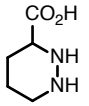
Nicholas Kramer

Piperazic Acid Synthesis

Bowers Lab

Piperazic Acid (hexahydropyridazine-3-carboxylic acid)(Piz); a unique motif observed in an array of architechturally complex secondary metabolites, predominantly within non-ribosomal peptide natural products (>75).

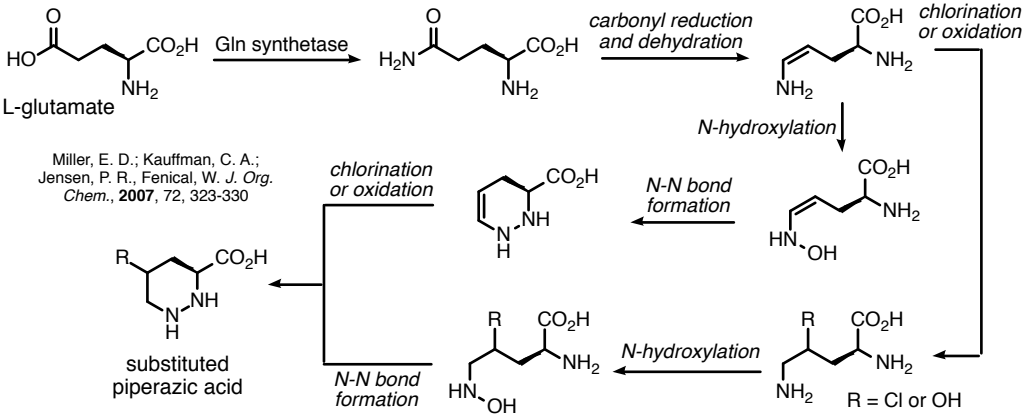


Useful Reviews:

- Ciufolini, M. A.; Xi, N. *Chem. Soc. Rev.*, **1998**, 27, 437-445
- XI, N.; Alemany, L. B.; Ciufolini, M. A. *J. Am. Chem. Soc.*, **1998**, 120, 80-86
- Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. *Nat. Prod. Rep.*, **2011**, 28, 1445-1471
- Waldman, A. J.; Ng, T. L.; Wang, P.; Balkus, E. P. *Chem. Rev.*, **2017**, 117, 5784-5863
- Küchenthal, C.-H.; Maison, W. *Synthesis*, **2010**, 5, 719-740

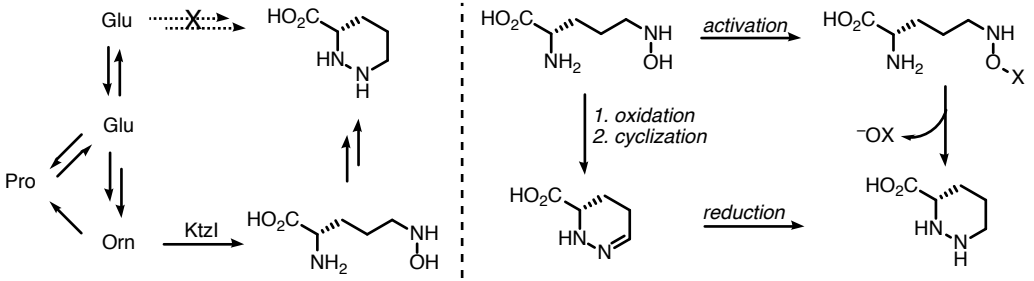
Background: Piperazic acid, a non-proteinogenic amino acid, was first identified in 1971 as a consitutent of the antibiotic monamycin (Bevan, K.; Davies, J. S.; Hassal, C. H.; Morton, R. B.; Phillips, D. A. S. *J. Chem. Soc. C.*, **1971**, 514-522). Studies on the biosynthesis of piperazic acid have been conducted, specifically within the context monamycin and polyoxypeptin (Arroyo, V.; Hall, M. J.; Hassall, C. H.; Yamasaki, K. *J. Chem. Soc., Chem. Commun.*, **1976**, 845-846 and Jiang, W.; Heemstra, J. R., Jr.; Forseth, R. R.; Neumann, C. S.; Manaviazar, S.; Schroeder, F. C.; Hale, K. J.; Walsh, C. T. *Biochemistry*, **2011**, 50, 6063-6072, respectively).

Piperazic Acid Biosynthesis (Fenical):



Miller, E. D.; Kauffman, C. A.; Jensen, P. R., Fenical, W. *J. Org. Chem.*, **2007**, 72, 323-330

Piperazic Acid Biosynthesis (Walsh): Other investigations have indicated that piperazic acid is synthesized biosynthetically from ornithine, not glutamine in *Kutzneria spp. 744*. Also discussed is the homology of *Streptomyces hygroscopicus* within the gene cluster that encodes for the production of himistatin, and thus may have a similar biosynthesis of Piz (Neumann, C. S.; Jiang, W.; Heemstra, J. R., Jr.; Gontang, E. A.; Kolter, R.; Walsh, C. T. *ChemBioChem.*, **2012**, 13, 972-976).



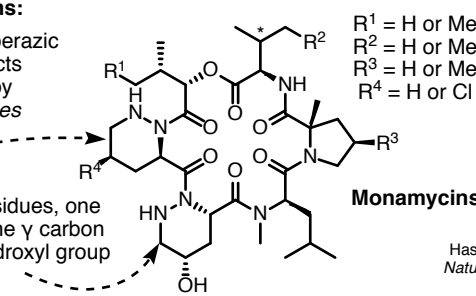
Piperazic Acid Biosynthesis: Other works (Fujimori, D. G.; Hrvatin, C. S.; Neumann, M.; Strieker, M. A. Marahiel; Walsh, C. T. Proc. *Natl. Acad. Sci U. S. A.*, **2007**, 104, 16498-16503 and Umezawa, K.; Ikeda, Y.; Kawase, O.; Naganawa, H.; Kondo, S. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1550-1553) have focused on elucidating the biosynthetic pathways of piperazic acid synthesis, yet much of these processes remains to be discovered.

Biological Significance of some Piperazic Acid-Containing Natural Products:

- Sanglifehrin A: Immunosuppressant agent/ inhibitory effects against hepatitus C.
- Lydiamycins A-C: Inhibitory effects against Gram-positive and Gram-negative bacteria, yeasts, and fungi.
- Luzopeptins/Quinoxapeptins: Inhibit HIV reverse transcriptase at sub-cytotoxic concentrations. Luzopeptin was also found to exhibit anti-tumor activity.
- Azinothicin: Exhibit potent antibacterial and antitumor activity as well as anti-inflammatory properties.
- Hiastatin: Found to exhibit *in vivo* antitumor activity against P388 leukemia and B16 melanoma in mice.
- Anthrimycin A: Demonstrated antibiotic activity toward *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*.
- Piperazimycins: Showns cyctotoxic activity against human colon carcinoma cell line HCT-116. Piperazimycin A showed activity against an oncologically diverse 60 cancer cell line panel at NCI as well.
- Chloptosin: Induces viability both in apoptosis-resistant human pancreatic adenocarcinoma cell line AsPC-I and in several apoptosis-sensitive cancer cell lines.
- L-156,605: Anti-inflammatory agent that inhibits binding of anaphilatoxin C5a to its receptor.
- L-156,373: Potent oxytoxin antagonist; high affinity for oxytocin receptor (OTR).

Historical Take – Monamycins:

Monamycins were the first piperazic acid-containing natural products discovered, isolated in 1959 by Hassall et al from *Streptomyces jamaicensis*.

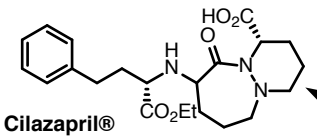


Contain two piperazic acid residues, one sometimes containing Cl on the γ carbon and the other containing a hydroxyl group on the γ carbon.

Monamycins A-I *(14 examples)*

Hassall, C. H.; Magnus, K. E. *Nature*, **1959**, 184, 1223-1224

A Non-Natural Small Molecule Drug Containing Piperazic Acid: Cilazapril®



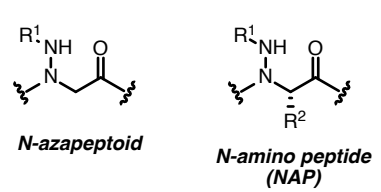
Cilazapril®

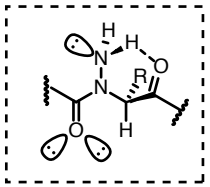
This anti-hypertensive agent features a bicyclic system containing piperazic acid amended to a 7-membered ring.

Attwood, M. R.; Hassall, C. H.; Kröhn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1011

Piperazic Acids – Conformation:

Recent studies of N-aminated peptides (NAPs) have shown a high level of torsional rigidity compard to their slightly more flexible glycine derivatives, rendering conformational implications regarding beta sheet/strand stabilization.



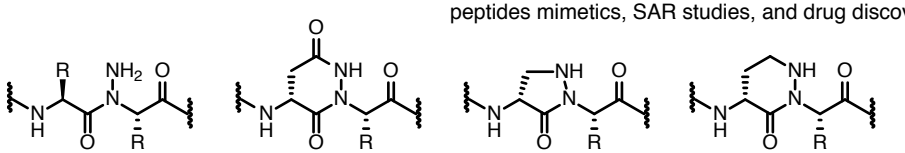


Kang, C. W.; Sarnowski, M. P.; Ranatunga, S.; Wojtas, L.; Metcalf, R. S.; Guida, W. C.; Del Valle, J. R. *Chem. Commun.*, **2015**, 51, 16259-16262

Sarnowski, M. P.; Kang, C. W.; Elbatrawi, Y. M.; Wojtas, L.; Del Valle, J. R. *Angew. Chem. Int. Ed.*, **2017**, 56, 2083-2086

Sarnowski, M. P.; Pedretty, K. P.; Giddings, N.; Woodcock, H. L.; Del Valle, J. R. *Bioorganic & Medicinal Chemistry*, **2017**, 26, 1162-1166

Due to these unique conformational factors, piperazic acid and similar moeities may play an important role in the future of peptides mimetics, SAR studies, and drug discovery efforts.



β-sheet orthotics

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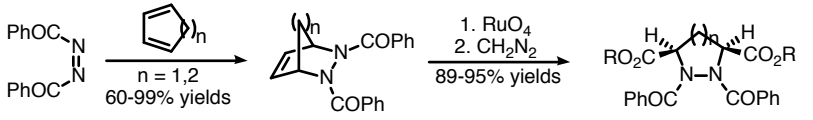
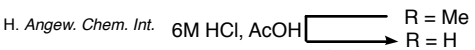
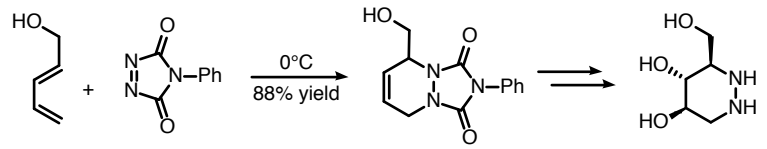
[4+2] Diels-Alder Reactions: Diels-Alder cycloadditions using azidodicarboxylates as dienophiles with 1,3-butadiene derivatives have been of the most frequent methods for piperazic acid formation.



Armbruster, J.; Grabowski, S.; Ruch, T.; Prinzbach, H. *Angew. Chem. Int. Ed.*, **1998**, 37, 2242

Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S.; *Chem. Pharm. Bull.*, **1998**, 46, 674



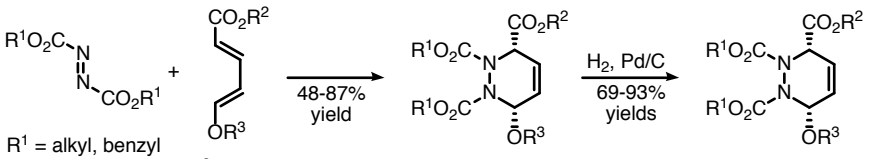


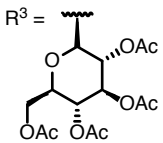
Bols, M.; Hazell, R. G.; Thomsen, I. B. *Chem. Eur. J.*, **1997**, 3, 940

Jimenez, R.; Sanz, A. M.; Gomez-Contreras, F.; Cano, M. C.; Yunta, M. J. R.; Pardo, M.; Campayo, L. *Heterocycles*, **2004**, 63, 1299

1-azafogomine

Auxilliary approach to piperazic acids:

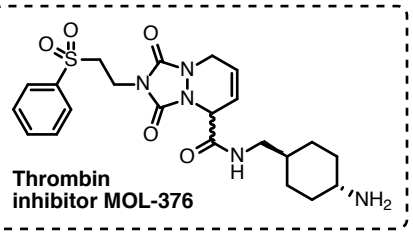




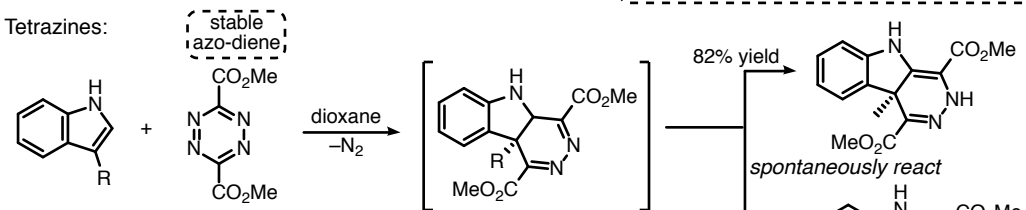
Diastereoselective approach toward chiral piperazic acid derivatives. Such an approach was used in the total synthesis of Thrombin.

Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2591

Methew, J.; Farber, K.; Nakanishi, H.; Qabar, M. *Tetrahedron Lett.*, **2003**, 44, 83

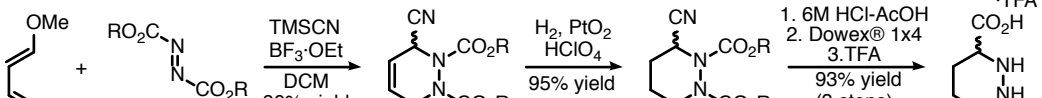


Tetrazines:



Benson, S. C.; Lee, L.; Snyder, J. K. *Tetrahedron Lett.*, **1996**, 37, 5061

Domino Synthesis:

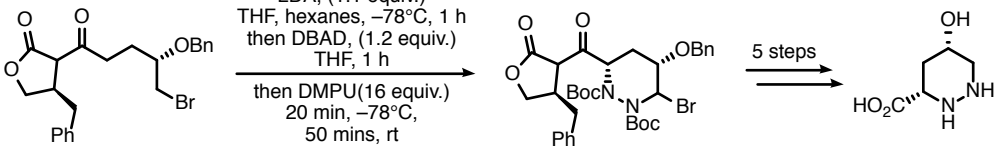


Kaname, M.; Yamada, M.; Yoshifuji, S.; Shashida, H.; *Chem. Pharm. Bull.*, **2009**, 57, 49

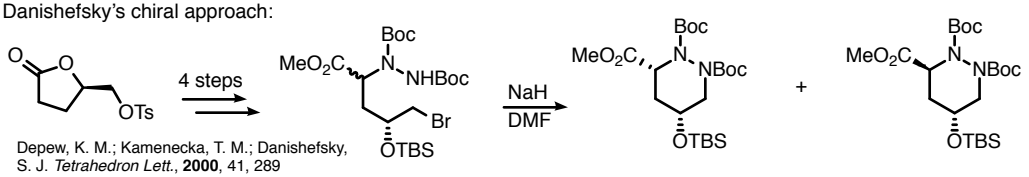
Progress: Many more examples of [4+2] Diels-Alder cycloaddition reactions for the purpose of accessing Piz derivatives exist in the literature. Due to the necessity for electron-donating and electron-withdrawing groups incorporated onto the Diels-Alder retrons, this method seems viable for the synthesis of substituted and structurally complex derivatives, yet lacks the scope for Piz incorporation into peptides.

Intramolecular Nucleophilic Displacement: Substitution reactions reactions have been employed to access Piz and its derivatives.

Hale, K. J.; Jogiya, N.; Manaviazar, S. *Tetrahedron Lett.*, **1998**, 39, 7163



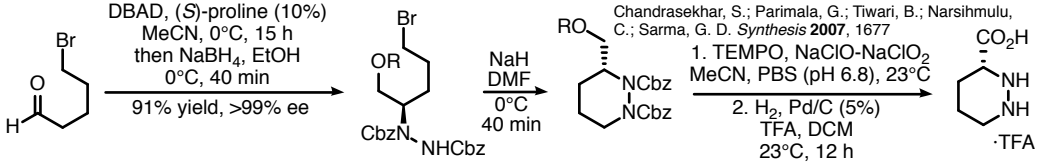
Danishefsky's chiral approach:



Depew, K. M.; Kamenecka, T. M.; Danishefsky, S. J. *Tetrahedron Lett.*, **2000**, 41, 289

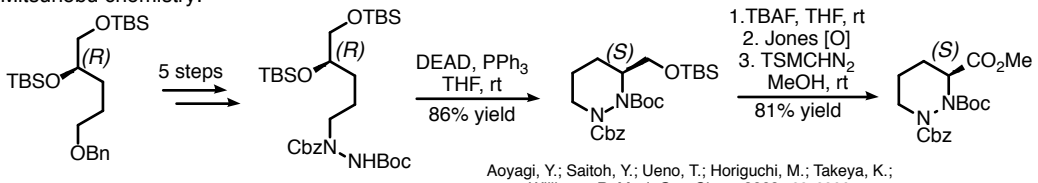
These piperazic acids were used in the total synthesis of himastatines (Kamenecka, T. M.; Danishefsky, S. J. *Chem. Eur. J.*, **2001**, 7, 41).

Organocatalytic:



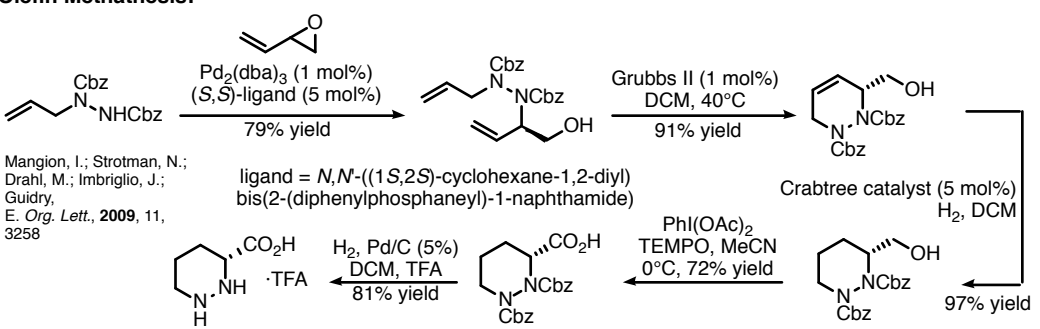
Chandrasekhar, S.; Parimala, G.; Tiwari, B.; Narsihmulu, C.; Sarma, G. D. *Synthesis* **2007**, 1677

Mitsunobu chemistry:



Aoyagi, Y.; Saitoh, Y.; Ueno, T.; Horiguchi, M.; Takeya, K.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 6899

Olefin Methathesis:



Mangion, I.; Strotman, N.; Drahl, M.; Imbriglio, J.; Guidry, E. *Org. Lett.*, **2009**, 11, 3258

ligand = *N,N'*-((1*S*,2*S*)-cyclohexane-1,2-diyl) bis(2-(diphenylphosphaneyl)-1-naphthamide)

Summary: Alternative methods for traditional synthesis of piperazic acid and its derivatives include intramolecular lactam formation, intramolecular hydrazone formation, intramolecular N-arylation, and more.

See Maison's review and earlier works (Ciufolini) for a more detailed comprehensive review of Piz synthesis as well as insights into their conformational implications.

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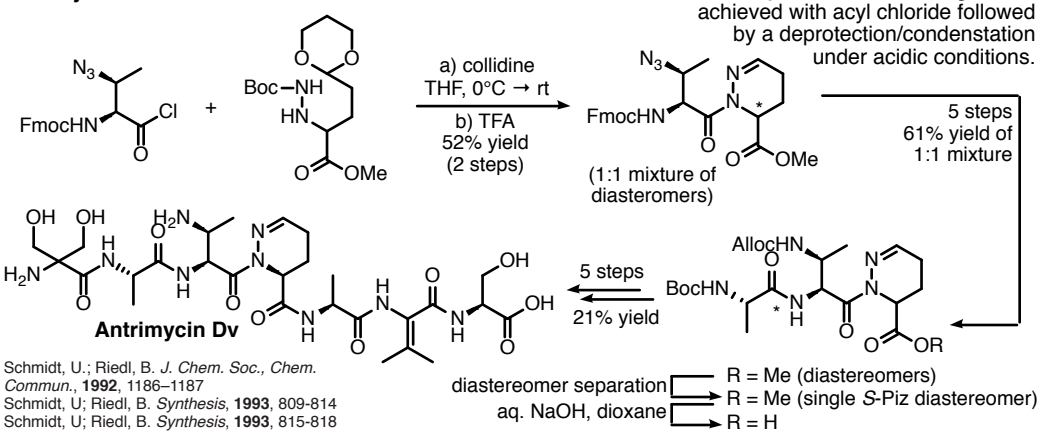
Piperazic Acids in Natural Product Total Synthesis:

Current Limitations:

- Piperazic acid-containing peptide natural products are difficult to prepare using preformed piperazic acid building blocks due to stereoelectronic and steric factors associated with the motif.
- Current methods (i.e. Diels-Alder, olefin methathesis, nucleophilic displacements) pose inherent problems regarding peptide synthesis – protecting group and functional group tolerance.

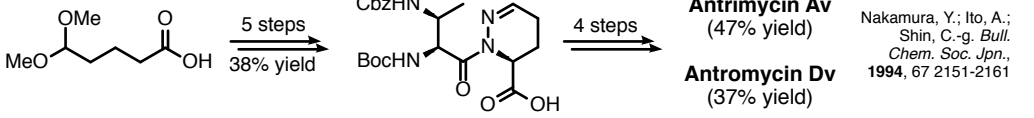
This summary will showcase a some of the highlights from the following review: Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. *Nat. Prod. Rep.*, **2011**, 28, 1445-1471. Refer to this for a full perspective on piperazic acid-containing NPs, their isolation, total syntheses, and biological relevance.

Antrimycins – Schmidt & Riedl:



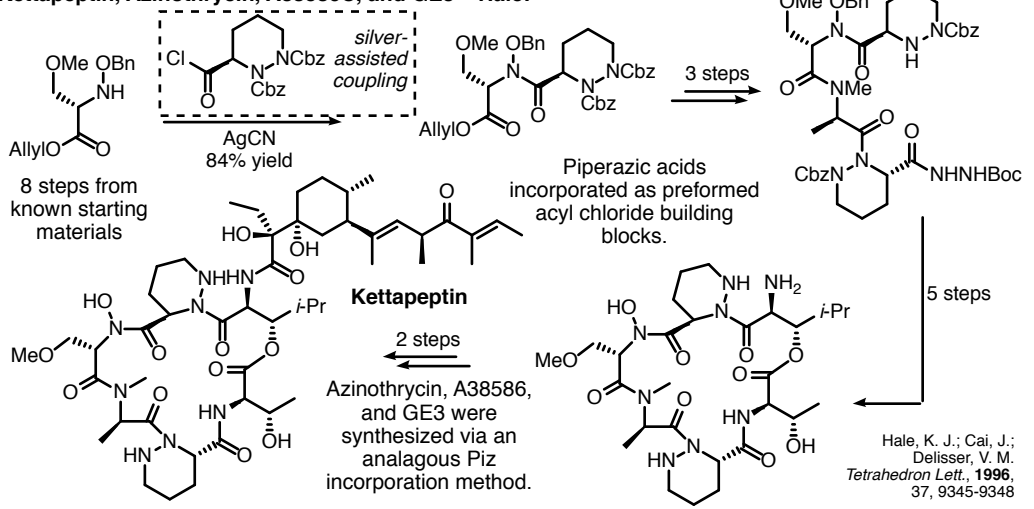
Schmidt, U.; Riedl, B. *J. Chem. Soc., Chem. Commun.*, **1992**, 1186–1187
Schmidt, U; Riedl, B. *Synthesis*, **1993**, 809-814
Schmidt, U; Riedl, B. *Synthesis*, **1993**, 815-818

Antrimycins – Nakamura: Nakamura et al incorporated their piperazic acid moeity in an alalagous method to that of Schmidt & Riedl, synthesizing and using the intermediate shown below to access Antrimycins Av & Dv.



Nakamura, Y.; Ito, A.; Shin, C.-g. *Bull. Chem. Soc. Jpn.*, **1994**, 67 2151-2161

Kettapeptin, Azinothrycin, A38586C, and GE3 – Hale:



Hale, K. J.; Cai, J. *Chem. Commun.*, **1997**, 2319-2320

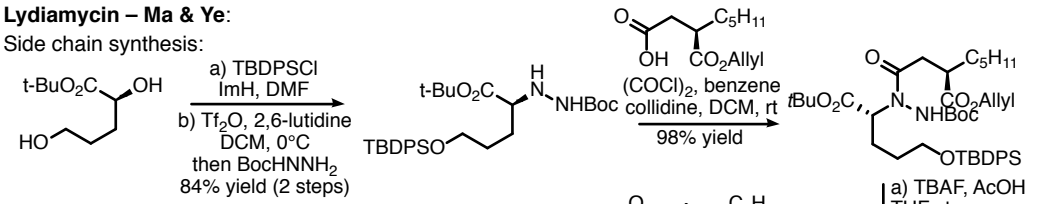
Hale, K. J.; Lazarides, L. *Org. Lett.*, **2002**, 4, 1903-1906

Hale, K. J.; Manaviazar, S.; George, J. H.; Walters, M. A.; Dalby, S. M. *Org. Lett.*, **2009**, 11, 733-736

Hale, K. J.; Cai, J.; Delisser, V. M. *Tetrahedron Lett.*, **1996**, 37, 9345-9348

Lydiamycin – Ma & Ye:

Side chain synthesis:



This method for Piz formation was employed in the attempt at the divergent synthesis of the Lydiamycins, however, complications from stereocenter misassignments prevented completions of the total synthesis. Regardless, intramolecular condensation reactions have been a key strategy in Piz derivative formation.

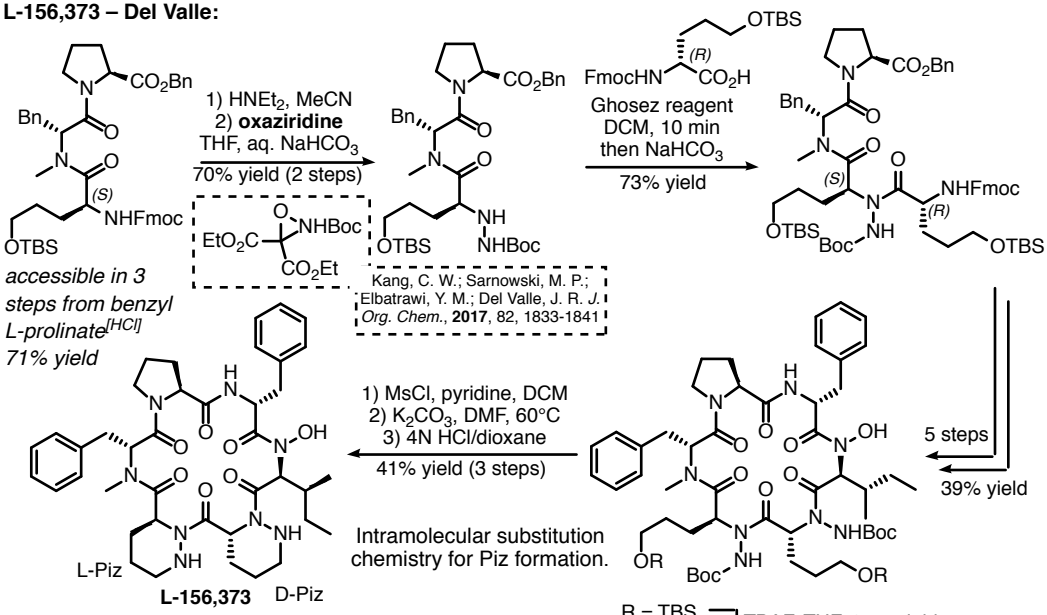
Schmidt, U.; Braun, C.; Sutoris, H. *Synthesis*, **1996**, 223-229

Hoffmann, R.; Kim, H.-O. *Tetrahedron Lett.*, **1990**, 31, 2953

Tamaki, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. *Tetrahedron Lett.*, **1993**, 34, 683-686

Tamaki, K.; Kurihara, S.; Oikawa, T.; Tanzawa, K.; Sugimura, Y. *J. Anitbiot.*, **1994**, 47, 1481-1492

L-156,373 – Del Valle:



Kang, C. W.; Sarnowski, M. P.; Elbatrawi, Y. M.; Del Valle, J. R. *J. Org. Chem.*, **2017**, 82, 1833-1841

Elbatrawi, Y. M.; Kang, C. W.; Del Valle, J. R. *Org. Lett.*, **2018,** 20, 2707-2710

Del Valle has recently published the synthesis of L-156,373, a non-ribosomal natural product isolated from the fermentation broth of *Streptomyces silvensis*, which exhibits binding affinity for the oxytocin receptor (OTR). Also synthesized was an oxoPiz derivative, highlighting late chemical diversification of Piz residues.

Highlights of the synthesis:

- Access to α-hydrazino amino acids including canonical amino acids (previous methodlogy – see above, regarding Armstrong's oxaziridine & new conditions).
- Late-stage Piz formation via seemingly facile substitution chemistry may allow for convenient access of piperazic acid derivatives, while cirumventing the limitations associated with the sterically and stereoelectronically-hindered preformed building blocks.

Conclusion:

This review has offered highlights into the syntheses of piperazic acids as well as a brief introduction into the unique nature of this non-canonical amino motif. While this review is not a compilation of all of the literature examples, the cited reviews offer an in-depth analysis of the vast literature on piperaciz acids.

Future:

With the advancements in organic synthesis of piperazic acid and its derivatives, specifically within the recent literature, natural product targets containing Piz may be increasingly more accessible, both in solution and on solid support.