First off – What are peptides, and who cares?
– Peptide ('peptid') - any of various amides that are derived from 2+ amino acids via the joining of one acid with another free amine
– BUT much more variability can be had than in canonical cases:

- As drug compounds, peptides often boast potency, selectivity, solubility and low toxicity
- Typically have low oral bio-availability, plasma/cellular stability, t1/2
- Downsides of linear peptides (enzymatic stability can often be overcome via cyclization
- Beautiful/unique structures not seen in other classes of 2° metabolites

What to expect from this GM:
– Coverage of some key issues in complex peptide small molecule synthesis
  – Key methodology (tactics) to address problems
  – Case studies of relevant syntheses
  – Discussion of strategies towards atroposelectivity
  – Focus on small molecule peptides vs. 20+ AA peptides

Topics not covered:
– Peptide couplings, macrocyclizations, ligations; see Reisberg, 2020 & Malins, 2016 GMs
– Exhaustive coverage of every interesting peptide NP or strategy
– Directed evolution or engineered enzyme ncAA synthesis
– In-depth treatment of every methodology shown

Key Strategic Problems:
(1) Noncanonical Amino Acid (ncAA) Problem
Common ncAAs (not exhaustive – see ACIE, 2013, 52, 7098)

hydroxy amino acids
- α-OH-Gly
- β-OH-Xaa

methylation amino acids
- aminoisobutyric acid (Aib)
- Ser(Me)

homo-amino acids
- hPhe, hTyr
- piperolic acids (Pip)

N-containing side chain
- ornithine (Orn)

Factors to Consider:
– Commercial availability often low
– Self-reactive ncAAs (i.e. Orn)
– How to synthesize asymmetrically - racemization (Phg)

(2) The (Het)Arene Connection Problem

Factors to Consider:
– Order of connection
  - pre- or post- peptide bond
  – Atroposelectivity + choreography
  – Inherent reactivity of (het)arene
  – Synthesis of AA analogues

These 2 problems are, of course, intertwined
### Bank 1: Asymmetric Strecker Reactions

**2 reviews:**
- Chem. Rev. 2011, 111, 6947
- Chem. Rev. 2003, 103, 2795

**Chiral Non-Racemic Imines**
- Tet. Lett. 1995, 36, 2859

**Chiral Lactic Aldehydes**

**Takeaways:**
- Many ways to accomplish this (sulfinimines, transition metals, organocatalysis)
- Downsides: hydrolysis is sometimes difficult, CN use

### Bank 2: Asymmetric Hydrogenation of Dehydroaminoacids

**Review:** Synthesis 2006, 1, 1

**Case Study: Dong’s Method + Dichotomine E Synthesis**

**Dichotomine E**
- 20:1 d.r.

**Note:**
- chAA as turn-inducing element for macrocyclization

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**Chiral Amine Auxiliaries**

**Nature 1963, 200, 1201**

**Takeaways:**
- Many ways to accomplish this (sulfinimines, transition metals, organocatalysis)
- Downsides: hydrolysis is sometimes difficult, CN use
Tactics and Strategies in Complex Peptide Synthesis

Bank 3: Multi-Component Reactions
Application of Passerini Reaction to Cyclotheonamides A–E

Bank 4: Auxiliary Use
Use of Garner’s Aux for the key ncAA in Lucentamycin A

**OL 2001, 3, 3301**
- Peculiar α-keto homoAA moiety
- Potent (nM), slow-binding serine protease covalent inhibitors

**JOC, 2012, 77, 9859**
- Unique 4-ethylidene-3-methylproline (Emp)
- Showed no significant cytotoxicity

Takeaways:
- Aux use allows logical, low-risk prep of ncAAs
- BUT many steps required, lots of redox manipulations and PG swaps

**what are more elegant ways to accomplish this?**
**Tactics and Strategies in Complex Peptide Synthesis**

Alexandros S. Pollatos

Baran Group Meeting

04/23/2022

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**α-amanitin**
- Among deadliest toxins known (LD$_{50}$ 50-100 µg/kg – 20x KCN!)

**Synthetic Challenges:**
1) oxidatively delicate tryptathione
2) enantiosel. synthesis of DHIle
3) diastereosel. sulfoxidation

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**α-amanitin**
- Made by C-H borylation
- Immobilized B p-orbital avoids deg.

**Trp Problem**
- MIDAB
- SPPS

---

**DHIle Synthesis**

1. crotylation
2. TBSOTf, lut.
3. OsO$_4$, NMO
4. NaI$_4$

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**DHIle**

1. TBAF
2. LiOH
3. methylimino-diacetic acid (MIDA)
4. Me

---

**Compare to Süßmuth’s:**

**JOC 2021**, 86, 5362

1. SAE
2. TsCl, TEA
3. NaI, Zn(Cu)
4. Boc$_2$O, NaH
5. Tfa-G-OrBu
6. LHMDS, [Ru]
7. NaBH$_4$
8. K$_2$OsO$_4$, NMO
9. TBSCl
10. TMSOTf

---

**Müller’s synthesis employs very similar transform here:**

**ACIE 2020**, 59, 11390

1. TFA
2. KOH
3. mCPBA
40% over 3 steps

4. DHIle coupling
5. Et$_3$NH
6. TBAF
7. macrocycl. 15%/4 steps

---

**α-amanitin**
- Made by C-H borylation
- 85% 1:1 syn-cis : anti-cis pushed both fwd

---

**Bank 5: C-H Activations**

**Case Study: Total Synthesis of α-amanitin**

Perrin *JACS*, 2018, 140, 6513

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**OH**
- 1. SAE
- 2. TsCl, TEA
- 3. NaI, Zn(Cu)
- 4. Boc$_2$O, NaH
- 5. Tfa-G-OrBu
- 6. LHMDS, [Ru]
- 7. NaBH$_4$
- 8. K$_2$OsO$_4$, NMO
- 9. TBSCl
- 10. TMSOTf

---

**More solvent-exposed l.p. use bulky oxidant**

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**Immobilized B p-orbital avoids deg.**

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**Müller’s synthesis employs very similar transform here:**

**ACIE 2020**, 59, 11390
Total Synthesis of α-amanitin (continued)

Süssmith's non-Savige-Fontana

BocHN
\[\text{OtBu} \downarrow \text{SO}_2\text{Cl}_2 \]
BocHN
\[\text{OtBu} \downarrow \text{Cl} \]

form Eastern macrocycle, then same end-game

\[\text{α-amanitin}\]

Indole C-H Borylation

see: Veruculogen JACS 2015, 137, 10160
Teleocidins JACS 2019, 141, 1494
+ Hartwig’s work

\[\text{[Ir] dimer \ ligand (bpy, phen-type)}\]

\[\text{HBPin, B}_2\text{Pin}_2\]

\[\text{PinB}\]

\[\text{6-sp}^3\text{-H Activation}\]

\[\text{Pd(OAc)}_2 (20\% \text{ oxone, Mn(OAc)}_2, \text{Ac}_2\text{O or Ar-I}}\]

\[\text{MeNO}_2, 80 \degree \text{C}\]

\[\text{X = Ar, OAC}\]

\[\text{R = Leu, Phe, Ala, ethylGly}\]

\[\text{OL 2006, 8, 3391}\]

D.G. free variant:
ACIE 2017, 56, 1506

Case Study: Celogentin C-H Activation vs

Chen: ACIE 2010, 49, 958

Castle: JACS 2010, 132, 1159

\[\text{Chen uses C-H activation}\]

\[\text{Castle opts for Knoevenagel + 1,4 add’}n\]

\[\text{TiCl}_4, \text{NMM} \quad 68\%\]

\[\text{We will return to this compound for Oxidative Coupling discussion}\]
(2) Arene Connection Problem


Many arene-arene peptide natural products are formed via oxidative couplings between Phe, Tyr, Trp, & His – how can this strategy be applied?

**Harran’s Diazonamide A** – *ACIE* 2003, 42, 4961

see also: Nicolaou’s synthesis – Classics vol. 2, ch. 20

**Strategy:** Form D-E juncture in presence of pre-formed A-F system.

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**Revisiting the Celogetins**

Castle: *JACS* 2010, 132, 1159

Chen: *ACIE* 2010, 49, 958

**Strategy:** Form D-E juncture in presence of pre-formed A-F system.

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Tactics and Strategies in Complex Peptide Synthesis

Bank 6: Oxidative Couplings (cont.)

Arylomycins *JACS, 2018, 140*, 2072
original: *JACS, 2007, 127*, 15830

![Chemical structure of Arylomycins](image)

The Atropisomer Problem

- Atropisomers can arise in isopeptides from hindered rotation about single bonds
- How can one control chirality in the absence of stereogenic atoms?

Main strategies include:
1. Atropisomeric ‘recycling’ by equilibration and separation
2. Modern atrop-selective cross-couplings
3. Point-to-axial chirality transfer

**Key:** Order of bond formations is crucial, but difficult to predict

Bank 7: Larock Annulation

**Original Larock Annulation**

- **Pd(0) or Pd(II) + ligand, inorg. base,**
- **Naseseazines:** *JACS 2013, 135*, 5557
- **Psychotrimine:** *JACS 2008, 130*, 10886
- **Kapakahine:** *JACS 2009, 131*, 6360

**Applications in synthesis:**

- **Naseseazines:** *JACS 2013, 135*, 5557
- **Psychotrimine:** *JACS 2008, 130*, 10886
- **Kapakahine:** *JACS 2009, 131*, 6360

**Important applications in the synthesis of strained indole macrocycles:**

- **Streptide:** *JACS 2019, 141*, 17361
- **Chloropeptin:** case study forthcoming

**This area is intentionally left blank**
Larock Case Study: Complestatin & Chloropeptin I (*)

Key Fragments:

1. Schollkopf aux.
2. HCl
3. Boc₂O
4. LiOH

Strategy:

- $S_N$Ar in presence of D-F system

Takeaways:

- Larock ligand and soluble base key for Ar-Br
- 1st Larock macrocyclization
- Use of AA to generate Phg analogues powerful
A Comparison of Approaches: Classic vs. Modern Vancomycin (Boger)

Strategy: Disconnect D-E first since isom. will not affect A-B & C-D

Key finding: $E_a$ of atropisomers: $D$-$E < A$-$B < C$-$D$

Original approach: JACS 1999, 121, 10004

60% 1:1 at C-D but recyclable

Sandmeyer $R = NO_2$ to Cl then Suzuki 77% (2 steps) 1:1.3 at A-B but 3:1 on isom.

CsF, DMSO 65-75% 8:1 at D-E, 1:1 on isom.

Deprotections; peptide couplings

7 steps
A Comparison of Approaches: Classic vs. Modern Vancomycin (Boger)

The Modern Approach: Strategically similar, tactical improvements

JACS 2020, 142, 16039

Improvements to ncAA Synthesis

A-Ring Precursor

original route: low %ee, scalability issues

B2eg2 = \[\begin{array}{c}
\text{O} \\
\text{B} \\
\text{O} \\
\text{O}
\end{array}\]

C Ring Precursor

from phenylglycine

D Ring Precursor

clear fragment improvements, but how did the key connections change?

original fragment synthesis:

JOC 1997, 62, 4721
A Comparison of Approaches: Classic vs. Modern Vancomycin (Boger)

**Strategy:**
- Disconnection order preserved
- Ligand-controlled atroposelective Suzuki followed by relay

**Modern Approach:**

\[
\text{Pd}_{2}\text{dba}_{3}, \quad (R)-\text{BINAP(O)}
\]

72-89% ≤ 8g scale

\[
\text{or Pd(OAc)}_{2}, \quad (R)-\text{BINAP}
\]

82-93% ≤ 25g scale

slow addition

\[
\text{DMTMM(H)}
\]

used in couplings
- suppress epim.
- strained lactams

**Key Takeaways:**
- Original disconnection strategy worked well
- Modern tactics enable better material throughput, kinetic control
- In cases of atropisomeric biaryls, empirical evidence is required (i.e. E\textsubscript{a}’s)
- See also: Nicolaou’s and Evans’ syntheses (Classics, vol. 2, ch. 9)
**Tactics and Strategies in Complex Peptide Synthesis**

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**(3) A Look to the Novel Approaches**

**Bank 8: Chemoenzymatic Oxidation**


**Hydroxylation as a Handle**

expanded scope:

- HO
  - R = Me, OH
  - R = H, Me, Et, CH$_2$N$_3$, CO$_2$Me

**Method**

*JACS* 2018, 140, 1165

Polyoxypeptin & Cavinafungin B

*Tetrahedron* 2019, 75, 3253

*Tetrahedron* 2018, 74, 6469

**Biocatalytic DKR-amino transfer**

*ACIE*, 2021, 60, 17680–17685.

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**Case Study: Tambromycin – C-H Functionalization vs. Chemoenzymatics**

**Thomson and Renata Synthesis**

1. I$_2$, KOH
2. TIPSCI, LHMDS
3. i-PrMgCl•LiCl

56% over 3 steps

9. Deoxo-Fluor
10. BBr$_3$

41% over 2 steps

3 steps

**Tambroline Route – Renata**

1. KDO1, aKG, Fe$^{2+}$, O$_2$
2. Boc$_2$O
3. BnBr
4. SOCl$_2$, cat. RuCl$_3$, NaIO$_4$

5. DMA, $\Delta$

36%/4 steps

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- Two routes with identical disconnection
- Renata employs enzymatic transforms
- Thomson uses auxiliary

**Renata**: *ACIE*, 2018, 57, 5037

**Thomson**: *OL*, 2018, 20, 2369.

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**Meso-pyrrolidines**

- MAO, O$_2$, FAD(H), buffer
- then hydrolyze

ACIE, 2010, 49, 2182

**β,γ-difunct. proline**

**δ-oxidation on γ-methyleleucine,**

in situ

NH$_3^+$/BH$_3$

75-88%

**β-epimer reacts faster**

yields ≥70%, >90% ee

**β-branched Phe analogues**
Case Study: Tambromycin (con’t)

**Tambroline Route – Thomson**

1. nBuLi, BuCOCl, Evans aux
2. KHMDS, trisyl azide
3. H₂O₂, LiOH

~$900/g

**Takeaways**

– Chemoenzymatic approach consists of more steps but traces to more available S.M.
– Traditional approach 13 steps LLS, chemoenzymatic 10 steps LLS

**Bank 9: Electrochemical Peptide Functionalizations**

excellent reviews: *Peptide Science* 2018, 110, e24049
*JACS* 2022, 144, 23
Application to synthesis: *Chem. Sci.* 2020, 39, 10752

**Parting Thoughts:**

– Largest unaddressed problem in the field is ncAA synthesis
– Typical metrics of evaluating syntheses seem not to apply as cleanly
– Other unsolved issues: large-scale structural/shape control, minimization of PGs

**and much more**