β-Amino Acids: Function and Synthesis

- Conformations of β-Peptides
- Biological Significance
- Asymmetric Synthesis

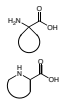
Sean Brown
MacMillan Group Meeting
November 14, 2001

Lead References: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.
Enantioselective Synthesis of β-Amino Acids; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.
Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.
Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, 56, 8033.

α-Amino Acids vs. β-Amino Acids

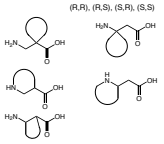
α-Amino acids

3 substitution positions
2 configurations: (R), (S)



β-Amino acids

5 substitution positions
8 configurations: (2R), (2S), (3R), (3S), (R,R), (R,S), (S,R), (S,S)

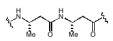


- β-Amino acids allow for greater diversity.
- Extra C-C bond potenially allows for increased diversity in secondary structures.

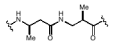
Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.

Helical Secondary Structures of α and β-Peptides

poly-Ala



poly-β^3-hAla

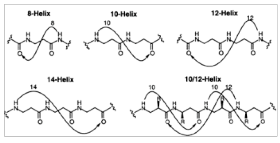


poly-(β^3-hAla-β^2-hAla)

- A greater number of helical structures are avaliable from β-peptides.

Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

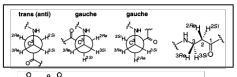
Nomenclature for β-Peptide Helices



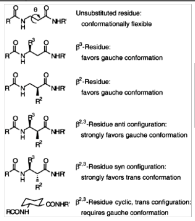
- The nomenclature for β-peptide helices is based on the number of atoms in the ring formed by the H-bond.

Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

Conformational Preferences



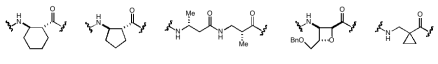
Partial Charge Stabilization



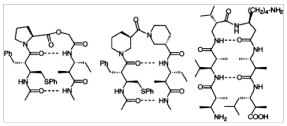
- Gauche conformation encourages helix formation.
- Electrostatic interaction between the partial charges of the carbonyl carbon and the amide nitrogen preferentially stabilizes the gauche conformation.
- Trans confomation promotes sheetlike formation.

Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

β-Peptide Conformations



14-Helix 12-Helix 10/12-Helix 10-Helix 8-Helix

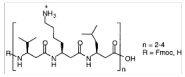


β-Peptide Sheets

- Small differences in *β*-amino acid structure can give rise to different secondary structures.
- *β*-Peptides containing *syn* substituted *β*-amino acids separated by turn-stabilizing residues can form sheets .

Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

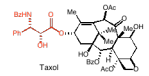
β-Peptide as Antimicrobial



- *β*-Peptides can exibit similar physiochemical properties to *α*-peptides.
- *β*-Peptides are stable to proteolytic degradation.

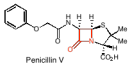
Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

Biologically Active β-Amino Acids

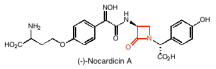


Taxol

(-)-Cocaine



Penicillin V

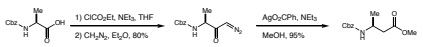


(-)-Nocardicin A

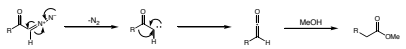
- *β*-Amino acids are found in many biologically active natural products and drugs.
- *β*-Lactams are prevalent structural moieties in antibiotics.

β^3 Substituted β-Amino Acids

Arndt-Eistert Reaction



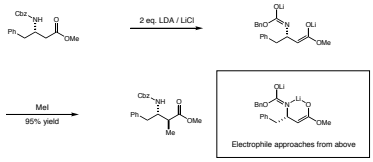
Wolff Rearrangement



- Enantiomercally pure β-amino acids are prepared from the appropriate α-amino acid.
- Rearrangement occurs with retention of stereochemistry.
- Epimerization is rarely observed.

Enantioselective Synthesis of β-Amino Acids; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

$\beta^{2,3}$ Substituted β-Amino Acids

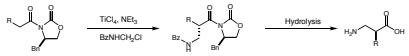


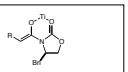
Electrophile approaches from above

- β^3-Amino acids derived from the Arndt-Eistert method can be further elaborated to $\beta^{2,3}$-amino acids.
- High diastereoselectivities are observed in alkylations.

Enantioselective Synthesis of β-Amino Acids; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

β^2 Substituted β-Amino Acids



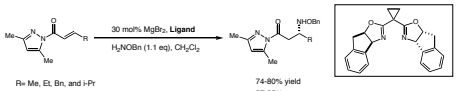


Electrophile approaches from below

- Evans' chiral auxiliary alkylation produces β^2-amino acids of high enantiomeric purity.

Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

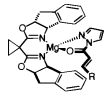
Catalytic Asymmetric Addition of O-Benzylhydroxylamine



R= Me, Et, Bn, and i-Pr

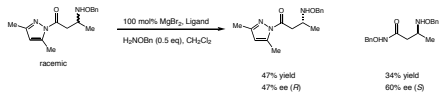
74-80% yield
87-95% ee

- This is the first highly enantioselective catalytic conjugate amine addition.
- The other enatiomeric series can be accessed through use of $Y(OTf)_3$ or $Yb(OTf)_3$ though ee's are below 60%.
- Substitution on olefin limited to alkyl groups.
- High catalyst loading.



Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, 120, 6615.

Kinetic Resolution of β-Amino Amide

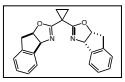


racemic

47% yield
47% ee (*R*)

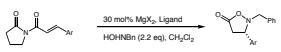
34% yield
60% ee (*S*)

- ee of entioselective reaction increases over time but yield decreases.
- Minor enantiomer undergoes aminolysis faster than major enantiomer.

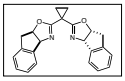


Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, 120, 6615.

Amine Conjugate Additions to Cinnamates



53-87% yield
60-96% ee

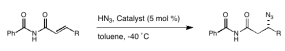


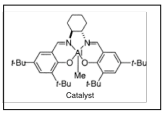
X= I, (ClO_4)

- First highly enantioselective conjugate amine addition to cinnamates.
- N-Benzylhydroxylamine is more reactive than O-benzylhydroxylamine and the pyrrolidinone cinnamate also more reactive than the corresponding pyrazole substrate.

Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, 2, 3393.

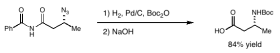
Enantioselective Conjugate Addition of Hydrazoic Acid





Catalyst

R	yield (%)	ee (%)
Me	96	96
t-Bu	99	97
CH_2Bn	93	96
Ph	60	58

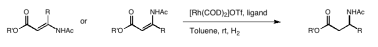


84% yield

- Works well for alkyl substituents, but low yield and enantioselectivity for aryl substituents.
- Hydrazoic acid is toxic and difficult to use.

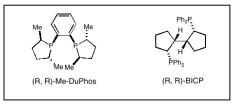
Myers, J. K.; Jacobsen, E. N. J. *Am. Chem. Soc.* **1999**, 121, 8959.

Asymmetric Hydrogenation of an Enamide



100% conv.
>90% ee

R= Me, Et, Pr, i-Bu, i-Pr

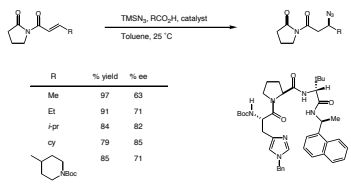


(R, R)-Me-DuPhos (R, R)-BICP

- (Z) olefins need higher pressures of hydrogen and are generally less selective.
- (R, R)-Me-DuPhos gives poor enantiomeric excess from the (Z) olefin.
- Poor enantioselectivity when R is aryl (65% ee).

Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* ***1999****, 64,* 6907-6910.

Organocatalytic Addittion of Azide

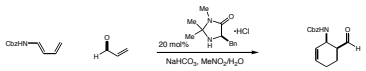


R	% yield	% ee
Me	97	63
Et	91	71
i-pr	84	82
cy	79	85
	85	71

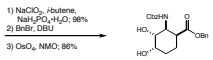
- Catalyst is an organic molecule which gives it obvious benefits.
- β-Turn is necessary for selectivity.

Guerin, D. J.; Horstmann, T. E.; Miller, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635.

Organocatalytic Approach To Cyclic β-Amino Acids



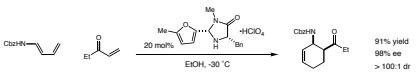
68% yield
89% ee



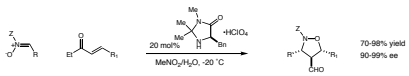
- O.C. gives quick access to highly functionalized β-amino acids.

Wipf, P.; Wang, X. *Tetrahedron. Let.* **2000**, *41*,8747-8751.

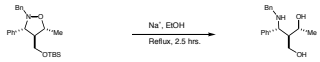
Organo Catalytic Approachs To β-Amino Carbonyls



91% yield
98% ee
> 100:1 dr



70-98% yield
90-99% ee



80% yield

Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875.

Summary

- Lengthening α-amino acids by one carbon does not lead to chaos, but new secondary folding structures.
- β-Peptides form secondary structures with greater stability than α-peptides.
- The metabolic stability of β-peptides can be utilized in drug design.
- Asymmetric catalysis should provide inexpensive and quick access to novel β-amino acids.