Forskerdatabase), Jonsdottir, S. O. (Intern), Kristiansen, K. (Forskerdatabase)
Pages: 923-937
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Main Research Area: Technical/natural sciences

**Publication information**

Journal: Journal of Chemical Information and Modeling
Volume: 53
Issue number: 4
ISSN (Print): 1549-9596
Ratings:
- BFI (2018): BFI-level 1
- Web of Science (2018): Indexed yes
- BFI (2017): BFI-level 1
- Scopus rating (2017): SNIP 1.206 SJR 1.349 CiteScore 3.9
- Web of Science (2017): Indexed yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): CiteScore 3.84 SJR 1.474 SNIP 1.193
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 1.575 SNIP 1.281 CiteScore 4.27
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 1.433 SNIP 1.244 CiteScore 3.88
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 1.654 SNIP 1.334 CiteScore 4.4
- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 1.518 SNIP 1.342 CiteScore 4.22
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 1.326 SNIP 1.31 CiteScore 4.3
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 1.424 SNIP 1.265
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 1.039 SNIP 1.227
- Web of Science (2009): Indexed yes
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 1.14 SNIP 1.099
- Scopus rating (2007): SJR 0.984 SNIP 1.298
- Scopus rating (2006): SJR 1.006 SNIP 1.337
- Web of Science (2006): Indexed yes
- Scopus rating (2005): SJR 0.846 SNIP 1.144
- Web of Science (2005): Indexed yes
Extracellular DNA Shields against Aminoglycosides in Pseudomonas aeruginosa Biofilms

Within recent years, it has been established that extracellular DNA is a key constituent of the matrix of microbial biofilms. In addition, it has recently been demonstrated that DNA binds positively charged antimicrobials such as aminoglycosides and antimicrobial peptides. In the present study, we provide evidence that extracellular DNA shields against aminoglycosides in Pseudomonas aeruginosa biofilms. We show that exogenously supplemented DNA integrates into P. aeruginosa biofilms and increases their tolerance toward aminoglycosides. We provide evidence that biofilms formed by a DNA release-deficient P. aeruginosa quorum-sensing mutant are more susceptible to aminoglycoside treatment than wild-type biofilms but become rescued from the detrimental action of aminoglycosides upon supplementation with exogenous DNA. Furthermore, we demonstrate that exposure to lysed polymorphonuclear leukocytes, which are thought to be a source of extracellular DNA at sites of infections, increases the tolerance of P. aeruginosa biofilms toward aminoglycosides. Although biofilm-associated aminoglycoside tolerance recently has been linked to extracellular DNA-mediated activation of the pmr genes, we demonstrate that the aminoglycoside tolerance mediated by the presence of extracellular DNA is not caused by activation of the pmr genes in our P. aeruginosa biofilms but rather by a protective shield effect of the extracellular DNA.
Bacteria communicate by means of small signal molecules in a process termed quorum sensing (QS). QS enables bacteria to organize their activities at the population level, including the coordinated secretion of virulence factors. Certain small-molecule compounds, known as quorum-sensing inhibitors (QSIs), have been shown to effectively block QS and subsequently attenuate the virulence of Pseudomonas aeruginosa, as well as increasing its susceptibility to both antibiotics and the immune system. In this study, a structure-based virtual screening (SB-VS) approach was used for the discovery of novel QSI candidates. Three-dimensional structures of 3,040 natural compounds and their derivatives were obtained, after which molecular docking was performed using the QS receptor LasR as a target. Based on docking scores and molecular masses, 22 compounds were purchased to determine their efficacies as quorum-sensing inhibitors. Using a live reporter assay for quorum sensing, 5 compounds were found to be able to inhibit QS-regulated gene expression in P. aeruginosa in a dose-dependent manner. The most promising compound, G1, was evaluated by isobaric tag for relative and absolute quantitation (iTraq)-based proteomic analysis, and it was found to significantly affect the abundance of 46 proteins (19 were upregulated; 27 were downregulated) in P. aeruginosa PAO1. It specifically reduced the expression of
several quorum-sensing-regulated virulence factors, such as protease IV, chitinase, and pyoverdine synthetases. G1 was also able to reduce extracellular DNA release and inhibited the secretion of the virulence factor, elastase, whose expression is regulated by LasR. These results demonstrate the utility of SB-VS for the discovery of target-specific QSI.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Singapore Centre on Environmental Life Sciences Engineering, National University of Singapore
Authors: Tan, S. Y. (Ekstern), Chua, S. (Ekstern), Chen, Y. (Ekstern), Rice, S. A. (Ekstern), Kjelleberg, S. (Ekstern), Nielsen, T. E. (Intern), Yang, L. (Ekstern), Givskov, M. C. (Ekstern)
Pages: 5629-5641
Publication date: 2013
Main Research Area: Technical/natural sciences

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Journal: Antimicrobial Agents and Chemotherapy
Volume: 57
Issue number: 11
ISSN (Print): 0066-4804
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.263 SJR 2.291 CiteScore 4.15
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.21 SJR 2.275 SNIP 1.328
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.343 SNIP 1.361 CiteScore 4.28
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.361 SNIP 1.428 CiteScore 4.45
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.423 SNIP 1.411 CiteScore 4.67
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.363 SNIP 1.5 CiteScore 4.88
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.523 SNIP 1.574 CiteScore 5.02
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.458 SNIP 1.54
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.424 SNIP 1.65
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.45 SNIP 1.448
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.167 SNIP 1.49
Web of Science (2007): Indexed yes
Identification of LasR Ligands through a Virtual Screening Approach

With the widespread occurrence of bacterial resistance to antibiotics, the development of new strategies beyond conventional treatments is a pursuit taken by public health institutions worldwide. LasR, a transcription factor that controls quorum sensing in Pseudomonas aeruginosa, has emerged as an attractive therapeutic target for the next generation of antimicrobial agents. In the present study, a virtual screening workflow combining pharmacophore- and structure-based approaches was used to identify new LasR ligands. Five novel inducers and three inhibitors of LasR activity were validated experimentally by use of a cell-based assay. Interestingly, these compounds are molecularly distinct from the native signal molecule, N-3-oxododecanoyl-L-homoserine lactone (OHN), and may serve as lead structures for the design of new drugs. The binding modes of these compounds to the OHN binding site in LasR were predicted and used to identify the key interactions that contribute to the induction and inhibition of LasR activity.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry, Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Technical University of Denmark
Pages: 157-163
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: ChemMedChem
Volume: 8
Issue number: 1
ISSN (Print): 1860-7179
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.805 SJR 1.137 CiteScore 2.91
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.156 SNIP 0.904 CiteScore 3.11
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.151 SNIP 0.902 CiteScore 3
BFI (2014): BFI-level 1
In-bead screening
The present invention relates to screening of one-bead-one-compound (OBOC) combinatorial libraries which is useful for the discovery of compounds displaying molecular interactions with a biological or a physicochemical system, such as substrates and inhibitors of enzymes and the like. The invention provides a method for screening a library of compounds for their interaction with a physico-chemical or biological system and a corresponding kit for performing the method of screening a one-bead-one-compound library of compounds.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Nielsen, T. E. (Intern), Qvortrup, K. (Intern)
Publication date: 2013

Publication information
IPC: G01N33/50
Patent number: WO2013057188
Date: 18/10/2012
Original language: English
Electronic versions:
WO2013057188A1.pdf
Photolabile linker for the synthesis of hydroxamic acids

The present invention relates to a photolabile hydroxamate linker based on the o-nitroveratryl group and its application for multistep solid-phase synthesis and controlled photolytic release of hydroxamic acids. The invention provides a method for producing a solid support comprising a hydroxylamine-functionalized photolabile linker, and the so produced hydroxylamine-functionalized photolabile solid support. The invention further provides a method for synthesizing a one-bead-one compound library of hydroxamic acid derivatives on a photolabile linker, as well as a method for screening a library of hydroxamic acid derivatives.

Ruthenium Hydride/Brønsted Acid-Catalyzed Tandem Isomerization/N-Acyliminium Cyclization Sequence for the Synthesis of Tetrahydro-β-carbolines

This paper describes an efficient tandem sequence for the synthesis of 1,2,3,4-tetrahydro-β-carbolines (THBCs) relying on a ruthenium hydride/Brønsted acid-catalyzed isomerization of allylic amides to N-acyliminium ion intermediates which are trapped by a tethered indolenineophile. The methodology provides not only a convenient "aldehyde-free" alternative to the classical Pictet−Spengler reaction but also attractive possibilities for total synthesis, including rapid generation of molecular complexity and formation of quaternary stereogenic centers. TBHCs can also be accessed by harnessing the Suzuki cross-coupling reaction to the isomerization/N-acyliminium cyclization sequence. Finally, diastereo- and enantioselective versions of the title reaction have been examined using substrate control (with dr >15: 1) and asymmetric catalysis (ee up to 57%), respectively.
Solid-phase iminium cyclization reactions for the synthesis of natural product-like diketopiperazines

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, R. (Intern), Le Quement, S. T. (Intern), Nielsen, T. E. (Intern)
Publication date: 2013
Synthesis and biological evaluation of triazole-containing N-acyl homoserine lactones as quorum sensing modulators

Many bacterial species are capable of assessing their local population densities through a cell–cell signaling mechanism termed quorum sensing (QS). This intercellular communication process is mediated by small molecule or peptide ligands and their cognate protein receptors. Numerous pathogens use QS to initiate virulence once they achieve a threshold cell number on a host. Consequently, approaches to intercept QS have attracted considerable attention as potential anti-infective therapies. Our interest in the development of small molecule tools to modulate QS pathways motivated us to evaluate triazole-containing analogs of natural N-acyl l-homoserine lactone (AHL) signals as non-native QS agonists and antagonists in Gram-negative bacteria. We synthesized 72 triazole derivatives of five broad structure types in high yields and purities using efficient Cu(i)-catalyzed azide–alkyne couplings. These compounds were evaluated for their ability to activate or inhibit two QS receptors from two prevalent pathogens – LasR from Pseudomonas aeruginosa and AbaR from Acinetobacter baumannii – using bacterial reporter strains. Several triazole derivatives were identified that were capable of strongly modulating the activity of LasR and AbaR. These compounds represent a new and synthetically accessible class of AHL analogs, and could find utility as chemical tools to study QS and its role in bacterial virulence.
Publication information
Journal: Organic & Biomolecular Chemistry
Volume: 11
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ISSN (Print): 1477-0520
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 3.32 SJR 1.281 SNIP 0.767
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 3.39 SJR 1.382 SNIP 0.805
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.391 SNIP 0.85 CiteScore 3.47
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.396 SNIP 0.903 CiteScore 3.5
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.492 SNIP 0.892 CiteScore 3.55
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.653 SNIP 0.939 CiteScore 3.47
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.759 SNIP 0.967 CiteScore 3.71
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.803 SNIP 0.951
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.868 SNIP 1.077
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.989 SNIP 1.054
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.88 SNIP 0.983
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.594 SNIP 0.963
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.293 SNIP 1.105
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.314 SNIP 0.999
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.1
Web of Science (2003): Indexed yes
Original language: English
Synthesis of heterocycles through ruthenium-catalyzed ring-closing metathesis and isomerization reactions

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Publication date: 2013
Conference: 245th National Spring Meeting of the American-Chemical-Society, New Orleans, LA, United States, 07/04/2013 - 07/04/2013
Main Research Area: Technical/natural sciences

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Journal: Abstracts of Papers of the American Chemical Society
Volume: 245
Article number: 327
ISSN (Print): 0065-7727
Ratings:
Web of Science (2018): Indexed yes
Web of Science (2017): Indexed Yes
Scopus rating (2014): SJR 0.101 SNIP 0.013
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 0.101 SNIP 0.003
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 0.1 SNIP 0
Scopus rating (2011): SJR 0.101 SNIP 0
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 0.102 SNIP 0
Scopus rating (2009): SJR 0.102 SNIP 0
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.102 SNIP 0
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.102 SNIP 0
Scopus rating (2006): SJR 0.102
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.104
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.104 SNIP 0.028
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.123 SNIP 0.013
Scopus rating (2002): SJR 0.141 SNIP 0.096
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.112 SNIP 0.037
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 0.111
Original language: English
Publication: Research - peer-review › Conference abstract in journal – Annual report year: 2013

Tandem ring-closing metathesis/isomerization reactions for the total synthesis of violacein

General information
State: Published
Tandem Ring-Closing Metathesis/Isomerization Reactions for the Total Synthesis of Violacein

A series of 5-substituted 2-pyrrolidinones was synthesized through a one-pot ruthenium alkylidene-catalyzed tandem RCM/isomerization/nucleophilic addition sequence. The intermediates resulting from RCM/isomerization showed reactivity toward electrophiles in aldol condensation reactions which provided a new entry for the total synthesis of the antileukemic natural product violacein.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, M. T. (Intern), Nielsen, T. E. (Intern)
Pages: 1986-1989
Publication date: 2013
Main Research Area: Technical/natural sciences

Publication information
Journal: Organic Letters
Chapter 1. Build/Couple/Pair Strategy Combining the Petasis 3-Component Reaction with Ru-Catalyzed Ring-Closing Metathesis

A “build/couple/pair” strategy for the efficient and concise (2-5 step) synthesis of structurally distinct skeletons is described. A Petasis 3-component reaction is used to synthesize anti-amino alcohols displaying pairwise reactive combinations of alkene moieties. Upon treatment with a ruthenium alkylidene catalyst, these dienes selectively undergo ring-closing metathesis reactions to form skeletally distinct heterocycles. In addition, a ruthenium-catalyzed tandem RCM/isomerization/N-alkyliminium cyclization sequence to hitherto unknown oxazabicyclooctane derivatives is developed, which grants an extra element of skeletal diversity. Further skeletal diversification reactions utilizing palladium-catalyzed ring-contraction and intramolecular Diels-Alder reactions are also demonstrated.


A multifunctional catalysis approach, involving a ruthenium-catalyzed tandem ring-closing metathesis/isomerization/N-acyliminium cyclization sequence, is described. Double bonds created during ring-closing metathesis isomerize to generate reactive Nacyliminium intermediates which undergo intramolecular cyclization reactions with tethered heteroatom and carbon nucleophiles. In the tandem process, two new rings are formed, where a single metal catalyzes two mechanistically distinct reactions in one chemical operation. In this way, a series of interesting indolizidinones are formed in good yields with excellent diastereoselectivities, including a formal total synthesis of the antiparasitic natural product harmicine and the first total synthesis of mescalotam. Furthermore, preliminary asymmetric variants of the tandem process have been identified, affording indolizinindoles in up to 60% ee.
Fluorescence-Based Reporter for Gauging Cyclic Di-GMP Levels in Pseudomonas aeruginosa

The increased tolerance toward the host immune system and antibiotics displayed by biofilm-forming Pseudomonas aeruginosa and other bacteria in chronic infections such as cystic fibrosis bronchopneumonia is of major concern. Targeting of biofilm formation is believed to be a key aspect in the development of novel antipathogenic drugs that can augment the effect of classic antibiotics by decreasing antimicrobial tolerance. The second messenger cyclic di-GMP is a positive regulator of biofilm formation, and cyclic di-GMP signaling is now regarded as a potential target for the development of antipathogenic compounds. Here we describe the development of fluorescent monitors that can gauge the cellular level of cyclic di-GMP in P. aeruginosa. We have created cyclic di-GMP level reporters by transcriptionally fusing
the cyclic di-GMP-responsive cdrA promoter to genes encoding green fluorescent protein. We show that the reporter constructs give a fluorescent readout of the intracellular level of cyclic di-GMP in P. aeruginosa strains with different levels of cyclic di-GMP. Furthermore, we show that the reporters are able to detect increased turnover of cyclic di-GMP mediated by treatment of P. aeruginosa with the phosphodiesterase inducer nitric oxide. Considering that biofilm formation is a necessity for the subsequent development of a chronic infection and therefore a pathogenicity trait, the reporters display a significant potential for use in the identification of novel antipathogenic compounds targeting cyclic di-GMP signaling, as well as for use in research aiming at understanding the biofilm biology of P. aeruginosa.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, University of Washington, H. Lundbeck A/S, University of Copenhagen
Pages: 5060-5069
Publication date: 2012
Main Research Area: Technical/natural sciences

Publication information
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Volume: 78
Issue number: 15
ISSN (Print): 0099-2240
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 3.99
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.08
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.914 SNIP 1.455 CiteScore 4.12
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.887 SNIP 1.436
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.972 SNIP 1.528
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.156 SNIP 1.572
An application of readily available hydrazides in the Petasis 3-component coupling reaction is presented. An investigation of the substrate scope was performed to establish a general, synthetically useful protocol for the formation of hydrazido alcohols, which were selectively converted to oxazolidinone and oxadiazolone ring systems through triphosgene-mediated cyclization reactions.

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**Publication information**
Journal: Organic Letters
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ISSN (Print): 1523-7060
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.197 SJR 2.853 CiteScore 6.16
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.32 SJR 2.985 SNIP 1.216
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.005 SNIP 1.324 CiteScore 6.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Solid-Phase Iminium Cyclization Reactions for the Synthesis of Natural Product-Like Diketopiperazines

The development of methodology for the solid-phase synthesis of fused 2,5-diketopiperazines with an emphasis on structural and stereochemical control, has been accomplished through two different approaches. The first approach was based on a highly trans-stereoselective (82% d.e.) intramolecular N-acyliminium ion cyclization of N-terminal peptide glyoxylamides, assembling the complete molecular skeleton in a single step. The second approach aimed for the use of a cis-stereoselective intermolecular Pictet-Spengler cyclization to construct the first part of the ringsystem and a subsequent diketopiperazine formation to close the second ring.

In the first approach, four different methods for accessing the glyoxylamide cyclization precursor were developed; oxidative cleavage of a serine, dihydroxylation/oxidative cleavage of an acrylamide, oxidation of a glycolamide and acidic release from a diethoxy acetamide.

The scope of the methodology was found to be broad, allowing for numerous variations in the western amino acid part, including components such as proline, homoproline and Nmethylated amino acids, delivering products in moderate to...
The acetylation pattern could also be detected using a quantitative ninhydrin assay. The ethyl acetylated route was found to be nonstereoselective but well-suited for the synthesis of diastereoisomeric mixtures of 2,5-diketopiperazine[6,1-a]tetrahydroisoquinolines in high purities (74 to 90%), allowing for the separation of the cis-diastereoisomers. The route based on glyoxylic acid was found to be cis-stereoselective (1:2) generating the 2,5-diketopiperazine[6,1-a]tetrahydroisoquinoline product in a high purity (71%). Unfortunately an issue with incomplete conversion in the final step (20%) rendered separation of the diastereoisomers, by preparative RP-HPLC, problematic. Employing the developed methods, a diastereoisomeric matrix of aminomethylthiophene hydroxamic acid biased HDAC inhibitors based on the 2,5-diketopiperazine[6,1-a]tetrahydroisoquinoline scaffold was prepared and subsequently evaluated for biologically activity. The compounds showed inhibitory activity against a nuclear extract of HeLa cells, on average 200-fold lower than the activity of SAHA. When screened towards HDAC 1 the compounds showed a lower inhibitor activity, compared to the nuclear extract, except for one of the compounds which showed increased activity. The compound represents a clear case of stereodifferentiation. Finally, and most importantly, when screening the compounds towards HDAC 8 an activity which was on average 5-fold higher than the activity of SAHA was found. The profound difference in HDAC 1 and HDAC 8 inhibitor activity identifies the compounds as potential sub-type inhibitors.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Petersen, R. (Intern), Nielsen, T. E. (Intern)
Number of pages: 212
Publication date: 2012

Solid-Phase Synthesis of Modified Peptides as Putative Inhibitors of Histone Modifying Enzymes
The role of histone modifications in the tight regulation of gene expression is emerging as a new area within drug discovery. The misregulation of histone modification levels has been linked with several life-threatening diseases, including cancer and diabetes, and reverting these irregularities may improve the prognosis of patients suffering from these diseases.

The development of methodologies to modify peptides for use as peptide-based inhibitors of histone modifying enzymes is presented. Several different approaches for both N and C-terminal modification have been developed. Two broadly useful acid-labile traceless azido handles for the solid-phase synthesis of N H-1,2,3-triazoles are presented. A variety of alkynes were efficiently immobilised on a range of polymeric supports by Cu(I)-mediated azide-alkyne cycloadditions. Supported triazoles showed excellent compatibility with subsequent peptide chemistry. Release of pure material from the solid support was readily achieved by treatment with aqueous TFA. In parallel, an azido donor protection group for the synthesis of N H-1,2,3-triazoles was developed for use in both solid-phase and solution-phase chemistry. The N H-1,2,3-triazoles were cleanly deprotected by treatment with TFA (CH2Cl2). Four different libraries of histone demethylase inhibitor candidates have been synthesised based on metal chelation, cofactor mimicking and radial stabilising inhibition strategies. The libraries have all been synthesised on solid-phase using various handle strategies for the clean release of products. Two cofactor mimicking inhibitor candidates, which were synthesised using a safety-catch benzyl hydrazide handle, were found to inhibit the histone demethylase JMJD2C with IC50-values of 23.5µM and 24µM.

Two mild and selective methods for the solid-phase synthesis of thiourea- and guanidinemodified peptides are presented. By activating N,N'-di-Boc-thiourea with Mukaiyama’s reagent or HgCl2, the N-terminal of solid-supported peptides could be cleanly converted into the corresponding thiourea or guanidine derivative. The reactions were found to be compatible with all 20 naturally occurring amino acids, and were furthermore feasible on several commercially used polymeric supports. By using dilute SnCl4 for N-Boc deprotection, and NaOH for the release of material from the solid support, N-modified peptides were cleanly obtained in excellent yields and purities.

Libraries of histone H2B tail pieces were synthesised using both parallel and split-pool synthesis protocols. Changes in the acetylation pattern of the individual library members upon treatment with HDAC3 enzyme were measured using LCMS-MS techniques. An MSMS deconvolution strategy was employed in the identification of individual library members. Changes in the acetylation pattern could also be detecting using a quantitative ninhydrin assay.
Solid-Phase Synthesis of Structurally Diverse Heterocycles by an Amide–Ketone Condensation/N-Acyliminium Pictet–Spengler Sequence

An efficient approach for the solid-phase synthesis of structurally diverse heterocyclic compounds is presented. Under acidic reaction conditions, peptidic levulinamides undergo intramolecular ketone–amide condensation reactions to form cyclic N-acyliminium intermediates. In the presence of a tethered nucleophile, a second cyclization reaction results in the formation of a fused bicyclic ring system. The scope of the methodology was demonstrated by several combinations of substituted ketones and nucleophiles, the latter conveniently originating from amino acids with functionalized side chains, such as tryptophan, substituted phenylalanines, and cysteine. The cyclization sequence provides diastereomerically pure products in high yields. In one extension of the methodology, the resulting relative stereochemistry of the products enables the formation of bridged ring systems by a unique cyclative release mechanism.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry, University of Copenhagen
Authors: Komnatnyy, V. V. (Intern), Givskov, M. C. (Ekstern), Nielsen, T. E. (Intern)
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Journal: Chemistry: A European Journal
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Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.02 SJR 2.265 CiteScore 4.9
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.03 SJR 2.352 SNIP 1.068
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.461 SNIP 1.195 CiteScore 4.99
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.526 SNIP 1.222 CiteScore 5.51
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.643 SNIP 1.239 CiteScore 5.68
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.935 SNIP 1.291 CiteScore 5.55
ISI indexed (2012): ISI indexed yes
Solid-supported synthesis: From pharmacologically relevant heterocycles to biologically active surfaces

The present PhD thesis consists of an introduction part and two separate parts covering selected research projects during the PhD study.

The introduction part describes the concept of solid-supported synthesis and combinatorial chemistry. The chapter covers recent achievements in materials for solid-phase synthesis, methods for on- and off-bead screening of combinatorial libraries and their application to various biological targets.

The first part of the thesis is dedicated to the development of methodology for the synthesis of structurally diverse heterocyclic scaffolds via N-acyliminium intermediates on solid support. In Chapter 1.1, an intermolecular Mannich-type reaction of solid-supported N-acyliminium ions is reported. The method is useful for the solid-supported synthesis of substituted ?-lactames, which constitute a class of pharmacologically relevant small molecule scaffolds. Chapter 1.2, in turn, utilizes readily available ketones as precursors for solid-supported N-acyliminium ions. Under acidic reaction conditions, peptidic levulinamides undergo intramolecular ketone amide condensation reactions to form cyclic N-acyliminium intermediates, which in the presence of tethered nucleophiles bring about a second cyclization and the formation of a fused, bicyclic ring system.

The second part of the thesis deals with the topical problem of bacterial biofilm-related infections in manufacturing and use of indwelling medical devices, such as catheters and implants. In Chapter 2.1, new methods for the controlled organo-functionalization of titanium, one of the most prominent materials in medicinal device industry, have been suggested. Initial acidic and oxidative treatment of the metal surface generates reactive hydroxyl moieties, which are subsequently modified with synthetically versatile amine-containing reagents. Subsequent applications in antimicrobial peptide synthesis, metal-catalysis, release from the surface, and polymer grafting, are also presented.

Solid-supported synthesis: From pharmacologically relevant heterocycles to biologically active surfaces

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Synthesis of tetrahydro-β-carbolines via isomerization of N-allyltryptamines: a metal-catalyzed variation on the Pictet–Spengler theme

An efficient and broadly applicable alternative to the classical Pictet–Spengler synthesis of tetrahydro-β-carbolines is presented. The method relies on metal-catalyzed isomerization of allylic amines to form reactive iminium intermediates which can be trapped by a tethered indole nucleophile.
A convenient procedure for the solid-phase synthesis of hydroxamic acids on PEGA resins

An efficient method for the solid-phase synthesis of hydroxamic acids is described. The method comprises the nucleophilic displacement of esters immobilized on PEGA resins with hydroxylamine/sodium hydroxide in isopropanol. The hydroxyaminolysis protocol is compatible with a broad range of PEGA-supported peptide and peptidomimetic esters. The methodology was found to be compatible with two new strategies for the synthesis of solid-supported lactams and diketopiperazines, respectively, both relying on the high inter- and intramolecular reactivity of cyclic N-acyliminium ions with electron-rich aromatics and heteroaromatics, ultimately affording hydroxamic acid derivatives in high purities.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, University of Copenhagen
Authors: Nandurkar, N. S. (Intern), Petersen, R. (Intern), Qvortrup, K. (Intern), Komnatnyy, V. V. (Intern), Taveras, K. (Intern), Le Quement, S. T. (Intern), Frauenlob, R. (Ekstern), Givskov, M. (Ekstern), Nielsen, T. E. (Intern)
Pages: 7121-7124
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Tetrahedron Letters
Volume: 52
A photolabile linker for the solid-phase synthesis of 4-substituted NH-1,2,3-triazoles

A novel photolabile linker for solid-phase synthesis is presented. The linker displays an azido handle for copper-catalyzed azide–alkyne cycloaddition reactions with a variety of alkynes, remains intact under typical solid-phase reaction conditions, and enables a mild photolytic release of 4-substituted NH-triazoles in high purity and yield.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry
Authors: Qvortrup, K. (Intern), Nielsen, T. E. (Intern)
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Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Chemical Communications
Volume: 47
Issue number: 11
ISSN (Print): 1359-7345
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 6.03 SJR 2.555 SNIP 1.127
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.06 SJR 2.538 SNIP 1.16
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.601 SNIP 1.295 CiteScore 6.7
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.692 SNIP 1.436 CiteScore 6.83
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.752 SNIP 1.372 CiteScore 6.73
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.118 SNIP 1.35 CiteScore 6.21
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.889 SNIP 1.323 CiteScore 5.96
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.781 SNIP 1.255
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.669 SNIP 1.31
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Chemical synthesis on SU-8

In this paper we describe a highly effective surface modification of SU-8 microparticles, the attachment of appropriate linkers for solid-supported synthesis, and the successful chemical modification of these particles via controlled multi-step organic synthesis leading to molecules attached in an unambiguous manner to the support surface.

General information

State: Published
Organisations: Organic Chemistry, Department of Chemistry, 2CureX
Authors: Qvortrup, K. (Intern), Taveras, K. (Intern), Thastrup, O. (Ekstern), Nielsen, T. E. (Intern)
Pages: 1309-1311
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Main Research Area: Technical/natural sciences

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Journal: Chemical Communications
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Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 6.03 SJR 2.555 SNIP 1.127
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.06 SJR 2.538 SNIP 1.16
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 2.601 SNIP 1.295 CiteScore 6.7
Levulinic acid derivatives: Building blocks for solid-phase synthesis of diverse heterocyclic scaffolds

General information
Solid-phase synthesis of an apoptosis-inducing tetrapeptide mimicking the Smac protein

An approach for the solid-phase synthesis of apoptosis-inducing Smac peptidomimetics is presented. Using a Rink linker strategy, tetrapeptides mimicking the N-4-terminal residue of the Smac protein [(N-Me)AVPF sequence] were synthesized on PEGA resin in excellent purities and yields. Following two synthetic routes, a known tetrapeptide, incorporating a substituted proline, previously shown to exhibit excellent biological activity in vitro as well as low toxicity, was synthesized effectively on a solid support.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry, Technical University of Denmark
Authors: Le Quement, S. T. (Intern), Ishøy, M. (Intern), Petersen, M. T. (Intern), Simonsen, P. M. (Forskerdatabase), Holck, N. S. (Ekstern), Nielsen, T. E. (Intern)
Pages: 7049-7053
Publication date: 2011
Main Research Area: Technical/natural sciences

Publication information
Journal: Tetrahedron Letters
Volume: 52
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ISSN (Print): 0040-4039
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.571 SJR 0.683 CiteScore 2.04
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.13 SJR 0.754 SNIP 0.637
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.748 SNIP 0.739 CiteScore 2.3
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.796 SNIP 0.791 CiteScore 2.41
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.908 SNIP 0.793 CiteScore 2.4
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.094 SNIP 0.84 CiteScore 2.45
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.217 SNIP 0.93 CiteScore 2.76
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.245 SNIP 0.912
Web of Science (2010): Indexed yes
Solid-Phase Synthesis of Smac Peptidomimetics Incorporating Triazoloprolines and Biarylalanines

Apoptotic induction mechanisms are of crucial importance for the general homeostasis of multicellular organisms. In cancer the apoptotic pathways are downregulated, which, at least partly, is due to an abundance of inhibitors of apoptosis proteins (IAPs) that block the apoptotic cascade by deactivating proteolytic caspases. The Smac protein has an antagonistic effect on IAPs, thus providing structural clues for the synthesis of new pro-apoptotic compounds. Herein, we report a solid-phase approach for the synthesis of Smac-derived tetrapeptide libraries. On the basis of a common (N-Me)AVPF sequence, peptides incorporating triazoloprolines and biarylalanines were synthesized by means of Cu(I)-catalyzed azide–alkyne cycloaddition and Pd-catalyzed Suzuki cross-coupling reactions. Solid-phase procedures were optimized to high efficiency, thus accessing all products in excellent crude purities and yields (both typically above 90%). The peptides were subjected to biological evaluation in a live/dead cellular assay which revealed that structural decorations on the AVPF sequence indeed are highly important for cytotoxicity toward HeLa cells.
Synthesis of Heterocycles through a Ruthenium-Catalyzed Tandem Ring-Closing Metathesis/Isomerization/N-Acyliminium Cyclization Sequence

Tandem bicycle: In the title reaction double bonds created during ring-closing metathesis isomerize to generate reactive iminium intermediates that undergo intramolecular cyclization reactions with tethered heteroatom and carbon nucleophiles. In this way, a series of biologically interesting heterocyclic compounds can be made, including a known precursor for the total synthesis of the antiparasitic natural product harmicine.
Synthesis of Heterocycles through a Ruthenium-Catalyzed Tandem Ring-Closing Metathesis/Isomerization/N-Acyliminium Cyclization Sequence

Erfolgreiches Tandem: In der Titelreaktion isomerisieren Doppelbindungen, die bei der Ringschlussmetathese erzeugt werden, wobei reaktive Iminiumintermediate entstehen, die in intramolekularen Cyclisierungen mit Seitenketten-Heteroatom- und -Kohlenstoffnucleophilen reagieren. So wurde eine Reihe biologisch interessanter heterocyclischer Verbindungen hergestellt, darunter eine bekannte Vorstufe für die Totalsynthese des Antiparasitikums Harmicin.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry, Department of Organic Chemistry
Authors: Ascic, E. (Intern), Jensen, J. F. (Intern), Nielsen, T. E. (Intern)
Pages: 5294-5297
Publication date: 2011
Main Research Area: Technical/natural sciences

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Issue number: 22
ISSN (Print): 1433-7851
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.165 SJR 6.155 CiteScore 11.31
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 10.8 SJR 5.954 SNIP 2.146
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.888 SNIP 2.225 CiteScore 11.13
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.811 SNIP 2.307 CiteScore 10.84
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.702 SNIP 2.198 CiteScore 10.7
ISI indexed (2013): ISI indexed yes
N-Acyliminium Intermediates in Solid-Phase Synthesis

N-Acyliminium ions are powerful intermediates in synthetic organic chemistry. Examples of their use are numerous in solution-phase synthesis, but there are unmerited few reports on these highly reactive electrophiles in solid-phase synthesis. The present review covers the literature to date and illustrates the methods used to generate N-acyliminium intermediates on solid support and their further elaboration to a range of pharmacologically interesting peptidomimetics, heterocycles, and other small molecules.

Bibliographical note
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General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry
Authors: Quement, S. T. L. (Intern), Petersen, R. (Intern), Meldal, M. (Ekstern), Nielsen, T. E. (Intern)
Traceless Azido Linker for the Solid-Phase Synthesis of NH-1,2,3-Triazoles via Cu-Catalyzed Azide-Alkyne Cycloaddition Reactions

A broadly useful acid-labile traceless azido linker for the solid-phase synthesis of NH-1,2,3-triazoles is presented. A variety of alkynes were efficiently immobilized on a range of polymeric supports by Cu(I)-mediated azide-alkyne cycloadditions. Supported triazoles showed excellent compatibility with subsequent peptide chemistry. Release of pure material (typically >95%) from the solid support was readily achieved by treatment with aqueous TFA.

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry
Authors: Cohrt, A. E. (Intern), Jensen, J. F. (Intern), Nielsen, T. E. (Intern)
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.197 SJR 2.853 CiteScore 6.16
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.32 SJR 2.985 SNIP 1.216
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 3.005 SNIP 1.324 CiteScore 6.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.964 SNIP 1.324 CiteScore 6.18
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.157 SNIP 1.322 CiteScore 6.12
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.338 SNIP 1.355 CiteScore 5.7
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.267 SNIP 1.356 CiteScore 5.81
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.014 SNIP 1.304
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.061 SNIP 1.37
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 3.319 SNIP 1.299
Web of Science (2008): Indexed yes
Solid-phase synthesis of complex and pharmacologically interesting heterocycles

Efficient routes for the creation of heterocycles continue to be one of the primary goals for solid-phase synthesis. Recent advances in this field rely most notably on transition-metal-catalysis and N-acyliminium chemistry to mediate a range of cyclization processes for the generation of compounds with significant structural complexity and diversity. This review describes some of the most systematic solid-phase approaches that are potentially suited for pharmaceutical applications, that is, the methods described are useful for the synthesis of compound collections, and exhibit tunable stereochemistry, scaffold structure, and appendage modification.
An Experimental and Theoretical Study of the Mechanism of Stannylcupration of α,β-Acetylenic Ketones and Esters

The title reaction has been investigated by experimental and computational (DFT) techniques, and subsequently compared to the corresponding carbocupration reaction, with particular emphasis on the stereoselectivity. For stannylcupration of an ynone substrate, only the anti-addition product is observed, whereas for the corresponding ynoate substrate, the stereoselectivity can be affected by the reaction conditions: in the presence of methanol as proton donor, the initial syn-addition product can be trapped, whereas a syn/anti mixture is obtained in a non-protic solvent. This is in sharp contrast to the carbocupration of the same ynone substrate with a cyanocuprate (RCu(CN)Li), which is highly selective for syn-addition. The product selectivities can be understood from a detailed computational characterization of the reaction paths, and in particular from the relative stabilities of the vinyl cuprate and allenolate intermediates. It is suggested that the stereodetermining step is protonation of vinyl cuprate intermediates.

General information
State: Published
Organisations: Department of Chemistry, Technical University of Denmark
Authors: Ahlquist, M. S. G. (Intern), Nielsen, T. E. (Intern), Le Quement, S. (Ekstern), Tanner, D. A. (Intern), Norrby, P. (Intern)
Synthesis of the Zoanthamine ABC Ring System: Some Surprises from Intramolecular Diels-Alder Reactions

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry
Authors: Juhl, M. (Intern), Nielsen, T. E. (Intern), Le Quement, S. T. (Intern), Tanner, D. A. (Intern)
Pages: 265-280
Publication date: 2006
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of Organic Chemistry
Volume: 71
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 0.997 SJR 1.846 CiteScore 4.55
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.59 SJR 2.001 SNIP 1.035
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.997 SNIP 1.166 CiteScore 4.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.007 SNIP 1.219 CiteScore 4.69
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.092 SNIP 1.169 CiteScore 4.51
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 2.286 SNIP 1.223 CiteScore 4.31
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 2.265 SNIP 1.239 CiteScore 4.43
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.127 SNIP 1.169
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 2.198 SNIP 1.251
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.349 SNIP 1.217
Web of Science (2008): Indexed yes
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 2.249 SNIP 1.296
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 2.03 SNIP 1.284
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.956 SNIP 1.299
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 1.912 SNIP 1.333
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 2.188 SNIP 1.417
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 2.048 SNIP 1.36
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 2.024 SNIP 1.342
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 1.943 SNIP 1.339
Original language: English
Source: orbit
Source-ID: 192107
Publication: Research - peer-review › Journal article – Annual report year: 2006

Pd-Catalyzed Silastannation of Secondary Propargylic Alcohols and Their Derivatives

General information
State: Published
Organisations: Organic Chemistry, Department of Chemistry
Authors: Nielsen, T. E. (Intern), Le Quement, S. T. (Intern), Tanner, D. A. (Intern)
Pages: 1381 - 1390
Publication date: 2004
Main Research Area: Technical/natural sciences

Publication information
Journal: Synthesis
Issue number: 9
Original language: English
Source: orbit
Source-ID: 154375
Publication: Research - peer-review › Journal article – Annual report year: 2004

Highly stereoselective addition of stannylcuprates to alkynones
The addition of stannylcuprate reagents such as (Bu3Sn)(PhS)CuLi to alkynones has been found to proceed in high yield and with excellent stereoselectivity for the Z isomer of the product (>95%). The behavior of the stannylcuprates is thus very different from that of their "carbocuprate" counterparts such as Me2CuLi or Me2Cu(CN)Li-2 which are nonstereoselective. Furthermore, in contrast to the reactions of (R3Sn)(PhS)CuLi with the corresponding alkynoates, the presence of a proton source in the reaction medium has no effect on the stereoselectivity of the reaction of alkynones.

General information
State: Published
Organisations: Department of Chemistry
Authors: Nielsen, T. E. (Intern), de Dios, M. (Ekstern), Tanner, D. A. (Intern)
Pages: 7309-7313
Publication date: 2002
Main Research Area: Technical/natural sciences
Stereoselective synthesis of (E)-beta-tributylstannyl-alpha,beta-unsaturated ketones: Construction of a key intermediate for the total synthesis of zoanthamine

(E)-beta-Trialkylstannyl-alpha,beta-unsaturated ketones are readily available from secondary propargylic alcohols via a two-step sequence involving highly regio- and stereoselective Pd(0)-catalyzed hydrostannation followed by mild oxidation (TPAP). The methodology has been applied to the synthesis of enantiomerically pure enone 12 which is a key intermediate for the total synthesis of zoanthamine, a structurally complex marine natural product.
Stannylcupration of (alpha, beta)-Unsaturated Ketones

General information
State: Published
Organisations: Department of Chemistry
Authors: Nielsen, T. E. (Intern), Tanner, D. A. (Intern)
Publication date: 2001
Event: Poster session presented at ACS National Meeting, Chicago, USA, .
Main Research Area: Technical/natural sciences
Source: orbit
Source-ID: 50532
Publication: Research › Poster – Annual report year: 2001

Projects:

Development of receptors for Aqueous Carbohydrate Recognition
Department of Chemistry
Period: 01/01/2016 → 31/12/2018
Number of participants: 4
Phd Student:
Baj, Vanessa (Intern)
Supervisor:
Behrens, Carsten (Ekstern)
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Beeren, Sophie (Intern)

Financing sources
In-Bead Diagnostics and Screening

Department of Chemistry
Period: 15/09/2013 → 31/10/2014
Number of participants: 2
PhD Student:
Væring, Philip (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt EU-finansieret
Project: PhD

Microfabrication and Chemical Functionalization of Tailor-made Materials for Biomedical Applications

Department of Chemistry
Period: 01/09/2013 → 21/06/2017
Number of participants: 6
PhD Student:
Mortensen, Kim Thollund (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Qvortrup, Katrine (Intern)
Examiner:
Tanner, David Ackland (Intern)
Meldal, Morten (Ekstern)
Spring, David Robert (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Relations
Publications:
Development of a UV-Cleavable Protecting Group for Hydroxylamines, Synthesis of a Structurally Wide Variety of Hydroxamic Acids, and Identification of Histone Deacetylase Inhibitors
Project: PhD

Ruthenium-Catalyzed Tandem RCM/Isomerization Sequences

Department of Chemistry
Period: 15/03/2012 → 03/06/2015
Number of participants: 6
PhD Student:
Ishøy, Mette (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Andresen, Thomas Lars (Intern)
Poulsen, Thomas Bjørn (Intern)
Nelson, Adam S. (Ekstern)
Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Total synthesis of Sioboldine A
Department of Chemistry
Period: 15/03/2012 → 02/09/2015
Number of participants: 6
Phd Student:
Olsen, Lasse Bohn (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Duus, Jens Øllgaard (Intern)
Craig, Donald (Ekstern)
Nielsen, John (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Catalysis Orchestration: One Catalysts with multiple modes of Action
Department of Chemistry
Period: 01/03/2012 → 03/06/2015
Number of participants: 6
Phd Student:
Ohm, Ragnhild Gaard (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Fristrup, Peter (Intern)
Andersson, Pher G. (Ekstern)
Nielsen, Mogens Brøndsted (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Ligand assisted Site-Specific Modification of Proteins
Department of Chemistry
Period: 01/01/2012 → 30/09/2015
Number of participants: 6
Phd Student:
Bang, Claus Gunnar (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Gotfredsen, Charlotte Held (Intern)
Heinis, Christian (Ekstern)
Jensen, Knud Jørgen (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: ErhvervsPhD-ordningen VTU
Project: PhD

Synthesis of Antibacterial Tetrahydro-b-Carbolines via Metal-Catalyzed N-Allylamine Isomerization/N-Alkyliminium Cyclization Sequence
Department of Chemistry
Period: 01/11/2011 → 04/02/2015
Number of participants: 6
Phd Student: Hansen, Casper Lykke (Intern)
Supervisor: Nielsen, Thomas Eiland (Intern)
Main Supervisor: Tanner, David Ackland (Intern)
Examiner: Fristrup, Peter (Intern)
Meldal, Morten (Ekstern)
Stockman, Robert A. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Synthesis of novel antibacterial agents via combinatorial solid-phase synthesis
Department of Chemistry
Period: 01/11/2011 → 13/05/2015
Number of participants: 6
Phd Student: Flagstad, Thomas (Intern)
Supervisor: Nielsen, Thomas Eiland (Intern)
Main Supervisor: Tanner, David Ackland (Intern)
Examiner: Madsen, Robert (Intern)
Jensen, Knud Jørgen (Intern)
Ovaa, Huib (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Synthesis of Antimicrobial Natural Product Derivatives on Photolabile Solid Support
Department of Chemistry
Period: 15/10/2011 → 26/05/2016
Number of participants: 6
Phd Student: Mikkelsen, Remi Jacob Thomsen (Intern)
Supervisor: Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Duus, Jens Øllgaard (Intern)
Nielsen, John (Intern)
Ovaa, Huib (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.

Relations
Publications:
Solid-Phase Synthesis for the Construction of Biologically Interesting Molecules and the Total Synthesis of Trioxacarcin DC-45-A2
Project: PhD

Ruthenium-catalyzed tandem reactions
Department of Chemistry
Period: 01/09/2011 → 03/06/2015
Number of participants: 6
Phd Student:
Petersen, Mette Terp (Intern)
Supervisor:
Nielsen, Thomas Eiland (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Clausen, Mads Hartvig (Intern)
Skrydstrup, Troels (Ekstern)
Spring, David Robert (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Azumamide E and Analogs as Epigenetic Modulators
Department of Chemistry
Period: 01/11/2010 → 07/05/2014
Number of participants: 5
Phd Student:
Maolanon, Alex (Intern)
Main Supervisor:
Olsen, Christian Adam (Intern)
Examiner:
Nielsen, Thomas Eiland (Intern)
Poulsen, Thomas B. (Ekstern)
Szpilman, Alex M. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Eksternt finansieret virksomhed
Project: PhD

Organic Synthesis of antimicrobial agents and antibiotics
Department of Chemistry
Integrated Chemical Synthesis and Cell Screening In Patient Cells
Department of Chemistry
Period: 15/10/2009 → 31/03/2014
Number of participants: 2
Phd Student:
Taveras, Kennedy (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)
Examiner:
Nielsen, John (Intern)
Stockman, Robert A. (Ekstern)
Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.
Project: PhD

Diversity-Oriented Synthesis of Small Molecules Trageting Bacterial Biofilm
Department of Chemistry
Period: 01/08/2009 → 17/12/2012
Number of participants: 4
Phd Student:
Komnatnyy, Vitaly V. (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)
Examiner:
Tanner, David Ackland (Intern)
Spring, David Robert (Ekstern)
Financing sources
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering
Project: PhD

Diversity-Oriented Synthesis of Composite Antomicrobial Agents
Department of Chemistry
Period: 01/05/2009 → 17/08/2012
Number of participants: 5
Phd Student:
Ascic, Erhad (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)
Examiner:
Madsen, Robert (Intern)
Nelson, Adam S. (Ekstern)
Design, Synthesis and Biological Evaluation of Histone Demethylase Inhibitors

Department of Chemistry
Period: 01/03/2009 → 20/08/2012
Number of participants: 5
PhD Student:
Cohrt, Anders Emil O'Hanlon (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)
Examiner:
Olsen, Christian Adam (Intern)
Benito, Juan M. (Ekstern)
Nielsen, John (Intern)

Development of New Methods for the Synthesis of Biologically Active small Molecules

Department of Chemistry
Period: 01/10/2008 → 18/04/2012
Number of participants: 5
PhD Student:
Petersen, Rico (Intern)
Main Supervisor:
Nielsen, Thomas Eiland (Intern)
Examiner:
Tanner, David Ackland (Intern)
Jensen, Knud Jørgen (Intern)
Looper, Ryan E. (Ekstern)

Tools for Chemical Biology: New Macrocyclic Antibiotics from Diversity Oriented Synthesis

Department of Chemistry
Period: 01/04/2007 → 24/11/2010
Number of participants: 6
PhD Student:
Madsen, Charlotte Marie (Intern)
Supervisor:
Gottfredsen, Charlotte Held (Intern)
Main Supervisor:
Clausen, Mads Hartvig (Intern)
Examiner:
Nielsen, Thomas Eiland (Intern)
Nelson, Adam S. (Ekstern)
Nielsen, John (Intern)
Financing sources
Source: Internal funding (public)
Name of research programme: Institut/centerfinansieret
Project: PhD

Syntetiske GLP-1 analoger
Department of Chemistry
Period: 01/01/2007 → 21/04/2010
Number of participants: 6
Phd Student:
Storgaard, Morten (Intern)
Supervisor:
Peschke, Bernd (Ekstern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Nielsen, Thomas Eiland (Intern)
Greve, Daniel R. (Intern)
Rademann, Jörg (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: ErhvervsPhD-ordningen VTU
Project: PhD

Metalorganiske reaktioner med aldehyder og kulhydrater
Department of Chemistry
Period: 01/09/2005 → 25/02/2009
Number of participants: 5
Phd Student:
Monrad, Rune Nygaard (Intern)
Main Supervisor:
Madsen, Robert (Intern)
Examiner:
Nielsen, Thomas Eiland (Intern)
Bols, Mikael (Ekstern)
Thiem, Joachim Erich (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: DTU-lønnet stipendie
Project: PhD

Alkenytltin Chemistry: Method Development and Applications in Organic Synthesis
Department of Chemistry
Period: 01/03/1999 → 16/07/2002
Number of participants: 6
Phd Student:
Nielsen, Thomas Eiland (Intern)
Supervisor:
Kjær, Anders (Intern)
Main Supervisor:
Tanner, David Ackland (Intern)
Examiner:
Madsen, Robert (Intern)
Frejd, Torbjørn (Ekstern)
Skrydstrup, Troels (Ekstern)
Financing sources
Source: Internal funding (public)
Name of research programme: DTU-lønnet stipendie
Project: PhD