JOC Article

Synthesis of 2,6-Bridged Piperazine-3-ones by *N*-Acyliminium Ion Chemistry

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Several 2-substituted and 2,5-disubstituted piperazine-3,6-diones were synthesized starting from readily available α-amino acids. After activation of a lactam carbonyl via introduction of a methoxycarbonyl group onto nitrogen, this carbonyl was selectively reduced. Treatment of the resulting urethane with protic acid generated the corresponding *N*-acyliminium ion, which was trapped by a nucleophilic C2-side chain to provide 2,6-bridged piperazine-3-ones. Several aromatic, heteroaromatic, and nonaromatic side chains were used as π-nucleophiles. In addition, the effect of the presence of a C5-methyl group on the stereochemical outcome of the cyclization was examined.

Introduction

A common structural element found in neurotransmitters such as serotonine **1** and dopamine **2** is the 2-arylethylamine moiety **3** (Chart 1). Deregulation of these neurotransmitters, usually caused by malfunctions in the central nervous system (CNS), may result in several human mood disorders such as depression and schizophrenia. The treatment of (some symptoms of) these diseases involves the blocking (by antagonists) or stimulation (by agonists) of certain neurotransmitter receptors. Many drugs and other compounds showing CNS activity such as flesinoxan (**4**)[1] and eltoprazine (**5**)[2] contain an 1-arylpiperazine moiety (viz. **6**), which acts as a conformationally restricted bioisosteric replacement of the 2-arylethylamine moiety to enhance the selectivity of the bioactivity toward specific neurotransmitters.[3]

Substituted piperazines are not only found in CNS active drugs. One example is prazosin (**7**),[4] which is used to lower blood pressure. A second example is the 1,4-disubstituted piperazine-2-one **8**, which is a dual inhibitor of farnesyl transferase/geranyl geranyltransferase I and is used as a cancer chemotherapeutic agent.[5]

Considering the importance of the piperazine scaffold in a broad range of applications, we anticipated that it might be worthwhile to rigidify the piperazine core, and thus provide potentially valuable insight into the biologically active conformation. One way to achieve an enhanced rigidity is by introducing a 2,6-bridge over the piperazine ring, thus lowering its conformational freedom.

Interestingly, the 2,6-bridged piperazine moiety is also encountered as a key structural element in several natural products (Chart 2).

Examples are the safracins,[6] ecteinascidin 743 (**9**),[7] the saframycins,[8] and quinocarcin A (**10**).[9] All of these compounds show antitumor or antibiotic activity, of which ecteinascidin 743 (**9**) is the most potent one. Remarkably, in all cases the carbon substituent at the C5-position of the piperazine moiety has a cis relationship with the 2,6-bridging substituent. In total syntheses of these natural products, the bridge was usually constructed via an *N*-acyliminium ion cyclization. A limited study of the scope of the nucleophile in such cyclizations, all lacking a C5-substituent, was reported by Kurihara and Mishima (eq 1).[10]

Using both nonactivated (**11a**) and activated benzylic side chains (**11b** and **11c**) as the nucleophile, they demonstrated that selective closure onto the C6-carbon took place to form the products **12a**−**c**; no cyclization onto the C5-carbon was observed.

In conjunction with this work, and building on *N*-acyliminium ion technology that has been previously

(1) Zuideveld, K. P.; van Gestel, A.; Peletier, L. A.; Van der Graaf, P. H.; Danhof, M. *Eur. J. Pharmacol.* **2002**, *445*, 43 and references therein.
(2) Sijbesma, H.; Schipper, J.; Dekloet, E. R. *Eur. J. Pharmacol.* **1990**, *177*, 55.
(3) Neal, N. J. *Medical pharmacology at a glance*, 2nd ed.; Blackwell Scientific Publications: Oxford, 1992.
(4) Cushman, W. C.; Materson, B. J.; Williams, D. W.; Reda, D. J. *Hypertension* **2001**, *38*, 953.
(5) Bergman, J. M.; Abrams, M. T.; Davide, J. P.; Greenberg, I. B.; Robinson, R. G.; Buser, C. A.; Huber, H. E.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Graham, S. L.; Hartman, G. D.; Williams, T. M.; Dinsmore, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1411.
(6) Saito, N.; Tachi, M.; Seki, R.; Kamayachi, H.; Kubo, A. *Chem. Pharm. Bull.* **2000**, *48*, 1549 and references therein.
(7) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993.
(8) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**, *26*, 1765.
(9) (a) Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196. (b) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *35*, 4065.
(10) Kurihara, H.; Mishima, H. *Heterocycles* **1982**, *17*, 191.

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CHART 1

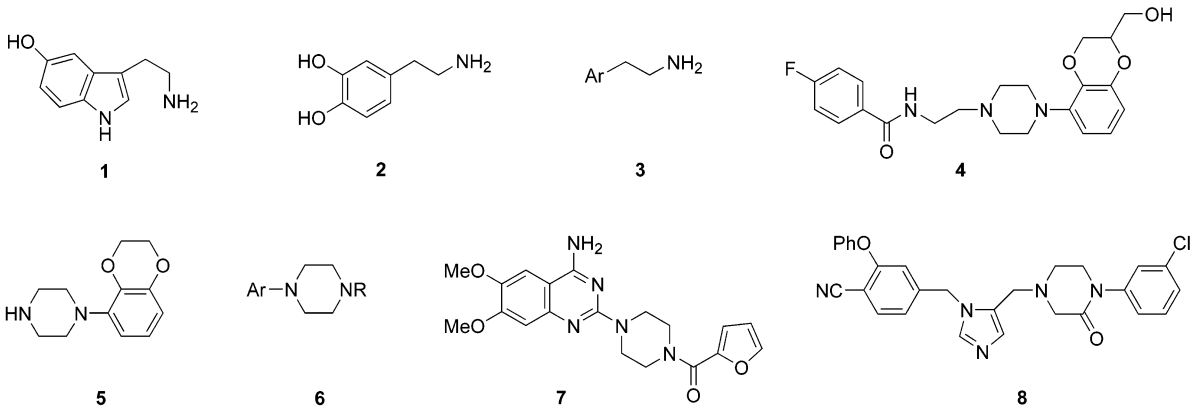
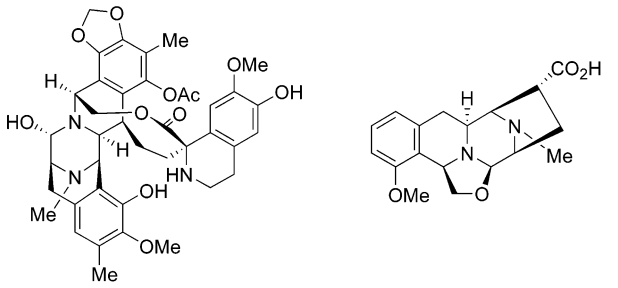


CHART 2

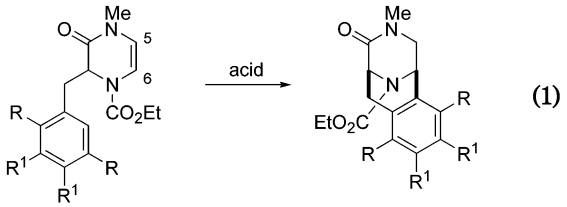


developed in our group,[11,12] we wish to report a thorough study addressing the following two issues: (i) determine the scope of π-nucleophiles in the cyclization reaction **16** → **13** and (ii) study the influence of a C5-substituent on the stereochemical outcome of the cyclization **16** → **13** (Scheme 1).[13] The key starting diketopiperazines **16** were easily obtained by straightforward condensation of the suitably protected commercially available amino acids **18** and **19** to **17** and subsequent cyclization, followed by activation of the carbonyl of the resulting secondary amide by introduction of a methoxycarbonyl group.

Results and Discussion

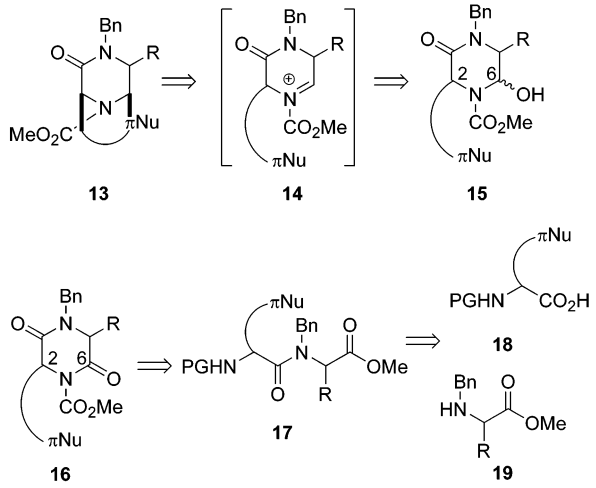
The synthesis of the required *N*-methoxycarbonyl-substituted piperazine-2,5-diones **16** (Scheme 1) started with the coupling of a benzyloxycarbonyl (Cbz)- or *tert*-butoxycarbonyl (Boc)-protected amino acid (**20a**−**f**) with *N*-benzylglycine methyl ester (**21a**) or (*S*)-*N*-benzylalanine methyl ester (**21b**). The latter compounds were both obtained via reductive amination of the corresponding amino esters with benzaldehyde (Table 1).[14]

The results are collected in Table 1. The amino acids containing an aromatic R group (**20a**−**c**) were protected



(1)

SCHEME 1. Retrosynthetic Strategy



as a benzyl carbamate. Dipeptide formation was effected using standard peptide coupling protocols. Hydrogenolytic removal of the Cbz group followed by cyclization provided the desired piperazinediones. Both the products with R^1 = H (**23a**−**c**; Table 1, entries 1−3) and R^1 = Me (**26a**,**c**; Table 1, entries 8−10) were obtained in good overall yields. The amino acids containing an unsaturated R-group (**20e**,**f**) or a benzyl protecting group (**20d**) were derivatized with a *tert*-butoxycarbonyl group and subsequently coupled with *N*-benzylglycine methyl ester.

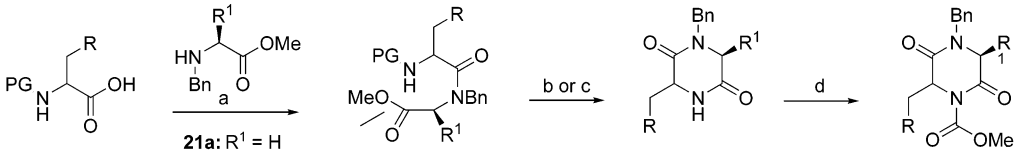
(11) For reviews, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) De Koning, H.; Speckamp, W. N. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffman, R. W., Mulzer, J.; Schaumann, E., Eds.; 1995; Vol. E21b, p 1953. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, 1047.

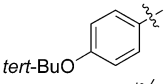
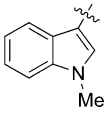
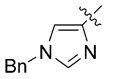
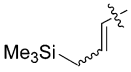
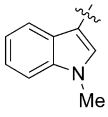
(12) For recent entries, see, e.g.: (a) Veerman, J. J. N.; Klein, J.; Aben, R. W. M.; Scheeren, J. W.; Kruse C. G.; Van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra H. *Eur. J. Org. Chem.* **2002**, 3133. (b) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317. (c) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes F. P. J. T. *Chem. Commun.* **2000**, 699. (d) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, *1127*, 7. (e) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157.

(13) Despite several attempts, intermolecular coupling of nucleophiles such as allyltrimethylsilane failed.

(14) Pikul, S.; McDow Dunham, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Fei, G.; Mieling, G. E. *J. Med. Chem.* **1999**, *42*, 87.

TABLE 1[a]



entry	substrate	PG	R	R^1	dipeptide	diketopiperazine (yield)[b]	product (yield)
1	(*S*)-**20a**	Cbz		H	**22a**	(*S*)-**23a** (76%)	(*S*)-**24a** (76%)
2	(*S*)-**20b**	Cbz		H	**22b**	(*S*)-**23b** (57%)	(*S*)-**24b** (82%)
3	(*S*)-**20c**	Cbz		H	**22c**	(*S*)-**23c** (50%)	(*S*)-**24c** (50%)
4	(*S*)-**20d**	Boc		H	**22d**	(*S*)-**23d** (84%)	(*S*)-**24d** (72%)
5	*rac*-**20e**	Boc		H	**22e**	*rac*-**23e** (64%)	*rac*-**24e** (84%)
6	*rac*-**20f**	Boc		H	**22f**	*rac*-**23f** (90%)	*rac*-**24f** (75%)
7	*rac*-**24f**			H			*rac*-**24g** (52%)[c]
8	(*R*)-**20a**	Cbz		Me	(*R,S*)-**25a**	(*R,S*)-**26a** (54%)	(*R,S*)-**27a** (38%)
9	(*S*)-**20a**	Cbz		Me	(*S,S*)-**25a**	(*S,S*)-**26a** (65%)	(*S,S*)-**27a** (62%)
10	(*S*)-**20c**	Cbz		Me	(*S,S*)-**25c**	(*S,S*)-**26c** (60%)	(*S,S*)-**27c** (40%)

[a] Reagents and conditions: (a) EDCI, HOAt, CH_2Cl_2, rt, 24 h; (b) Pd/C, H_2, EtOH, rt; (c) TFA/CH_2Cl_2 (1:1, v/v), rt, 4 h, then saturated aq $NaHCO_3$/EtOAc (1:1, v/v), rt, 20 h; (d) MeO_2CCl, NEt_3, DMAP, CH_2Cl_2, rt, 20 h. [b] Yield over two steps. [c] After cross-metathesis with allyl$SiMe_3$/Cl_2Ru=CHPh (2-(1,3-mesitylimidazolidinyl)(PCy_3) (10 mol %), toluene, 80 °C, 20 h.

The resulting dipeptides were deprotected with TFA and treated with base to afford the desired piperazinediones **23d**−**f** in good yields (Table 1, entries 4−6). Cross-metathesis of *rac*-**24f** with allyltrimethylsilane using the second-generation Grubbs catalyst[15] provided cyclization precursor *rac*-**24g** containing the nucleophilic 2-allylsilane moiety in reasonable yield as an inseparable 2:1 mixture of (*E*)/(*Z*)-isomers (Table 1, entry 7).

Introduction of the methoxycarbonyl group onto the secondary lactam nitrogen was effected using a literature procedure.[16] Although this reaction usually did not give full conversion, the products were isolated in reasonable to good yields and the remaining starting materials could be easily recovered. The yields for the alanine-derived piperazinediones (**27a**,**c**) were somewhat lower, which was probably caused by increased steric hindrance by the C5-methyl group.

With this array of substrates available, the scene was set to study the scope of the *N*-acyliminium ion cyclization reaction. The activated C6-carbonyl of piperazinedione **16** was chemoselectively reduced using sodium borohydride in methanol.[17] The resulting hydroxylactam **15** was, without further purification, treated with either formic acid or TFA to generate the reactive *N*-acyliminium ion **14**, which was trapped by the nucleophilic R-group to yield the desired 2,6-bridged-piperazine-3-ones **28**−**36**. The results are summarized in Table 2.

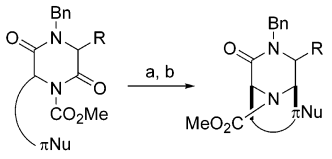
The first substrates to be cyclized were the piperazinediones with a nonactivated aromatic side chain (Table 2, entries 1 and 2). The activated amide group of (*S*)-**24a** was reduced with sodium borohydride in methanol. The resulting crude urethane was dissolved in TFA to generate the *N*-acyliminium ion intermediate. Gratifyingly, the phenyl ring smoothly cyclized to provide the 2,6-bridged 3-ketopiperazine **28** in high yield (76%) over two steps. Use of formic acid also led to formation of the

(15) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153 and references therein.

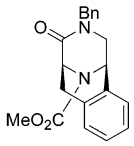
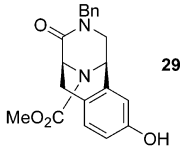
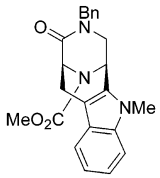
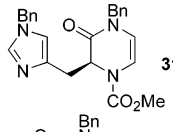
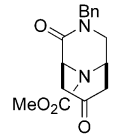
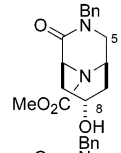
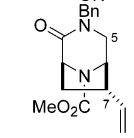
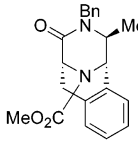
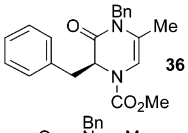
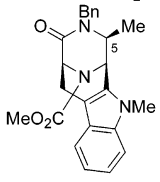
(16) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295.

(17) Lee, B. H.; Clothier, M. F. *Tetrahedron Lett.* **1999**, *40*, 643.

TABLE 2 [a]



24a-g, 27a,c **28-37**

entry	substrate	solvent	time	product (yield)
1	(*S*)-**24a**	TFA	24 h	 **28** (76%)
2	(*S*)-**24b**	TFA	72 h	 **29** (88%)
3	(*S*)-**24c**	HCO_2H	2 h	 **30** (80%)
4	(*S*)-**24d**	TFA	24 h	 **31** (77%)
5	*rac*-**24e**	HCO_2H	24 h	 **32** (17%)
6	*rac*-**24f**	HCO_2H	24 h	 [b]96% **33**[c] (50%)
7	*rac*-**24g**	HCO_2H	24 h	 **34** (64%)
8	(*R,S*)-**27a**	TFA	24 h	 **35** (74%)
9	(*S,S*)-**27a**	TFA	24 h	 **36** (60%)
10	(*S,S*)-**27c**	TFA	24 h	 **37** (71%)

[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1 h; (b) HCO_2H, rt or TFA, rt. [b] TPAP, NMO, rt, 1 h. [c] After aminolysis of the corresponding formate: NH_3, MeOH, rt, 1 h.

desired product, albeit at a much slower rate (72 h for complete conversion). A very important issue in the synthesis of the 2,6-bridged 3-ketopiperazines is the integrity of the stereocenter at the C2-position. Therefore, as a reference, compound **28** was also synthesized starting from racemic **24a**. Pleasingly, chiral HPLC analysis confirmed that no racemization had occurred at any step of the synthesis. Subjection of the tyrosine derivative (*S*)-**24b** to the same sequence resulted in the formation of O-deprotected product **29** in an even higher yield of 88%. In this case, the cyclization took 3 days to reach completion, which was probably caused by the electron-withdrawing oxygen substituent at the deactivating meta position. Next, two substrates with a heteroaromatic side chain were subjected to cyclization conditions (Table 2, entries 3 and 4). As expected, the very nucleophilic *N*-methylindole moiety of (*S*)-**24c** rapidly cyclized onto the *N*-acyliminium ion using either formic acid or TFA to give product **30** in 80% yield. Unfortunately, reduction/cyclization of the histidine-derived piperazinedione (*S*)-**24d** failed, and not even a trace of the desired tricyclic product was obtained; instead, the enamide **31** was isolated. This result can be explained by assuming protonation of the basic imidazole side chain, resulting in a deactivated nucleophile leading to elimination to the enamide. Use of the weaker formic acid or elevation of the temperature gave the same result. Finally, Lewis acid-mediated generation of the *N*-acyliminium ion was attempted, for which the corresponding urethanes were required. Unfortunately, attempts to introduce an ethoxy group on the C6-position by stirring **31** in acidic ethanol failed and only starting material was isolated.

Having studied the scope with respect to aromatic nucleophiles, some nonaromatic π-nucleophiles were examined (Table 2, entries 5 and 6). Subjection of the propargyl-substituted precursor *rac*-**24e**, after reduction of the endocyclic imide carbonyl, to formic acid treatment at room temperature did not result in the formation of ketone **32**. Elevation of the temperature to 100 °C indeed yielded some cyclized product, albeit in poor yield (17%), and together with several unidentified side products. Most likely, the acetylene moiety is too rigid to be in close proximity to the *N*-acyliminium ion. Better results were obtained using the more flexible allyl-substituted precursor *rac*-**24f**. Reduction and subsequent formic acid-induced π-cyclization led to a cationic intermediate that was trapped as the formate. Treatment of this product with ammonia in methanol provided the alcohol **33** in reasonable yield (50%) as a single diastereomer. The stereochemistry was confirmed using ^{1}H NMR: NOE enhancements were observed between H8 and H5eq of the ketopiperazine ring, the methylene of the *N*-benzyl, and the ortho protons of the *N*-benzyl substituent, respectively. When TFA was used to induce cyclization, the corresponding trifluoroacetate was formed, which upon treatment with ammonia gave some of the desired product **33**. Furthermore, elimination products were formed. Oxidation of the secondary alcohol with TPAP/NMO[18] proceeded in almost quantitative yield to provide ketone **32**, which was previously prepared by using the propargyl nucleophile (*rac*-**24e**). Reduction/cyclization of

(18) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

rac-**24g** (entry 7) afforded piperazinone **34** in fair yield (64%) as a single diastereomer. NOE enhancements were detected between H7 and H5eq, the methylene hydrogens, and the *ortho*-hydrogens of the *N*-benzyl substituent, respectively, thus proving the stereochemistry. In this case, the cyclization to a five-membered ring occurred, resulting in a further rigidified molecule.

Because the naturally occurring bridged piperazinediones usually contain a substituent at the C5-position, the effect of the introduction of a methyl group at this position on the cyclization was examined (Table 2, entries 8−10). As expected, reduction/cyclization of the trans-2,5-disubstituted piperazinedione (*R*,*S*)-**27a** (Table 2, entry 8) proceeded smoothly to give product **35**, with the C5-methyl substituent positioned trans with respect to the 2,6-bridge. Unfortunately, subjection of the cis-substituted analogue (*S*,*S*)-**27a** (Table 2, entry 9) to the same conditions resulted in elimination to enamide **36**. The steric hindrance of the *cis*-5-methyl group in combination with the weakly nucleophilic phenyl group slowed the cyclization to such an extent that elimination to the enamide **36** was favored. Elevation of the temperature to 100 °C furnished some of the enantiomer of trans-substituted piperazinone **35** in poor yield (30%). Probably, protonation of the enamide mainly took place at the C6-position, leading to a more stable, but significantly less reactive, tertiary *N*-acyliminium ion. Because the C5−C6 cis configuration is encountered in natural products, we were eager to synthesize this isomer via cationic chemistry. Analogous to the nucleophiles present in these natural products, we turned to a more nucleophilic side chain. For this purpose, precursor (*S*,*S*)-**27c** (Table 2, entry 10), containing the highly nucleophilic *N*-methylindole moiety, was subjected to the reduction/cyclization sequence. Gratifyingly, the desired all *cis*-substituted piperazinone **37** was obtained in good yield (71%). The stereochemistry was proven by the presence of a NOE-contact between the *N*-methyl group of the indole and the equatorial C5-methyl group. Because all related natural compounds combine a C5−C6 cis relationship with the presence of an electron-rich phenyl group, we assume that the biosynthetic route occurs via a cationic pathway.

Conclusions

In conclusion, a convenient route to 2,6-bridged-piperazine-3-ones was developed using an *N*-acyliminium ion cyclization as the key step. The cyclization precursors were efficiently synthesized in three steps starting from readily available amino acids as starting materials. The scope with respect to the π-nucleophilic side chain was studied. It was found that aromatic, heteroaromatic, and unsaturated α-*H*-amino acids could be used as nucleophiles in the cyclization reaction. Additionally, introduction of a methyl substituent at the C5-position of the piperazinone was possible, leading to bridged products with the same stereochemistry as found in related natural products.

Experimental Section

General Information. All reactions were carried out under an inert atmosphere of dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for transfer of air-sensitive reagents and dry solvents. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{245}) with the aforementioned solvent (mixture) unless noted otherwise. Chromatographic purification refers to flash chromatography[19] using the indicated solvent (mixture) and ACROS silica gel (particle size 35−70 μm). Infrared spectra (IR) were recorded using a Bruker IFS 28 spectrophotometer, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained using a Bruker ARX 400 (400 and 100 MHz, respectively) unless indicated otherwise. Spectra are reported in units of ppm on the δ scale. HRMS measurements were performed on a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis und Kolbe Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany. Melting points are uncorrected. Dry CH_2Cl_2 was distilled from CaH_2 and stored over MS 4 Å under a dry nitrogen atmosphere. Triethylamine was dried and distilled from KOH pellets. Reagents were purchased at highest commercial quality and used without further purification unless stated otherwise.

***N*$^{\alpha}$-Cbz-*N*^{ind}-methyl-(*S*)-tryptophan ((*S*)-20c).** To a solution of *N*^{ind}-methyl-(*S*)-tryptophan[20] (0.95 g, 4.4 mmol) and $Na_2CO_3 \cdot 10H_2O$ (2.44 g, 8.75 mmol) in water/dioxane (20 mL, 1:1, v/v) at 0 °C was added dropwise benzyl chloroformate (0.58 mL, 4.3 mmol). The temperature was allowed to warm to room temperature, and the mixture was stirred for 20 h. Then, the reaction mixture was extracted with ether (20 mL), and the resulting organic layer was extracted with 0.5 M NaOH (20 mL). The combined aqueous layers were acidified with 6 M HCl to pH 1 and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated to afford (*S*)-**20c** (1.13 g, 73%) as a light brown solid after purification by chromatography (EtOAc). R_f = 0.45. Mp = 61 °C. $[\alpha]^{21}_D$ = +20.4 (*c* 0.99, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 11.5 Hz, 1 H), 7.05−7.38 (m, 8 H), 6.89 (s, 1H), 5.11 (s, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 4.72 (br m, 1H), 3.71 (s, 3H), 3.34 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 156.0, 136.8, 136.1, 128.4, 128.2, 128.1, 128.0, 127.6, 121.7, 119.2, 118.7, 109.2, 108.0, 67.1, 54.5, 32.5, 27.4. IR (film): ν 3315, 3058, 1714. HRMS (FAB): calcd for $C_{20}H_{21}N_2O_2$ (MH^+) 353.1501, found 353.1507.

General Procedure A for Dipeptide Synthesis. To a solution of the *N*-Cbz- or *N*-Boc-protected amino acid in dry, ethanol-free CH_2Cl_2 (0.2 M) were added EDCI (1.1 equiv), HOAt (0.1 equiv), and the *N*-benzyl amino acid methyl ester (2.0 equiv). After being stirred at room temperature for 24 h, the reaction mixture was poured out on water, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were consecutively washed with 0.1 M HCl and brine and dried ($MgSO_4$), and the solvent was evaporated to yield the crude dipeptide.

General Procedure B for the Deprotection and Cyclization of the Dipeptides. To a solution of the *N*-Cbz-protected dipeptide in methanol (0.1 M) was added 10% palladium on carbon (10 mass %). The reaction mixture was stirred under an H_2 atmosphere (balloon) at room temperature until the conversion was complete (TLC). Filtration through Celite and solvent evaporation gave the virtually pure diketopiperazines.

General Procedure C for the Deprotection and Cyclization of the Dipeptides. To a solution of the *N*-Boc-protected dipeptide in CH_2Cl_2 (0.1 M) was added an equal volume of TFA. After being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo. Residual

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traces of TFA were azeotropically removed with toluene. The resulting crude product was dissolved in a mixture of saturated aqueous $NaHCO_3$/EtOAc (0.1 M, 1:1, v/v) and stirred at room temperature for 20 h. Subsequently, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to afford the virtually pure diketopiperazines.

(3*S*)-1,3-Dibenzylpiperazine-2,5-dione ((*S*)-23a). According to general procedure A, coupling of *N*-Cbz-(*S*)-phenylalanine ((*S*)-**20a**, 0.30 g, 1.0 mmol) with **21a**, followed by cyclization according to general procedure B, afforded (*S*)-**23a** (223 mg, 76%) as a white solid. $[\alpha]^{21}_D = -40$ (*c* 1.0, CH_2Cl_2). Mp = 179−181 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.12 (m, 10H), 5.98 (br s, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 4.42−4.30 (m, 1H), 3.56 (d, *J* = 17.5 Hz, 1H), 3.22 (dd, *J* = 4.3, 13.6 Hz, 1H), 3.14 (dd, *J* = 6.7, 13.6 Hz, 1H), 3.07 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 165.2, 134.8, 134.7, 130.0, 128.9, 128.7, 128.6, 128.1, 127.4, 56.4, 49.6, 48.4, 40.1. IR: 3224, 1652. HRMS (FAB): calcd for $C_{18}H_{19}N_2O_2$ (MH^+) 295.1447, found 295.1437.

(3*S*)-1-Benzyl-3-(4-*tert*-butoxybenzyl)piperazine-2,5-dione ((*S*)-23b). According to general procedure A, coupling of *N*-Cbz-(*S*)-4-*tert*-butyltyrosine dicyclohexylamine ((*S*)-**20b**, 1.13 g, 2.01 mmol) with **21a**, followed by cyclization according to general procedure B, afforded (*S*)-**23b** (0.42 g, 57%) as a white solid. $[\alpha]^{21}_D = -29$ (*c* = 1.0, CH_2Cl_2). Mp = 177−179 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35−7.19 (m, 5H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.98 (br s, 1H), 4.58 (d, *J* = 14.5 Hz, 1H), 4.39 (d, *J* = 14.5 Hz, 1H), 4.40−4.29 (m, 1H), 3.54 (d, *J* = 17.5 Hz, 1H), 3.20−3.10 (m, 2H), 3.02 (d, *J* = 17.5 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 165.4, 134.6, 130.5, 129.4, 128.7, 128.6, 127.9, 124.0, 78.4, 56.3, 49.5, 48.1, 39.7, 28.7. IR: ν 3254, 1650.

(3*S*)-1-Benzyl-3-(1-methyl-1*H*-indol-3-ylmethyl)piperazine-2,5-dione ((*S*)-23c). According to general procedure A, coupling of (*S*)-**20c** (0.31 g, 0.88 mmol) with **21a**, followed by cyclization according to general procedure B, afforded (*S*)-**23c** (0.15 g, 50%) as a white solid. $[\alpha]^{21}_D = +38.6$ (*c* 0.73, MeOH). Mp = 249 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.9 Hz, 1H), 7.33−7.10 (m, 8H), 6.91 (s, 1H), 5.84 (br s, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.39−4.33 (m, 1H), 4.27 (d, *J* = 14.5 Hz, 1H), 3.74 (s, 3H), 3.60 (d, *J* = 17.6 Hz, 1H), 3.47 (dd, *J* = 3.6, 14.5 Hz, 1H), 3.25 (d, *J* = 17.6 Hz, 1H), 3.24 (dd, *J* = 7.9, 14.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 165.5, 137.1, 135.0, 128.8, 128.5, 128.4, 128.0, 127.4, 122.2, 119.6, 119.0, 109.4, 107.6, 55.7, 49.5, 48.7, 32.8, 30.7. IR: ν 3239, 1652. HRMS (FAB): calcd for $C_{21}H_{22}N_3O_2$ (MH^+) 348.1712, found 348.1717. Aanal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.51; H, 5.96; N, 11.95.

(3*S*)-1-Benzyl-3-(1-benzyl-1*H*-imidazol-4-ylmethyl)-piperazine-2,5-dione ((*S*)-23d). According to general procedure A, coupling of (*S*)-**20d** (0.50 g, 1.44 mmol) with **21a**, followed by cyclization according to general procedure C, afforded (*S*)-**23d** (0.45 g, 84%) as a white solid. $[\alpha]^{21}_D = -1.0$ (*c* 1.0, CH_2Cl_2). Mp = 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.42 (s, 1H), 7.38−7.23 (m, 8H), 7.15−7.10 (m, 2H), 6.70 (s, 1H), 4.99 (s, 2H), 4.57 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 4.32−4.30 (m, 1H), 3.77 (d, *J* = 17.5 Hz, 1H), 3.63 (d, *J* = 17.5 Hz, 1H), 3.33 (dd, *J* = 2.8, 14.8 Hz, 1H), 2.92 (dd, *J* = 8.9, 14.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 165.2, 137.8, 135.8, 135.2, 129.0, 128.8, 128.4, 128.3, 128.0, 127.4, 117.3, 55.2, 50.9, 49.6, 49.0, 31.6. IR: ν 3230, 1678, 1653. HRMS (FAB): calcd for $C_{22}H_{23}N_4O_2$ (MH^+) 375.1821, found 375.1817. Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.46; H, 5.87; N, 14.89.

1-Benzyl-3-prop-2-ynylpiperazine-2,5-dione (*rac*-23e). According to general procedure A, coupling of *rac*-**20e** (0.90 g, 4.23 mmol)[21] with **21a**, followed by cyclization according to general procedure C, afforded *rac*-**23e** (0.65 g, 64%) as an oil after purification by chromatography (MeOH/EtOAc, 1/19). R_f = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.26 (m, 5H), 6.89 (br s, 1H), 4.76 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 4.21−4.18 (m, 1H), 3.96 (dd, *J* = 0.9, 17.8 Hz, 1H), 3.82 (dd, *J* = 0.9, 17.8 Hz, 1H), 2.84−2.81 (m, 2H), 2.02 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 164.3, 134.8, 128.9, 128.5, 128.2, 78.5, 72.6, 53.8, 49.8, 49.0, 25.2. IR: 3282, 3250, 2245, 1683, 1650. HRMS (FAB): calcd for $C_{14}H_{15}N_2O_2$ (MH^+) 243.1134, found 243.1129.

3-Allyl-1-benzylpiperazine-2,5-dione (*rac*-23f). According to general procedure A, coupling of *rac*-**20f** (1.7 g, 7.9 mmol) with **21a**, followed by cyclization according to general procedure C, afforded *rac*-**23f** (1.74 g, 90%) as a white solid after purification by chromatography (EtOAc). R_f = 0.35. Mp = 91 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40−7.23 (m, 5H), 6.43 (br s, 1H), 5.85−5.65 (m, 1H), 5.27−5.18 (m, 2H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 4.12−4.09 (m, 1H), 3.94−3.75 (m, 2H), 2.83−2.70 (m, 1H), 2.62−2.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 165.4, 135.0, 131.4, 128.7, 128.3, 128.0, 120.5, 54.5, 49.5, 48.8, 38.5. IR: 3244, 1687, 1660. HRMS (FAB): calcd for $C_{14}H_{17}N_2O_2$ (MH^+) 245.1290, found 245.1278. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.74; H, 6.68; N, 11.37.

(3*S*,6*S*)-1,3-Dibenzyl-6-methylpiperazine-2,5-dione ((*S*,*S*)-26a). According to general procedure A, coupling of (*S*)-**20a** (303 mg, 1.01 mmol) with **21b**, followed by cyclization according to general procedure B, afforded (*S*,*S*)-**26a** (203 mg, 65%) as a white solid after purification by chromatography (EtOAc). R_f = 0.31. $[\alpha]^{21}_D = -100.9$ (*c* 1.0, CH_2Cl_2). Mp = 173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.16 (m, 10 H), 6.12 (br s, 1H), 5.32 (d, *J* = 14.8 Hz, 1H), 4.35−4.31 (m, 1H), 3.92 (d, *J* = 14.8 Hz, 1H), 3.76 (q, *J* = 7.0 Hz, 1H), 3.25 (dd, *J* = 3.8, 13.6 Hz, 1H), 3.12 (dd, *J* = 7.9, 13.6 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 165.0, 135.4, 135.3, 130.0, 128.9, 128.8, 128.3, 128.0, 127.5, 57.0, 54.1, 46.9, 41.3, 18.2. IR: ν 3230, 1682, 1654. HRMS (FAB): calcd for $C_{19}H_{21}N_2O_2$ (MH^+) 309.1603, found 309.1605. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.93; H, 6.57; N, 9.02.

(3*R*,6*S*)-1,3-Dibenzyl-6-methylpiperazine-2,5-dione ((*R*,*S*)-26a). According to general procedure A, coupling of (*R*)-**20a** (301 mg, 1.0 mmol) with **21b**, followed by cyclization according to general procedure B, afforded (*R*,*S*)-**26a** (166 mg, 54%) as a white solid after purification by chromatography (EtOAc). R_f = 0.36. $[\alpha]^{21}_D = +54.6$ (*c* 1.0, CH_2Cl_2). Mp = 116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.14 (m, 10H), 5.94 (br s, 1H), 5.24 (d, *J* = 14.9 Hz, 1H), 4.32−4.28 (m, 1H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.75 (q, *J* = 7.0 Hz, 1H), 3.58 (dd, *J* = 3.6, 14.1 Hz, 1H), 2.96 (dd, *J* = 9.4, 14.1 Hz, 1H), 1.41 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 165.7, 135.6, 129.5, 129.2, 128.9, 128.0, 127.9, 127.5, 55.2, 54.9, 47.4, 38.7, 17.6. IR: ν 3223, 1682, 1660. HRMS (FAB): calcd for $C_{19}H_{21}N_2O_2$ (MH^+) 309.1603, found 309.1605. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.84; H, 6.68; N, 8.95.

(3*S*,6*S*)-1-Benzyl-6-methyl-3-(1-methyl-1*H*-indol-3-ylmethyl)piperazine-2,5-dione ((*S*,*S*)-26c). According to general procedure A, coupling of (*S*)-**20c** (409 mg, 1.16 mmol) with **21b**, followed by cyclization according to general procedure B, afforded (*S*,*S*)-**26c** (250 mg, 60%) as a white solid after purification by chromatography (EtOAc). R_f = 0.35. $[\alpha]^{21}_D = -84.5$ (*c* 0.78, CH_2Cl_2). Mp = 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.32−7.12 (m, 8H), 6.94 (s, 1H), 6.76 (br s, 1H), 5.27 (d, *J* = 14.9 Hz, 1H), 4.36−4.32

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(m, 1H), 3.85 (d, J = 14.9 Hz, 1H), 3.74 (q, J = 7.0 Hz, 1H), 3.73 (s, 3H), 3.41 (dd, J = 3.7, 14.5 Hz, 1H), 3.28 (dd, J = 7.7, 14.5 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 165.6, 137.0, 135.5, 128.8, 128.4, 128.2, 127.9, 127.6, 122.0, 119.5, 119.1, 109.3, 108.0, 56.5, 54.1, 32.6, 31.5, 18.1. IR: ν 3229, 1683, 1654. HRMS (FAB): calcd for $C_{22}H_{22}N_3O_2$ (MH^+) 362.1869, found 362.1871.

General Procedure D for Carbamate Protection of Diketopiperazines. To a solution of the diketopiperazine, DMAP (2 equiv), and triethylamine (2 equiv) in dry, ethanol-free CH_2Cl_2 (0.5 M) at 0 °C was added dropwise methyl chloroformate (4 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The organic layer was washed with 1 M HCl and brine, dried ($MgSO_4$), and evaporated to give the protected diketopiperazine.

(2*S*)-2,4-Dibenzyl-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*)-24a). According to general procedure D, protection of (*S*)-**23a** (0.21 g, 0.71 mmol) afforded (*S*)-**24a** (0.19 g, 76%) as a white amorphous solid after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.30. $[\alpha]^{21}_D$ = +96 (*c* 1.0, CH_2Cl_2). Mp = 115−117 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31−6.89 (m, 10H), 5.19−5.09 (m, 1H), 4.40 (br s, 2H), 3.88 (s, 3H), 3.35 (d, J = 18.3 Hz, 1H), 3.32 (dd, J = 3.6, 13.9 Hz, 1H), 3.22 (dd, J = 4.8, 13.9 Hz, 1H), 2.17 (d, J = 18.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3, 164.4, 152.5, 134.1, 134.0, 130.1, 128.9, 128.6, 128.5, 128.0, 127.5, 60.0, 54.3, 49.3, 49.1, 38.7. HRMS (FAB): calcd for $C_{20}H_{21}N_2O_4$ (MH^+) 353.1501, found 353.1506.

(2*S*)-4-Benzyl-2-(4-*tert*-butoxybenzyl)-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*)-24b). According to general procedure D, protection of (*S*)-**23b** (0.27 g, 0.74 mmol) afforded (*S*)-**24b** (0.26 g, 82%) as a clear oil after purification by chromatography (PE/EtOAc, 2/3). R_f = 0.47. $[\alpha]^{21}_D$ = +87 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29−7.14 (m, 5H), 6.82 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 5.10−4.99 (m, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.31 (d, J = 14.3 Hz, 1H), 3.86 (s, 3H), 3.35 (d, J = 18.2 Hz, 1H), 3.27 (dd, J = 3.4, 16.0 Hz, 1H), 3.16 (dd, J = 4.8, 16.0 Hz, 1H), 2.19 (d, J = 18.2 Hz, 1H), 1.21 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.5, 164.3, 154.9, 152.5, 134.3, 130.7, 128.9, 128.8, 128.6, 128.1, 124.1, 78.3, 60.1, 54.7, 49.3, 49.1, 38.0, 28.6.

(2*S*)-4-Benzyl-2-(1-methyl-1*H*-indol-3-ylmethyl)-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*)-24c). According to general procedure D, protection of (*S*)-**23c** (100 mg, 0.29 mmol) afforded (*S*)-**24c** (59 mg, 50%) as a white solid after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.23. $[\alpha]^{21}_D$ = +107.5 (*c* 1.0, CH_2Cl_2). Mp = 147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.9 Hz, 1H), 7.29−7.13 (m, 6H), 7.00−6.96 (m, 2H), 6.72 (s, 1H), 5.15−5.13 (m, 1H), 4.80 (d, J = 14.6 Hz, 1H), 3.92 (s, 3H), 3.66 (s, 3H), 3.65 (dd, J = 2.9, 15.1 Hz, 1H), 3.41 (dd, J = 4.9, 15.1 Hz, 1H), 3.36 (d, J = 14.6 Hz, 1H), 3.22 (d, J = 18.3 Hz, 1H), 2.06 (d, J = 18.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 165.0, 152.7, 136.9, 134.4, 129.6, 128.7, 128.5, 128.0, 127.5, 122.2, 119.7, 119.1, 109.3, 106.3, 54.4, 49.3, 48.8, 32.7, 28.8. IR: ν 1781, 1730, 1667. HRMS (FAB): calcd for $C_{23}H_{24}N_3O_2$ (MH^+) 406.1767, found 406.1771.

(2*S*)-4-Benzyl-2-(1-benzyl-1*H*-imidazol-4-ylmethyl)-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*)-24d). According to general procedure D, protection of (*S*)-**23d** (253 mg, 0.63 mmol) afforded (*S*)-**24d** (159 mg, 72%) as a white solid after purification by chromatography (MeOH/EtOAc, 1/20). R_f = 0.21. $[\alpha]^{21}_D$ = +16.6 (*c* 1.0, CH_2Cl_2). Mp = 58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 9H), 7.11−7.08 (m, 2H), 6.59 (d, J = 1.1 Hz, 1H), 5.08 (dd, J = 3.7, 5.2 Hz, 1H), 4.91 (d, J = 15.1 Hz, 1H), 4.87 (d, J = 15.1 Hz, 1H), 4.51 (d, J = 14.5 Hz, 1H), 4.24 (d, J = 14.5 Hz, 1H), 3.87 (s, 3H), 3.50 (d, J = 18.2 Hz, 1H), 3.31 (dd, J = 3.7, 14.8 Hz, 1H), 3.21 (dd, J = 5.2, 14.8 Hz, 1H), 2.84 (d, J = 18.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 165.2, 152.7, 136.1, 135.9, 134.8, 129.0, 128.8, 128.7, 128.4, 128.0, 127.3, 118.4, 59.4, 54.3, 50.8, 49.9, 48.9, 31.4. IR: ν 1781, 1729, 1667, 1268. HRMS (FAB): calcd for $C_{24}H_{25}N_4O_4$ (MH^+) 433.1876, found 433.1861.

4-Benzyl-3,6-dioxo-2-prop-2-ynylpiperazine-1-carboxylic Acid Methyl Ester (*rac*-24e). According to general procedure D, protection of *rac*-**23e** (0.64 g, 2.64 mmol) afforded *rac*-**24e** (0.66 g, 84%) as a clear sticky oil after purification by chromatography (Et_2O). R_f = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.29 (m, 5H), 4.89 (t, J = 4.1 Hz, 1H), 4.86 (d, J = 14.5 Hz, 1H), 4.41 (d, J = 14.5 Hz, 1H), 4.28 (d, J = 18.4 Hz, 1H), 3.92 (s, 3H), 3.86 (d, J = 18.4 Hz, 1H), 3.06−3.03 (m, 2H), 1.91 (t, J = 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 164.4, 152.7, 134.5, 128.9, 128.6, 128.3, 78.1, 73.3, 57.3, 54.6, 50.8, 49.4, 24.0. IR (film): 3285, 2250, 1718, 1655. HRMS (FAB): calcd for $C_{16}H_{17}N_2O_4$ (MH^+) 301.1188, found 301.1183.

2-Allyl-4-benzyl-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester (*rac*-24f). According to general procedure D, protection of *rac*-**23f** (0.43 g, 1.77 mmol) afforded *rac*-**24f** (0.40 g, 75%) as a clear sticky oil after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.22 (m, 5H), 5.77−5.67 (m, 1H), 5.16−5.09 (m, 2H), 4.96 (t, J = 3.9 Hz, 1H), 4.80 (d, J = 14.4 Hz, 1H), 4.37 (d, J = 14.4 Hz, 1H), 3.98 (d, J = 18.5 Hz, 1H), 3.90 (s, 3H), 3.84 (d, J = 18.5 Hz, 1H), 2.72−2.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 164.6, 152.5, 134.8, 130.8, 129.0, 128.5, 128.3, 121.0, 58.7, 54.4, 50.5, 49.3, 37.7. IR: 1783, 1731, 1671, 1275. HRMS (FAB): calcd for $C_{16}H_{19}N_2O_4$ (MH^+) 303.1345, found 303.1344.

((*E*)/(*Z*))-4-Benzyl-3,6-dioxo-2-(4-trimethylsilanylbut-2-enyl)piperazine-1-carboxylic Acid Methyl Ester (*rac*-24g). To solution of *rac*-**24f** (211 mg, 0.7 mmol) and allyltrimethylsilane (0.33 mL, 2.1 mmol) in dry toluene (15 mL) under argon, Ru-catalyst (59 mg, 70 μmol) was added and the reaction mixture was stirred at 80 °C for 20 h. Concentration of the reaction mixture and further purification by chromatography (PE/EtOAc, 1.2/1 → 1/1) afforded *rac*-**24g** (141 mg, 52%) as an oil. R_f = 0.40 (PE/EtOAc, 1.2/1). ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C, 3:1 mixture): δ 7.40−7.25 (m, 5H), 5.96−5.90 (m, 0.25H), 5.83−5.78 (m, 0.25H), 5.55−5.48 (m, 0.75H), 5.24−5.11 (m, 0.75H), 4.80−4.63 (m, 2H), 4.43−4.37 (m, 1H), 4.18−4.10 (m, 1H), 4.02−3.94 (m, 1H), 3.81 (s, 3H), 2.75−2.55 (m, 2H), 1.45−1.25 (m, 2H), 0.02 (s, 2.25H), −0.04 (s, 6.75H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C, 3:1 mixture): δ 164.9, 164.7, 163.7, 163.6, 151.8, 151.7, 139.2, 135.5, 131.2, 129.5, 128.1, 128.0, 127.5, 127.5, 127.1, 127.0, 120.9, 119.5, 58.6, 58.4, 57.9, 53.2, 50.0, 49.9, 48.0, 47.9, 35.4, 29.6, 21.9, 17.6, −2.1, −2.5. IR: ν 2953, 1783, 1731, 1668, 1271. HRMS (FAB): calcd for $C_{20}H_{29}N_2O_4Si$ (MH^+) 389.1897, found 389.1876.

(2*S*,5*S*)-2,4-Dibenzyl-5-methyl-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*,*S*)-27a). According to general procedure D, protection of (*S*,*S*)-**26a** (192 mg, 0.62 mmol) afforded (*S*,*S*)-**27a** (140 mg, 62%) as a colorless oil after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.42. $[\alpha]^{21}_D$ = +17.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.15 (m, 10H), 5.30 (d, J = 14.8 Hz, 1H), 5.16 (t, J = 5.3 Hz, 1H), 3.86 (q, J = 7.1 Hz, 1H), 3.83, (d, J = 14.8 Hz, 1H), 3.82 (s, 3H), 3.35 (dd, J = 5.3, 14.0 Hz, 1H), 3.29 (dd, J = 5.1, 14.0 Hz, 1H), 0.74 (d, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.4, 164.6, 135.1, 135.0, 130.4, 128.9, 128.8, 128.4, 128.1, 127.6, 60.2, 55.5, 54.4, 46.5, 39.6, 17.4. IR (film): ν 1781, 1730, 1660, 1256. HRMS (FAB): calcd for $C_{21}H_{23}N_2O_4$ (MH^+) 367.1658, found 367.1639.

(2*R*,5*S*)-2,4-Dibenzyl-5-methyl-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*R*,*S*)-27a). According to general procedure D, protection of (*R*,*S*)-**26a** (240 mg, 0.78 mmol) afforded (*R*,*S*)-**27a** (108 mg, 38%) as a colorless oil after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.41. $[\alpha]^{21}_D$ = −94.6 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.03 (m, 10H), 5.16 (t, J = 4.5 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.30 (d, J = 15.2 Hz, 1H), 3.90 (s, 3H), 3.38 (dd, J = 4.2, 14.0 Hz, 1H), 3.32 (dd, J = 4.8, 14.0 Hz, 1H), 2.88 (q, J = 7.0 Hz, 1H), 1.37 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 166.3, 152.9, 135.7, 134.4, 130.4, 128.7, 128.6,

128.0, 127.7, 127.6, 59.8, 55.2, 54.4, 46.6, 39.0, 18.3. IR (film): ν 1782, 1730, 1661, 1271. HRMS (FAB): calcd for $C_{21}H_{23}N_2O_4$ (MH^+) 367.1658, found 367.1659.

(2*S*,5*S*)-4-Benzyl-5-methyl-2-(1-methyl-1*H*-indol-3-ylmethyl)-3,6-dioxopiperazine-1-carboxylic Acid Methyl Ester ((*S*,*S*)-27c). According to general procedure D, protection of (*S*,*S*)-**26c** (250 mg, 0.69 mmol) afforded (*S*,*S*)-**27c** (116 mg, 40%) as a white solid after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.25. $[\alpha]^{21}_D$ = −84.5 (*c* 0.78, CH_2Cl_2). Mp = 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.29−7.11 (m, 8H), 6.85 (s, 1H), 5.27 (d, *J* = 14.9 Hz, 1H), 5.18 (t, *J* = 4.7 Hz, 1H), 3.77 (s, 3H), 3.74 (q, *J* = 7.1 Hz, 1H), 3.71 (s, 3H), 3.60 (dd, *J* = 4.5, 14.9 Hz, 1H), 3.56 (d, *J* = 14.9 Hz, 1H), 3.44 (dd, *J* = 4.9, 14.9 Hz, 1H), 0.44 (d, *J* = 7.1 Hz, 3H). IR (film): ν 1779, 1729, 1659, 1255. HRMS (FAB): calcd for $C_{24}H_{26}N_3O_4$ (MH^+) 420.1923, found 420.1921.

General Procedure E for Reduction/Cyclization. To a solution of the methoxycarbonyl-protected diketopiperazine in MeOH (0.1 M) at 0 °C was added sodium borohydride (3 equiv) in portions. After being stirred for 1 h, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to yield the crude *N*,*O*-acetal. This crude product was dissolved in TFA or formic acid (0.05 M) and stirred at room temperature. The solvent was evaporated, and residual traces of acid were azeotropically removed with toluene to yield the crude products.

(1*S*,9*S*)-11-Benzyl-10-oxo-11,13-diazatricyclo[7.3.1.0^{2,7}]-trideca-2(7),4,6-triene-13-carboxylic Acid Methyl Ester (28). According to general procedure E, reduction/cyclization of (*S*)-**24a** (62.0 mg, 176 μmol) afforded **28** (45 mg, 76%) as an amorphous white solid after purification by chromatography (PE/EtOAc, 2/3). R_f = 0.45. $[\alpha]^{21}_D$ = −21 (*c* 0.5, CH_2Cl_2). Mp = 109−111 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.28−7.05 (m, 7H), 6.70 (d, *J* = 7.3 Hz, 2H), 5.37 (d, *J* = 3.9 Hz, 1H), 4.82 (d, *J* = 5.9 Hz, 1H), 4.71 (d, *J* = 15.1 Hz, 1H), 4.17 (d, *J* = 15.1 Hz, 1H), 3.84 (dd, *J* = 4.4, 12.0 Hz, 1H), 3.70 (s, 3H), 3.23 (dd, *J* = 6.1, 16.4 Hz, 1H), 3.16 (d, *J* = 12.0 Hz, 1H), 3.06 (d, *J* = 16.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C): δ 166.7, 153.4, 135.8, 134.1, 132.2, 128.3, 127.7, 127.1, 126.3, 126.3, 126.2, 126.0, 53.2, 52.5, 52.2, 48.9, 47.9, 31.6. IR: ν 2922, 2359, 1703, 1637. HRMS (FAB): calcd for $C_{20}H_{21}N_2O_3$ (MH^+) 337.1552, found 337.1559.

(1*S*,9*S*)-11-Benzyl-4-hydroxy-10-oxo-11,13-diazatricyclo-[7.3.1.0^{2,7}]trideca-2(7),4,6-triene-13-carboxylic Acid Methyl Ester (29). According to general procedure E, reduction/cyclization of (*S*)-**24b** (257 mg, 600 μmol) afforded **29** (185 mg, 88%) as an amorphous white solid after purification by chromatography (PE/EtOAc, 1/2). R_f = 0.32. $[\alpha]^{21}_D$ = −26 (*c* 0.5, CH_2Cl_2). Mp = 112−114 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 8.93 (br s, 1H), 7.16−7.09 (m, 3H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.78−6.71 (m, 3H), 6.62 (d, *J* = 2.2 Hz, 1H), 5.26 (d, *J* = 4.2 Hz, 1H), 4.79 (d, *J* = 5.9 Hz, 1H), 4.70 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.4 Hz, 1H), 3.80 (dd, *J* = 4.4, 12.2 Hz, 1H), 3.69 (s, 3H), 3.14 (d, *J* = 12.0 Hz, 1H), 3.10 (dd, *J* = 6.1, 16.1 Hz, 1H), 2.94 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C): δ 166.9, 155.6, 153.4, 135.9, 134.9, 129.1, 127.7, 126.3, 126.2, 122.2, 115.0, 112.6, 53.2, 52.8, 52.1, 49.0, 47.9, 30.7. IR: ν 3309, 2926, 1708, 1635. HRMS (FAB): calcd for $C_{20}H_{21}N_2O_4$ (MH^+) 353.1501, found 353.1519.

Cyclization Product 30. According to general procedure E, reduction/cyclization of (*S*)-**24c** (26 mg, 60 μmol) afforded **30** (20 mg, 80%) as an amorphous white solid after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.24. $[\alpha]^{21}_D$ = +19.7 (*c* 0.35, CH_2Cl_2). Mp = 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 150 °C): δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.24−7.20 (m, 1H), 7.12−7.06 (m, 2H), 6.93−6.89 (m, 2H), 6.69 (d, *J* = 7.6 Hz, 2H), 5.62−5.60 (m, 1H), 4.96−4.95 (m, 1H), 4.78 (d, *J* = 15.1 Hz, 1H), 4.22 (d, *J* = 15.1 Hz, 1H), 3.92 (dd, *J* = 4.2, 12.4 Hz, 1H), 3.76 (s, 3H), 3.53 (s, 3H), 3.28 (d, *J* = 12.4 Hz, 1H), 3.17−3.15 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 150 °C): δ 166.9, 153.2, 136.8, 135.8, 131.3, 127.2, 126.1, 126.0, 125.3, 120.9, 118.4, 117.1, 108.6, 106.8, 53.1, 51.8, 50.0, 47.8, 44.7, 28.4, 25.0. IR: ν 1706, 1651. HRMS (FAB): calcd for $C_{23}H_{24}N_3O_3$ (MH^+) 390.1818, found 390.1815.

(2*S*)-4-Benzyl-2-(1-benzyl-1*H*-imidazol-4-ylmethyl)-3-oxo-3,4-dihydro-2*H*-pyrazine-1-carboxylic Acid Methyl Ester (31). According to general procedure E, reduction/cyclization of (*S*)-**24d** (156 mg, 0.36 mmol), followed by aqueous basic workup, afforded **31** (115 mg, 77%) as an amorphous white solid after purification by chromatography (MeOH/EtOAc, 1/10). R_f = 0.40. $[\alpha]^{21}_D$ = +5.3 (*c* 0.33, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6, 150 °C): δ 7.54 (s, 1H), 7.39−7.20 (m, 10H), 6.79 (s, 1H), 6.18 (d, *J* = 6.0 Hz, 1H), 5.69 (d, *J* = 6.0 Hz, 1H), 5.12 (s, 2H), 4.88 (t, *J* = 8.8 Hz, 1H), 4.67 (d, *J* = 12.9 Hz, 1H), 4.61 (d, *J* = 12.9 Hz, 1H), 3.60 (s, 3H), 2.88 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 150 °C): δ 163.4, 152.2, 136.8, 136.4, 136.1, 135.4, 128.0, 127.9, 127.1, 126.8, 126.7, 116.9, 112.5, 107.8, 56.9, 52.1, 49.3, 47.9, 28.0. IR: 1713, 1679, 1445. HRMS (FAB): calcd for $C_{24}H_{25}N_4O_3$ (MH^+) 417.1927, found 417.1924.

3-Benzyl-2,7-dioxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylic Acid Methyl Ester (32). According to general procedure E, reduction/cyclization of *rac*-**24e** (114 mg, 0.38 mmol) at 100 °C afforded **32** (20 mg, 17%) as an oil after purification by chromatography (PE/EtOAc 1:1 → 0:1). R_f = 0.54 (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C): δ 7.34−7.27 (m, 3H), 7.17−7.13 (m, 2H), 4.83−4.79 (m, 2H), 4.68 (d, *J* = 14.6 Hz, 1H), 4.32 (d, *J* = 14.6 Hz, 1H), 3.74 (s, 3H), 3.57 (dd, *J* = 5.1, 12.4 Hz, 1H), 3.12 (d, *J* = 12.4 Hz, 1H), 2.86−2.81 (m, 2H), 2.46 (d, *J* = 15.1 Hz, 1H), 2.24 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C): δ 203.4, 165.7, 153.4, 135.8, 127.9, 127.2, 126.8, 53.2, 52.4, 50.3, 48.4, 46.0, 43.9, 43.4. IR (film): ν 1701, 1686, 1655. **32 from 33.** To a solution of **33** (25 mg, 82 μmol) in acetone (2 mL) were added TPAP (2.9 mg) and *N*-methylmorpholine *N*-oxide (NMO, 10.6 mg, 104 μmol), and the mixture was stirred for 2 h at room temperature. Filtration of the reaction mixture over a short path of silica afforded **32** (24 mg, 96%) as a clear oil after purification by chromatography.

3-Benzyl-7-hydroxy-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylic Acid Methyl Ester (33). According to general procedure E, reduction/cyclization of *rac*-**24f** (155 mg, 0.38 mmol) afforded **33** (78 mg, 50%) as an oil after purification by chromatography (EtOAc). R_f = 0.25. ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C): δ 7.37−7.25 (m, 5H), 4.60 (d, *J* = 14.4 Hz, 1H), 4.52−4.48 (m, 2H), 4.44 (d, *J* = 14.4 Hz, 1H), 3.77−3.73 (m, 1H), 3.67 (s, 3H), 3.54 (dd, *J* = 6.6, 12.4 Hz, 1H), 3.10 (d, *J* = 12.4 Hz, 1H), 2.16−2.13 (m, 1H), 1.91−1.88 (m, 1H), 1.50−1.40 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C): δ 166.6, 153.6, 136.3, 127.9, 127.5, 126.8, 61.1, 53.2, 52.0, 48.3, 45.2, 40.0, 38.8, 36.2. IR (film): ν 3404, 1702, 1639, 1453. HRMS (FAB): calcd for $C_{16}H_{21}N_2O_4$ (MH^+) 305.1501, found 305.1481.

3-Benzyl-2-oxo-6-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylic Acid Methyl Ester (34). According to general procedure E, reduction/cyclization of *rac*-**24g** (105 mg, 0.27 mmol) afforded **34** (52 mg, 64%) as an oil after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$, 4:1 mixture of rotamers, data of the major): δ 7.34−7.16 (m, 5H), 5.80−5.70 (m, 1H), 4.98−4.95 (m, 2H), 4.80−4.58 (m, 2H), 4.22 (br s, 2H), 3.70 (s, 3H), 3.56 (br s, 1H), 2.91 (d, *J* = 11.6 Hz, 1H), 2.63−2.56 (m, 1H), 2.44−2.39 (m, 1H), 1.99−1.93 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C): δ 168.3, 154.0, 140.2, 136.4, 128.1, 128.0, 126.7, 113.5, 59.0, 57.7, 51.9, 50.8, 47.6, 44.6, 36.5. IR: ν 1710, 1664. HRMS (FAB): calcd for $C_{17}H_{21}N_2O_3$ (MH^+) 301.1552, found 301.1550.

(1*R*,9*R*,12*S*)-11-Benzyl-12-methyl-10-oxo-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylic Acid Methyl Ester (35). According to general procedure E, reduction/cyclization of (*R*,*S*)-**27a** (20 mg, 50 μmol) afforded **35** (14 mg, 74%) as an oil after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.26. $[\alpha]^{21}_D$ = −5.9 (*c* 59, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 7.30−7.26 (m, 1H), 7.21−7.13 (m, 3H), 7.09−7.05 (m, 1H), 6.99−6.95 (m, 2H),

6.53−6.51 (m, 2H), 5.12 (s, 1H), 5.05 (d, J = 15.5 Hz, 1H), 4.79 (d, J = 5.8 Hz, 1H), 3.89 (d, J = 15.5 Hz, 1H), 3.73 (s, 3H), 3.44−3.42 (m, 1H), 3.22 (dd, J = 5.8, 16.5 Hz, 1H), 3.03 (d, J = 16.5 Hz, 1H), 1.39 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C): δ 166.4, 134.2, 132.1, 128.2, 127.3, 127.0, 126.1, 125.9, 58.5, 54.1, 52.2, 52.0, 45.7, 31.6, 17.4. IR: ν 1706, 1651, 1451. HRMS (FAB): calcd for $C_{21}H_{23}N_2O_3$ (MH^+) 351.1709, found 351.1705.

(2*S*)-2,4-Dibenzyl-5-methyl-3-oxo-3,4-dihydro-2*H*-pyrazine-1-carboxylic Acid Methyl Ester (36). According to general procedure E, reduction/cyclization of (*S*,*S*)-**27a** (140 mg, 0.38 mmol) afforded **36** (79 mg, 60%) as a white amorphous solid after purification by chromatography (PE/EtOAc, 2/1). R_{xa6} = 0.41. $[\alpha]^{21}_D$ = +40 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 7.37−7.17 (m, 10H), 6.11 (s, 1H), 5.04 (d, J = 16.1 Hz, 1H), 4.92−4.87 (m, 1H), 4.67 (d, J = 16.1 Hz, 1H), 3.51 (s, 3H), 3.01−2.94 (m, 2H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C): δ 164.6, 152.3, 137.3, 135.6, 128.8, 127.9, 127.4, 126.4, 126.0, 125.8, 120.5, 105.7, 57.4, 52.0, 43.8, 35.3, 14.6. IR: ν 1715, 1669. HRMS (FAB): calcd for $C_{21}H_{23}N_2O_3$ (MH^+) 351.1709, found 351.1712.

Cyclization Product 37. According to general procedure E, reduction/cyclization of (*S*,*S*)-**27c** (110 mg, 0.26 mmol) afforded **37** (74 mg, 71%) as a white amorphous solid after purification by chromatography (PE/EtOAc, 1/1). R_f = 0.29. $[\alpha]^{21}_D$ = −16.7 (*c* 0.45, CH_2Cl_2). Mp = 58 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 110 °C): δ 7.52 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.25−7.07 (m, 7H), 5.56 (d, J = 4.3 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 4.95 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H), 4.13−4.10 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.19 (dd, J = 6.1, 15.9 Hz, 1H), 3.14 (d, J = 15.9 Hz, 1H), 1.20 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 110 °C) δ 168.4, 153.6, 137.5, 137.1, 130.7, 127.6, 126.2, 126.1, 125.5, 121.3, 118.7, 117.4, 109.2, 107.1, 55.9, 52.3, 52.1, 48.7, 44.2, 30.4, 24.9, 15.3. IR: ν 1706, 1651, 1451. HRMS (FAB): calcd for $C_{24}H_{26}N_3O_3$ (MH^+) 404.1974, found 404.1982.

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Supporting Information Available: Representative ^{1}H and ^{13}C NMR spectra and chiral HPLC spectra for compound **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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