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Asymmetric Michael Addition Induced by (*R*)-*tert*-Butanesulfinamide and Syntheses of Chiral Pyrazolidinone Derivatives

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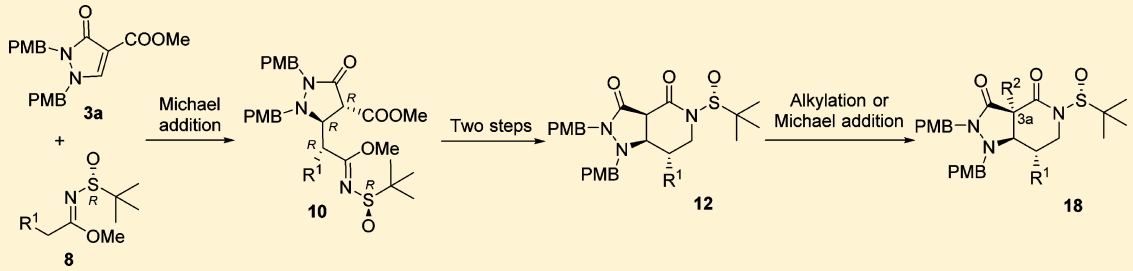
Supporting Information



ABSTRACT: A highly diastereoselective Michael addition of (*R*)-*N*-*tert*-butanesulfinyl imidates **8** to *α*,*β*-unsaturated pyrazolidinone **3a** has been developed to afford pyrazolidinones **10** possessing three contiguous stereocenters with good to excellent yield and excellent diastereoselectivity. A two-step conversion of reduction and cyclization provides the bicyclic pyrazolopiperidine **12** in a good yield. A series of pyrazolopiperidine derivatives **18** with a quaternary carbon center at C-3a are stereoselectively synthesized via alkylation or Michael addition.

Nitrogen-containing molecules are extremely important because of their abundance in various natural products, pharmaceuticals, and synthetic organic compounds that have shown interesting biological activities.[1] In this context, tremendous endeavors have been devoted not only to preparing the nitrogen-containing heterocycles in optically pure forms but also to introduce multiple functional groups onto these compounds mainly through carbon−carbon bond formation.[2] *N*-*tert*-Butanesulfinyl imidates are privileged chiral sources for synthesizing nitrogen-containing compounds and have been widely investigated in organic synthesis.[3] For instance, the groups of Ellman,[4] Kimpe,[5] and Poisson[6] have, respectively, explored the *α*-alkylation, Mannich-type addition, and aldol addition of *N*-*tert*-butanesulfinyl imidates. Recently, Liu et al.[7] and our group[8] have reported the synthesis of chiral indanones or butyrolactonimidates from *N*-*tert*-butanesulfinyl imidates and *α*,*β*-unsaturated diesters through highly stereoselective Michael addition. Despite great success, development of efficient methods for the preparation of nitrogen-containing heterocycles with multiple chiral centers is still highly desirable. 4,5-Disubstituted pyrazolidinones and corresponding ring-fused derivatives play an essential role in biologically active compounds.[9] Here, we report the synthesis of multisubstituted chiral pyrazolidinones **10** via Michael addition between different *N*-*tert*-butanesulfinyl imidates **8** and 4-methoxycarbonyl-substituted *α*,*β*-unsaturated pyrazolidinone **3**, which simultaneously generates three contiguous stereocenters in one step. The obtained products have shown to be versatile for synthesizing novel heterocyclic derivatives.

Preparation of both substrates, *α*,*β*-unsaturated pyrazolidinones **3** and *N*-*tert*-butanesulfinyl imidates **8**, is illustrated in Scheme 1. Condensation of 1,2-bis(4-methoxybenzyl)hydrazine (**1**) with methyl enol ether **2** in the presence of DBU, followed by lactamization under the acidic conditions, provided 4-methoxycarbonyl-substituted *α*,*β*-unsaturated pyrazolidinone **3a**,[10] and the 4-phenyl-substituted **3c** was prepared in a similar way between **4** and **5**.[11] Decarboxylation of **3a** employing LiCl/DMSO led to the derivative **3b**. On the other hand, according to the method reported in the literature,[4c,12] imidates **8a**−**e**,**j**,**k** were synthesized through condensation of *N*-*tert*-butanesulfinamide **7** with the corresponding orthoesters **6** in the presence of *p*-TsOH without solvent. Additionally, imidates **8f**−**i** were prepared from **8k** by *α*-alkylation with the corresponding halides **9**.[13]

With both *α*,*β*-unsaturated pyrazolidinones and *N*-*tert*-butanesulfinyl imidates in hand, we started to investigate the Michael addition reaction employing **3a** and **8a** as partners. Initial experiment using 1.5 equiv of LiHMDS at −78 °C in THF (Table 1, entry 1) gave the Michael adduct **10a** in moderate yield with excellent diastereoselectivity (75% yield, dr

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Scheme 1. Preparation of *α,β*-Unsaturated Pyrazolidinones 3 and *N-tert*-Butanesulfinyl Imidates 8

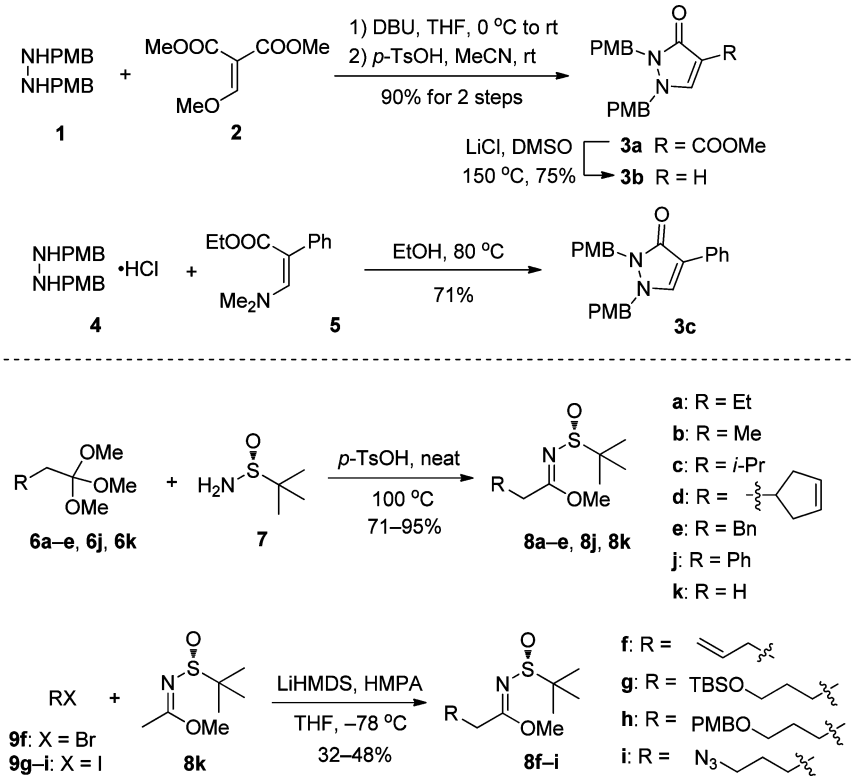
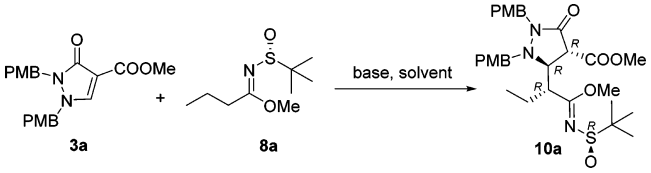


Table 1. Optimization of Conditions for the Michael Addition[a]



entry	base	solvent	T (°C)	yield[b] (%)	dr[c]
1[d]	LiHMDS	THF	−78	75	97:3
2[e]	*n*-BuLi	THF	−78	94	95:5
3[f]	*t*-BuLi	THF	−78	84	95:5
4[g]	LDA	THF	−78	92	97:3
5	LDA	DME	−78	12	88:12
6	LDA	Et_2O	−78	NR	
7	LDA	toluene	−78	trace	54:46
8	LDA	CH_2Cl_2	−78	NR	
9	LDA	THF	−40	10	79:21
10	LDA	THF	−20	trace	73:27
11	LDA	THF	0	NR	

[a]Unless noted otherwise, reactions were performed with **3a** (0.13 mmol), **8a** (0.2 mmol), and base (0.2 mmol) at −78 °C in 2.0 mL of corresponding solvent. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]1.0 mol/L of LiHMDS in THF was used as base. [e]2.5 mol/L of *n*-BuLi in *n*-hexane was used as base. [f]1.3 mol/L of *t*-BuLi in *n*-pentane was used as base. [g]1.5 mol/L of LDA in THF/ethylbenzene/heptane was used as base.

= 97:3). X-ray crystallographic analysis of the single crystal of **10a** unambiguously indicated the absolute configuration of the three newly generated stereocenters to be (*R*,*R*,*R*).[14] Replacement of LiHMDS with *n*-BuLi resulted in an improved yield (94%) but slightly decreased diastereoselectivity (dr = 95:5, entry 2). Using *t*-BuLi as base, the yield was substantially reduced to 84% with the same dr value (dr = 95:5, entry 3). To our delight, compound **10a** was obtained in high yield (92%) and excellent diastereoselectivity (dr = 97:3, entry 4) when LDA was used. Further condition screening revealed that solvent had a remarkable influence on both the conversion and diastereoselectivity. Only THF was found to give a clean reaction, while other tested solvents, such as DME, Et_2O, toluene, and CH_2Cl_2, provided inferior results (entries 5−8). Furthermore, the yields decreased when the reaction was performed at higher temperatures and, not surprisingly, accompanied by poorer diastereoselectivity (entries 9−11).

We next explored the scope of the Michael reaction with different *α,β*-unsaturated pyrazolidinones **3** and *N-tert*-butanesulfinyl imidates **8** using the optimized conditions (1 equiv of **3**, 1.5 equiv of **8**, 1.5 equiv of LDA, THF, −78 °C). As described in Table 2, a variety of novel pyrazolidinones **10a−i** were prepared with moderate to excellent yield and excellent diastereoselectivity except for the product **10c**. The reason that substrate **8c** bearing a bulky isopropyl substituent afforded **10c** in a dramatically decreased yield and diastereoselectivity compared to other tested substrates was probably due to its increased steric repulsion. The reaction was usually compatible with imidates bearing various alkyl and functional alkyl side chains. Interestingly, slightly more base (2 equiv of LDA) was needed for the imidates **8d**, **8g**, and **8i** to obtain a substantially improved yield in the addition reaction. Note that only a trace amount of Michael adduct was observed when **3a** and **8j** were used as reaction partners. Additionally, we found that the reaction employing Michael acceptors **3b** and **3c** did not proceed under the same conditions, which might be caused by their lower reactivity compared to that of **3a**.

Pyrazolidinone **10a** was then used as a model compound for converting to bicyclic pyrazolo[4,3-*c*]piperidine **16b**.[15] The

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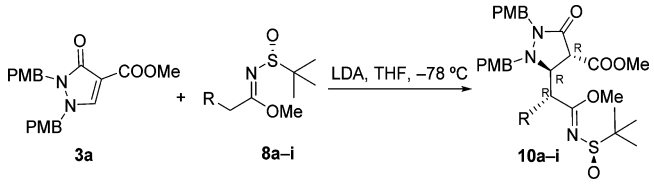
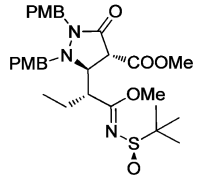
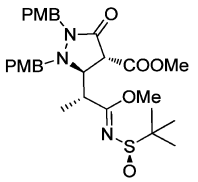
Table 2. Asymmetric Michael Addition of 3 with 8[a]

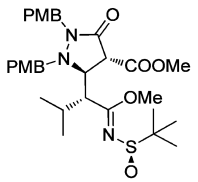




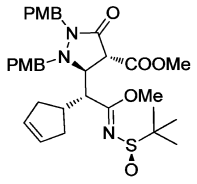
10a (92%; dr = 97:3)



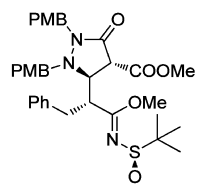
10b (91%; dr = 90:10)



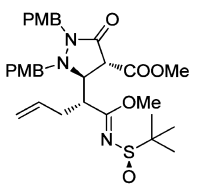
10c (26%; dr = 60:40)



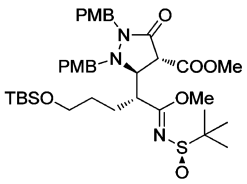
10d (72%; dr = 93:7)
10d (92%; dr = 94:6)[b]



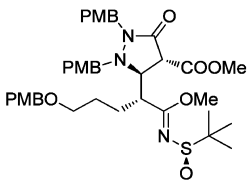
10e (80%; dr = 96:4)



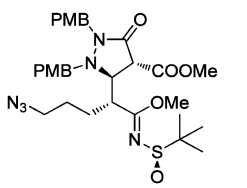
10f (88%; dr = 97:3)



10g (73%; dr = 96:4)
10g (90%; dr = 97:3)[b]



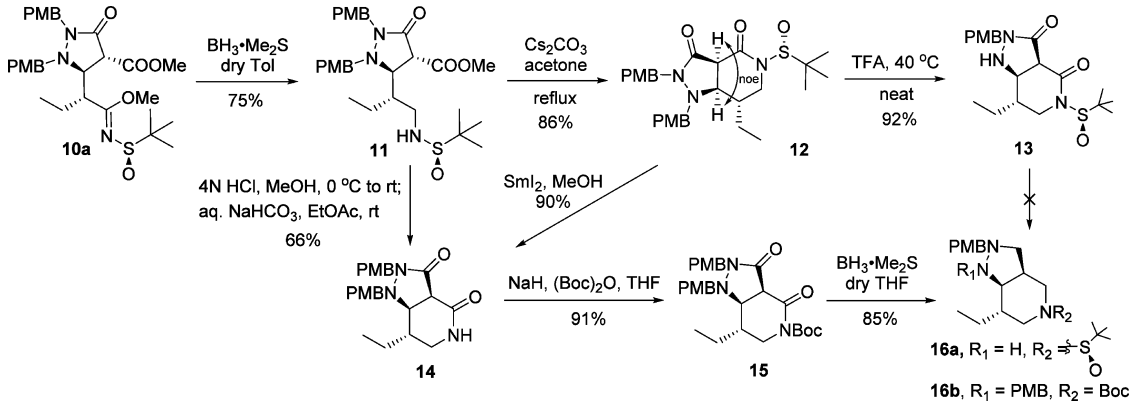
10h (70%;dr = 96:4)
10h (75%;dr = 97:3)[b]



10i (75%;dr = 96:4)
10i (92%;dr = 97:3)[b]

[a]Unless noted otherwise, reactions were performed with **3a** (0.13 mmol), **8** (0.2 mmol), and LDA (0.2 mmol) in THF (2.0 mL) at −78 °C for 1 h. The dr value was determined by HPLC. [b]0.26 mmol of LDA was used.

Scheme 2. Synthesis of the Pyrazolo[4,3-*c*]piperidine 16b



preparation of such ring-fused derivatives bearing multiple stereogenic centers with high enantio- and diastereoselectivity has been a challenging task. As illustrated in Scheme 2, treatment of **10a** with $BH_3{\cdot}Me_2S$ in toluene resulted in reduction of the imidate functional group to afford amine **11**. Upon exposure to Cs_2CO_3, amine **11** was converted to the bicyclic lactam **12** in 86% yield. Extensive NOE experiments clearly indicated a *cis*-fused pyrazolo[4,3-*c*]piperidine ring system of lactam **12**, demonstrating that epimerization of the ester in **11** occurred under the reaction conditions. Subsequently, selective deprotection of the PMB group in **12** was realized in neat TFA to afford amine **13**. Since attempts to reduce the carbonyl groups in **13** to form **16a** were unsuccessful, we switched the *tert*-butanesulfinyl group in **12** to a *tert*-butoxycarbonyl (Boc) group via the free lactam intermediate **14** in high yield, leading to compound **15**. Alternatively, bicyclic **14** could be prepared directly from **11** by treatment with 4 N HCl and subsequent aqueous $NaHCO_3$. Finally, reduction of the two lactam functional groups in **15** by

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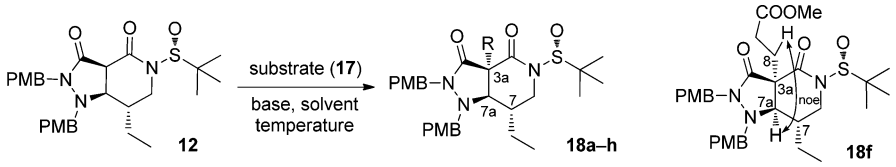
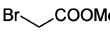
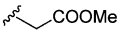
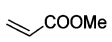
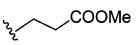
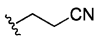
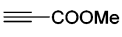
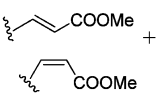
Table 3. Construction of a New Quaternary Carbon Center on C-3a[a]



entry	substrate	base	solvent	T (°C)	time	product	R	yield (%)[b]
1[c]		Cs_2CO_3	Me_2CO	60	14 h	**18a**		92
2		NaH	THF	0	0.5 h	**18b**		94
3		NaH	THF	0	0.5 h	**18c**		95
4		NaH	THF	0	0.5 h	**18d**		87
5[d]		NaH	THF	0	0.5 h	**18e**		81
6[d]		Cs_2CO_3	Me_2CO	24	12 h	**18f**		80
7		NaH	THF	0	0.5 h	**18g**		91
8[d]		Cs_2CO_3	Me_2CO	24	10 h	*trans*-**18ha** *cis*-**18hb**		86 (*trans*/*cis* =5/1)

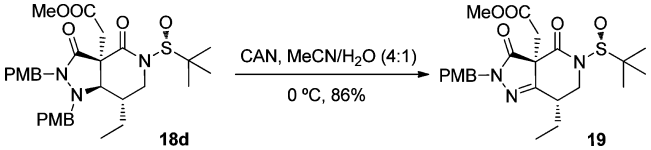
[a]Unless noted otherwise, reactions were performed with **12** (0.095 mmol), **17** (0.19 mmol), and base (0.19 mmol) in 5 mL of solvent. [b]Yield of isolated product. [c]Reactions were performed with **12** (0.095 mmol), **17** (0.475 mmol), and base (0.475 mmol). [d]Reactions were performed with **12** (0.095 mmol), **17** (0.285 mmol), and base (0.285 mmol).

BH_3·Me_2S led to the pyrazolo[4,3-*c*]piperidine **16b** in 85% yield.

Moreover, the potential nucleophilicity of bicyclic lactam **12** provided further opportunities to access structurally diverse derivatives through introduction of various side chains at C-3a. As shown in Table 3, all of the tested electrophilic substrates, such as alkyl halides (entries 1−4), acetyl chloride (entry 5), *α*,*β*-unsaturated ester (entry 6), and acrylonitrile (entry 7), underwent the desired transformation smoothly with **12**, leading to the corresponding products **18a**−**g** in good yields using NaH or Cs_2CO_3 as base. When methyl propiolate was used as an electronphile, separable geometric *trans*-**18ha** and *cis*-**18hb** were isolated in 86% total yield and a 5:1 ratio (entry 8). The absolute configuration of **18** was determined to be (3a*S*,7*S*,7a*R*) by NOE experiments.

Subjecting **18** (such as **18d**) to CAN resulted in deprotection of PMB group followed by amine oxidation to afford imine **19** (Scheme 3). Having a side chain at C-3a installed, we sought to prepare more complex heterocyclic derivatives from intermediate **18**. Taking **18f** as an example (Scheme 4), the ester and lactam groups in **18f** were reduced by $LiAlH_4$ in THF, concomitant removal of the *tert*-butanesulfinyl group, to afford tricyclic aminal **20** (51% yield) and alcohol **21** (28% yield).

Scheme 3. Formation of Imine 19 from Compound 18d



Gratifyingly, after screening different reduction conditions (Ni/EtOH/H_2, Et_3SiH/BCl_3/DCM, $NaBH_4$/THF, BH_3·Me_2S/THF), we were able to convert aminal **20** to alcohol **21** using BH_3·Me_2S in 80% yield. Next, the free hydroxyl group in **21** was activated as a mesylate in the presence of MsCl/DMAP/NEt_3. Without purification, heating the unstable **22** in methanol at 50 °C resulted in the formation of ammonium salt **23**, which was further converted to the tricyclic amide **24** in 47% yield in three steps under conditions of H_2/PtO_2 in MeOH.

In summary, we have reported an asymmetric Michael addition reaction between (*R*)-*N*-*tert*-butanesulfinyl imidates **8** and *α*,*β*-unsaturated pyrazolidinone **3** to generate pyrazolidinones **10** possessing three contiguous stereogenic centers with moderate to excellent yield and excellent diastereoselectivity. A two-step conversion including reduction and cyclization

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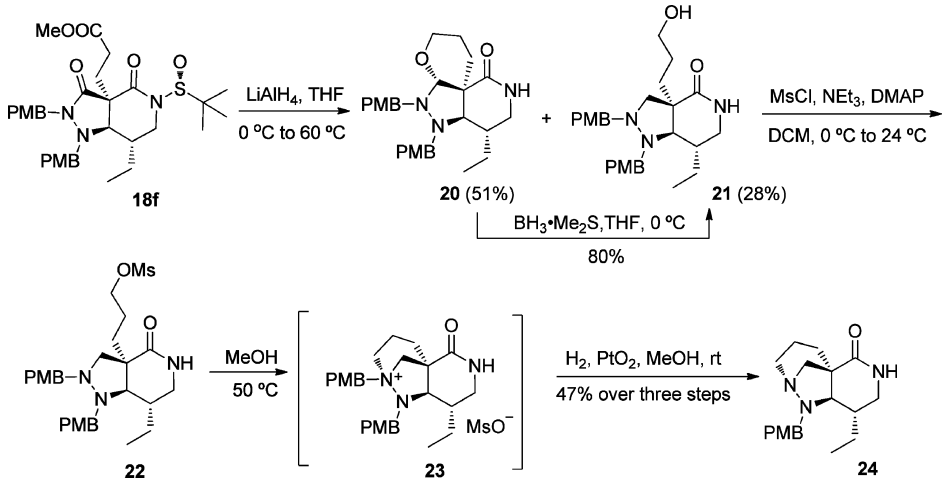
Scheme 4. Synthesis of Tricyclic Amide 24 from Compound 18f



provided bicyclic pyrazolopiperidine **12** in a good yield. In addition, a series of pyrazolopiperidine derivatives **18a–h** with a quaternary carbon center at C-3a were prepared by stereoselective alkylation or Michael addition from **12** with good to excellent yield. Moreover, the synthesized chiral bicyclic pyrazolopiperidines with multiple functional groups could be used as starting materials for constructing more complex ring systems and potential building blocks for medicinal chemistry study.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were used without further purification. All solvents were dried and distilled before use; THF, DME, and Et_2O were distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; toluene was dried and distilled from sodium; MeOH was distilled from magnesium/iodine. Chromatography was conducted by using 200–300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. HRMS spectra were obtained by the ESI-TOF method. IR spectra were recorded on an FT IR spectrometer. HPLC was equipped with a DAD detector.

*Methyl 1,2-Bis(4-methoxybenzyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (**3a**).* Under N_2, to a solution of **1** (1.0 g, 3.67 mmol) in dry THF (30 mL) was added DBU (1.4 mL, 9.20 mmol) at 0 °C. After the resulting solution was maintained at 0 °C for 0.5 h, a solution of **2** (533 mg, 3.06 mmol) in dry THF (20 mL) was slowly added. The mixture was then stirred at 0 °C for 0.5 h and warmed to 25 °C for another 2 h. The reaction was quenched by addition of saturated NH_4Cl (50 mL) at 0 °C. Then the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. To a solution of the above crude product in CH_3CN (20 mL) was added *p*-TsOH (700 mg, 3.67 mmol) at 25 °C. The solution was further stirred for 0.5 h at 25 °C before it was quenched by addition of saturated $NaHCO_3$ (100 mL). Then the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column eluting with EtOAc/petroleum ether (3:1) to give **3a** (1.05 g, 90% for two steps) as a white solid: mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.88–6.84 (m, 4H), 4.97 (s, 2H), 4.73 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 162.1, 160.2, 159.4, 141.2, 129.0, 129.0, 128.2, 128.2, 127.4, 123.6, 114.7, 114.7, 114.3, 114.3, 99.4, 55.3, 55.2, 53.1, 51.4, 44.8 ppm; IR (neat) ν_{max} = 2951, 1725, 1647, 1555, 1514, 1251, 1174, 1031, 786 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{21}H_{22}N_2NaO_5$ 405.1421, found 405.1410.

*1,2-Bis(4-methoxybenzyl)-1H-pyrazol-3(2H)-one (**3b**).* To a solution of **3a** (50 mg, 0.13 mmol) in DMSO (2 mL) was added LiCl (11.0 mg, 0.26 mmol) at 25 °C. The mixture was then heated at 150 °C for 24 h before being quenched by addition of water at 25 °C. Then the aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to a silica gel column eluting with petroleum ether: EtOAc (1:3) to give **3b** (31.8 mg, 75%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 3.2 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.86–6.82 (m, 4H), 5.54 (d, J = 3.6 Hz, 1H), 4.95 (s, 2H), 4.58 (s, 2H), 3.80 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 159.8, 159.2, 140.6, 128.7, 128.7, 128.3, 128.3, 128.2, 125.5, 114.4, 114.4, 114.2, 114.2, 96.2, 55.3, 55.2, 52.8, 44.8 ppm; IR (neat) ν_{max} = 2924, 2854, 1611, 1513, 1454, 1257, 1175, 1013, 908, 792, 732, 697 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{19}H_{20}N_2NaO_3$ 347.13661, found 347.13673.

*1,2-Bis(4-methoxybenzyl)-4-phenyl-1H-pyrazol-3(2H)-one (**3c**).* To a solution of **5** (497 mg, 2.27 mmol) in EtOH (25 mL) was added **4** (500 mg, 1.62 mmol) at 25 °C. The mixture was heated at 80 °C for 5 h and then quenched by addition of saturated $NaHCO_3$ at 25 °C. The aqueous layer was extracted with EtOAc (3 × 50 mL). After the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, subjection of the residue to a silica gel column eluting with petroleum ether/EtOAc (2:1) gave **3c** (464.0 mg, 71%) as a light yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 2H), 7.52 (s, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.85–6.83 (m, 4H), 5.02 (s, 2H), 4.63 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.8, 159.3, 136.5, 131.6, 128.9, 128.9, 128.5, 128.5, 128.5, 128.5, 128.2, 126.2, 125.4, 125.1, 125.1, 114.4, 114.4, 114.2, 114.2, 109.3, 55.3, 55.3, 53.1, 45.1 ppm; IR (neat) ν_{max} = 2926, 1612, 1513, 1462, 1345, 1294, 1248, 1176, 1030, 819, 733 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{25}H_{24}N_2NaO_3$ 423.16791, found 423.16780.

General Procedure for the Preparation of 8a–e,j,k. To a round-bottomed flask charged with *tert*-butanesulfinamide **7** (1.0 g, 8.3 mmol) were added orthoester **6** (25.0 mol) and *p*-TsOH (7.6 mg, 0.04 mmol). The reaction mixture was stirred at 100 °C for 3 h. Volatile materials were removed in vacuo, and the crude oil was purified by silica gel chromatography.

*Methyl (R,Z)-N-(tert-Butylsulfinyl)-3-methylbutanimidate (**8c**).* Compound **8c** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:10) as a colorless oil: 1.375 g, 76% yield. $[\alpha]_D^{20}$ = −117.3 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.61–2.37 (m, 2H), 2.11–2.04 (m, 1H), 1.14 (s, 9H), 0.88 (t, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 55.6, 53.8, 41.0, 26.6, 22.3, 22.3, 21.8,

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21.8, 21.8 ppm; IR (neat) ν_{max} = 2956, 2925, 2854, 1617, 1460, 1295, 1207, 1083, 1019, 796, 586 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{10}H_{21}NNaO_2S$ 242.1185, found 242.1188.

*Methyl (R,Z)-N-(tert-Butylsulfinyl)-2-(cyclopent-3-en-1-yl)-acetimidate (**8d**).* Compound **8d** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:10) as a light yellow oil: 1.426 g, 71% yield; $[\alpha]_D^{20}$ = −109.7 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 2H), 3.78 (s, 3H), 2.95−2.63 (m, 3H), 2.62−2.36 (m, 2H), 2.12−2.02 (m, 2H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 129.6, 129.2, 55.6, 53.9, 38.5, 38.4, 38.2, 34.8, 21.8, 21.8, 21.8 ppm; IR (neat) ν_{max} = 2923, 1611, 1458, 1261, 1083, 796, 592 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{12}H_{21}NNaO_2S$ 266.1185, found 266.1178.

General Procedure for the Preparation of 8f−i. Under N_2, to a solution of dry THF (5 mL) were added LiHMDS (680 μL, 1.0 M in THF) and HMPA (135 μL, 0.68 mmol) at −78 °C. After the resulting solution was maintained at −78 °C for 0.5 h, a solution of **8k** (100 mg, 0.56 mmol) in dry THF (2.5 mL) was slowly added. The resulting mixture was maintained at −78 °C for 0.5 h, and the solution of **9** (0.56 mmol) in dry THF (2.5 mL) was added slowly. Then the mixture was further stirred for 2 h at −78 °C before it was quenched by addition of saturated NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography to afford **8f−i**.

*Methyl (R,Z)-N-(tert-Butylsulfinyl)pent-4-enimidate (**8f**).* Compound **8f** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:10) as a colorless oil: 59 mg, 48% yield; $[\alpha]_D^{20}$ = −115.4 (*c* 0.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.87−5.72 (m, 1H), 5.14−4.95 (m, 2H), 3.77 (s, 3H), 2.78 (m, 2H), 2.48−2.35 (m, 2H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 136.2, 115.9, 55.7, 54.0, 31.9, 30.2, 21.8, 21.8, 21.8 ppm; IR (neat) ν_{max} = 2926, 2853, 1619, 1458, 1083, 589 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{10}H_{19}NNaO_2S$ 240.1029, found 240.1027.

*Methyl (R,Z)-5-((tert-Butyldimethylsilyl)oxy)-N-(tert-butylsulfinyl)-pentanimidate (**8g**).* Compound **8g** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:10) as a colorless oil: 67 mg, 34% yield; $[\alpha]_D^{20}$ = −82.1 (*c* 0.32, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.77−2.60 (m, 2H), 1.72−1.67 (m, 2H), 1.58−1.51 (m, 2H), 1.21 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 62.4, 55.6, 54.0, 54.0, 32.3, 32.3, 25.9, 25.9, 25.9, 22.8, 21.8, 21.8, 21.8, −5.3, −5.3 ppm; IR (neat) ν_{max} = 2929, 2858, 1615, 1461, 1256, 1090, 837, 777 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{16}H_{35}NNaO_3SSi$ 372.2005, found 372.2012.

*Methyl (R,Z)-N-(tert-Butylsulfinyl)-5-((4-methoxybenzyl)oxy)-pentanimidate (**8h**).* Compound **8h** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:10) as a light yellow oil, 84 mg, 42% yield. $[\alpha]_D^{20}$ = −66.2 (*c* 0.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.71−2.67 (m, 2H), 1.80−1.70 (m, 2H), 1.70−1.59 (m, 2H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 158.9, 130.5, 129.1, 129.1, 113.7, 113.7, 72.5, 69.3, 55.6, 55.2, 54.0, 32.3, 29.2, 23.1, 21.8, 21.8, 21.8 ppm; IR (neat) ν_{max} = 2925, 2854, 2199, 1250, 1094, 778 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{18}H_{29}NNaO_4S$ 378.1710, found 378.1692.

*Methyl (R,Z)-5-azido-N-(tert-butylsulfinyl)pentanimidate (**8i**).* Compound **8i** was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:8) as a colorless oil: 47 mg, 32% yield; $[\alpha]_D^{20}$ = −122.4 (*c* 0.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.71 (td, *J* = 7.2, 3.6 Hz, 2H), 1.81−1.71 (m, 2H), 1.68−1.59 (m, 2H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 55.8, 54.1, 50.9, 31.9, 28.4, 23.5, 21.9, 21.9, 21.9 ppm; IR (neat) ν_{max} = 2934, 2095, 1612, 1457, 1260, 1077, 797, 591 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{10}H_{20}N_4NaO_2S$ 283.1199, found 283.1192.

General Procedure for the Preparation of 10. Under N_2, to a solution of **8** (0.20 mmol, 1.5 equiv) in dry THF (1 mL) was added LDA (1.5 M in THF/ethylbenzene/heptane, 0.20 mmol, 1.5 equiv) at −78 °C. After the resulting solution was stirred at −78 °C for 1 h, a solution of **3a** (50 mg, 0.13 mmol) in THF (1 mL) was slowly added. Stirring was maintained for 1 h at −78 °C before the mixture was quenched by addition of saturated NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue through chromatography afforded **10**.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxybutan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10a**):* white solid; 70 mg, 92% yield; mp 64−65 °C; $[\alpha]_D^{20}$ = −48.8 (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.87 (d, *J* = 14.4 Hz, 1H), 4.17 (d, *J* = 14.4 Hz, 1H), 3.88 (d, *J* = 12.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.70−3.65 (m, 2H), 3.64 (s, 3H), 3.48 (s, 1H), 2.86 (td, *J* = 9.4, 4.6 Hz, 1H), 1.14−1.15 (m, 10H), 1.06−0.87 (m, 1H), 0.43 (d, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 169.7, 166.6, 159.1, 159.0, 131.4, 131.4, 130.3, 130.3, 128.9, 127.9, 113.7, 113.7, 113.6, 113.6, 62.0, 60.50, 55.6, 55.2, 55.2, 53.9, 53.0, 50.9, 47.6, 47.4, 22.1, 21.9, 21.9, 21.9, 11.0 ppm; IR (neat) ν_{max} = 2954, 1737, 1695, 1610, 1514, 1458, 1246, 1175, 1073, 772 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{30}H_{41}N_3NaO_7S$ 610.2557, found 610.2534. Isomer of **10a**: light yellow oil, 2.1 mg, 3% yield; $[\alpha]_D^{20}$ = +2.9 (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.66 (d, *J* = 14.8 Hz, 1H), 3.87−3.80 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.59 (s, 2H), 3.42 (s, 1H), 3.35−3.26 (m, 4H), 1.48−1.40 (m, 1H), 1.30−1.25 (m, 1H), 1.20 (s, 9H), 0.72 (t, *J* = 7..2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 169.5, 166.3, 159.0, 159.0, 131.4, 131.4, 130.3, 130.3, 129.1, 127.8, 113.8, 113.8, 113.6, 113.6, 62.9, 61.2, 55.9, 55.2, 55.1, 53.9, 53.1, 50.8, 48.9, 47.5, 22.1, 22.1, 22.1, 21.1, 11.8 ppm; IR (neat) ν_{max} = 2925, 1694, 1612, 1514, 1245, 1076, 772 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{30}H_{41}N_3NaO_7S$ 610.2557, found 610.2541. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (isomer of **10a**) = 18.67 min, t_R (**10a**) = 20.60 min.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxypropan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10b**):* light yellow oil; 67 mg, 91% yield; $[\alpha]_D^{20}$ = −29.4 (*c* 0.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 14.4 Hz, 1H), 4.28 (d, *J* = 14.4 Hz, 1H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.69 (d, *J* = 12.0 Hz, 1H), 3.64 (s, 4H), 3.43 (s, 1H), 3.02−2.90 (m, 1H), 1.17 (s, 9H), 0.62 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 169.7, 166.5, 159.2, 159.1, 131.4, 131.4, 130.3, 130.3, 128.7, 127.9, 113.8, 113.8, 113.7, 113.7, 62.7, 60.6, 55.7, 55.2, 55.2, 54.1, 53.0, 51.1, 47.8, 40.3, 21.8, 21.8, 21.8, 14.4 ppm; IR (neat) ν_{max} = 2925, 2853, 1738, 1695, 1615, 1515, 1250, 666 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{29}H_{39}N_3NaO_7S$ 596.2401, found 596.2383. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (isomer of **10b**) = 12.28 min, t_R (**10b**) = 15.26 min.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxy-3-methylbutan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10c**):* light yellow oil; 21 mg, 26% yield; $[\alpha]_D^{20}$ = −10.4 (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4, 2H), 6.79 (d, *J* = 8.4, 2H), 5.18 (d, *J* = 14.8 Hz, 1H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.59−3.47 (m, 3H), 3.38 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.30 (s, 3H), 1.93−1.88 (m, 1H), 1.24 (s, 9H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.8, 166.5, 159.0, 158.9, 131.2, 131.2, 130.0, 130.0, 129.5, 128.3, 113.8, 113.8, 113.5, 113.5, 61.8, 61.5, 56.2, 55.2, 55.1, 53.5, 53.2, 50.7, 50.6, 49.7, 27.8, 22.2, 22.2, 22.2, 21.0, 18.7 ppm; IR (neat) ν_{max} = 2926, 1735, 1695, 1611, 1513, 1458, 1247, 1175, 1075, 1035, 773 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{43}N_3NaO_7S$ 624.2714, found 624.2690. Isomer of

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10c: light yellow oil; 13.1 mg, 17% yield; $[\alpha]_D^{20}$ = −25.6 (*c* 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 4H), 6.87−6.83 (m, 4H), 4.73 (d, *J* = 14.4 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.81−3.81 (m, 4H), 3.77 (s, 3H), 3.68 (s, 3H), 3.58 (s, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 1H), 1.71−1.62 (m, 1H), 1.21 (s, 9H), 0.58 (d, *J* = 6.8 Hz, 3H), 0.48 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 169.9, 166.4, 159.1, 158.9, 131.5, 131.5, 130.3, 130.3, 129.3, 128.0, 113.8, 113.8, 113.6, 113.6, 61.0, 60.2, 55.7, 55.2, 55.1, 53.7, 53.1, 52.2, 49.7, 48.1, 27.1, 22.2, 22.2, 22.2, 20.1, 20.0 ppm; IR (neat) ν_{max} = 2924, 2854, 1696, 1608, 1514, 1461, 1247, 1174, 1080 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{43}N_3NaO_7S$ 624.2714, found 624.2683. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10c**) = 27.80 min, t_R (isomer of **10c**) = 30.99 min.

*Methyl (3R,4R)-3-((R,Z)-2-(((R)-tert-butylsulfinyl)imino)-1-(cyclopent-3-en-1-yl)-2-methoxyethyl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10d**):* light yellow oil; 76 mg, 92% yield; 2.0 equiv of LDA was used; $[\alpha]_D^{20}$ = −26.1 (*c* 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 4H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.48 (s, 2H), 4.73−4.62 (m, 2H), 3.85−3.84 (m, 4H), 3.79 (s, 3H), 3.75−3.74 (m, 4H), 3.66 (s, 4H), 3.50 (d, *J* = 12.0 Hz, 1H), 3.05 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.27−2.17 (m, 1H), 2.17−2.06 (m, 1H), 1.93−1.87 (m, 1H), 1.78−1.66 (m, 1H), 1.49−1.43 (m, 1H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 169.9, 166.3, 159.1, 158.9, 131.5, 131.5, 130.3, 130.3, 129.4, 129.4, 129.3, 127.9, 113.8, 113.8, 113.6, 113.6, 61.3, 61.1, 55.7, 55.2, 55.1, 53.9, 53.1, 50.1, 49.4, 48.3, 37.3, 36.3, 35.6, 22.1, 22.1, 22.1 ppm; IR (neat) ν_{max} = 2923, 2852, 1736, 1695, 1608, 1513, 1459, 1252, 1174, 1083, 1033, 799, 758 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{33}H_{43}N_3NaO_7S$ 648.2714, found 648.2683. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10d**) = 30.60 min, t_R (isomer of **10d**) = 37.93 min.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxy-3-phenylpropan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10e**):* light yellow oil; 70 mg, 80% yield; $[\alpha]_D^{20}$ = −43.8 (*c* 0.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.10−7.08 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.54−6.46 (m, 2H), 5.07 (d, *J* = 14.4 Hz, 1H), 4.09−3.96 (m, 2H), 3.87−3.83 (m, 9H), 3.79−3.71 (m, 2H), 3.59 (s, 3H), 3.53 (s, 1H), 3.15 (td, *J* = 10.4, 4.8 Hz, 1H), 2.51 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.00−1.89 (m, 1H), 0.87 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.6, 166.2, 159.2, 159.2, 137.8, 131.5, 131.5, 130.4, 130.4, 129.0, 128.8, 128.8, 128.0, 128.0, 127.7, 126.3, 114.0, 114.0, 113.7, 113.7, 62.0, 60.2, 55.2, 55.1, 54.9, 53.7, 52.9, 50.8, 48.2, 46.7, 35.7, 21.5, 21.5, 21.5 ppm; IR (neat) ν_{max} = 2924, 1696, 1610, 1513, 1249, 1173, 772 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{35}H_{43}N_3NaO_7S$ 672.2714, found 672.2696. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10e**) = 23.79 min, t_R (isomer of **10e**) = 20.89 min.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxypent-4-en-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10f**):* light yellow oil; 69 mg, 88% yield; $[\alpha]_D^{20}$ = −47.8 (*c* 0.73, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.26−5.06 (m, 1H), 4.91 (d, *J* = 14.4 Hz, 1H), 4.79 (d, *J* = 10.0 Hz, 1H), 4.70 (d, *J* = 17.2 Hz, 1H), 4.12 (d, *J* = 14.4 Hz, 1H), 3.91 (d, *J* = 12.0 Hz, 1H), 3.86−3.75 (m, 9H), 3.70 (d, *J* = 11.2 Hz, 2H), 3.61 (s, 3H), 3.51 (s, 1H), 3.04 (td, *J* = 9.6, 4.8 Hz, 1H), 1.89−1.85 (m, 1H), 1.65−1.54 (m, 1H), 1.18 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.6, 166.4, 159.2, 159.0, 134.2, 131.4, 131.4, 130.3, 130.3, 128.8, 127.8, 117.1, 113.8, 113.8, 113.7, 113.7, 61.8, 60.4, 55.7, 55.2, 55.1, 53.8, 52.9, 50.9, 47.4, 45.8, 33.5, 21.9, 21.9, 21.9 ppm; IR (neat) ν_{max} = 2950, 1697, 1611, 1513, 1250, 1173, 1033, 771 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{41}N_3NaO_7S$ 622.2557, found 622.2538. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10f**) = 31.24 min, t_R (isomer of **10f**) = 29.06 min.

*Methyl (3R,4R)-3-((R,Z)-5-((tert-butyldimethylsilyl)oxy)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxypentan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10g**):* light yellow oil; 86 mg, 90% yield; 2.0 equiv of LDA was used; $[\alpha]_D^{20}$ = −34.3 (*c* 0.62, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 3.85−3.75 (m, 10H), 3.69 (d, *J* = 8.8 Hz, 1H), 3.65−3.62 (m, 4H), 3.51 (s, 1H), 3.32−3.18 (m, 2H), 2.93−2.92 (m, 1H), 1.17 (s, 9H), 1.09−0.92 (m, 4H), 0.83 (s, 9H), − 0.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 169.7, 166.6, 159.2, 159.0, 131.4, 131.4, 130.3, 130.3, 128.9, 127.9, 113.7, 113.7, 113.6, 113.6, 62.3, 62.2, 60.8, 55.6, 55,1, 55.1, 53.9, 53.0, 50.7, 47.8, 45.8, 29.9, 25.8, 25.8, 25.8, 25.3, 21.9, 21.9, 21.9, 18.1, − 5.4, − 5.4 ppm; IR (neat) ν_{max} = 2929, 2857, 1736, 1699, 1611, 1513, 1459, 1251, 1176, 1082, 1035, 838, 776 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{37}H_{57}N_3NaO_8SSi$ 754.3528, found 754.3502. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10g**) = 32.79 min, t_R (isomer of **10g**) = 31.80 min.

*Methyl (3R,4R)-3-((R,Z)-1-(((R)-tert-butylsulfinyl)imino)-1-methoxy-5-((4-methoxybenzyl)oxy) pentan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10h**):* light yellow oil; 72 mg, 75% yield; 2.0 equiv of LDA was used; $[\alpha]_D^{20}$ = −35.8 (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.91−6.80 (m, 6H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.30 (s, 2H), 4.21 (d, *J* = 14.4 Hz, 1H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.70−3.65 (m, 2H), 3.62 (s, 3H), 3.52 (s, 1H), 3.07−3.06 (m, 2H), 3.00−2.94 (m, 1H), 1.18 (s, 9H), 1.12−0.98 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 169.7, 166.5, 159.2, 159.0, 159.0, 131.4, 131.4, 130.4, 130.3, 130.3, 129.0, 129.0, 128.8, 127.8, 113.8, 113.8, 113.6, 113.6, 113.6, 113.6, 72.4, 69.4, 62.1, 60.6, 55.7, 55.2, 55.1, 55.1, 54.0, 53.0, 50.8, 47.6, 45.7, 26.8, 25.6, 21.9, 21.9, 21.9 ppm; IR (neat) ν_{max} = 2928, 2854, 1697, 1612, 1514, 1248, 1176, 1084, 754 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{39}H_{51}N_3NaO_9S$ 760.3238, found 760.3240. The dr value was determined by HPLC (ODS-3, H_2O/CH_3CN = 40/60, flow rate 1.0 mL/min, λ = 280 nm, t_R (**10h**) = 35.19 min, t_R (isomer of **10h**) = 36.54 min.

*Methyl (3R,4R)-3-((R,Z)-5-azido-1-(((R)-tert-butylsulfinyl)imino)-1-methoxypentan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**10i**):* light yellow oil; 78 mg, 92% yield; 2.0 equiv of LDA was used; $[\alpha]_D^{20}$ = −52.7 (*c* 0.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.98 (d, *J* = 14.4 Hz, 1H), 4.05 (d, *J* = 14.4 Hz, 1H), 3.94 (d, *J* = 12.0 Hz, 1H), 3.86−3.77 (m, 9H), 3.74−3.64 (m, 2H), 3.63 (s, 3H), 3.45 (s, 1H), 2.92−2.79 (m, 3H), 1.20 (s, 9H), 1.14−0.92 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.7, 166.4, 159.4, 159.2, 131.6, 131.6, 130.5, 130.5, 128.8, 127.8, 113.8, 113.8, 113.7, 113.7, 61.8, 60.1, 56.0, 55.3, 54.9, 54.1, 53.1, 51.3, 50.9, 47.2, 45.4, 26.4, 26.0, 21.9, 21.9, 21.9 ppm; IR (neat) ν_{max} = 2939, 2099, 1736, 1697, 1611, 1514, 1457, 1250, 1175, 1070, 1032, 754 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{42}N_6NaO_7S$ 665.2728, found 665.2711. The dr value was determined by HPLC (Chiralpak AS-H, *n*-hexane/*i*-PrOH = 10/90−30/70, flow rate 1.0 mL/min, λ = 254 nm, t_R (**10i**) = 9.82 min, t_R (isomer of **10i**) = 10.50 min.

*Methyl (3R,4R)-3-((S)-1-(((R)-tert-Butylsulfinyl)amino)butan-2-yl)-1,2-bis(4-methoxybenzyl)-5-oxopyrazolidine-4-carboxylate (**11**).* To a 250 mL flask were added **10a** (2.0 g, 3.40 mmol) and dry toluene (100 mL) under an atmosphere of N_2 followed by slow addition of $BH_3{\cdot}Me_2S$ (2.04 mL, 10 M in THF) at 0 °C. The resulting mixture was further stirred for 2 h at 25 °C before it was quenched by addition of saturated NH_4Cl (100 mL) at 0 °C. Then the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was subjected to a silica gel column chromatography eluting with EtOAc to give **11** (1.43 g, 75%) as a light yellow oil: $[\alpha]_D^{20}$ = −14.2 (*c* 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.83 (d, *J* = 14.8 Hz, 1H), 4.19 (d, *J* = 14.8 Hz,

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1H), 4.02 (d, J = 12.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 6H), 3.70 (d, J = 12.0 Hz, 1H), 3.58 (d, J = 5.6 Hz, 1H), 3.30 (s, 1H), 2.87−2.83 (m, 2H), 2.80−2.68 (m, 1H), 1.06 (s, 9H), 1.05−0.99 (m, 2H), 0.61−0.59 (m, 1H), 0.53 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 166.4, 159.3, 159.3, 131.3, 131.3, 130.4, 130.4, 128.2, 127.6, 113.9, 113.9, 113.8, 113.8, 61.2, 60.1, 55.7, 55.2, 55.1, 53.1, 51.3, 46.7, 45.4, 44.0, 22.4, 22.4, 22.4, 19.3, 11.3 ppm; IR (neat) ν_{max} = 2925, 2853, 1736, 1687, 1612, 1513, 1460, 1250, 1175, 828 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{29}H_{41}N_3NaO_6S$ 582.2608, found 582.2592.

*(3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-dione (**12**).* To a stirred solution of **11** (25 mg, 0.0447 mmol) in acetone (3 mL) was added Cs_2CO_3 (21.8 mg, 0.0670 mmol) at 0 °C. The mixture was stirred for another 5 h at 50 °C before being quenched by addition of saturated NH_4Cl (10 mL). Then the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was subjected to a silica gel column chromatography eluting with EtOAc/petroleum ether (1:1) to give **12** (20 mg, 86%) as a white solid: mp 155−156 °C; $[\alpha]_D^{20}$ = −66.8 (c 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.93 (d, J = 14.4 Hz, 1H), 4.03 (d, J = 12.8 Hz, 1H), 3.97 (d, J = 14.4 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.75−3.71 (m, 2H), 3.25−3.14 (m, 1H), 2.85 (dd, J = 13.6, 6.4 Hz, 1H), 2.67 (dd, J = 13.6, 2.0 Hz, 1H), 1.30−1.25 (m, 1H), 1.14 (s, 9H), 1.09−1.02 (m, 1H), 0.79 (dt, J = 14.0, 7.2 Hz, 1H), 0.47 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.1, 159.5, 159.4, 130.8, 130.8, 130.6, 130.6, 128.1, 127.0, 114.1, 114.1, 113.6, 113.6, 61.5, 61.3, 59.1, 55.2, 55.2, 48.9, 46.9, 39.8, 38.4, 22.4, 22.3, 22.3, 22.3, 10.5 ppm; IR (neat) ν_{max} = 2925, 1701, 1513, 1259, 1275, 1091, 766, 750 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{28}H_{37}N_3NaO_5S$ 550.2346, found 550.2325.

*(3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-7-ethyl-2-(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-dione (**13**).* A solution of **12** (20 mg, 0.038 mmol) in TFA (2 mL) was stirred for 3 h at 40 °C. Then the mixture was cooled at 0 °C and quenched by addition of saturated $NaHCO_3$ (10 mL). After the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product over a silica gel column chromatography eluting with EtOAc gave **13** (14 mg, 92%) as a light yellow oil: $[\alpha]_D^{20}$ = −4.7 (c 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.83 (br, 1H), 4.57−4.45 (m, 2H), 3.79−3.77 (m, 4H), 3.56−3.53 (m, 1H), 3.29 (dd, J = 13.6, 6.4 Hz, 1H), 3.03 (dd, J = 13.6, 3.2 Hz, 1H), 1.55 (s, 1H), 1.44−1.35 (m, 1H), 1.19 (s, 9H), 1.19−1.10 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.5, 159.3, 130.2, 130.2, 127.4, 113.9, 113.9, 61.3, 56.7, 55.2, 52.0, 48.1, 40.3, 38.1, 22.7, 22.4, 22.4, 22.4, 11.0 ppm; IR (neat) ν_{max} = 2962, 1694, 1611, 1514, 1461, 1394, 1248, 1091, 1034, 771 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{20}H_{29}N_3NaO_4S$ 430.1771, found 430.1762.

*(3aR,7S,7aR)-7-Ethyl-1,2-bis(4-methoxybenzyl)tetrahydro-1H-pyrazolo[4,3-c]pyridine-3,4(2H,3aH)-dione (**14**).* (Method A) Under N_2, to a solution of **12** (50 mg, 0.095 mmol) in dry MeOH (3 mL) was added SmI_2 (2.9 mL, 0.1 M in THF) at 0 °C. After the resulting solution was stirred at 25 °C for 0.5 h, it was quenched by addition of water at 0 °C. Then the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue through a silica gel column eluting with DCM/MeOH (15:1 to 10:1) gave **14** (36 mg, 90%) as a light yellow oil. (Method B) To a solution of **11** (8.0 mg, 0.014 mmol) in MeOH (1 mL) was added HCl solution (4 M solution in 1,4-dioxane, 35 μL, 0.14 mmol) at 0 °C. After the solution was stirred at 25 °C for 3 h, saturated $NaHCO_3$ (1 mL) and EtOAc (1 mL) was added to the mixture, which continued to stir for another 2 h at 25 °C. Then the aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification as above provided **14** (4.0 mg, 66%) as a light yellow oil: $[\alpha]_D^{20}$ = −70.0 (c 0.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.89−6.85 (m, 4H), 6.00 (s, 1H), 4.97 (d, J = 14.4 Hz, 2H), 3.96−3.89 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.75 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 7.2 Hz, 1H), 3.09−3.03 (m, 2H), 2.65−2.61 (m, 1H), 1.37−1.33 (m, 1H), 0.95−0.93 (m, 1H), 0.61−0.57 (m, 1H), 0.41 (t, J = 7.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 166.2, 159.5, 159.3, 130.9, 130.9, 130.9, 130.9, 128.5, 127.6, 114.0, 114.0, 113.7, 113.7, 62.0, 58.2, 55.3, 55.2, 46.7, 45.2, 43.0, 35.7, 21.8, 10.5 ppm; IR (neat) ν_{max} = 2933, 2325, 1706, 1612, 1513, 1264, 1248, 1175, 1034, 732, 702, 565 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{24}H_{29}N_3NaO_4$ 446.20503, found 446.20470.

*tert-Butyl (3aR,7S,7aR)-7-Ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-5H-pyrazolo[4,3-c]piperidine-5-carboxylate (**15**).* To a solution of **14** (36 mg, 0.085 mmol) in 5 mL of THF was added NaH (11.4 mg, 0.285 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 0.5 h before $(Boc)_2O$ (62 mg, 0.285 mmol) was added. The reaction was stirred for another 1.5 h at 25 °C and quenched by addition of saturated NH_4Cl (10 mL). Then the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to a silica gel column chromatography eluting with MeOH/DCM (1:20) to give **15** (41 mg, 91%) as a light yellow oil: $[\alpha]_D^{20}$ = −128.0 (c 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.94 (d, J = 14.4 Hz, 1H), 4.00 (d, J = 14.4 Hz, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.81 (s, 6H), 3.71 (d, J = 12.8 Hz, 1H), 3.65 (d, J = 7.2 Hz, 1H), 3.56 (dd, J = 13.6, 4.0 Hz, 1H), 3.07−3.03 (m, 1H), 2.86 (dd, J = 13.2, 10.4 Hz, 1H), 1.65−1.56 (m, 1H), 1.50 (s, 9H), 1.16−0.99 (m, 1H), 0.77−0.61 (m, 1H), 0.46 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 164.0, 159.5, 159.3, 152.5, 130.8, 130.8, 130.7, 130.7, 128.2, 127.3, 114.1, 114.1, 113.8, 113.8, 83.5, 61.8, 58.3, 55.3, 55.2, 48.8, 46.8, 46.3, 37.1, 27.9, 27.9, 27.9, 22.0, 10.5 ppm; IR (neat) ν_{max} = 1771.7, 1723.8, 1611.2, 1512.1, 1300.9, 1244.2, 1148.1, 1111.2, 1032.6, 731.4 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{29}H_{37}N_3NaO_6$ 546.2575, found 546.2561.

*tert-Butyl (3aR,7S,7aR)-7-Ethyl-1,2-bis(4-methoxybenzyl)-octahydro-5H-pyrazolo[4,3-c]piperidine-5-carboxylate (**16b**).* Under N_2, to a 10 mL flask were added **15** (20 mg, 0.083 mmol) and dry THF (2 mL), followed by slow addition of $BH_3{\cdot}Me_2S$ (19 μL, 10 M in THF) at 0 °C. The mixture was stirred for 2 h at 25 °C before it was quenched by addition of saturated NH_4Cl (10 mL) at 0 °C. After the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified through a silica gel column chromatography eluting with EtOAc/petroleum ether (2:1) to give **16b** (16 mg, 85%) as a light yellow oil: $[\alpha]_D^{20}$ = −19.0 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 4.09 (br, 2H), 3.96 (br, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (d, J = 12.4 Hz, 1H), 3.57 (d, J = 12.0 Hz, 1H), 3.49 (d, J = 12.4 Hz, 1H), 3.21 (s, 1H), 3.01 (s, 1H), 2.63 (s, 1H), 2.59−2.41 (m, 2H), 2.14 (d, J = 8.0 Hz, 1H), 1.45 (s, 9H), 0.79−0.57 (m, 5H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 158.5, 155.1, 131.6, 131.0, 131.0, 131.0, 131.0, 130.8, 113.4, 113.4, 113.2, 113.2, 79.4, 65.4, 64.8, 63.8, 55.6, 55.2, 55.2, 46.6, 42.6, 40.0, 36.8, 28.4, 28.4, 28.4, 22.7, 10.8 ppm; IR (neat) ν_{max} = 1694.5, 1512.5, 1249.6, 1034.6 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{29}H_{41}N_3NaO_4$ 518.2989, found 518.2974.

General Procedure for the Preparation of 18a,f,h. Under an atmosphere of N_2, to a solution of **12** (50 mg, 0.095 mmol, 1.0 equiv) in dry acetone (5 mL) was added Cs_2CO_3 (93 mg, 0.285 mmol, 3.0 equiv) at 0 °C. After the resulting mixture was maintained at 0 °C for 0.5 h, **17** (0.285 mmol, 3.0 equiv) was slowly added. Then the reaction was stirred for another 12−14 h at the corresponding temperature as shown in Table 3 before it was quenched by addition of saturated NH_4Cl (10 mL). Next, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue via column chromatography afforded **18a,f,h**.

(3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-3a,7-diethyl-1,2-bis(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-

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*dione (**18a**)*. Compound **18a** (48 mg, 92% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a light yellow oil (5.0 equiv of Cs_2CO_3 and iodoethane were used): $[\alpha]_D^{20} = -70.4$ (*c* 0.41, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.98 (d, *J* = 14.8 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.23−3.20 (m, 2H), 2.52−2.47 (m, 1H), 1.56−1.51 (m, 1H), 2.33−2.30 (m, 1H), 1.25−1.23 (m, 1H), 1.07 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.86−0.70 (m, 2H), 0.43 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 167.8, 159.6, 159.4, 130.9, 130.9, 130.8, 130.8, 128.0, 127.1, 114.1, 114.1, 113.8, 113.8, 63.1, 60.9, 59.5, 57.9, 55.3, 55.2, 46.3, 42.6, 35.9, 28.3, 22.5, 22.5, 22.5, 21.3, 10.6, 9.6 ppm; IR (neat) ν_{max} = 2960, 2925, 2348, 1691, 1611, 1512, 1461, 1303, 1249, 1176, 1091, 1073, 1031, 804, 758, 580 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{30}H_{41}N_3NaO_5S$ 578.2659, found 578.2646.

*Methyl 3-((3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-3aH-pyrazolo[4,3-c]pyridin-3a-yl)propanoate (**18f**)*. Compound **18f** (47 mg, 80% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a white solid: mp 110−111 °C; $[\alpha]_D^{20} = -42.2$ (*c* 0.47, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 14.8 Hz, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.18 (d, *J* = 14.8 Hz, 1H), 3.84−3.79 (m, 7H), 3.69 (s, 3H), 3.24 (d, *J* = 13.2 Hz, 1H), 3.13 (s, 1H), 2.77−2.51 (m, 2H), 2.29−2.11 (m, 2H), 2.00−1.85 (m, 1H), 1.28−1.25 (m, 1H), 1.06 (s, 9H), 0.85−0.79 (m, 1H), 0.70−0.63 (m, 1H), 0.41 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.8, 167.0, 159.5, 159.4, 130.9, 130.9, 130.8, 130.8, 127.7, 127.0, 114.1, 114.1, 113.8, 113.8, 64.1, 61.0, 59.3, 56.6, 55.2, 55.1, 51.7, 46.4, 43.0, 35.7, 30.4, 30.0, 22.4, 22.4, 22.4, 21.6, 10.5 ppm; IR (neat) ν_{max} = 2926, 1692, 1513, 1461, 1250, 1176, 1092, 802, 760 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{32}H_{43}N_3NaO_7S$ 636.2714, found 636.2722.

*Methyl (E)-3-((3aS,7S,7aR)-5-((R)-tert-butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-3aH-pyrazolo[4,3-c]-pyridin-3a-yl)acrylate (**18ha**)*. Compound **18ha** (41 mg, 71% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:3) as a light yellow oil: $[\alpha]_D^{20} = -47.2$ (*c* 0.32, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.08 (d, *J* = 16.0 Hz, 1H), 5.00 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 12.4 Hz, 1H), 4.15 (d, *J* = 14.4 Hz, 1H), 3.84−3.76 (m, 9H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.31 (s, 1H), 3.24−3.15 (m, 1H), 2.29−2.32 (m, 1H), 1.32 (s, 1H), 1.08 (s, 9H), 0.88−0.81 (m, 2H), 0.45 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.8, 164.7, 159.6, 159.5, 144.4, 131.0, 131.0, 130.7, 130.7, 127.5, 126.6, 123.8, 114.2, 114.2, 113.8, 113.8, 65.7, 61.3, 59.1, 59.0, 55.2, 55.2, 51.8, 46.7, 42.3, 36.1, 22.4, 22.4, 22.4, 22.0, 10.5 ppm; IR (neat) ν_{max} = 2925, 2349, 1695, 1611, 1513, 1462, 1251, 1177, 1092, 1032, 803, 755, 576 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{32}H_{41}N_3NaO_7S$ 634.2557, found 634.2539.

*Methyl (Z)-3-((3aS,7S,7aR)-5-(tert-Butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-3aH-pyrazolo[4,3-c]pyridin-3a-yl)acrylate (**18hb**)*. Compound **18hb** (9 mg, 15% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a light yellow oil: $[\alpha]_D^{20} = -99.2$ (*c* 0.122, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 11.2 Hz, 1H), 6.16 (d, *J* = 11.2 Hz, 1H), 4.97 (d, *J* = 14.4 Hz, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.85 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.71−3.63 (m, 4H), 3.22 (d, *J* = 10.0 Hz, 1H), 3.08 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.98−2.95 (m, 1H), 1.25 (s, 1H), 1.15 (s, 9H), 0.90−0.73 (m, 1H), 0.74−0.60 (m, 1H), 0.35 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.8, 165.3, 159.4, 159.4, 146.6, 130.9, 130.9, 130.8, 130.8, 128.2, 127.7, 122.3, 113.9, 113.9, 113.7, 113.7, 68.3, 61.3, 60.1, 59.5, 55.2, 51.9, 47.5, 39.7, 38.3, 30.9, 22.4, 22.2, 22.2, 22.2, 10.3 ppm; IR (neat) ν_{max} = 2923, 2325, 1714, 1513, 1461, 1259, 1088, 1016, 795, 662 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{32}H_{41}N_3NaO_7S$ 634.2557, found 634.2553.

General Procedure for the Preparation of 18b−e,g. To a solution of **12** (50 mg, 0.095 mmol, 1.0 equiv) in dry THF (5 mL) was added NaH (0.19 mmol, 2.0 equiv) under N_2 at 0 °C. The resulting solution was maintained at 0 °C for 0.5 h before **17** (0.19 mmol, 2.0 equiv) was slowly added. The mixture was stirred for another 0.5 h at 0 °C and quenched by addition of saturated NH_4Cl (10 mL). After the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **18b−e,g**.

*(3aS,7S,7aR)-3a-Allyl-5-((R)-tert-butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-dione (**18b**)*. Compound **18b** (51 mg, 94% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a light yellow oil: $[\alpha]_D^{20} = -51.8$ (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.74−5.64 (m, 1H), 5.20−5.14 (m, 2H), 4.99 (d, *J* = 14.4 Hz, 1H), 4.33 (d, *J* = 12.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (d, *J* = 12.0 Hz, 1H), 3.31−3.15 (m, 3H), 2.37−2.21 (m, 2H), 1.26−1.21 (m, 1H), 1.06 (s, 9H), 0.80−0.64 (m, 2H), 0.37 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.9, 159.5, 159.4, 134.0, 130.8, 130.8, 130.8, 130.8, 127.9, 127.0, 119.6, 114.0, 114.0, 113.8, 113.8, 62.8, 60.8, 59.2, 57.1, 55.3, 55.2, 46.3, 42.6, 40.1, 35.8, 22.5, 22.5, 22.5, 21.2, 10.5 ppm; IR (neat) ν_{max} = 2924, 1693, 1512, 1459, 1248, 1091, 757 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{41}N_3NaO_5S$ 590.2659, found 590.2634.

*(3aS,7S,7aR)-3a-Benzyl-5-((R)-tert-butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-dione (**18c**)*. Compound **18c** (56 mg, 95% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:3) as a light yellow oil: $[\alpha]_D^{20} = -81.8$ (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 7H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.84−6.82 (m, 4H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.10 (d, *J* = 14.8 Hz, 1H), 3.97 (d, *J* = 12.0 Hz, 1H), 3.79 (s, 6H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.26−3.15 (m, 3H), 2.41 (d, *J* = 13.2 Hz, 1H), 2.30 (d, *J* = 11.8 Hz, 1H), 1.07 (s, 9H), 1.02 (s, 1H), 0.75−0.70 (m, 1H), 0.54−0.50 (m, 1H), 0.23 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 165.9, 159.3, 159.3, 136.8, 130.9, 130.9, 130.7, 130.7, 130.7, 130.7, 128.7, 128.7, 127.9, 127.4, 127.0, 113.8, 113.8, 113.8, 113.8, 62.3, 60.8, 58.6, 58.0, 55.2, 55.1, 46.2, 42.1, 40.4, 35.4, 22.5, 22.5, 22.5, 20.6, 10.5 ppm; IR (neat) ν_{max} = 2927, 2325, 1693, 1513, 1462, 1302, 1250, 1176, 1091, 707 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{35}H_{43}N_3NaO_5S$ 640.2821, found 640.2836.

*Methyl 2-((3aS,7S,7aR)-5-((R)-tert-butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-3aH-pyrazolo[4,3-c]pyridin-3a-yl)acetate (**18d**)*. Compound **18d** (50 mg, 87% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a white solid: mp 69−70 °C; $[\alpha]_D^{20} = -81.8$ (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.93 (d, *J* = 14.4 Hz, 1H), 4.25 (d, *J* = 12.8 Hz, 1H), 4.09 (d, *J* = 14.4 Hz, 1H), 3.85−3.79 (m, 7H), 3.67 (s, 3H), 3.55 (s, 1H), 3.49 (d, *J* = 17.2 Hz, 1H), 3.16 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.39 (d, *J* = 16.8 Hz, 1H), 2.32−2.26 (m, 1H), 1.30−1.21 (m, 1H), 1.20−1.10 (m, 1H), 1.08 (s, 9H), 0.95−0.84 (m, 1H), 0.48 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.7, 166.9, 159.6, 159.5, 130.9, 130.9, 130.8, 130.8, 127.6, 127.1, 114.1, 114.1, 113.7, 113.7, 63.9, 61.1, 59.3, 55.3, 55.2, 55.1, 51.9, 46.7, 43.5, 38.5, 36.6, 22.4, 22.4, 22.4, 21.8, 10.6 ppm; IR (neat) ν_{max} = 2924, 2324, 1692, 1512, 1462, 1247, 1176, 1092, 1032, 805, 751 cm^{-1}; HRMS $[M + Na]^+$ calcd for $C_{31}H_{41}N_3NaO_7S$ 622.2557, found 622.2550.

*(3aR,7S,7aR)-3a-Acetyl-5-((R)-tert-butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)hexahydro-3H-pyrazolo[4,3-c]piperidine-3,4(3aH)-dione (**18e**)*. Compound **18e** (44 mg, 81% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:3) as a light yellow oil (3.0 equiv of NaH and acetyl chloride were used): $[\alpha]_D^{20} = -67.2$ (*c* 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.30−7.23 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.94 (d, *J* =

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14.4 Hz, 1H), 4.07 (d, J = 14.0 Hz, 1H), 4.04 (d, J = 11.6 Hz, 1H), 3.88 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.35 (d, J = 12.0 Hz, 1H), 3.00 (dd, J = 14.0, 4.8 Hz, 1H), 2.58 (s, 3H), 2.33 (dd, J = 14.0, 2.4 Hz, 1H), 1.20 (s, 1H), 1.12 (s, 9H), 0.89 (dt, J = 14.4, 7.2 Hz, 1H), 0.75 (dt, J = 14.4, 7.2 Hz, 1H), 0.40 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 166.1, 164.0, 159.5, 159.5, 131.0, 131.0, 130.9, 130.9, 127.6, 126.9, 114.0, 114.0, 113.8, 113.8, 69.4, 61.8, 61.4, 59.3, 55.2, 55.2, 47.3, 41.3, 37.4, 28.6, 22.4, 22.4, 22.4, 22.0, 10.4 ppm; IR (neat) ν_{max} = 2922, 2853, 1694, 1513, 1461, 1303, 1258, 1094, 1033, 803, 758 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{30}H_{39}N_3NaO_6S$ 592.2452, found 592.2440.

*3-((3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-7-ethyl-1,2-bis(4-methoxybenzyl)-3,4-dioxooctahydro-3aH-pyrazolo[4,3-c]pyridin-3a-yl)propanenitrile (**18g**).* Compound **18g** (50 mg, 91% yield) was obtained through purification by silica gel column chromatography eluting with EtOAc/petroleum ether (1:2) as a light yellow oil: $[\alpha]_D^{20}$ = −71.1 (c 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.97 (d, J = 14.4 Hz, 1H), 4.28 (d, J = 12.8 Hz, 1H), 4.21 (d, J = 14.8 Hz, 1H), 3.89 (d, J = 12.8 Hz, 1H), 3.83(s, 3H), 3.80 (s, 3H), 3.31−3.26 (m, 2H), 2.62−2.51 (m, 1H), 2.49−2.30 (m, 2H), 2.20−2.16 (m, 1H), 1.77−1.61 (m, 1H), 1.38 (s, 1H), 1.05 (s, 9H), 0.92−0.79 (m, 1H), 0.77−0.70 (m, 1H), 0.53 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 165.9, 159.8, 159.6, 131.0, 131.0, 130.9, 130.9, 127.3, 126.1, 119.3, 114.3, 114.3, 113.9, 113.9, 64.2, 61.0, 58.7, 56.0, 55.3, 55.1, 46.4, 43.1, 35.5, 31.1, 22.4, 22.4, 22.4, 21.6, 13.4, 10.6 ppm; IR (neat) ν_{max} = 2924, 2853, 1691, 1611, 1512, 1462, 1302, 1251, 1177, 1091, 1073, 1031, 804, 758, 580 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{31}H_{40}N_4NaO_5S$ 603.2612, found 603.2596.

*Methyl 2-((3aS,7S,7aR)-5-((R)-tert-Butylsulfinyl)-7-ethyl-2-(4-methoxybenzyl)-3,4-dioxo-2,3,4,5,6,7-hexahydro-3aH-pyrazolo[4,3-c]-pyridin-3a-yl)acetate (**19**).* To a solution of **18d** (50 mg, 0.083 mmol) in 4:1 MeCN/H_2O (5 mL) was added CAN (183.0 mg, 0.33 mmol) at 0 °C. After the resulting solution was stirred at 0 °C for 0.5 h, the mixture was quenched by addition of saturated $NaHCO_3$ at 0 °C. Then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to a silica gel column eluting with petroleum ether/EtOAc (2:1) to give **19** (34 mg, 86%) as a white solid: mp 158−159 °C; $[\alpha]_D^{20}$ = +186.4 (c 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.83 (s, 2H), 3.91−3.96 (m, 1H), 3.78 (s, 3H), 3.51 (s, 3H), 3.43 (d, J = 17.6 Hz, 1H), 3.12−2.94 (m, 3H), 1.56−1.53 (m, 2H), 1.14 (s, 9H), 1.02 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.2, 165.3, 159.1, 157.2, 129.4, 129.4, 128.2, 113.9, 113.9, 61.4, 59.1, 55.2, 52.4, 47.9, 40.9, 38.7, 35.7, 25.5, 22.2, 22.2, 22.2, 11.3 ppm; IR (neat) ν_{max} = 2924, 2855, 1728, 1514, 1458, 1361, 1259, 1205, 1081, 1027, 800, 757, 664 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{23}H_{31}N_3NaO_6S$ 500.18258, found 500.18197.

*(4S,4aR,6aR,10aS)-4-Ethyl-5,6-bis(4-methoxybenzyl)octahydro-8H-pyrano[3′,2′:4,5]pyrazolo [4,3-c]pyridin-1(2H)-one (**20**) and (3aR,7S,7aR)-7-Ethyl-3a-(3-hydroxypropyl)-1,2-bis(4-methoxybenzyl)octahydro-4H-pyrazolo[4,3-c]pyridin-4-one (**21**).* Under N_2, to a solution of **18f** (50 mg, 0.081 mmol) in dry THF (5 mL) was added LAH (31 mg, 0.81 mmol) at 0 °C. The mixture was heated at 60 °C for 1 h before it was quenched by addition of saturated Na_2SO_4 (a few drops). The resultant mixture was filtered with Celite, and the combined filtrates were concentrated in vacuo. Purification of the residue by silica gel column chromatography eluting with EtOAc/petroleum ether (1:1) provided **20** (19 mg, 51%) and **21** (10.7 mg, 28%) as a light yellow oil. Conversion of **20** to **21** was conducted as follows: to a solution of **20** (20 mg, 0.041 mmol) in dry THF (2 mL) was slowly added BH_3·Me_2S (41 μL, 10 M in THF) at 0 °C. The reaction was quenched with saturated NH_4Cl (10 mL) after 1 h. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. After the crude product was refluxed in MeOH (2 mL) for 2 h and evaporated in vacuo, the residue was subjected to column chromatography eluting with EtOAc/acetone (2:1) to give **21** (16 mg, 80%). Compound **20**: $[\alpha]_D^{20}$ = −62.7 (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.81−6.76 (m, 4H), 5.93 (s, 1H), 4.58 (s, 1H), 3.40−3.93 (m, 3H), 3.81−3.76 (m, 7H), 3.62 (d, J = 12.4 Hz, 1H), 3.46−3.40 (m, 2H), 3.29 (s, 1H), 3.06 (dd, J = 11.6, 3.6 Hz, 1H), 2.27 (td, J = 14.0, 4.8 Hz, 1H), 2.00 (d, J = 14.4 Hz, 1H), 1.84−1.70 (m, 1H), 1.55−1.31 (m, 4H), 0.86 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 158.7, 158.6, 131.5, 130.8, 130.8, 130.7, 130.7, 130.5, 113.5, 113.5, 113.4, 113.4, 93.7, 66.0, 65.5, 65.0, 60.0, 55.2, 55.2, 53.0, 42.3, 36.9, 29.3, 22.5, 20.8, 12.7 ppm; IR (neat) ν_{max} = 2923, 2325, 1658, 1612, 1512, 1463, 1302, 1248, 1173, 1884, 1034, 803, 755 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{27}H_{35}N_3NaO_4$ 488.2520, found 488.2504. Compound **21**: $[\alpha]_D^{20}$ = −10.9 (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.2 Hz, 2H), 6.03 (s, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.82−3.78 (m, 8H), 3.61−3.54 (m, 2H), 3.43 (d, J = 12.4 Hz, 1H), 3.39−3.31 (m, 1H), 3.03 (q, J = 10.8 Hz, 2H), 2.86 (d, J = 10.4 Hz, 1H), 2.81 (d, J = 8.4 Hz, 1H), 1.86−1.80 (m, 2H), 1.64−1.54 (m, 1H), 1.50−1.43 (m, 2H), 0.99−0.85 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 158.8, 158.6, 131.2, 131.0, 131.0, 130.6, 130.5, 130.5, 113.4, 113.4, 113.4, 113.4, 71.0, 62.6, 62.3, 62.3, 61.3, 55.2, 55.2, 54.2, 42.6, 42.4, 34.4, 28.7, 22.9, 11.5 ppm; IR (neat) ν_{max} = 2921, 1654, 1511, 1249, 1034, 806, 750 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{27}H_{37}N_3NaO_4$ 490.2676, found 490.2663.

*(2R,5aR,9S,9aR)-9-Ethyl-1-(4-methoxybenzyl)hexahydro-3H-2,5a-methanopyrido[4,3-c][1,2]diazepin-6(1H)-one (**24**).* Under N_2, to a solution of **21** (13 mg, 0.028 mmol) in dry DCM (2 mL) were added Et_3N (12 μL, 0.084 mmol) and DMAP (1 mg, 0.0084 mmol) at 0 °C. After the resulting solution was maintained at 0 °C for 0.5 h, MsCl (6.5 μL, 0.084 mmol) was slowly added. The reaction was quenched 1 h later by addition of saturated NH_4Cl (5 mL) at 0 °C. Then the aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were dried and concentrated. The crude product **22** was dissolved in MeOH (2 mL) and stirred for 1 h at 50 °C. After addition of PtO_2 (1 mg, 0.0028 mmol), the resulting mixture was stirred for 36 h under an atmosphere of H_2 at room temperature. Then the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. Purification of the residue over silica gel column eluting with EtOAc/acetone (2:1) gave **24** (4 mg, 47% for three steps) as a light yellow oil: $[\alpha]_D^{20}$ = +8.0 (c 0.10, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.90 (br, 1H), 4.08−3.91 (m, 2H), 3.79 (s, 3H), 3.47 (d, J = 12.6 Hz, 1H), 3.32 (br, 1H), 3.24 (br, 1H), 3.02−2.95 (m, 2H), 2.85 (d, J = 4.2 Hz, 1H), 2.70 (s, 1H), 2.34−2.20 (m, 1H), 1.82−1.55 (m, 3H), 1.47 (s, 2H), 1.32−1.20 (m, 1H), 0.86 (br, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 158.8, 130.8, 129.2, 129.2, 113.8, 113.8, 70.4, 62.8, 55.3, 53.1, 49.8, 47.2, 42.3, 41.3, 31.6, 23.1, 19.3, 11.3 ppm; IR (neat) ν_{max} = 3414, 2959, 2923, 2854, 1653, 1458, 1260, 1093, 1022, 799 cm^{-1}; HRMS [M + Na]$^+$ calcd for $C_{19}H_{27}N_3NaO_2$ 352.1996, found 352.1980.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and HPLC chromatograms for **10** and crystallographic data for compound **10a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01237.

^{1}H and ^{13}C NMR spectra for all new compounds and HPLC chromatograms for **10** (PDF)

Crystallographic data for compound **10a** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Gupta, L.; Chauhan, P. M. S. *Chem. Biol. Interface* **2011**, *1*, 1. (c) Bawa, S.; Ali, R.; Afzal, O.; Akhtar, M. J.; Azad, B.; Kumar, R.; Andalip; Siddiqui, N. A. *J. Pharm. BioAllied Sci.* **2011**, *3*, 194. (d) Joule, J. A.; Alvarez, M.; Salas, M. *Heterocycles* **1991**, *32*, 1391. (e) Kucukguzel, S. G.; Senkardes, S. *Eur. J. Med. Chem.* **2015**, *97*, 786.

(2) For relevant reviews, see: (a) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (b) Bariwal, J.; Van der Eycken, E. V. D. *Chem. Soc. Rev.* **2013**, *42*, 9283. (c) Naito, T. *Chem. Pharm. Bull.* **2008**, *56*, 1367. (d) Fesenko, A. A.; Shutalev, A. D. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2013**, *49*, 827. (e) Golantsov, N. E.; Karchava, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2008**, *44*, 263. (f) Lubczak, J. *Curr. Trends Polymer Sci.* **2003**, *8*, 73.

(3) For reviews, see: (a) Liu, G. C.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (d) Dong, H.-Q.; Xu, M.-H.; Feng, C.-G.; Sun, X.-W.; Lin, G.-Q. *Org. Chem. Front.* **2015**, *2*, 73. (e) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (f) Brinner, K.; Ellman, J. A. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley, 2005; p 181.

(4) (a) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.

(5) (a) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. D. *J. Org. Chem.* **2011**, *76*, 234. (b) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 3792. (c) Colpaert, F.; Mangelinckx, S.; Debrabandere, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2204.

(6) Bartrum, H. E.; Viceriat, A.; Carret, S.; Poisson, J.-F. *Org. Lett.* **2014**, *16*, 1972.

(7) Wang, J. F.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X. J.; Liu, H. *Org. Lett.* **2013**, *15*, 1508.

(8) Wang, H.-J.; Tang, P.; Zhou, Q.-L.; Zhang, D.; Chen, Z.-T.; Huang, H.-X.; Qin, Y. *J. Org. Chem.* **2015**, *80*, 2494.

(9) (a) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053. (b) Caruso, F.; Rossi, M.; Tanski, J.; Sartori, R.; Sariego, R.; Moya, S.; Diez, S.; Navarrete, E.; Cingolani, A.; Marchetti, F.; Pettinari, C. *J. Med. Chem.* **2000**, *43*, 3665. (c) Caruso, F.; Pettinari, C.; Marchetti, F.; Natanti, P.; Phillips, C.; Tanski, J.; Rossi, M. *Inorg. Chem.* **2007**, *46*, 7553. (d) Savini, L.; Massarelli, P.; Nencini, C.; Pellerano, C.; Biggio, G.; Maciocco, A.; Tuligi, G.; Carrieri, A.; Cinone, N.; Carotti, A. *Bioorg. Med. Chem.* **1998**, *6*, 389. (e) Ferlin, M. G.; Chiarelotto, G.; Dall'Acqua, S.; Maciocco, E.; Mascia, M. P.; Pisu, M. G.; Biggio, G. *Bioorg. Med. Chem.* **2005**, *13*, 3531. (f) Lehmann, F.; Holm, M.; Laufer, S. *J. Comb. Chem.* **2008**, *10*, 364.

(10) Bromn, M. J. *Synthesis, Structure and Functionalisation of 1,2-Diazetidines*; University of Warwick, 2011.

(11) Salaheldin, A. M.; Abdullah Al-Sheikh, M. *Molecules* **2010**, *15*, 4359.

(12) Casy, G.; Patterson, J. W.; Taylor, R. J. K. *Org. Synth.* **1989**, *67*, 193.

(13) (a) Han, J. C.; Liu, L. Z.; Chang, Y. Y.; Yue, G. Z.; Guo, J.; Zhou, L. Y.; Li, C. C.; Yang, Z. *J. Org. Chem.* **2013**, *78*, 5492. (b) Coelho, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647. (c) Fall, A.; Sene, M.; Gaye, M.; Gomez, G.; Fall, Y. *Tetrahedron Lett.* **2010**, *51*, 4501.

(14) See the Supporting Information for details. CCDC 1460861 (**10a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

(15) Page, P.; Laleu, B.; Gaggini, F.; Orchard, M. Preparation of pyrazolo piperidine derivatives as NADPH oxidase inhibitors. Eur. Pat. Appl. EP 2361911A1, Aug 31, 2011.

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