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Symposium-in-Print

Tetrahedron Young Investigator Award 2009

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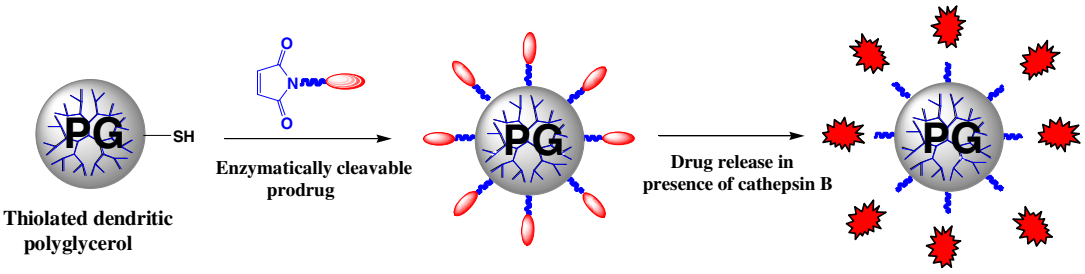
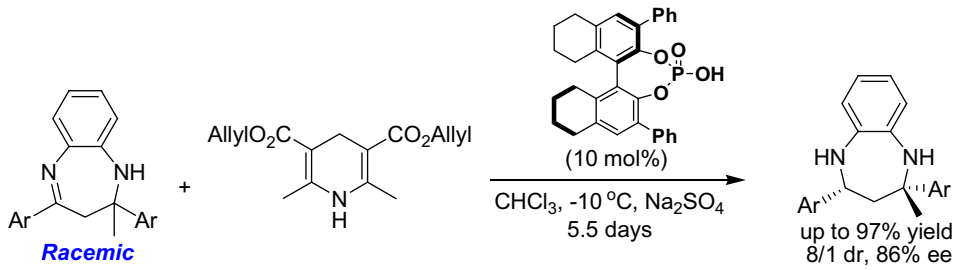
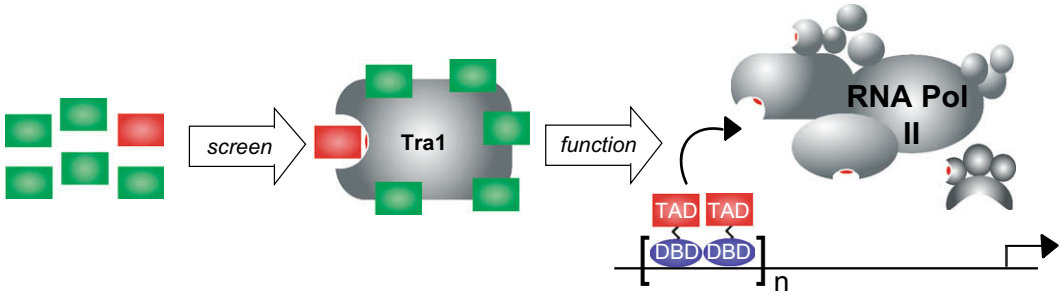
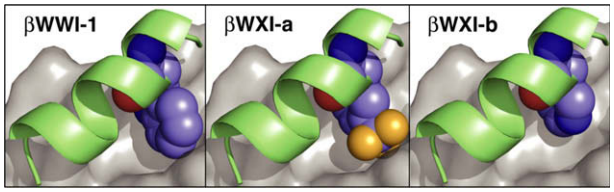
Edited by: Dale L. Boger

Contents

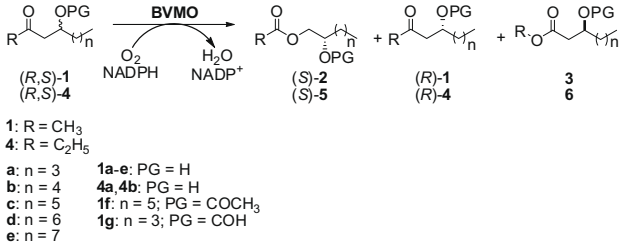




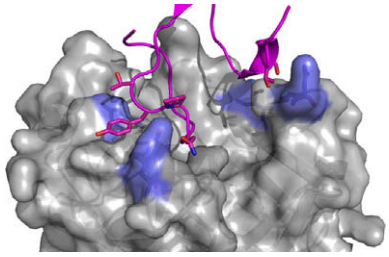




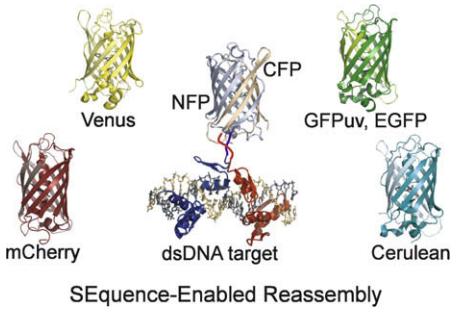
We recently reported a β^3-decapeptide, βWWI-1, that binds a validated gp41 model in vitro and inhibits gp41-mediated fusion in cell culture. Here we report six analogs of βWWI-1 containing a variety of non-natural side chains in place of the central tryptophan of the WWI-epitope. These analogs are compared on the basis of both gp41 affinity in vitro and fusion inhibition in live, HIV-infected cells. One new β^3-peptide, βWXI-a, offers a significantly improved CC_{50}/EC_{50} ratio in the live cell assay.

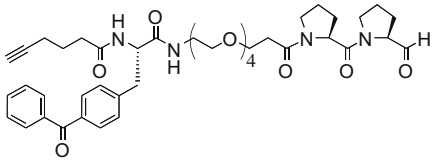


Kinetic resolution of linear aliphatic β-substituted ketones with engineered *Escherichia coli* cells expressing BVMOs of different bacterial origin is reported. Regioselectivity as well as enantioselectivity of the biotransformation are examined in detail.

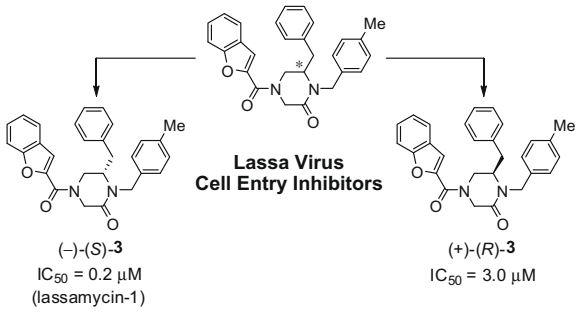


Small antigenic differences between the human and mouse versions of MT-SP1 greatly affect the binding of an anti-MT-SP1 antibody. The cross-reactivity of the antibody was improved by making computationally-designed point mutants of antibody residues that contact these divergent residues.

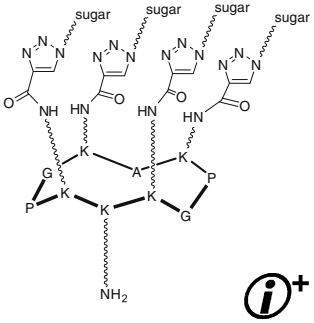


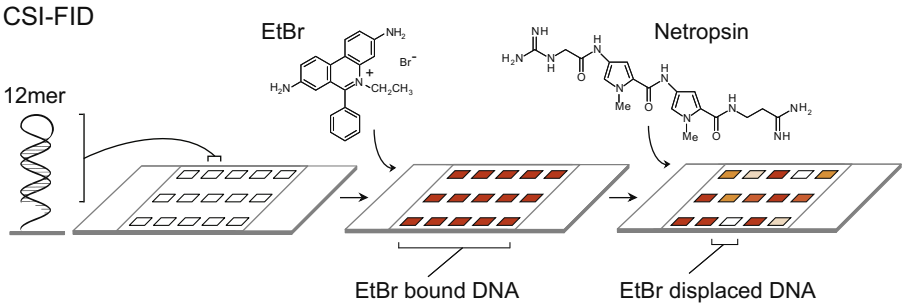


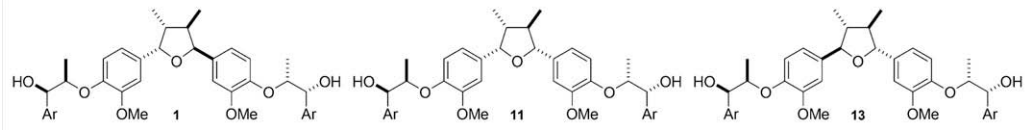
The potential of peptidyl aldehydes as emerging activity-based probes is reported here for the first time.



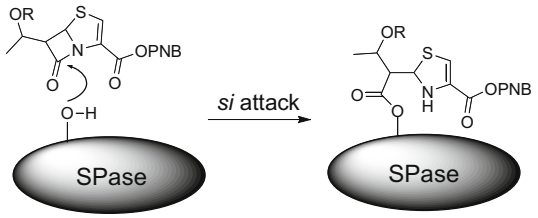
A facile synthesis of cyclopeptide-centered multivalent glycoclusters using Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes, so called 'click chemistry', has been developed. The affinities of mannose-specific protein Concanavalin A (Con A) toward two synthetic glycoclusters respectively bearing divalent or tetravalent mannoses were investigated by surface plasmon resonance.



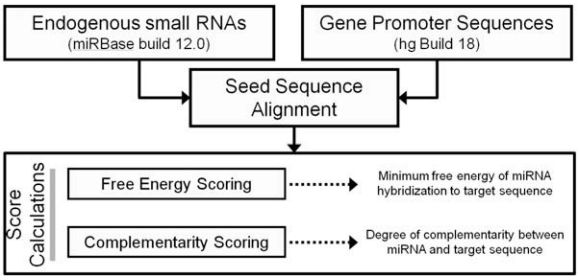




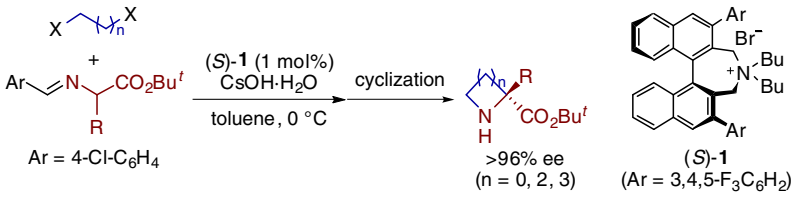
HIF-1 inhibition by manassantin A (**1**) and analogues with modified tetrahydrofuran configurations (**11** and **13**) is reported.

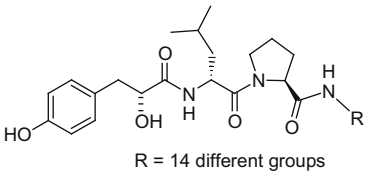


The synthesis of a 5*S* penem inhibitor of bacterial signal peptidase is reported and shown to have activity against human pathogens and to be potentially optimizable for spectrum and activity.



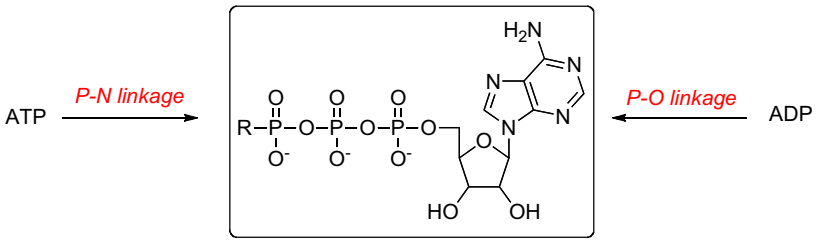
A method for detecting potential microRNA target sites within gene promoters.

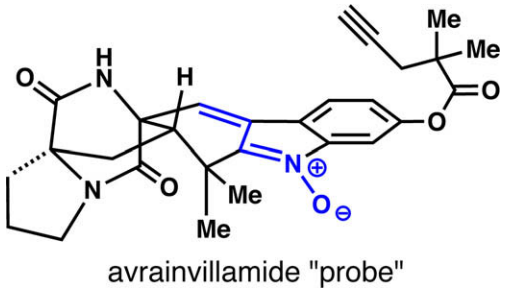


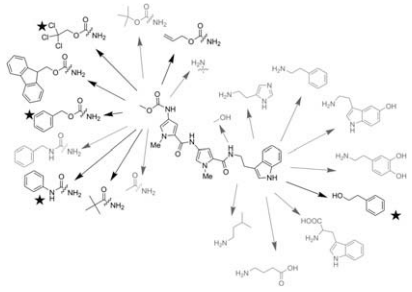


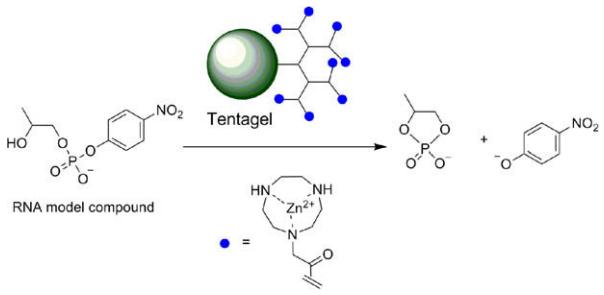
R = 14 different groups

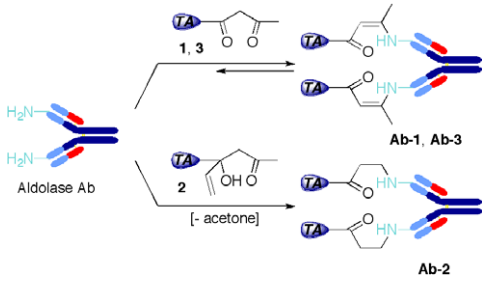
Simpler analogs of aeruginosin 298-A

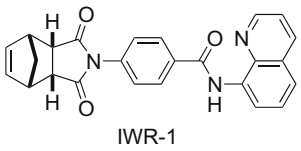






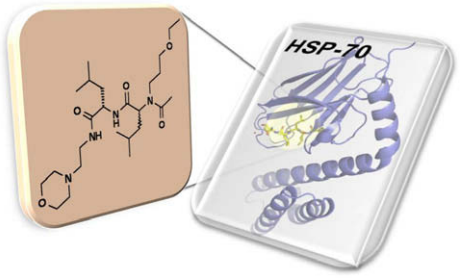


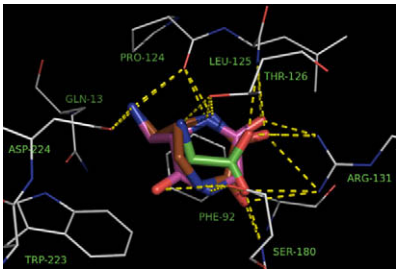


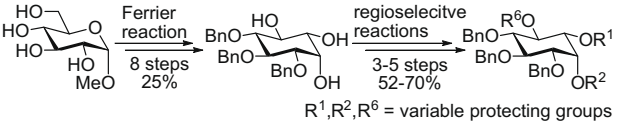


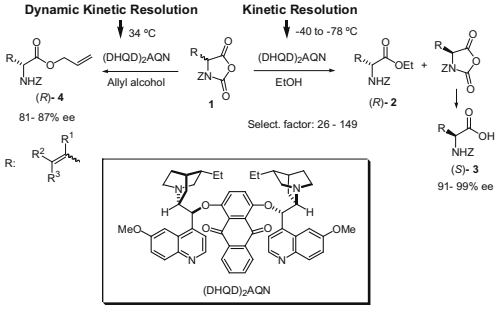
IWR-1

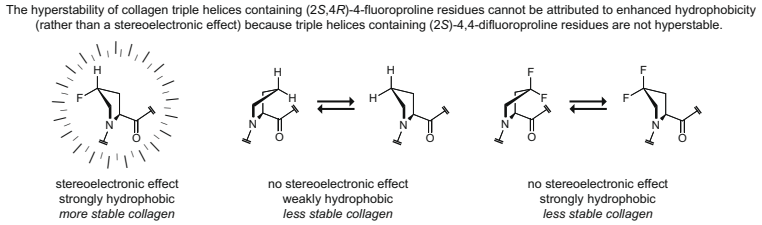
SAR studies of IWR-1 are described.



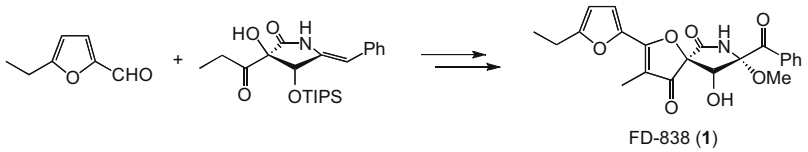




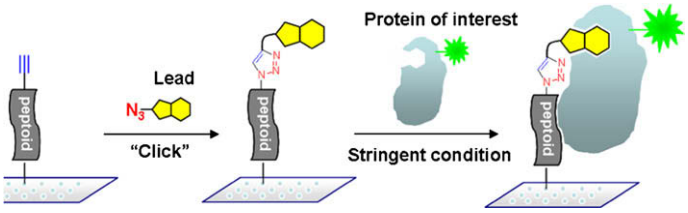




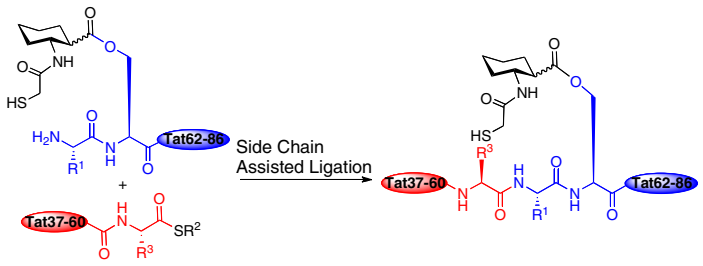
(2*S*,4*R*)-4-Fluoroproline residues stabilize the collagen triple helix by the gauche effect—a stereoelectronic effect that enforces a Cg-exo ring pucker and thus properly preorganizes the torsion angles in the backbone.

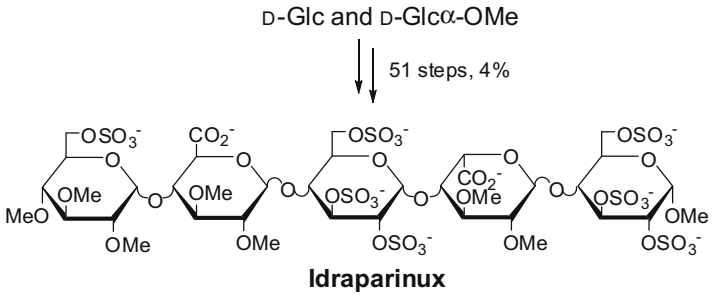


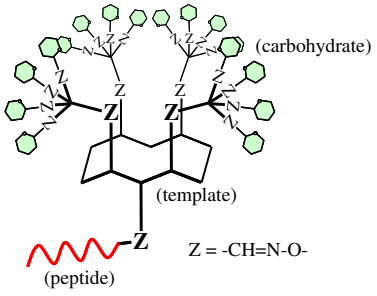
First asymmetric total synthesis of FD-838, a naturally occurring azaspirobicyclic product, has been accomplished allowing determination of its absolute stereochemistry.



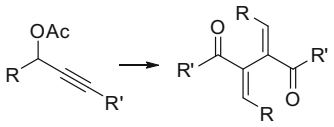
A rapid array-based protocol is presented by which a modest affinity protein-binding small molecule can be appended to a library of peptoids via click chemistry. The array can then be screened for improved ligands that exhibit a higher affinity for the protein target.



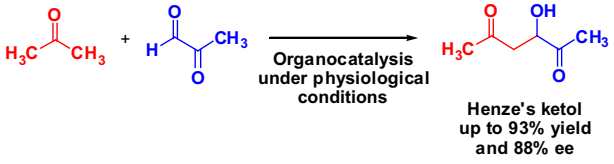




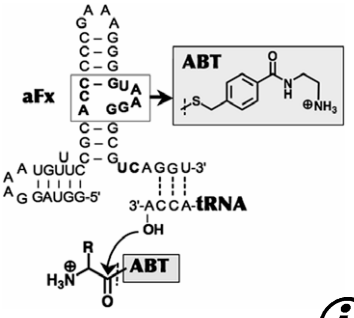
We report an iterative oxime-based procedure for the assembly of biologically relevant carbohydrates and peptides onto a cyclopeptidic scaffold.

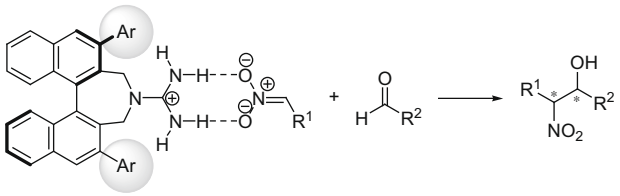


A highly efficient homogeneous gold-catalyzed oxidative dimerization of propargylic acetates is described.

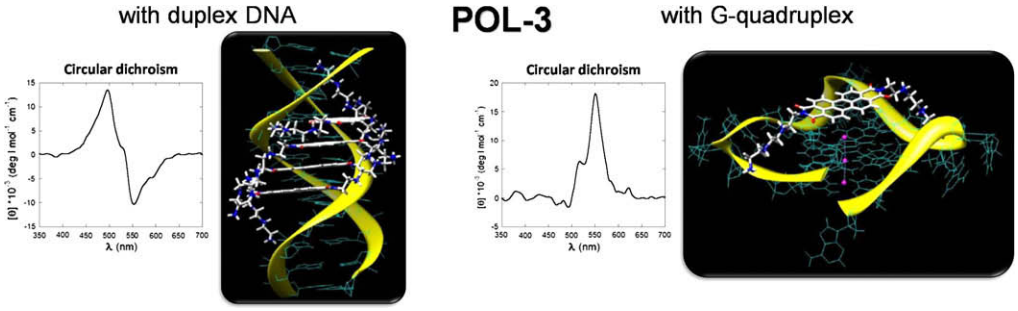


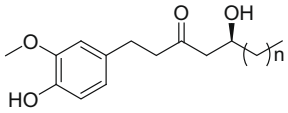
Here, we report a new flexizyme (a flexible de novo tRNA acylation ribozyme) system, a pair of amino-derivatizing benzyl thioester (ABT) and amino flexizyme (aFx). This new flexizyme system enables for tRNA aminoacylation with hydrophobic amino acids that are difficult to dissolve in the aqueous reaction buffer, which has been problematic to perform the reaction using the parental flexizyme and the substrate pairs.





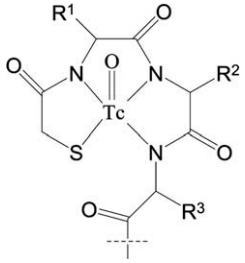
Diastereo- and enantioselective Henry reaction of nitroalkanes with aldehydes catalyzed by axially chiral guanidines is accomplished on the basis of complexation between chiral guanidinium and nitronate through two hydrogen bonds.



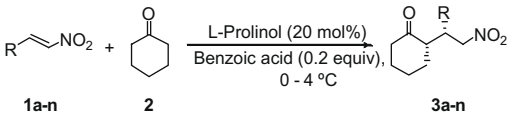


n=4, (+)-(*S*)-[6]-Gingerol (**1a**)
n=6, (+)-(*S*)-[8]-Gingerol (**1b**)
n=8, (+)-(*S*)-[10]-Gingerol (**1c**)

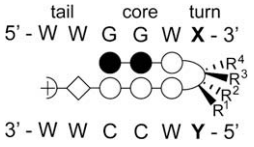
An enantioselective approach to (+)-(*S*)-[*n*]-gingerols (**1a**–**c**) has been developed.

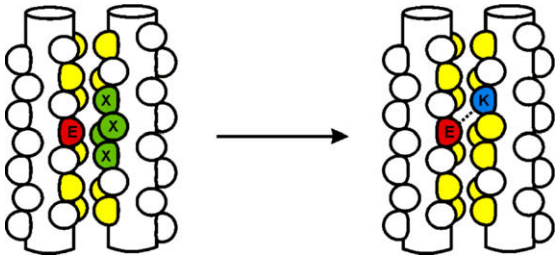


HER2-binding Affibody molecules carrying internally positioned ^{99m}Tc chelators have been synthesized and compared to N-terminally modified analogues as tumor targeting agents. The effects of chelator composition and position are discussed.

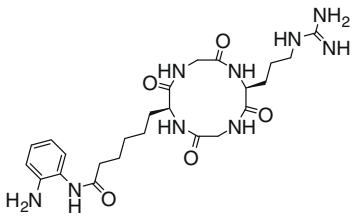


The first L-prolinol catalyzed asymmetric Michael addition of cyclohexanone to nitroolefins in the presence of benzoic acid to afford Michael adducts with high diastereoselectivities (87:13–>99:1) and enantioselectivities (82–96%) was described.

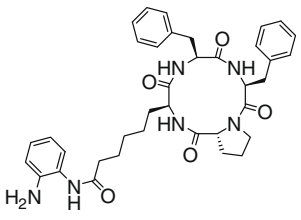




Using phage display technology, a stable coiled coil pair of novel primary structure was selected. A staggered salt bridge within the hydrophobic core allows the highly specific interaction of both α-helices.



1



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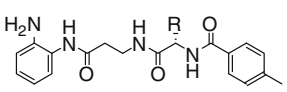
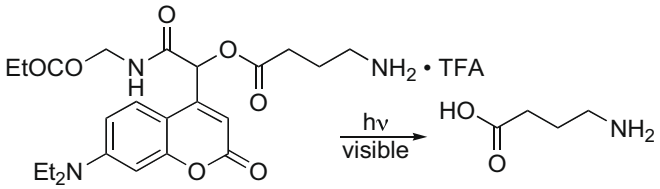
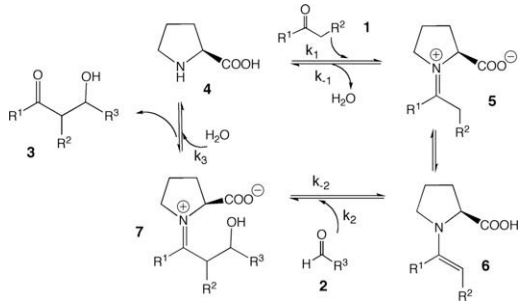
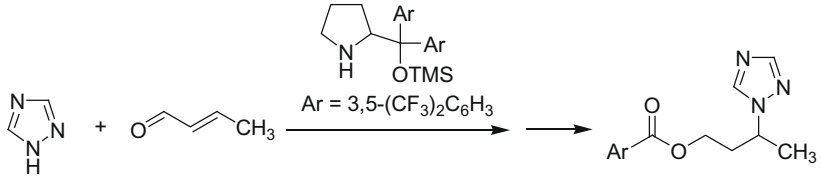


15 R = H
16 R = $(CH_2)_3NHC(NH)NH_2$

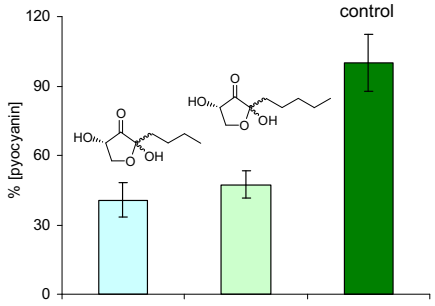
Novel hybrid benzamide–peptide histone deacetylase inhibitors have been synthesized and structural–activity relationships are detailed, along with enzyme and cellular activities.



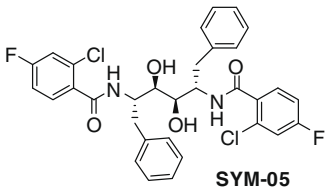




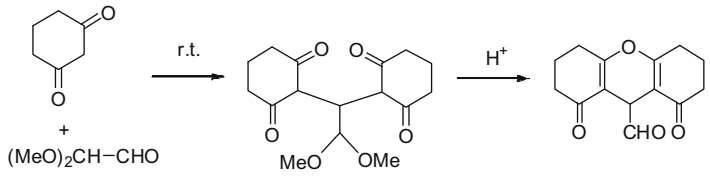
1*H*-1,2,4-Triazole reacted with 2-butenal in the presence of diaryl prolinol silyl ether **3** and benzonic acid to give 3-(1*H*-1,2,4-triazol-1-yl)butanal **4**, which was subsequently reduced and then treated with various acyl chloride to generate enantioriched 3-(1*H*-1,2,4-triazol-1-yl)butyl benzoates **6**. Some of triazoles **6** exhibited strong binding interactions with the cytochrome P450-dependent sterol 14α-demethylase (CYP51). For example, compound (*R*)-**6f** showed the best binding activity with K_d 0.3381 μM.



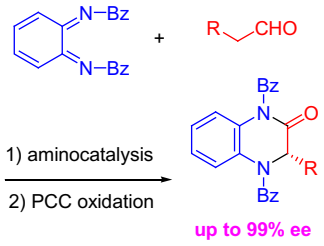
AI-2 analogs with extended alkyl substitutions at C-2 of dihydroxypentanedione (DPD) function as synergistic agonists of quorum sensing (QS) in *Vibrio harveyi* and as inhibitors of QS in *Pseudomonas aeruginosa*.



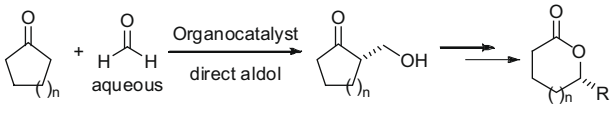
A solid-phase strategy for rapid preparation of small molecule-based, symmetric and asymmetric diols is described, and of the 75 diols synthesized, one was found to be a potent and selective inhibitor (K_i = 400 nM) against HIV-1 protease.

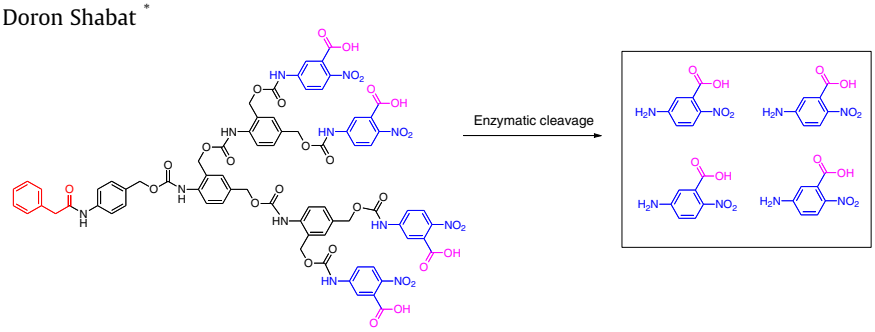


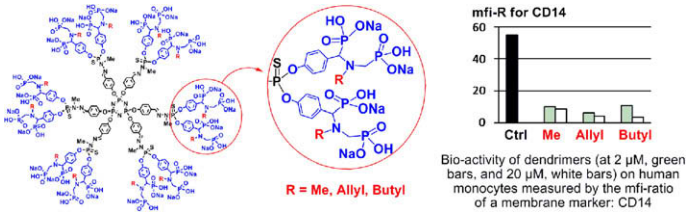
Catalyst-free tandem aldol condensation/Michael addition of enolizable aldehydes with 1,3-cyclohexanediones are described.

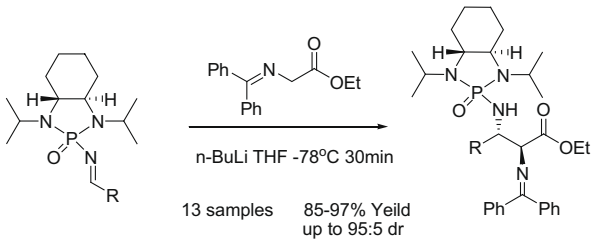


A highly enantioselective inverse electron demand hetero-Diels–Alder reaction of *o*-benzoquinone diimide and aldehydes has been developed.

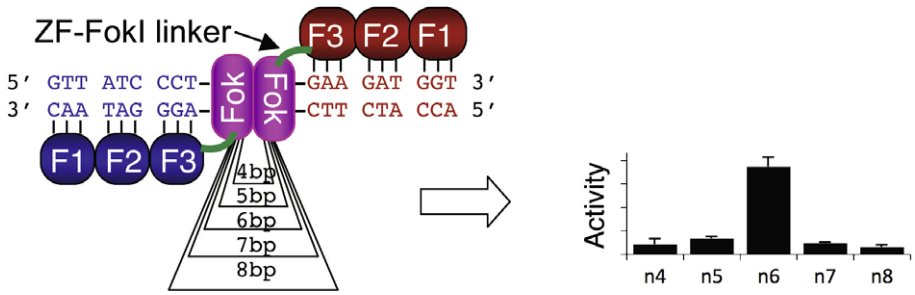


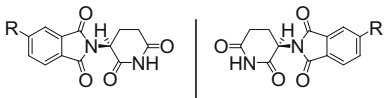






Chiral phosphonyl imines having *N*-isopropyl groups in the auxiliary were found to react with lithium glycine enolates in good yields and high diastereoselectivity.

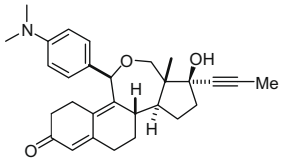




(*S*)-**1**; R=H
(*S*)-**2**; R=OH

(*R*)-**1**; R=H
(*R*)-**2**; R=OH

The first asymmetric synthesis of (*S*)- and (*R*)-5-hydroxythalidomides (**2**), one of thalidomide's major metabolites, was achieved. Configurational stability and stereochemical biological evaluation of (*S*)- and (*R*)-**1** and **2** were investigated.



Pseudo steroid, **1c**

OTHER CONTENTS

*Corresponding author
Supplementary data available via ScienceDirect

COVER

The cover depicts a chemically programmed antibody acting on a cancer cell. Chemically programmed antibodies are a new class of drugs currently in clinical trials for cancer and diabetes. [Gavrilyuk, J. I.; Wuellner, U.; Salahuddin, S.; Goswami, R. K.; Sinha, S. C.; Barbas III, C. F. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 3716.]

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