

ASSEMBLY OF PEPTIDOMIMETICS BY MULTICOMPONENT REACTIONS

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PEPTIDES AND PEPTIDOMIMETICS

- 1922 - treatment of a patients with type I diabetes with insulin
- Low metabolic stability, lack of oral activity, rapid excretion, and low cell membrane permeability
- Backbone modifications vs side-chain modifications
- Non-canonical amino acids, non-peptidic scaffolds
- Structural and functional mimicry of bioactive peptides
- 60 peptide-based drugs on the market, more that 140 in clinical pipeline

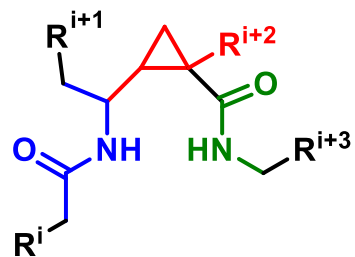
PEPTIDOMIMETICS

Structural and functional mimicry of peptides



FUNCTIONAL PEPTIDOMIMETICS

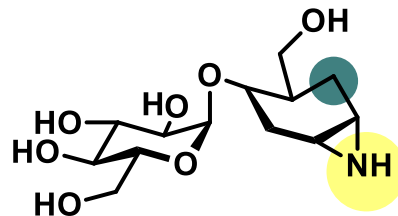
NON-NATURAL AMINO ACIDS



cyclopropane-based
peptidomimetics

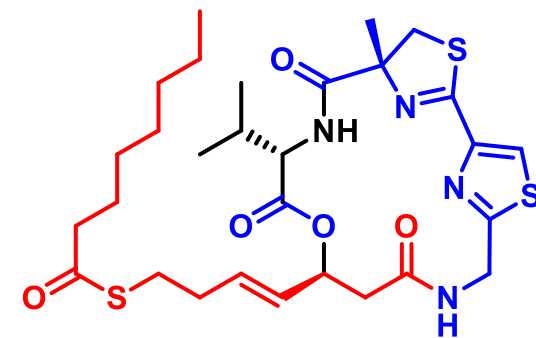
Chem. Eur. J. **23** (2017) 3159-3168

STRUCTURAL MIMETICS



Org. Lett. **20** (2018) 7488-7492

MACROCYCLIZATION



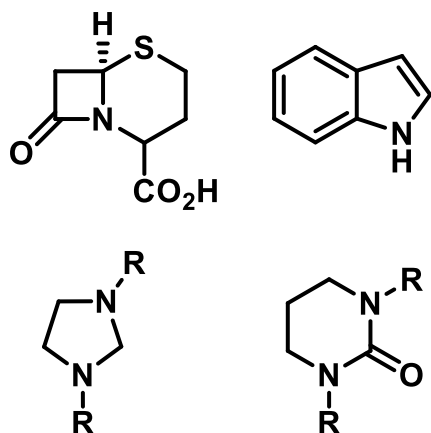
LARGAZOLE

J. Am. Chem. Soc. **141** (2019) 4167-4181

OUR APPROACH

HETEROCYCLICS

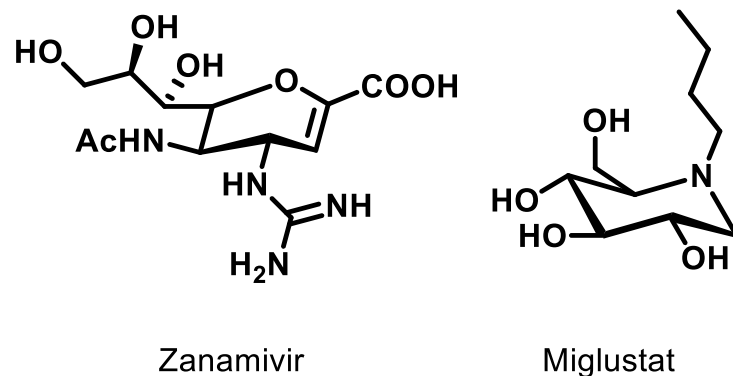
60 % (640) of U.S. FDA approved small-molecule drugs are nitrogen-containing heterocyclics



Org. Biomol. Chem. **17** (2019) 3670-3708
J. Med. Chem. **57** (2014) 10257-10274

PEPTIDE-CARBOHYDRATE ADDUCTS

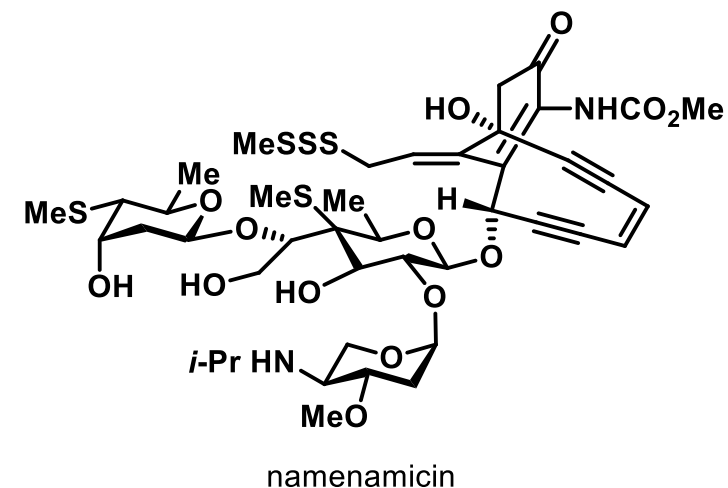
60 peptide-based drugs
131 carbohydrate drugs
diagnostics, vaccines, therapeutics



Chem. Eur. J. **21** (2015) 10616-10628
Drug Discov. Ther. **9** (2015) 79-87

PEPTIDE-ENEDIYNE ADDUCTS

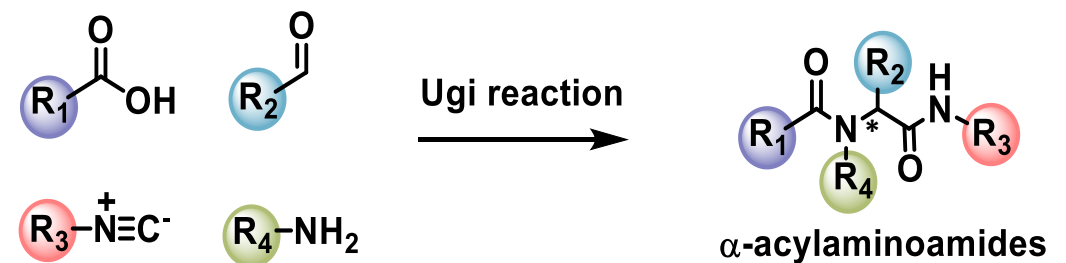
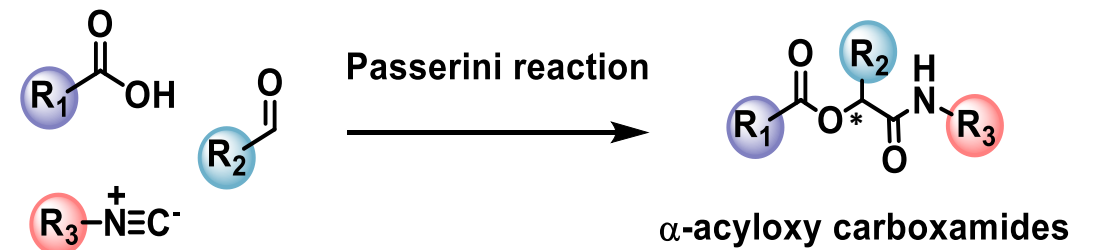
among the most potent natural products with antitumor and antibiotic activity



Bioorg. Med. Chem. Lett. **25** (2015) 9-15
J. Am. Chem. Soc. **141** (2019) 118-122

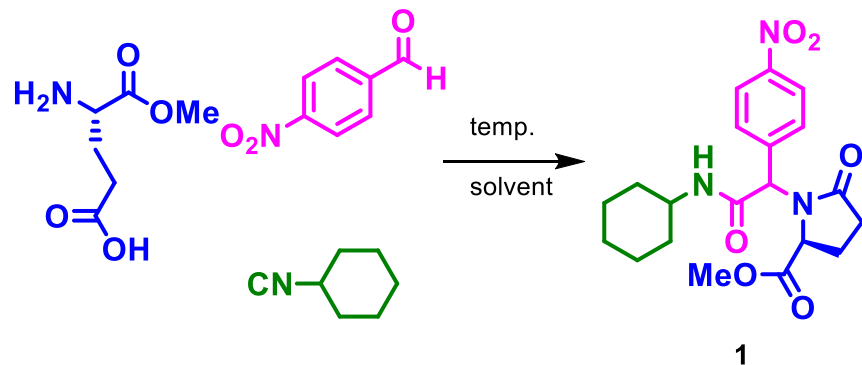
MULTICOMPONENT REACTIONS (MCRs)

- diversity and complexity
- isocyanide-based MCRs
- access to libraries and new building blocks

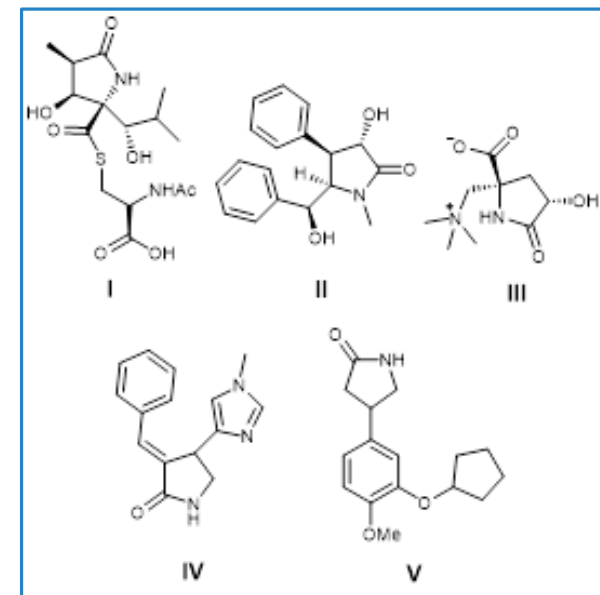
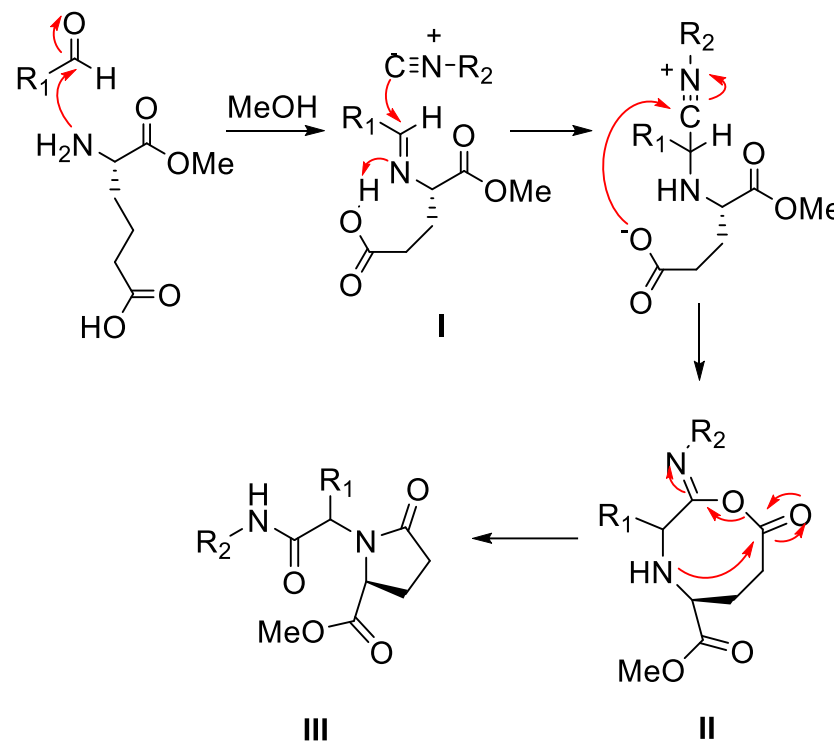


HETEROCYCLIC COMPOUNDS by MCRs

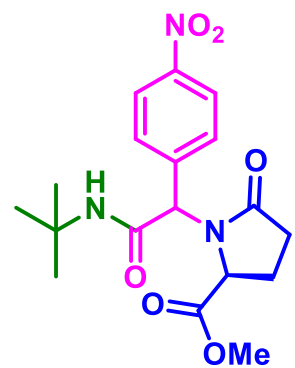
γ -LACTAMS



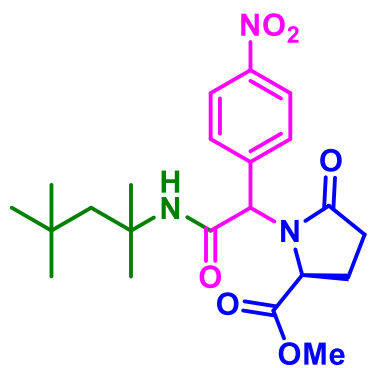
Entry	Solvent	T/ °C	Time/h	Yield/% ^b
1	DCM	RT	24	-
2	DCM/MeOH (10:1)	RT	48	28
3	MeOH	RT	24	22
4	MeOH	60	48	47
5	TFE	RT	24/72	68/70
6	TFE	60	24/72	75/83
7	HFIP	RT	24	80
8	HFIP	60	24	84



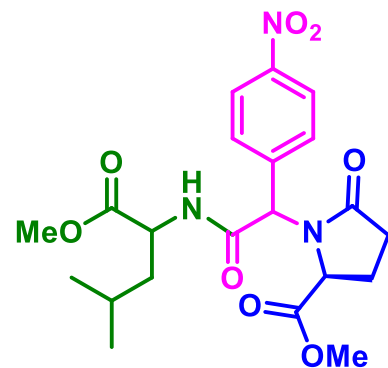
28 examples
up to 84 % yield



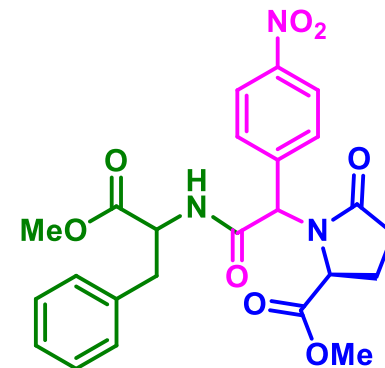
2 (53 %)



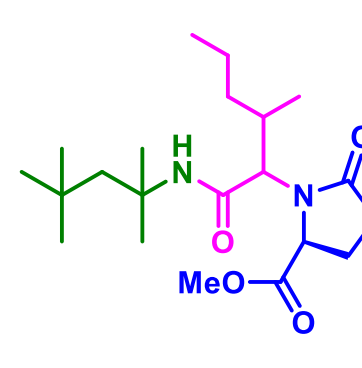
3 (83 %)



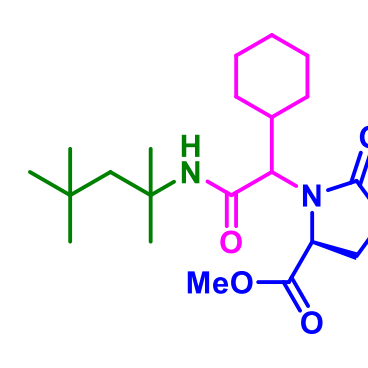
4 (80 %)



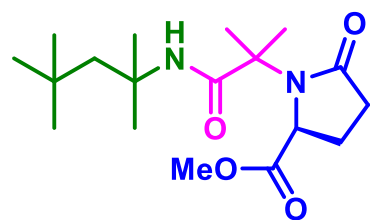
5 (63 %)



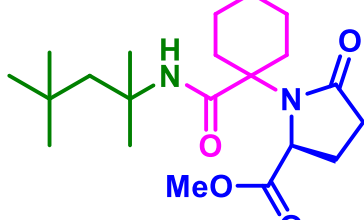
6 (62 %)



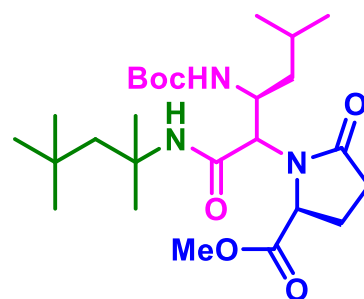
7 (89 %)



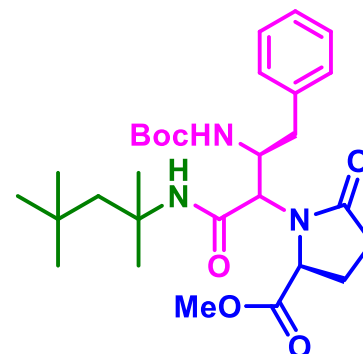
8 (24 %)



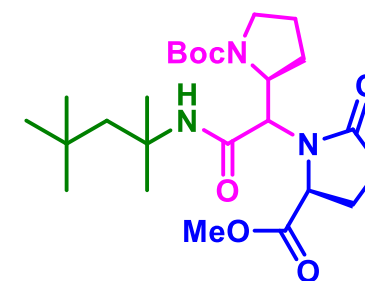
9 (74 %)



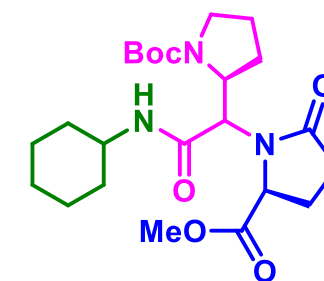
10 (75 %)



11 (84 %)



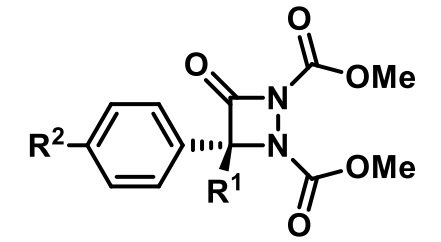
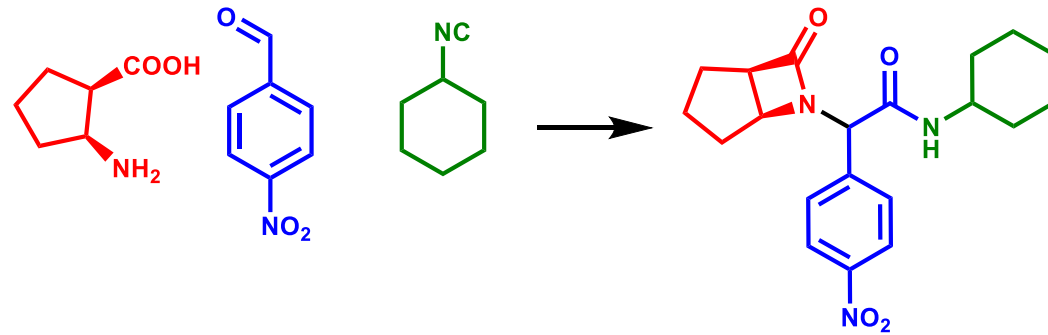
12 (22 %)



13 (58 %)

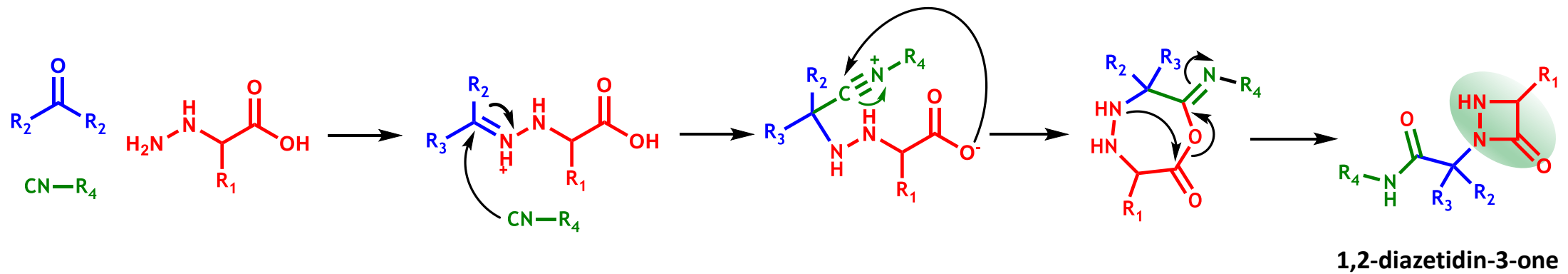
J. Suć Sajko, V. Ljoljić Bilić, I. Kosalec, I. Jerić, *ACS Comb. Sci.* **21** (2019) 28–34

1,2-DIAZETIDIN-3-ONES

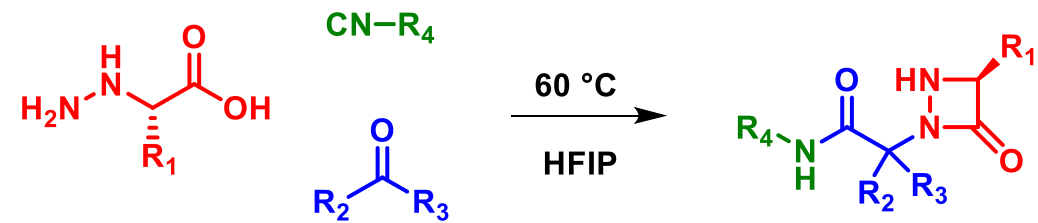


phosphatase methylesterase-1 inhibitor

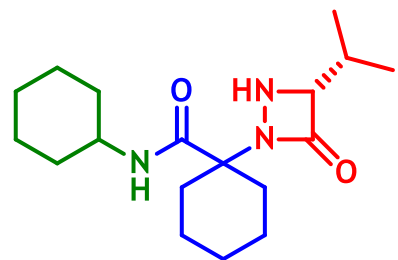
S. Gedey, J. Van der Eycken, F. Fülöp, *Org. Lett.* **4** (2002) 1967–1969



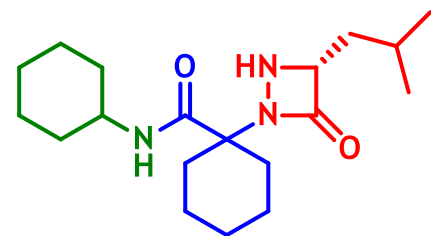
1,2-diazetidone



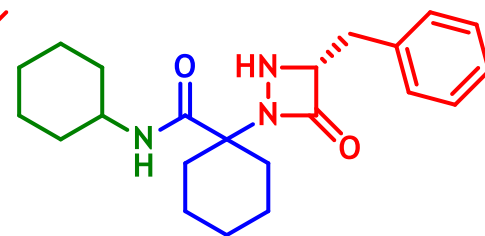
30 examples
up to 93 % yield



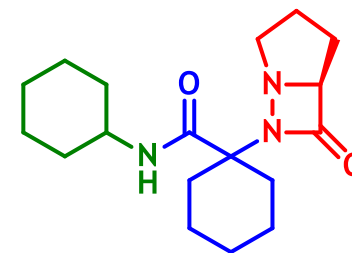
16 (80 %)



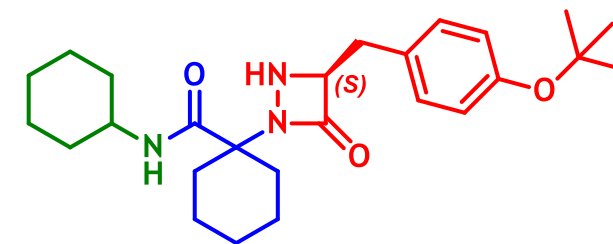
17 (83 %)



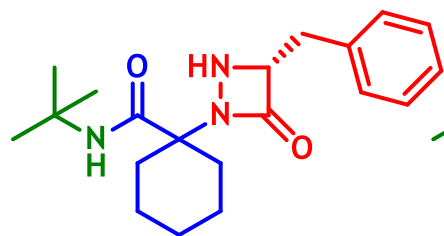
18 (87 %)



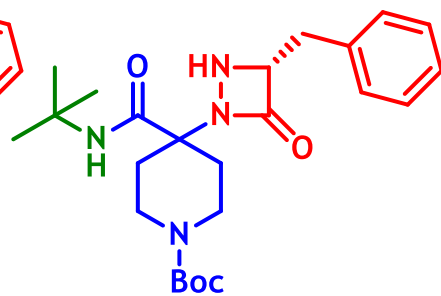
19 (48 %)



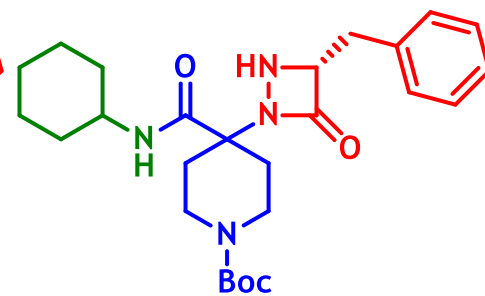
20 (32 %)



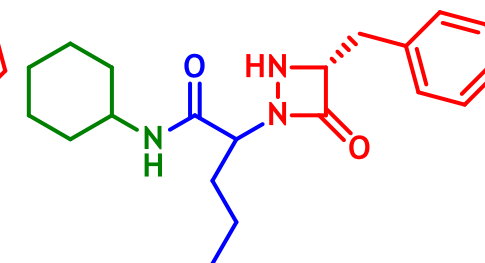
21 (27 %)



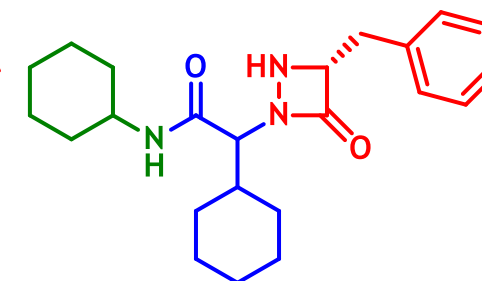
22 (30 %)



23 (89 %)



24 (48 %)

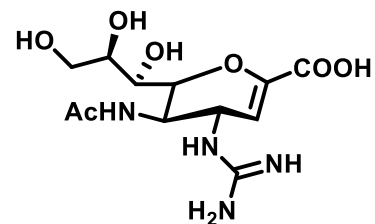


25 (68 %)

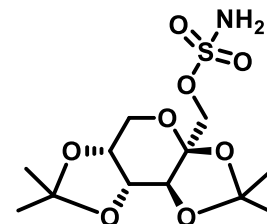
J. Suć Sajko, I. Jerić - unpublished results

PEPTIDE-CARBOHYDRATE ADDUCTS by MCRs

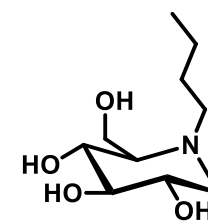
- privileged scaffolds in drug development
- intrinsic building block diversity
- stereochemically rich
- chemical transformations



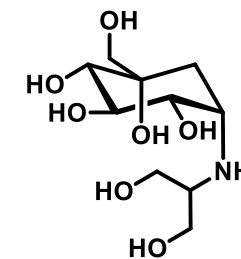
Zanamivir



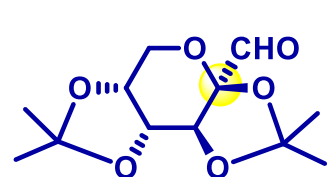
Topiramate



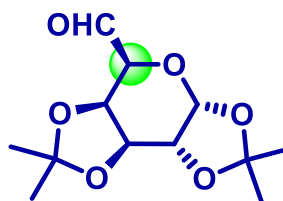
Miglustat



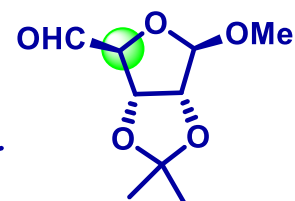
Voglibose



D-fructose



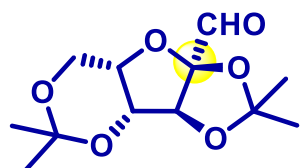
D-galactose



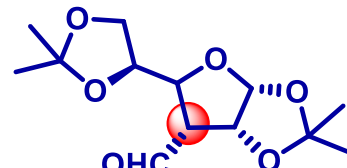
D-ribose



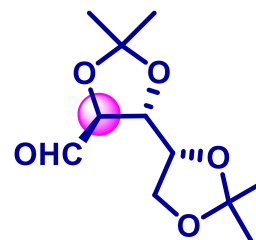
D-xylose



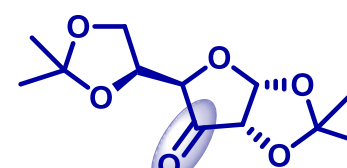
L-sorbose



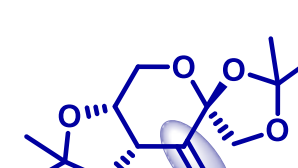
D-allose



D-arabinose

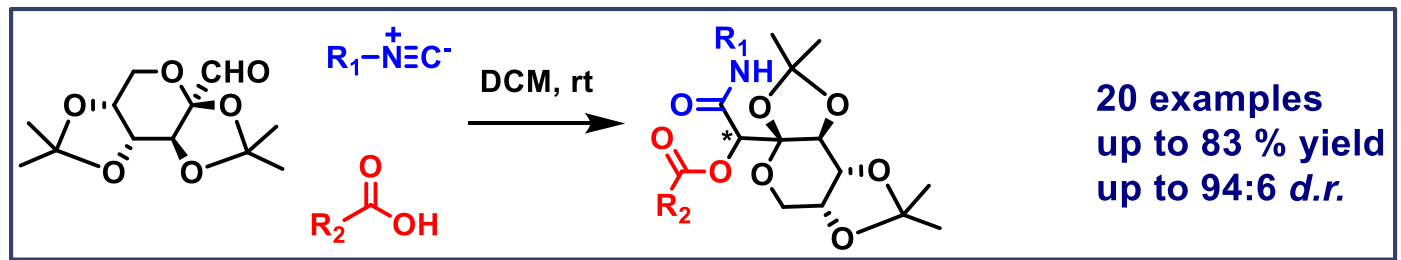


D-glucose

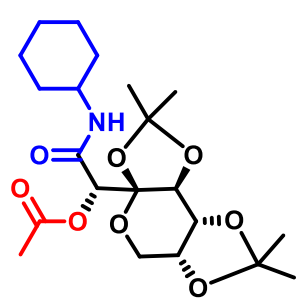


D-fructose

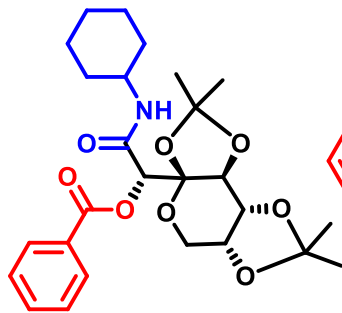
PASSERINI PRODUCTS



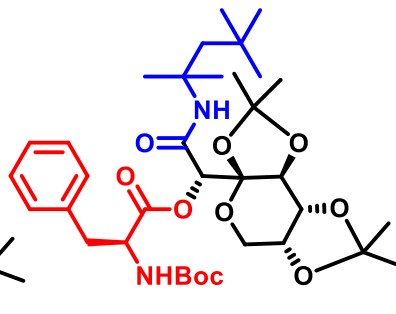
20 examples
up to 83 % yield
up to 94:6 *d.r.*



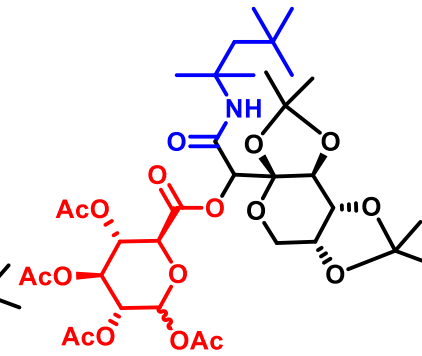
26 (72 %)
d.r. 91:9



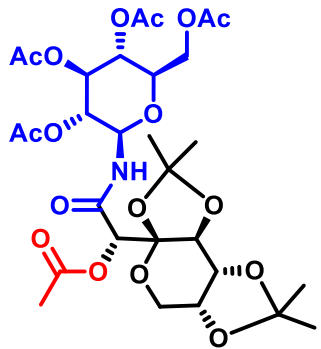
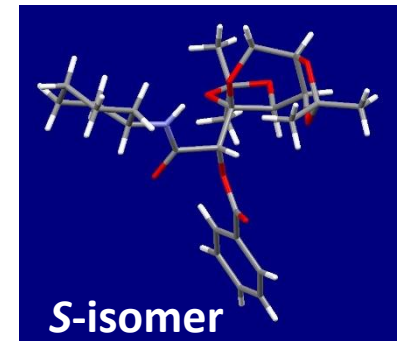
27 (83 %)
d.r. 89:11



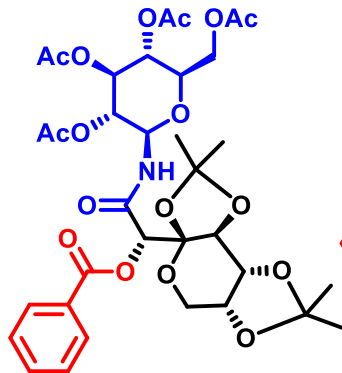
28 (79 %)
d.r. 91:9



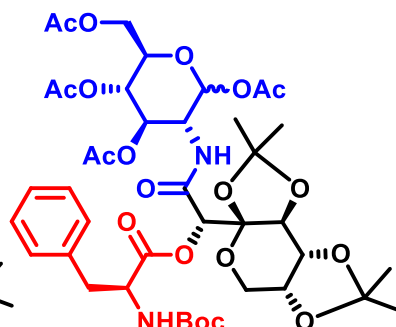
29 (70 %)
d.r. 94:6



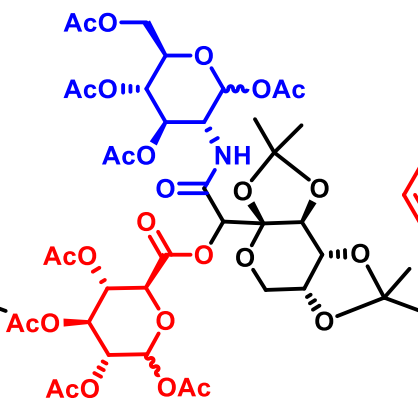
30 (80 %)
d.r. 90:10



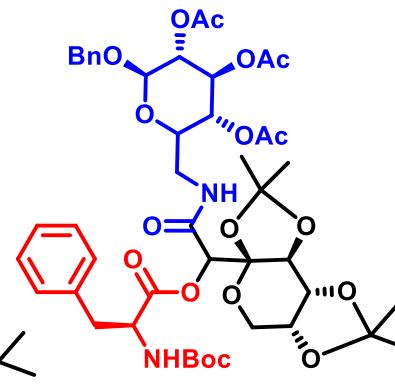
31 (57 %)
d.r. 91:9



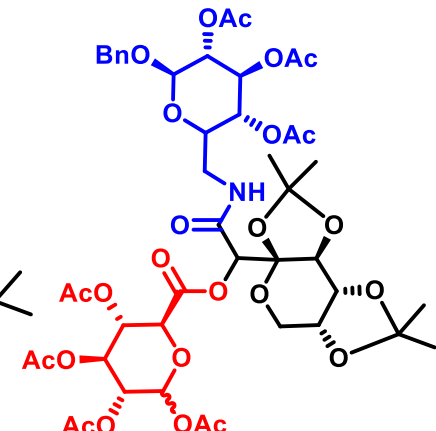
32 (68 %)



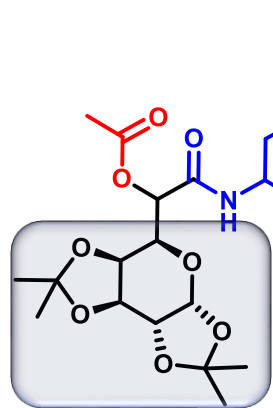
33 (75%)



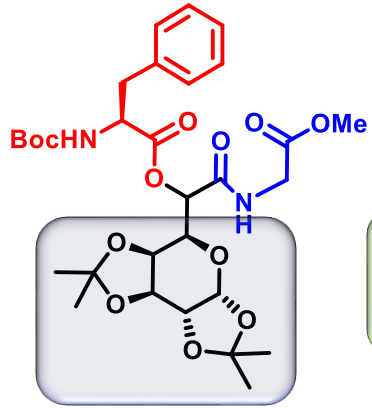
34 (70 %)
d.r. 90:10



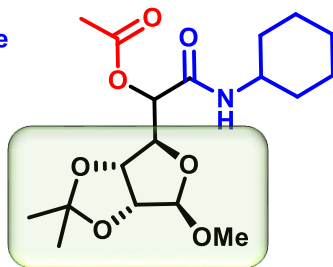
35 (75 %)



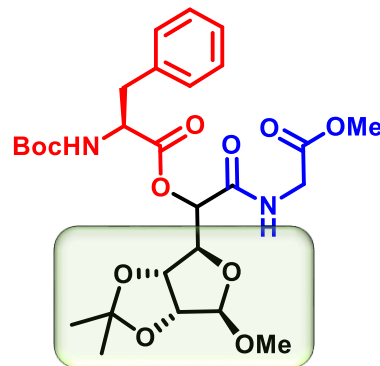
36 (81 %)
d.r. 80:20



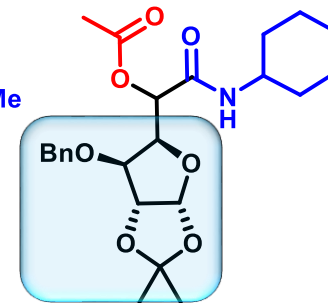
37 (80 %)
d.r. 70:30



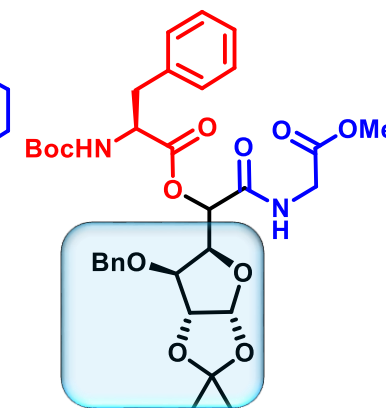
38 (82 %)
d.r. 77:23



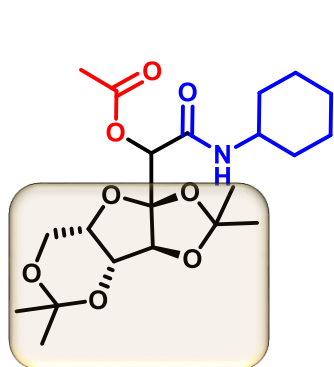
39 (78 %)
d.r. 77:23



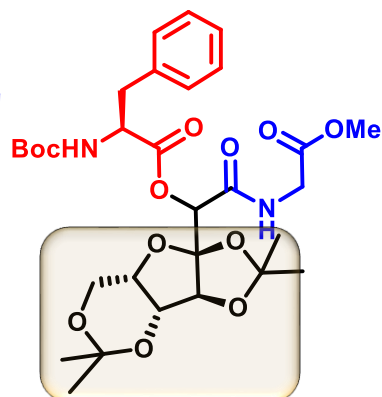
40 (79 %)
d.r. 77:23



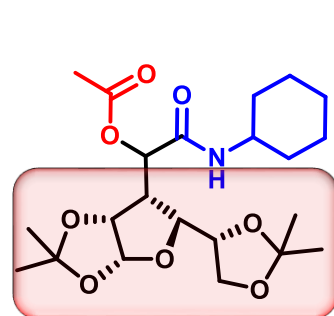
41 (75 %)
d.r. 77:23



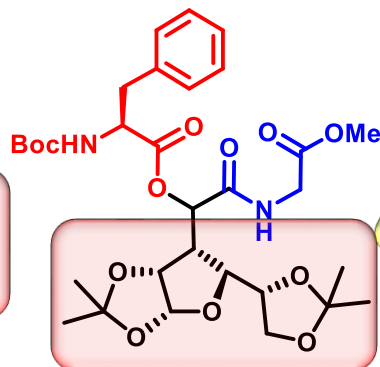
41 (66 %)
d.r. 90:10



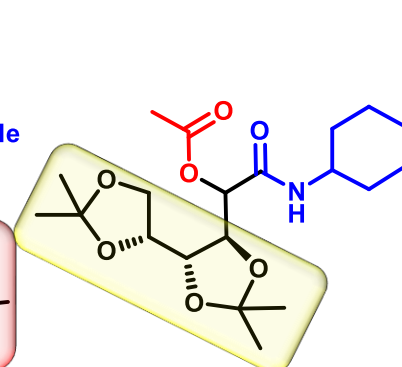
42 (65 %)
d.r. 90:10



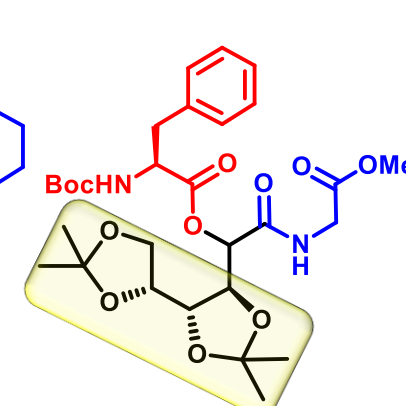
43 (72 %)
d.r. 90:10



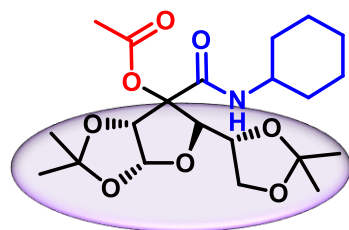
44 (77 %)
d.r. 90:10



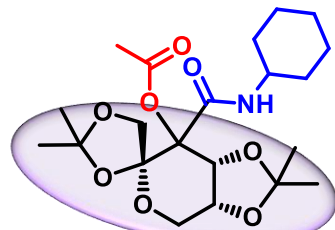
45 (81 %)
d.r. 55:45



46 (78 %)
d.r. 55:45



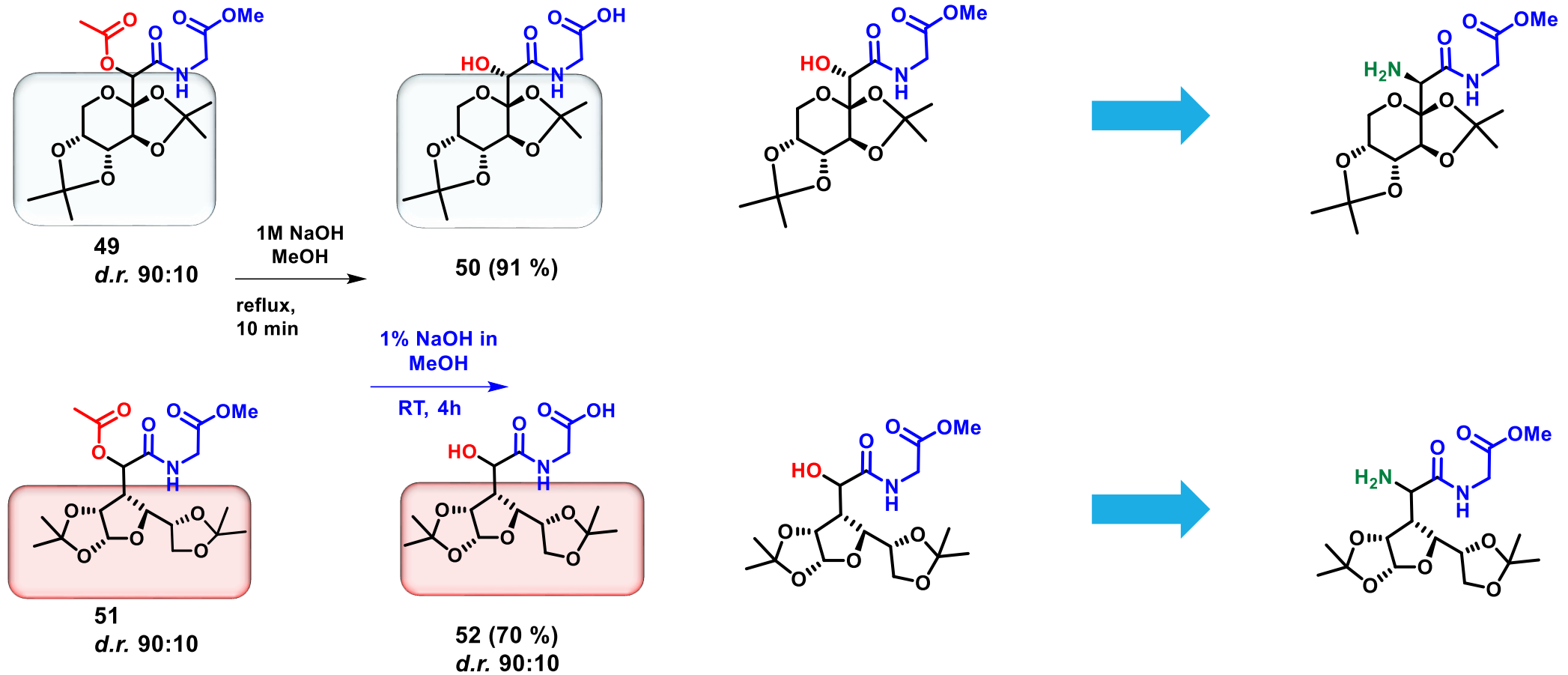
47 (67 %)
d.r. 55:45



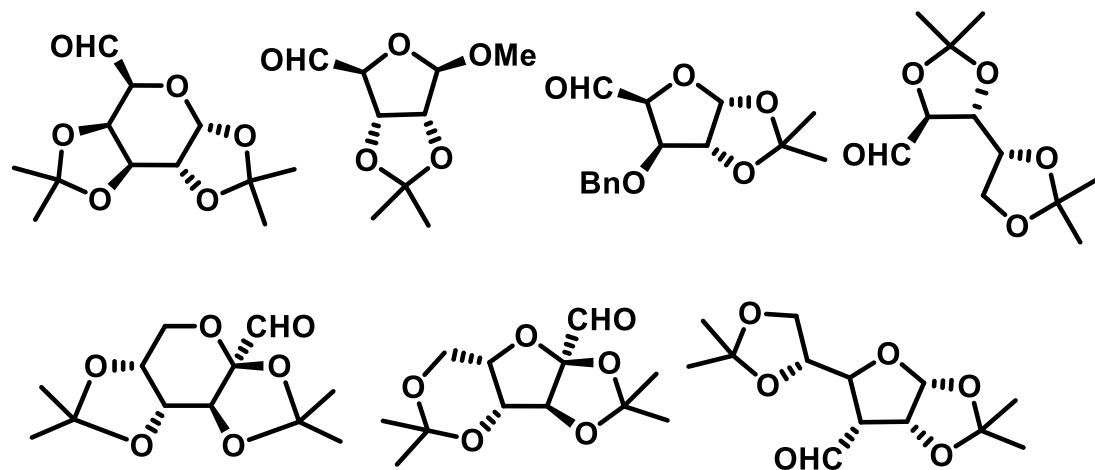
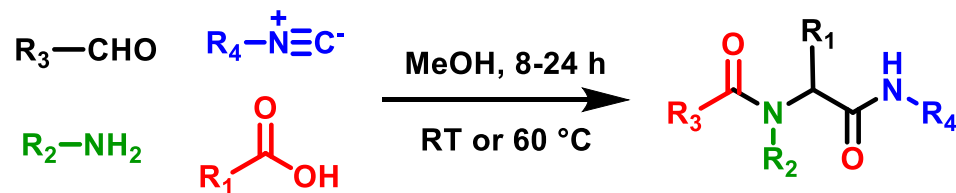
48 (51 %)
d.r. 55:45

23 examples
up to 82 % yield
up to 90:10 *d.r.*

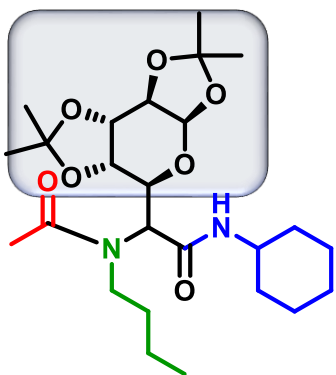
POST-CONDENSATION MODIFICATIONS



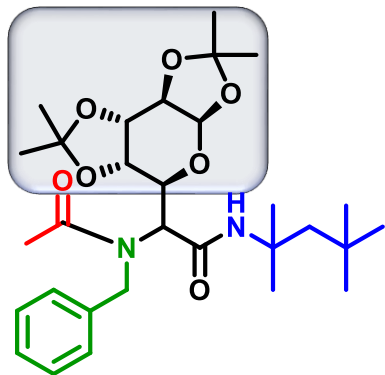
UGI PRODUCTS



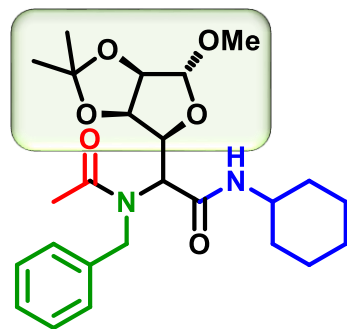
33 examples
up to 85 % yield
up to 86:14 *d.r.*



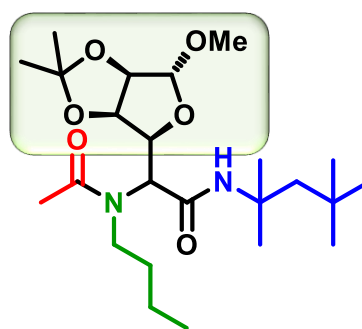
53 (75 %)
d.r. 80:20



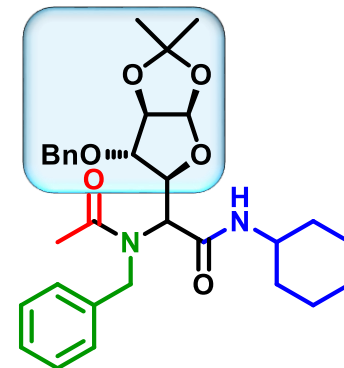
54 (76 %)
d.r. 78:22



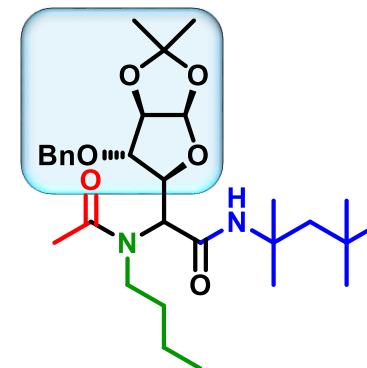
55 (78 %)
d.r. 54:46



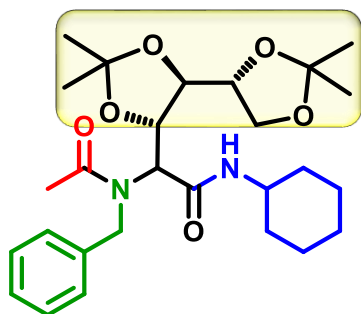
56 (74%)
d.r. 54:46



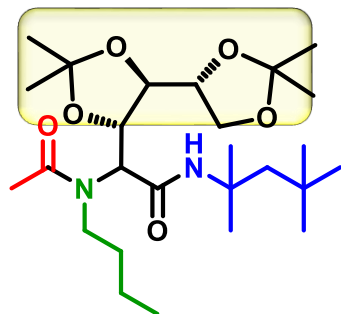
57 (69 %)
d.r. 67:33



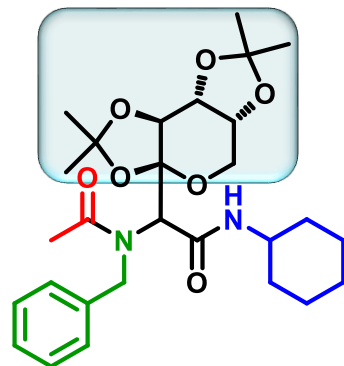
58 (63 %)
d.r. 65:35



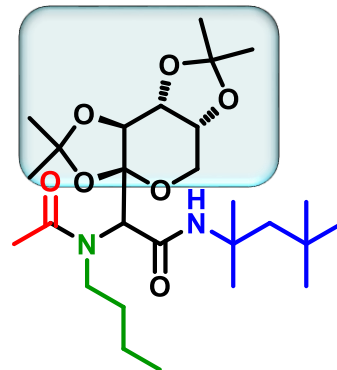
59 (71 %)
d.r. 65:35



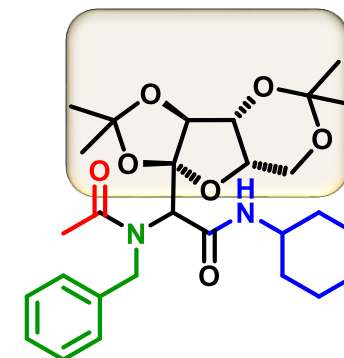
60 (65 %)
d.r. 65:35



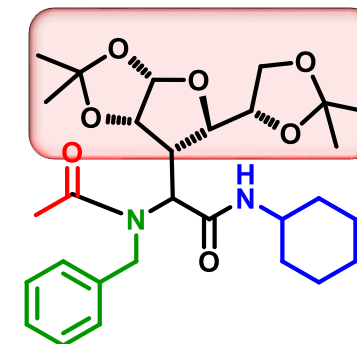
61 (46 % major)
d.r. nd



62 (34 % major)
d.r. nd



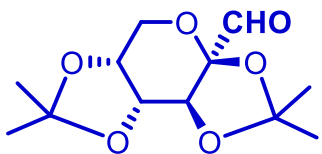
63 (59 %)
d.r. nd



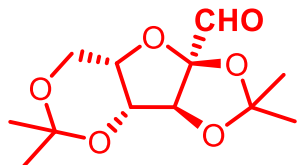
64 (57 %)
d.r. nd

K. Vlahoviček-Kahlina, Z. Štefanić, I. Jerić – unpublished results

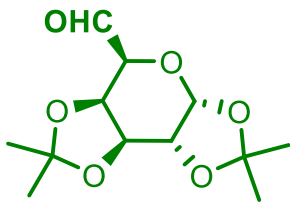
FRUCTOSE

 $R_1\text{-CHO}$

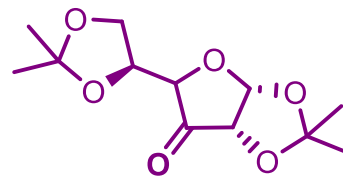
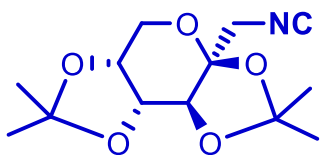
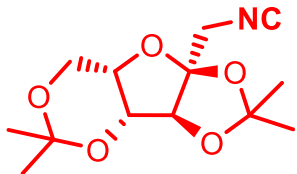
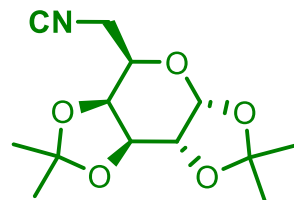
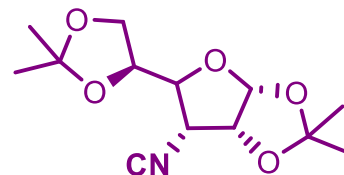
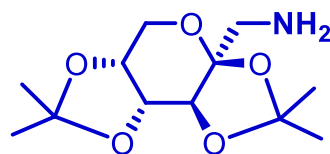
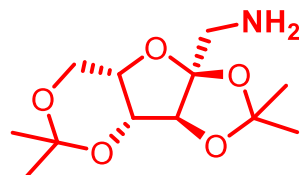
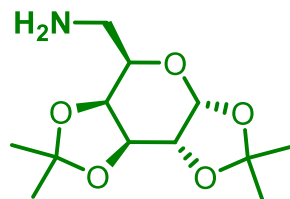
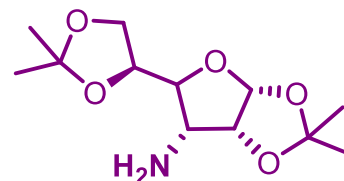
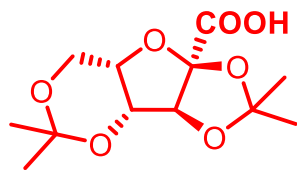
SORBOSE

 $R_2\text{-CHO}$

GALACTOSE

 $R_3\text{-CHO}$

ALLOSE

 $R_4\text{-C=O}$  $R_1\text{-CH}_2\text{NC}$  $R_2\text{-CH}_2\text{NC}$  $R_3\text{-CH}_2\text{NC}$  $R_4\text{-NC}$  $R_1\text{-CH}_2\text{NH}_2$  $R_2\text{-CH}_2\text{NH}_2$  $R_3\text{-CH}_2\text{NH}_2$  $R_4\text{-NH}_2$  $R_2\text{-COOH}$ Other carboxylic acid components:

acetyl acid

benzoic acid

Boc-Phe-OH

Boc-Tyr(Boc)-OH

Other amine components:

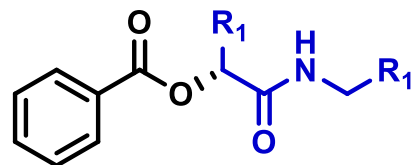
benzyl amine

H-Phe-OMe

H-Tyr-OBn

PASSERINI AND UGI PRODUCTS

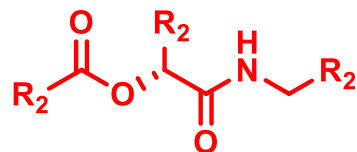
41 examples
up to 78 % yield



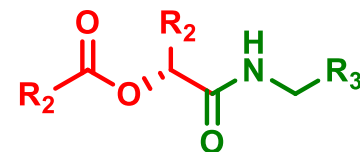
65 (69 %)
d.r. 89:11



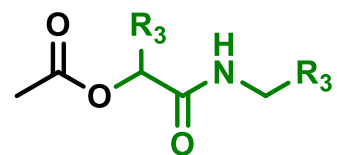
66 (39 %)
d.r. >99:1



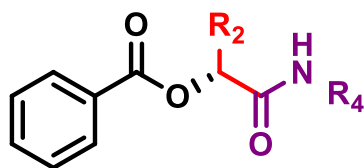
67 (43 %)
d.r. 89:11



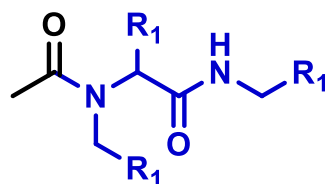
68 (42 %)
d.r. >99:1



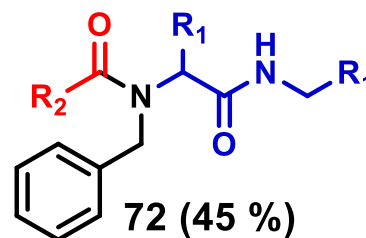
69 (53 %)
d.r. 85:15



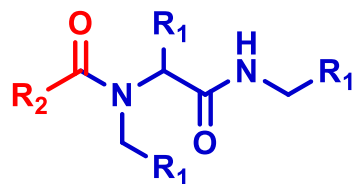
70 (71 %)
d.r. >99:1



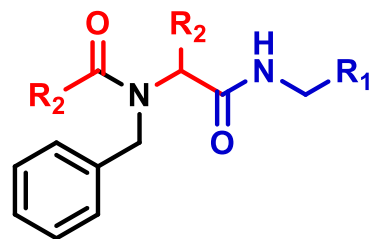
71 (52 %)
d.r. 51:49



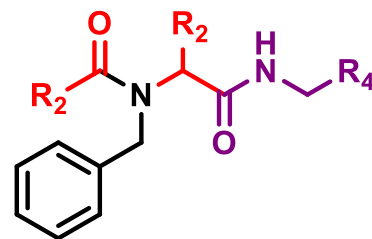
72 (45 %)
d.r. 51:49



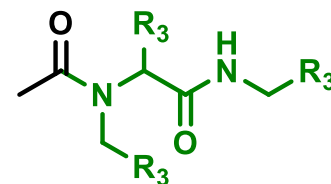
73 (32 %)
d.r. 53:47



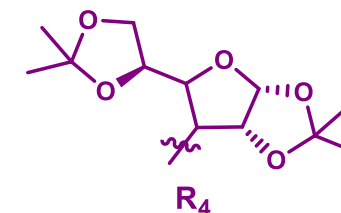
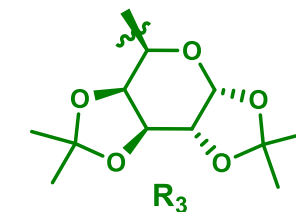
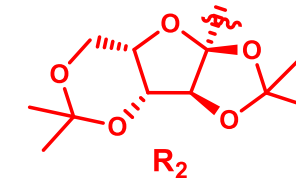
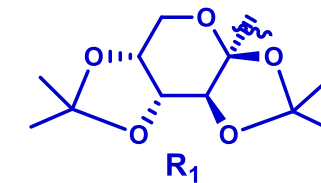
74 (60 %)
d.r. 55:45



75 (40 %)
d.r. 63:37

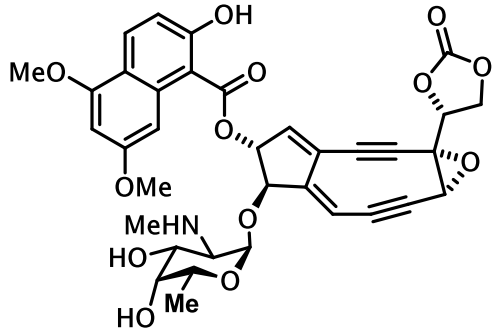
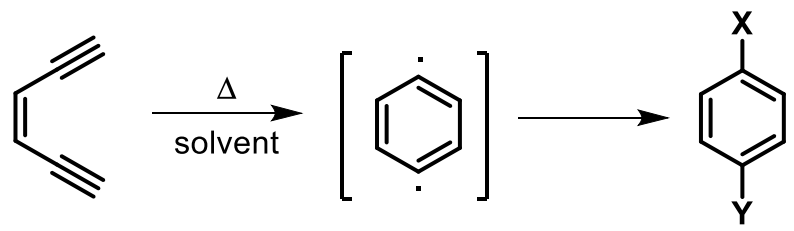


76 (64 %)
d.r. 77:23

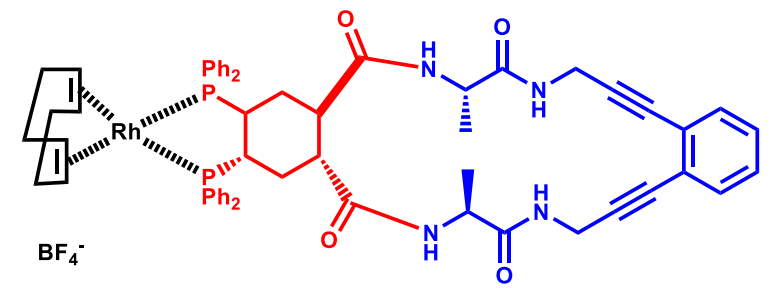
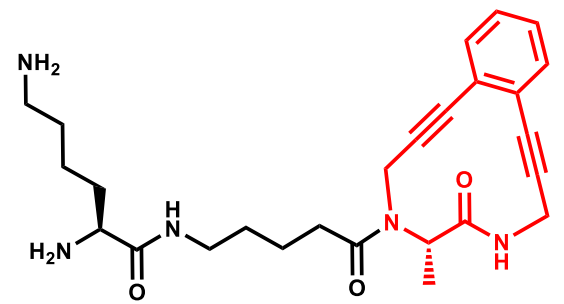
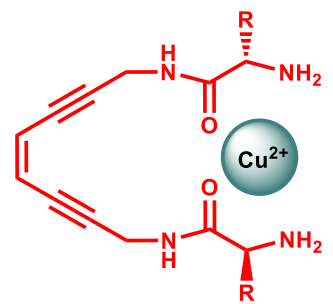


PEPTIDE-ENEDIYNE ADDUCTS by MCRs

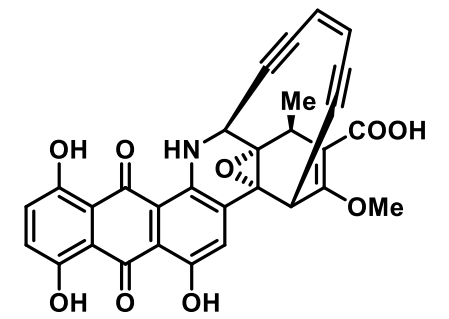
ENEDIYNE COMPOUNDS



Neocarnizostatin

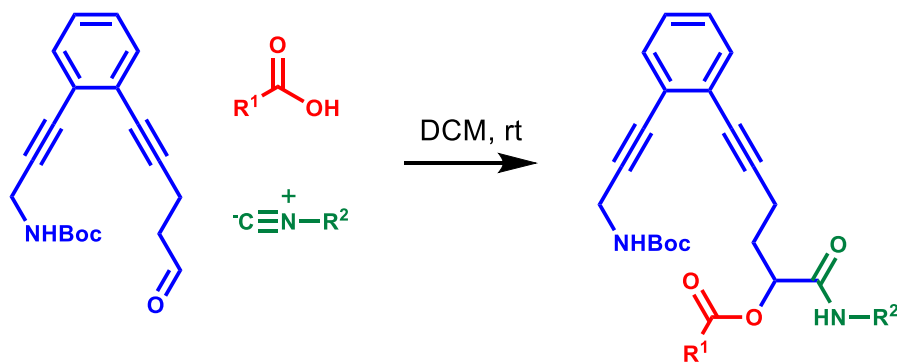
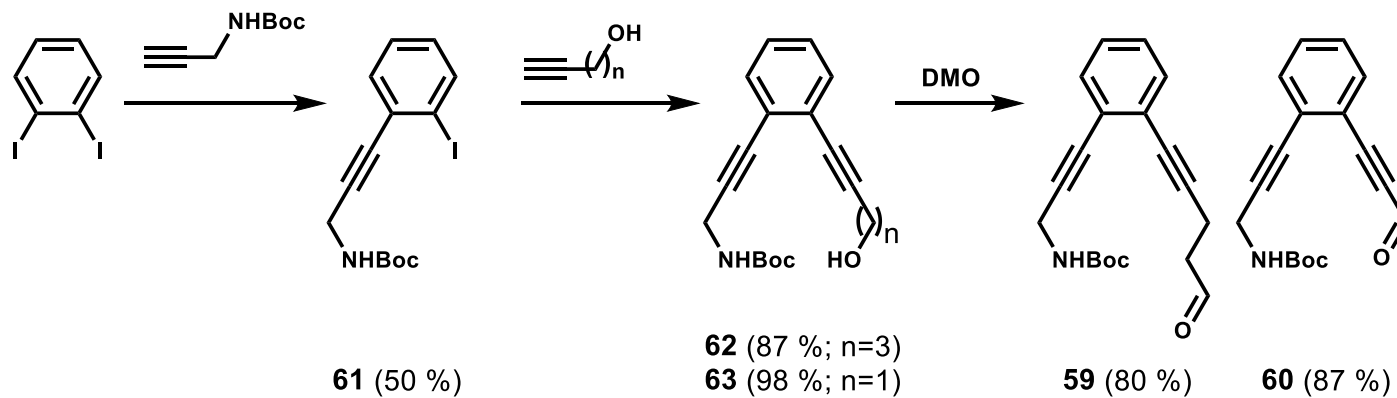
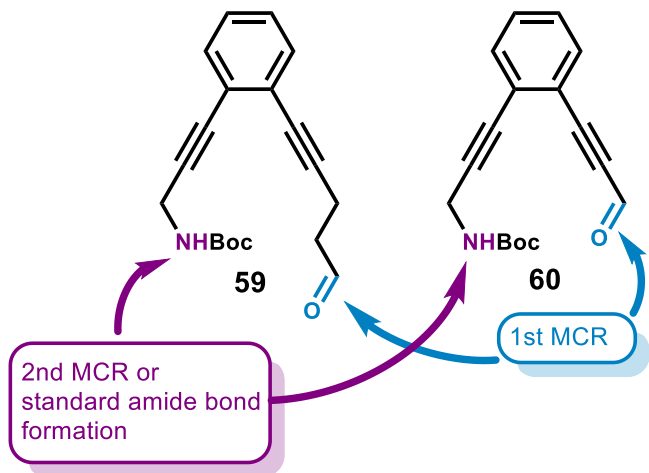


BF₄⁻

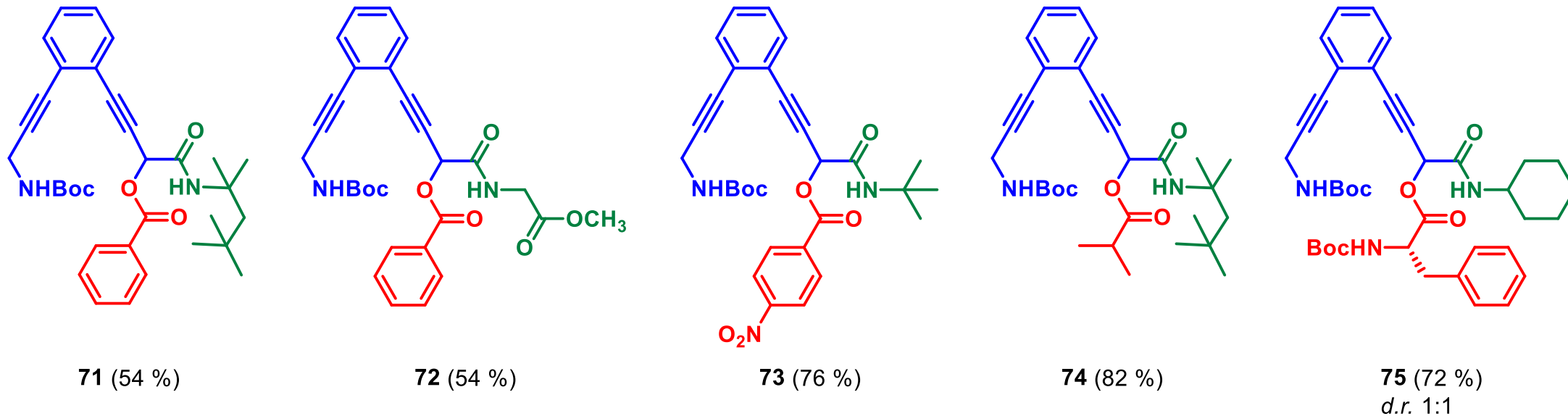
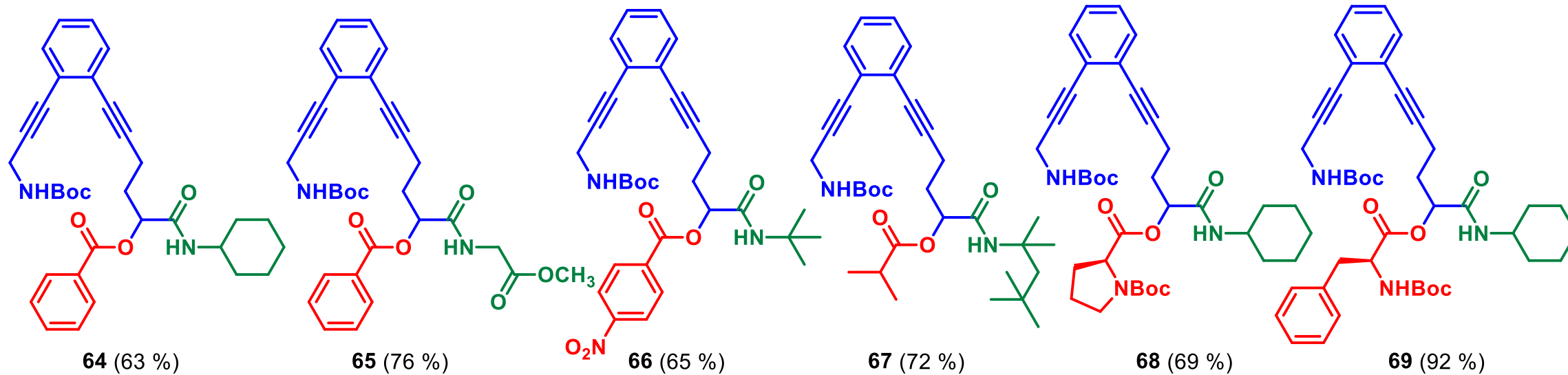


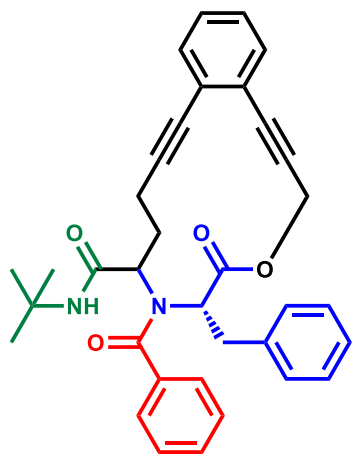
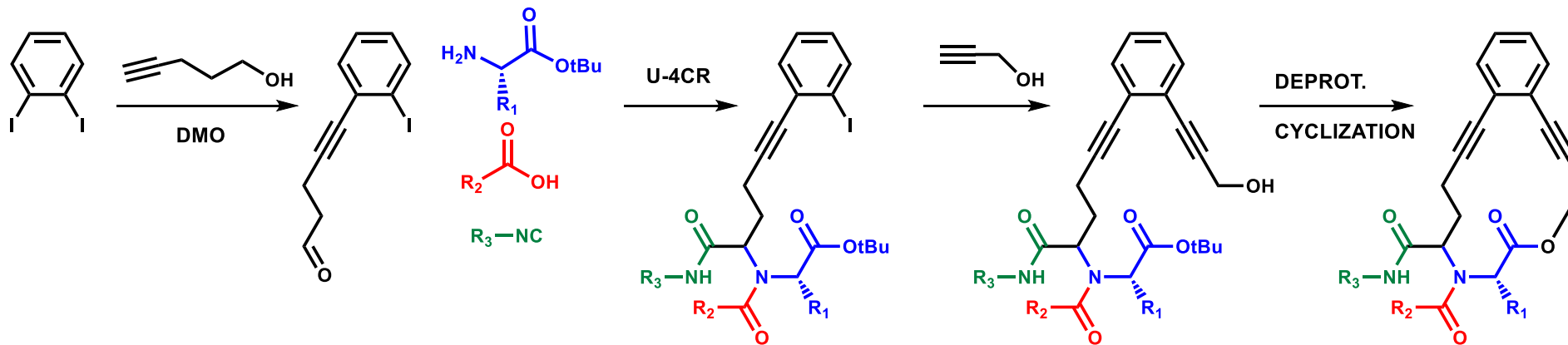
Dinemicin A

Gredičak et al. *J. Inorg. Biochem.* **116** (2012) 45-52
 Gredičak et al. *Amino Acids*, **43** (2012) 2087-100
 Kokan et al. *Organometallics*, **33** (2014) 4005-4015

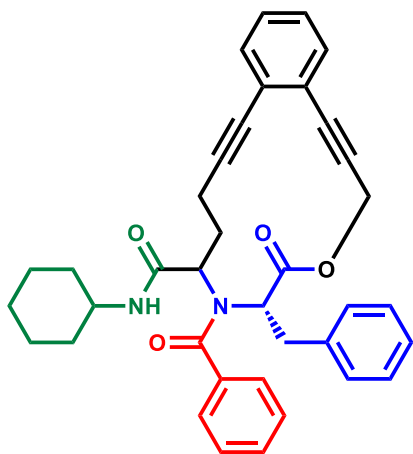


21 examples
up to 92 % yield

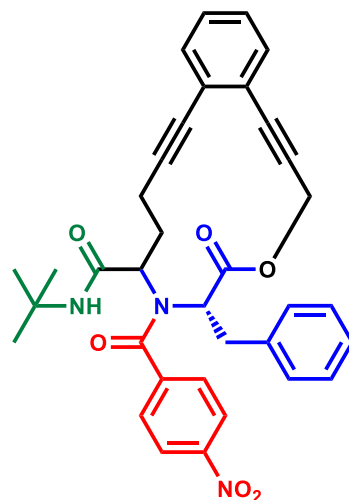




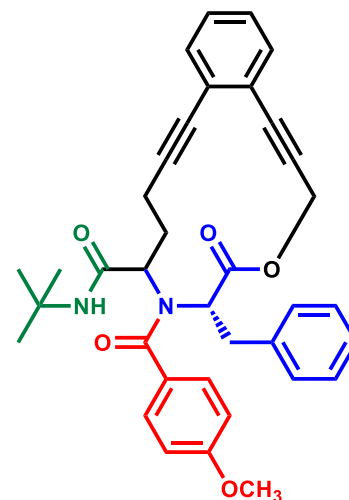
76 (68 %)
d.r. 76:24



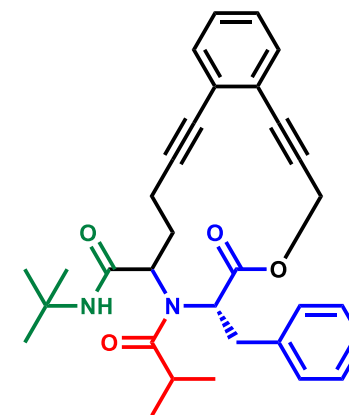
77 (43 %)



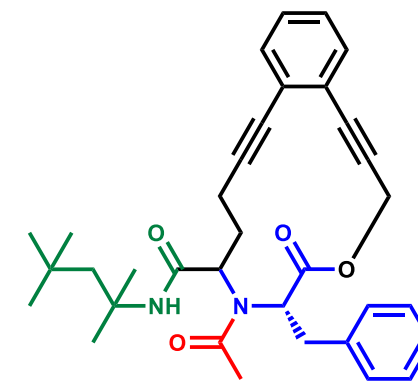
78 (57 %)
d.r. 78:22



79 (40 %)
d.r. 50:50



80 (9 %)
d.r. > 20:1



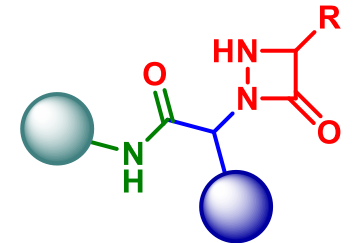
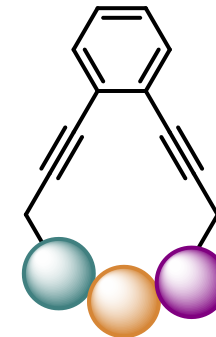
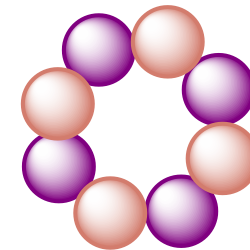
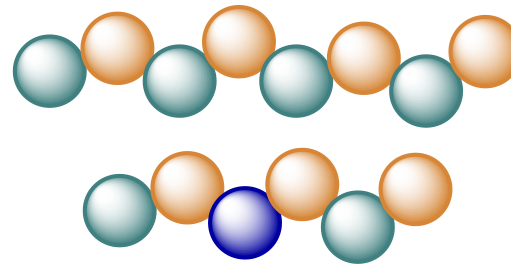
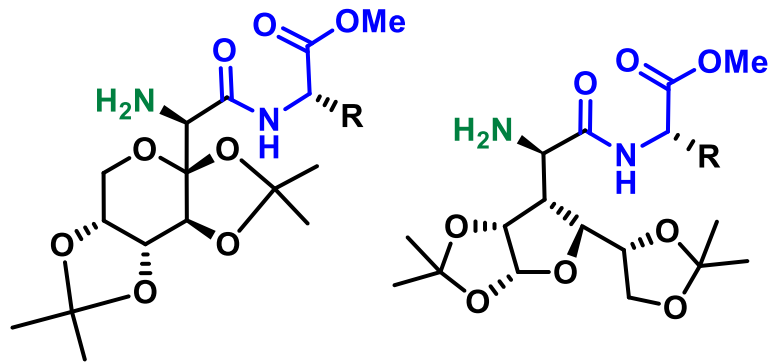
81 (16 %)
d.r. > 20:1

CONCLUSIONS AND PERSPECTIVE

- robust access to libraries of structurally diverse compounds



- construction of **adaptable molecular architectures**
 - **secondary structure**
 - **self-assembly**
- **Nature-mimicking systems**



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Laboratory for biomimetic chemistry

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Mario Vazdar
Vilko Smrečki

CSF project: The assembly of peptidomimetics by multicomponent reactions (IP-2014-09-3102)

