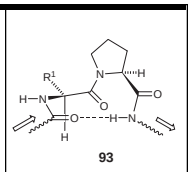
Synthesis, chemistry and conformational properties of piperazic acids



CHEMICAL SOCIETY REVIEWS

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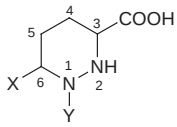
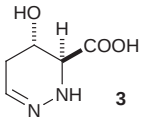
We review methods for the preparation of piperazic acids ("*piz*") and significant aspects of their chemistry. Special attention is devoted to issues relating to acylation of these non-proteinogenic amino acids, given the importance of these operations for the synthesis of *piz*-containing oligopeptides. We also provide an account of the unique conformational properties of piperazic acids and discuss their behavior as rigid proline equivalents that should be quite useful for the creation and study of peptide turn mimics.

1 Introduction

Piperazic acids ("*piz*") are non-proteinogenic, cyclic α-hydrazino acids of general structure **1**, **2**. Compound **1**, the first



1 X = Y = H
2 X, Y = π bond



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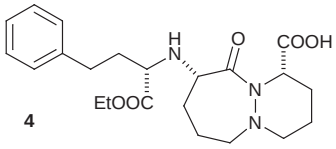
member of the family to be described in the literature, was discovered by Hassall and coworkers as a component of monamycins, a group of cyclodepsipeptide natural products.[1] In the intervening years, piperazic acids and their C-4 oxygenated variants, **3**, have been detected in several other peptide natural substances,[2,3] the number of which continues to grow.[4] The majority of these compounds display remarkable biological properties. For instance, antrimycins[2b] are tuberculostatic agents; GE3 and GE3B[4a] are antitumor antibiotics that inhibit the progression of cell cycle from the G1 to the S phase; L-156,373[3] is a potent oxytocin antagonist; L-156,602[3] is an antiinflammatory agent that inhibits binding of anaphilatoxin C5a to its receptor; luzopeptins[5] and quinoxapeptins[5] are strongly active against HIV.[6] Appreciable biological activity is found even at the level of *piz*-containing structures much simpler than those of the above natural products. For instance, the antihypertensive agent, cilazapril®, **4**,[7] features a unique



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bicyclic derivative of **1** as a key subunit, while piperazic acid **1** itself appears to interfere with γ-aminobutyric acid ("GABA") uptake.[8]

Our own interest in **1**–**3** developed in connection with work directed toward the total synthesis of luzopeptins. These efforts have provided us with much opportunity to explore the preparation, chemistry and conformational properties of piperazic acids, especially the unsaturated variants, **2** and **3**, and their N-2 acyl derivatives. Our own work, and that of other researchers before us, has unveiled a number of interesting properties of these molecules. Aspects of their synthesis, chemistry, and unusual conformational properties are reviewed herein.

2 The chemistry of piperazic acids

2.1 Synthesis of the *piz* framework

A number of methods for the synthesis of piperazic acids are currently available, undoubtedly as a result of their growing importance in natural products chemistry and of their potential in pharmaceutical research. In general, the *piz* framework is assembled by cyclization of a suitable α-hydrazino acid precursor, which, in turn, may be obtained either by *N*-amination of an α-amino acid derivative or by delivery of a complete hydrazine unit to an appropriate substrate.

Marco Ciufolini

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Ning Xi

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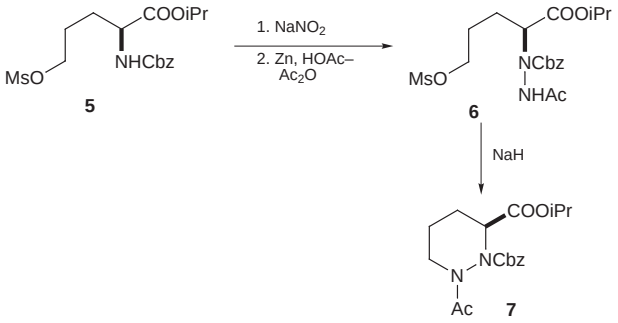
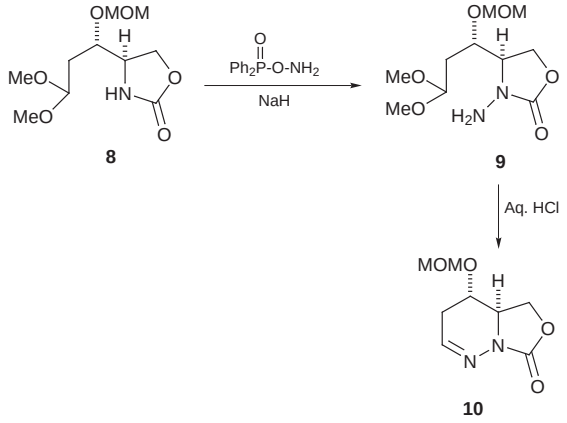
A typical route to piperazic acids through *de novo* construction of the hydrazine unit is exemplified in the conversion of **5** to **7**. Thus, a classical *N*-nitrosation of compound **5** followed by nitroso group reduction and *in situ* acetylation were carried out as a prelude to cyclization to **7** (Scheme 1).[9] Hydrazines may be



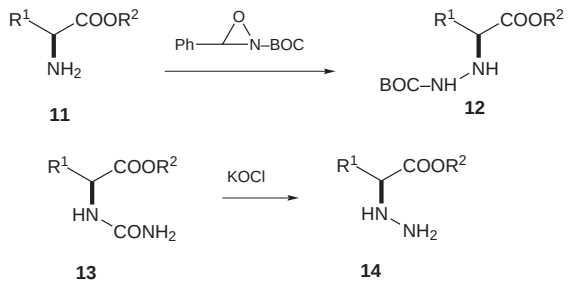
Scheme 1

assembled even more expeditiously thanks to contemporary methodology for *N*-amination. This is illustrated in a recent synthesis of piperazic acid analogs, a central feature of which was the reaction of oxazolone **8** with *O*-(diphenylphosphinyl)hydroxylamine. The emerging **9** was then cyclized to **10** with aqueous acid (Scheme 2).[10] The recently described Collet



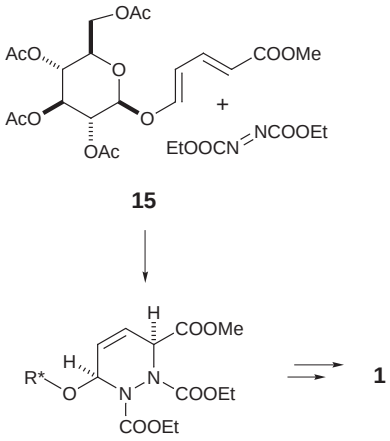
Scheme 2

oxaziridines[11a] seem to hold excellent potential for the creation of the hydrazine unit of an ultimate piperazic acid, as apparent from the successful *N*-amination of various α-amino acids (*cf.* **11** → **12**). Similar transformations should also be possible through the so-called Shestakov reaction, an analog of the Hoffman rearrangement that utilizes ureas as substrates. Improved protocols for the conduct of this reaction with hydantoic acids are now available (*cf.* **13** → **14**, Scheme 3).[11b]



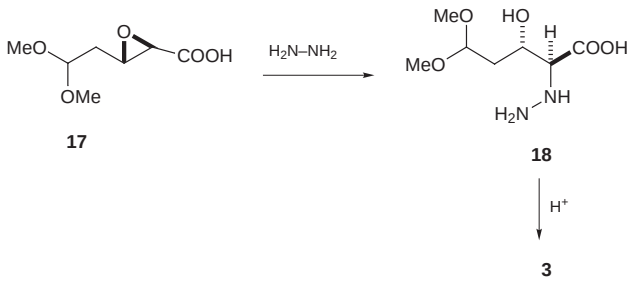
Scheme 3

Most known routes to piperazic acids, however, involve delivery of a complete hydrazine subunit to a suitable acceptor. The heterocycloaddition between dienes and azodicarboxylate esters, or cyclic variants thereof, constitutes one of the earliest synthetic methods for **1** and **2**.[12] As shown in Scheme 4, the reaction may be conducted in an enantioselective mode; *e.g.*, by the use of dienes displaying a glucose-derived chiral auxiliary (Scheme 4).[13] A different strategy rests on the regioselective



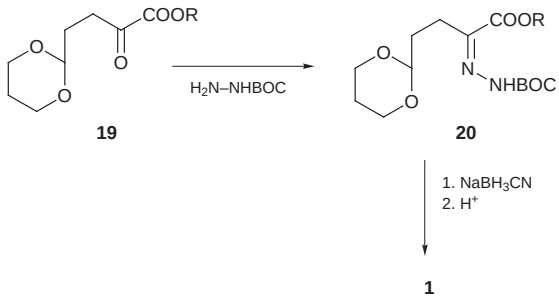
Scheme 4

hydrazinolysis of the oxirane ring of an α,β-epoxy acid, prepared in turn from the corresponding allylic alcohol by enantioselective Sharpless methodology and oxidation. This approach was demonstrated in a landmark synthesis of a piperazic acid component of luzopeptins (Scheme 5).[14] It is



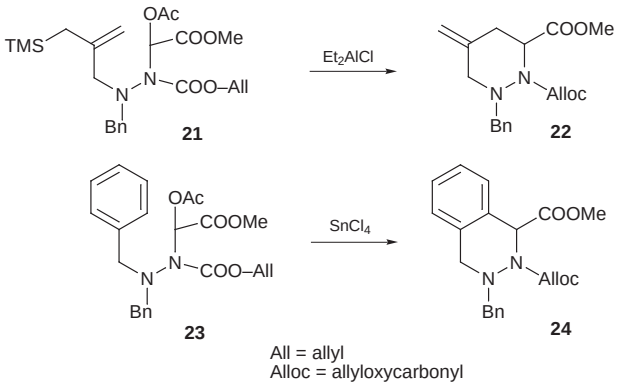
Scheme 5

noteworthy that the regioselectivity of nucleophilic opening of epoxides bearing an electron-withdrawing substituent at one of the oxiranyl carbons may be weak, and it is often in favor of the β-carbon relative to the substituent in question. In the present case, however, complete α-selectivity was observed. This may be due to conversion of the substrate acid to the corresponding carboxylate salt prior to oxirane cleavage, since the presence of a carboxylate anion on the epoxy ring is known to promote good α-selectivity.[15] A related approach involves reduction of the imino subunit of a hydrazone obtained from an α-ketoester and an alkyl carbazate (Scheme 6).[16] An interesting route to *piz*



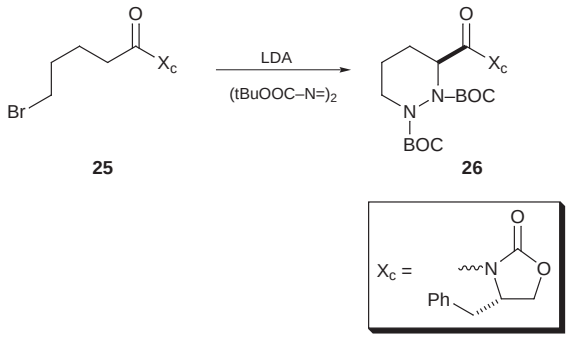
Scheme 6

frameworks through Speckamp-type intramolecular amidoalkylation reaction of *N*- acylhydrazinium species is shown in Scheme 7. This technique also allows preparation of benzo analogs **24** of piperazic acids.[17a]



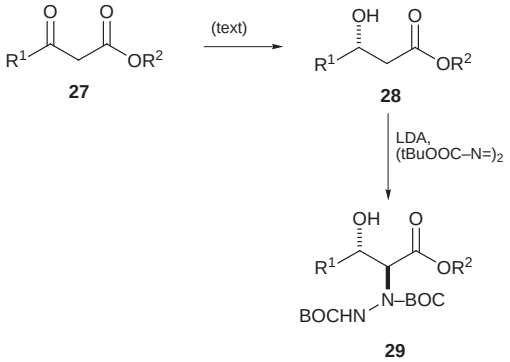
Scheme 7

Especially versatile avenues to **1**–**3** have emerged[18] with the advent of methods for electrophilic hydrazination of enolates.[19] This chemistry may well represent the most practical avenue to piperazic acids currently available, especially when combined with protocols for asymmetric derivatization of enolates; *e.g.*, through the use of Evans chiral auxiliaries. In many cases, the azodicarboxylate component is the bis *tert*-butyl ester ("DBAD"), though other azodicarboxylates may also be employed. A variant of this reaction leads directly to the perhydropyridazine ring system through condensation of azodicarboxylates with enolates of 4-halobutyrate esters (Scheme 8).[20]



Scheme 8

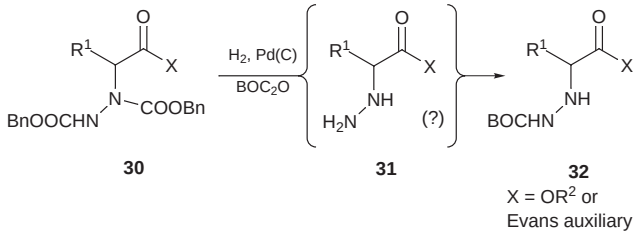
Luzopeptins and quinoxapeptins incorporate piperazic acids that display a free OH or an acyloxy group at C-4. Very direct asymmetric syntheses of these materials may be accomplished by diastereoselective hydrazination of the dianions of scalemic β-hydroxyesters (Scheme 9).[21] Diastereomeric excesses ob-

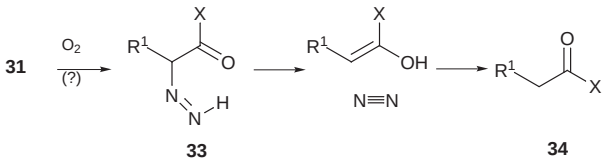


Scheme 9

served in the course of these reactions are good to excellent (94% in our hands). In turn, the hydroxyester substrates are readily available by enantioselective reduction of the corresponding β-ketoesters, either by Noyori-type hydrogenation or by treatment with fermenting bakers' yeast.[22]

It will be seen shortly that the preparation of piperazic acid for an ultimate incorporation into a peptide chain often requires access to terminally blocked α-hydrazino acid intermediates of the type **32**. Compounds of this type may be obtained from DBAD adducts by release of both BOC units (TFA) and treatment of the intervening free hydrazino acid with BOC_2O. The terminal NH_2 of the hydrazine is considerably more reactive than the inner NH group, so that product **32** is obtained with excellent regioselectivity. However this procedure is inefficient.[23] It is much better to start with adducts **30** of dibenzyl azodicarboxylate. Hydrogenolysis of the benzyl carbamates in the presence of BOC_2O leads to **32** in excellent yields.[24] Similar procedures have been described as a "transprotection".[17b] It is not clear whether the free hydrazine **31** is an intermediate in these reactions, but if so, its reaction with BOC_2O must be considerably faster than its hydrogenolysis. It should be noted that hydrazines such as **31** are quite sensitive to oxidation. Exposure to the atmosphere causes deazoniation, probably through the series of events depicted in Scheme 10. Transprotection bypasses the need to handle sensitive intermediates during blocking group exchange.

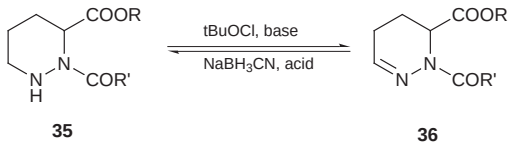




Scheme 10

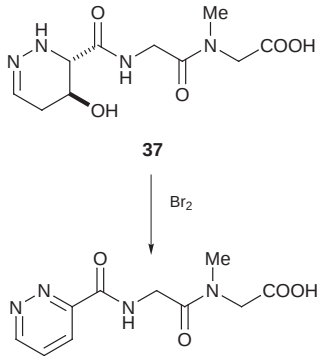
2.2 Reactivity of piperazic acids

Saturated and unsaturated variants of piperazic acids may be readily interconverted when the N-2 position is acylated; therefore, any method leading to one type of compound is readily adaptable to the creation of the other. Acidic $NaBH_3CN$ easily reduces the imino unit of structures of the type **2**,[23] while oxidation of molecules of the type **1** may be effected with *tert*-butyl hypochlorite (Scheme 11).[25a] It should be noted that controlled oxidations may be difficult to induce if the N-2 position is not acylated, in which case the substrate tends to undergo aromatization to a pyridazine. This is shown with compound **37**, a product of partial hydrolysis of luzopeptins. Reaction with Br_2 furnished **38** (Scheme 12).[26]



Scheme 11

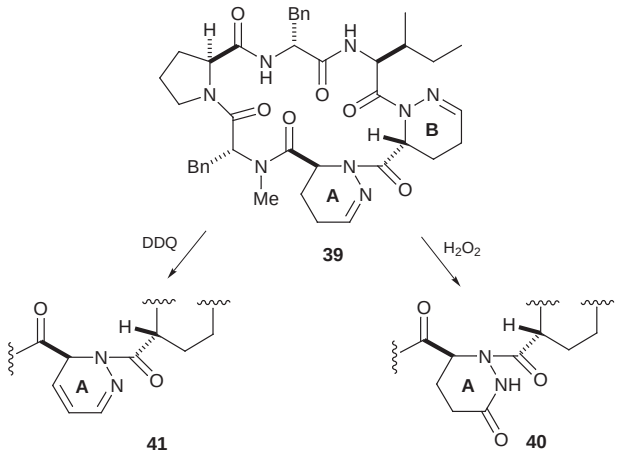
Oxidation of *N*-acylpiperazic acids with other mild agents may lead to useful derivatives. Bock and coworkers have described several noteworthy transformations of compound **39**, a potent oxytocin antagonist.[25b] This material reacts regioselectively at the piperazic acid **A** unit under a variety of conditions. Treatment with hydrogen peroxide attacks the imino linkage in ring **A**, resulting in the formation of cyclic hydrazide **40**; while reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoqui-



37 38

Scheme 12

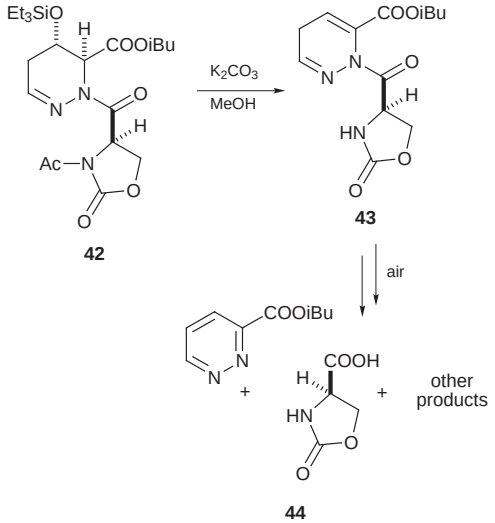
none ("DDQ") produces **41**, apparently as a relatively stable compound (Scheme 13). By contrast, we find that compounds



39 41 40

Scheme 13

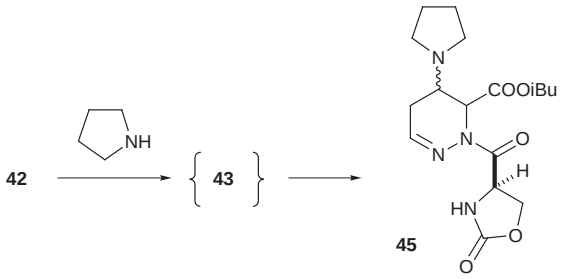
of the type **43**, which are regioisomers of **41**, are fragile substances.[27] These materials may be obtained upon β-elimination of C-4-oxygenated piperazic acids and their esters, *e.g.*, **42**. It will be seen later that this reaction is often facile and it constitutes a major stumbling block in sequences directed toward the incorporation of fragments **3** in growing peptide chains. Exposure of **43** to the atmosphere tends to promote aromatization with concomitant release of the N-2 acyl unit, as well as other reactions (Scheme 14). On the other hand,



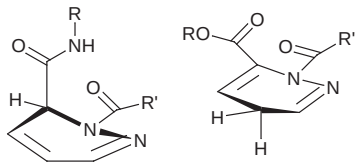
42 43 44

Scheme 14

43 may be intercepted *in situ* with nucleophilic amines, *e.g.*, pyrrolidine, to furnish products of conjugate addition in moderate yield (Scheme 15).[24] The difference in stability between structures **41** and **43** is probably due to a stereoelectronic effect. Compound **44** favors a conformation **46** which places the sole ring hydrogen at a pseudoequatorial position. Improper alignment of the C–H σ orbital with the ring π system retards removal of this H atom by radical species such as, *e.g.*, ground- state, triplet O_2. Compound **43**, by contrast, exists in a conformation, **47**, wherein a hydrogen atom is always pseudoaxial and properly aligned with the ring π system for facile abstraction (Scheme 16).



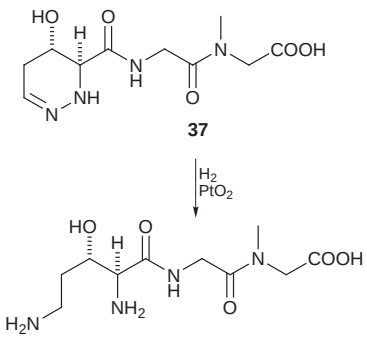
Scheme 15



46 47

Scheme 16

The N–N linkage of piperazic acids is susceptible to hydrogenolysis, especially if the N-2 position is free. Thus, reaction of **37** with H_2 in the presence of PtO_2 leads to **48** (Scheme 17).[26] It is likely that this transformation involves an

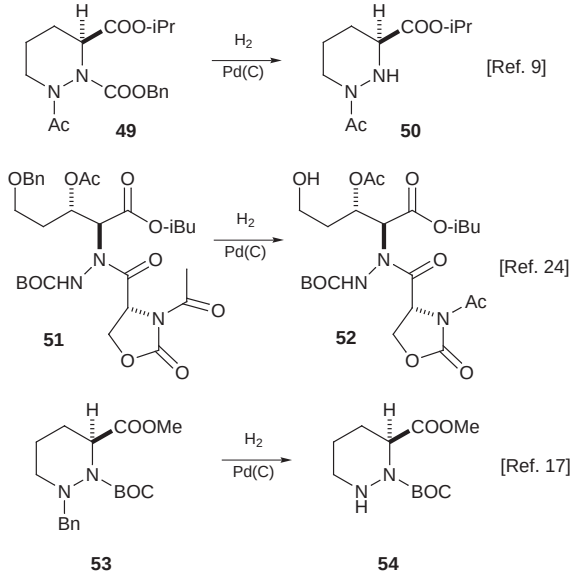


37 48

Scheme 17

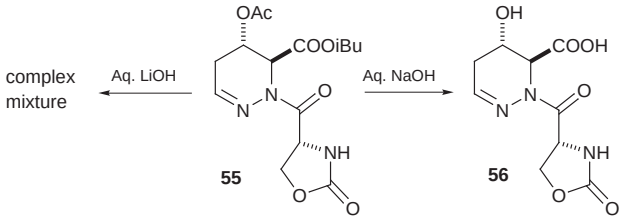
initial reduction of the imino linkage, followed by a faster cleavage of the N–N bond. However, hydrogenolysis of benzyl groups may be effected without rupture of the N–N bond in monoacyl derivatives of **1**, as well as in acyclic α-hydrazino ester precursors to piperazic acids. Even *N*-benzyl groups may be cleaved under appropriate conditions, without harm to the N–N linkage (Scheme 18; see also Scheme 10).

Piperazic acids are relatively stable to acidic reagents. Even some of the C-4 oxygenated analogs survive exposure to strong trifluoroacetic acid solutions for short periods of time (10–15 min). Tolerance to basic agents is likewise good; however, either free acids or esters of general structure **3** may suffer β-elimination under basic conditions. This propensity complicates the task of incorporating fragments containing **3** into growing peptide chains, since even the weakly basic agents required during these rections (*e.g.*, *N*-methylmorpholine) may



Scheme 18

cause unwanted side reactions. Occasionally, β-elimination may be controlled by the judicious choice of conditions. To illustrate, attempted hydrolysis of **55** with aqueous LiOH produced complex mixtures; however, hydroxy acid **56** was obtained in essentially quantitative yield after 5 minutes of contact time with aqueous NaOH (Scheme 19).[24] Of course,

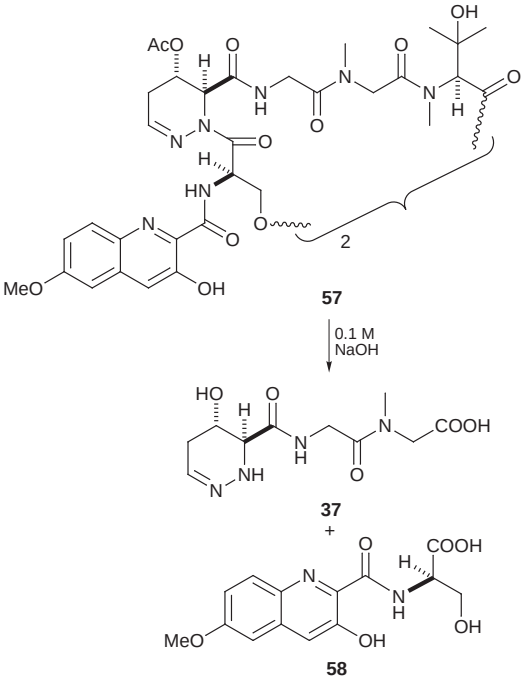


Scheme 19

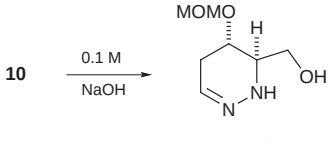
longer exposure also resulted in decomposition. It is noteworthy that hydrolytic cleavage of N-2 acyl substituents in piperazic acids of the type **2** and **3** occurs considerably more readily than one would expect for an amide linkage. Thus, prolonged reaction of luzopeptin A, **57**, with 0.1 M aqueous NaOH at 37 °C yields fragment **37** (Scheme 20).[26] Identical treatment induced hydrolysis of the oxazolone ring in compound **10**, a transformation that normally requires considerably more vigourous conditions (Scheme 21).[10]

The ease of N-2 deacylation in piperazic acid derivatives may be due to resonant dispersal of the negative charge accumulating on N- 2 during framentation of a tetrahedral intermediate such as **60** into the adjacent imino linkage (Scheme 22). It is also possible that the inductive effect of the imino nitrogen aids the fragmentation of **60** by diminishing the basicity of the departing nitrogen anion. Notice that formation of **37** occurs without β-elimination within the oxygenated piperazic acid. This may be due to the fact that the *piz* unit is now present as a secondary amide, instead of a free acid or an ester. The considerably diminished ability of secondary amides to undergo carbonyl α-deprotonation is probably responsible for the survival of the otherwise sensitive C-4 oxygenated functionality. This is also apparent in the examples of Scheme 23. We were unable to suppress β-elimination of the piperazic acid unit, and subsequent decomposition of the substrates, during Kunieda-type cleavage of the oxazolone ring in *piz* esters **62**. By contrast, secondary amide **63** underwent the reaction cleanly and in high yield.[24]

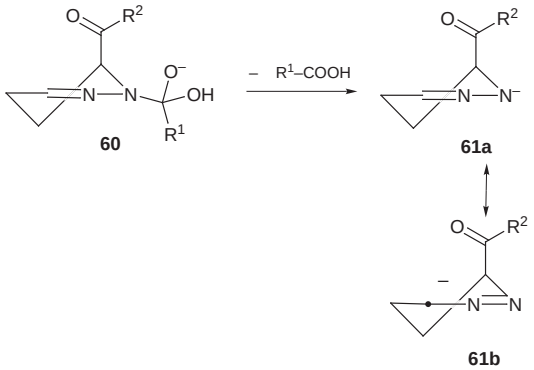
Piperazic acids occur in nature only as components of peptide natural products, and in all known cases, they are found as N-2



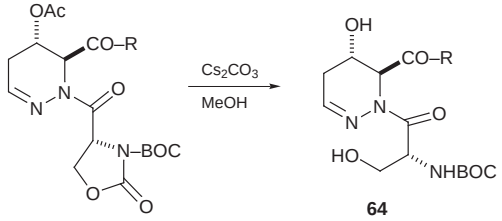
Scheme 20



Scheme 21

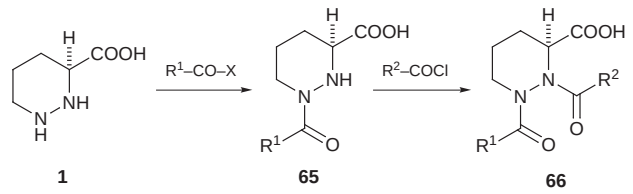


Scheme 22



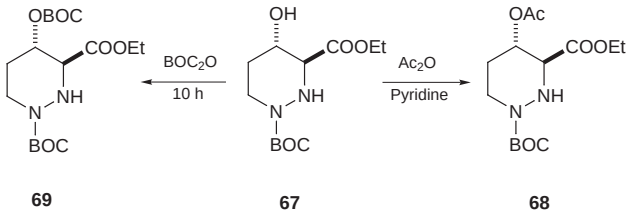
Scheme 23

acyl derivatives. Interestingly, N-2 acylation of a free piperazic acid is problematic. As early as 1979, it was observed that **1** reacts selectively at N-1 with various acylating agents, and that N-2 acylation of the resultant **65** is possible only with acid chlorides (Scheme 24).[12a] In support of these observations, we



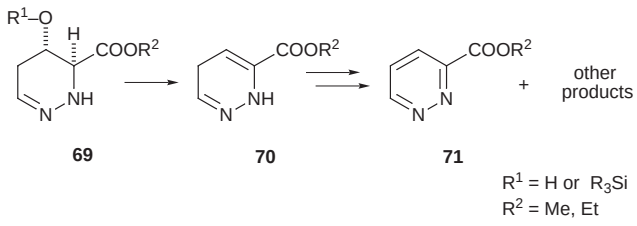
Scheme 24

found that **67** is inert toward carboxylic acids activated by a variety of common peptide coupling agents, and even toward carboxylic anhydrides.[23] Thus, **68** is the exclusive product of reaction with Ac_2O and pyridine, while prolonged treatment with BOC_2O yields **69** (Scheme 25). The weak nucleophilicity



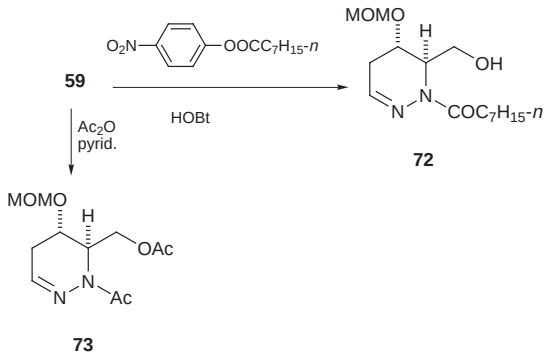
Scheme 25

of the N-2 site is reduced even further in structures of the type **2**. Attempted acylation of these molecules under gentle conditions normally fails, while more vigorous conditions severely damage the substrate. This is especially true of oxygenated variants of the type **69**, which tend to undergo β-elimination when exposed to several basic agents necessary for the conduct of acylation reactions. The resulting **70** then decomposed by a variety of pathways, as indicated above (Scheme 26). Notice that the decrease in N-2 nucleophilicity in **69** is consonant with the ease of N-2 deacylation discussed earlier.



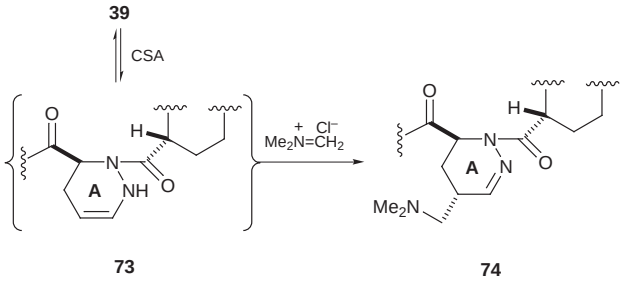
Scheme 26

The reasons for the unusually poor nucleophilicity of piperazic acids have been researched in some detail.[10] The fact that the N atom to be acylated is now part of a 6-membered ring suggests a parallel between *piz* and pipecolinic acid derivatives. While the latter are notoriously troublesome substrates in peptide-forming reactions, they are nonetheless considerably more reactive than *piz*. For example, pipecolinic units may be *N*-derivatized with carboxylic acids activated by *N*-methyl-2-chloropyridinium chloride,[28] while piperazic acids are completely inert under these conditions. In pipecolinic acid derivatives, the difficulty of *N*-acylation may be due primarily to a stereoelectronic effect.[29] In piperazic acids, stereoelectronic problems appear to be greatly exacerbated by inductive erosion of N-2 nucleophilicity by the carboxy group, but not by steric or conformational effects. Indeed, compound **59**, which is sterically and conformationally very similar to **2** or **3**, reacts at N-2 even with weak acylating agents; *e.g.*, 4- nitrophenyl esters in the presence of N-hydroxybenzotriazole ("HOBt"). It is also worthy of note that reaction of **59** with Ac_2O in pyridine delivers only diacetyl compound **73**, with no evidence of N-1 acylation and consequent enamide formation, or of tautomerization to an enamine and C-6-acylation (Scheme 27).[10] As an



Scheme 27

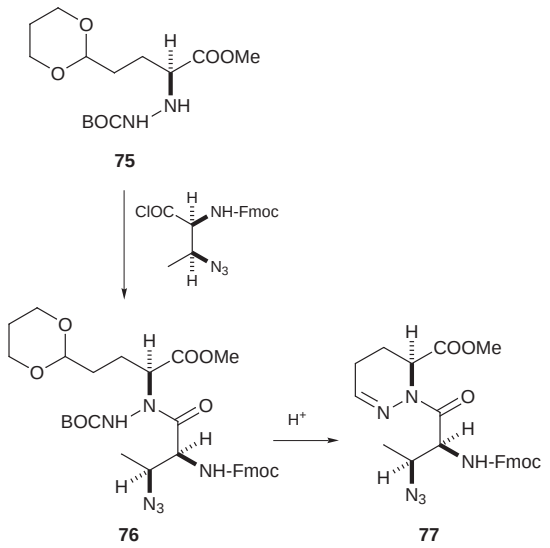
interesting aside, it should be mentioned that hydrazone tautomerization and consequent C-6 derivatization in N-2 acyl variants of **1** and **2** are possible under more vigorous conditions. In particular, reaction of **39** with camphorsulfonic acid ("CSA") and *N*,*N*-dimethylimmonium chloride ("Eschenmoser's salt") produces Mannich-type derivative **74**.[25b] Presumably, CSA serves to promote conversion to ene hydrazine **73** by protonation of the imino nitrogen and prototropic shift (Scheme 28). To our knowledge, however, no examples of C-6 acylation of **2** or **3** are known.



Scheme 28

The foregoing difficulties greatly complicate the creation of peptides incorporating N-2 acyl piperazic acids. Early methods for N-2 acylation of intermediates of the type **65** seem now less attractive than more recent techniques involving acylation of a terminally monoprotected α-hydrazino acid derivative such as **32**. The free NH group of these substances also displays abnormally low nucleophilicity, necessitating the use of highly reactive acid chlorides. This is exemplified by the conversion **75** →**77** in Scheme 29.[16] The sequence leading to **77** also reflects recent advances in the preparation and use of acyl chlorides of Fmoc-protected amino acids.[30] Hydrazines of general type **32** have also been acylated by an alternative technique involving condensation of their N-TMS derivatives with acyl fluorides. This is exemplified by the reaction of compound **78** with **79** (Scheme 30).[31] As of this writing, however, this method does not appear to have been used for the preparation of peptides incorporating piperazic acids.

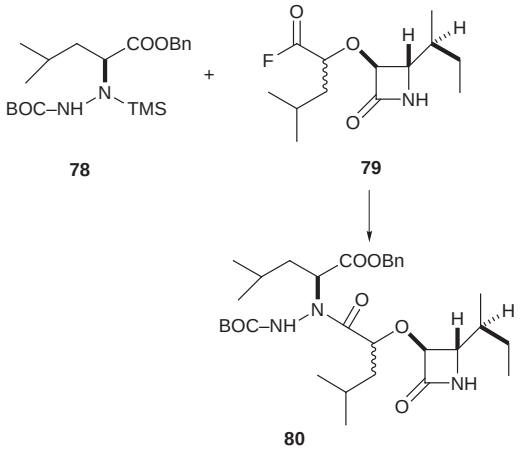
The creation of N-2 serinyl derivatives of *piz* is especially problematic, due to the propensity of many serinyl chlorides to undergo β-elimination of the protected oxygen functionality under the conditions of the acylation reaction. Yet, the N-2 serinyl *piz* is a crucial motif of synthetically appealing targets such as luzopeptins and quinoxapeptins. This difficulty may be remedied by the use of reagent **81** (D configuration shown), wherein β-elimination is retarded on stereoelectronic grounds.[32] The availability of this serinylating agent was central



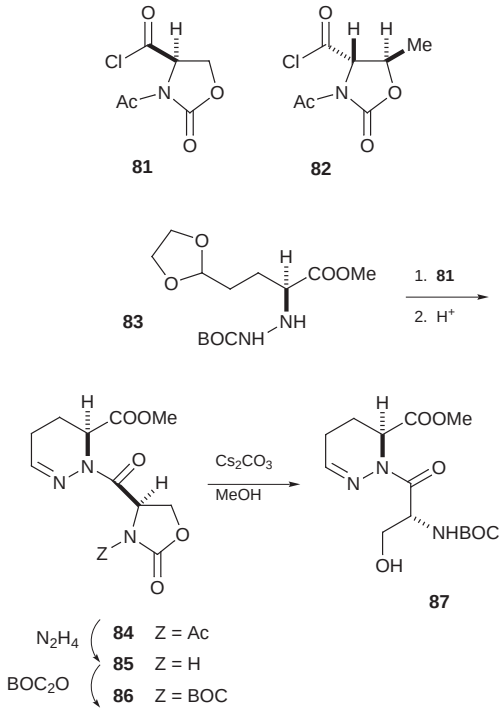
Scheme 29

to the success of the synthesis of compounds **62**–**64**,[24] heretofore elusive dipeptide components of many luzopeptins and of quinoxapeptins. Its use is detailed below in the context of a synthesis of **87** (Scheme 31),[33] a dipeptide subunit of the E series of luzopeptins. It is likely that acyl chloride **82** may be likewise employed for the preparation of N-2 threoninyl piperazic acids.

The advent of reliable technology for the preparation of N-2 acyl *piz* frameworks has revealed a unique property of these susbtances. Briefly, peptides incorporating proline or pipecolinic acid exist as mixtures of rotamers of the tertiary amide. As shown in Table 1, conformation **A** is always favored over **B**, typically to the extent of 1.5:1 to 5:1 (NMR), though in some cases this preference may be stronger (*cf*. **90**). In sharp contrast, analogous *piz* amides and peptides are rigidly fixed as rotamer **A** around the N-2-acyl bond.[33] This preference is calculated to be especially strong in peptides based on unsaturated piperazic acids **2** and **3**. Indeed, variable temperature NMR experiments with some derivatives of **2** and **3** failed to reveal significant motion about the N-2-acyl bond in a temperature range from −89 °C to +120 °C, suggesting also that the conformational energy barrier is large. The rigidity of these molecules may be attributed to an electrostatic interaction between the N-1 nitrogen and the N-2 acyl oxygen atoms that greatly disfavors conformer **B**, thereby strongly reinforcing the molecules innate preference for **A** (Fig. 1). More recently, we have confirmed the calculated preferences of a number of *piz* derivatives by single crystal X-ray diffractometry.[34]



Scheme 30



Scheme 31

Table 1

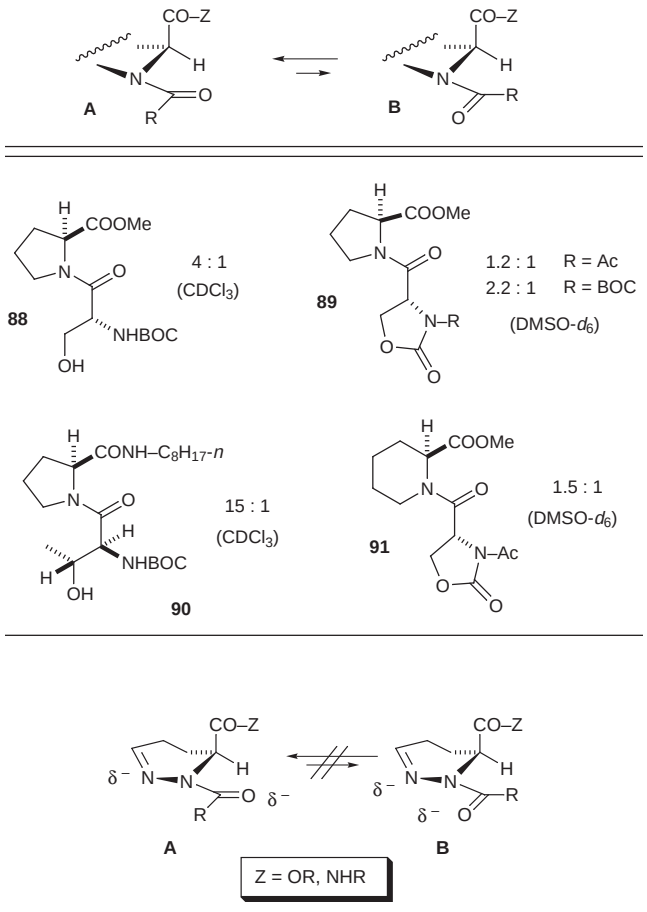


Fig. 1

These observations may have significant ramifications in problems relating to peptide secondary structure. A number of important aspects of protein structure and function are currently perceived to be intimately related to the presence of turn motifs

in peptide chains; that is, of regions where a peptide chain reverses its direction.[35] A diagram representing a typical peptide turn appears in Fig. 2. Such turns are believed to be key structural features of β-sheet architectures and of binding domains involved in ligand–receptor interactions, including those between proteins and nucleic acids. Accordingly, functional, structural, and mimicry aspects of turns motifs have commanded considerable attention, and remain to this day exceptionally active areas of scientific inquiry.[36]

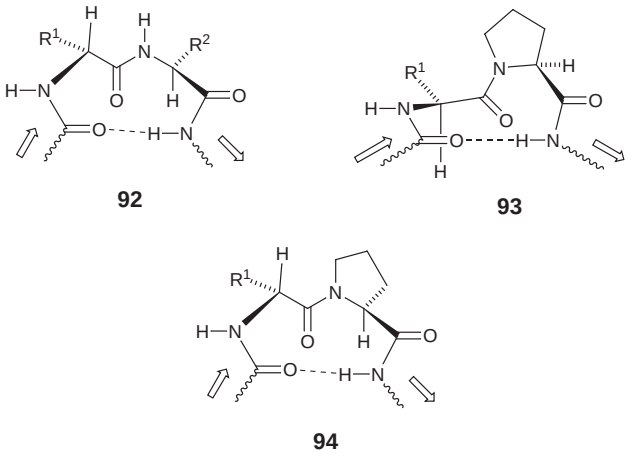


Fig. 2

Strain is often present in proximity of the amino acids occupying the peripheral position of a turn. This strain may be relieved by replacement of a secondary amide with a conformationally more flexible teriary amide at a turn site, *e.g.*, by the introdution of proline ("*pro*", *cf.* **93**). Indeed, this amino acid appears often at turn sites, probably because it can readily accommodate a conformation of the type **A** (Fig. 1), which is conducive to turn formation. Turns are even more greatly favored if the peripheral amino acids are of opposite α-configuration, the resulting structure being often described as a "heterochiral" sequence. Not surprisingly, a heterochiral sequence of the type, *e.g.*, *N*-(D-aminoacyl)-L-*pro* (*cf.* **94**) constitutes an especially good turn promoter. Indeed, similar heterochiral sequences have been utilized extensively in turn mimicry. However, the introduction of a proline within a peptide chain, even in a heterochiral mode, is insufficient to force a turn, because as detailed above, *N*-acyl *pro* generally do not manifest a sufficiently great preference for turn-promoting conformer **A**. Thus, artificial peptide turns must be further stabilized by a significant number of other intramolecular interactions (multiple hydrogen bonds, metal coordination, disulfide bridges, rigid templates, *etc*.).[37] Heterochiral as well as homochiral sequences wherein *pro* is replaced by a piperazic acid, especially an unsaturated one like **2** or **3**, display vector properties of a peptide turn. Recall, N-2 *piz* peptides are *locked* in a conformation of the type **A**; therefore, it seems plausible that these entities may be utilized to *force* turns in peptide chains. *Piz* peptides may thus become useful, perhaps exceedingly so, as building blocks for turn mimetics consisting of just a handful of amino acids. The resulting small molecule (mass < 500 Dalton) mimics of turn motifs may well find significant applications in various aspects of life science and health care. These are currently areas of intense research in our group.

Structural evidence in support of the turn-forming ability of *piz* may be identified in a seminal paper by Bock and collaborators at Merck & Co., USA.[25b] The X-ray crystal structure of oxytocin antagonist **39** reveals turn motifs at the level of the *piz* subunits, which interestingly are each part of a heterochiral sequence. An additional turn motif occurs at the level of the proline. The Merck scientists also observed significant changes in the biological activity of **39** upon reduction of the imino groups. It is conceivable that removal of the imino subunit renders the molecule more flexible and consequently less apt to assume a conformation suitable for binding to the oxytocin receptor. This would be consistent with the calculated greater rigidity of unsaturated *piz* peptides *vs*. their unsaturated analogs.

A further potential benefit of *piz*-based turns is implicit in Fig. 3, which shows an overlay of the calculated (PM3) structures of an L-*pro* peptide and of the corresponding L-**2** analog. Proline and piperazic acid seem sufficiently similar that turn mimics based on **2** should display only marginal differences relative to their naturally occurring originals, increasing the likelihood that sufficiently strong interactions will sussist once the "counterfeit" turn docks with a natural receptor site.

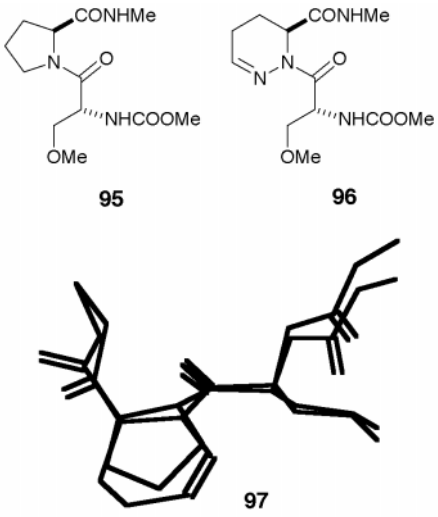


Fig. 3

3 Conclusions and outlook

Our interest in piperazic acids developed as a result of observations made during a synthetic venture in the luzopeptin domain. Of course, it is our expectation that the climax of this endeavor, the total synthesis of at least some of the luzopeptins, will soon be forthcoming. This accomplishment is likely to provide the scientific community with the means necessary to investigate details of the mechanism of action of the natural products and to conduct medicinal chemistry and SAR studies. An equally important payoff of our work, perhaps one of even greater importance, is the discovery of the unusual conformational properties of *piz* units and their potential as turn-inducing instruments. Further research in this area will probably reveal interesting and novel aspects of peptide secondary structure, and indeed, the exploration of these issues is well underway in our group as of this writing. The chronology of the piperazic acid story just narrated provides also compelling evidence that an area of organic chemistry too often suspected of having already seen its heydays, Synthesis, has once again proven to be as central as ever in delivering new and potentially valuable research leads to the scientific community.

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Received 21st May 1998
Accepted 8th June 1998