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General Approach to Nitrogen-Bridged Bicyclic Frameworks by Rh-Catalyzed Formal Carbenoid Insertion into an Amide C−N Bond

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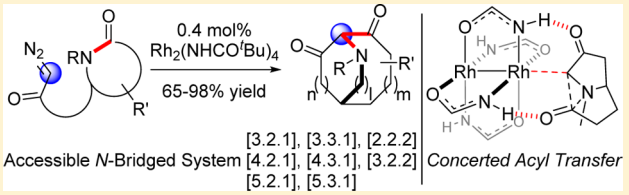
Supporting Information

ABSTRACT: Various nitrogen-bridged bicyclic skeletons are found in bioactive natural products and pharmaceuticals. The development of a new reaction to construct these molecular frameworks has attracted considerable attention in synthetic organic chemistry. We developed a novel synthetic method for obtaining a wide variety of nitrogen-bridged bicyclic compounds with a catalytic process, Rh-catalyzed formal carbenoid insertion into an amide C−N bond. Using 0.1−0.4 mol % $Rh_2(NHCO^tBu)_4$ catalyst, various azabicyclo[*X.Y.Z*]alkane derivatives were obtained in good to excellent yield, successfully demonstrating the broad substrate scope of the developed process. Experimental and computational studies to elucidate the reaction mechanism revealed that the formal insertion reaction of a carbenoid into an amide C−N bond proceeded via the formation of Rh-associated *N*-ylides, followed by an acyl group-selective Stevens [1,2]-shift through a concerted addition/elimination process on the sp^2-hybridized carbon.



INTRODUCTION

Nitrogen-bridged bicyclic skeletons are ubiquitous structures in biologically active alkaloids, and various azabicyclic skeletons are found in this class of natural products (Figure 1).[1] The development of a new reaction to construct these molecular frameworks has attracted considerable attention in synthetic organic chemistry because such reactions can be utilized as pivotal transformations in complex molecule synthesis. In addition, these azabicyclic frameworks are attractive scaffolds for drug discovery because of their potentially diverse bioactivities.[2] Extensive efforts are therefore focused on this research topic.

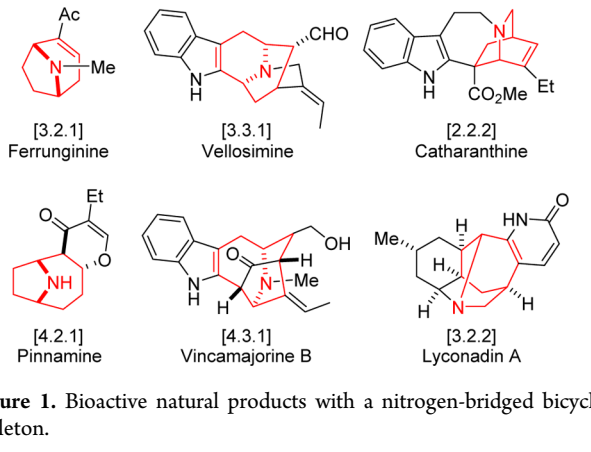


Figure 1. Bioactive natural products with a nitrogen-bridged bicyclic skeleton.

The reaction of amines with a metal carbenoid provides the corresponding *N*-ylide intermediates, generally followed by a Stevens [1,2]-shift to give substituent-rearranged amine derivatives.[3] The present reaction sequence is equivalent to formal carbenoid insertion into a C−N single bond. Stevens [1,2]-shifts generally proceed through diradical intermediates.[4] Therefore, this transformation is the preferred process for benzylic ylides. On the other hand, the metal carbenoid-mediated *N*-ylide formation−Stevens rearrangement cascade using amides as substrates has very limited applications,[5] in part because of the competitive formation of an *O*-ylide intermediate via the reaction of the carbonyl oxygen with a metal carbenoid.[6,7] Detailed investigation of the reactivity of *N*-ylides generated from amide or urea derivatives in the presence of a Rh catalyst by Padwa and co-workers indicated that α-diazo esters containing an amide in the γ-position react with a Rh(II) dimer complex, producing a transition metal-mediated equilibrium mixture of the *N*-ylide and *O*-ylide intermediates (Scheme 1a).[5a] *O*-Ylides efficiently react with dipolarophiles to give the corresponding cycloaddition adducts. *N*-Ylides are formed as thermodynamically more stable intermediates in the absence of dipolarophiles and undergo sigmatropic rearrangement or fragmentation reactions. When the tetrahydroisoquinolyl amide derivative **1** was treated with a catalytic amount of $Rh_2(OCOMe)_4$, a Stevens [1,2]-shift of the most reactive benzylic substituent proceeded preferentially from the corresponding *N*-ylide intermediate to give the product with an isoindolobenzazepine ring system, leading to formal carbenoid insertion into a benzylic C−N bond (Scheme 1b).[5b]

In the course of our synthetic studies aimed at (−)-agelastatin A,[8] we investigated the construction of the tricyclic framework

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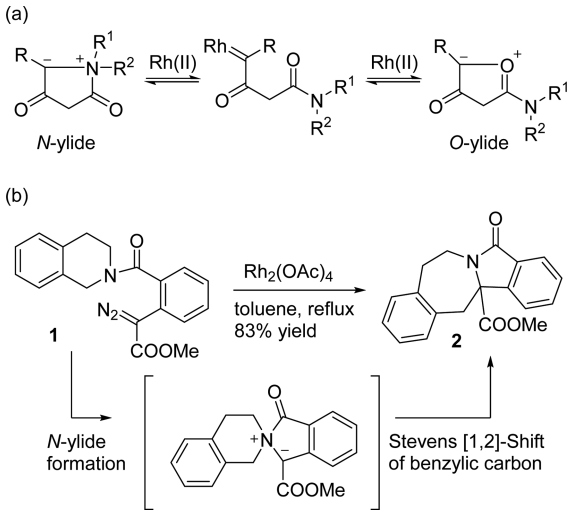
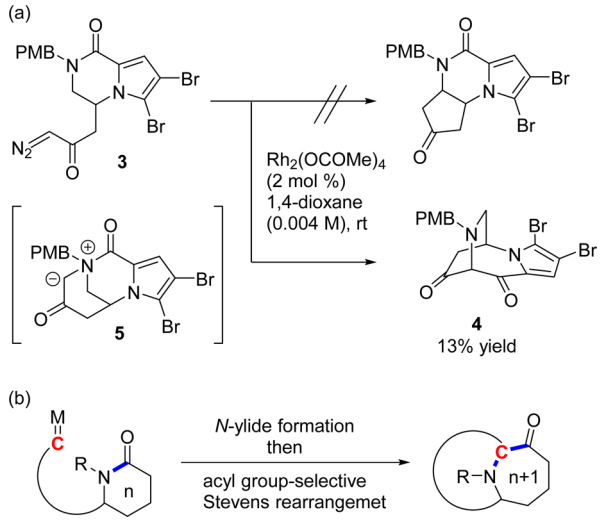
Scheme 1. An Example of a Precedent Metal Carbenoid-Mediated *N*-Ylide Formation−Stevens Rearrangement Cascade Using Amide Substrates



via Rh-catalyzed C−H insertion of functionalized pyrrole derivative **3**. The reaction was performed using 2 mol % $Rh_2(OCOMe)_4$ in 1,4-dioxane at room temperature. Although the desired transformation did not proceed, an unexpected product with an azabicyclo[3.2.2]nonane framework **4** was isolated as a major product (13% yield) (Scheme 2a). The

Scheme 2. Formation of an Unexpected Product with an Azabicyclic Framework



product structure indicated that Rh carbenoid-mediated *N*-ylide formation occurred preferentially over the conventional five-membered ring formation through Rh-catalyzed C−H insertion, and after the formation of *N*-ylide intermediate **5**, the Stevens [1,2]-shift of the acyl group occurred selectively even in the presence of a *p*-methoxybenzyl group on the amide nitrogen.[9] The observed transformation is an unexplored reaction in the field of metal carbenoid chemistry, formal carbenoid insertion into an amide C−N bond. We hypothesized that establishing a practical catalyst system for this transformation would provide general access to nitrogen-bridged bicyclic skeletons (Scheme 2b). This background led us to investigate the present Rh-catalyzed skeletal rearrangement process. Herein, we report the first formal carbenoid insertion into an amide C−N bond using a Rh(II) dimer complex, which was successfully applied to the construction of diverse nitrogen-bridged bicyclic frameworks. Experimental and computational studies performed to elucidate the reaction mechanism are also described.

RESULTS AND DISCUSSION

Optimization of the Reaction Conditions. The reaction conditions were optimized using compound **6a** as a model substrate (Table 1). On the basis of the unexpected findings shown in Scheme 2, a solution of **6a** and 2 mol % $Rh_2(OCOMe)_4$ in 1,4-dioxane was stirred for 2 h at room temperature, affording the desired product **7a** in 38% yield (entry 1). We first screened the source of metal catalysts. When the reaction was performed using Rh(I) or Rh(III) complexes, the desired product **7a** was not obtained (entries 2 and 3). The use of other metal complexes, such as $Fe(acac)_3$,[10] $Cu(OTf)_2$,[11] and $(2,4\text{-}^tBu_2C_6H_4O)_3PAuSbF_6$,[12] also gave unsatisfactory results (entries 4−6). Thus, we examined the reaction in detail using Rh(II) dimer complexes. Compared with the results obtained using $Rh_2(carboxylate)_4$ complexes (entries 1 and 7−9), the target skeletal rearrangement proceeded more efficiently using 2 mol % $Rh_2(NHCOMe)_4$ complex, and compound **7a** was obtained in 74% yield (entry 10).[13] Screening of other $Rh_2(carboxamidate)_4$ complexes revealed that the electronic and structural properties of the carboxamidate ligands affected the catalytic activity. The best result (92% yield) was obtained when the reaction was catalyzed by $Rh_2(NHCO^tBu)_4$, which was prepared from $Rh_2(OCOMe)_4$ and pivalamide using a protocol analogous to that used to prepare $Rh_2(carboxamidate)_4$.[13b] Compared with the reactions using Rh(II) dimer complexes bearing primary carboxamidate ligands (entries 10−12), there was a significant decrease in the yield when $Rh_2(caprolactamate)_4$ was utilized as the catalyst, suggesting that hydrogen in the carboxamidate ligands has an important role in promoting the reaction (entry 13). Solvent effect studies revealed that the use of a mixed solvent (1:1 1,4-dioxane/CH_2Cl_2) gave more satisfactory results (95% yield) (entry 15). The yield was further improved when the reaction was performed at 40 °C (98% yield) (entry 16), and 0.4 mol % catalyst was sufficient to promote this skeletal rearrangement process without any decrease in the yield (entry 17).

Scope and Limitations of the Developed Rh Catalysis. Having identified the optimal reaction conditions, we next examined the scope of the insertion reaction with respect to the substrate. The substrate generality of the synthesis of 9-azabicyclo[4.2.1]nonane derivatives is summarized in Scheme 3. When compound **6b** possessing a quaternary carbon center at the α-position of the amide group was utilized as a substrate, the reaction proceeded smoothly in the presence of 0.4 mol % $Rh_2(NHCO^tBu)_4$, affording compound **7b** in 94% yield. β-Substituted lactams **6c** and **6d**, as well as a benzo-fused lactam **6e**, were also suitable substrates for this reaction, and the corresponding azabicyclic compounds **7c−e** were produced in 70−85% yield. In addition, compound **7f** bearing a tetrasubstituted carbon center at the ring junction could be synthesized in 85% yield. Substrates possessing an *N*-benzyl group (**6g**) and an *N*-butyl group (**6h**) could also be applied to this reaction, providing compounds **7g** and **7h** in 96 and 90% yield, respectively.

To demonstrate the practicality of this catalytic synthetic method, we performed the experiments shown in Scheme 4.

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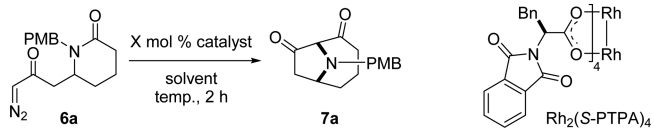
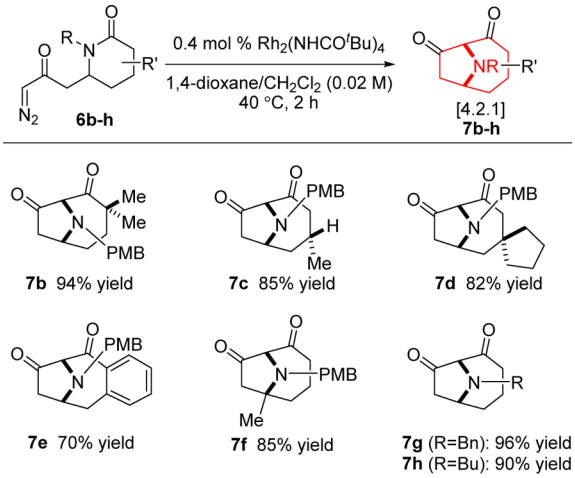
Table 1. Optimization of the Reaction Conditions



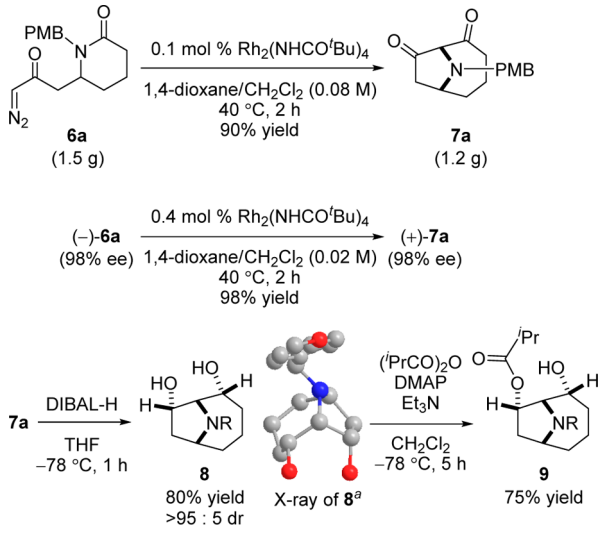
entry	X (mol %)	catalyst	solvent	concn (M)	temp	yield (%)
1	2	$Rh_2(OCOMe)_4$	1,4-dioxane	0.004	rt	38
2	2	$Rh(acac)(ethylene)_2$	1,4-dioxane	0.004	rt	0
3	2	$RhCl_3(H_2O)_3$	1,4-dioxane	0.004	rt	0
4	20	$Fe(acac)_3$/NaBArF	PhCl	0.004	100 °C	0
5	20	$Cu(OTf)_2$	PhCl	0.004	100 °C	trace
6	10	$(ArO)_3PAuSbF_6$	PhCl	0.004	100 °C	0
7	2	$Rh_2(OCOCPh_3)_4$	1,4-dioxane	0.004	rt	26
8	2	$Rh_2(S\text{-PTPA})_4$	1,4-dioxane	0.004	rt	27
9	2	$Rh_2(OCOCF_3)_4$	1,4-dioxane	0.004	rt	0
10	2	$Rh_2(NHCOMe)_4$	1,4-dioxane	0.004	rt	74
11	2	$Rh_2(NHCOCF_3)_4$	1,4-dioxane	0.004	rt	55
12	2	$Rh_2(NHCO^tBu)_4$	1,4-dioxane	0.004	rt	92
13	2	$Rh_2(caprolactamate)_4$	1,4-dioxane	0.004	rt	38
14	2	$Rh_2(NHCO^tBu)_4$	CH_2Cl_2	0.004	rt	88
15[a]	2	$Rh_2(NHCO^tBu)_4$	1,4-dioxane/CH_2Cl_2	0.004	rt	95
16[a]	2	$Rh_2(NHCO^tBu)_4$	1,4-dioxane/CH_2Cl_2	0.004	40 °C	98
17[a]	0.4	$Rh_2(NHCO^tBu)_4$	1,4-dioxane/CH_2Cl_2	0.020	40 °C	98

[a]In 1:1 (v/v) 1,4-dioxane/CH_2Cl_2. *S*-PTPA is *N*-phthaloyl-(*S*)-phenylalaninate. Ar is 2,4-$^tBu_2C_6H_4$. BArF is $B[C_6H_3(CF_3)_2]_4$.

Scheme 3. Synthesis of 9-Azabicyclo[4.2.1]nonane Derivatives



Scheme 4. Demonstration of the Practicality



[a]H atoms have been omitted for the sake of clarity.

It is noteworthy that this catalysis could be performed on a gram scale (1.5 g of **6a**) using 0.1 mol % catalyst in 0.08 M solvent, producing compound **7a** in 90% yield. Slow addition of the diazo substrate using a syringe pump was not required for this catalysis, making the process more accessible. Optically active diazo substrate (−)-**6a** with a 98% ee was prepared and treated under the optimized conditions. Product (+)-**7a** was obtained in 98% yield without a noticeable loss of optical purity, demonstrating its applicability to asymmetric synthesis of azabicyclic compounds.[14] Discrimination of the two ketones in **7a** was further explored. Reduction of the ketones in **7a** with DIBAL-H proceeded in a highly diastereoselective manner (>95:5), providing compound **8** in 80% yield. The structure of **8** was confirmed by X-ray crystallography. Subsequent acylation of **8** with isobutyric anhydride at −78 °C proceeded site-selectively to afford monoacylated compound **9** in 75% yield.

To evaluate the substrate generality of the developed process, synthesis of other nitrogen-bridged bicyclic compounds with azabicyclo[*X*.*Y*.1]alkane skeletons was further investigated (Scheme 5). When ethylene-tethered-type diazocarbonyl compound **6i** was used as a substrate, benzo-fused 8-azabicyclo[3.2.1]octane **7i** was obtained in 90% yield. Azabicyclo[3.2.1]octanes with a methyl group at the α-position of ketones **7j** and **7k** were also accessible without epimerization of the stereogenic center (65 and 96% yield, respectively). Similarly, compound **6l** bearing a tetrasubstituted carbon center at the benzylic carbon was a suitable substrate, affording azabicyclo[3.2.1]octane derivative **7l** in 77% yield. 10-Azabicyclo[4.3.1]decanes **7m** and **7n** and 9-azabicyclo[3.3.1]-nonane **7o** were also accessible from the corresponding

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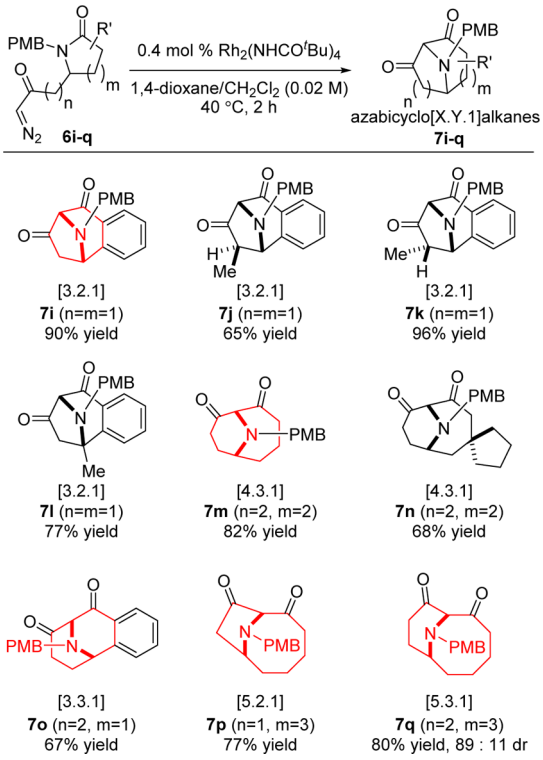
Scheme 5. Synthesis of Azabicyclo[*X.Y.*1]alkanes[a]



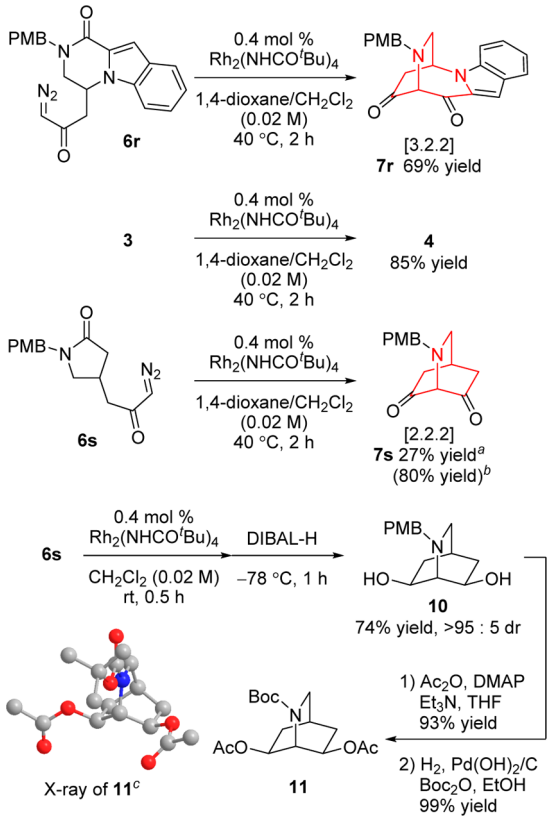
[a]Products were obtained as a single diastereomer unless otherwise noted. dr is the diastereomeric ratio.

diazocarbonyl compounds **6m**–**o** under the same reaction conditions (**7m**, 82% yield; **7n**, 68% yield; **7o**, 67% yield). Furthermore, when *ε*-caprolactam derivatives **6p** and **6q** were utilized as the substrates, the Rh-catalyzed skeletal rearrangement occurred in a diastereoselective manner,[15] affording 10-azabicyclo[5.2.1]decane **7p** and 11-azabicyclo[5.3.1]-undecane **7q** in 77 and 80% yield, respectively.

Synthesis of azabicyclo[*X.Y.*2]alkanes was next examined using substrates bearing a diazocarbonyl substituent at the *β*-position of the amide nitrogen (Scheme 6). The optimized conditions for the synthesis of azabicyclo[*X.Y.*1] skeletons were also effective for this purpose. Using indole and pyrrole-fused substrates **6r** and **3**, the corresponding 6-azabicyclo[3.2.2]-nonanes **7r** and **4** were obtained in 69 and 85% yield, respectively. Although the reaction of *γ*-lactam derivative **6s** also proceeded smoothly under the same reaction conditions, the corresponding 2-azabicyclo[2.2.2]octane **7s** was isolated in only 27% yield because of the gradual decomposition of **7s** during the silica gel column purification. Therefore, after the construction of the 2-azabicyclo[2.2.2]octane core using the developed skeletal rearrangement, DIBAL-H was directly added to the reaction mixture to give diol **10** in 74% yield with excellent diastereoselectivity. The relative configuration of **10** was confirmed by X-ray crystallography after it had been converted into an *N*-Boc diacetate derivative **11**.

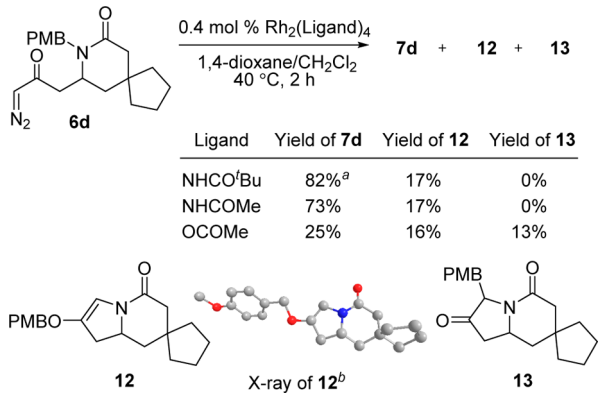
Mechanistic Investigation into the Developed Rh Catalysis. During studies of the substrate scope, we observed the formation of [1,4]-PMB transfer products[16] such as **12** in some entries, which most likely occurred because of a dissociation–recombination mechanism from the *N*-ylide intermediate.[4] To gain insight into the reaction mechanism, product compositions were analyzed using the reaction of **6d** as

Scheme 6. Synthesis of Azabicyclo[*X.Y.*2]alkanes



[a]Isolated yield determined by silica gel column chromatography. [b]Estimated yield determined by ^{1}H NMR using Ph_3CH as an internal standard. [c]H atoms have been omitted for the sake of clarity.

Scheme 7. Experiments To Elucidate the Reaction Mechanism



Ligand	Yield of **7d**	Yield of **12**	Yield of **13**
NHCO^{t}Bu	82%[a]	17%	0%
NHCOMe	73%	17%	0%
OCOMe	25%	16%	13%

[a]From Scheme 3 for comparison. [b]H atoms have been omitted for the sake of clarity.

a model system (Scheme 7). When the reaction was performed under optimal conditions, **7d** was obtained in 82% yield, accompanied by the formation of **12** in 17% yield. Similar results were obtained using $Rh_2(NHCOMe)_4$ as a catalyst. On the other hand, the use of $Rh_2(OCOMe)_4$ affected the product compositions. In addition to **7d** (25% yield) and **12** (16% yield), compound **13**, the product presumably formed by the Stevens [1,2]-shift of the PMB group involving a radical pair intermediate,[4] was isolated in 13% yield. The product compositions were affected by the structure of the Rh(II) dimer

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complex, strongly indicating the intermediacy of the Rh-associated *N*-ylide.[17] Moreover, as shown in Table 1, remarkable differences in the catalyst activity were observed between Rh(II) dimer complexes with primary carboxamidate ligands and those with secondary carboxamidate ligands, suggesting that the amide hydrogen was involved in the transition state of the N → C acyl transfer step. These experimental findings led us to propose the transition state model shown in Figure 2 for Rh-catalyzed formal carbenoid

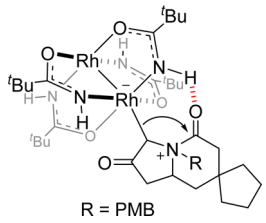


Figure 2. Proposed transition state model.

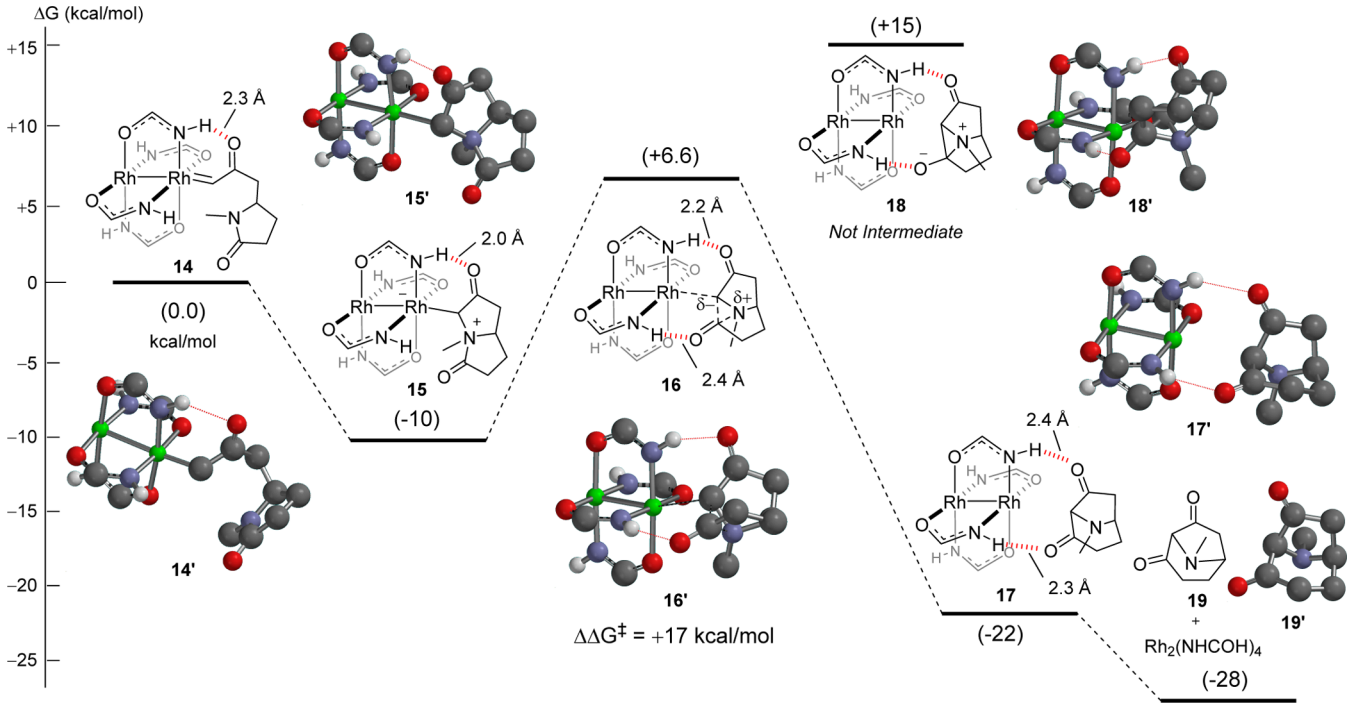
insertion into an amide C−N bond, where the Stevens [1,2]-shift of the acyl group is facilitated by a hydrogen bonding interaction between the amide carbonyl group and the hydrogen in the carboxamidate ligand.

To test the validity of our transition state model, density functional theory calculations were performed using a structurally simplified model (Scheme 8).[18] The geometry of the proposed structures was calculated at the RB3LYP level with the LANL2DZ basis set for Rh and the 6-31G* basis set for C, H, N, and O.[19,20] Computational analyses of the generation of Rh carbenoids from diazo compounds have been well-investigated by the Nakamura group.[20] Thus, we began our calculations from Rh carbenoid **14**.[21] The distance between the oxygen atom of the carbonyl group and the hydrogen atom of the amide in the energy-minimized structure is approximately 2.3 Å, indicating the existence of a hydrogen bonding interaction.[22] Nucleophilic attack of the nitrogen atom on the carbenoid carbon gives Rh-associated *N*-ylide **15**, which was calculated to be 10 kcal/mol more stable than complex **14**. Subsequent N → C acyl transfer was initiated by nucleophilic attack of the carbon associated with Rh metal, providing transition state **16**. The calculated structure indicated that hydrogen bond networks (2.2 and 2.4 Å) stabilized the transition state.[23] The activation energy was reasonably low (17 kcal/mol), supporting the reaction pathway via model **16**. Intrinsic reaction coordinate analysis[24] demonstrated that this step is a nonsynchronous concerted process,[25] suggesting the direct production of **17** from **16**. In addition, the postulated zwitterionic intermediate **18** was calculated to be a highly unstable complex, leading us to conclude that the [1,2]-acyl transfer proceeded via a concerted addition/elimination process on the sp^2 carbon.[26] Dissociation of the Rh(II) dimer complex easily occurred from **17**, affording the final product **19**. Both the nucleophilicity of the carbon associated with a Rh metal and the hydrogen bond donating activity of the hydrogen in the carboxamidate ligands were affected by the substituent in the carbonyl group of the carboxamidate ligands. Apposite balance of these properties would realize the efficient promotion of the formal carbenoid insertion into an amide C−N bond via a selective Stevens [1,2]-shift of the acyl groups.

CONCLUSION

We developed a novel synthetic method for obtaining a wide variety of nitrogen-bridged bicyclic compounds with Rh-catalyzed formal carbenoid insertion into an amide C−N bond. Using 0.1−0.4 mol % $Rh_2(NHCO^tBu)_4$ catalyst, various azabicyclo[*X.Y.Z*]alkane derivatives were obtained in good to excellent yield, successfully demonstrating the broad substrate

Scheme 8. Energy Profile Calculated at the RB3LYP/LANL2DZ and 6-31G(d) Level of Theory[a]



[a]H atoms of the C−H bonds have been omitted for the sake of clarity.

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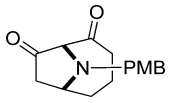
generality of the developed process. Experimental and computational studies to elucidate the reaction mechanism revealed that the formal insertion reaction of a carbenoid into an amide C−N bond proceeded via the formation of Rh-associated *N*-ylides, followed by an acyl group-selective Stevens [1,2]-shift through a concerted addition/elimination process on the sp^2 carbon. The developed method provides a general approach to nitrogen-bridged bicyclic frameworks and can be applied to the synthesis of complex natural products and pharmaceutical agents.

EXPERIMENTAL SECTION

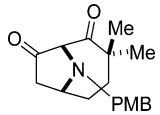
General Information. Analytical thin layer chromatography was performed on Kieselgel 60F254, 0.25 mm thickness plates. Column chromatography was performed with silica gel 60 N (spherical, neutral 63-210 mesh). Reactions were conducted in dry solvent. Other reagents were purified by the usual methods.

General Procedure A for the Insertion Reaction. To a stirred solution of $Rh_2(NHCO^tBu)_4$ (0.48 mg, 0.8 μmol) in 1,4-dioxane (5 mL) and CH_2Cl_2 (3 mL) was added a solution of α-diazocarbonyl compound **6** (0.2 mmol) in CH_2Cl_2 (2 mL) over 3 min at 40 °C. After being stirred for 2 h at 40 °C, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel to afford nitrogen-bridged compound **7**.

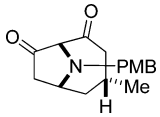
Characterization of Products 7a−s, 4, and 10−13.



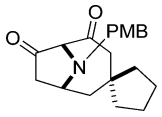
*9-(4-Methoxybenzyl)-9-azabicyclo[4.2.1]nonane-2,8-dione (**7a**).* Prepared according to general procedure A and isolated as white powder (98% yield, 53.3 mg): mp 79−81 °C; R_f = 0.7 (*n*-hexane/EtOAc, 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (m, 1H), 1.73 (m, 1H), 1.81 (m, 1H), 2.10 (m, 1H), 2.24 (d, *J* = 18.0 Hz, 1H), 2.44 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.73 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.88 (ddd, *J* = 15.6, 14.0, 2.4 Hz, 1H), 3.74 (s, 1H), 3.79 (s, 3H), 3.81 (m, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 34.7, 40.1, 42.4, 52.2, 57.1, 57.8, 80.5, 114.0, 129.5, 129.9, 159.1, 206.9, 210.9; IR (ATR) ν 2930, 1751, 1697, 1610, 1510, 1240, 1173, 1134, 1096, 1031, 814 cm^{-1}; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{20}NO_3^+$ *m*/*z* 274.1438, found *m*/*z* 274.1439.



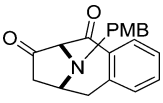
*9-(4-Methoxybenzyl)-3,3-dimethyl-9-azabicyclo[4.2.1]nonane-2,8-dione (**7b**).* Prepared according to general procedure A and isolated as a colorless oil (94% yield, 56.3 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.46 (s, 3H), 1.49−1.66 (m, 3H), 2.21 (d, *J* = 18.4 Hz, 1H), 2.26 (m, 1H), 2.68 (dd, *J* = 18.4, 8.4 Hz, 1H), 3.67−3.86 (m, 4H), 3.80 (s, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 28.9, 31.3, 32.2, 38.8, 46.7, 55.2, 57.7, 59.1, 81.8, 113.9, 129.6, 130.1, 159.0, 208.7, 213.1. IR (ATR) ν 2934, 1749, 1693, 1511, 1245 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{18}H_{23}NNaO_3^+$ *m*/*z* 324.1570, found *m*/*z* 324.1564.



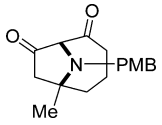
*rac-(1S,4S,6R)-9-(4-Methoxybenzyl)-4-methyl-9-azabicyclo-[4.2.1]nonane-2,8-dione (**7c**).* Prepared according to general procedure A and isolated as a colorless oil (85% yield, 49 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.8 Hz, 3H), 1.59 (m, 1H), 2.21−2.35 (m, 4H), 2.71 (dd, *J* = 18.8, 9.6 Hz, 1H), 3.38 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.70 (s, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.81 (s, 3H), 3.82 (m, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 27.3, 40.5, 40.9, 47.5, 55.2, 58.6, 58.7, 81.4, 114.0, 129.5, 130.1, 159.1, 206.8, 211.8; IR (ATR) ν 2961, 2912, 1753, 1696, 1511, 1244 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{21}NNaO_3^+$ *m*/*z* 310.1414, found *m*/*z* 310.1417.



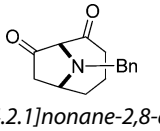
*9-(4-Methoxybenzyl)-9-azaspiro[bicyclo[4.2.1]nonane-3,1′-cyclopentane]-5,7-dione (**7d**).* Prepared according to general procedure A and isolated as a colorless oil (82% yield, 53.6 mg): R_f = 0.6 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19−1.68 (m, 9H), 2.16 (d, *J* = 12.8 Hz, 1H), 2.24−2.35 (m, 2H), 2.67 (m, 1H), 3.34 (d, *J* = 12.8 Hz, 1H), 3.68 (s, 1H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.80 (s, 3H), 3.81 (m, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.0, 36.6, 38.7, 42.9, 43.9, 47.3, 49.7, 55.2, 59.1 (2C), 81.8, 114.0, 129.5, 130.2, 159.1, 206.0, 211.7; IR (ATR) ν 2951, 1751, 1693, 1510, 1244 cm^{-1}; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{20}H_{26}NO_3^+$ *m*/*z* 328.1907, found *m*/*z* 328.1889.



*3,4-Benzo-9-(4-methoxybenzyl)-9-azabicyclo[4.2.1]nonane-2,8-dione (**7e**).* Prepared according to general procedure A and isolated as a colorless oil (70% yield, 45 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (d, *J* = 18.4 Hz, 1H), 2.81−2.89 (m, 2H), 3.81 (s, 3H), 3.87−3.97 (m, 3H), 4.03 (s, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.29 (m, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 42.5, 52.3, 55.1, 55.3, 77.6, 113.9, 127.2, 128.6, 129.8, 130.7, 132.0, 132.7, 135.8, 137.7, 159.1, 200.2, 210.1; IR (ATR) ν 2927, 2835, 1752, 1672, 1610, 1510, 1243 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_3^+$ *m*/*z* 344.1257, found *m*/*z* 344.1266.



*9-(4-Methoxybenzyl)-6-methyl-9-azabicyclo[4.2.1]nonane-2,8-dione (**7f**).* Prepared according to general procedure A and isolated as white powder (85% yield, 48.6 mg): mp 99−101 °C; R_f = 0.6 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3H), 1.57 (m, 1H), 1.80 (m, 1H), 1.89 (m, 1H), 2.09 (m, 1H), 2.46 (m, 1H), 2.55 (s, 2H), 2.65 (dd, *J* = 16.8, 5.2 Hz, 1H), 3.68 (d, *J* = 13.6 Hz, 1H), 3.78 (s, 3H), 3.81 (s, 1H), 4.17 (d, *J* = 13.6 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 27.0, 38.9, 44.1, 47.3, 50.4, 55.2, 61.4, 78.9, 113.8, 129.2, 129.8, 158.8, 207.5, 208.6; IR (ATR) ν 2930, 1752, 1696, 1611, 1510, 1457, 1242, 1171, 1032, 814 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{21}NNaO_3^+$ *m*/*z* 310.1414, found *m*/*z* 310.1413.



*9-Benzyl-9-azabicyclo[4.2.1]nonane-2,8-dione (**7g**).* Prepared according to general procedure A and isolated as a colorless oil (96% yield, 46.9 mg): R_f = 0.2 (*n*-hexane/EtOAc, 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 1H), 1.73 (m, 1H), 1.82 (m, 1H), 2.12 (m, 1H), 2.26 (d, *J* = 18.4 Hz, 1H), 2.46 (dd, *J* = 15.6, 6 Hz, 1H), 2.76 (dd, *J* = 18.4, 8.4 Hz, 1H), 2.91 (m, 1H), 3.76 (s, 1H), 3.81 (m, 1H), 3.92 (d, *J* = 14 Hz, 1H), 3.98 (d, *J* = 14 Hz, 1H), 7.25−7.36 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 34.6, 40.1, 42.4, 57.7, 57.9, 80.6, 127.5, 128.2, 128.5, 137.9, 206.9, 210.8; IR (ATR) ν 2928, 1752,

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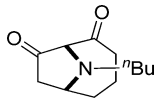
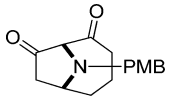
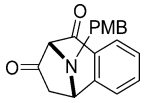
1697, 1495, 1455, 1409, 1322, 1239, 1133, 1078 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{30}H_{34}N_2NaO_4^+$ m/z 509.2411, found m/z 509.2418.



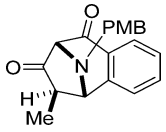
*9-Butyl-9-azabicyclo[4.2.1]nonane-2,8-dione (**7h**).* Prepared according to general procedure A and isolated as a pale yellow oil (90% yield, 37.7 mg): R_f = 0.6 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.32−1.51 (m, 5H), 1.73−1.80 (m, 2H), 2.12 (m, 1H), 2.27 (d, J = 18.0 Hz, 1H), 2.45 (dd, J = 16.0, 5.6 Hz, 1H), 2.64−2.84 (m, 4H), 3.77 (s, 1H), 3.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.0, 20.1, 30.7, 34.1, 40.8, 42.5, 52.3, 58.4, 80.4, 207.8, 211.0; IR (ATR) ν 3649, 2928, 1753, 1698, 1457, 1410, 1313, 1238, 1137, 1084 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{24}H_{38}N_2NaO_4^+$ m/z 441.2724, found m/z 441.2725.



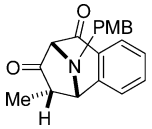
*(+)-(1S,6R)-9-(4-Methoxybenzyl)-9-azabicyclo[4.2.1]nonane-2,8-dione [(+)-**7a**].* Prepared according to general procedure A and isolated as white powder (98% yield, 53.7 mg): mp 94−96 °C; $[\alpha]^{23}_D$ + 213.7° (*c* 1, $CHCl_3$). The enantiomeric excess was determined to be 98% after reduction to **8**.



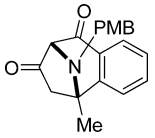
*3,4-Benzo-8-(4-methoxybenzyl)-8-azabicyclo[3.2.1]octane-2,7-dione (**7i**).* Prepared according to general procedure A and isolated as a pale yellow oil (90% yield, 52.1 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (d, J = 17.6 Hz, 1H), 3.00 (dd, J = 17.6, 6.8 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.80 (s, 3H), 3.87 (d, J = 13.2 Hz, 1H), 3.96 (s, 1H), 4.52 (d, J = 6.8 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.44 (dd, J = 7.2, 7.2 Hz, 1H), 7.61 (dd, J = 7.2, 7.2 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0, 52.5, 55.2, 59.7, 78.5, 113.9, 126.4, 126.5, 128.5, 128.6, 129.9, 130.0, 135.6, 142.7, 159.1, 189.9, 207.6; IR (ATR) ν 2958, 2835, 1759, 1691, 1512, 1244, 701 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{19}H_{18}NO_3^+$ m/z 308.1281, found m/z 308.1285.



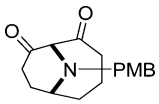
*rac-(1S,5R,6R)-3,4-Benzo-8-(4-methoxybenzyl)-6-methyl-8-azabicyclo[3.2.1]octane-2,7-dione (**7j**).* Prepared according to general procedure A and isolated as a pale yellow oil (65% yield, 41.9 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, J = 7.2 Hz, 3H), 2.47 (q, J = 7.6 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.81 (s, 3H), 3.90 (d, J = 13.2 Hz, 1H), 3.98 (s, 1H), 4.06 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 7.2 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.61 (dd, J = 7.6, 7.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 48.7, 51.7, 55.2, 65.8, 78.6, 113.9, 126.3, 126.6, 128.4, 128.9, 129.8 (2C), 135.8, 142.4, 159.0, 190.4, 209.9; IR (ATR) ν 2972, 2934, 1758, 1687, 1601, 1512, 1246 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}NO_3^+$ m/z 322.1438, found m/z 322.1448.



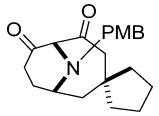
*rac-(1S,5R,6S)-3,4-Benzo-8-(4-methoxybenzyl)-6-methyl-8-azabicyclo[3.2.1]octane-2,7-dione (**7k**).* Prepared according to general procedure A and isolated as pale yellow powder (96% yield, 61.4 mg): mp 80−81 °C; R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J = 6.8 Hz, 3H), 3.06 (qd, J = 6.8, 6.4 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.80 (s, 3H), 3.90 (d, J = 13.2 Hz, 1H), 4.02 (s, 1H), 4.40 (d, J = 6.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.2 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.61 (dd, J = 7.6, 7.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 46.5, 52.1, 55.2, 64.2, 78.5, 113.9, 126.6, 128.4, 128.6, 128.9, 130.0, 130.6, 135.1, 139.7, 159.1, 190.1, 210.3; IR (ATR) ν 2969, 2934, 1758, 1689, 1611, 1601, 1512, 1243 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}NO_3^+$ m/z 322.1438, found m/z 322.1445.



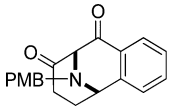
*cis-3,4-Benzo-8-(4-methoxybenzyl)-5-methyl-8-azabicyclo[3.2.1]-octane-2,7-dione (**7l**).* Prepared according to general procedure A and isolated as a pale yellow oil (77% yield, 49.2 mg): R_f = 0.7 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.55 (d, J = 17.2 Hz, 1H), 2.80 (d, J = 17.2 Hz, 1H), 3.44 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.86 (s, 1H), 3.96 (d, J = 13.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.66 (dd, J = 7.6, 7.6 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 48.1, 51.0, 55.2, 62.7, 78.1, 113.9, 125.4, 126.3, 128.3, 129.1, 129.9, 130.1, 135.9, 144.7, 159.0, 190.9, 206.5; IR (ATR) ν 2974, 2834, 1760, 1688, 1598, 1512, 1250 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}NO_3^+$ m/z 322.1438, found m/z 322.1427.



*10-(4-Methoxybenzyl)-10-azabicyclo[4.3.1]decane-2,9-dione (**7m**).* Prepared according to general procedure A and isolated as white powder (82% yield, 47 mg): mp 89−90 °C dec; R_f = 0.5 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−1.76 (m, 3H), 1.85−2.00 (m, 2H), 2.11 (m, 1H), 2.30−2.49 (m, 3H), 3.12 (m, 1H), 3.31 (m, 1H), 3.63 (s, 1H), 3.80 (s, 3H), 3.82 (d, J = 13.2 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 22.7, 31.7, 34.6, 42.1, 54.7, 55.2, 59.7, 76.7, 113.9, 129.4, 129.9, 159.1, 206.0, 208.7; IR (ATR) ν 2935, 1728, 1697, 1610, 1510, 1242, 1031 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3^+$ m/z 310.1414, found m/z 310.1418.



*10-(4-Methoxybenzyl)-10-azaspiro[bicyclo[4.3.1]decane-3,1′-cyclopentane]-5,7-dione (**7n**).* Prepared according to general procedure A and isolated as a colorless oil (68% yield, 46 mg): R_f = 0.3 (*n*-hexane/EtOAc, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (m, 1H), 1.62−2.04 (m, 10H), 2.16 (d, J = 11.2 Hz, 1H), 2.39−2.60 (m, 3H), 3.12 (d, J = 11.2 Hz, 1H), 3.26 (m, 1H), 3.43 (s, 1H), 3.74 (d, J = 12.8 Hz, 1H), 3.80 (s, 3H), 3.89 (d, J = 12.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.4, 25.5, 34.3, 39.8, 40.7, 42.1, 43.0, 51.8, 53.5, 55.2, 57.8, 75.9, 113.9, 129.3, 130.3, 159.1, 206.6, 208.8; IR (ATR) ν 2951, 2872, 1727, 1699, 1512, 1247 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{21}H_{27}NNaO_3^+$ m/z 364.1883, found m/z 364.1880.



*3,4-Benzo-9-(4-methoxybenzyl)-9-azabicyclo[3.3.1]nonane-2,8-dione (**7o**).* Prepared according to general procedure A and isolated as a pale yellow oil (67% yield, 43.1 mg): R_f = 0.6 (*n*-hexane/EtOAc,

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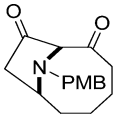
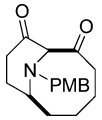
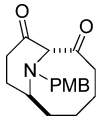
3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (m, 1H), 2.33 (m, 1H), 2.50 (m, 1H), 2.67 (m, 1H), 3.75 (s, 2H), 3.80 (s, 3H), 3.97 (s, 1H), 4.16 (m, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 7.6, 7.6 Hz, 1H), 7.65 (dd, J = 7.6, 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 34.9, 54.9, 55.3, 57.0, 78.6, 113.9, 126.3, 127.4, 128.1, 128.7, 130.0, 130.3, 135.4, 141.6, 159.2, 192.1, 201.1; IR (ATR) ν 2947, 2835, 1724, 1681, 1512, 1246 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}NO_3^+$ m/z 322.1438, found m/z 322.1447.



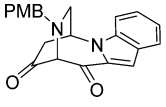
cis-10-(4-Methoxybenzyl)-10-azabicyclo[5.2.1]decane-2,9-dione (***7p***). Prepared according to general procedure A and isolated as pale yellow powder (77% yield, 44 mg): mp 111−113 °C; R_f = 0.7 (*n*-hexane/EtOAc, 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (m, 1H), 1.46 (m, 1H), 1.60−2.10 (m, 6H), 2.65 (dd, J = 18.0, 7.6 Hz, 1H), 3.42 (m, 1H), 3.43 (s, 1H), 3.53 (m, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.82 (s, 3H), 3.93 (d, J = 13.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 30.8, 35.8, 39.1, 39.3, 55.2, 59.4, 60.3, 77.2, 114.0, 130.1, 130.4, 159.2, 209.9, 211.1; IR (ATR) ν 2929, 2855, 1757, 1698, 1611, 1512, 1247, 1032 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{34}H_{42}N_2NaO_6^+$ m/z 597.2935, found m/z 597.2944.



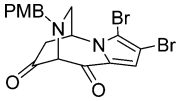
*cis-11-(4-Methoxybenzyl)-11-azabicyclo[5.3.1]undecane-2,10-dione (cis-**7q**)*. Prepared according to general procedure A and isolated as a colorless oil (80% yield, 89:11 dr, 42.6 mg). Major diastereomer: R_f = 0.5 (*n*-hexane/EtOAc, 4/1); ^{1}H NMR (400 MHz, CD_3CN, 50 °C) δ 1.38−2.22 (m, 9H), 2.48−2.64 (m, 2H), 2.93−3.02 (m, 2H), 3.36 (s, 1H), 3.82 (s, 3H), 3.84 (d, J = 13.2 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN, 50 °C) δ 25.6, 28.1, 31.8, 32.9, 35.8, 40.6, 56.1, 58.0, 60.1, 78.2, 115.0, 131.9 (2C), 160.5, 209.5, 215.5; IR (ATR) ν 2930, 1720, 1698, 1610, 1510, 1244, 1154, 1032 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{36}H_{46}N_2NaO_6^+$ m/z 625.3248, found m/z 625.3240.



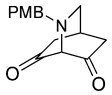
*trans-11-(4-Methoxybenzyl)-11-azabicyclo[5.3.1]undecane-2,10-dione (trans-**7q**)*. Prepared according to general procedure A and isolated as colorless blocks (80% yield, 89:11 dr, 5.4 mg): mp 111−113 °C. Minor diastereomer: R_f = 0.4 (*n*-hexane/EtOAc, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 1H), 1.61 (m, 1H), 1.84−2.31 (m, 7H), 2.51−2.67 (m, 3H), 3.02 (m, 1H), 3.39 (d, J = 13.2 Hz, 1H), 3.49 (s, 1H), 3.81 (s, 3H), 3.85 (d, J = 13.2 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 26.1, 26.9, 27.0, 38.7, 44.4, 48.4, 55.3, 58.3, 79.6, 114.0, 129.1, 130.6, 159.1, 207.0, 211.6; IR (ATR) ν 2939, 1723, 1697, 1512, 1246 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{36}H_{46}N_2NaO_6^+$ m/z 625.3248, found m/z 625.3254.



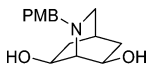
*rac-(6S,9S)-12-(4-Methoxybenzyl)-6H-9,6-(epiminomethano)-azepino[1,2-a]indole-8,10(7H,9H)-dione (**7r**)*. Prepared according to general procedure A and isolated as yellow powder (69% yield, 49.6 mg): mp 168−169 °C dec; R_f = 0.5 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (m, 1H), 2.91 (d, J = 12.0 Hz, 1H), 3.07 (dd, J = 13.2, 3.2 Hz, 1H), 3.69 (d, J = 12.0, 5.6 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.80 (s, 3H), 3.93 (d, J = 13.2 Hz, 1H), 4.21 (s, 1H), 5.33 (m, 1H), 6.86 (d, J = 8.0 Hz, 2H), 7.18−7.47 (m, 6H), 7.74 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3, 48.2, 55.0, 55.2, 58.3, 79.2, 109.6, 110.4, 113.9, 121.6, 123.8, 126.47, 126.51, 128.4, 130.2, 134.4, 137.7, 159.1, 184.7, 202.0; IR (ATR) ν 2919, 1729, 1658, 1512, 1354, 1327, 1243, 1168, 1031 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{22}H_{20}N_2NaO_3^+$ m/z 383.1366, found m/z 383.1373.



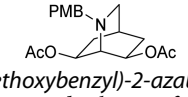
*rac-(5S,8S)-2,3-Dibromo-10-(4-methoxybenzyl)-5H-8,5-(epiminomethano)pyrrolo[1,2-a]azepine-7,9(6H,8H)-dione (**4**)*. Prepared according to general procedure A and isolated as pale yellow powder (85% yield, 79.7 mg): mp 137−138 °C dec; R_f = 0.6 (*n*-hexane/EtOAc, 3/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (m, 1H), 2.88 (d, J = 12.0 Hz, 1H), 2.94 (dd, J = 18.0, 3.2 Hz, 1H), 3.59 (d, J = 12.0, 5.6 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.80 (s, 3H), 3.89 (d, J = 13.2 Hz, 1H), 4.11 (s, 1H), 5.30 (m, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.20 (s, 1H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5, 53.2, 54.6, 55.3, 58.3, 79.1, 102.8, 112.1, 114.0, 119.6, 128.2, 130.2, 132.0, 159.3, 180.2, 200.8; IR (ATR) ν 2917, 2836, 1733, 1652, 1513, 1378, 1331, 1245 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{18}H_{16}Br_2N_2NaO_3^+$ m/z 488.9420, found m/z 488.9431.



2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-6,7-dione (***7s***). Prepared according to general procedure A (27% yield, 14.1 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (dd, J = 18.0, 1.2 Hz, 2H), 2.48 (dd, J = 18.0, 3.2 Hz, 2H), 2.65 (m, 1H), 2.93 (dd, J = 1.2, 1.2 Hz, 2H), 3.40 (s, 1H), 3.65 (d, J = 3.2 Hz, 2H), 3.80 (s, 3H), 6.85 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 42.6, 53.7, 55.2, 59.7, 74.7, 113.8, 129.5, 130.1, 159.0, 203.6; IR (ATR) ν 2919, 1740, 1715, 1611, 1511, 1245, 1173, 1077, 1031 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{18}NO_3^+$ m/z 260.1281, found m/z 260.1269.



(1s,4r,6R,7S)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-6,7-diol (***10***). To a solution of $Rh_2(NHCO^tBu)_4$ (0.48 mg, 0.8 μmol) in CH_2Cl_2 (8 mL) was added **6s** (57.5 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) over 3 min at room temperature. After being stirred for 30 min, the reaction mixture was cooled to −78 °C, and DIBAL-H (1.02 M in hexane, 0.78 mL, 0.80 mmol) was added. After the mixture had been stirred for 1 h at −78 °C, the reaction was quenched with a 2 M aqueous Rochelle salt solution and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 15/1 to 5/1) to afford **10** as pale yellow powder (74% yield, 38.8 mg): mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, J = 12.8 Hz, 2H), 1.82−1.91 (m, 3H), 2.79 (s, 1H), 2.85 (s, 2H), 3.86 (s, 3H), 3.90 (m, 2H), 4.01 (s, 2H), 6.86 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 36.3, 55.1, 55.2, 61.6, 61.8, 68.5, 113.8, 129.8, 131.6, 158.7; IR (ATR) ν 3395, 2930, 1611, 1512, 1245, 1177, 1035, 1006, 831 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{22}NO_3^+$ m/z 264.1594, found m/z 264.1592.



(1s,4r,6R,7S)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-6,7-diyl Diacetate (***s1***). To a stirred solution of **10** (75.6 mg, 0.29 mmol), DMAP (3.7 mg, 0.03 mmol), and triethylamine (0.09 mL, 0.64 mmol) in THF (5.8 mL) was added acetic anhydryde (0.06 mL, 0.64 mmol) at 0 °C. After the mixture had been stirred for 1 h at room temperature, the reaction was quenched with saturated aqueous

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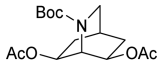
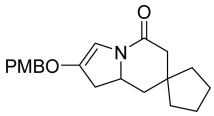
$NaHCO_3$ and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/AcOEt, 3/1) to afford **s1** as a colorless oil (93% yield, 92.2 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56−1.59 (m, 2H), 1.90−2.03 (m, 3H), 2.11 (s, 6H), 2.87 (s, 2H), 3.02 (dd, J = 2.4, 2.4 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 2H), 4.85 (ddd, J = 9.6, 2.8, 2.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.2, 32.6, 54.8, 55.2, 55.3, 60.5, 71.9, 113.4, 129.4, 132.0, 158.5, 170.5; IR (ATR) ν 2935, 1735, 1611, 1510, 1440, 1364, 1239, 1170, 1024, 832 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_5^+$ m/z 370.1625, found m/z 370.1625.



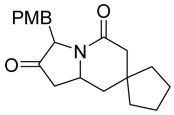
*(1s,4r,6R,7S)-2-(tert-Butoxycarbonyl)-2-azabicyclo[2.2.2]octane-6,7-diyl Diacetate (**11**).* A solution of **s1** (92.2 mg, 0.27 mmol), Boc_2O (471.4 mg, 2.16 mmol), and 20% $Pd(OH)_2/C$ (20.3 mg) in EtOH (9 mL) was stirred under a H_2 atmosphere. After 13 h, the reaction mixture was filtered through a short pad of Celite and concentrated *in vacuo*. The obtained residue was purified by flash chromatography on silica gel (hexane/AcOEt, 2/1) to afford **11** as a white powder (99% yield, 83.2 mg): mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 1.43−1.52 (m, 11H), 2.00−2.11 (m, 9H), 3.35−3.39 (m, 2H), 4.36 (dd, J = 2.8, 2.8 Hz, 1H), 4.85−4.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer) δ 21.0, 25.4, 28.5, 32.0, 48.0, 50.6, 68.9, 79.4, 156.0, 170.3; IR (ATR) ν 1737, 1687, 1410, 1363, 1227, 1175, 1114, 1023, 907 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO_6^+$ m/z 350.1574, found m/z 350.1565.

The structure of **11** could be confirmed by X-ray diffraction analysis (CCDC number 1404663)



*2′-(4-Methoxybenzyloxy)-8′,8a′-dihydro-1′H-spiro[cyclopentane-1,7′-indolizin]-5′(6′H)-one (**12**).* Prepared according to general procedure A using $Rh_2(OCOMe)_4$, instead of $Rh_2(NHCO^tBu)_4$, and isolated as colorless blocks in 16% yield: mp 120−121 °C; R_f = 0.3 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46−1.90 (m, 10H), 2.18 (d, J = 17.6 Hz, 1H), 2.36 (d, J = 17.6 Hz, 1H), 2.59−2.71 (m, 2H), 3.81 (s, 3H), 4.13 (m, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.75 (d, J = 10.8 Hz, 1H), 6.38 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.9, 36.7, 38.1, 39.6, 41.2, 41.7, 43.0, 55.3, 55.8, 72.2, 102.1, 114.0, 127.9, 129.6, 150.3, 159.7, 164.7; IR (ATR) ν 3111, 2927, 1653, 1616, 1516, 1468, 1247, 1173 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{26}NO_3^+$ m/z 328.1907, found m/z 328.1916.

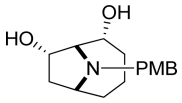
The structure of **12** could be confirmed by X-ray diffraction analysis (CCDC number 1035392)



*3′-(4-Methoxybenzyl)dihydro-1′H-spiro[cyclopentane-1,7′-indolizine]-2′,5′(3′H,6′H)-dione (**13**).* Prepared according to general procedure A using $Rh_2(OCOMe)_4$, instead of $Rh_2(NHCO^tBu)_4$, and isolated as a colorless oil in 9% yield: R_f = 0.3 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.75 (m, 10H), 2.10−2.28 (m, 3H), 2.46 (d, J = 14.4 Hz, 1H), 2.86 (m, 1H), 3.20 (dd, J = 14.0, 2.8 Hz, 1H), 3.29 (dd, J = 14.0, 5.6 Hz, 1H), 3.77 (s, 3H), 4.50 (m, 1H), 6.78 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.3, 34.4, 35.9, 40.8, 41.0, 41.1, 44.0, 45.0, 53.4, 55.3, 63.3, 114.0, 128.6, 130.9, 158.7, 168.8, 212.6; IR (ATR) ν 2945, 2863, 1756, 1638, 1512, 1456, 1249 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{20}H_{25}NNaO_3^+$ m/z 350.1727, found m/z 350.1733.

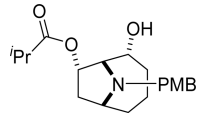
Procedure for the Insertion Reaction on a Gram Scale. To a stirred solution of $Rh_2(NHCO^tBu)_4$ (3.0 mg, 5 μmol) in 1,4-dioxane (31.5 mL) and CH_2Cl_2 (25 mL) was added **6a** (1.5 g, 5.0 mmol) in CH_2Cl_2 (6 mL) over 5 min at 40 °C. After being stirred for 2 h at 40 °C, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 3/1) to afford **7a** in 90% yield (1.22 g, 4.5 mmol).

Recognition of Diketone (Scheme 4).



*rac-(1S,2R,6R,8S)-9-(4-Methoxybenzyl)-9-azabicyclo[4.2.1]nonane-2,8-diol (**8**).* To a stirred solution of **7a** (55 mg, 0.2 mmol) in THF (1.3 mL) was added 1.0 M DIBAL-H in hexane (0.8 mL, 0.8 mmol) at −78 °C. After the mixture had been stirred at −78 °C for 1 h, 0.2 M potassium sodium (+)-tartrate (aqueous) was added and stirring was continued at room temperature for an additional 1 h. The reaction mixture was filtered through Celite, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc/MeOH, 36/12/1) to afford **8** in 80% yield (>95:5 dr, 44.4 mg, 0.16 mmol) as white powder: mp 99−101 °C; R_f = 0.4 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.46 (m, 1H), 1.57 (m, 1H), 1.70−1.80 (m, 2H), 1.87 (m, 1H), 1.94−2.02 (m, 2H), 2.72 (m, 1H), 3.21 (m, 1H), 3.36 (dd, J = 6.8, 4.4 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.78 (s, 3H), 3.86 (m, 1H), 3.96 (br s, 1H), 4.05 (br s, 1H), 4.69 (m, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 33.7, 34.2, 43.1, 55.2, 57.7, 58.6, 65.6, 74.0, 75.9, 113.5, 129.1, 132.5, 158.5; IR (ATR) ν 3339, 2923, 1611, 1510, 1458, 1243, 1168, 1026, 822 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{32}H_{46}N_2NaO_6^+$ m/z 577.3248, found m/z 577.3251.

The structure of **8** could be confirmed by X-ray diffraction analysis (CCDC number 1034017)



*rac-(1R,5R,6S,7S)-5-Hydroxy-9-(4-methoxybenzyl)-9-azabicyclo-[4.2.1]nonan-7-yl Isobutyrate (**9**).* To a stirred solution of **8** (55.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol), and Et_3N (0.033 mL, 0.24 mmol) in CH_2Cl_2 (5 mL) was added $(^iPrCO)_2O$ (0.093 mL, 0.56 mmol) at −78 °C. After the mixture had been stirred at −78 °C for 5 h, H_2O was added and the reaction mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel ($CHCl_3/CH_3CN$, 20/1) to afford **9** in 75% yield (52.1 mg, 0.15 mmol) as a pale yellow oil: R_f = 0.4 ($CHCl_3/CH_3CN$, 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 1.34−1.52 (m, 2H), 1.72−1.87 (m, 3H), 1.93 (m, 1H), 2.02 (m, 1H), 2.46−2.60 (m, 2H), 2.99 (m, 1H), 3.27 (m, 1H), 3.52 (m, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.76−3.86 (m, 5H), 5.38 (m, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.1, 21.0, 33.5, 34.0, 34.2, 40.7, 55.2, 57.8, 58.1, 65.5, 75.5, 75.9, 113.6, 129.1, 132.1, 158.6, 176.2; IR (ATR) ν 3483, 2929, 1727, 1611, 1510, 1467, 1242, 1160, 1035, 822 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{30}NO_4^+$ m/z 348.2169, found m/z 348.2166.

Synthesis and Characterization of $Rh_2(NHCO^tBu)_4$. *Dirhodium Tetrapivalamidate.* The mixture of $Rh_2(OAc)_4$ (100 mg, 0.23 mmol) and H_2NCO^tBu (300 mg, 3 mmol) in chlorobenzene (10 mL) was heated to reflux for 12 h, and then the solvent was distilled off by heating at a rate such that ∼5 mL of the solvent was removed per hour. After 2 h, chlorobenzene (10 mL) was added to the mixture, and the solvent was distilled off at the same rate for 2 h. This process was repeated one additional time, and the residue was purified by flash chromatography on silica gel ($EtOAc/CH_2Cl_2$, 2/3) to afford the titled compound in 74% yield (102 mg, 0.17 mmol) as black powder: mp >300 °C; R_f = 0.2 (CH_2Cl_2/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 36H), 4.81 (br s, 4H); ^{13}C NMR

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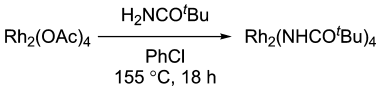
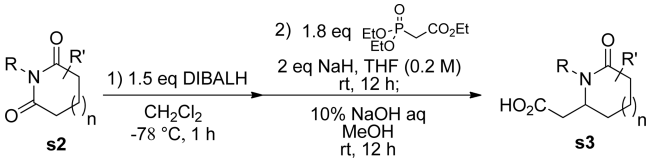
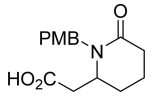
(100 MHz, DMF-d_7, 50 °C) δ 27.9, 39.4, 180.7; IR (ATR) ν 3352, 2961, 2863, 1570, 1485, 1447, 1356, 1258, 1170 cm^{-1}; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{20}H_{41}N_4O_4Rh_2^+$ m/z 607.1232, found m/z 607.1239.



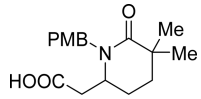
Synthesis and Characterization of Substrates. *General Procedure B for Preparing Carboxylic Compound* ***s3***.



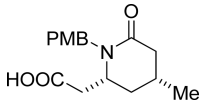
To a stirred solution of **s2** in CH_2Cl_2 was added DIBAL-H (1.0 M solution in *n*-hexane, 1.5 equiv) at −78 °C. After the mixture had been stirred at −78 °C for 1 h, 0.2 M potassium sodium (+)-tartrate (aqueous) was added and stirring was continued at room temperature for 1 h. The reaction mixture was filtered through Celite, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used for the next reaction without further purification. To a stirred suspension of NaH (2 equiv, 60% dispersion in mineral oil) in THF was added triethylphosphonoacetate (1.8 equiv) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Hydroxylactam was added to the reaction mixture, and the whole was stirred at room temperature for 12 h. NaOH (aqueous, 10%) was added, and stirring was continued at room temperature for 12 h. The reaction mixture was acidified with 6 N aqueous HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford **s3**.



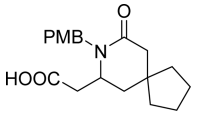
*2-[1-(4-Methoxybenzyl)-6-oxopiperidin-2-yl]acetic Acid (**s3a**).* Prepared according to general procedure B and isolated as white powder (69% yield, two steps): mp 168−170 °C; R_f = 0.4 ($CHCl_3$/MeOH, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.95 (m, 4H), 2.45−2.60 (m, 3H), 2.69 (dd, J = 16, 3.6 Hz, 1H), 3.78 (s, 3H), 3.86 (m, 1H), 3.94 (d, J = 14.8 Hz, 1H), 5.21 (d, J = 14.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 9.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 26.9, 31.2, 37.3, 47.5, 52.2, 55.2, 114.0, 128.8, 129.2, 158.9, 171.3, 174.0; IR (ATR) ν 2951, 1713, 1581, 1511, 1413, 1355, 1243, 1176, 1032, 909 cm^{-1}; HRMS (ESI-TOF) [2M + Na]$^+$ calcd for $C_{30}H_{38}N_2NaO_8^+$ m/z 577.2520, found m/z 577.2530.



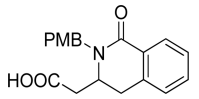
*2-[1-(4-Methoxybenzyl)-5,5-dimethyl-6-oxopiperidin-2-yl]acetic Acid (**s3b**).* Prepared according to general procedure B and isolated as white powder (50% yield, two steps): mp 161−162 °C; R_f = 0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.26 (s, 3H), 1.54−1.92 (m, 4H), 2.56 (dd, J = 15.6, 10.0 Hz, 1H), 2.71 (dd, J = 15.6, 3.2 Hz, 1H), 3.78 (s, 3H), 3.80 (m, 1H), 3.84 (d, J = 14.8 Hz, 1H), 5.21 (d, J = 14.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.8, 27.9, 31.7, 37.4, 38.2, 47.6, 52.7, 55.2, 114.0, 129.0, 129.5, 158.9, 175.1, 176.8; IR (ATR) ν 2924, 1723, 1579, 1511, 1172 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{23}NNaO_4^+$ m/z 328.1519, found m/z 328.1527.



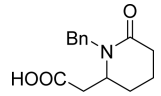
*cis-2-[1-(4-Methoxybenzyl)-4-methyl-6-oxopiperidin-2-yl]acetic Acid (**s3c**).* Prepared according to general procedure B and isolated as white powder (30% yield, two steps): mp 157−160 °C; R_f = 0.2 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 0.99 (d, J = 6.8 Hz, 3H), 1.25−1.46 (m, 2H), 1.84 (m, 1H), 2.04−2.11 (m, 2H), 2.40 (dd, J = 15.6, 8.4 Hz, 1H), 2.44 (m, 1H), 2.71 (dd, J = 15.6, 4.0 Hz, 1H), 3.71 (m, 1H), 3.74 (s, 3H), 4.26 (d, J = 15.6 Hz, 1H), 5.04 (d, J = 15.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.3, 27.6, 38.4, 39.9, 41.7, 47.0, 54.4, 55.7, 115.1, 129.9, 130.4, 160.5, 174.0 (2C); IR (ATR) ν 3286, 2952, 2912, 1712, 1602, 1577, 1514, 1252, 1201 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_4^+$ m/z 314.1363, found m/z 314.1371.



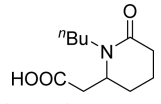
*2-[8-(4-Methoxybenzyl)-9-oxo-8-azaspiro[4.5]decan-7-yl]acetic Acid (**s3d**).* Prepared according to general procedure B and isolated as white powder (51% yield, two steps): mp 164−166 °C; R_f = 0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.92 (m, 10H), 2.32−2.45 (m, 2H), 2.49 (dd, J = 15.6, 8.4 Hz, 1H), 2.72 (dd, J = 15.6, 3.2 Hz, 1H), 3.65 (m, 1H), 3.79 (s, 3H), 4.09 (d, J = 14.8 Hz, 1H), 5.28 (d, J = 14.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.6, 35.0, 38.7, 40.0, 40.1, 40.2, 44.5, 45.9, 50.8, 55.2, 114.0, 128.8, 129.2, 158.9, 171.6, 174.3; IR (ATR) ν 2945, 2860, 1720, 1610, 1513, 1246 cm^{-1}; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{19}H_{26}NO_4^+$ m/z 332.1856, found m/z 332.1851.



*2-[2-(4-Methoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl]acetic Acid (**s3e**).* Prepared according to general procedure B and isolated as white powder (51% yield, two steps): mp 147−148 °C; R_f = 0.3 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44−2.55 (m, 2H), 2.80 (dd, J = 16.4, 1.6 Hz, 1H), 3.20 (dd, J = 16.4, 5.6 Hz, 1H), 3.79 (s, 3H), 4.05 (d, J = 14.8 Hz, 1H), 4.06 (m, 1H), 5.37 (d, J = 14.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 7.6, 7.6 Hz, 1H), 7.43 (dd, J = 8.0, 7.6 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 36.0, 48.3, 51.3, 55.2, 114.1, 127.4, 128.1, 128.3, 128.6, 129.4, 129.5, 132.3, 135.4, 159.1, 164.0, 175.3; IR (ATR) ν 3080, 2951, 1723, 1619, 1510, 1471, 1244 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{19}H_{19}NNaO_4^+$ m/z 348.1206, found m/z 348.1200.



*2-(1-Benzyl-6-oxopiperidin-2-yl)acetic Acid (**s3g**).* Prepared according to general procedure B and isolated as white powder (37% yield, two steps): mp 124−126 °C; R_f = 0.5 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75−1.95 (m, 4H), 2.45−2.60 (m, 3H), 2.70 (dd, J = 16 Hz, 1H), 3.85 (m, 1H), 4.03 (d, J = 15.2 Hz, 1H), 5.26 (d, J = 15.2 Hz, 1H), 7.22−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 26.8, 31.1, 37.3, 48.1, 52.6, 127.4, 127.7, 128.6, 136.6, 171.5, 173.9; IR (ATR) ν 2946, 1719, 1590, 1485, 1452, 1413, 1254, 1188, 1072, 960 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{17}NNaO_3^+$ m/z 270.1101, found m/z 270.1094.



*2-(1-Butyl-6-oxopiperidin-2-yl)acetic Acid (**s3h**).* Prepared according to general procedure B and isolated as white powder (32% yield, two steps): mp 86−88 °C; R_f = 0.5 ($CHCl_3$/MeOH, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.24−1.39 (m, 2H), 1.47−1.63 (m, 2H), 1.74−1.88 (m, 4H), 2.35−2.60 (m, 3H),

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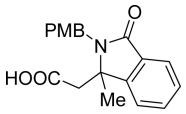
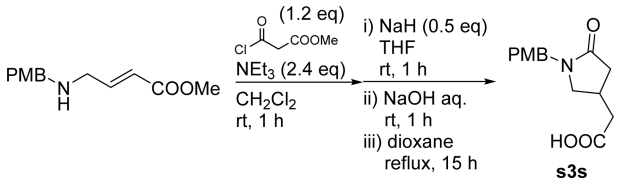
2.68−2.82 (m, 2H), 3.83−3.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.6, 20.2, 26.9, 29.5, 31.3, 37.6, 45.6, 53.2, 170.7, 174.3; IR (ATR) ν 2956, 1721, 1589, 1487, 1415, 1353, 1297, 1249, 1193, 1087 cm^{-1}; HRMS (ESI-TOF) [2M + Na]$^+$ calcd for $C_{22}H_{38}N_2NaO_6^+$ m/z 449.2622, found m/z 449.2622.

2-[2-(4-Methoxybenzyl)-3-oxoisoindolin-1-yl]acetic acid (**s3i**) was prepared by a reported procedure.[27]



*2-[2-(4-Methoxybenzyl)-1-methyl-3-oxoisoindolin-1-yl]acetic Acid (**s3l**).* To a stirred solution of 2-(4-methoxybenzyl)isoindoline-1,3-dione (2.4 g, 9 mmol) in THF (100 mL) was added MeLi (10.8 mmol, 1.1 M solution in Et_2O). After the mixture had been stirred at −78 °C for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed under reduced pressure. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used for the next reaction without further purification. To a stirred suspension of NaH (900 mg, 22.5 mmol, 60% dispersion in mineral oil) in THF was added triethylphosphonoacetate (3.6 mL, 18 mmol) at room temperature, and the mixture was stirred for 30 min. The residue was added to the reaction mixture, and the whole was stirred at 130 °C for 5 h. NaOH (aqueous, 10%) was added, and stirring was continued at 50 °C for 12 h. The reaction mixture was acidified with 6 N aqueous HCl, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford **s3l** as a colorless gum (383 mg, 13% yield, three steps): R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 2.82 (d, J = 14.8 Hz, 1H), 2.88 (d, J = 14.8 Hz, 1H), 3.75 (s, 3H), 4.44 (d, J = 15.6 Hz, 1H), 4.94 (d, J = 15.6 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.42 (dd, J = 7.6, 7.6 Hz, 1H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 9.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 42.2, 42.5, 55.2, 64.0, 113.8, 121.1, 123.8, 128.5, 129.2, 129.9, 130.7, 131.9, 148.9, 158.8, 168.8, 172.2; IR (ATR) ν 3368, 2932, 1726, 1647, 1613, 1513, 1246 cm^{-1}; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{19}H_{20}NO_4^+$ m/z 326.1385, found m/z 326.1391.

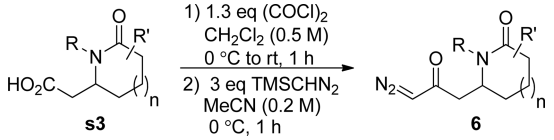


*2-[1-(4-Methoxybenzyl)-5-oxopyrrolidin-3-yl]acetic Acid (**s3s**).* To a solution of (*E*)-methyl 4-[(4-methoxybenzyl)amino]but-2-enoate[28] (15 mmol) and triethyamine (5.0 mL, 36 mmol) in CH_2Cl_2 (75 mL) was added methyl malonyl chloride (1.9 mL, 18 mmol) at 0 °C, and the resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude residue.

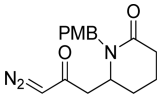
To a stirred solution of NaH (60% in oil, 272 mg, 6.8 mmol) in THF (30 mL) was added the crude residue at −78 °C, and the reaction mixture was stirred for 1 h at room temperature. Aqueous NaOH (2 M) was added, and stirring was continued for 1 h at room temperature. The reaction was quenched with 1 N aqueous HCl, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure.

A solution of the crude residue in 1,4-dioxane (34 mL) was refluxed for 15 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (hexane/AcOEt/MeOH, 8/8/1 to 1/1/1) to afford **s3s** as white powder (38%, 1.5 g): mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (dd, J = 15.6, 5.6 Hz, 1H), 2.43 (dd, J = 16.4, 7.6 Hz, 1H), 2.50 (dd, J = 16.8, 6.0 Hz, 1H), 2.66−2.77 (m, 2H), 2.95 (dd, J = 9.6, 6.0 Hz, 1H), 3.47 (dd, J = 10.4, 8.0 Hz, 1H), 3.80 (s, 3H), 4.38 (s, 2H), 6.86 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 37.2, 38.3, 46.0, 51.8, 55.3, 114.1, 128.1, 129.5, 159.1, 173.7, 175.4; IR (ATR) ν 2923, 1719, 1684, 1637, 1513, 1420, 1246, 1175, 1032, 847 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{17}NNaO_4^+$ m/z 286.1050, found m/z 286.1056.

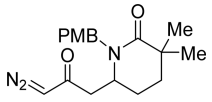
*General Procedure C for Preparing Diazocarbonyl Compound **6**.*



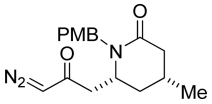
To a stirred solution of the carboxylic acid in CH_2Cl_2 was added $(COCl)_2$ (1.3 equiv) at 0 °C, and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give crude acid chloride. The residue was dissolved in CH_3CN, and $TMSCHN_2$ (2.0 M solution in Et_2O, 3 equiv) was added to the solution at 0 °C. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel to afford α-diazocarbonyl compound **6**.



*6-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)piperidin-2-one (**6a**).* Prepared according to general procedure C and isolated as yellow powder (87% yield, two steps): mp 83−85 °C; R_f = 0.2 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.90 (m, 4H), 2.38−2.54 (m, 3H), 2.64 (dd, J = 15.2, 3.2 Hz, 1H), 3.79 (s, 3H), 3.92−3.98 (m, 1H), 4.00 (d, J = 14.8 Hz, 1H), 5.10 (d, J = 14.8 Hz, 1H), 5.19 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 27.2, 31.7, 43.6, 47.5, 52.3, 55.2, 55.5, 113.9, 129.2, 129.5, 158.9, 170.0, 191.6; IR (ATR) ν 2949, 2099, 1624, 1510, 1462, 1359, 1242, 1174, 1031, 969, 814 cm^{-1}; HRMS (ESI-TOF) [2M + Na]$^+$ calcd for $C_{32}H_{38}N_6NaO_6^+$ m/z 625.2745, found m/z 625.2748.



*6-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)-3,3-dimethylpiperidin-2-one (**6b**).* Prepared according to general procedure C and isolated as a colorless oil (74% yield, two steps): R_f = 0.3 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.26 (s, 3H), 1.57−2.04 (m, 4H), 2.46−2.65 (m, 2H), 3.79 (s, 3H), 3.89 (d, J = 14.4 Hz, 1H), 3.90 (m, 1H), 5.11 (d, J = 14.4 Hz, 1H), 5.21 (s, 1H), 6.84 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 27.9, 28.0, 32.0, 38.1, 43.7, 47.6, 52.8, 55.2, 55.5, 113.9, 129.0, 129.8, 158.8, 176.3, 191.7; IR (ATR) ν 3067, 2955, 2100, 1624, 1510, 1374, 1245 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{18}H_{23}N_3NaO_3^+$ m/z 352.1632, found m/z 352.1626.



*cis-6-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)-4-methylpiperidin-2-one (**6c**).* Prepared according to general procedure C and isolated as a colorless oil (73% yield, two steps): R_f = 0.2 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 4.8 Hz, 3H), 1.24 (m, 1H), 1.80−2.26 (m, 4H), 2.53−2.77 (m, 2H), 3.80 (s, 3H), 3.83 (m, 1H), 4.35 (d, J = 15.6 Hz, 1H), 4.88 (d, J = 15.6 Hz, 1H), 5.07 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 26.5, 37.9, 41.1, 46.1, 46.6, 53.4, 55.2, 55.6, 114.0, 128.6, 129.6, 158.7, 171.3, 191.4; IR (ATR) ν 3087, 2953, 2104, 1630, 1512, 1368, 1245 cm^{-1}; HRMS (ESI-TOF)

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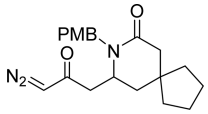
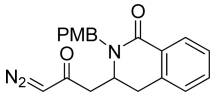
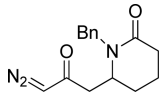
$[M + Na]^+$ calcd for $C_{17}H_{21}N_3NaO_3^+$ m/z 338.1475, found m/z 338.1467.



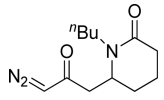
*9-(3-Diazo-2-oxopropyl)-8-(4-methoxybenzyl)-8-azaspiro[4.5]-decan-7-one (**6d**).* Prepared according to general procedure C and isolated as a colorless oil (73% yield, two steps): R_f = 0.3 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31−1.68 (m, 9H), 1.85 (m, 1H), 2.25−2.43 (m, 3H), 2.75 (m, 1H), 3.80 (s, 3H), 3.80 (m, 1H), 4.24 (d, J = 14.8 Hz, 1H), 5.02 (d, J = 14.8 Hz, 1H), 5.10 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.4, 34.9, 40.1, 40.3, 40.5, 44.7, 45.6, 46.3, 51.5, 55.2, 55.5, 113.9, 129.0, 129.3, 158.7, 170.9, 191.4; IR (ATR) ν 2950, 2102, 1624, 1511, 1355, 1243 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{20}H_{25}N_3NaO_3^+$ m/z 378.1788, found m/z 378.1786.



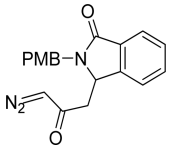
*3-(3-Diazo-2-oxopropyl)-2-(4-methoxybenzyl)-3,4-dihydroisoquinolin-1-one (**6e**).* Prepared according to general procedure C and isolated as a pale yellow oil (79% yield, two steps): R_f = 0.3 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36−2.42 (m, 2H), 2.75 (m, 1H), 3.18 (dd, J = 16.0, 5.6 Hz, 1H), 3.79 (s, 3H), 4.07 (d, J = 14.4 Hz, 1H), 4.17 (m, 1H), 5.09 (s, 1H), 5.18 (d, J = 14.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.37 (dd, J = 7.6, 7.2 Hz, 1H), 7.43 (dd, J = 7.6, 7.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5, 42.2, 48.2, 51.4, 55.2, 55.5, 114.0, 127.2, 127.9, 128.2, 129.0, 129.5, 129.7, 132.0, 135.7, 159.0, 163.5, 191.6; IR (ATR) ν 3067, 2952, 2101, 1635, 1510, 1371, 1243 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{20}H_{19}N_3NaO_3^+$ m/z 372.1319, found m/z 372.1322.



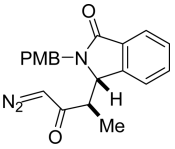
*6-(3-Diazo-2-oxopropyl)-1-benzylpiperidin-2-one (**6g**).* Prepared according to general procedure C and isolated as yellow powder (85% yield, two steps): mp 87−89 °C; R_f = 0.2 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.93 (m, 4H), 2.40−2.55 (m, 3H), 2.63 (dd, J = 15.2, 3.2 Hz, 1H), 3.95 (m, 1H), 4.10 (d, J = 15.2 Hz, 1H), 5.13 (d, J = 15.2 Hz, 1H), 5.19 (s, 1H), 7.22−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 27.3, 31.7, 43.6, 48.2, 52.6, 55.5, 127.3, 127.7, 128.5, 137.3, 170.1, 191.5; IR (ATR) ν 2948, 2097, 1622, 1495, 1450, 1414, 1328, 1136, 1071, 967 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{30}H_{34}N_6NaO_4^+$ m/z 565.2534, found m/z 565.2543.



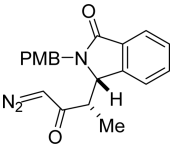
*1-Butyl-6-(3-diazo-2-oxopropyl)piperidin-2-one (**6h**).* Prepared according to general procedure C and isolated as a yellow oil (74% yield, two steps): R_f = 0.2 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.25−1.37 (m, 2H), 1.47−1.60 (m, 2H), 1.72−1.90 (m, 4H), 2.30−2.53 (m, 3H), 2.62−2.73 (m, 2H), 3.84−3.91 (m, 1H), 3.97−4.01 (m, 1H), 5.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 17.0, 20.2, 27.1, 29.6, 31.7, 43.7, 45.3, 52.9, 55.7, 169.6, 191.7; IR (ATR) ν 3486, 2954, 2099, 1618, 1474, 1415, 1362, 1296, 1136, 1083 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{24}H_{38}N_6NaO_4^+$ m/z 497.2847, found m/z 497.2855.



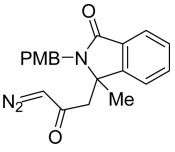
*3-(3-Diazo-2-oxopropyl)-2-(4-methoxybenzyl)isoindolin-1-one (**6i**).* Prepared according to general procedure C and isolated as a pale yellow oil (61% yield, two steps): R_f = 0.4 (*n*-hexane/EtOAc, 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (dd, J = 7.2, 16.0 Hz, 1H), 2.80 (dd, J = 5.2, 16.0 Hz, 1H), 3.78 (s, 3H), 4.43 (d, J = 17.2 Hz, 1H), 4.97 (m, 1H), 5.00 (s, 1H), 5.02 (d, J = 17.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.48 (dd, J = 7.2, 7.2 Hz, 1H), 7.53 (dd, J = 7.2, 7.2 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 44.0, 55.2, 55.7, 56.0, 114.0, 122.5, 123.8, 128.5, 129.2 (2C), 131.7 (2C), 145.1, 159.0, 168.3, 190.7; IR (ATR) ν 3457, 2931, 2101, 1674, 1611, 1510, 1408, 1373, 1330, 1243 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{19}H_{18}N_3O_3^+$ m/z 336.1343, found m/z 336.1347.



*rac-(S)-3-[(R)-4-Diazo-3-oxobutan-2-yl]-2-(4-methoxybenzyl)-isoindolin-1-one (**6j**).* Prepared according to general procedure C using 2-[2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl]propanoic acid prepared according to general procedure B using triethyl 2-phosphonopropionate, instead of triethylphosphonoacetate, and isolated as a colorless oil (75% yield, 2:1 dr, two steps): R_f = 0.4 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (d, J = 7.2 Hz, 3H), 3.09 (m, 1H), 3.79 (s, 3H), 4.16 (d, J = 17.2 Hz, 1H), 4.92 (m, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.27 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.46−7.50 (m, 2H), 7.88 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7, 43.5, 43.9, 55.0, 55.2, 60.0, 114.2, 123.7 (2C), 128.4, 128.6, 129.4, 131.5, 132.6, 142.1, 159.1, 168.6, 194.7; IR (ATR) ν 3080, 2934, 2104, 1681, 1612, 1512, 1361, 1245 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}N_3O_3^+$ m/z 350.1499, found m/z 350.1492.



*rac-(S)-3-[(S)-4-Diazo-3-oxobutan-2-yl]-2-(4-methoxybenzyl)-isoindolin-1-one (**6k**).* Prepared according to general procedure C using 2-[2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl]propanoic acid prepared according to general procedure B using triethyl 2-phosphonopropionate, instead of triethylphosphonoacetate, and isolated as white powder (75% yield, 2:1 dr, two steps): mp 150−151 °C dec; R_f = 0.4 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 7.6 Hz, 3H), 3.00 (m, 1H), 3.76 (s, 3H), 4.17 (d, J = 17.2 Hz, 1H), 4.94 (m, 1H), 5.21 (d, J = 17.2 Hz, 1H), 5.22 (s, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.46 (dd, J = 7.2, 7.2 Hz, 1H), 7.52 (dd, J = 7.2, 7.2 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 44.1, 47.0, 54.7, 55.2, 60.2, 113.8, 121.9, 123.8, 128.5, 129.1, 129.5, 131.8, 132.4, 144.1, 158.9, 169.2, 194.4; IR (ATR) ν 3076, 2933, 2108, 1678, 1623, 1512, 1375, 1245 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}N_3O_3^+$ m/z 350.1499, found m/z 350.1500.



*3-(3-Diazo-2-oxopropyl)-2-(4-methoxybenzyl)-3-methylisoindolin-1-one (**6l**).* Prepared according to general procedure C and isolated as a colorless oil (30% yield, two steps): R_f = 0.3 (*n*-hexane/EtOAc,

DOI: 10.1021/acs.joc.5b01954
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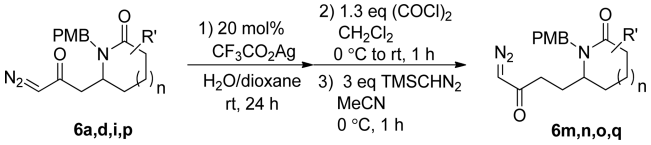
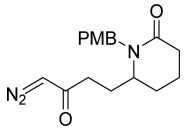
1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.71 (d, J = 14.8 Hz, 1H), 2.83 (d, J = 14.8 Hz, 1H), 3.77 (s, 3H), 4.55 (s, 1H), 4.63 (d, J = 16.0 Hz, 1H), 4.84 (d, J = 16.0 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.2 Hz, 1H), 7.48 (dd, J = 7.2, 7.2 Hz, 1H), 7.55 (dd, J = 7.2, 7.2 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 42.5, 48.3, 55.2, 55.8, 64.4, 113.8, 121.2, 123.9, 128.5, 129.4, 130.3, 131.0, 131.8, 149.0, 158.8, 168.0, 189.6; IR (ATR) ν 3074, 2972, 2932, 2100, 1676, 1633, 1511, 1365, 1244 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{20}H_{20}N_3O_3^+$ m/z 350.1499, found m/z 350.1501.

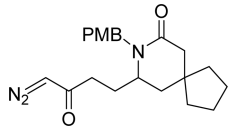


6a,d,i,p **6m,n,o,q**

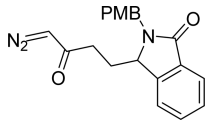
General Procedure D. To a stirred solution of **6** in dioxane and H_2O (9/1) was added CF_3COOAg (20 mol %), and the whole was stirred at room temperature for 12 h. EtOAc, toluene, and H_2O were successively added to the reaction mixture, and the aqueous layer was extracted with a 10% NaOH solution. The combined aqueous layer was acidified with a 10% HCl solution; the organic layer was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was used for the next reaction without further purification. To a stirred solution of the carboxylic acid in CH_2Cl_2 was added $(COCl)_2$ (1.3 equiv) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give crude acid chloride. The residue was dissolved in CH_3CN, and $TMSCHN_2$ (2.0 M solution in Et_2O, 3 equiv) was added to the solution at 0 °C. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel to afford α-diazocarbonyl compounds **6m**, **6n**, and **6o**.



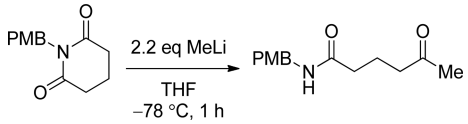
*6-(4-Diazo-3-oxobutyl)-1-(4-methoxybenzyl)piperidin-2-one (**6m**).* Prepared according to general procedure D and isolated as a pale yellow oil (72% yield, three steps): R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–2.44 (m, 10H), 3.30 (m, 1H), 3.78 (s, 3H), 3.91 (d, J = 14.4 Hz, 1H), 5.27 (s, 1H), 5.30 (d, J = 14.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 25.8, 26.5, 31.7, 36.3, 46.4, 54.0, 54.4, 55.0, 113.6, 129.0, 129.5, 158.5, 169.9, 193.2; IR (ATR) ν 2952, 2100, 1617, 1510, 1352, 1242 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{21}N_3NaO_3^+$ m/z 338.1475, found m/z 338.1473.



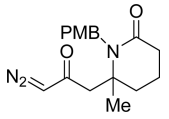
*9-(4-Diazo-3-oxobutyl)-8-(4-methoxybenzyl)-8-azaspiro[4.5]decan-7-one (**6n**).* Prepared according to general procedure D and isolated as a colorless oil (68% yield, three steps): R_f = 0.3 (n-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.68 (m, 10H), 1.92–1.97 (m, 2H), 2.24–2.49 (m, 4H), 3.35 (m, 1H), 3.79 (s, 3H), 3.96 (d, J = 14.4 Hz, 1H), 5.18 (s, 1H), 5.37 (d, J = 14.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.6, 27.6, 34.4, 34.6, 39.4, 40.1, 40.2, 44.7, 45.0, 52.0, 54.5, 55.1, 113.8, 129.1, 129.4, 158.7, 171.1, 193.6; IR (ATR) ν 2945, 2861, 2100, 1624, 1510, 1344, 1242 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{21}H_{27}N_3NaO_3^+$ m/z 392.1945, found m/z 392.1953.



*3-(4-Diazo-3-oxobutyl)-2-(4-methoxybenzyl)isoindolin-1-one (**6o**).* Prepared according to general procedure D and isolated as a pale yellow oil (74% yield, three steps): R_f = 0.4 (n-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.84 (m, 2H), 2.29–2.45 (m, 2H), 3.78 (s, 3H), 4.13 (d, J = 17.2 Hz, 1H), 4.52 (m, 1H), 4.87 (s, 1H), 5.20 (d, J = 17.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.48 (dd, J = 7.2, 7.2 Hz, 1H), 7.54 (dd, J = 7.2, 7.2 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 32.7, 43.2, 54.4, 55.2, 57.7, 114.0, 122.2, 123.7, 128.3, 129.0, 129.5, 131.7, 132.4, 144.0, 159.0, 168.4, 193.2; IR (ATR) ν 2925, 2104, 1684, 1649, 1512, 1246 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{20}H_{19}N_3NaO_3^+$ m/z 372.1319, found m/z 372.1317.



*N-(4-Methoxybenzyl)-5-oxohexanamide (**s4**).* To a stirred solution of 1-(4-methoxybenzyl)-piperidine-2,6-dione (933 mg, 4 mmol) in THF (200 mL) was added MeLi (8.8 mmol, 1.1 M solution in Et_2O). After being stirred at −78 °C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the solvent was removed under reduced pressure. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (n-hexane/EtOAc/MeOH, 12/8/1) to afford **s4** (837 mg, 84%) as white powder: mp 107–109 °C; R_f = 0.3 (n-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (tt, J = 6.8 Hz, 2H), 2.11 (s, 3H), 2.21 (t, J = 6.8 Hz, 2H), 2.50 (t, J = 6.8 Hz, 2H), 3.79 (s, 3H), 4.34 (d, J = 5.6 Hz, 2H), 6.01 (br s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 29.8, 35.1, 42.3, 42.8, 55.1, 113.9, 129.0, 130.3, 158.8, 172.1, 208.5; IR (ATR) ν 3299, 1701, 1637, 1545, 1511, 1303, 1246, 1160, 1027, 819 cm^{-1}; HRMS (ESI-TOF) $[2M + Na]^+$ calcd for $C_{28}H_{38}N_2NaO_6^+$ m/z 521.2622, found m/z 521.2621.



*6-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)-6-methylpiperidin-2-one (**6f**).* To a stirred suspension of NaH (2 equiv, 60% dispersion in mineral oil) in THF was added triethylphosphonoacetate (1.8 equiv) at 0 °C, and the mixture was stirred at 0 °C for 30 min. **s4** (499 mg, 2 mmol) was added and the mixture stirred in refluxing THF for 35.5 h. After the mixture had cooled to room temperature, NaOH (aqueous, 10%) was added, and stirring was continued at room temperature for 2 h. The reaction mixture was acidified with 6 N aqueous HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used for the next reaction without further purification. To a stirred solution of the crude carboxylic acid in CH_2Cl_2 was added $(COCl)_2$ (1.3 equiv) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give crude acid chloride. The residue was dissolved in CH_3CN, and $TMSCHN_2$ (2.0 M solution in Et_2O, 3 equiv) was added to the solution at 0 °C. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (n-hexane/EtOAc/MeOH, 16/8/1) to afford **6f** as a yellow oil (13% yield, three steps): R_f = 0.3 (n-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.72–1.90 (m, 3H), 2.18 (m, 1H), 2.48–2.56 (m, 4H), 3.77 (s, 3H), 4.50 (d, J = 15.6 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 5.20 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 27.0, 32.2, 35.0, 44.7, 49.1, 55.2, 56.6, 59.6, 113.7, 128.1, 131.2, 158.3, 171.1, 191.2; IR (ATR) ν 2948, 2098, 1616, 1510, 1441, 1352, 1242, 1174, 1031 cm^{-1}; HRMS (ESI-TOF)

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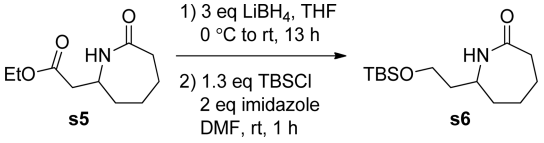
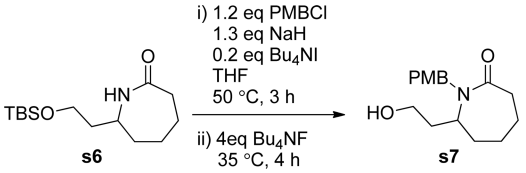
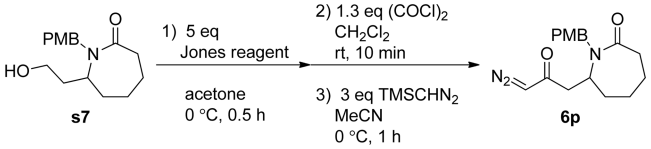
[M + Na]$^+$ calcd for $C_{17}H_{21}N_3NaO_3^+$ m/z 338.1475, found m/z 338.1470.



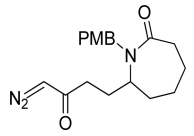
*7-[2-(tert-Butyldimethylsilyloxy)ethyl]azepan-2-one (**s6**).* To a stirred solution of **s5**[29] (600 mg, 3.3 mmol) in THF (30 mL) was added $LiBH_4$ (215 mg, 9.8 mmol) at 0 °C, and the whole was allowed to warm to room temperature. After 13 h, MeOH, H_2O, and saturated aqueous NH_4Cl were successively added to the mixture; the organic layer was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (5 mL), and to the stirred solution were added imidazole (449 mg, 6.6 mmol) and TBSCl (648 mg, 4.3 mmol) at 0 °C. The whole was stirred at room temperature for 1 h, and saturated aqueous NH_4Cl was added to the mixture. The organic layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (*n*-hexane/EtOAc, 6/5 to 3/7) gave **s6** (433 mg, 49%, two steps) as a colorless oil: R_f = 0.6 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.36−2.04 (m, 8H), 2.45 (m, 2H), 3.53 (m, 1H), 3.68−3.79 (m, 2H), 6.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −5.5, 18.1, 23.2, 25.8, 29.7, 35.6, 36.8, 38.4, 51.8, 60.0, 177.6; IR (ATR) ν 3221, 2927, 2855, 1660, 1441, 1100, 831 cm^{-1}; HRMS (ESI-TOF) [2M + H]$^+$ calcd for $C_{28}H_{59}N_2O_4Si_2^+$ m/z 543.4008, found m/z 543.4017.



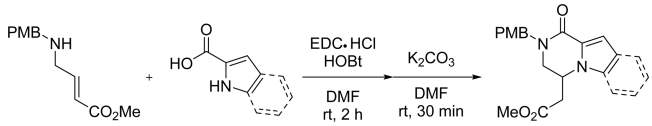
*7-(2-Hydroxyethyl)-1-(4-methoxybenzyl)azepan-2-one (**s7**).* To a stirred solution of **s6** (409 mg, 1.5 mmol) and tetrabutylammonium iodide (111 mg, 0.30 mmol) in THF (15 mL) was added NaH (79 mg, 2.0 mmol, 60% dispersion in mineral oil) at 0 °C. After 0.5 h, PMBCl (0.25 mL, 1.8 mmol) was added to the mixture, and the whole was stirred at 50 °C for 3 h. Tetrabutylammonium fluoride (1.6 g, 6.0 mmol) in THF (6 mL) was added to the reaction mixture, and the whole was stirred at 35 °C for 4 h. Saturated aqueous NH_4Cl was added to the mixture; the organic layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (EtOAc) gave **s7** (310 mg, 74%) as a colorless oil: R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−2.05 (m, 9H), 2.53 (ddd, J = 14.4, 12.8, 1.6 Hz, 1H), 2.68 (ddd, J = 12.8, 6.8, 1.6 Hz, 1H), 3.59 (t, J = 6.0 Hz, 2H), 3.69 (m, 1H), 3.79 (s, 3H), 4.10 (d, J = 14.4 Hz, 1H), 5.02 (d, J = 14.4 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.0, 31.9, 34.3, 37.8, 51.1, 53.8, 55.2, 59.4, 113.7, 129.7, 130.4, 158.8, 175.5; IR (ATR) ν 3386, 2928, 1606, 1511, 1245, 1034 cm^{-1}; HRMS (ESI-TOF) [2M + Na]$^+$ calcd for $C_{32}H_{46}N_2NaO_6^+$ m/z 577.3248, found m/z 577.3242.



*7-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)azepan-2-one (**6p**).* To a stirred solution of **s7** (277 mg, 1.0 mmol) in acetone (10 mL) was added Jones reagent (2.0 mL, 2.5 M) at 0 °C, and the whole was stirred for 0.5 h. ^{i}PrOH, EtOAc, toluene, and H_2O were successively added to the reaction mixture, and the aqueous layer was extracted with a 10% NaOH solution. The combined aqueous layer was acidified with a 10% HCl solution; the organic layer was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (1.0 mL), and to the stirred solution was added $(COCl)_2$ (0.11 mL, 1.3 mmol) at 0 °C. The whole was stirred at room temperature for 10 min and concentrated. The residue was dissolved in MeCN (4.5 mL), and to the stirred solution was added $TMSCHN_2$ (342 mg, 3 mmol) in Et_2O (1.5 mL) at 0 °C. The whole was stirred for 1 h and concentrated. The residue was purified by column chromatography (*n*-hexane/EtOAc/MeOH, 3/7/0 to 0/9/1) to give **6p** (69% yield, 242 mg, three steps) as a colorless oil: R_f = 0.3 (*n*-hexane/EtOAc, 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−1.80 (m, 6H), 2.44−2.78 (m, 4H), 3.78 (s, 3H), 3.87 (m, 1H), 4.17 (d, J = 14.8 Hz, 1H), 4.92 (d, J = 14.8 Hz, 1H), 5.21 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 24.2, 32.0, 37.8, 42.6, 50.5, 53.6, 55.0, 55.3, 113.7, 129.5, 130.0, 158.7, 174.9, 191.3; IR (ATR) ν 2932, 2099, 1611, 1510, 1367, 1244 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{21}N_3NaO_3^+$ m/z 338.1475, found m/z 338.1477.

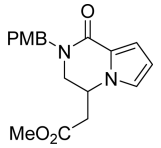


*7-(4-Diazo-3-oxobutyl)-1-(4-methoxybenzyl)azepan-2-one (**6q**).* Prepared according to general procedure D and isolated as a colorless oil (76% yield, three steps): R_f = 0.5 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−2.31 (m, 10H), 2.55 (ddd, J = 14.4, 12.4, 2.4 Hz, 1H), 2.69 (ddd, J = 14.4, 6.8, 2.0 Hz, 1H), 3.43 (m, 1H), 3.79 (s, 3H), 4.09 (d, J = 14.4 Hz, 1H), 4.96 (d, J = 14.4 Hz, 1H), 5.14 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 23.7, 26.5, 31.6, 37.4, 37.7, 51.1, 54.4, 55.2, 56.8 113.7, 129.8, 130.3, 158.8, 175.2, 193.5; IR (ATR) ν 2931, 2098, 1610, 1510, 1356, 1243, 1173, 1031 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{18}H_{23}N_3NaO_3^+$ m/z 352.1632, found m/z 352.1639.



General Procedure E. To a solution of (*E*)-methyl 4-[(4-methoxybenzyl)amino]but-2-enoate and carboxylic acid (1.1 equiv) in DMF (0.5 M) were added EDC·HCl (1.2 equiv) and HOBt (0.3 equiv), and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude residue that could be utilized in the next step without further purification.

To a solution of the crude residue in DMF (0.5 M) was added K_2CO_3 (10 mol %), and the mixture was stirred for 30 min at room temperature. Then H_2O was added, and the reaction mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford cyclized ester.



*Methyl 2-[2-(4-methoxybenzyl)-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazin-4-yl]acetate (**s8a**).* Prepared according to general procedure E and isolated as a white solid (77% yield, 82.9 mg, two steps): mp 101−102 °C; R_f = 0.2 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (dd, J = 16.8, 7.6 Hz, 1H), 2.60 (dd, J = 16.8, 6.0 Hz, 1H), 3.35 (dd, J = 13.2, 2.8 Hz, 1H), 3.58 (s, 3H), 3.79 (s, 3H), 3.80 (dd, J = 13.2, 4.0 Hz, 1H), 4.27 (d, J = 14.0 Hz, 1H), 4.58 (dddd, J = 7.6, 6.0, 4.0, 2.8 Hz, 1H), 5.00 (d, J = 14.0 Hz, 1H), 6.21 (dd, J = 4.0, 2.4 Hz, 1H), 6.73 (dd, J = 2.4, 1.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.96 (dd, J = 4.0, 1.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.5, 48.2, 48.3, 50.2, 51.9, 55.2, 110.3, 114.0, 122.0, 123.7, 128.9, 129.9, 130.0, 159.0, 159.1, 170.6; IR

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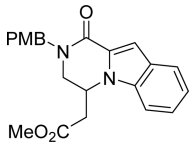
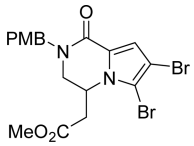
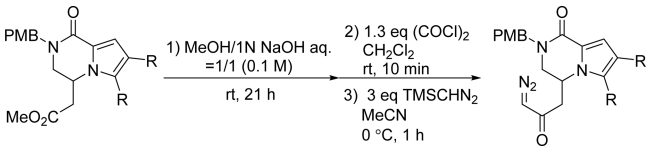
(ATR) ν 2952, 1732, 1634, 1544, 1510, 1433, 1328, 1302, 1242, 1173 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{18}H_{20}N_2NaO_4^+$ m/z 351.1315, found m/z 351.1323.



*Methyl 2-[2-(4-Methoxybenzyl)-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-a]indol-4-yl]acetate (**s8b**).* Prepared according to general procedure E and isolated as a colorless oil (59% yield, 200.8 mg, two steps): R_f = 0.4 (*n*-hexane/EtOAc, 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (dd, J = 16.8, 5.2 Hz, 1H), 2.53 (dd, J = 16.8, 8.4 Hz, 1H), 3.50 (s, 3H), 3.56 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.94 (dd, J = 13.2, 4.0 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 4.88 (m, 1H), 5.16 (d, J = 14.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.16 (m, 1H), 7.27−7.34 (m, 5H), 7.71 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 47.1, 47.8, 48.5, 51.8, 55.2, 107.0, 109.4, 114.1, 120.9, 122.8, 124.7, 127.6, 128.1, 128.5, 130.1, 135.1, 159.2, 159.5, 170.7; IR (ATR) ν 2951, 1731, 1645, 1610, 1547, 1510, 1433, 1328, 1302, 1242, 1173 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{22}H_{22}N_2NaO_4^+$ m/z 401.1472, found m/z 401.1477.

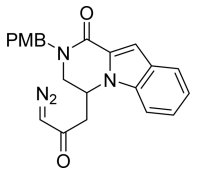


*Methyl 2-[6,7-Dibromo-2-(4-methoxybenzyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl]acetate (**s8c**).* To a stirred solution of **s8a** (781.7 mg, 2.38 mmol) in MeOH (4.3 mL) and THF (4.3 mL) was added 1.3-dibromo-5,5-dimethylhydrantoine (408.9 mg, 1.43 mmol) at −40 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $NaSO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography using silica gel to afford **s8c** as a white solid (14% yield, 162.7 mg): mp 106−107 °C; R_f = 0.5 (*n*-hexane/EtOAc, 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.38−2.56 (m, 2H), 3.52 (m, 1H), 3.53 (s, 3H), 3.80 (s, 3H), 3.82 (m, 1H), 4.12 (d, J = 14.0 Hz, 1H), 4.59 (m, 1H), 5.07 (d, J = 14.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.01 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 46.9, 48.2, 48.8, 51.8, 55.2, 103.7, 112.8, 114.1, 114.7, 124.9, 128.6, 130.1, 158.1, 159.1, 170.1; IR (ATR) ν 2952, 1731, 1644, 1543, 1511, 1468, 1428, 1370, 1324, 1241 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{18}H_{18}Br_2N_2NaO_4^+$ m/z 506.9526, found m/z 506.9515.

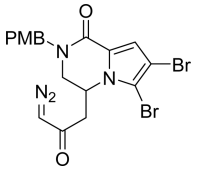


General Procedure F. A solution of ester **s8** in a 1/1 MeOH/1 N aqueous NaOH mixture (0.1 M) was stirred for 21 h at room temperature, and the reaction mixture was acidified with 1 N aqueous HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude carboxylic acid.

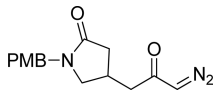
To a stirred solution of the crude carboxylic acid in CH_2Cl_2 was added $(COCl)_2$ (1.3 equiv) at room temperature, and the mixture was stirred for 10 min. The reaction mixture was concentrated under reduced pressure to give crude acid chloride. The residue was dissolved in CH_3CN (0.2 M), and $TMSCHN_2$ (2.0 M solution in Et_2O, 3 equiv) was added to the solution at 0 °C. After the mixture had been stirred for 1 h, saturated aqueous $NaHCO_3$ was added and the reaction mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the α-diazocarbonyl compound.



*4-(3-Diazo-2-oxopropyl)-2-(4-methoxybenzyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**6r**).* Prepared according to general procedure F and isolated as brown blocks (14% yield, 180.9 mg, three steps): mp 104−106 °C; R_f = 0.2 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (m, 2H), 3.51 (d, J = 13.2 Hz, 1H), 3.78 (s, 3H), 3.92 (dd, J = 13.2, 3.6 Hz, 1H), 4.08 (d, J = 14.4 Hz, 1H), 4.58 (s, 1H), 5.00 (m, 1H), 5.27 (d, J = 14.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.14 (m, 1H), 7.26−7.29 (m, 5H), 7.69 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3, 47.1, 47.9, 48.4, 55.2, 55.4, 106.9, 109.6, 114.0, 120.9, 122.7, 124.7, 127.5, 128.1, 128.9, 130.4, 135.1, 159.3, 159.4, 190.8; IR (ATR) ν 2933, 2101, 1633, 1546, 1509, 1430, 1350, 1316, 1239, 1173 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{22}H_{20}N_4NaO_3^+$ m/z 411.1428, found m/z 411.1433.

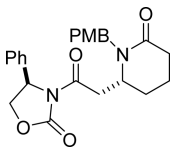


*6,7-Dibromo-4-(3-diazo-2-oxopropyl)-2-(4-methoxybenzyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (**3**).* Prepared according to general procedure F and isolated as a pale yellow oil (67% yield, 63 mg, three steps): R_f = 0.4 (*n*-hexane/EtOAc, 3/2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (m, 2H), 3.51 (dd, J = 13.2, 0.8 Hz, 1H), 3.79 (s, 3H), 3.83 (dd, J = 13.2, 3.6 Hz, 1H), 3.99 (d, J = 14.0 Hz, 1H), 4.69 (s, 1H), 4.74 (m, 1H), 5.15 (d, J = 14.0 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.0, 46.9, 48.3, 50.0, 55.25, 55.31, 101.0, 105.3, 114.1, 116.0, 125.3, 128.7, 130.4, 157.0, 159.4, 190.0; IR (ATR) ν 2933, 2105, 1639, 1512, 1377, 1327, 1245 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{18}H_{16}Br_2N_4NaO_3^+$ m/z 516.9481, found m/z 516.9486.



*4-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (**6s**).* Prepared according to general procedure C and isolated as a brown oil (65%, two steps): ^1H NMR (400 MHz, $CDCl_3$) δ 2.12 (dd, J = 16.8, 7.2 Hz, 1H), 2.30−2.50 (m, 2H), 2.64 (dd, J = 16.8, 8.8 Hz, 1H), 2.78 (m, 1H), 2.91 (dd, J = 9.6, 6.0 Hz, 1H), 3.46 (dd, J = 10.0, 8.8 Hz, 1H), 3.79 (s, 3H), 4.34 (d, J = 14.8 Hz, 1H), 4.38 (d, J = 14.8, 1H), 5.24 (s, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 37.3, 44.9, 45.9, 51.8, 55.0, 55.3, 114.0, 128.4, 129.5, 159.1, 173.3, 192.3; IR (ATR) ν 2015, 1682, 1637, 1513, 1442, 1355, 1246, 1176, 1032 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{15}H_{17}N_3NaO_3^+$ m/z 310.1162, found m/z 310.1165.

*Preparation of (−)-**6a**.*



*(R)-3-{2-[(R)-1-(4-Methoxybenzyl)-6-oxopiperidin-2-yl]acetyl}-4-phenyloxazolidin-2-one [(−)-**s9**].* A solution of **s3a** (554.6 mg, 2 mmol), (*R*)-4-phenyl-2-oxazolidinone (326 mg, 2 mmol), DMAP (122 mg, 1 mmol), and *N*-ethyl-*N*′-[3-(dimethylamino)propyl]-carbodiimide (EDC) HCl salt (460 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 36 h. The reaction

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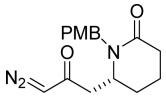
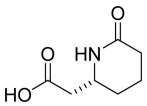
mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (*n*-hexane/EtOAc/MeOH, 16/8/1) to afford **s9** as a colorless gum (39% yield, 330.9 mg). The absolute configuration of the piperidinone ring was determined by converting it to **s10**: R_f = 0.3 (*n*-hexane/EtOAc/MeOH, 8/8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (m, 1H), 1.64−1.80 (m, 2H), 1.92 (m, 1H), 2.42 (m, 1H), 2.53 (m, 1H), 3.08 (dd, J = 16.4, 8.4 Hz, 1H), 3.37 (dd, J = 16.4, 4.4 Hz, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.18 (d, J = 14.8 Hz, 1H), 4.26 (dd, J = 9.2, 3.6 Hz, 1H), 4.63 (dd, J = 9.2, 8.4 Hz, 1H), 4.94 (d, J = 14.8 Hz, 1H), 5.28 (dd, J = 8.4, 3.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.25 (dd, J = 7.6, 0.8 Hz, 2H), 7.31−7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 27.6, 31.6, 38.9, 47.8, 52.0, 55.2, 57.6, 69.9, 113.8, 125.8, 128.9, 129.2 (2C), 129.7, 138.7, 153.4, 158.7, 169.9, 170.0; IR (ATR) ν 2946, 1775, 1700, 1631, 1511, 1458, 1382, 1324, 1243, 1199, 1039 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_5^+$ m/z 423.1914, found m/z 423.1915; $[\alpha]^{20}_D$ − 79.0° (c 1.0, $CHCl_3$)



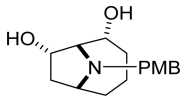
*(R)-6-(3-Diazo-2-oxopropyl)-1-(4-methoxybenzyl)piperidin-2-one [(−)-**6a**].* To a stirred solution of **s9** (659.2 mg, 1.56 mmol) in THF (6.2 mL) were added LiOH (93.4 mg, 3.9 mmol) and 30% aqueous H_2O_2 (0.35 mL, 3.1 mmol) in H_2O (1.7 mL) at 0 °C. After the mixture had been stirred for 1 h at 0 °C, saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the aqueous layer was washed with EtOAc. The aqueous layer was acidified with 1 N aqueous HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude (*R*)-**s3a**.

(*R*)-**s3a** was converted to (−)-**6a** according to general procedure C and isolated as yellow powder (37% yield, 174.3 mg, three steps): mp 101−103 °C; $[\alpha]^{23}_D$ − 34.0° (c 1, $CHCl_3$). The enantiomeric excess was determined to be 98% by analytical chiral HPLC. Nineteen min, 21 min (OJ-H column, 85/15 *n*-hexane/^{i}PrOH, 1 mL/min, 254 nm).

Determination of the Absolute Configuration and Enantiomeric Excess.



*(R)-2-(6-Oxopiperidin-2-yl)acetic Acid [(−)-**s10**].* A solution of (*R*)-**s3a** (49.6 mg, 0.18 mmol) in trifluoroacetic acid was refluxed for 12 h, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and basified with saturated aqueous $NaHCO_3$, and the aqueous layer was washed with CH_2Cl_2. The aqueous layer was acidified with 6 N aqueous HCl, washed with CH_2Cl_2, concentrated under reduced pressure, and extracted with $CHCl_3$. The extract was filtered through Celite and washed with Et_2O to afford (−)-**s10** as colorless powder (78% yield, 21.1 mg, two steps): mp 117−119 °C; $[\alpha]^{24}_D$ − 21.2° (c 0.5, EtOH). (*S*)-2-(6-Oxopiperidin-2-yl)acetic acid [(+)-**s10**}: $[\alpha]_D$ + 17.8° (c 1, EtOH).[30]



*(1S,2R,6R,8S)-9-(4-Methoxybenzyl)-9-azabicyclo[4.2.1]nonane-2,8-diol [(−)-**8**].* Prepared via the same procedure for the synthesis of **8** and isolated as white powder: mp 74−76 °C; $[\alpha]^{20}_D$ − 14.1° (c 1, $CHCl_3$). The enantiomeric excess was determined to be 98% by analytical chiral HPLC. Eighteen min, 21 min (AD-H column, 95/5 *n*-hexane/^{i}PrOH, 1 mL/min, 254 nm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01954.

Computational details and charts of spectra (PDF)

X-ray crystallographic data (CIF)

X-ray crystallographic data (CIF)

X-ray crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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