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Diastereoselective Synthesis of Diketopiperazine Bis-α,β-epoxides

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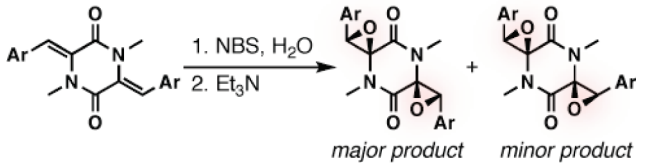

Functionalized diketopiperazines (dioxopiperazines) are an important class of molecules in medicinal chemistry and material science. Herein we report a diastereoselective synthesis of diketopiperazine bis-α,β-epoxides via the oxidation of exocyclic olefins. Although six diastereomers may be formed by this approach, only one or two of them were observed.

2,5-Diketopiperazines (also known as piperazine-2,5-diones and 2,5-dioxopiperazines) are cyclic dipeptides and part of many biologically active natural products that include polythiodiketopiperazines MPC1001s,[1,2] emestrin,[3] and bionectin[4] among others.[5] The 2,5-diketopiperazine has been an important scaffold in material science[6−8] and medicinal chemistry[9,10] and is often utilized for biological properties associated with its mimicry of peptidic pharmacophores, conformational rigidity, hydrogen bond donor and acceptor groups, and resistance to proteolysis in vivo.[11−13] The structural complexity and the promising biological activities associated with such diketopiperazines continue to inspire synthetic chemists.

While 2,5-diketopiperazine has been the subject of synthetic studies dating back to the 1900s by Emil Fischer et al.,[14] it has been studied more intensively in recent years. Typically, chiral amino acid derivatives are dimerized and cyclized, allowing for substitution at the C_3 and C_6 positions.[13,15] As a means to introduce desired substituents at the 3 and 6 positions of the 2,5-diketopiperazines, a majority of synthetic studies have been devoted to the elimination−nucleophilic attack of compounds **A** in the presence of nucleophiles, often under acidic conditions, to form **B** (Scheme 1a).[16] This approach was employed in the synthetic studies of diketopiperazine natural products,[17−21] including the landmark total synthesis by Kishi and co-workers.[22]

We became interested in alternative approaches toward functionalizing 2,5-diketopiperazines (Scheme 1b). Monoepoxide variants of **C** have been previously reported as a means to further elaborate the DKP framework.[23−25] Our group set out to establish a method for accessing bis-epoxides **C**, which we thought would serve as a precursor to more complex DKPs. Specifically, we wished to exploit the dual reactivity of bis-epoxides **C** under acidic and basic conditions to control the regioselectivity of the subsequent ring-opening. We envisioned that under acidic conditions, compounds **D** could be formed from **C** via acyliminium ion intermediates similarly to Scheme 1a. Under basic conditions, compounds **E** could be formed by nucleophilic attack at the less-hindered carbons of compounds **C**. In order to test this hypothesis, it was necessary to synthesize compounds **C**. Herein, we report a diastereoselective method to prepare a variety of bis-epoxides **C** using a two-step bromohydration−etherification pathway. As we will describe in a separate report in due course, these bis-epoxides are pivotal intermediates for complex 2,5-diketopiperazines.

The attempted condensation of piperazine-2,5-dione **1** with benzaldehyde under various conditions did not yield the corresponding aldol product **5a**, which is consistent with the literature

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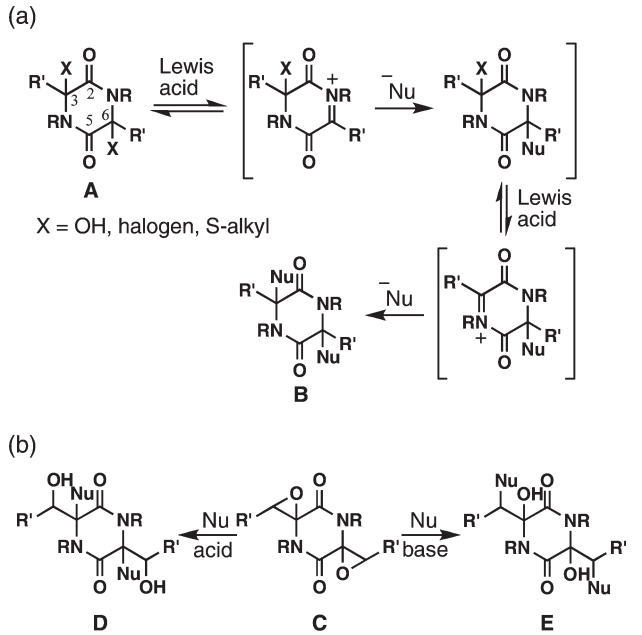
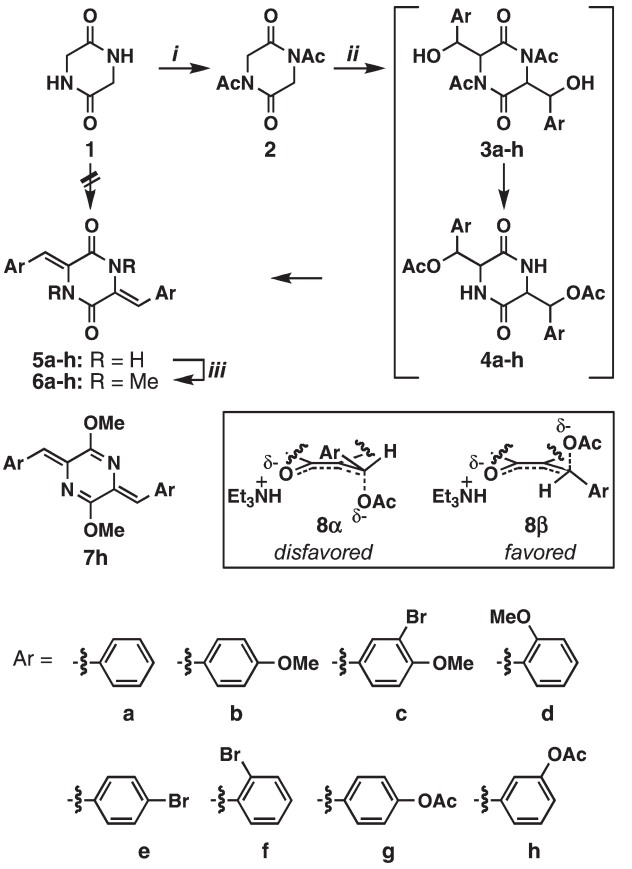
SCHEME 1. (a) Approach Employed by Others To Access Substituted Diketopiperazines; (b) Our Proposed Approach



(Scheme 2).[26] However, the *N*-acetylated derivative **2** could be coupled with benzaldehyde under basic conditions (Et_3N in DMF, 120 °C) to form alkene **5a** in 72% yield.[26] Other aromatic aldehydes also reacted smoothly to form **5b**−**h** in 52−96% yields (Table 1). The acetyl group drove the otherwise thermodynamically unfavorable aldol reaction to completion by the aldol addition−acetyl migration−elimination cascade (**2** to **5** via **3** and **4**) to form exclusively cis products as shown in Scheme 2.[26] One plausible explanation for the cis selectivity is an E1cb pathway through the transition state **8*β***. An alternative transition state, **8α**, is presumably disfavored due to the steric repulsion between the ion pair and the aromatic ring. This mechanism would mitigate an undesired stereospecific E2 pathway, accounting for high yields in some cases. As has been observed with similar diketopiperazines, the alkene intermediates **5a**−**h** were readily crystallized and exhibited extraordinarily poor solubility in a variety of protic and aprotic solvents.[27−29] This is presumably due to the combination of intermolecular hydrogen bonding and $\pi-\pi$ stacking capabilities, which promote tight crystal packing.[29,30] Due to the poor solubility, the products from this reaction were crystallized and used in the following step without ^{13}C NMR analysis.

We have been interested in the MPC1001 class of natural products, all of which are *N*-alkylated in the diketopiperazine rings.[1,2] Thus, we proceeded to methylate the secondary amides **5a**−**h** with MeI and NaH or K_2CO_3 to form the tertiary amides **6a**−**h** in 45−89% yields (Table 1).[31] The most notable

SCHEME 2. Preparation of Compounds 6a−h[a]



[a]Conditions: (i) Ac_2O (neat), reflux, 5 h, 90%; (ii) ArCHO (2.5 equiv), Et_3N (3.0 equiv), DMF, 120 °C, 7−17 h; see Table 1 for isolated yields; (iii) MeI (4.0 equiv), NaH (for **5a**−**f**) or K_2CO_3 (for **5g** and **5h**) (3.0 equiv), DMF, 25 °C, 12 h; see Table 1 for isolated yields.

TABLE 1. Isolated Yields for the Formation of Compounds 5 and 6

product	yield (%)	product	yield (%)
5a	72	**6a**	60
5b	52	**6b**	61
5c	68	**6c**	89
5d	56	**6d**	78
5e	88	**6e**	45
5f	96	**6f**	46
5g	54	**6g**	60
5h	68	**6h**	50

side products from this reaction were the result of *O*-methylation to form highly conjugated imidates, as represented by **7h**. These *O*-methylated byproducts were significantly more hydrophobic than their *N*-methylated counterparts and could be readily separated by silica gel chromatography.

With the *N*-methylated intermediates in hand, our studies continued with an examination of epoxidation conditions for the phenyl-substituted compound **6a**. The use of both nucleophilic and electrophilic reagents such as *m*-CPBA,[25] DMDO,[24] H_2O_2/NaOH, and TBHP/VO(acac)$_2$ either showed no reaction or resulted in monoepoxidation. The desired bisepoxidation could be accomplished by means of a two-step sequence involving bromohydration with NBS and H_2O, followed by epoxide ring closing of the crude bromohydrin under basic conditions (Table 2).[23] Of the six potential

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SCHEME 3. Control Experiments To Examine the Reversibility of the Two-Step Sequence: (a) Possible Bromide-Promoted Conversion of *S,S,S,R*-9a to *S,S,S,S*-9a; (b) Possible Base-Catalyzed Epimerization between *syn*-F and *anti*-F

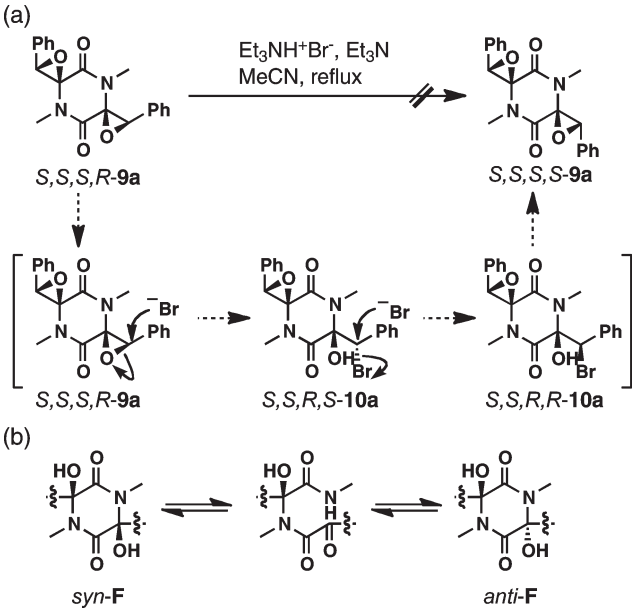
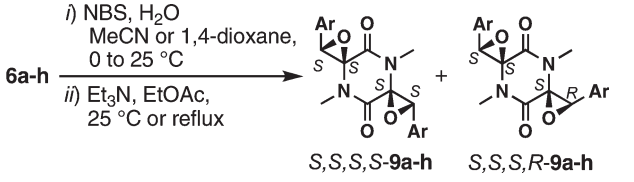


TABLE 2. Observed Diastereoselectivity in the Bis-epoxidation of 6



			yield[a] (%)	
product	solvent (step i)	temp (°C) (step ii)	*SSSS*	*SSSR*
9a	MeCN	25	34	60
9b	1,4-dioxane	25	62	< 1
9c	1,4-dioxane	reflux	56	< 1
9d	MeCN	reflux	51	< 1
9e	MeCN	25	54	24
9f[b]	MeCN	25	6	55
9g	MeCN	25	75	< 10
9h	MeCN	25	42	37

[a]Isolated yield. [b]Isolated as a mixture of *S,S,S,S*- and *S,S,S,R*-**9**.

diastereomeric epoxides (Figure 1), only two were observed for the phenyl-substituted analogue. The X-ray crystallographic analysis of these two compounds (Figures S54 and S55 in the Supporting Information) showed that they were the C_2-symmetric compound *S,S,S,S*-**9a** (and its enantiomer) and the asymmetric compound *S,S,S,R*-**9a** (and its enantiomer). The two-step epoxidation strategy was applied to the substrates shown in Table 2. For most substrates, the major product was the C_2-symmetric diastereomer *S,S,S,S*-**9** (and its enantiomer) rather than the asymmetric diastereomer *S,S,S,R*-**9** (and their enantiomers). Scheme S1 in the Supporting Information shows the compounds that did not provide the desired bis-epoxides.

The relative stereochemistry of *S,S,S,S*-**9b**−**h** was determined by ^{1}H NMR spectroscopic analysis. All of these

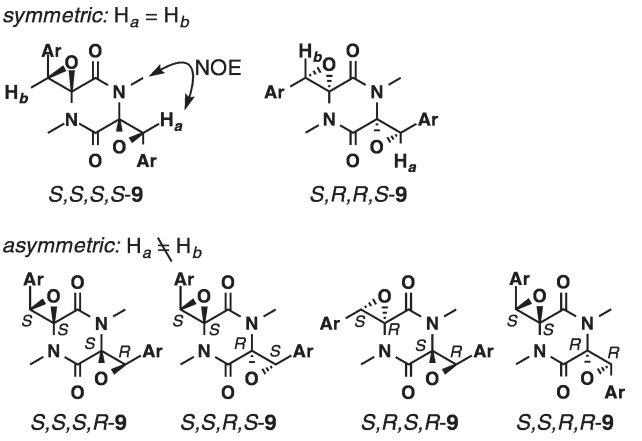


FIGURE 1. Structures of six possible bis-epoxides.

compounds showed one peak for the methine hydrogen atoms, indicating C_2 symmetry (*S,S,S,S*-**9b**−**h** or *S,R,R,S*-**9b**−**h**, Figure 1). All of these compounds also exhibited strong NOE signals between the *N*-methyl groups and methine protons, indicating the cis relationship between them. The only structures that could be consistent with these data were *S,S,S,S*-**9b**−**h**.

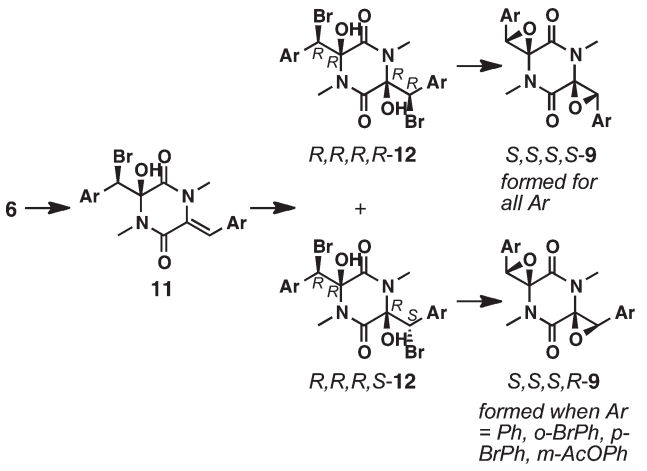
The relative stereochemistry of *S,S,S,R*-**9b**−**h** was determined in a slightly different manner. These compounds showed a significant difference on the chemical shift of the two *N*-methyl groups ($\Delta\delta$ = ~0.7 ppm in all of the cases; Table S1, Supporting Information), indicating that the two *N*-methyl groups in each compound were in different proximity to the aromatic rings. This excluded *S,R,S,R*-**9** and *S,S,R,R*-**9**. NOE experiments would not distinguish between *S,S,S,R*-**9** and *S,S,R,S*-**9**. However, the ^{1}H NMR analysis of a derivative (cf. compound **D** in Scheme 1b) of compound *S,S,S,R*-**9a** revealed that the relative stereochemistry at the two benzylic positions after epoxide opening was opposite.[32] All together, the structures that are most consistent with these spectroscopic data are *S,S,S,R*-**9b**−**h**. To further support the structures, we compared the ^{1}H NMR spectra of these compounds with that of *S,S,S,R*-**9a** (confirmed by X-ray crystallographic analysis) as shown in Table S1 (Supporting Information).

The observed diastereoselectivity clearly demonstrates that there is some steric or electronic bias directing the stereochemical outcome. Although we cannot rule out the possibility that some of the six possible diastereomers (see Scheme S2 in the Supporting Information) decomposed in a stereospecific manner, it is surprising that only one or two diastereomers were isolated. When the aromatic moieties were phenyl groups, the asymmetric compound *S,S,S,R*-**9a** was the major product (60% yield). The minor and symmetric product, *S,S,S,S*-**9a** might be more thermodynamically favored because neither of the phenyl groups is proximal to the *N*-methyl group. Therefore, with the phenyl group, the reaction might be kinetically controlled.

With a π-donor (Br or O) at the ortho or para position (compounds **6b**, **6c**, **6d**, **6e**, and **6g**), the symmetric compounds *S,S,S,S*-**9** were the major products (Table 2). This suggested that the two-step process might be reversible with these π-donors at the ortho or para position, which would

(32) Ando, S.; Koide, K. Submitted for publication.

SCHEME 4. Possible Pathways Leading to *S,S,S,S*-9 and *S,S,S,R*-9



enable isomerization from the asymmetric *S,S,S,R*-**9** to symmetric *S,S,S,S*-**9**. The reversibility appeared to stem from the enhanced reactivity of the benzylic epoxides toward $Et_3NH^+Br^-$ (Scheme 3a, S,*S,S,R*-**9a** to *S,S,R,S*-**10a** and *S,S,R,S*-**10a** to *S,S,R,R*-**10a**). To test this hypothesis, asymmetric compound *S,S,S,R*-**9a** was treated with $Et_3NH^+Br^-$ and Et_3N in refluxing MeCN. Under these conditions, no reaction appeared to take place, invalidating our hypothesis, at least when Ar = Ph.

Another mechanistic possibility was that Et_3N-catalyzed epimerizations of carbinol carbon stereocenters were involved in the stereocontrol (Scheme 3b). Thus, we treated **12a** with Ag_2O in the absence of base. In this reaction, bromide ions should be sequestered from the reaction mixture as insoluble AgBr, excluding the transformations shown in Scheme 3a. Under these conditions, *S,S,S,S*-**9a** and *S,S,S,R*-**9a** were formed in a 1:2 ratio.[33] Because the Ag_2O- and Et_3N-promoted reactions provided the two epoxides in similar ratios, the origin of diastereoselectivity using Et_3N is unlikely to involve the aforementioned epimerizations.

The preference for a syn relationship between the two hydroxy groups is a well-documented phenomenon in the synthesis of similar diketopiperazines.[18,34,35] Therefore, our working hypothesis is that syn diols are the reactive intermediates after the bromohydration step. Because S_N2 reactions are stereospecific, the origin of stereoselectivity would be the formation of bromohydrins **12** (Scheme 4). More specifically, it would be during the second bromohydration that the syn- or antirelationship between the two bromide groups would be established (**11** to **12**). Further studies are needed to thoroughly understand the origin of the diastereoselectivity in this step.

In this study, we achieved the synthesis of diketopiperazine bis-α,β-epoxides **9** in four steps from inexpensive glycine anhydride **1**. The bromohydration−cyclization sequence favored the formation of the C_2-symmetric diastereomer. Although other methods for the preparation of piperazine-2,5-diones have been reported, our route is notable for its ability to produce a variety of aromatic analogues and promises accessibility to more complex α- and β-substituted substrates. Our progress toward achieving the goal depicted in Scheme 1b will be reported in due course.

(33) See the Supporting Information for the details of this experiment.
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Experimental Section

Preparation of Compounds *S,S,S,S*-9a and *S,S,S,R*-9a (Racemic). NBS (78 mg, 0.44 mmol) was added to a suspension of compound **6a** (64 mg, 0.20 mmol) in H_2O/MeCN (2.2 mL of 1:10 mixture) while on an ice bath with stirring. The resulting mixture was then allowed to warm to 25 °C and stirred for 18 h at the same temperature. EtOAc (4.0 mL) was added to the reaction mixture, and the resulting solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture of diastereomers was used for the next step. The crude residue was dissolved in EtOAc (2.0 mL), and Et_3N (0.20 mL, 1.4 mmol) was added to the resulting mixture at 25 °C under a nitrogen atmosphere. After being stirred for 23 h at 25 °C, the reaction mixture was filtered to remove the insoluble salts. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (10−40% EtOAc in hexanes) on silica gel (12 mL) to afford compound *S,S,S,S*-**9a** (racemic mixture, 25 mg, 36%) as a white solid and compound *S,S,S,R*-**9a** (racemic mixture, 42 mg, 60%) as a colorless crystalline. To prepare samples for X-ray crystallography, compound *S,S,S,S*-**9a** (racemic) was recrystallized from EtOAc, and compound *S,S,S,R*-**9a** (racemic) was recrystallized from hexanes−EtOAc. **Data for compound *S,S,S,S*-9a (racemic):** mp = 140−142 °C; R_f = 0.29 (30% EtOAc in hexanes); IR (KBr pellet) ν_{max} = 3063, 2935, 1694 (C=O), 1455, 1429, 1378, 1271, 1167, 1072, 762, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K, Figure S23, Supporting Information) δ = 7.49−7.38 (m, 10H), 4.02 (s, 2H), 2.89 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, Figure S24, Supporting Information) δ = 160.7, 130.4, 129.1, 128.4, 126.8, 71.4, 63.0, 26.3; HRMS (EI+) calcd for $C_{20}H_{18}N_2O_4$ $[M]^+$ 350.1267, found 350.1264. **Data for compound *S,S,S,R*-9a (racemic):** mp = 179−181 °C; R_f = 0.20 (30% EtOAc in hexanes); IR (KBr pellet) ν_{max} = 3055, 2925, 2854, 1693 (C=O), 1453, 1427, 1373, 1272, 1160, 933, 877, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K, Figure S25, Supporting Information) δ = 7.57−7.52 (m, 2H), 7.43−7.38 (m, 3H), 7.21 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.07 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.02 (dd, *J* = 7.2, 7.2 Hz, 2H), 4.38 (s, 1H), 4.33 (s, 1H), 3.10 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, Figure S26, Supporting Information) δ = 164.3, 160.6, 131.1, 130.5, 129.4, 129.1, 128.8, 128.5, 127.5, 127.0, 71.8, 7.05, 62.8, 62.6, 29.7, 26.5; HRMS (EI+) calcd for $C_{20}H_{18}N_2O_4$ $[M]^+$ 350.1267, found 350.1265.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and additional figures, schemes, and X-ray crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.(33) See the Supporting Information for the details of this experiment.