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Recent advances in the synthesis of diketopiperazines

Christopher J. Dinsmore and Douglas C. Beshore*

Merck Research Laboratories, Department of Medicinal Chemistry, WP14-2, P.O. Box 4, Sumneytown Pike, West Point, PA 19486, USA

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1. Introduction

The use of peptide and peptide-like structures is frequently required in the course of drug discovery. Optimization of potential drug candidates often precludes the use of peptides because of their poor physical and metabolic properties. As a result of the structural similarity of diketopiperazines (DKPs) to peptides,[1] their appearance in biologically active natural products has inspired medicinal chemists to use DKPs to circumvent the limitations of peptides. Constraining the nitrogen atoms of an α-amino amide into a DKP ring (Fig. 1) alters physical properties, reduces susceptibility to metabolic amide bond cleavage reactions and reduces conformational mobility. As a result of the change in structural and physical characteristics, DKPs can confer more drug-like properties to molecules and enhance favorable interactions with macromolecules.

From efforts directed toward the syntheses of natural products and potential drug candidates, new routes to DKPs continue to emerge. While isomers **1**–**3** share a piperazine core, optimal strategies for their syntheses differ. This report will examine the synthetic methods used to construct each isomer, distinguishing between intramolecular C–N cyclization reactions and tandem reactions, in which multiple bonds are formed in a single transformation. Recent reports from the literature are highlighted, as are the syntheses of biologically active compounds.

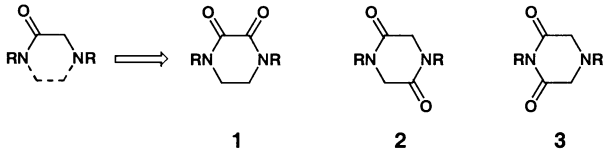

Figure 1.

Keywords: diketopiperazines; peptides; cyclization; dioxopiperazines; review.

* Corresponding author. Tel.: +1-215-652-7474; fax: +1-215-652-7310; e-mail: douglas_beshore@merck.com

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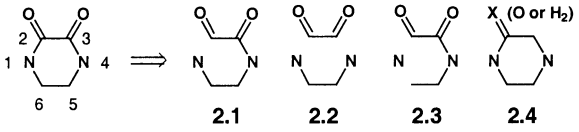


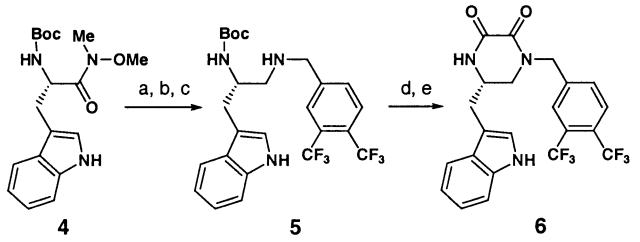
Scheme 1. 2,3-DKP synthesis strategies, with review section indicated.

2. 2,3-Diketopiperazines

2,3-DKPs have been used frequently in medicinal chemistry and can also be found in natural products such as the antibiotics piperacillin,[2,3] cefoperazone[4] and bicyclomycin.[5,6] A survey of the literature shows that the construction of 2,3-DKPs can be divided into the four main strategies depicted in Scheme 1.

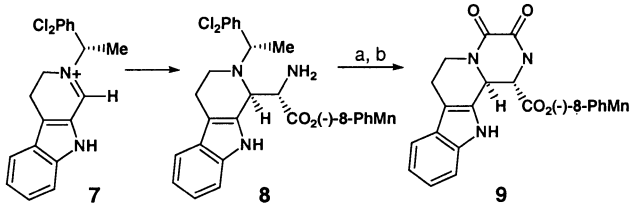
2.1. Intramolecular formation of N_1–C_2

Most methods of intramolecular cyclization reactions to produce 2,3-DKPs proceed via formation of the N_1–C_2 amide bond rather than the N_1–C_6 linkage. This strategy generally employs a sequence of reactions involving the treatment of a mono-protected 1,2-diamine with an alkyl chlorooxoacetate to give an oxamate, followed by *N*-deprotection and cyclization, often in a one-pot transformation. For example, in a report by Lewis et al.,[7] the readily available Weinreb amide of *N*-α-Boc-L-tryptophan **4** (Scheme 2) was reduced to the corresponding aldehyde, then condensed with a substituted benzylamine. Reduction of the resultant imine provided the mono-*N*-Boc diamine **5** in good yield. Reaction with methyl chlorooxoacetate provided a carbamate ester that, in the presence of methanolic hydrogen chloride, underwent deprotection and cyclization to provide the NK_1 antagonist **6** in good yield.

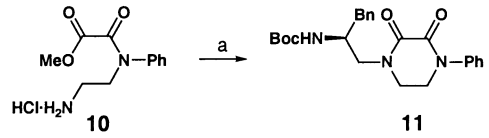


Scheme 2. *Reagents*: (a) $LiAlH_4$; (b) $BnNH_2$, $MgSO_4$; (c) $NaBH_4$ (55%); (d) $ClCOCO_2Me$, Et_3N, DCM; (e) HCl, MeOH (64%).

In a report by Polniaszek and Bell,[8] the chiral tryptamine-derived iminium ion **7** (Scheme 3) was treated with a glycine-(−)-8-phenylmenthol [(−)-8-PhMn] ester enolate to produce the adduct **8** in a double diastereodifferentiating reaction. This was acylated with methyl chlorooxoacetate and subjected to hydrogenolysis, whereupon the resulting amine underwent spontaneous intramolecular acylation to afford the tetracycle **9**.



Scheme 3. *Reagents*: (a) $ClCOCO_2Me$, DMAP; (b) NH_4CO_2H, 10% Pd/C.



Scheme 4. *Reagents*: (a) *N*-Boc-phenylalanal, $Na(AcO)_3BH$, 4 Å mol. Sieves, DCE, 0°C–rt (60%).

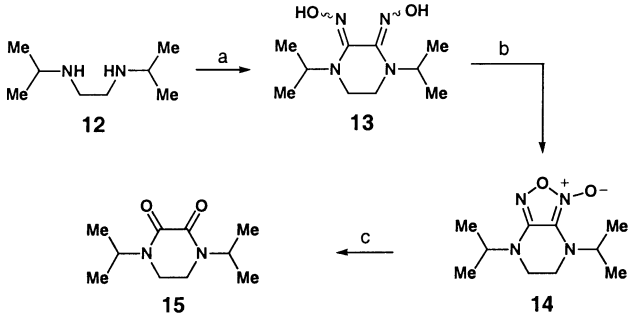
Dinsmore and Bergman developed a strategy in which introduction of substitution at N_1 and DKP cyclization were accomplished in a single-pot transformation.[9] By treating the easily accessible, stable amine hydrochloride **10** (Scheme 4) with alkyl and aryl aldehydes in the presence of sodium triacetoxyborohydride, *N*-substituted 2,3-DKPs were produced in moderate to good yields. For example, *N*-Boc-phenylalanal was reductively aminated with **10** to provide **11** in 60% yield. While aryl ketones resulted in premature cyclization of **10** to give the corresponding N_1-unsubstituted 2,3-DKP, benzaldehydes and cyclic ketones were good substrates for the reaction. This alkylation–cyclization protocol was later applied to the synthesis of *N*-aryl-2,3-DKP inhibitors of farnesyltransferase.[10]

2.2. Tandem formation of N_1–C_2/C_3–N_4

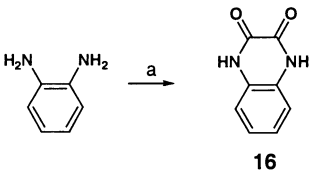
The most commonly reported route to 2,3-DKP construction utilizes the facile reaction of a 1,2-diamine with either oxalyl chloride,[8] dialkyl oxalate,[11] or 1,1′-oxalyldiimidazole[12] to simultaneously form the N_1–C_2 and C_3–N_4 bonds. By matching one of the aforementioned oxalates appropriately with a desired diamine, tandem formation of 2,3-DKPs can be constructed with great efficiency. As a result, this method of tandem bond formation continues to be the preferred method of 2,3-DKP ring construction today, as it has been since it was pioneered by Bischoff in 1889.[13]

The use of a more unusual oxalate synthon, reported by Willer and Moore,[14] entailed a three step procedure in which diamine **12** (Scheme 5) was reacted with dichloroglyoxime in methanol to afford dioxime **13** in good yield. Cyclization afforded the oxadiazole **14**, which was then hydrolyzed to DKP **15** excellent yield.

Another interesting dicarbonyl equivalent was reported by



Scheme 5. *Reagents*: (a) dichloroglyoxime, MeOH, −60°C (75%); (b) NaOH, $K_3Fe(CN)_6$, (90%); (c) $EtOH/H_2O$, Δ (100%).



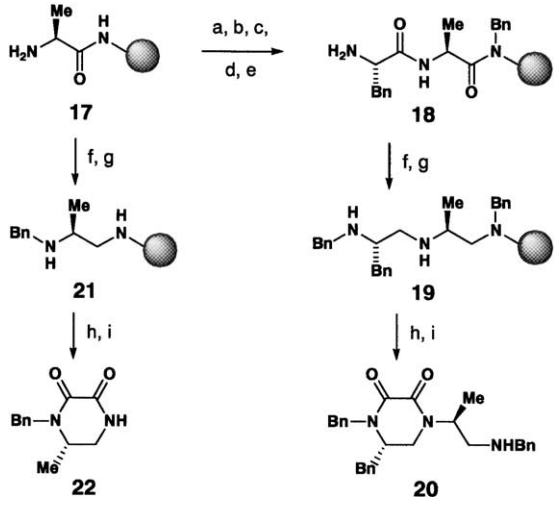
Scheme 6. *Reagent*: (a) imidazolin-2,4,5-trione, EtOH, Δ (24%).

Kollenz et al.[15] 1,2-Phenylenediamine (Scheme 6) was treated with the easily prepared imidazoline-2,4,5-trione in refluxing ethanol to provide DKP **16** in 24% yield.

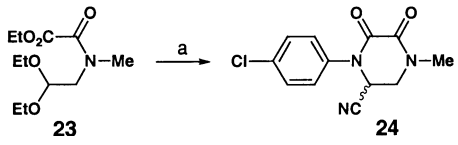
The advent of solid phase methods in organic synthesis has enabled the rapid generation of compound arrays from diverse structural classes, including DKPs. A general approach to DKPs was recently reported by Houghten et al.,[12] in which 1,4,6-trisubstituted 2,3-DKPs and 1,6-disubstituted 2,3-DKPs were constructed on a *p*-methylbenzhydrylamine (MBHA) resin (Scheme 7). Backbone construction began with **17**, derived from resin acylation with *N*-Fmoc-alanine followed by amine deprotection. Amide benzylation followed by peptide homologation provided the resin-bound dipeptide **18**. Terminal amine acylation, followed by exhaustive borane reduction provided the diamine **19**, which underwent bis-acylation with 1,1′-oxalyldiimidazole and HF mediated resin cleavage to provide **20** in >75% yield, based upon original resin loading. N_4-Unsubstituted 2,3-DKPs were produced by a related, truncated synthetic sequence. Acylation and borane reduction of **17** produced diamine **21**, which underwent analogous bis-acylation and resin cleavage to afford 2,3-diketo-4[*H*]-piperazine **22**.

2.3. Tandem formation of C_2–N_1–C_6

An attractive feature of a strategy involving the tandem formation of the N_1–C_2 and N_1–C_6 bonds is the facile assembly of unsymmetrical 2,3-DKPs. In a report by Lucas,[16] ester acetal **23** (Scheme 8) was heated in the



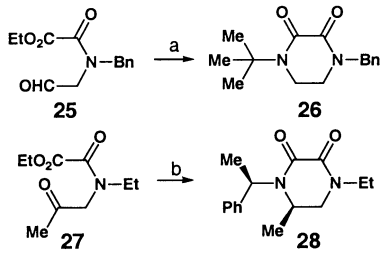
Scheme 7. *Reagents*: (a) TrCl, DIEA, DCM; (b) BnBr, *t*-BuOLi, DMSO; (c) 2% TFA in DCM, DIEA, DCM; (d) Fmoc-Phe-OH, DIPCDI, DMF; (e) 20% piperidine in DMF; (f) $PhCO_2H$, DIPCDI, DMF; (g) BH_3·THF, 65°C; (h) 1,1′-oxalyldiimidazole, DMF; (i) HF/anisole.



Scheme 8. *Reagents*: (a) KCN, *p*-$ClArNH_2$, AcOH, H_2O, Δ (43%).

presence of potassium cyanide and *p*-chloroaniline to produce the racemic 6-substituted 2,3-DKP **24**. Presumably, acetal hydrolysis and Staudinger reaction are followed by in situ ring closure.

In a report by Beshore and Dinsmore,[17] a reductive amination–cyclization strategy was employed as an efficient method to introduce diverse N_1-substituents. The ester aldehyde **25** (Scheme 9) was treated with primary aliphatic and aromatic amines in the presence of sodium triacetoxyborohydride, acetic acid and molecular sieves. For example, *t*-butylamine and **25** were combined to produce the 2,3-DKP **26** in good yield. In addition, reaction of the chiral auxiliary-bearing amine (*R*)-α-methylbenzylamine and the methyl ketone **27** produced the (*R*)-6-methyl-2,3-DKP **28** with 6:1 diastereoselectivity.

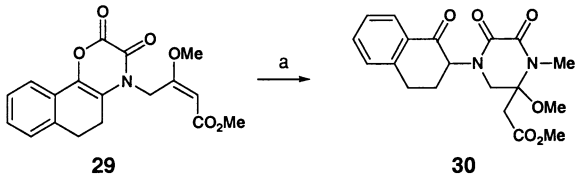


Scheme 9. *Reagents*: (a) *t*-$BuNH_2$, $Na(AcO)_3BH$, AcOH, 4 Å mol. sieves, DCE, 0°C–rt–Δ (80%); (b) (*R*)-α-methyl benzylamine, AcOH, $Na(AcO)_3BH$, 4 Å mol. sieves, DCE, 0°C–rt (90%).

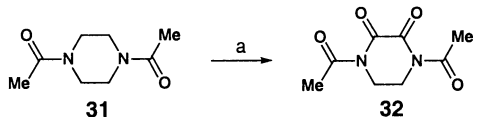
In a report by Bowman,[18] the morpholinedione **29** (Scheme 10) was treated with methylamine in aqueous solution to provide the β-keto-2,3-DKP **30** in 90% yield, by conjugate addition of the amine to the enoate moiety followed by ring-opening intramolecular *N*-acylation.

2.4. Oxidation of piperazine derivatives

There are several examples of the use of oxidative strategies to install the dicarbonyl motif present in 2,3-DKPs, some of which were developed in the context of natural product total syntheses. Regioselective oxidation can be affected directly on an appropriately functionalized piperazine derivative. *N*,*N*′-Diacetylpiperazine (**31**, Scheme 11) was treated with RuO_4 generated in situ, to provide a quantitative yield of



Scheme 10. *Reagents*: (a) $MeNH_2$, H_2O (90%).

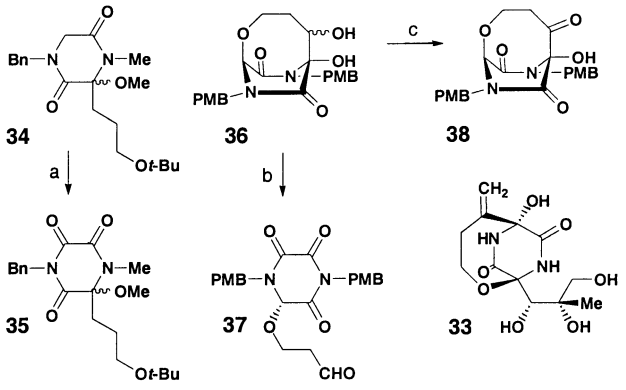


Scheme 11. *Reagents*: (a) $NaIO_4$, RuO_2, CCl_4/H_2O (100%).

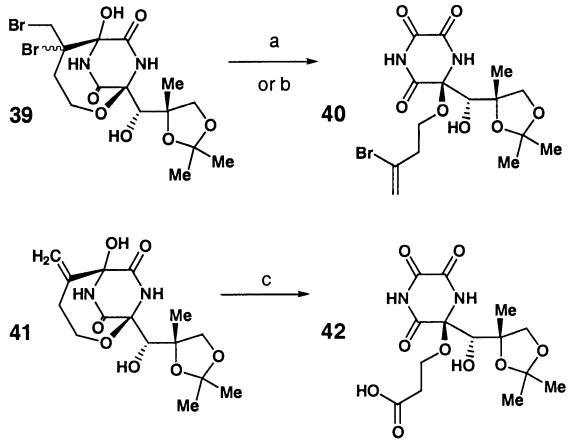
2,3-DKP **32**.[19] Interestingly, when the corresponding *N*,*N*-dibenzylpiperazine was subjected to the same reaction conditions, only 5% of the desired 2,3-DKP was formed.

The most commonly reported piperazine ring oxidation involves oxidation of 2,5-DKPs to 2,3,5-triketopiperazines, sometimes inadvertently. Nonetheless, the precedent that is set for the construction of 2,3-DKPs is apparent. In studies directed toward bicyclomycin (**33**) (Scheme 12) by Shin and co-workers,[20] a triketopiperazine intermediate was required. The 2,5-DKP **34** was treated with NBS in aqueous chloroform to produce the triketopiperazine **35** in moderate yield. In another report by Yoshimura in which bicyclomycin's core ring had already been constructed,[21] PCC oxidation of the diol **36** produced the undesired ring cleavage product **37** in good yield, while Swern oxidation provided the desired ketone **38** in 91% yield.

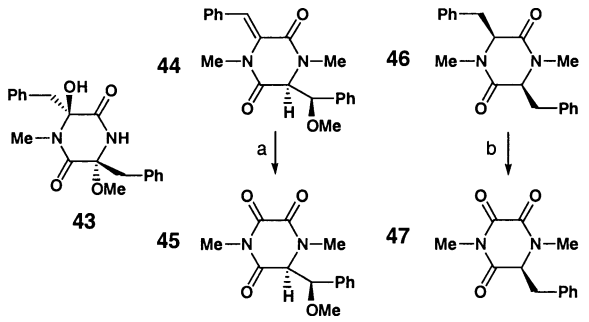
Kohn and colleagues reported in their additional studies of



Scheme 12. PMB=*para*-methoxybenzyl. *Reagents*: (a) NBS (1.1 equiv.), $CHCl_3/H_2O$ (23%). (b) PCC (61%); (c) $(COCl)_2$, DMSO, Et_3N, DCM (91%).



Scheme 13. *Reagents*: (a) DBU, THF (71%); (b) KF, 18-C-6, DMF (48%); (c) $NaIO_4$, OsO_4, dioxane (67%).



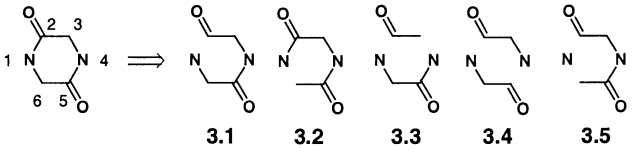
Scheme 14. *Reagents*: (a) O_3, then Me_2S, DCM, −78°C–rt (87%); (b) $FeCl_3$, $h\nu$, $(CH_3)_2CO/H_2O$ (30%).

bicyclomycin and its derivatives the conversion of dibromide **39** (Scheme 13) to the ring-cleaved triketopiperazine **40** by treatment with base.[22] In a related example,[23] the vinyl group in **41** was subjected to oxidative cleavage with $NaIO_4$ and OsO_4, to produce the ring-opened acid **42** in good yield.

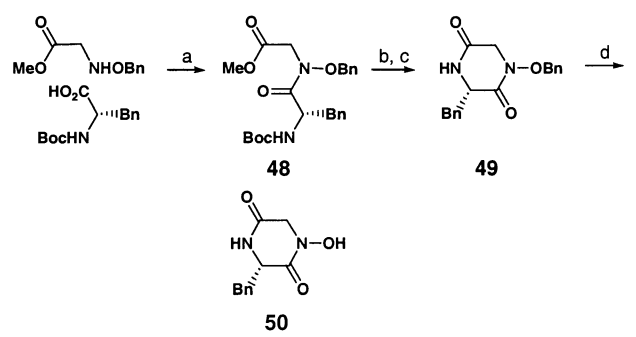
Other oxidative methods to 2,3-DKP formation have arisen from studies directed toward the synthesis and structural elucidation of picroroccellin (**43**) and its derivatives (Scheme 14).[24] The styrene **44** was ozonolyzed to produce the triketopiperazine **45** in 87% yield. In a report by Barbier,[25] the *N*,*N*-dimethyl-2,5-DKP **46** underwent $FeCl_3$-promoted photooxidation to produce the piperazinetrione **47** in moderate yield.

3. 2,5-Diketopiperazines

The 2,5-DKPs, head-to-tail dipeptide dimers, are a common naturally occurring structural motif.[1] They are also frequently generated as unwanted byproducts or degradation products in the syntheses of oligopeptides.[26–28] Correspondingly (Scheme 15), synthetic strategies have often taken advantage of the large pool of available natural and unnatural amino acids as enantiopure starting materials.



Scheme 15. 2,5-DKP synthesis strategies, with review section indicated.

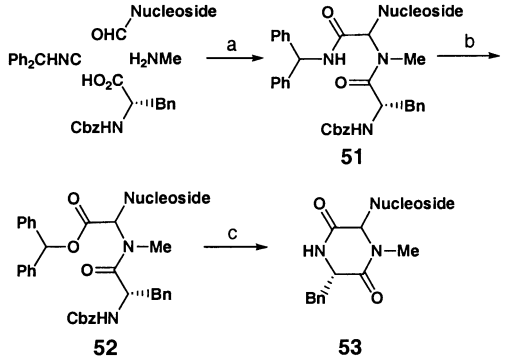


Scheme 16. *Reagents*: (a) *i*-BuOCOCl, Et_3N, THF/DCM (69%); (b) TFA, DCM; (c) 5% aqueous $NaHCO_3$ (86%); (d) H_2, Pd/C, EtOH (85%).

3.1. Intramolecular formation of N_1–C_2

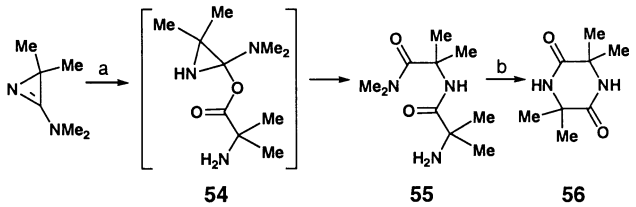
2,5-DKP formation via intramolecular cyclization of the N_1–C_2 bond is well represented in the literature as an efficient route to ring closure that has been readily adapted to solid supported synthesis. Typically, construction of these head-to-tail dipeptides involves the coupling of an *N*-protected α-amino acid to an α-amino ester, followed by *N*-deprotection and cyclization, which occurs either in situ or with elevated temperature.[29] While there are many examples of this sequence in the literature, a report by Akiyama and co-workers describing the synthesis and spectroscopic properties of *N*-hydroxy-2,5-DKPs is illustrative (Scheme 16).[30] The dipeptide **48** was produced by coupling the requisite protected amino acids. In a two-step procedure, the *N*-Boc protecting group was removed under acidic conditions and the resultant amine was intramolecularly acylated under mildly basic conditions to afford the 2,5-DKP **49** in good yield. Further deprotection of the *O*-benzyl protecting group with palladium on activated carbon provided **50**.

An interesting example of N_1–C_2 construction was reported by Boehm and Kingsbury in their syntheses of polyoxin antibiotics (Scheme 17).[31] Utilization of the Ugi four component coupling strategy provided the benzhydryl amide **51**. Nitrosation and rearrangement to the benzhydryl ester was accomplished with N_2O_4 to afford the cyclization precursor **52**. Removal of the Cbz protecting group and in situ cyclization provided 2,5-DKP **53**.

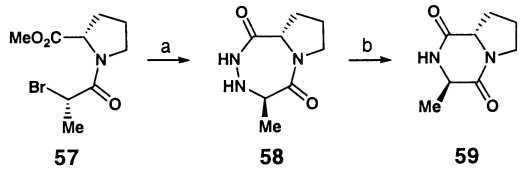


Scheme 17. *Reagents*: (a) MeOH, H_2O; (b) N_2O_4, NaOAc, DCM; (c) HCO_2H, Pd black, MeOH, (100%).

Obrecht and Heimgartner reported the use of a 2-aminoazirene as an activated acylating group for 2,5-DKP synthesis (Scheme 18).[32] Upon treatment with α-amino-*iso*-butyric acid in refluxing acetonitrile, 3-(dimethylamino)-2,2-dimethyl-2*H*-azirene underwent conversion to the



Scheme 18. *Reagents*: (a) α-amino-*iso*-butyric acid hydrochloride, ACN, Δ (90%); (b) *N*-Me-pyrrolidine, 170°C (40%).

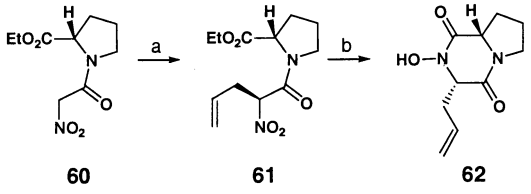


Scheme 19. *Reagents*: (a) $H_2NNH_2{\cdot}H_2O$, EtOH, Δ; (b) Na/NH_3(liq), −68°C.

N,*O*-orthoimide adduct **54**.[33] Isomerization of **54** provided the 2,5-DKP precursor **55** in excellent yield. Thermal cyclization at 170°C afforded **56** in moderate yield.

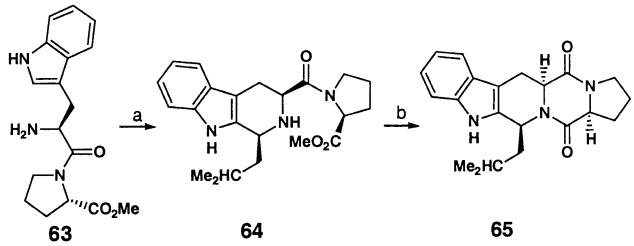
Construction of pyrrolopyrazine-1,4-diones as *cis*-peptidyl-proline amide mimetics has been accomplished through utilization of a cyclic hydrazide precursor (Scheme 19).[34] Bromoester **57**, obtained from the acylation of proline methyl ester with (*S*)-α-bromopropionic acid, was treated with hydrazine to produce the cyclic hydrazide **58**. Dissolving metal reductive cleavage provided an intermediate amino amide which underwent spontaneous cyclization with loss of ammonia to provide the 2,5-DKP **59**.

Another approach to pyrrolopyrazine-1,4-diones, reported by Rajappa and co-workers,[35–37] features the stereoselective introduction of a sidechain substituent. Allylation of the *N*-(α-nitroacetyl)proline **60** (Scheme 20) produced the α-substituted nitroacetamide **61** with moderate diastereoselectivity (25% de).[35] Partial zinc reduction provided the *N*-hydroxy-2,5-DKP **62** in good yield. This method was also applied to acyclic dipeptide precursors to furnish 6-substituted-N_1-hydroxy-2,5-DKPs.

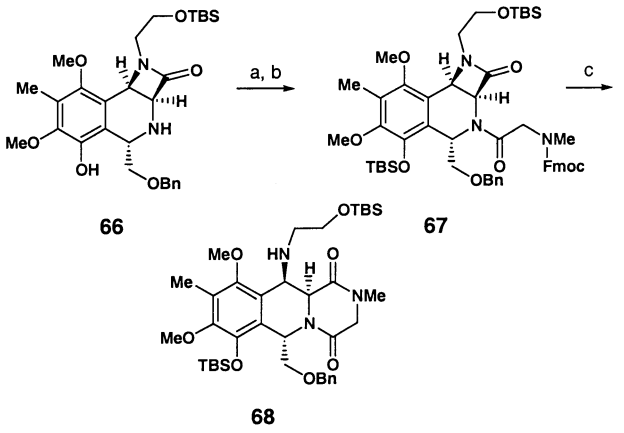


Scheme 20. *Reagents*: (a) DBU, $Pd(dba)_2$, PPh_3, allyl acetate, ACN, 30°C; (b) Zn, NH_4Cl (aq), EtOH, Δ, 25% de (80%).

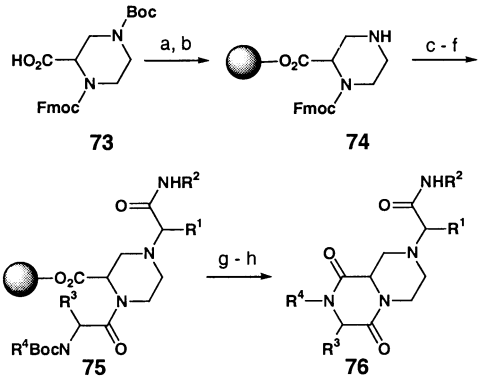
Syntheses of representatives of the fumitremorgin family of heptacyclic 2,5-DKP fungal isolates are described extensively in the literature. In a report by Harrison and Sharma,[38] model studies were conducted to synthesize this class of natural products. The easily prepared tryptophan-proline dipeptide **63** (Scheme 21) was treated with 3-methylbutanal in refluxing benzene to produce the Pictet–Spengler



Scheme 21. *Reagents*: (a) 3-methylbutanal, TFA, 4 Å mol. sieves, DCM, 0°C–rt (dr 85:15); (b) HCO_2H, *i*-BuOH, toluene, Δ (40%).



Scheme 22. *Reagents*: (a) TBSCl, Et_3N, THF; (b) *N*-Fmoc-sarcosine acid chloride, DMAP, DCM (86% over 2 steps); (c) piperidine, ACN (>99%).



Scheme 24. *Reagents*: (a) hydroxymethylpolystyrene resin, PPh_3, DEAD, THF; (b) 40% TFA/DCM; (c) $HCOCO_2H{\cdot}H_2O$, R^1-$B(OH)_2$, DCM; (d) DIC, R^2NH_2, DCM; (e) 25% piperidine/DMF; (f) $(R^4)BocNCH(R^3)CO_2H$, PyBOP, DMF; (g) 25% TFA/DCM; (h) 2 M AcOH/*i*-BuOH, 50°C.

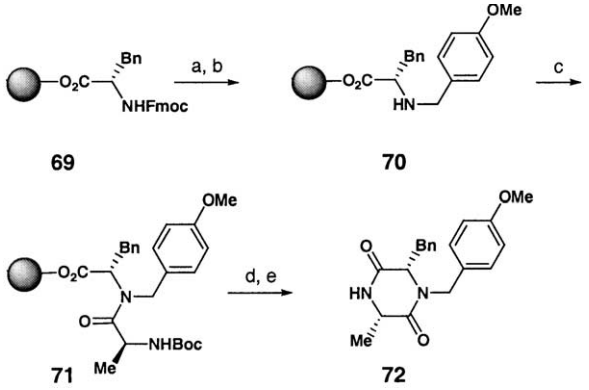
cyclization product **64**, producing an 85:15 ratio of diastereomers. Acid-promoted cyclization, followed by fractional crystallization from ethanol, provided diastereomerically pure 2,5-DKP **65** in 40% yield from **63**. This facile route to this family of natural products has led to the assembly a combinatorial library of fumitremorgin analogues.[39]

Azetidinone ring opening reactions have also been used to construct 2,5-DKPs (Scheme 22).[40] In a report by Williams et al., the tricyclic intermediate **66** was silylated, then acylated with Fmoc-sarcosine acid chloride to provide **67**. Deprotection with piperidine unmasked the amine, which underwent spontaneous azetidinone ring cleavage with concomitant 2,5-DKP ring formation to provide **68** in quantitative yield.

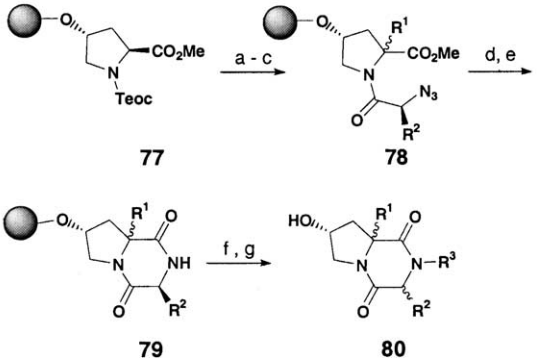
Gordon and Steele reported the efficient synthesis of a trisubstituted 2,5-DKP library on solid support (Scheme 23).[41] Esterification of an Fmoc protected amino acid with Wang resin gave **69**. Piperidine-mediated Fmoc removal provided the primary amine, which underwent reductive alkylation with *p*-methoxybenzaldehyde to provide the secondary amine **70**. This was acylated with *N*-Boc alanine in the presence of PyBOP to provide **71**. Exposure to neat trifluoroacetic acid deprotected the amino group and released the acyclic precursor from the resin. Cyclization to the 2,5-DKP **72** was accomplished by briefly refluxing the acyclic precursor in toluene. Using this general sequence, combined with standard split and pool techniques, 1000 variously substituted 2,5-DKPs were synthesized, incorporating both polar and non-polar functionality from both aromatic and aliphatic aldehydes, as well as varying the amino acid derivative.

Another example of solid phase synthesis of 2,5-DKPs comes from efforts to identify biologically active β-turn peptide mimetics.[42–44] Golebiowski and co-workers developed the synthesis of a bicyclic 2,5-DKP with four variable substituents. The orthogonally protected piperazine **73** (Scheme 24) was attached to Merrifield resin under Mitsunobu conditions and the *N*-Boc protecting group was removed with trifluoroacetic acid, affording the resin-bound amine **74**. Introduction of R^1 and R^2 substituents was accomplished by Petasis reaction, followed by amide coupling. Fmoc removal and amino acid coupling provided **75**, which was subjected to deprotection and cyclization with simultaneous resin cleavage afforded the 2,5-DKP **76** in good yield and purity.

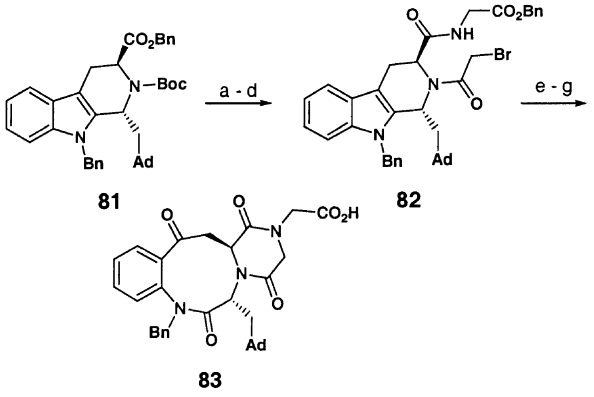
Resin release that does not incorporate concominant cyclization has allowed for further elaboration of the resin-bound DKP backbone.[45] This strategy has been utilized to



Scheme 23. *Reagents*: (a) 40% piperidine in DMF; (b) *p*-MeO-ArCHO, $Na(OAc)_3BH$, DCM, sonicate, 2 cycles; (c) Boc-AA-OH, PyBOP, DIEA, DCM, 2 cycles; (d) TFA; (e) toluene, reflux (42%).



Scheme 25. *Reagents*: (a) LiHMDS, R^1X, THF; (b) TBAF, THF; (c) $N_3CH(R^2)COCl$, DIEA, DMF; (d) $SnCl_2$, Et_3N, PhSH, THF; (e) KCN(cat.), DMF, 50–55°C; (f) NaH, DMF, R^3X; (g) TFA/H_2O (8:2).

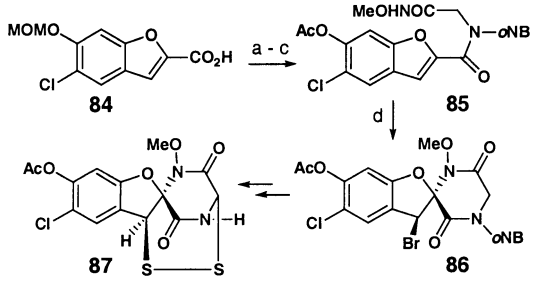


Scheme 26. Ad=Adamantyl. *Reagents*: (a) H_2, Pd/C, MeOH, THF; (b) $H_2NCH_2CO_2Bn$, PyBOP, DIEA, DCM; (c) TFA, DCM (94%); (d) $BrCH_2COCl$, Et_3N, DCM; (e) Cs_2CO_3, DMF (33%); (f) O_3, Me_2S, MeOH, DCM; (g) H_2, Pd/C, MeOH, THF.

synthesize fused hydroxyproline-2,5-DKPs on solid support, in which three points of variation are readily available.[46] The Ellman tetrahydropyranyl resin-bound ether **77** (Scheme 25)[47] was enolized with LiHMDS, and alkylated to establish the R^1 substituent with epimerization of the α-carbon center. Deprotection and acylation gave **78**, and tin(II)chloride reduction and cyclization provided the resin-bound 2,5-DKP **79**. Sodium hydride-mediated *N*-alkylation to install R^3 was accompanied by epimerization of the R^2-bearing stereocenter. Finally, under acidic conditions, the diketopiperazine was cleaved from the resin to provide **80** in >70% yield and 55–90% purity.

3.2. Intramolecular formation of N_1–C_6

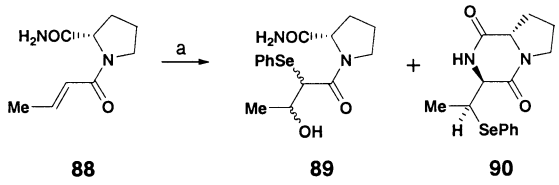
A less common mode of intramolecular cyclization to 2,5-DKPs involves formation of the N_1–C_6 bond. This route often employs acylation of glycinamide with an α-halo acid halide, followed by ring closure under basic conditions. A representative of this process was reported by McDonald and co-workers in the syntheses of non-peptidyl CCK_2 receptor antagonists (Scheme 26).[48] The Pictet–Spengler product **81**, three steps from L-tryptophan benzyl ester, was hydrogenolyzed and coupled to glycine benzyl ester. *N*-Boc removal and acylation with bromoacetyl chloride provided the cyclization precursor **82**. Treatment of **82** with cesium carbonate in DMF provided the corresponding 2,5-DKP, which was subjected to ozonolytic ring opening and debenzylation to provide tricycle **83**.



Scheme 27. *o*NB=*ortho*-nitrobenzyl. *Reagents*: (a) $(COCl)_2$, *N*-(*o*NB)-glycine methyl ester, $NaHCO_3$; HCl(aq), dioxane, Δ (84%); (b) Ac_2O, Py (95%); (c) ^{i}BuOCOCl, NMM, THF; $MeONH_2$ (70%); (d) NBS, $CHCl_3$ (67%).

Another approach to N_1–C_6 bond formation was successfully empolyed by Williams in the total synthesis of (±)-aspirochlorine (**87**, Scheme 27).[49] The benzofuran **84** was converted in three steps to the key cyclization precursor **85**. Treatment with NBS in chloroform provided the spirocyclic 2,5-DKP **86** in 67% yield, which was then converted in six steps to (±)-Aspirochlorine (**87**).

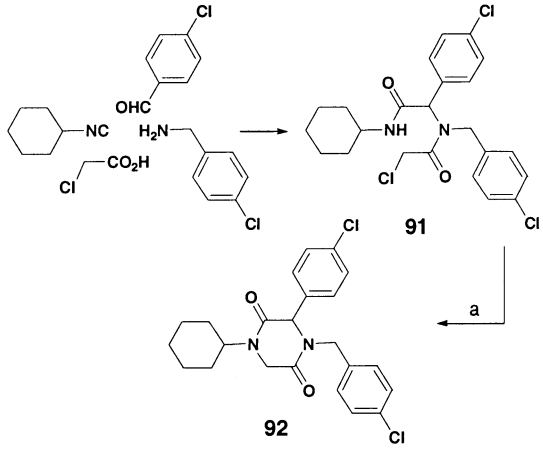
A similar transformation was reported as an oxidative byproduct of proline amide **88** (Scheme 28).[50,51] When treated with benzeneselenyl bromide and silver triflate, the acyclic mixture of diasteromers **89**, along with the 2,5-DKP **90** as a minor product, were formed. When the corresponding cinnamoylproline derivative was subjected to the same conditions, 7-*endo* cyclization ensued to form a hexahydro-1*H*-pyrrolo[1,2-*a*]diazepine-1,5(2*H*)-dione as the predominant product.



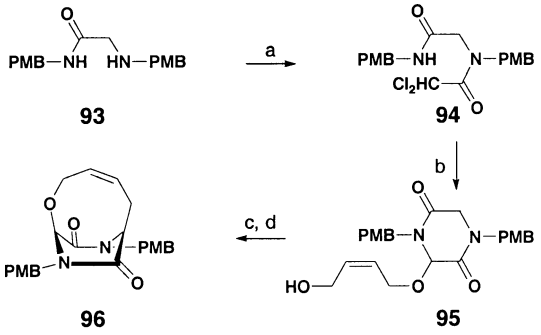
Scheme 28. *Reagents*: (a) PhSeBr, AgOTf, DMF, ACN (**89** (68%), **90** (17%, dr 3:1)).

A rapid two-step assembly of 2,5-DKPs was recently reported by Marcaccini et al.[52,53] in which the acyclic α-haloacetamide amide was prepared via utilization the Ugi four-component coupling strategy (Scheme 29). For example, *para*-chlorobenzylamine was mixed with *para*-chlorobenzaldehyde, cyclohexyl isocyanate and chloroacetic acid to provide the racemic chloroacetamide **91**. Sonication in the presence of potassium hydroxide in ethanol provided the 2,5-DKP **92** in 86% yield. Good yields in both steps were reported for the use of aliphatic and aromatic isocyanates, aliphatic amines and aromatic aldehydes.

In a report by Williams and Kwast,[54] intramolecular N_1–C_6 cyclization was achieved with simultaneous C_6-etherification for the construction of the core ring structure of



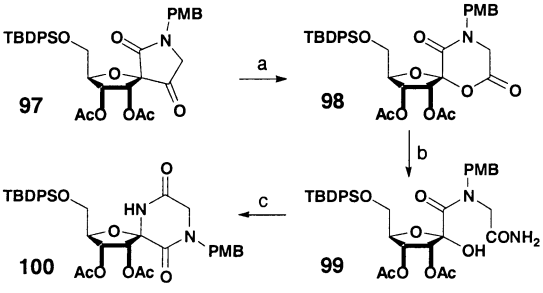
Scheme 29. *Reagents*: (a) KOH, EtOH, sonicate (86%).



Scheme 30. PMB=*para*-methoxybenzyl. *Reagents*: (a) $Cl_2CHCOCl$, K_2CO_3, DCM (88%); (b) *cis*-1,4-dihydroxy-2-butene, *t*-BuOK, THF, Δ (57%); (c) MsCl, LiCl, collidine, DMF (74%); (d) $(TMS)_2NLi$, THF, −78°C (81%).

bicyclomycin (Scheme 30). The glycinamide **93** was acylated with dichloroacetyl chloride, affording intermediate **94**. Treatment with *cis*-2-butene-1,4-diol in the presence of base gave the 2,5-DKP-aminal **95**. The allylic alcohol was converted to the corresponding chloride, then cyclized to the 2-oxa-7,9-diazabicyclo[4.2.2]deca-3-ene-8,10-dione **96** in good yield. Related bicyclic 2,5-DKPs were constructed in an analogous manner using alternative diols in the 2,5-DKP ring-forming reaction.

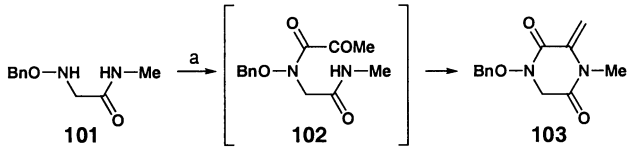
The synthesis of a spirocyclic 2,5-DKP by N_1–C_6 ring closure was reported by Paquette and co-workers.[55] Baeyer–Villager oxidation of the diacetate **97** (Scheme 31) produced the spirocyclic morpholinedione **98**. Ring opening was affected with ammonia in methanol, affording the primary amide **99**. Isomerization and cyclization–condensation in the presence of pyridinium *para*-toluenesulfonate afforded the 2,5-DKP **100** in 79% yield from **98**.



Scheme 31. *Reagents*: (a) *m*-CPBA, $NaHCO_3$, DCM (92%); (b) NH_3, MeOH, −20°C (c) PPTS, C_6H_6 (79%).

3.3. Tandem formation of N_1–C_2/C_3–N_4

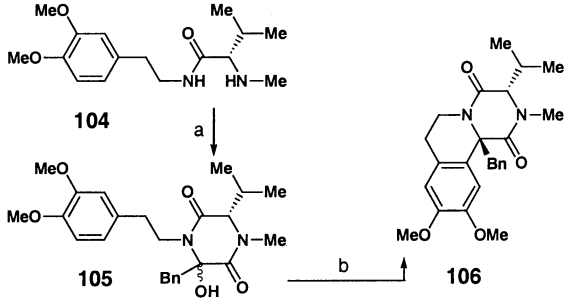
Tandem formation of the N_1–C_2 and C_3–N_4 bonds, although seldom used, is an efficient strategy that combines some of the methods used in the intramolecular cyclization approaches outlined in Sections 3.1 and 3.2. Typically, the transformation is accomplished by the reaction of an α-amino amide with a bivalent electrophile.[56,57] For example, Ottenheijm et al. reported a tandem acylation-condensation reaction of glycinamide **101** (Scheme 32) with pyruvoyl chloride in one pot, through the intermediacy of **102**, to provide the 2,5-DKP **103** in 58% yield. This same



Scheme 32. *Reagents*: (a) MeCOCOCl, Et_3N, CCl_4, then TFA (58%).

strategy was later extended to an approach to the neoechinulin family of fungal metabolites.[58] The DKP **103** and related compounds have the potential to undergo two-electron oxidation to form aromatic pyrazine-2,5-diones, offering an attractive route to their synthesis.[59]

A related acylation–condensation reaction was described by Czarnocki and co-workers (Scheme 33), who reported the diasteroselective synthesis of 1-benzyltetrahydroisoquinoline derivatives by diketopiperazine C_3,C_6-chirality transfer.[60,61] Treatment of α-amino amide **104** with phenylpyruvic acid provided the 6-hydroxy-2,5-DKP **105** as a mixture of diastereomers. Subsequent exposure to methanolic hydrogen chloride initiated an intramolecular condensation reaction to provide, as the sole diastereomer, the tricycle **106**.

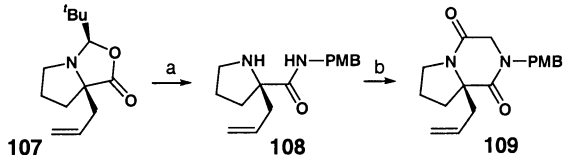


Scheme 33. *Reagents*: (a) $PhCH_2COCO_2H$, BOP, Et_3N, ACN (70%); (b) HCl, MeOH (>95%).

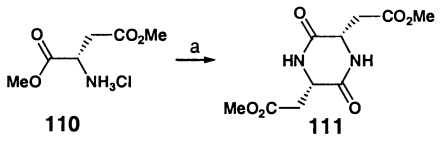
Another suitable electrophile for the single-pot α-amino amide to 2,5-DKP conversion is the α-halo acid halide. In an approach to brevianamide B by Williams and co-workers,[62] the optically active proline derivative **107**[63] (Scheme 34) was treated with lithium *para*-methoxyanilide to provide **108**. Conversion to **109** was achieved in high yield by one-pot *N*-acylation and amide alkylation of **108** with bromoacetyl bromide under basic conditions.

3.4. Tandem formation of N_1–C_2/N_4–C_5

Another tandem bond-forming strategy, in which simultaneous formation of both amide bonds of a 2,5-DKP occurs in a one-pot reaction from an α-amino ester derivative, often suffers from low yields. For example,[64] Taddei and



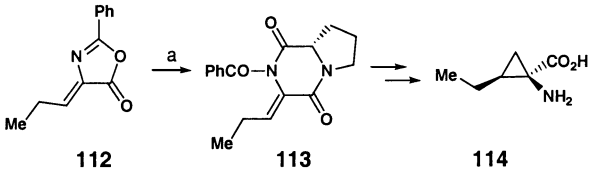
Scheme 34. PMB=*para*-methoxybenzyl. *Reagents*: (a) *p*-MeO-ArNHLi, THF (88%); (b) $BrCH_2COBr$, K_2CO_3/DCM, then NaOH, DCM (97%).



Scheme 35. *Reagents*: (a) NH_3, $CHCl_3$; workup then 65°C, 5 days (25%).

co-workers reported the dimerization of aspartic acid dimethyl ester **110** (Scheme 35) to produce the diketopiperazine **111** in 25% yield.

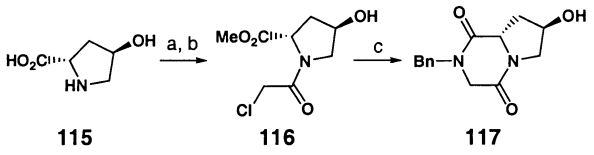
Fortunately, some modified α-amino acid derivatives are well behaved in this transformation. In a reported synthesis of (+)-allocoronamic acid (**114**, Scheme 36) by Bernabé and co-workers,[65] the oxazolone **112** was treated with (*S*)-proline under Schmidt conditions[66] to form the 2,5-DKP **113** in 50% yield. A similar approach was reported by Campbell and co-workers in a diastereoselective synthesis of cyclopropyl phenylalanines.[67]



Scheme 36. *Reagents*: (a) (*S*)-Proline, NaOH, H_2O/Me_2CO, then Ac_2O (50%).

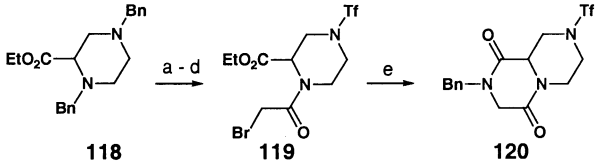
3.5. Tandem formation of $C_2–N_1–C_6$

The synthesis of 2,5-DKPs by simultaneous formation of the $N_1–C_2$ and $N_1–C_6$ bonds enables the facile introduction of N_1-substituents by the use of primary amines as reactants. A successful adaptation of this approach is the tandem acylation–alkylation of an amine with a suitable halo-ester. In a report by Tronche and co-workers,[68] hydroxyproline **115** (Scheme 37) was esterified and acylated with chloroacetyl chloride to provide the chloro ester **116**. Reaction with benzyl amine in the presence of triethylamine afforded the 2,5-dioxo-1,4-diazabicyclo[4.3.0]nonane **117** in 63% yield. Using this procedure, various aliphatic amines were introduced to the N_1-position in moderate to good yields.



Scheme 37. *Reagents*: (a) $SOCl_2$, MeOH (95%); (b) $ClCH_2COCl$, C_6H_6 (87%); (c) $BnNH_2$, Et_3N, EtOH (63%).

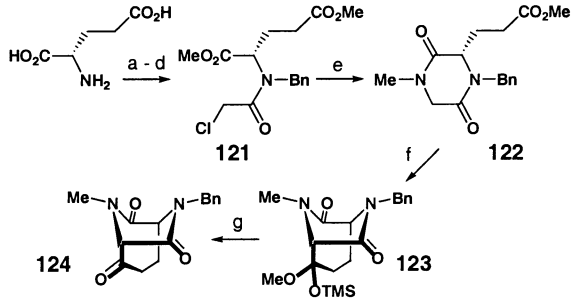
A related report by Gubert et al. utilized the α-bromoacetamide **119** to access saturated pyrazino[1,2-*a*]pyrazines (Scheme 38).[69] The *N*,*N*-dibenzylpiperazine **118** was readily converted to the cyclization substrate **119** by a series of protecting group adjustments, followed by acylation with bromoacetyl bromide. Treatment with aliphatic amines in cold ethanol afforded the octahydropyrazino[1,2-*a*]-



Scheme 38. *Reagents*: (a) MeCHClOCOCl, DCE 0°C-Δ; MeOH, Δ (70%); (b) Tf_2O, Et_3N, DCM, −78°C (94%); (c) H_2, Pd/C, AcOH, 40 psi (69%); (d) $BrCH_2COBr$, DCM/$NaHCO_3$, 0°C–rt (82%) (e) $BnNH_2$, EtOH, 0°C (46–57%).

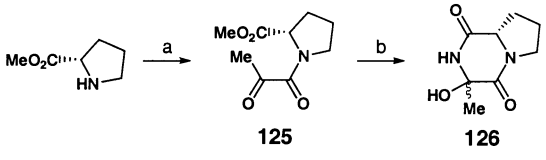
pyrazine-1,4-dione **120** in good yield. Treatment with $LiAlH_4$ in refluxing THF reduced the carbonyl groups and removed the triflate protecting group, readily providing the saturated heterocycle. By the introduction of aliphatic and aromatic amine moieties, this strategy has been used to access other bicyclic,[70] tricyclic[71] and tetracyclic[72] ring systems.

In a recent report by Weigl and Wünsch,[73] this approach was taken to prepare constrained 6,8-diazabicyclo[3.2.2]nonane derivatives (Scheme 39). From (*S*)-glutamic acid, esterification, benzylation and acylation with chloroacetyl chloride provided the 2,5-DKP precursor **121**. Reaction with methylamine provided **122** in 87% yield, and subsequent LiHMDS-induced transannular enolate acylation afforded **123** after silylation of the tetrahedral intermediate. Acidic aqueous media unmasked the ketone, providing diazabicyclo[3.2.2]nonane **124** in 82% yield from **122**.

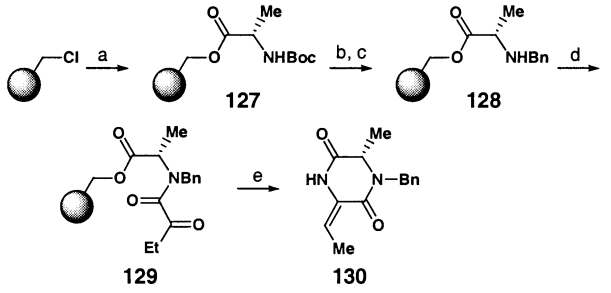


Scheme 39. *Reagents*: (a) TMSCl, MeOH; (b) PhCHO; (c) $NaBH_4$; (d) $ClCH_2COCl$; (e) $MeNH_2$ (87%); (f) LiHMDS, THF, then TMSCl; (g) TsOH, THF/H_2O (82%).

In analogy to reactions of halo-esters, keto-esters function well as electrophilic components in tandem $C_2–N_1–C_6$ bond constructions. In work directed toward brevianamides, paraherquamides and marcfortines, Sanz-Cervera et al. demonstrated the utility of a keto-ester in a tandem reaction.[74] Proline methyl ester was coupled with pyruvic acid to cleanly provide *N*-pyruvate amide **125** (Scheme 40).



Scheme 40. *Reagents*: (a) $MeCOCO_2H$, DCC, DCM (70%); (b) NH_3, DME (50%).



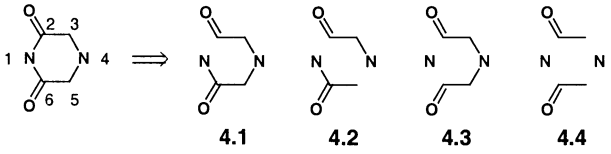
Scheme 41. *Reagents*: (a) *N*-Boc-Ala-OH, Cs_2CO_3, KI, DMF, Δ; (b) TFA, DCM; (c) PhCHO, $Na(OAc)_3BH$, AcOH, DCM; (d) $EtCOCO_2H$, DIC, DCM; (e) NH_4OAc, AcOH, toluene, Δ (53%).

Condensation with ammonia in DME provided the 6-hydroxy-2,5-DKP **126** in 50% yield.

A related method of 2,5-DKP formation adapted to solid phase synthesis has been reported by Li and Peng to facilitate the identification of potential tyrosine kinase inhibitors.[75] *O*-Alkylation of an *N*-Boc-amino acid with Merrifield chloromethyl resin provided adduct **127** (Scheme 41). Deprotection, followed by reductive alkylation with benzaldehyde, afforded the secondary amine **128**. Following amide coupling to pyruvic acid to give α-ketoamide **129**, exposure to ammonium acetate and catalytic acetic acid in refluxing toluene induced cyclization and concominant resin cleavage to afford the 2,5-DKP derivative **130** in 53% yield, based on initial loading. A library of intermediates related to **130** was converted to potential kinase inhibitor candidates.

4. 2,6-Diketopiperazines

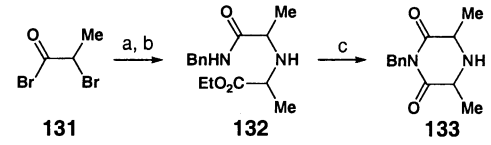
The third diketopiperazine isomer is the head-to-head cyclic dipeptide, or 2,6-DKP (Scheme 42). 2,6-DKPs have been the focus of much investigation as antiproliferative agents through the inhibition of DNA topoisomerase II.[76] As for the synthesis of the isomeric 2,5-DKPs, 2,6-DKP construction can often be tailored around the availability of amino acids as starting materials.



Scheme 42. 2,6-DKP synthesis strategies, with review section indicated.

4.1. Intramolecular formation of N_1–C_2

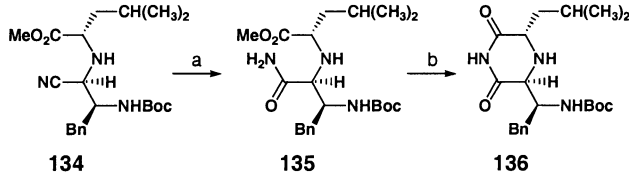
The intramolecular *N*-acylation reaction to form the N_1–C_2 bond is a common method of 2,6-DKP synthesis. Acyclic precursors generally contain a primary or secondary amide, frequently derived from a nitrile, as the nucleophilic nitrogen source and an acid (or equivalent) as the acylating group. From among the variations that have appeared in the literature, a wide array of reaction conditions for the cyclization has emerged to suit the demands of ring substitution.



Scheme 43. *Reagents*: (a) $BnNH_2$, $CHCl_3$, 0°C–rt (88%); (b) (±)-Ala-OMe, Et_3N, Tol, Δ, 18 h (65%); (c) 205°C, 3 h (85%).

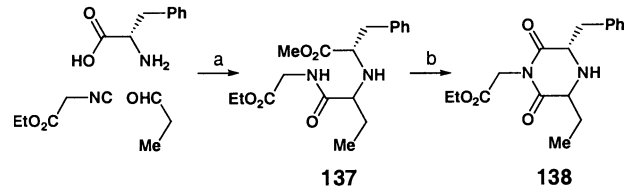
An early synthesis by Cignarella illustrates the efficiency with which one can construct the 2,6-DKP ring system by the cyclization of an amide onto an ester group.[77] The acid bromide **131** (Scheme 43) was sequentially coupled to an amine and an α-amino ester to give **132**, which was simply heated to provide the 2,6-DKP **133** in good yield.

A similar strategy was employed by Herranz et al. for the synthesis of (carbamoylmethylene)amino pseudopeptides (Scheme 44).[78] The nitrile **134**, isolated from a mixture of diastereomers prepared by a variation of the Strecker reaction, was hydrolyzed under phase transfer conditions to give primary amide **135**. Treatment with NaOH provided the corresponding 2,6-DKP **136** in high yield.

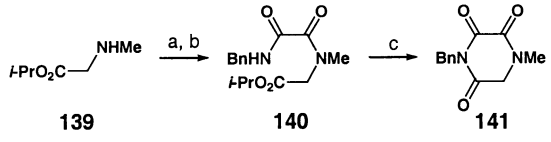


Scheme 44. *Reagents*: (a) *n*-Bu_4NHSO_4, 30% H_2O_2, DCM, 0°C; 24% NaOH, 4 h (70%); (b) 24% NaOH, *n*-Bu_4NHSO_4, 1 h (100%).

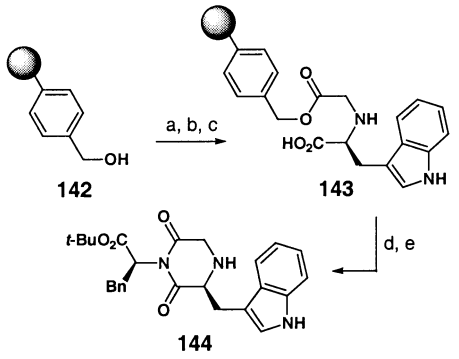
Rapid access to the 2,6-DKP cyclization precursor is enabled by utilization of the Ugi multi-component coupling strategy (Scheme 45).[79,80] An unprotected amino acid, isocyanate and an aldehyde were stored in methanol for three to fourteen days, affording the amido-ester **137**. The solvent was removed, and the residue dissolved in THF and refluxed for 3 days in the presence of base to provide the trisubstituted 2,6-DKP **138** 68% yield. When the coupling procedure was carried out using ketones instead of aldehydes, in the



Scheme 45. *Reagents*: (a) MeOH, 3–14 days, conc. in vacuo; (b) *t*-BuOK, THF, Δ, 3 days (68%).



Scheme 46. *Reagents*: (a) $ClCOCO_2Me$, Et_3N, 2:1 dioxane/DMF (56%); (b) $BnNH_2$, DMF, 130°C (87%); (c) Et_3N, MeOH, 2 days (79%).



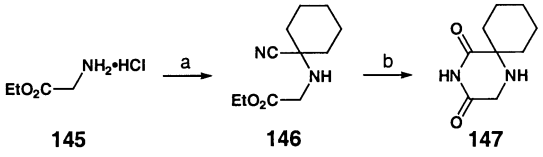
Scheme 47. *Reagents*: (a) $BrCH_2CO_2H$, DIC, DMAP, DMF, 3 h; (b) Trp-OPNB, Et_3N, DMSO, 20 h; (c) TBAF, THF, 1 h (70%); (d) Phe-O*t*-Bu, EDC, HOBt, *i*-Pr_2EtN, DMF, 16 h; (e) K_2CO_3, DMF, 70°C, 4 h (10%, 96% purity).

presence of 1 equiv. of triethylamine in refluxing methanol, 2,6-DKPs were obtained directly.

Mildly basic conditions were employed by Mulliez and Royer for the cyclization of amide–ester **140** (Scheme 46), prepared in two steps from amino ester **139**.[81] Treatment with triethylamine afforded the triketopiperazine **141** in good yield.

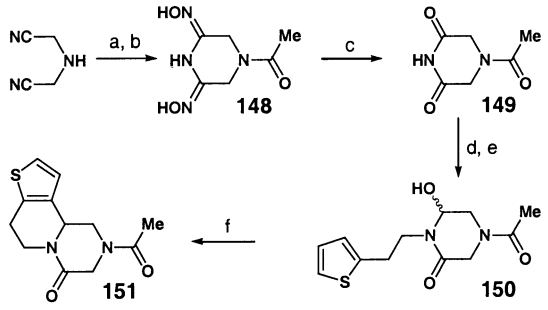
A solid phase method developed by Altamura et al. involves a resin-release cyclization strategy, analogous to reactions already described (vide supra).[82] The amino acid derivative **143** (Scheme 47), derived from the Wang resin **142**, was coupled to a second amino acid and subjected to a base-promoted cyclization-cleavage reaction to release the resin and provide the dipeptide analog **144** with negligible epimerization.

In a single pot reaction, a nitrile may be converted to the corresponding primary amide and cyclized onto an ester[83] or an amide[84,85] to form 2,6-DKPs. In an early example by Izzo and Safif,[86] the nitrile ester precursor was constructed via the Strecker reaction of amino ester **145** (Scheme 48) and cyclohexanone to give nitrile **146**. In a single subsequent step, **146** was heated in PPA to provide **147** directly. Similarly, a bis-nitrile may undergo direct conversion to a 2,6-DKP by sequential acid and base treatment.[87]

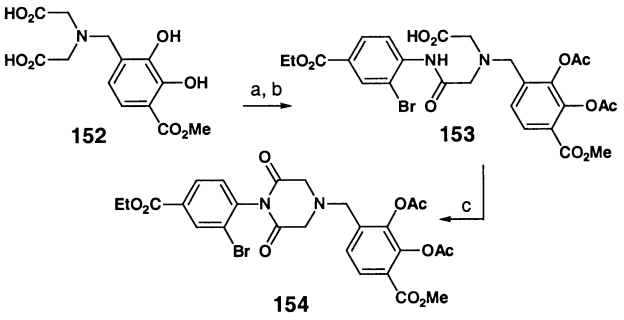


Scheme 48. *Reagents*: (a) Cyclohexanone, KCN, H_2O, MeOH; (b) PPA, 80–90°C, 45 min (66%).

In a report by Frehel and Maffrand[88] following an earlier report by Elvidge[89] (Scheme 49), iminodiacetonitrile was acylated with an acid chloride, then treated with ammonium hydroxide to produce the dioxime **148**. Treatment with sodium nitrite and acid unmasked the 2,6-DKP **149**. N_1-Alkylation and partial reduction of **145** afforded **150**, which was cyclized to produce the tricyclic product **151**.



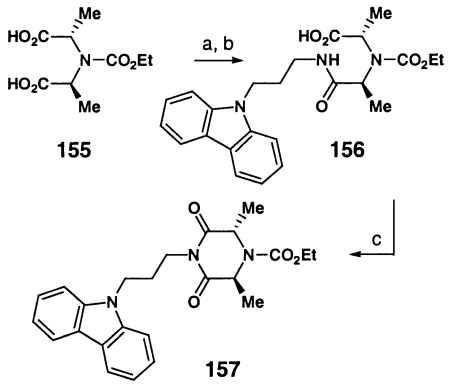
Scheme 49. *Reagents*: (a) AcCl, K_2CO_3, H_2O/DCM; (b) $NH_2OH{\cdot}HCl$, H_2O/MeOH, Δ; (c) $NaNO_2$, H_2O/AcOH, 0°C; (d) NaH, 2-thien-2-ylethyl benzenesulfonate, DMF, Δ; (e) $CuCl_2{\cdot}2H_2O$, $NaBH_4$, EtOH, 0°C; (f) 12N HCl, 0°C.



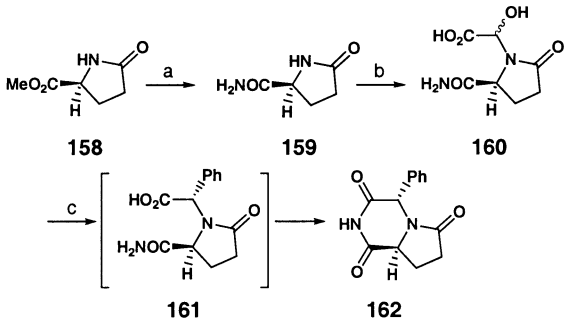
Scheme 50. *Reagents*: (a) Ac_2O, Py, 75°C, 10 h (57%); (b) $ArNH_2$, AcOH, 80°C, 4 h (70%); (c) Ac_2O, 80°C, 7 h (77%).

The cyclization of an amide onto an activated ester derived from an acid is a mild method of ring formation. 1-Aryl-2,6-DKPs were prepared by Li et al. and evaluated for antitumor activity.[90] The iminodiacetic acid **152** (Scheme 50) was converted to a cyclic anhydride and then treated with an aniline to afford amide–acid **153**. Warm acetic anhydride affected cyclization to provide the 2,6-DKP **154**, which showed potent in vitro inhibition of leukemia cell growth.

A similar synthetic pathway was developed by Harfenist et al. to prepare a neuroleptic agent (Scheme 51).[91] Dehydration of the diacid **155** to the corresponding epimerization-prone cyclic anhydride was accomplished using DCC. Subsequent aminolysis provided amide–acid **156**. While cyclodehydration using DCC resulted in epimerization, the



Scheme 51. *Reagents*: (a) DCC, THF, 1 h; (b) RNH_2, $CHCl_3$, tol, THF; (c) CDI, THF, reflux, 45 min (43%).

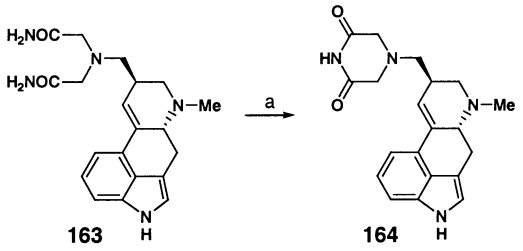


Scheme 52. *Reagents*: (a) 17% NH_3 in MeOH (84%); (b) $HCOCO_2H$, $(CH_3)_2CO$, Δ (77%); (c) C_6H_6, MsOH, 70°C, 48 h (83%).

use of 1,1′-carbonyldiimidazole proceeded smoothly to afford **157** in moderate yield.

An amidoalkylation method to access the amide–acid precursor to a 2,6-DKP was reported by Roth.[92] Methyl pyroglutamate **158** (Scheme 52) was converted to the primary carboxamide **159** by treatment with methanolic ammonia. Condensation with glycolic acid in refluxing acetone provided aminal **160** in good yield. A diastereoselective *N*-acyliminium ion-mediated electrophilic aromatic substitution of benzene in the presence of methanesulfonic acid produced intermediate **161**, which under the reaction conditions cyclized to provide bicyclic 2,6-DKP **162** in good yield.

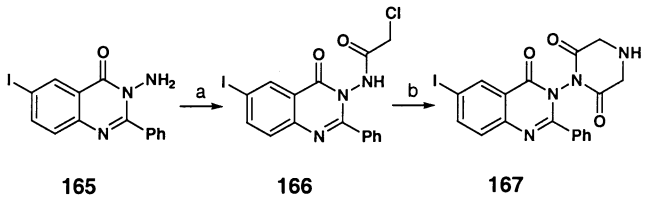
Several examples of bis-amide thermolysis to affect 2,6-DKP ring closure with liberation of an amine have been reported in the literature.[93–95] In a typical example, Mantegani et al.[93] prepared PNU 160260 (**164**, Scheme 53), a compound with activity against the D_2 receptor, by heating the di-amide **163** in phenol.



Scheme 53. *Reagents*: (a) PhOH, 160°C (63%).

4.2. Tandem formation of $N_1–C_2/N_4–C_5$

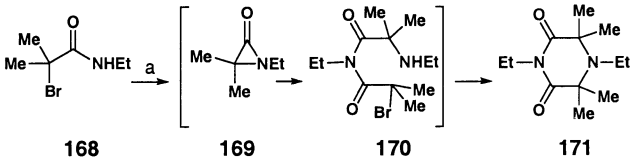
An efficient method to prepare 2,6-DKPs involves the tandem formation of the $N_1–C_2$ and $N_4–C_5$ bonds. In a



Scheme 54. *Reagents*: (a) $ClCOCH_2Cl$, DMF (83%); (b) $EtO_2CCH_2NH_2{\cdot}HCl$, C_5H_5N, Δ, 8 h (30%).

report by Abdel-Hamide directed toward the synthesis of new antimicrobial agents,[96] the 3-aminoquinazolinone **165** (Scheme 54) was acylated with chloroacetyl chloride, providing amide **166** in 83% yield. Reaction with ethylglycinate in refluxing pyridine provided the N_1-amino-2,6-DKP **167** in moderate yield.

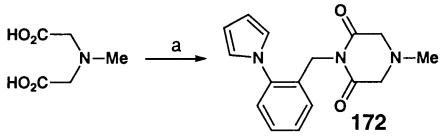
Previously, D'Angeli and co-workers reported the treatment of α-bromocarboxamide **168** (Scheme 55) with sodium hydride to produce the hexasubstituted 2,6-DKP **171**.[97] Formation of **171** was postulated to proceed through attack of aziridinone intermediate **169** by the anion of **168** to produce **170**, followed by intramolecular ring closure.



Scheme 55. *Reagents*: (a) NaH, THF.

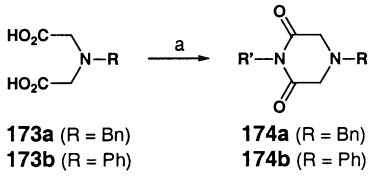
4.3. Tandem formation of $C_2–N_1–C_6$

The most common route to 2,6-DKP formation that relies on multiple bond-forming reactions involves construction of the $N_1–C_2$ and $N_1–C_6$ bonds of the imide group. Early reports focused upon elevated temperatures to drive the dehydration of diacids in the presence of various nitrogen sources, such as urea,[98] ammonia,[99] ammonium formate[100] and a primary amine.[101] In a milder procedure reported by Massa et al.[102] the synthesis of 1-substituted-2,6-DKP **172** (Scheme 56) was carried out by activation of *N*-methyliminodiacetic acid using acetic anhydride, addition of an aliphatic amine, and subsequent dehydration, again with acetic anhydride.

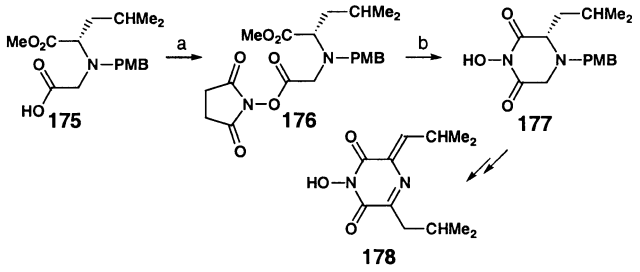


Scheme 56. *Reagents*: (a) Ac_2O, then RNH_2, then Ac_2O (54%).

Thorough evaluation of this type of process was reported by Kruse and Troost.[103] The benzyl or phenyl-substituted diacetic acids **173** (Scheme 57) were treated with primary aliphatic, aromatic and heteroaromatic amines under mild reaction conditions, using two equivalents of carbonyldiimidazole in refluxing tetrahydrofuran. Twenty five examples were reported with yields of 2,6-DKP **174** in the 63–99% range.



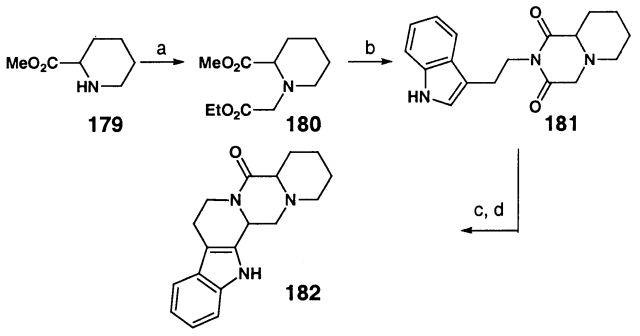
Scheme 57. *Reagents*: (a)$R'NH_2$, CDI (2 equiv.), THF or dioxane, Δ, 16 h.



Scheme 58. PMB=*para*-methoxybenzyl. *Reagents*: (a) *N*-OH-succinimide, DCC, Et_3N, DCM; (b) $NH_2OH{\cdot}HCl$, NaOH, H_2O/EtOH; 80–100°C (80% from **175**).

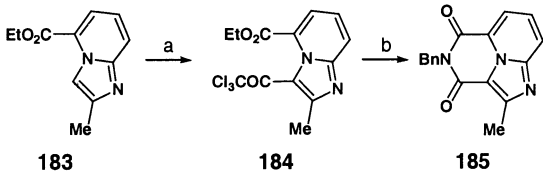
Esters also serve as useful partners in this coupling strategy. In a report by Singh,[104] the fungus-derived inhibitor of influenza A endonuclease flutimide (**178**) (Scheme 58) was synthesized starting from L-leucine methyl ester. Activation of the acid of **175** provided the *N*-hydroxysuccinimide ester **176**. Treatment with hydroxylamine provided a hydroxamide intermediate that underwent ring closure when heated to 80–100°C to provide intermediate **177** in 80% yield from **175**.

A similar strategy was employed by Valls et al. in the synthesis of the indole-based pentacycle **182** (Scheme 59).[105] Amino ester **179** was converted to the diester **180**, which was heated with tryptamine, affording the 2,6-DKP **181**. Regioselective partial reduction and cyclization provided the tetrasubstituted piperazinone **182** in good yield as a mixture of *cis* and *trans* isomers.



Scheme 59. *Reagents*: (a) $BrCH_2CO_2Et$, $NaHCO_3$, ACN, Δ (70%); (b) tryptamine, 175°C; EtOH, rt (79%); (c) $CuCl_2{\cdot}2H_2O$, $NaBH_4$, EtOH, 0°C (67%); (d) 12N HCl. 40°C (*trans* **182** 41%, *cis* **182** 33%).

In a report by Kawamoto and co-workers,[106] the 2,6-DKP-containing tricycle **185** (Scheme 60) and related derivatives were synthesized by acylation of the imidazo[1,2-*a*]pyridine **183** with trichloroacetyl chloride to produce the cyclization

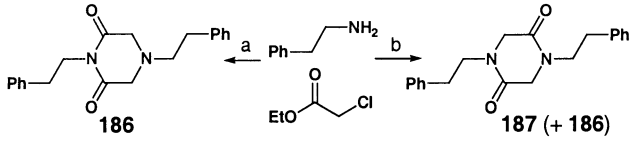


Scheme 60. *Reagents*: (a) Cl_3CCOCl, DMAP, THF, Δ, (40%); (b) $BnNH_2$, Et_3N, ACN (99%).

precursor **184**. Treatment with benzylamine at ambient temperature provided **185** in quantitative yield.

4.4. Simultaneous formation of four C–N bonds

Although arguably the most efficient mode of ring construction, a method involving simultaneous or sequential formation of all four C–N bonds in a single reaction vessel has not been developed extensively. Thus far, syntheses of non-symmetrical 2,6-DKPs have been absent from the literature. In a report by Das and Basu,[107] when equimolar amounts of phenethylamine and ethyl chloroacetate were heated in the absence of solvent, the product distributions were temperature dependent (Scheme 61). Upon heating at 170–175°C for three hours, the only isolated product, in nearly quantitative yield, was the 2,6-DKP **186**. However at 195–200°C, only a small amount of **186** was formed, and the 2,5-DKP adduct **187** was the major product.



Scheme 61. *Reagents*: (a) neat, 170–175°C, 3 h (97%); (b) neat 195–200°C, 4 h (**186** (4%), **187** (25%)).

5. Conclusion

As the need for biologically active molecules continues to grow, so does demand for new and improved methods to prepare small-ring heterocycles. A selection of versatile routes to their assembly allows the chemist to choose the bond disconnection strategy based on synthetic requirements. Diketopiperazines remain important in drug discovery because they contain constrained amino acids imbedded within their structures, without the unwanted physical and metabolic properties of peptides. In addition, recent advances in solid phase methodology have made this class of heterocycles even more attractive to combinatorial drug discovery efforts. DKPs are easily accessible, chirally enriched, naturally occurring heterocycles, whose synthesis and application to biologically relevant targets will continue with the rising demand for peptide alternatives.

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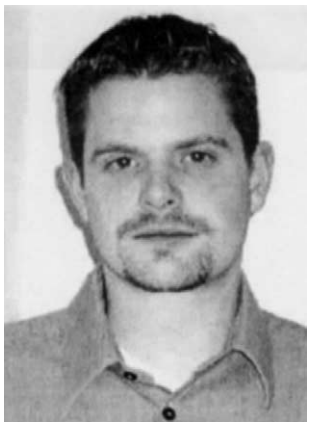
Biographical sketch

Christopher J. Dinsmore completed his undergraduate studies at Bowdoin College in 1987, then pursued doctoral studies under the direction of Thomas Hoye at the University of Minnesota, Minneapolis. In 1991 he moved to Harvard University, where he carried out postdoctoral research in the laboratory of David Evans. Since 1994, he has been a member of the Medicinal Chemistry Department at Merck Research Laboratories in West Point, Pennsylvania, where he has been associated with several drug discovery project teams.



Douglas C. Beshore was born in Camp Hill, Pennsylvania in 1975. While pursuing a Bachelor of Science in Biochemistry, he participated in the NSF-REU program at the University of Virginia in 1996. In 1997, he graduated with both collegiate and departmental honors from Albright College. Since matriculation, he has been a member of the Medicinal Chemistry Department at Merck Research Laboratories in West Point, Pennsylvania. He is concurrently pursuing doctoral studies at the University of Pennsylvania.