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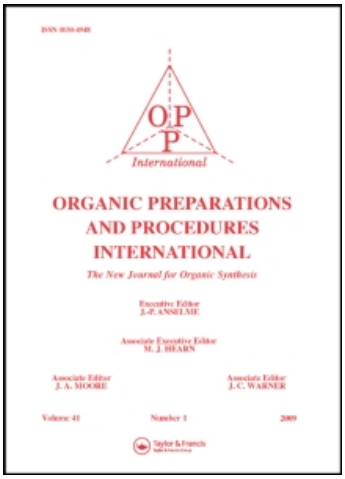

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SYNTHESES AND TRANSFORMATIONS OF PIPERAZINONE RINGS. A REVIEW

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Christopher J. Dinsmore* and Douglas C. Beshore

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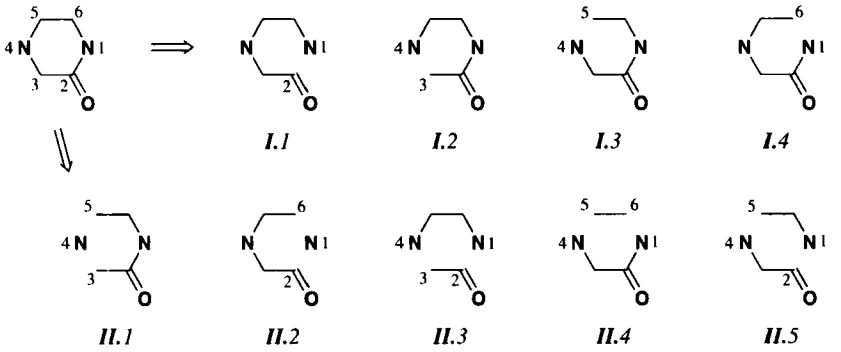
INTRODUCTION

The piperazinone ring has proven to be a valuable scaffold for the construction of biologically active molecules. Due in large part to their similarity to amino acids, piperazinones have been important tools for drug design and for evaluating interactions between natural ligands and macromolecules.[1,2] Piperazinones function as conformationally constrained peptidomimetics wherein the N_i and N_{i-1} positions of an amino acid backbone fragment (*e.g.* **1**, *Fig. 1*) are linked by an ethylene unit (*e.g.* **2**).[3,4] This ring constraint results in restriction of the ϕ_i, ψ_i and ω_i torsion angles,[5,6] confers protection

Fig. 1

from amino acid degrading enzymes, and alters the physicochemical properties by eliminating a hydrogen bond donor group. Furthermore, the additional carbons of the ring offer new positions for the placement of substituents capable of influencing ring conformation or engaging in binding interactions with macromolecules.

Driven largely by the demands of medicinal chemistry investigations, many approaches to the synthesis of piperazinones have been developed. To date, each of the synthetic strategies falls within one of several categories, defined by the C-N bond (or bonds) formed in the ring-forming reaction, as described in *Scheme 1* (review sections indicated). As such, the first chapter of this review focuses on intramolecular cyclizations, while the second describes tandem intermolecular/intramolecular reactions. In the third chapter, we highlight useful post-cyclization transformations of piperazinones. In general, the most recent developments are emphasized.



General strategies for the formation of piperazinone rings, with review section indicated.

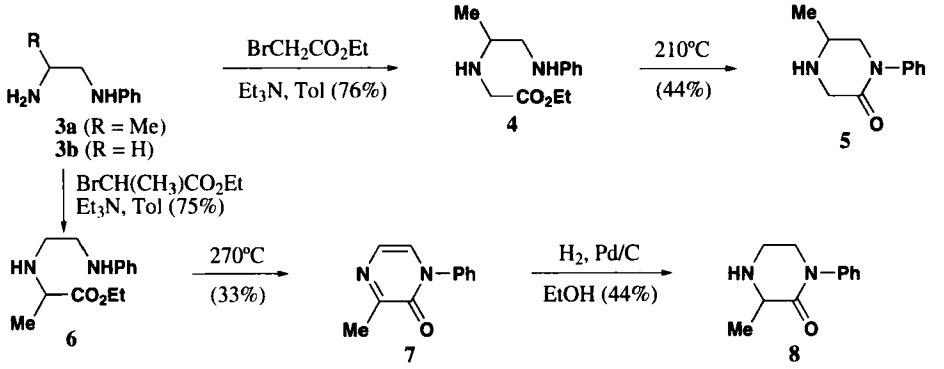
Scheme 1

I. INTRAMOLECULAR C-N BOND FORMING REACTIONS

Each of the four possible modes of intramolecular C-N bond formation to prepare a piperazinone ring (*Scheme 1*) is well represented in the literature. In general, methods involve the construction of cyclization precursors bearing the desired functionality, followed by a distinct ring-forming reaction. The wide range of available cyclization strategies and reaction conditions facilitates the incorporation of diverse functionality into the piperazinone ring structure.

1. Cyclization at N_1-C_2

One of the earliest developed and most widely used methods for the synthesis of piperazinones is the intramolecular addition of an amine to an acid or ester to form the N_1-C_2 bond. A report by Cignarella illustrates a strategy that begins with an unsymmetrical ethylenediamine (*Scheme 2*).[7]



Scheme 2

Alkylation of the 1,2-propanediamine **3a** provided ester **4**, which was heated at 210° to afford piperazinone **5** with loss of ethanol. However, the isomeric ester **6** required higher temperature, and gave the pyrazinone **7** by a dehydrogenation-cyclization-dehydrogenation sequence. Catalytic hydrogenation furnished the piperazinone **8**.

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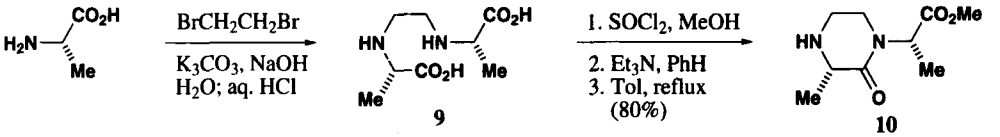
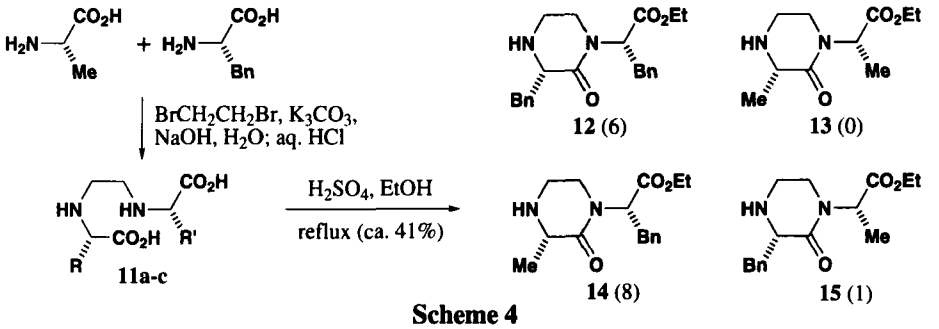
A method by Yamashita provides conformationally constrained dipeptide motifs from easily accessible 3,6-diaza-1,8-octanedioic acid derivatives.[8-12] Esterification of the symmetrical alanine-derived diacid **9** (*Scheme 3*) was followed by refluxing the free base in toluene to give the piperazinone ester **10** in good yield.[8] A similar di-tryptophan analog was recently prepared by Hansen.[13]



Scheme 3

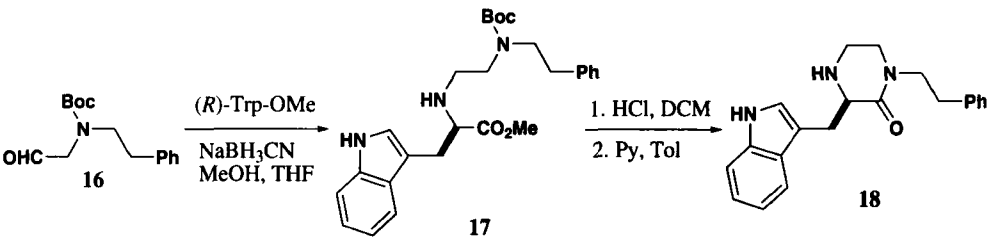
Generating the corresponding dipeptide mimetics from two different amino acids is more complex. An unsymmetrical substrate for the cyclization was produced by alkylating 1,2-dibromoethane with a mixture of alanine and phenylalanine to give the three possible compounds **11a-c** (*Scheme 4*).[12] Treating the mixture with acid gave, after purification, three of the four possible piperazinone products **12-15**, with di-alanine derivative **13** not isolated. Interestingly, the unsymmetrical



Scheme 4

substrate cyclized with 8:1 selectivity favoring intramolecular acylation of the phenylalanyl nitrogen (**14**) rather than the alanyl nitrogen (**15**), a surprising result since the unsymmetrical Phe-Gly variant of **11** produced only desmethyl-**15** and no desmethyl-**14** under the same reaction conditions.[14]

A common acyclic precursor to the piperazinone ring is a carbamate-protected amine, which is deprotected and cyclized under basic conditions. This strategy affords ample flexibility with regard to the synthesis of highly substituted analogs, and many recent methods rely on this reaction. A tachykinin receptor antagonist was prepared in a patent from Hoechst,[15] employing the Boc-glycinal derivative **16** (*Scheme 5*) in a reductive amination reaction to produce **17**. Acid-promoted deprotection and basification gave the desired **18**.



Scheme 5

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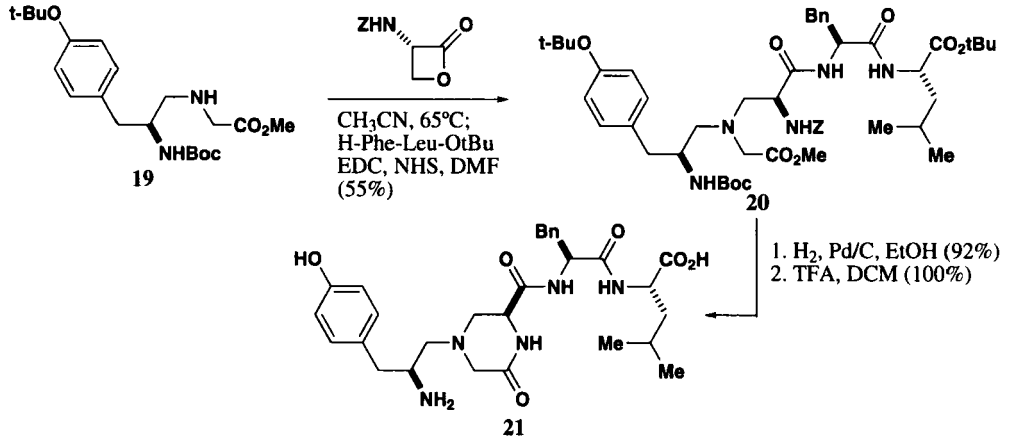
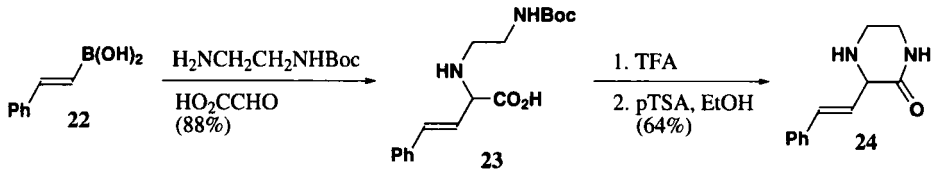
An alternative method for preparing the carbamate cyclization substrate is exemplified by Goodman's synthesis of the constrained Leu-enkephalin analog **21** (*Scheme 6*).[16] The amino ester **19** was used to ring-open the Vederas lactone, and the resulting free acid was directly coupled to a dipeptide to produce **20**. Catalytic hydrogenation promoted the cyclization reaction in high yield, which



Scheme 6

was followed by acid treatment to give tetrapeptide mimetic **21**. The mildness of the coupling and cyclization reaction conditions makes this an attractive method for inserting the piperazinone ring into polypeptide sequences.

A similarly attractive method reported by Hansen[13] utilizes the Petasis three-component coupling strategy to rapidly combine the required functionalities for cyclization (*Scheme 7*). Thus, boronic Mannich reaction of **22**, Boc-ethylene diamine and glyoxylic acid produced **23** in good yield, which was cyclized under acidic conditions to produce **24**.



Scheme 7

Functionality is also efficiently incorporated into the piperazinone architecture by employing a Ugi four-component coupling strategy. Two solution-based variations of this reaction were developed by Hulme for the preparation of piperazinone-based libraries (*Scheme 8*).[17,18] Isocyanocyclohexene was used as a key component to generate the acid-labile amide **25**.[17] Subsequent deprotection and methanolysis, presumably via an *N*-acyliminium ion intermediate, was followed by base-promoted cyclization to give **26**, all in one pot. Compounds bearing an amide rather than an alkyl substituent at C_3 were prepared in a method utilizing ethyl glyoxalate as the core reagent.[18] Thus, in another net three-step, one-pot sequence, the intermediate product **27** was deprotected and cyclized to produce piperazinone **28**.

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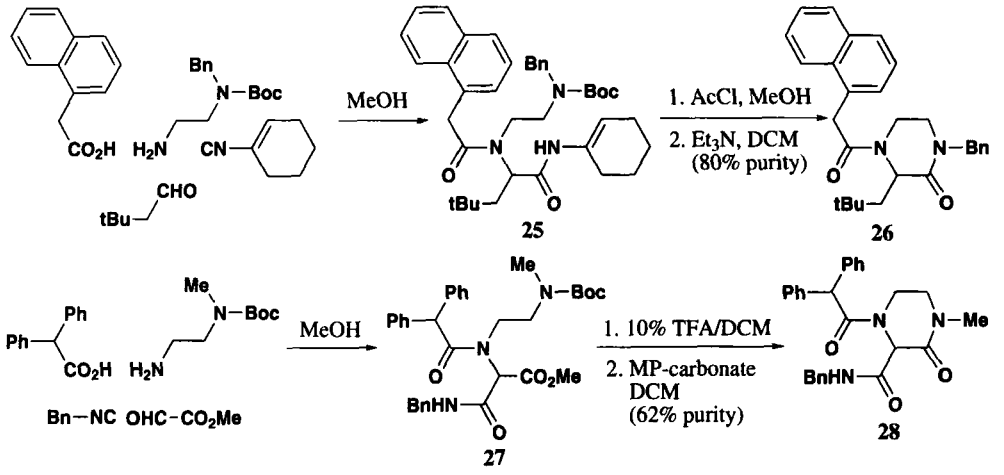
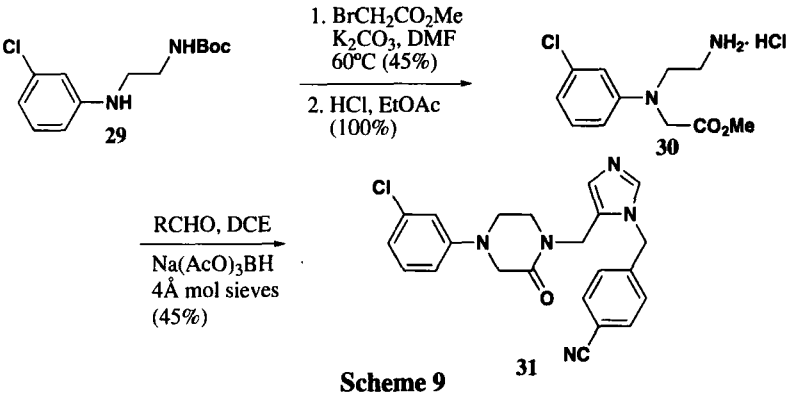


Scheme 8

The amine deprotection and intramolecular acylation strategy may be intercepted by an additional coupling reaction, as reported by Dinsmore *et al.* (*Scheme 9*).[19] Alkylation of the Boc-protected ethylenediamine **29** and treatment with acid gave the stable salt **30**. Under reductive amination conditions, in the presence of an imidazole carboxaldehyde, sequential reductive alkylation and intramolecular cyclization to give the farnesyltransferase inhibitor **31** occurred preferentially over premature cyclization of **30** to provide an N_1-unsubstituted piperazinone product.



Scheme 9

Several traceless solid-phase variants of intramolecular amine *N*-acylation reactions for piperazinone synthesis have been developed, each of which involves release of the resin from an acyl group. Examples of direct cyclocleavage reactions (*Scheme 10*) have solution-phase analogies. For instance, in a patent from Procter & Gamble,[20] Boc-glycine-Merrifield resin ester (**32**) was deprotected and reductively alkylated with a Boc-protected amino aldehyde to produce **33**, which was deprotected and cyclized under acidic conditions to release piperazinone **34** from the hydroxymethyl resin. Goodman's serine lactone alkylation method was used to functionalize Wang resin-bound Boc-glycine derivative **35**.[21] Amide coupling to give **36** was followed by cyclization to provide piperazinone **37**. Finally, the Ugi/de-Boc/cyclize sequence was carried out by Hulme on hydroxymethyl resin-bound amine **38** to produce, after acid treatment of **39**, the densely functionalized piperazinone **40**.[22]

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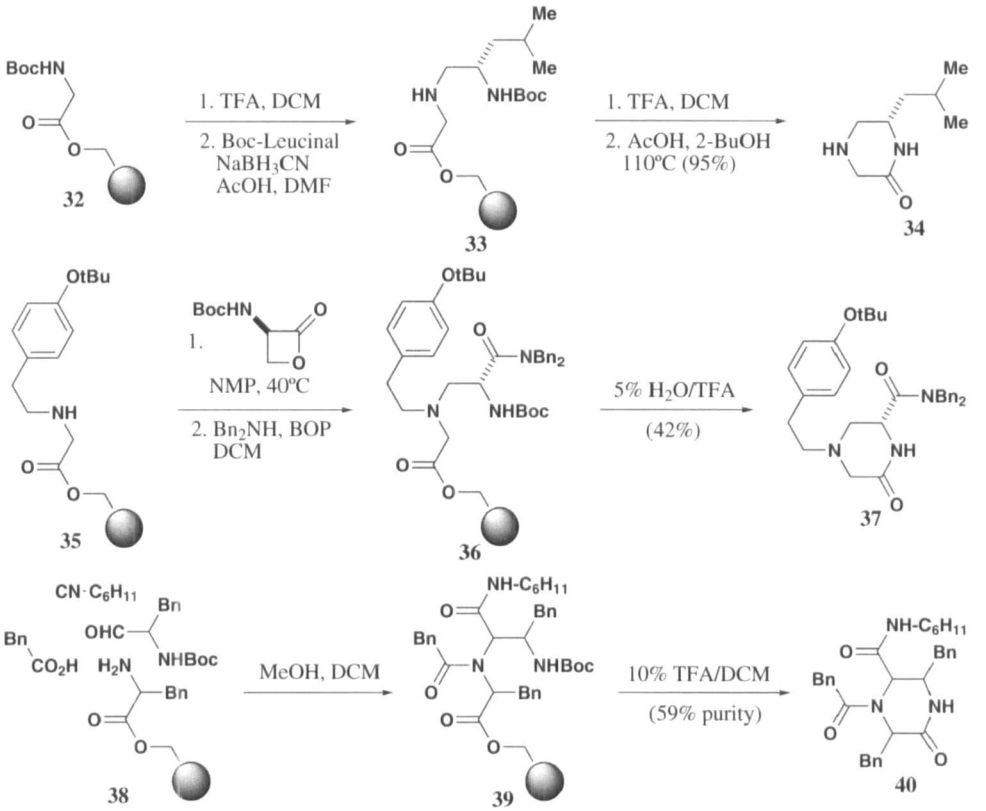
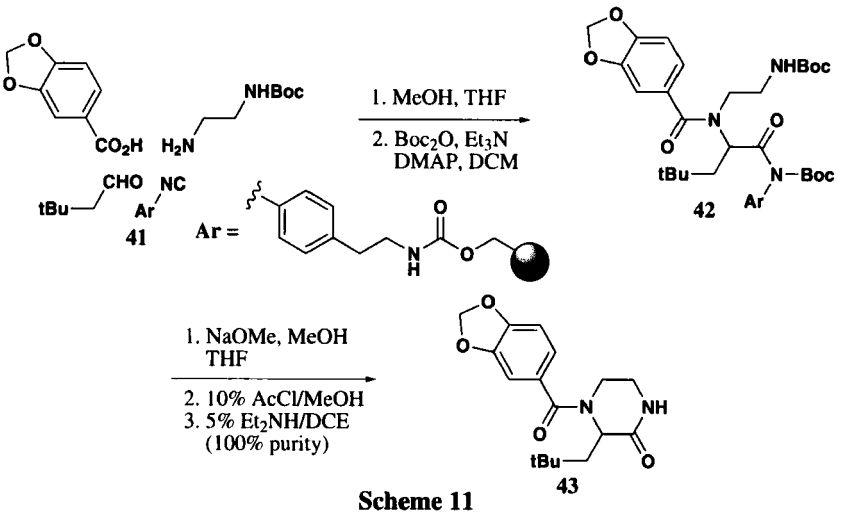


Scheme 10

Solid phase protocols that utilize "safety-catch" linkers have been developed for piperazinone synthesis to provide high-purity products. In a method developed by Hulme,[23] the Wang resin-bound isonitrile **41** (*Scheme 11*) was used in a Ugi four-component coupling reaction to give a



Scheme 11

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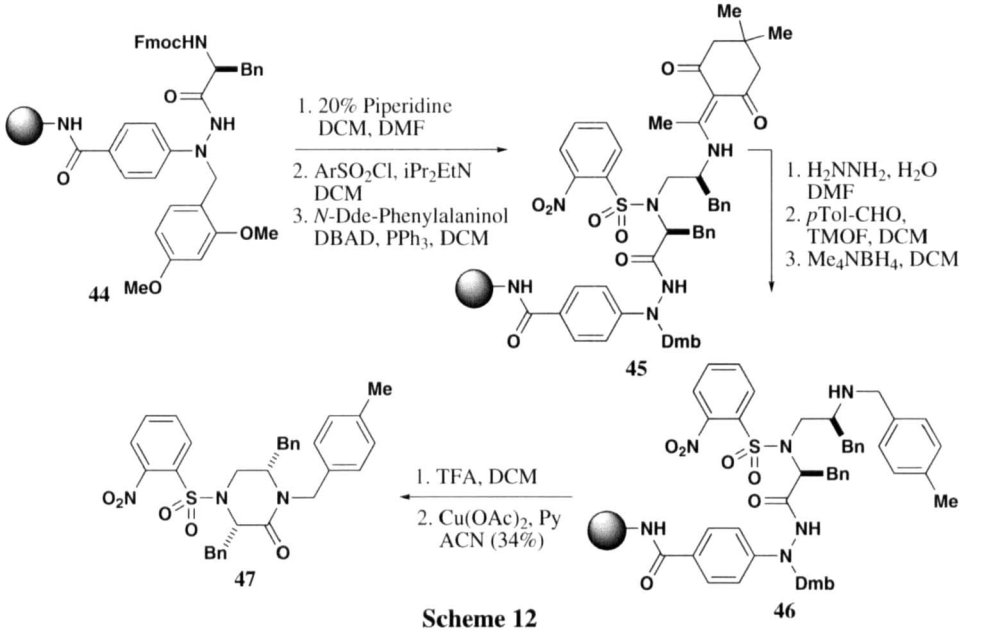
secondary amide, which was activated by acylation[24] to produce the resin-bound imide **42**. Following methanolysis to cleave the resin, deprotection and cyclization afforded piperazinone **43** in high purity.

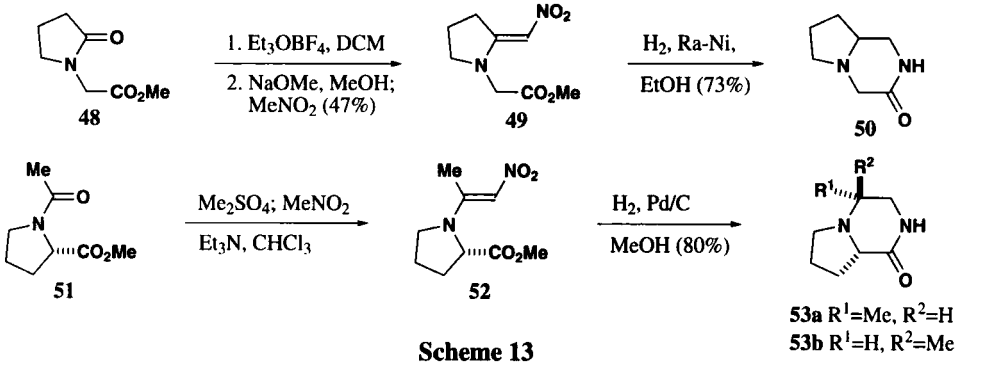
A latent form of an arylhydrazine "safety-catch" linker was developed by Berst *et al.* to enable solid-phase alkylation chemistry in the synthesis of piperazinones (*Scheme 12*).[25] ArgoGel™ amine resin, equipped with an aryl hydrazine linker protected by the acid-labile 2,4-dimethoxybenzyl



Scheme 12

group, was derivatized with an Fmoc amino acid to give starting compound **44**. This was converted to an *ortho*-nitrobenzene sulfonamide, then subjected to Mitsunobu alkylation to give **45**. Removal of the nitrogen protecting group and reductive alkylation provided **46**. Deprotection of the acylhydrazine was followed by oxidative cyclocleavage of the resin from piperazinone **47** via intramolecular *N*-acylation of an azocarboxylate intermediate.

Enforcing conformational rigidification of the piperazinone ring structure is achieved by joining substituents in a ring. In a method developed by Jain *et al.*, fused bicyclic piperazinones were prepared by intramolecular cyclizations of pyrrolidinone and *N*-acylpyrrolidine derivatives (*Scheme 13*).[26] Conversion of **48** to the corresponding lactam acetal was followed by condensation with



Scheme 13

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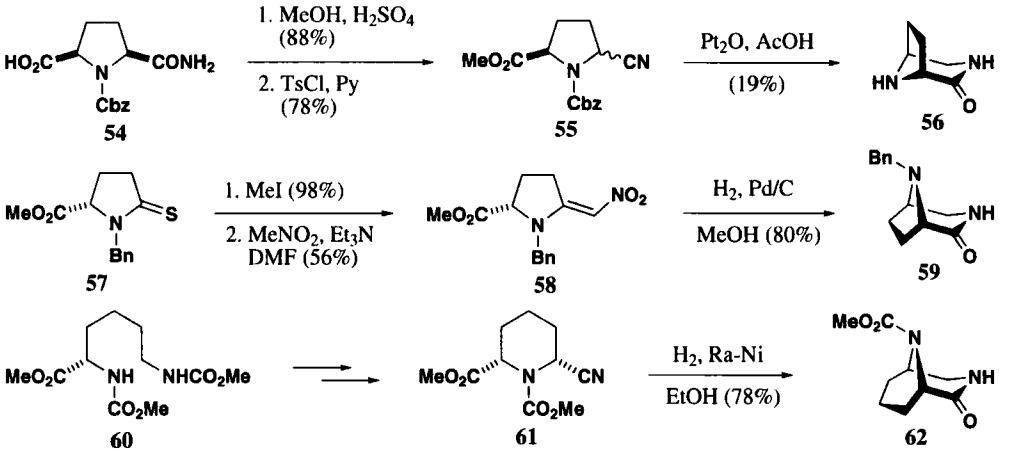
nitromethane to give the key nitro-olefin **49**. Reduction with spontaneous cyclization afforded the 1,4-diazabicyclo[4.3.0]nonan-3-one **50**. A similar sequence from acetamide **51** gave nitroolefin **52**, which was reduced to a 3:7 mixture of optically pure 1,4-diazabicyclo[4.3.0]nonan-5-ones **53a** and **53b**.

Non-fused bicyclic piperazinones have been prepared by similar methods involving reduction of amine precursors (*Scheme 14*). In a report by Cignarella,[7] the pyrrolidine **54** was esterified and

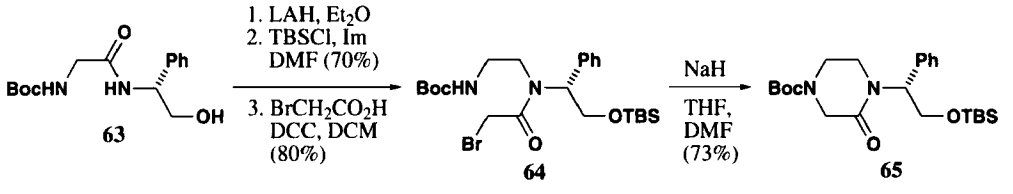


Scheme 14

dehydrated to give nitrile **55**, then reduced to give the 3,8-diazabicyclo[3.2.1]octan-2-one **56**. Optically pure analog **59** was produced by Jain *et al.* from the thiopyroglutamate **57** by conversion to the nitro compound **58**, and reduction as before.[26] In a report by Irie *et al.*,[27] the homologous diazabicyclo[3.3.1]nonan-2-one **62** was prepared by reduction of the nitrile **61**, available in three steps from the lysine derivative **60**.

2. Cyclization at C_3-N_4

An alternative mode of cyclization to form piperazinones, involving intramolecular *N*-alkylation to install the C_3-N_4 bond, has been of significant value for the preparation of biologically active compounds. Methods are particularly well suited to the synthesis of piperazinones with C_5 and/or C_6-substituents. As originally defined by Schanen *et al.* (*Scheme 15*),[28-30] an appropriate amino acid



Scheme 15

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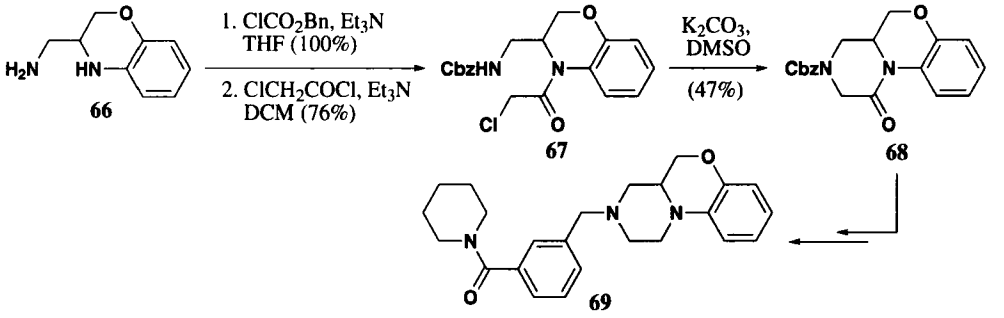
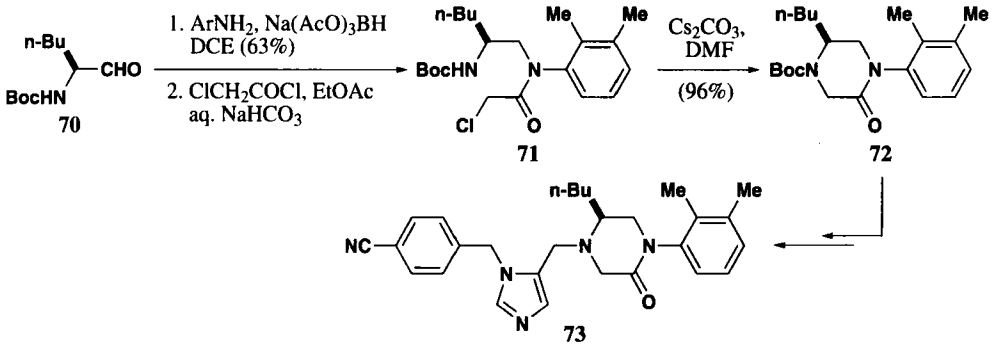
derivative (*e.g.* **63**) may be converted to an unsymmetrical 1,2-ethylenediamine, then acylated to give an α-haloacetamide cyclization precursor (*e.g.* **64**). Following deprotonation of the carbamate **64**, an intramolecular S_N2 displacement reaction provided the piperazinone **65** in good yield.

The versatility of this approach has been demonstrated in a number of recent examples. Transformation of diamine **66** (*Scheme 16*) to chloroacetamide **67** was followed by treatment with potassium carbonate to give the *N*-arylpiperazinone intermediate **68**.[31] This was used to prepare a



Scheme 16

constrained version (**69**) of the 5-HT_{1A} receptor binder mazapertine. An *N*-arylpiperazinone inhibitor of farnesyltransferase (**73**, *Scheme 17*) was prepared from aldehyde **70** using similar technology, employing a high-yielding cyclization of intermediate **71** with cesium carbonate to give intermediate **72**.[32]



Scheme 17

A related cyclization of α-haloacetamides involves carbamate deprotection prior to cyclization, rather than the reverse (*vide supra*). For example, in a report by Lewis *et al.* (*Scheme 18*),[33] aldehyde **74** was elaborated to the key intermediate **75**. This was treated with acid to reveal the corresponding amine, which subsequently cyclized to provide the NK_1 antagonist **76**.

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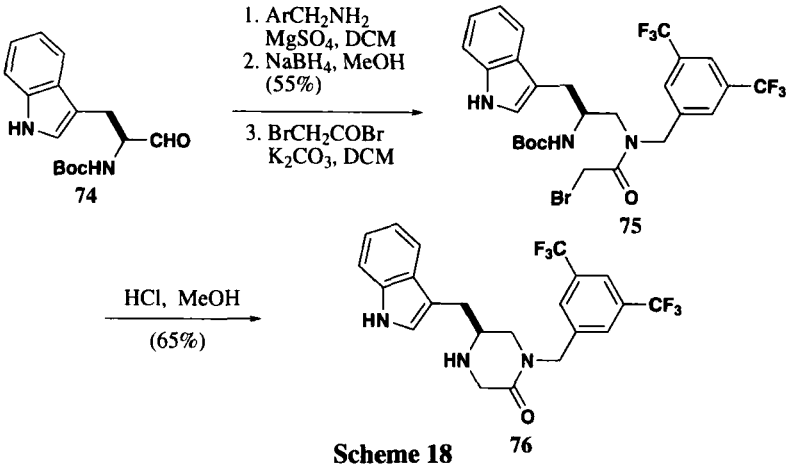
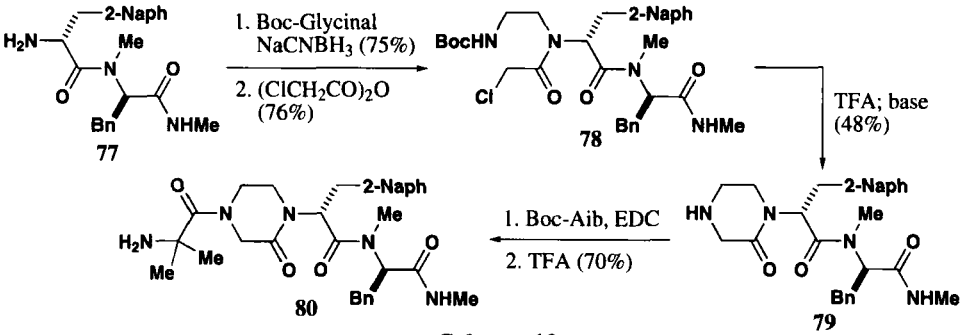


Scheme 18

A conformationally constrained analog (**80**) of growth hormone secretagogue NN703 was prepared in a similar fashion (*Scheme 19*),[13] by the conversion of dipeptide amine **77** to the chloroacetamide **78**, followed by carbamate deprotection and cyclization to provide piperazinone intermediate **79**.



Scheme 19

3. Cyclization at N_4-C_5

Intramolecular cyclization strategies to form the N_4-C_5 bond are numerous, and are often applied toward the syntheses of piperazinones bearing a substituent at C_3, the position resembling C_α of an amino acid. An early example, developed by DiMaio and Belleau,[5] typifies the incorporation of an amino acid into the cyclic framework to define the substituent and stereochemistry at C_3 (*Scheme 20*). From a glycinal dimethyl acetal derivative **81**, amide coupling gave dipeptide derivative **82**. Hydrolysis of the acetal led to cyclization and dehydration to give dihydropyrazinone **83**, which was subjected to catalytic olefin hydrogenation and carbamate hydrogenolysis to give the constrained Tyr-Gly peptidomimetic **84** in good overall yield.

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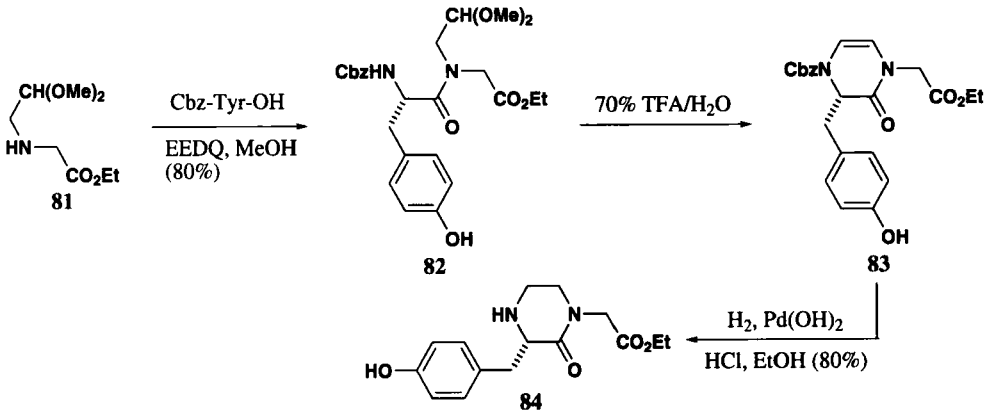
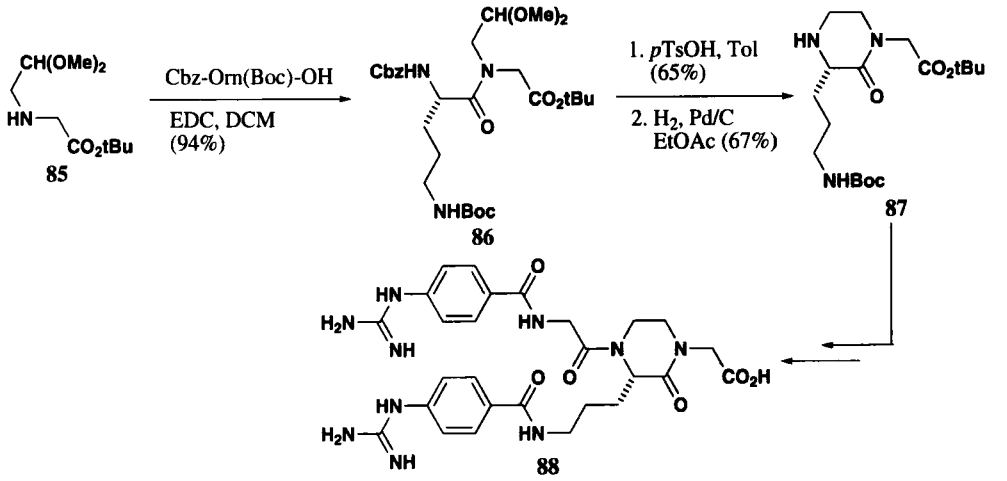


Scheme 20

Recent applications of this technology[34] include the synthesis of a dibasic GPIIb/IIIa antagonist by Kitamura *et al.* (*Scheme 21*).[35] The versatile acetal **85** was converted to **86**, then hydrolyzed and reduced as before to afford the protected diamine **87**. This was converted to the antithrombotic agent **88** by a sequence of steps involving amide coupling of **87** and Cbz-protected glycine, followed by global deprotection, and *bis*-*N*-acylation.



Scheme 21

A variation of this reaction by Giannis[6] allows the independent control of stereochemistry at both C_3 (from an amino acid) and at C_6 (from glucosamine) of the piperazinone ring (*Scheme 22*). The protected valine-glucosamine adduct **89** was reduced with concomitant ring closure by a reductive amination process, and then reprotected to give **90**. Periodate cleavage and aldehyde reduction afforded the *trans*-piperazinone **91**. A clever reversal of the sequence of reactions generated the alternative *cis*-piperazinone isomer **93** through the intermediacy of aldehyde **92**.

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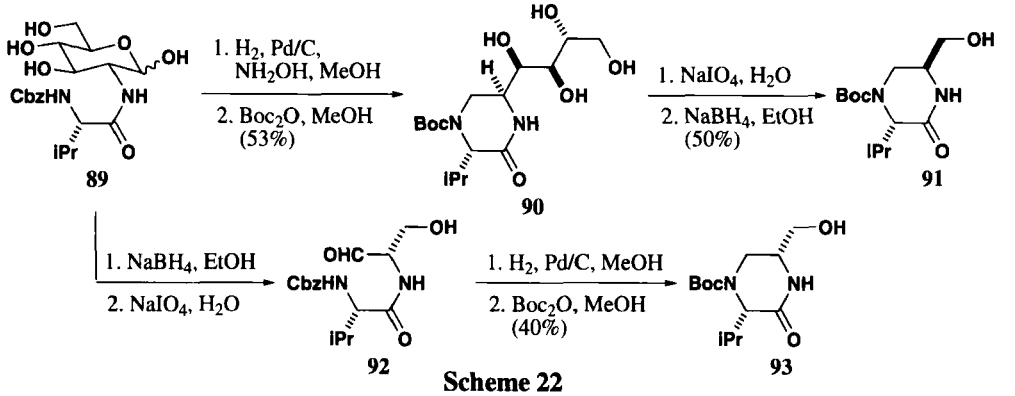
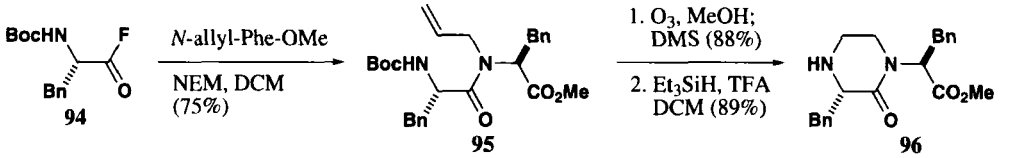


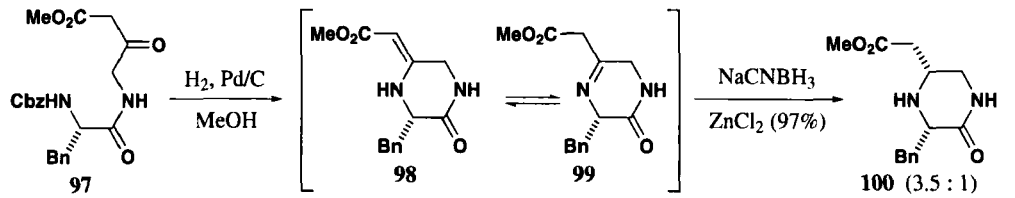
Scheme 22

A similar sequence of reactions by Moeller *et al.* gave a conformationally constrained Phe-Phe mimetic (*Scheme 23*).[36,37] Reaction of acid fluoride **94** with an *N*-allyl-amino ester provided olefin **95**. Ozonolysis and subsequent hydride addition to the resulting iminium ion gave **96** in good yield.



Scheme 23

A diastereoselective ketone reductive amination reaction was used by Muñiz *et al.* as an effective stereochemical relay from the C_3 amino acid substituent to the C_5 position of a piperazinone.[38,39] Ketone **97** (*Scheme 24*) was deprotected and cyclized in a catalytic hydrogenation



Scheme 24

reaction to give the intermediate enamine **98**. Filtration of the mixture and addition of sodium cyanoborohydride and Lewis acid promoted a reduction of imine **99** (deduced from isotopic labeling studies) to provide piperazinone **100** with predominantly *cis*-stereochemistry.

Construction of the N_4-C_5 bond by a Mitsunobu alkylation reaction was demonstrated in a report from Horwell *et al.* (*Scheme 25*).[34] The amine **101** was subjected to peptide coupling, followed by deprotection of hydroxyl and amino groups to provide the cyclization precursor **102**. Intramolecular Mitsunobu alkylation and acylation furnished the NK_1 binding piperazinone **103**.

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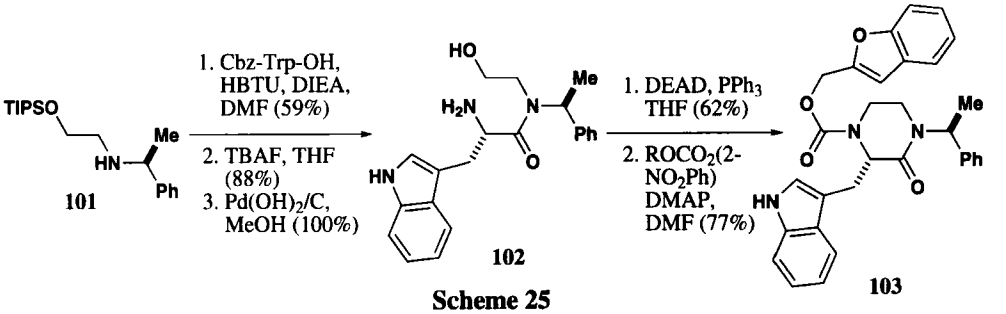
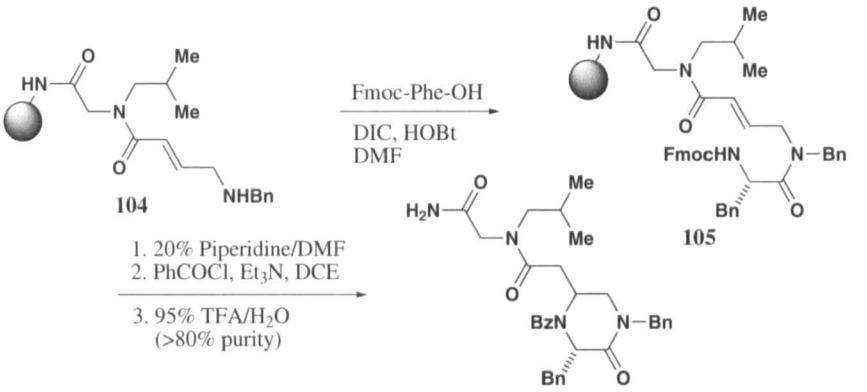


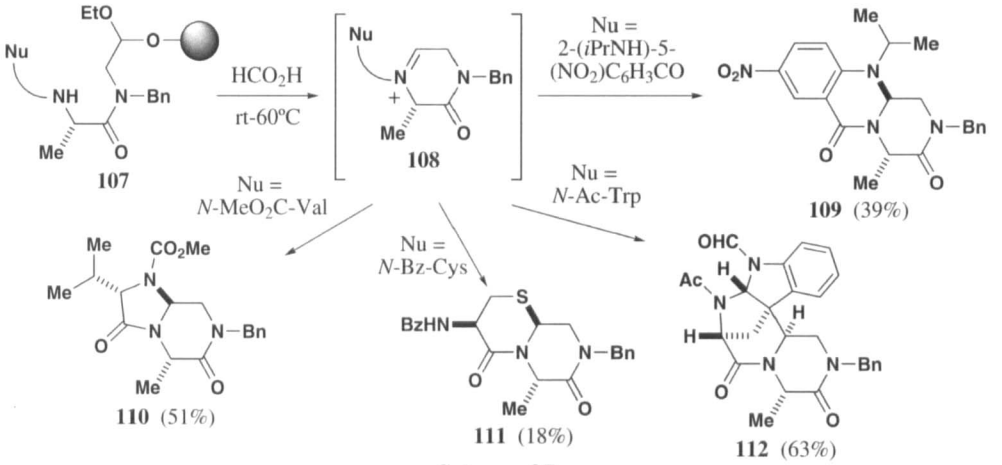
Scheme 25

Methods of forming the piperazinone N_4-C_5 bond by interesting transformations on solid phase have been recently developed. A report by Goff describes the use of the Rink amide-linked peptoid fragment **104** (*Scheme 26*).[40] *N*-acylation with an Fmoc amino acid to give **105** was followed by amine deprotection and intramolecular Michael addition under basic conditions. *N*-Acylation and cleavage from the resin afforded **106** in good purity (stereochemistry not indicated).



Scheme 26

A protecting group-type linker was used in a versatile synthesis of bicyclic piperazinones.[41] The TentaGel OH resin-bound acetal **107** (*Scheme 27*), bearing an amino acid functionalized with



Scheme 27

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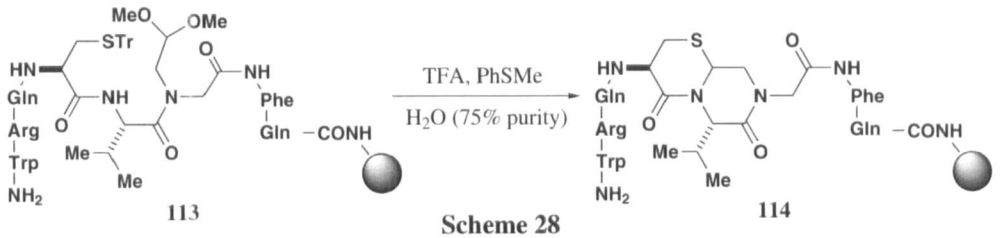
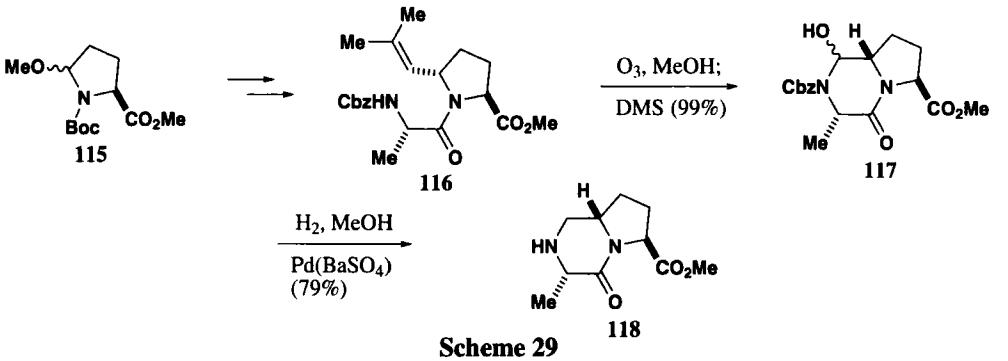
various nucleophilic groups, was activated with formic acid. Cyclization with release of the resin gave *N*-acyliminium ion intermediate **108**, which was quenched in a manner dependent on the pendant nucleophile. The amino group of a 2-aminobenzoyl substituent cyclized to afford **109**, and the nitrogen of a carbamate-protected amino acid fragment cyclized onto the iminium ion to give **110**. The side-chain substituent of the protected amino acid acted as the nucleophile in the case of cysteine (**111**; attack of the iminium ion by the sulfhydryl group) and tryptophan (**112**; attack of the iminium ion by the indole-C_3, cation quench at indole-C_2 by the protected amine, and indole-N_1-formylation).

In a recent report by Kohn,[42] bicyclic piperazinone-containing polypeptide compounds related to **111** were prepared in the manner outlined in *Scheme 28*. Simultaneous removal of the thioether and acetal protecting groups in **113**, along with cyclocondensation and cleavage from the RAM amide resin, gave octapeptide analog **114**.



Scheme 28

Bicyclic piperazinones have been prepared in solution by Moeller from proline derivatives,[36,37,43,44] employing the reductive strategy of DiMaio. The anodic oxidation product of proline methyl ester **115** (*Scheme 29*) was elaborated in several steps to give olefin **116**. Ozonolysis to give **117** was followed by catalytic hydrogenolysis to provide the 1,4-diazabicyclo[4.3.0]nonane-2-one **118**.



Scheme 29

A related transformation was reported by Corey and Martinez for the production of a key intermediate in the synthesis of an Ecteinascidin analogue (*Scheme 30*).[45] In a single pot transformation, the lactol **119** was treated with acid to induce stereoselective cyclization, affording the pentacyclic piperazinone **120** in high yield.

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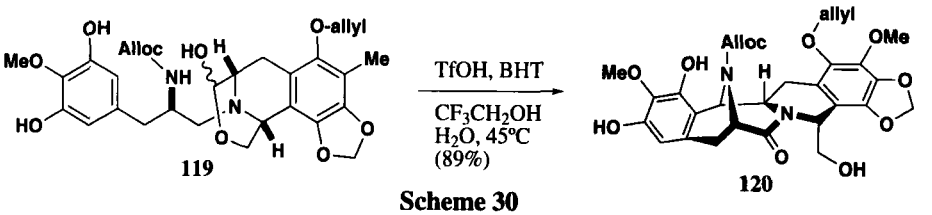
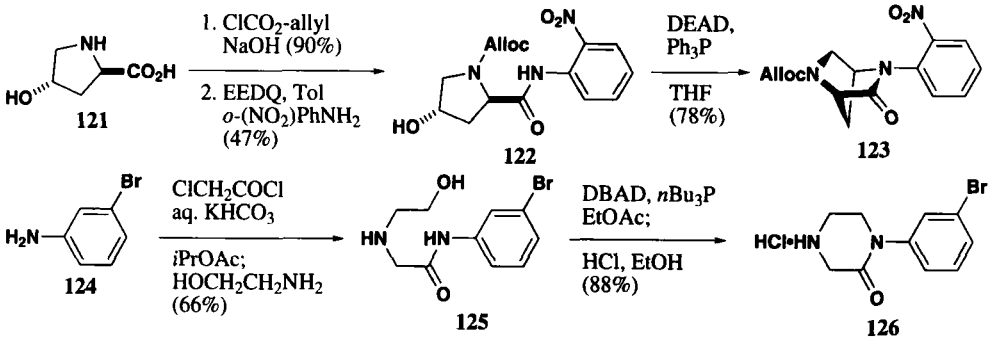


119 120

Scheme 30

4. Cyclization at C_6-N_1

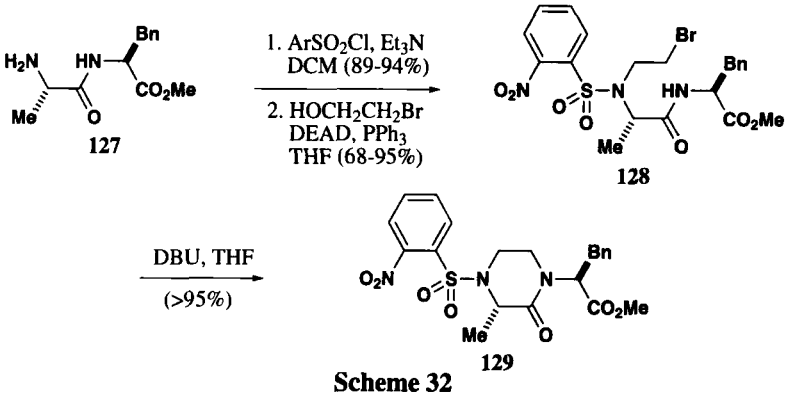
A less common mode of cyclization is that which forms the C_6-N_1 bond of a piperazinone ring. A very useful method is the cyclodehydration reaction of γ-hydroxy amides (*Scheme 31*). This was demonstrated by Hadfield *et al.*[46] to proceed under Mitsunobu reaction conditions, provided the amide is sufficiently acidic. For example, 4-hydroxyproline **121** was converted to anilide **122**, which



121 122 123 124 125 126

Scheme 31

was cyclized to provide the diazabicyclo[2.2.1]heptan-3-one **123** in good yield. A modified method by Weissman *et al.*[47] requires no protecting groups. In a single pot, the aniline **124** was converted to the corresponding 2-chloroacetamide, and the chloride displaced with ethanolamine to give **125**. Intramolecular Mitsunobu cyclodehydration proceeded smoothly to provide piperazinone **126**, with no evidence of an azetidine from attack of the secondary amino group. The method was useful for the preparation of *N*-arylpiperazinone inhibitors of farnesyltransferase.[48]



127 128 129

Scheme 32

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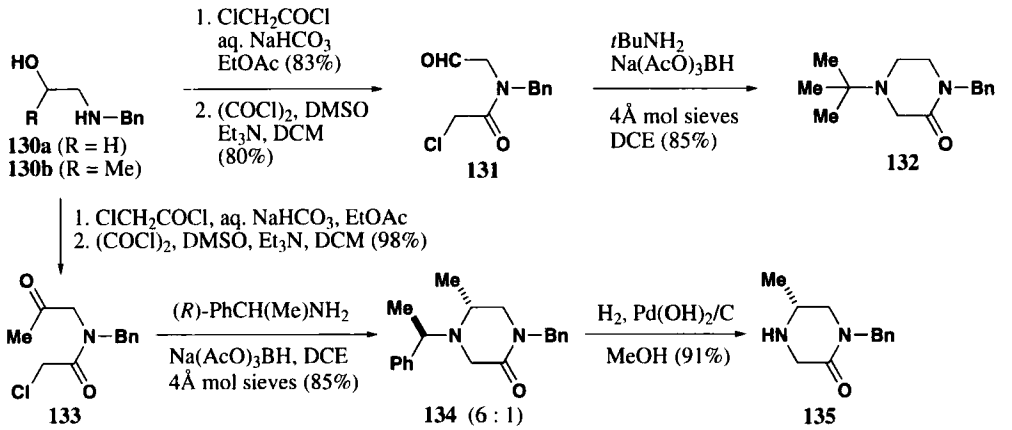
Intramolecular *N*-alkylation of a C_6-alkyl halide was demonstrated by Just *et al.* in a method utilizing dipeptide sulfonamides (*Scheme 32*).[49] Following sulfonylation of dipeptide ester **127**, Mitsunobu alkylation with 2-bromoethanol gave **128**. Treatment with base provided the Ala-Phe peptidomemetic piperazinone **129** in high yield.

II. TANDEM INTERMOLECULAR-INTRAMOLECULAR REACTIONS

A highly efficient construction of piperazinone rings involves the simultaneous formation of two bonds. In principle, such tandem reactions allow the rapid combination of two structural fragments in a single step, a feature that has implications for synthetic convergence and structural diversity. To date, five of the six possible synthetic strategies for joining two fragments in tandem C-N bond forming reactions have been demonstrated (*Scheme 1*).

1. Formation of C_3-N_4-C_5

A method of introducing an N_4 fragment in the form of an amine for simultaneous formation of C_3-N_4 and C_5-N_4 was developed by Dinsmore *et al.* (*Scheme 30*).[50] A key aldehyde intermediate **131** was prepared by 2-chloroacetylation and Swern oxidation of ethanolamine **130a**. Reductive amination of the aldehyde and an amine with *in situ* intramolecular S_N2 alkylation provided piperazinone **132** in good yield. In a similar fashion, a diastereoselective reductive amination of ketone **133** and α-methylbenzylamine gave **134**, which was deprotected to give the 5-methylpiperazinone **135** in optically pure form.



Scheme 33

A similar strategy for solid phase synthesis was reported by Goff (*Scheme 34*).[40] The Rink-amide peptoid **136** was 2-bromoacetylated to give **137**. Treatment with an amine resulted in tandem S_N2 displacement and conjugate addition reactions, and acidification removed the piperazinone product **138** from the resin.

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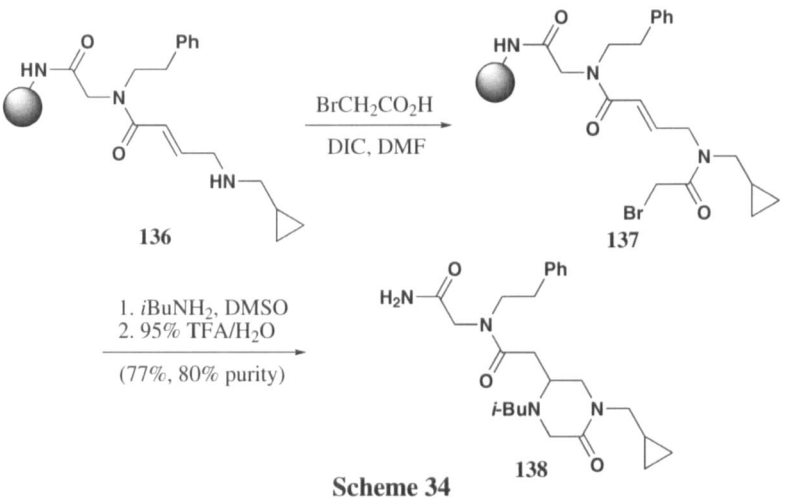

Scheme 34

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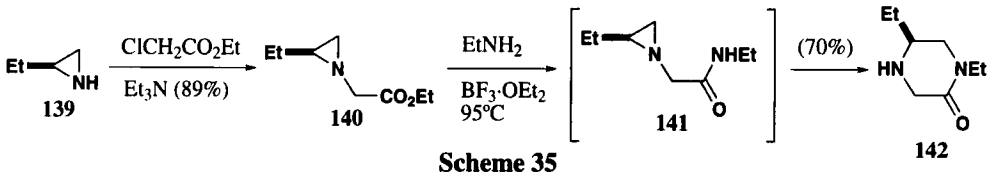
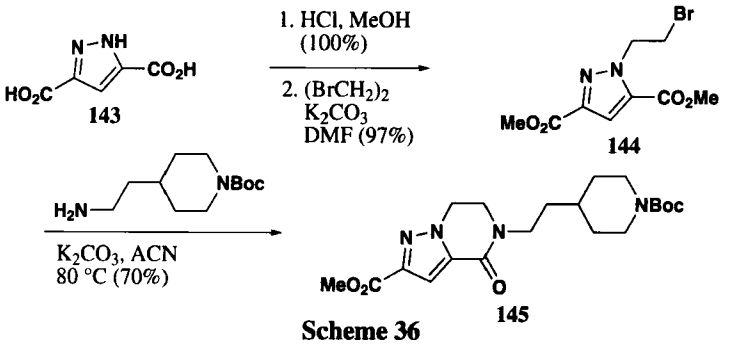
2. *Formation of C_2-N_1-C_6*

An analogous route to piperazinone formation is the installation of both the N_1-C_2 and C_6-N_1 bonds in one reaction, by combining an amine and a bivalent electrophile. The earliest example was reported by Yahiro,[51] in which ethylamine was acylated by the ester **140** (*Scheme 35*). The resultant amide **141**, in the presence of BF_3•OEt_2, isomerized via aziridine ring-opening to provide piperazinone **142** in good yield.



Scheme 35

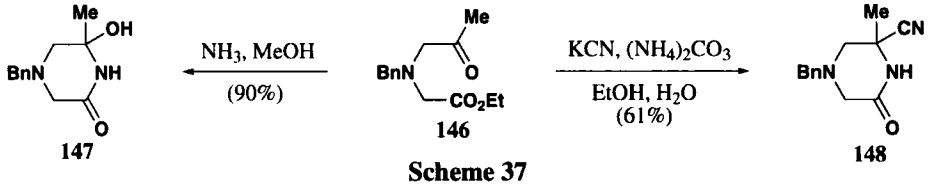
Another tandem amination-cyclization sequence was recently reported by Askew *et al.*[52] in their efforts to synthesize fibrinogen receptor antagonists. Commercially available di-acid **143** (*Scheme 36*) was esterified and *N*-alkylated, providing the piperazinone precursor **144**. In the presence



Scheme 36

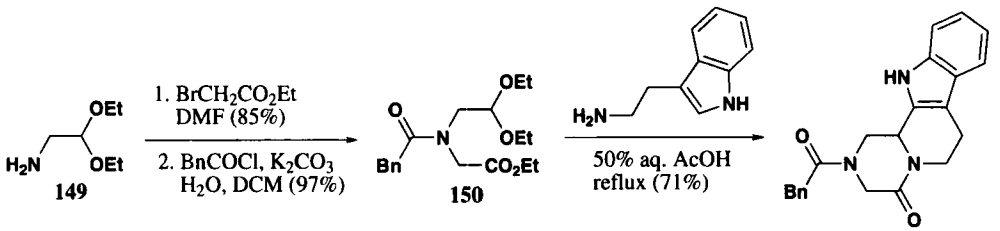
of a primary amine and K_2CO_3 in refluxing acetonitrile, bicyclic **145** was obtained in good yield. An analogous coupling reaction of methyl *N*-(2-bromoethyl)pyrrole-2-carboxylate and methylamine had been carried out by Brimble *et al.*[53]

A method reported by Georgiadis utilizes ketoester **146** in reactions with ammonia (*Scheme 37*).[54] Exposure of **146** to anhydrous ammonia in methanol gave the 6-hydroxypiperazinone **147** in good yield, while a Strecker-type reaction of the ketone gave the nitrile derivative **148.**



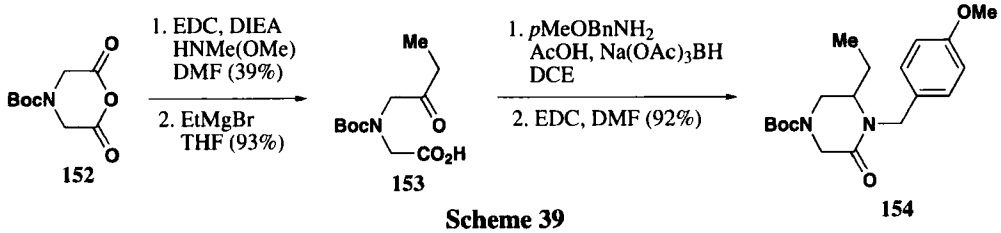
Scheme 37

Similar chemistry was reported by Valls *et al.*,[55] in which construction of the C_2-N_1-C_6 bonds of the piperazinone ring was accompanied by an additional C-C bond forming process. Aminoacetaldehyde diethyl acetal **149** (*Scheme 38*) was *N*-alkylated and then acylated under Schotten-Baumann conditions, providing the ester acetal **150**. With the addition of tryptophan in refluxing 50% aqueous acetic acid, Pictet-Spengler condensation followed by ring closure afforded the praziquantel analogue **151** in 71% yield.



Scheme 38

Finally, a route to a combinatorial library of 6-substituted piperazinones was published recently by Boger and coworkers.[56] *N*-Boc-iminodiacetic anhydride **152** (*Scheme 39*) was ring-opened to the Weinreb amide in the presence of EDC and DIEA. The ketone was then installed with ethyl Grignard, providing ketoacid **153**. Reductive amination with *p*-methoxybenzylamine and concentration of the crude reaction mixture was followed by treatment with EDC in DMF to close the piperazinone ring of **154** in excellent yield, with no further purification. Based upon this chemistry, various



Scheme 39

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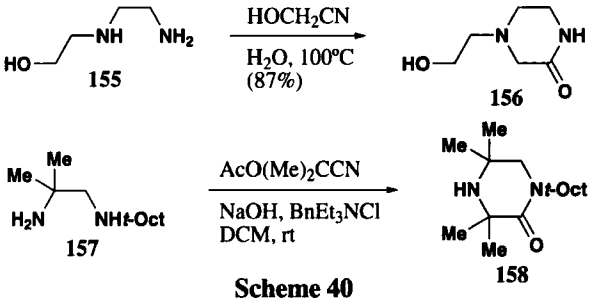
alkyl Grignard reagents (aryl ketones failed to react under reductive amination conditions) and alkyl amines were used to construct a diverse library targeted against LEF-1/β-Catenin-mediated transcription.

3. Formation of N_1-C_2 / C_3-N_4

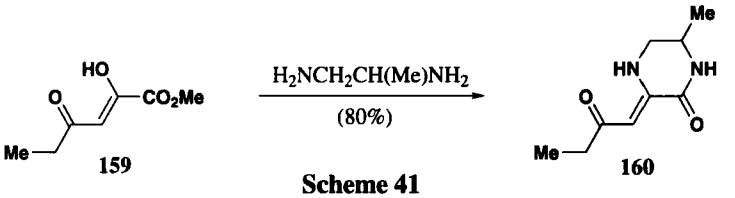
There are several reports of the reaction of a 1,2-diamine with a bivalent C_2-C_3 synthon to produce the N_1-C_2 and C_3-N_4 bonds of a piperazinone ring in one reaction. Reports from the patent literature describe processes involving regioselective Strecker reaction of one of the amino groups, and intramolecular nitrile amination and hydrolysis of the other. For example (*Scheme 40*), the



Scheme 40

unsymmetrical ethylenediamine **155** was treated with hot aqueous glycolonitrile to provide a good yield of **156**.[57] The sterically hindered piperazinone **158** was prepared from amine **157** and acetone cyanohydrin acetate under mild phase-transfer conditions, without detectable formation of the isomeric piperazinone.[58]

The condensation of a 1,2-diamine with an α,γ-diketoester provides, after loss of methanol and water, a piperazinone ring with unsaturation at C_3.[59-61] For example (*Scheme 41*),[61] ester **159** was treated with unsymmetrical 1,2-diaminopropane to produce **160** as a single regioisomeric product.



Scheme 41

Two reports of a conjugate addition-cyclization strategy employ a symmetrical ethylenediamine and a Michael acceptor bearing an ester (*Scheme 42*). In a procedure by Couladouros *et al.*,[62] the γ-keto-δ-crotonolactone **161** was treated with ethylenediamine to give, after intramolecular amination of lactone adduct **162**, the C_3-substituted piperazinone **163** as a mixture of diastereomers. A synthesis of C_3-methylene-substituted piperazinones (*e.g.* **166**) by Yamada *et al.*[63] involved conjugate addition of diamine **164** to *trans*-dimethyl dicyanobutenedioate to produce **165**, which underwent loss of HCN and methanol to give **166**. This finds precedent in a related reaction of a diamine with dimethylacetylenedicarboxylate (*vide infra*).[64]

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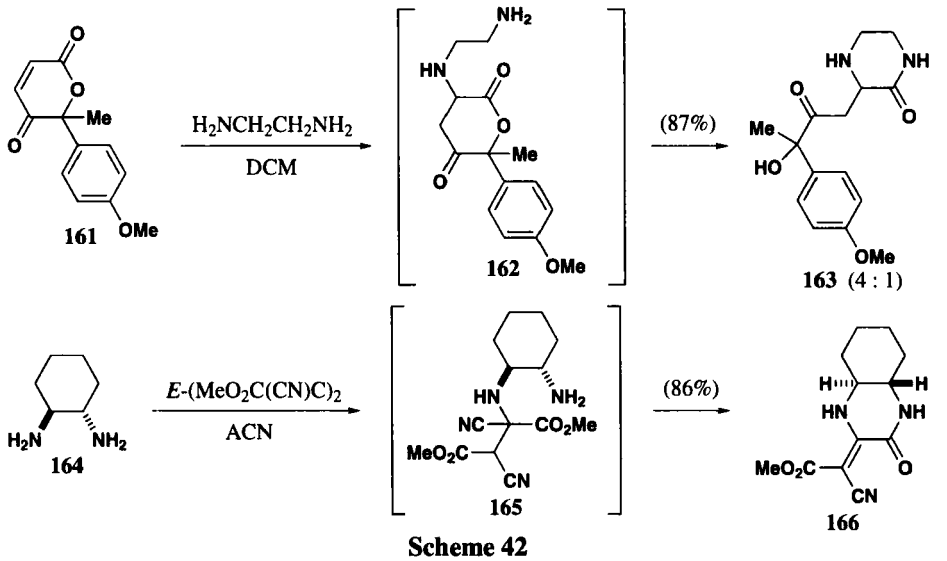
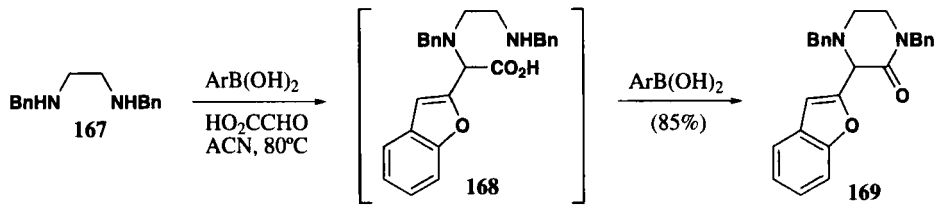


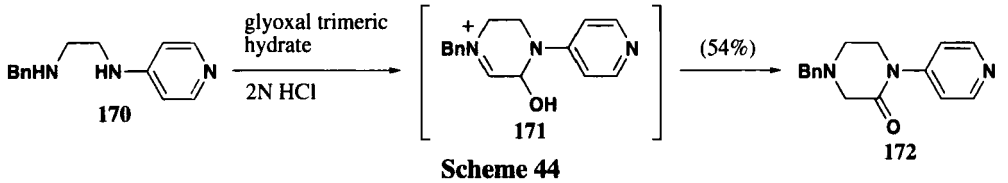
Scheme 42

In a highly efficient one-step synthesis of C_3-substituted piperazinones, Petasis and coworkers combined the boronic acid Mannich-type reaction with a cyclization reaction (*Scheme 43*).[65] The diamine **167** was treated with glyoxylic acid and an arylboronic acid to give intermediate **168**, which underwent cyclization to give **169** in good yield. Notable was the dual role of the boronic acid as both substrate for the reaction and catalyst for the cyclization.



Scheme 43

The condensation of an unsymmetrical 1,2-diamine with glyoxal under acidic conditions to produce piperazinones was pioneered by Chassonnery *et al.*[66] The application of this process to the synthesis of 1-heteroaryl-substituted piperazinones was found by Ridgill to be superior to alternative methods that would require the *N*-acylation of 2- or 4-aminoheteroaromatic derivatives (*e.g.* **170**, *Scheme 44*).[67] Treatment of **170** with glyoxal trimeric hydrate gave **172** as the exclusive isomer, presumably after tautomerization of the preferentially formed iminium ion **171**.



Scheme 44

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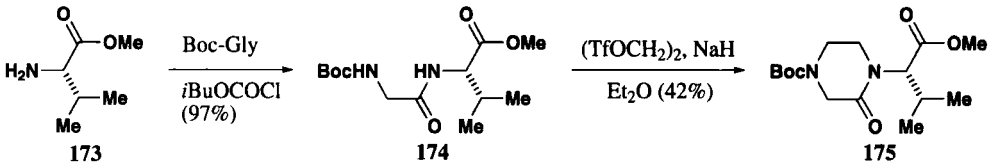
4. Formation of N_4-C_5 / C_6-N_1

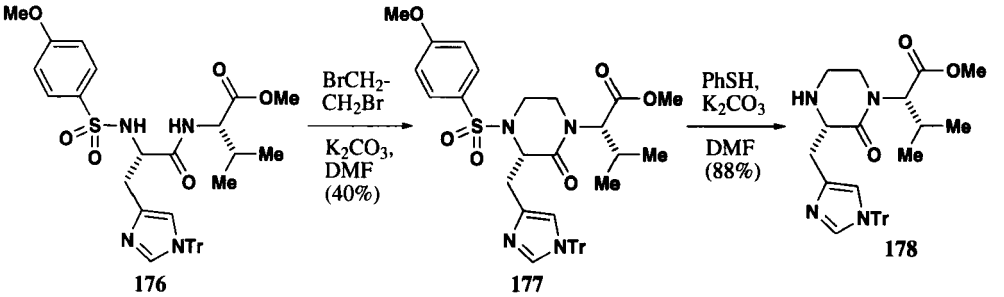
Piperazinones may also be constructed from α-aminoamides by bis-*N,N'*-alkylation, forming the N_4-C_5 and N_1-C_6 bonds in tandem. Common to the methods presented in this section is the use of carbamates or sulfonamides as N_4 protecting groups, which enables the use of mildly basic conditions to incorporate an ethylene group into the piperazinone core. The first report of the bis-*N,N'*-alkylation strategy by Pohlmann *et al.*[30] described the reaction of amidocarbamate **174** (*Scheme 45*) with ethylene glycol bis-triflate in the presence of NaH to provide piperazinone **175** in moderate yield.



173 → **174** → **175**

Scheme 45

Similarly, Bhatt and Just[68] utilized the reaction of 1,2-dibromoethane with amidosulfonamide **176** (*Scheme 46*). Ring closure was effected to afford piperazinone **177** in moderate yield. Deprotection of the N_4 amine was cleanly accomplished with thiophenol and potassium carbonate, providing the C_3-substituted piperazinone **178**. The same group reported a complimentary solid phase method[49] employing the same reaction conditions.



176 → **177** → **178**

Scheme 46

5. Formation of N_1-C_2 / N_4-C_5

A strategy reported by Beshore and Dinsmore, installs the N_1-C_2 and N_4-C_5 bonds in a tandem reductive amination-transamination-cyclization sequence.[69] This method was applied to the synthesis of a conformationally constrained macrocyclic inhibitor of farnesyltransferase (*Scheme 47*). Ethanolamine **179** was acylated and oxidized to the amidoaldehyde **180**, then treated with D-Ala-OMe in the presence of reducing agent to give intermediate **181**. Under the acidic reaction conditions, **181** equilibrated with intermediate **182**, whereupon intramolecular *N*-acylation provided **183** in good yield. *In situ* deprotection and cyclization provided the macrocyclic inhibitor **184**.

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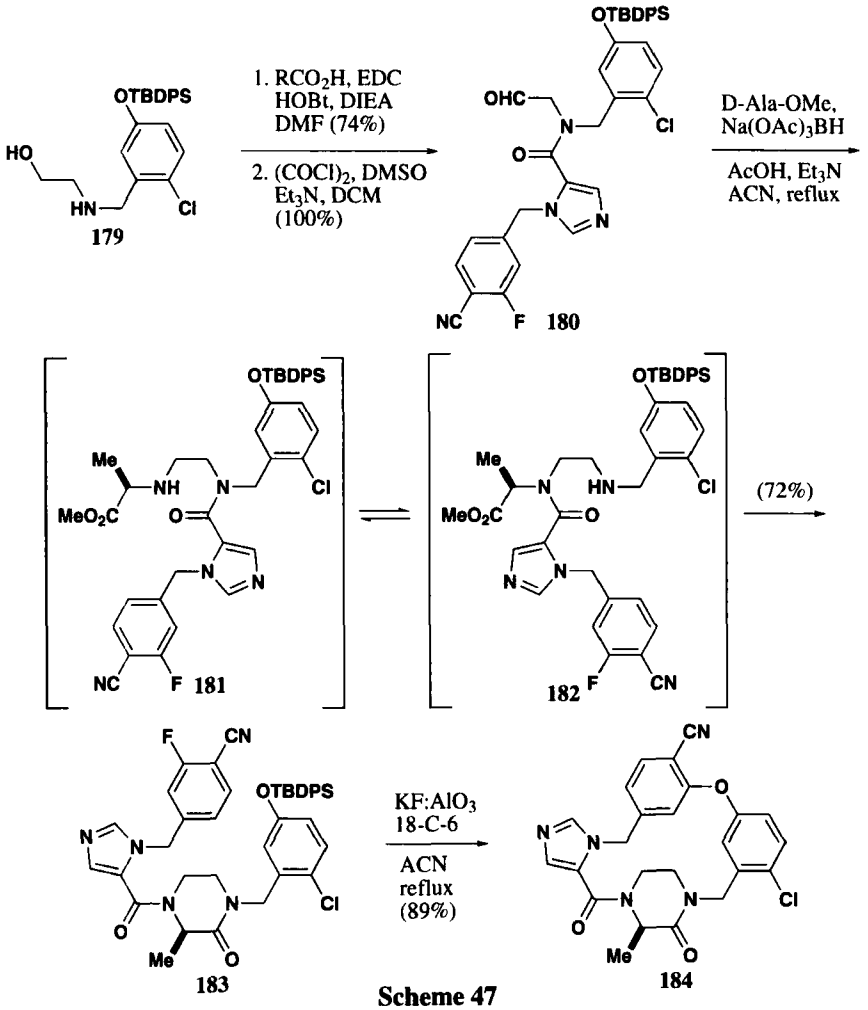

Scheme 47

III. PIPERAZINONE TRANSFORMATIONS

A variety of transformations have been carried out with piperazinone-containing compounds, many of which make use of the functionality embedded in the structure. Rather than discuss the common piperazinone *N*-alkylations and *N*-acylations, this section reviews many of the useful reactions involving changes to the carbon atoms of the piperazinone ring system.

1. Alkylation of Ring Carbons

A direct method of functionalizing the piperazinone ring is by C_3-alkylation, taking advantage of piperazinone enolate reactivity. In an early report, mono-, di- and tri-alkylations of 4-*N*-Boc-piperazinone dianion were carried out by Kane.[70] In a related approach, an auxilliary-controlled method was developed by Schanen *et al.* (*Scheme 48*),[28-30] employing the alkoxide-enolate of phenyl-

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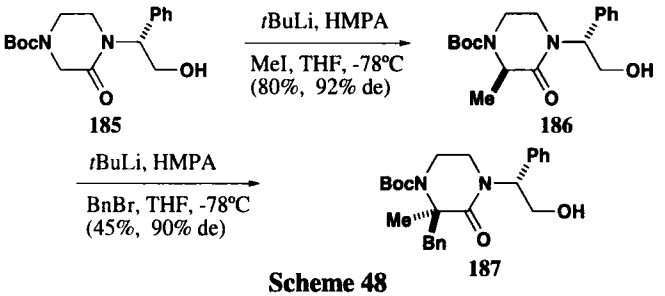
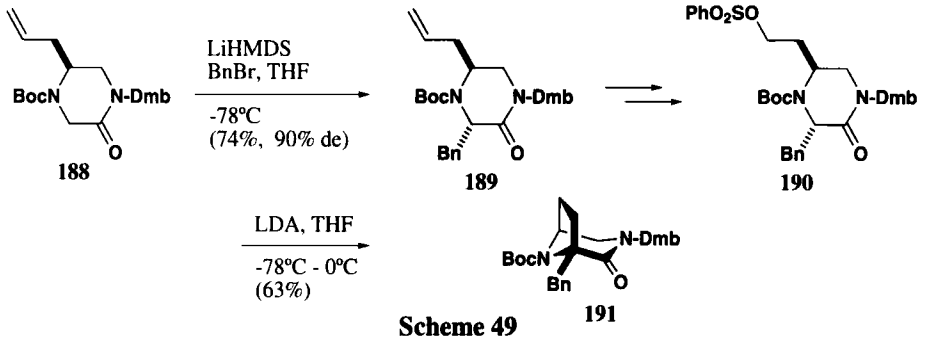
glycinol derivative **185** to prepare the methylated compound **186** in good yield and diastereoselection. A second enolization-alkylation was carried out with the same sense of face-selectivity to produce **187**. Amide reduction and auxilliary removal by catalytic hydrogenolysis gave optically pure piperazines.



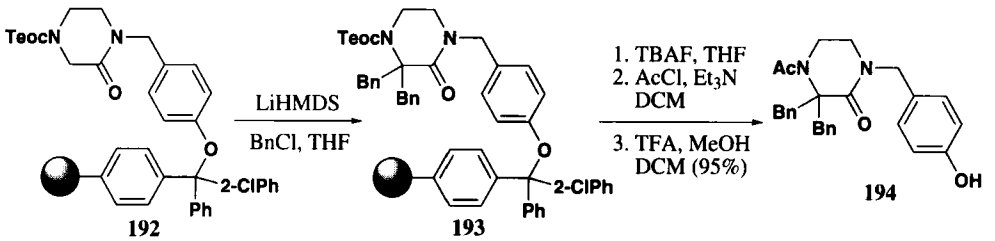
Scheme 48

Diastereoselective alkylation at C_3 was achieved with control by a C_5-substituent in a report by Dinsmore *et al.* (*Scheme 49*).[71] Benzylation of the lithium enolate of **188** gave *trans*-piperazinone **189**, presumably due to an axial disposition of the allyl group in the enolate by virtue of A(1,3)-strain.[72] Elaboration to the benzenesulfonate **190** was followed by a transannular enolate alkylation reaction to provide the diazabicyclo[3.2.1]octan-2-one **191**.



Scheme 49

Alkylation reactions on solid phase were utilized by Zhu in a study to produce a small combinatorial library of piperazinones.[73] The 2-chlorotrityl resin-bound intermediate **192** (*Scheme 50*) was alkylated to give **193**, then deprotected, acylated, and released from the resin to provide **194** in excellent overall yield.



Scheme 50

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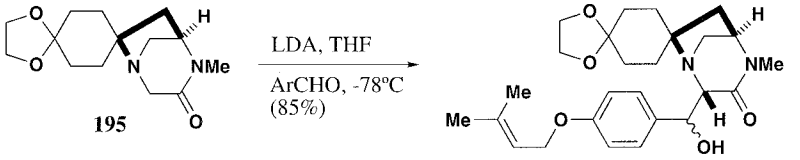
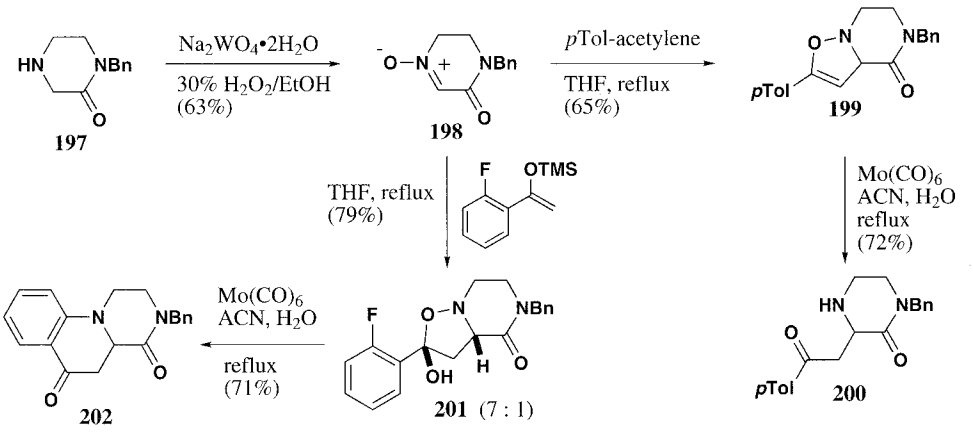
In a total synthesis of the antimuscarinic agent TAN1251A, Nagumo *et al.* reported an aldol reaction of bicyclic piperazinone **195** and an aromatic aldehyde to produce **196** (*Scheme 51*).[74] While attack of the lithium enolate occurred exclusively from the less hindered face, a mixture of benzylic hydroxyl epimers was obtained.



Scheme 51

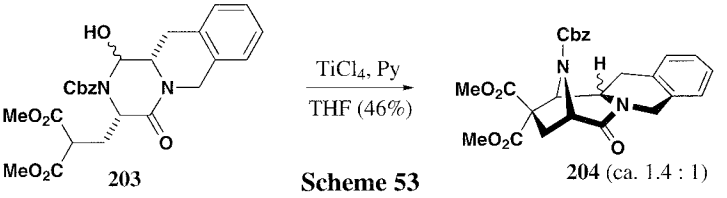
An alternative approach to C_3-substitution based on [3+2] cycloaddition chemistry was reported by Bernotas.[75,76] Oxidative conversion of piperazinone **197** (*Scheme 52*) to the nitrone **198** was followed by dipolar cycloaddition of an alkyne to provide the Δ^4-isoxazoline **199**. Reductive



Scheme 52

cleavage of the N-O bond gave the ketone **200**. The method was applied to the synthesis of a tricyclic system by incorporating an annulation reaction. Reaction of **198** and 2-fluoroacetophenone silyl enol ether gave predominantly *cis*-**201**. Reductive cleavage provided an intermediate C_3-substituted piperazinone which underwent intramolecular S_NAr reaction to give **202** in good yield.

Substituents may be added to the C_5-position of the piperazinone ring as nucleophilic components in amidoalkylation-type reactions of an *N*-acyl hemiaminal. An early example of this appeared in studies toward the synthesis of quinocarcin, carried out by Saito and Hirata (*Scheme 53*).[77]



Scheme 53

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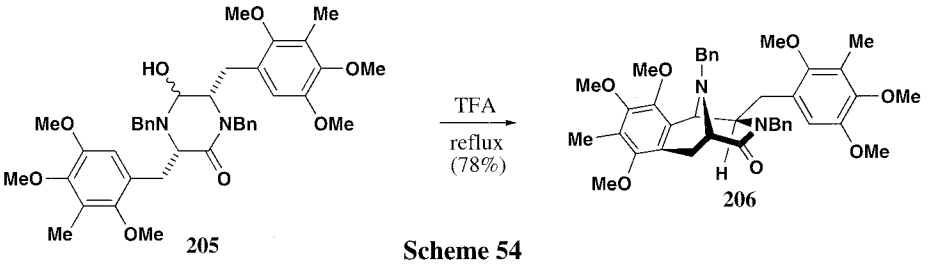
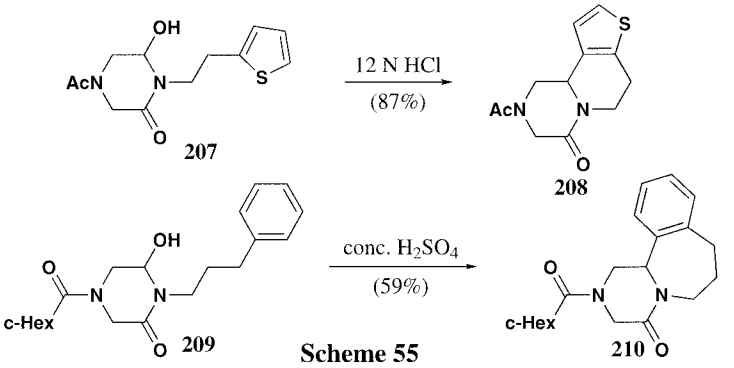
Lewis acid mediated addition of the pendant malonate group in **203** to the derived *N*-acyliminium ion afforded **204** in moderate yield, with epimerization at the C_6-position presumably due to equilibration of the iminium ion to an enamine.

Transformations carried out in saframycin synthetic studies feature an intramolecular Friedel-Crafts alkylation of an aromatic ring,[78-80] as exemplified in a report by Shawe and Liebeskind (*Scheme 54*).[81] Unfortunately, during acid-promoted cyclization of **205**, complete inversion of the stereochemistry at C_6 occurred to give undesired diastereomer **206**.



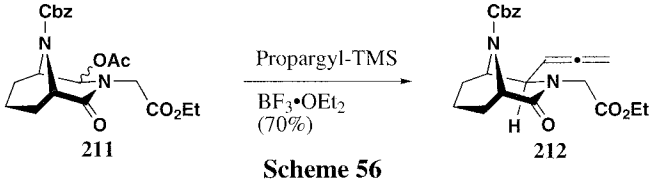
Scheme 54

Related reactions are used to install substituents at the piperazinone C_6-position. Acid-induced intramolecular substitution of an aromatic ring appended to the N_1-position appears to be a versatile method, as demonstrated by the work of Frehel[82] and Shekhter *et al.*,[83] who prepared the six-membered (**208**) and seven-membered (**210**) fused ring systems, respectively (*Scheme 55*).



Scheme 55

Intermolecular delivery of a nucleophile to the C_6-position was accomplished by Guo *et al.*[84] in the synthesis of FKBP-12 inhibitors (*Scheme 56*). Derivatization of a bicyclic *N*-acyl hemiaminal as its acetate gave **211**, which was subjected to attack by propargyltrimethylsilane after Lewis acid activation to give the allene **212** in good yield.



Scheme 56

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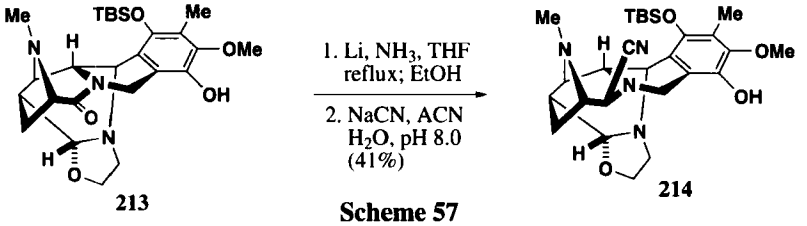
2. Reduction of the Carbonyl Group

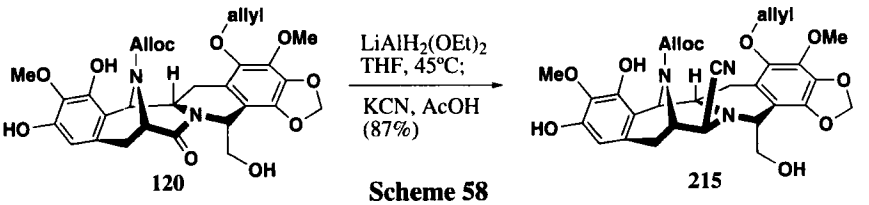
Two general modes of carbonyl group reduction have been applied to piperazinone rings, involving either partial reduction to a cyclic aminal or complete reduction to the useful piperazine ring structure. Partial reduction affords an intermediate capable of activation toward nucleophilic attack at the C_2-positon by nucleophiles. For example, in Evans's synthesis of (±)-cyanocycline,[85] the hexacyclic piperazinone **213** (*Scheme 57*) was reduced under dissolving metal conditions, and then directly subjected to a stereoselective cyanation reaction to provide the nitrile **214**. The same protocol was used by Garner in the preparation of an intermediate in the synthesis of (-)-quinocarcin.[86]



213 214

Scheme 57

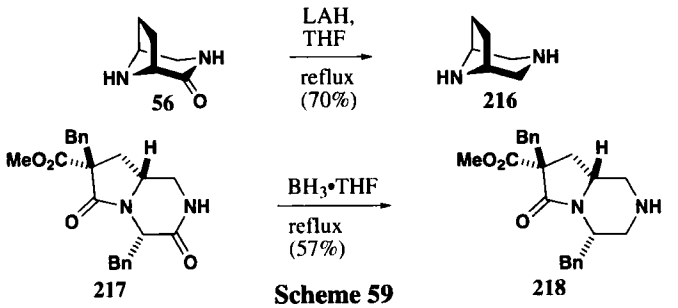
Very similar conditions employing hydride delivery to the carbonyl group and cyanation have been carried out,[77,87] including a recent example by Martinez and Corey in the synthesis of Ecteinascidin analogs (*Scheme 58*).[45] The hexacyclic derivative **120** was converted to the nitrile **215** in a high yielding one-pot transformation.



120 215

Scheme 58

There are numerous examples of the reduction of a piperazinone to a piperazine, typically using $LiAlH_4$,[88-92] AlH_3,[93,94] BH_3,[11,31,34,38,95-97] $NaBH_4$,[98] or sodium metal.[99] For example, reduction of **56** (*Scheme 59*) was carried out in refluxing $LiAlH_4$ in THF to give **216**,[88] and the bis-amide-ester **217** was selectively reduced with borane to provide **218**.[38]



56 216

217 218

Scheme 59

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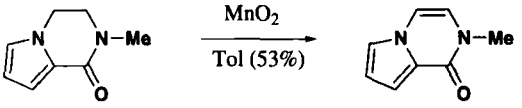
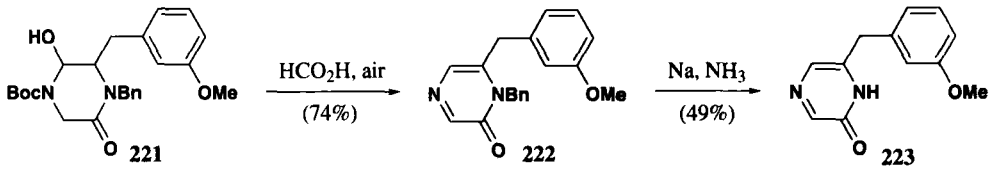
3. Oxidation Reactions

Oxidations of piperazinones can result in ring aromatization or oxygenation of a ring carbon. Inadvertent oxidative aromatization of a piperazinone to a pyrazinone by thermal dehydrogenation appeared in an early report by Cignarella[7] (*vide supra*, Scheme 2). A related oxidation was reported by Brimble *et al.* (*Scheme 60*),[53] in which **219** was oxidized at C_5-C_6 with manganese dioxide to provide the pyrrolo[1,2-*a*]pyrazinone **220** in moderate yield.



219 **Scheme 60** **220**

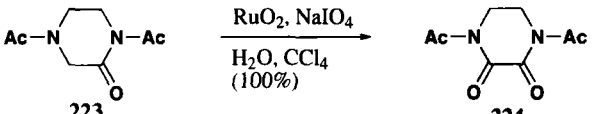
In studies directed toward the synthesis of the anti-tumor metabolite quinocarcin, Joule *et al.* reported the treatment of piperazinone **221** (*Scheme 61*) with formic acid and air to provide the deprotected and oxidized 1-benzyl-pyrazin-2-one **222**.[100] This was further deprotected under dissolving metal conditions to afford key intermediate **223**.



221 **222** **223**

Scheme 61

Vetuschi *et al.* reported the oxidation of piperazinones to 2,3-diketopiperazines using catalytic RuO_4 (*Scheme 62*).[101] While conversion of the *N,N'*-diacetyl derivative **223** to **224** was high-yielding, reaction of the corresponding *N,N'*-dibenzyl compound provided only 65% of crude 2,3-diketopiperazine.



223 **Scheme 62** **224**

4. Ring Cleavage Reactions

The most common ring cleaving reaction of a piperazinone is the hydrolysis of the N_1-C_2 amide bond. A report by Jain *et al.* illustrates this reaction in an efficient approach to the construction of substituted prolines (*Scheme 63*).[26] The bicyclic piperazinone **59** underwent solvolysis in methanolic HCl to provide the 5-aminomethylproline methyl ester **225** in excellent yield. Similarly, Martin-Martinez and co-workers reported the solvolysis of substituted 3,6-dioxyperhydropyrrolo[1,2-*d*]pyrazine **226** under basic conditions to provide the pyrrolodinone **227**.[102]

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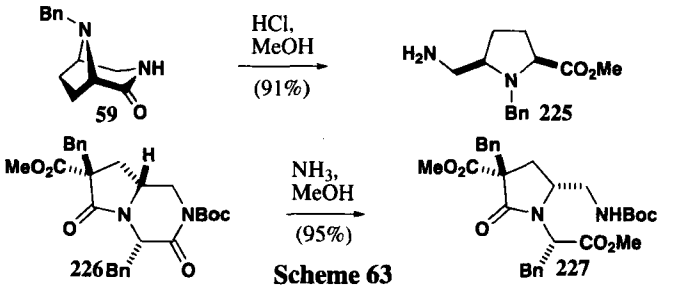
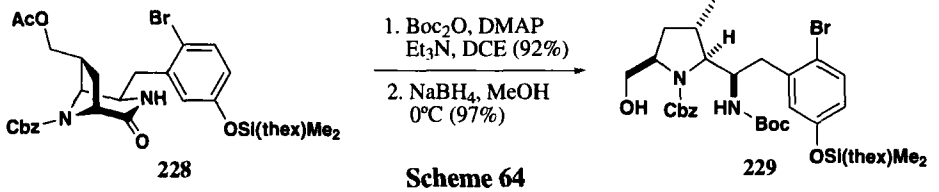


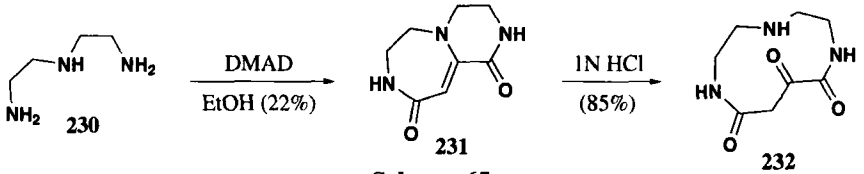
Scheme 63

Reductive cleavage of the amide N_1-C_2 bond was reported by Fukuyama,[103] using the *N*-Boc amide activation method of Greico.[24] The amide nitrogen in **228** (*Scheme 64*) was *N*-acylated, and the resultant imide reduced with $NaBH_4$ to afford the intermediate **229** in the total synthesis of (±)-quinocarcin. The same protocol was employed in the total synthesis of (±)-saframycin A.[80,103]



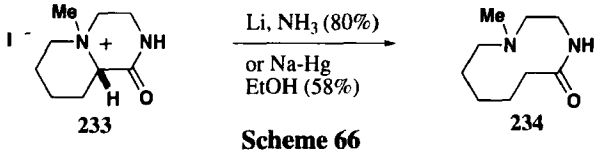
Scheme 64

Cleavage of the C_3-N_4 bond in piperazinone rings has been employed in the context of net ring-expansion strategies. For example, a hydrolysis method developed by Okawara *et al.* converts a C_3-methylene-substituted bicyclic piperazinone to a ketone (*Scheme 65*).[64] The reaction of triamine **230** with dimethyl acetylenedicarboxylate gave the tetrahydropyrazino[1,2-*d*]diazapinedione **231** via Michael addition followed by bis-intramolecular acylation. Upon treatment with aqueous acid, the C_3-N_4 bond was hydrolyzed to afford the triazacycloundecanetrione **232** in good yield.



Scheme 65

Dissolving metal reduction has also been used to cleave piperazinone rings. In another example of ring-expansion (*Scheme 66*), Arata and Nakagawa treated the methylammonium ion **233** with lithium metal in liquid ammonia to produce the 1,4-diazecan-5-one **213** in good yield.[104]



Scheme 66

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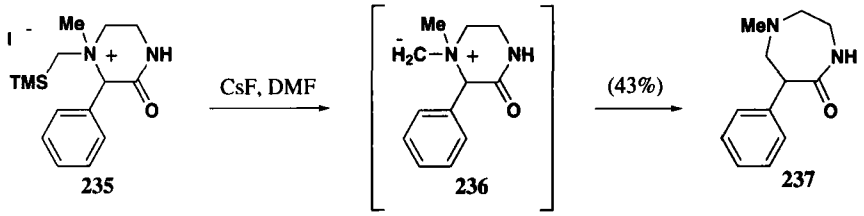
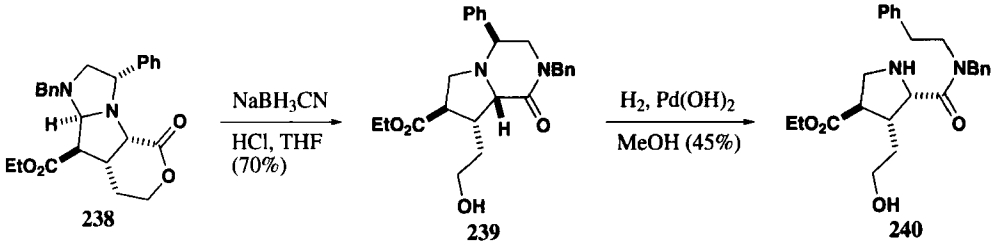
A report by Sato *et al.* described the rearrangement of an ammonium ylide as a strategy for piperazinone ring expansion.[105] The 3-phenyl-piperazinone **235** (*Scheme 67*) was treated with CsF to generate the ylide **236**, which rearranged to the 1,5-diazepan-2-one **237** in moderate yield. In contrast to the [1,2]-Stevens shift observed with piperazinone ylide **236**, the corresponding piperazine-ylide underwent [2,3]-Sommelet-Hauser rearrangement through the phenyl ring.



Scheme 67

A hydrogenolysis reaction has been used to cleave the N_4-C_5 bond of a piperazinone ring. In a report by Jones,[106] tricyclic lactone **238** (*Scheme 68*) was synthesized by intramolecular 1,3-dipolar cycloaddition of an imidazolinium ylide onto an olefin, then converted to piperazinone **239** by aminal reduction and intramolecular *N*-acylation. Reduction with Pearlman's catalyst cleaved the N_4-C_5 piperazinone bond, providing the 2,3,4-trisubstituted pyrrolidine **240** in moderate yield.



Scheme 68

IV. CONCLUSION

It is clear that an impressive array of methods is available for the construction of piperazinones, and that they form useful intermediates in the syntheses of peptidomimetic compounds and natural products. The ability to match an appropriate synthetic strategy to the structural requirements of a piperazinone target has become relatively simple, largely due to the breadth of recently developed reaction types that tolerate diverse functionality and stereochemistry. Notable recent advances include stereocontrolled bond constructions, which open opportunities to prepare non-proteinogenic piperazinone-peptidomimetics of ever-increasing complexity, and solid-phase protocols to facilitate syntheses of biologically active compound libraries. Due to the importance of constrained peptide mimetics in the investigation of biological phenomena, interest in the development and application of these and newer methods is likely to continue.

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V. LIST OF ABBREVIATIONS

ACN	acetonitrile
Alloc	allyloxycarbonyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
Cbz	carbonyloxybenzyl
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
Dde	1-(5,5-dimethyl-1,3-dioxocyclohexylidene)-1-ethyl
DEAD	diethyl azodicarboxylate
DIC	1,3-diisopropylcarbodiimide
DIEA	diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
Dmb	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Fmoc	9-fluorenylmethoxycarbonyl
HBTU	*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole hydrate
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
MP-carbonate	macroporous triethylammonium methylpolystyrene carbonate
Naph	naphthyl
NEM	*N*-ethylmorpholine
NHS	*N*-hydroxysuccinimide
NMP	*N*-methyl-2-pyrrolidinone
*p*TSA	*para*-toluenesulfonic acid
Py	pyridine

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Ra-Ni	Raney nickel
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
Tol	toluene
Tr	trityl
TsCl	*para*-toluenesulfonyl chloride

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