

Supporting Information

Synthesis of Chiral α -Hydroxy Acids via Palladium-Catalyzed C(sp³)-H Alkylation of Lactic Acid

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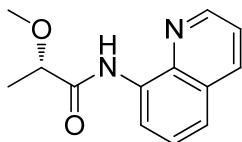
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General Information: Unless otherwise noted, all commercial materials were used without further purification. Anhydrous solvents obtained from Aladdin and Adamas were used directly without further purification, and solvents obtained from other commercial suppliers were used after purification as specified in *Purification of Laboratory Chemicals, 6th Ed.* Optical rotations were measured on a Perkin-Elmer 241 polarimeter equipped with a Na-lamp. HPLC analyses were performed on a Shimadzu SPD-20A. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AVANCE 400MHz instrument. ^1H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($\text{CHCl}_3 = 7.26$ (^1H NMR), DMSO = 2.50 (^1H NMR), $\text{CDCl}_3 = 77.16$ (^{13}C NMR)) unless otherwise noted. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High-resolution mass spectra for new compounds were recorded at Mass Spectrometry Facilities, Zhejiang University. X-ray diffraction experiments were performed at X-Ray Facilities, Zhejiang University.

Experimental Procedures:

Preparation of Lactic Acid Substrates

(*S*)-2-Methoxy-*N*-(quinolin-8-yl)propanamide (**1a**)



To a stirred solution of (*S*)-2-methoxypropanoic acid ¹ (10.41 g, 100 mmol) in dry dichloromethane (300 mL), 4-methylmorpholine (NMM, 11.5 mL, 105 mmol) was added slowly at 0 °C. After the solution was stirred for five minutes, *iso*-butyl carbonochloridate (13.3 mL, 105 mmol) was added dropwise slowly at 0 °C. The mixture was then stirred at room temperature for 1.5 h. A solution of 8-aminoquinoline (8.65 g, 60 mmol) in dry dichloromethane (50 mL) was slowly added to the reaction at 0 °C. After the reaction was stirred at room temperature overnight, the resulting mixture was then washed by aqueous HCl (100 mL, 0.1 M), saturated Na₂CO₃ (100 mL), brine (100 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by silica gel column chromatography in 6:3:1 petroleum ether: dichloromethane: ethyl acetate, afforded the pure 8-aminoquinoline amide **1a** (13.12 g, 95%) as a white solid. [α]_D²⁰ = -66.3 (CHCl₃, c=1.0). HPLC Chiralpak® AD-H column, n-hexane/isopropanol = 95: 5, flow rate = 1.00 mL/min, λ = 254 nm, 11.3 (minor), 12.1 (major), 97% ee. ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.80 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.46 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.58 (s, 3H), 1.55 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 170.89, 148.63, 138.92, 137.77, 136.20, 133.95, 129.51, 128.38, 128.03, 127.27, 126.60, 122.06, 121.69, 116.63, 84.55, 59.32, 39.58; HRMS (EI) *m/z*: 230.1058(M⁺), calc. for C₁₃H₁₄N₂O₂: 230.1055.

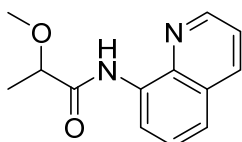
Chiral HPLC Data

HPLC Conditions

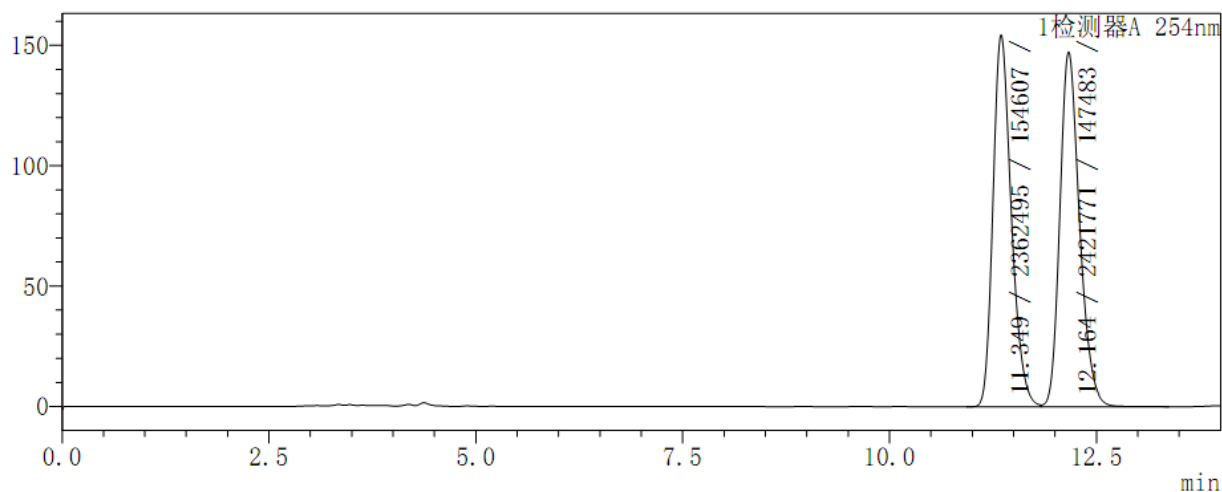
Chiral Stationary phase: Chiralpak® AD-H, n-hexane/isopropanol = 95:5, 1.00 mL/min

Signal: VWD1 A, Wavelength = 254 nm

rac-1a



mV

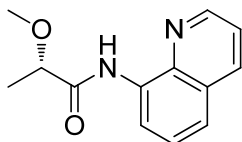


峰表

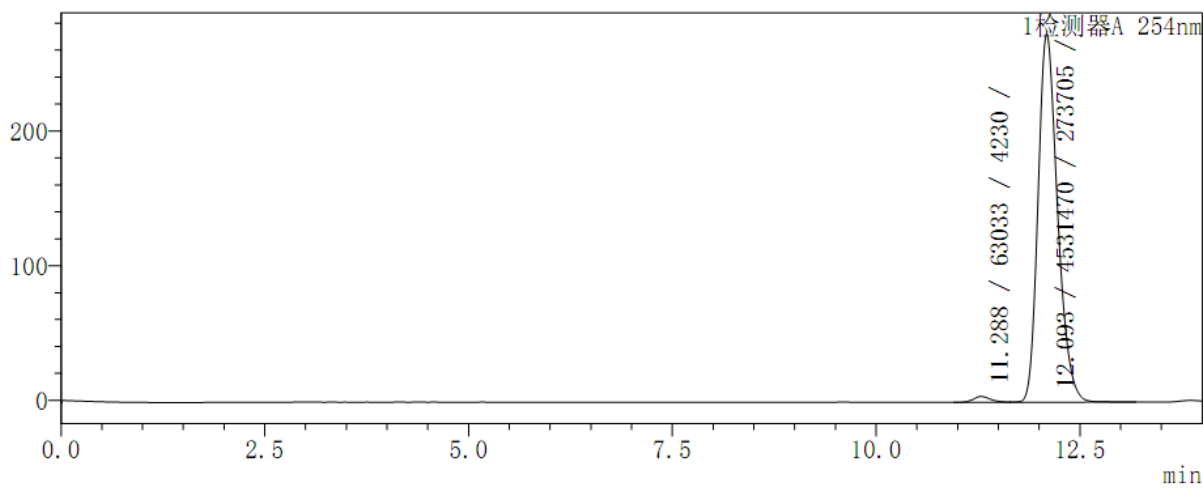
检测器A 254nm

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1	11.349	2362495	154607		49.381
2	12.164	2421771	147483	V	50.619
总计		4784266	302090		100.000

L-1a



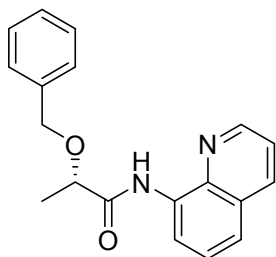
mV



峰表

检测器A 254nm

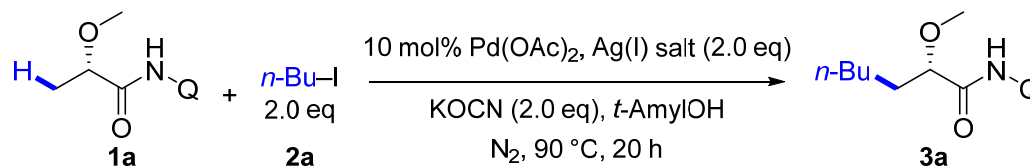
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1	11.288	63033	4230		1.372
2	12.093	4531470	273705	V	98.628
总计		4594504	277935		100.000

(S)-2-Benzyloxy-N-(quinolin-8-yl)propanamide (1b)

The preparation of **1b** followed the same procedure of **1a** except using (*S*)-2-benzyloxypropanoic acid instead of (*S*)-2-methoxypropanoic acid. The compound **1b** was obtained as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 11.09 (s, 1H), 9.16 – 8.69 (m, 2H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.79 – 7.51 (m, 4H), 7.51 – 7.27 (m, 4H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.22 (qd, *J* = 6.7, 6.7, 0.8 Hz, 1H), 1.62 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 172.04, 148.47, 138.98, 137.43, 136.23, 134.18, 128.56, 128.16, 128.07, 127.34, 121.93, 121.72, 116.54, 77.13, 72.47, 18.92; HRMS (EI) *m/z*: 306.1369(M⁺), calcd. for C₁₉H₁₈N₂O₂: 306.1368.

Optimization of Reaction Conditions for Mono-alkylation of **1a**

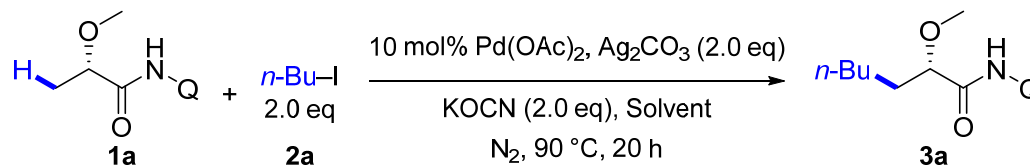
(1) Optimization of Silver Salts (KOCN and *t*-AmylOH used as Base and Solvent)



Entry	Ag(I) salt	Yield 3a	RSM
1	Ag ₂ CO ₃	34%	59%
2	AgF	<2%	>80%
3	AgOAc	<2%	>80%
4	AgOPiv	~3%	>80%
5	Ag ₂ O	22%	71%
6	Ag ₃ PO ₄	<2%	>80%
7	AgOCN	~3%	>80%
8	Ag ₂ SO ₄	<1%	>80%
9	AgSCN	<1%	>80%
10	/	0	>90%

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.40 mmol, 2.0 eq), Pd(OAc)₂ (0.02 mmol, 10 mol%), Ag(I) salt (0.40 mmol, 2.0 eq), KOCN (0.40 mmol, 2.0 eq), *t*-AmylOH (2.0 ml), reaction for 20 hours at 90 °C and under N₂ atmosphere.

(2) Optimization of Solvent (KOCN and Ag₂CO₃ used as Base and Silver Salt)

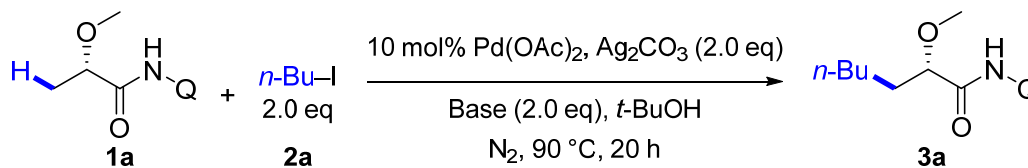


Entry	Solvent	Yield 3a	RSM
1	<i>t</i> -AmylOH	34%	59%
2	<i>t</i> -BuOH	49%	33%
3	<i>i</i> -PrOH	0	>90%
4	DMF	0	>80%
5	THF	<5%	>80%
6	2-Me-THF	<10%	>70%
7	Acetone	~10%	>70%
8	DME	~10%	>80%
9	AcOEt	22%	72%
10	CF ₃ CO ₂ Et	0	>90%
11	HFIP	0	>80%

12	PhMe	~2%	>80%
13	1,4-dioxane	~2%	>80%
14	MeCN	0	>80%
15	^t BuCN	0	>80%

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.40 mmol, 2.0 eq), Pd(OAc)₂ (0.02 mmol, 10 mol%), Ag₂CO₃ (0.40 mmol, 2.0 eq), KOCN (0.40 mmol, 2.0 eq), solvent (2.0 ml), reaction for 20 hours at 90 °C and under N₂ atmosphere.

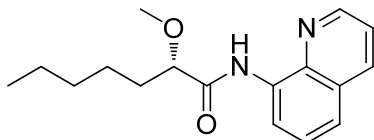
(3) Optimization of Base (*t*-BuOH and Ag₂CO₃ used as Solvent and Silver Salt)



Entry	Base	Yield 3a	RSM
1	/	~3%	>80%
2	KOCN	49%	33%
3	K ₂ CO ₃	61% (62%)	22%
4	K ₃ PO ₄	58%	27%
5	KF	43%	51%
6	KOAc	50%	44%
7	MesCO ₂ K	49%	43%
8	KTFA	45%	37%
9	Li ₂ CO ₃	~3%	>80%
10	Li ₃ PO ₄	~5%	>80%
11	LiOAc	~2%	>80%
12	Na ₂ CO ₃	33%	55%
13	Na ₃ PO ₄	29%	55%
14	NaOAc	20%	64%
15	Cs ₂ CO ₃	35%	54%
16	CsOAc	45%	46%
17	Rb ₂ CO ₃	61%	24%
18	RbOAc	53%	38%
19	K ₂ CO ₃ (1.0 eq)	61% (62%)	21%
19	K ₂ CO ₃ (0.5 eq)	58%	27%
20	K ₂ CO ₃ (0.2 eq)	53%	33%
21	K ₃ PO ₄ (0.2 eq)	32%	47%
22	KOAc (0.2 eq)	51%	38%
23	Rb ₂ CO ₃ (0.2 eq)	55%	32%
24 ^b	K ₂ CO ₃ (1.0 eq)	63% (64%)	21%

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.40 mmol, 2.0 eq), Pd(OAc)₂ (0.02 mmol, 10 mol%), Ag₂CO₃ (0.40 mmol, 2.0 eq), base (0.40 mmol, 2.0 eq), *t*-BuOH (2.0 ml), reaction for 20 hours at 90 °C and under N₂ atmosphere; ^a 100 °C; ^b Isolated yields indicated in the parentheses.

(S)-2-Methoxy-N-(quinolin-8-yl)heptanamide (3a)



The title compound was prepared under the optimized condition. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3a** as a colorless oil (36.9 mg, 64%) with **1a** (9.9 mg, 21%) recovered. $[\alpha]_D^{20} = -50.0$ (CHCl₃, *c*=1.0). HPLC Chiralpak® AD-H column, n-hexane/isopropanol = 95: 5, flow rate = 1.00 mL/min, $\lambda = 254$ nm, 9.0 (minor), 12.5 (major), 94% ee. ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.7, 2.1 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.84 (dd, *J* = 7.3, 4.4 Hz, 1H), 3.57 (s, 3H), 1.99 – 1.78 (m, 2H), 1.57 – 1.45 (m, 2H), 1.38 – 1.29 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.89, 148.70, 139.06, 136.28, 134.18, 128.14, 127.37, 121.94, 121.72, 116.65, 83.70, 58.85, 33.22, 31.79, 24.89, 22.63, 14.14; HRMS (EI) *m/z*: 286.1680 (M⁺), calc. for C₁₇H₂₂N₂O₂: 286.1681.

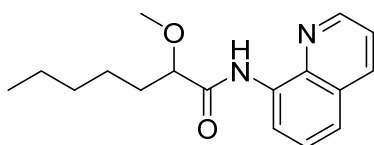
Chiral HPLC Data

HPLC Conditions

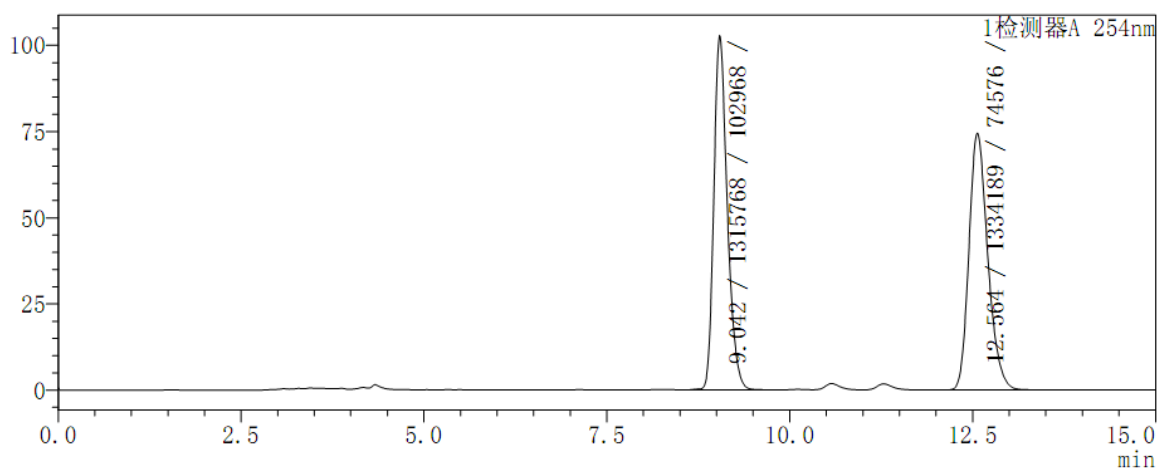
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Signal: VWD1 A, Wavelength = 254 nm

Rac-3a



mV

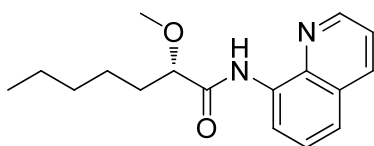


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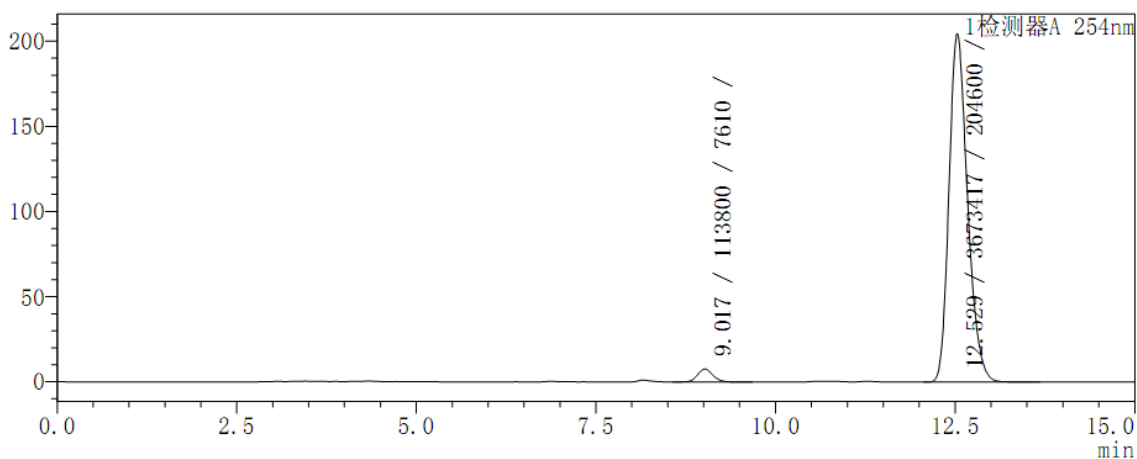
检测器A 254nm

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总计		2649956	177544		100.000

L-3a



mV



峰表

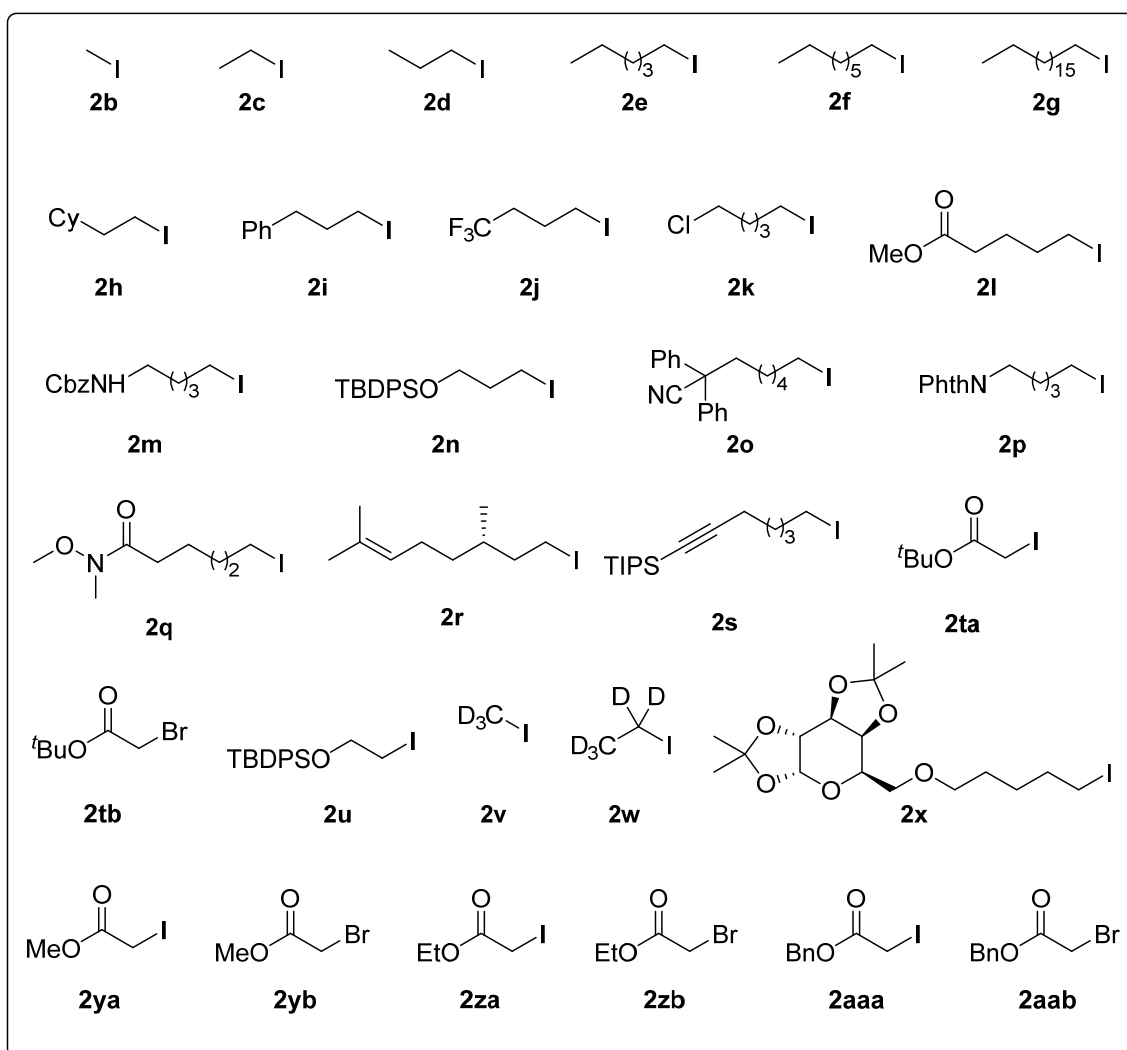
检测器A 254nm

峰号	保留时间	面积	高度	标记	面积%
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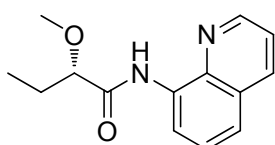
General Procedure (GP) for Mono-alkylation of Lactic Acid Derivative

To a 30-mL resealable Schlenk flask were added **1a** (46.1 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), alkyl iodide (0.4 mmol), Ag₂CO₃ (110.3 mg, 0.4 mmol), K₂CO₃ (27.6 mg, 0.2 mmol), and *t*-BuOH (2.0 mL). The Schlenk flask was charged with 1 atm of N₂. The mixture was stirred at 100 °C for 20 hours (for deuterated alkyl iodides, the reactions were run at 90 °C). The reaction vessel was allowed to cool to room temperature, and dichloromethane (5 mL) was added. The resulting mixture was filtered through a pad of Celite, which was subsequently washed with additional dichloromethane (20 mL). Evaporation of the organic solvent and purification by silica gel column chromatography gave the corresponding product.

Scope of alkyl iodides:

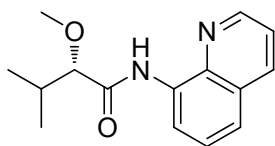


(*S*)-2-Methoxy-*N*-(quinolin-8-yl)butanamide (**3b**)



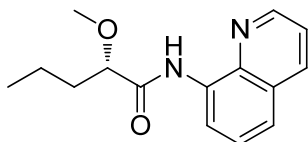
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3b** as a white solid (33.4 mg, 68%) [α]_D²⁰ = -88.2 (CHCl₃, c = 0.75), with **3b'** (10.2 mg, 20%) isolated. ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.82 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.82 (dd, *J* = 6.5, 4.5 Hz, 1H), 3.58 (s, 3H), 2.07 – 1.82 (m, 2H), 1.04 (d, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.60, 148.69, 139.05, 136.27, 134.15, 128.13, 127.35, 121.94, 121.71, 116.64, 84.46, 58.73, 26.07, 9.40; HRMS (EI) *m/z*: 244.1215 (M⁺); calc. for C₁₄H₁₆N₂O₂: 244.1212.

(S)-2-Methoxy-3-methyl-N-(quinolin-8-yl)butanamide (3b')



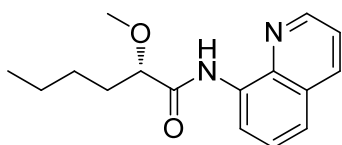
¹H NMR (400 MHz, CDCl₃) δ 10.75 (s, 1H), 8.86 (d, *J* = 4.1 Hz, 1H), 8.82 (dd, *J* = 6.7, 1.9 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.63 (d, *J* = 4.4 Hz, 1H), 3.59 (s, 3H), 2.31 – 2.18 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.38, 148.74, 139.11, 136.28, 134.13, 128.17, 127.40, 121.92, 121.74, 116.65, 88.67, 59.84, 32.12, 19.20, 17.34; HRMS (EI) *m/z*: 258.1369 (M⁺); calc. for C₁₅H₁₈N₂O₂: 258.1368.

(S)-2-Methoxy-N-(quinolin-8-yl)pentanamide (3c)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3c** as a colorless oil (30.3 mg, 59%). [α]_D²⁰ = -104.2 (CHCl₃, c = 1.0). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.86 (dd, *J* = 7.1, 4.6 Hz, 1H), 3.57 (s, 3H), 1.98 – 1.78 (m, 2H), 1.53 (dq, *J* = 14.9, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.89, 148.69, 139.04, 136.27, 134.16, 128.13, 127.36, 121.93, 121.72, 116.63, 83.48, 58.85, 35.30, 18.51, 14.01; HRMS (EI) *m/z*: 258.1366 (M⁺); calc. for C₁₅H₁₈N₂O₂: 258.1368.

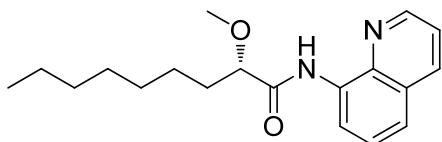
(S)-2-Methoxy-N-(quinolin-8-yl)hexanamide (3d)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3d** as

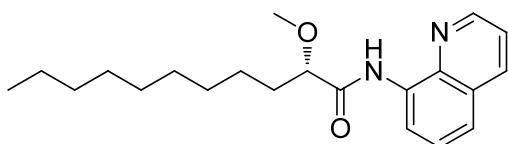
a colorless oil (32.4 mg, 59%). $[\alpha]_D^{20} = -94.6$ (CHCl₃, c = 0.5). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.8, 1.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.85 (dd, *J* = 7.1, 4.5 Hz, 1H), 3.57 (s, 3H), 2.00 – 1.78 (m, 2H), 1.48 (dt, *J* = 15.4, 7.5 Hz, 2H), 1.42 – 1.31 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.87, 148.69, 139.05, 136.26, 134.17, 128.13, 127.36, 121.93, 121.71, 116.63, 83.66, 58.83, 32.94, 27.32, 22.68, 14.06; HRMS (EI) *m/z*: 272.1529 (M⁺); calc. for C₁₆H₂₀N₂O₂: 272.1525.

(S)-2-Methoxy-N-(quinolin-8-yl)nonanamide (3e)



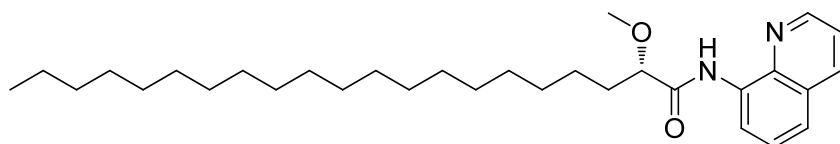
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 14:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3e** as a colorless oil (39.9 mg, 63%). $[\alpha]_D^{20} = -68.0$ (CHCl₃, c = 1.0). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.82 (dd, *J* = 6.8, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.62 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.85 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.58 (s, 3H), 2.00 – 1.77 (m, 2H), 1.57 – 1.44 (m, 2H), 1.36 – 1.23 (m, 8H), 0.86 (t, *J* = 6.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.88, 148.68, 139.05, 136.26, 134.18, 128.13, 127.37, 121.92, 121.71, 116.64, 83.69, 58.84, 33.26, 31.90, 29.56, 29.26, 25.21, 22.73, 14.18; HRMS (EI) *m/z*: 314.1997 (M⁺); calc. for C₁₉H₂₆N₂O₂: 314.1994.

(S)-2-Methoxy-N-(quinolin-8-yl)undecanamide (3f)



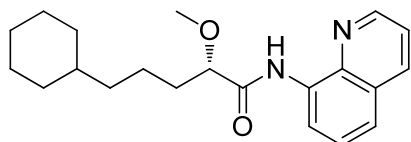
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 15:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3f** as a colorless oil (41.7 mg, 61%). $[\alpha]_D^{20} = -55.0$ (CHCl₃, c = 1.0). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.81 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.15 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.84 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.57 (s, 3H), 1.99 – 1.77 (m, 2H), 1.56 – 1.44 (m, 2H), 1.27 (s, 12H), 0.86 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.88, 148.69, 139.06, 136.27, 134.19, 128.14, 127.38, 121.92, 121.72, 116.65, 83.70, 58.85, 33.27, 31.99, 29.65, 29.60, 29.40, 25.21, 22.78, 14.22; HRMS (EI) *m/z*: 342.2306 (M⁺); calc. for C₂₁H₃₀N₂O₂: 342.2307.

(S)-2-Methoxy-N-(quinolin-8-yl)hencosanamide (3g)



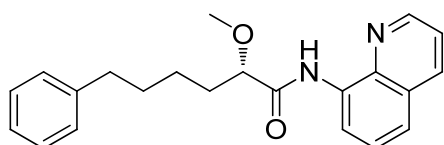
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 20:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3g** as a white solid (58.4 mg, 61%). $[\alpha]_D^{20} = -47.4$ (CHCl_3 , $c = 1.2$). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.79 (s, 1H), 8.85 (dd, $J = 4.0, 1.1$ Hz, 1H), 8.82 (dd, $J = 6.8, 1.6$ Hz, 1H), 8.14 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.61 – 7.47 (m, 2H), 7.44 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.85 (dd, $J = 7.2, 4.4$ Hz, 1H), 3.57 (s, 3H), 2.00 – 1.78 (m, 2H), 1.54 – 1.44 (m, 2H), 1.25 (s, 32H), 0.88 (t, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.87, 148.67, 139.06, 136.25, 134.19, 128.13, 127.37, 121.91, 121.70, 116.65, 83.70, 58.83, 33.27, 32.05, 29.83, 29.79, 29.76, 29.72, 29.61, 29.49, 25.22, 22.82, 14.24; HRMS (EI) m/z : 482.3876 (M^+); calc. for $\text{C}_{31}\text{H}_{50}\text{N}_2\text{O}_2$: 482.3872.

(S)-5-Cyclohexyl-2-methoxy-N-(quinolin-8-yl)pentanamide (3h)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 15:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3h** as a colorless oil (40.3 mg, 59%). $[\alpha]_D^{20} = -68.9$ (CHCl_3 , $c = 1.2$). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.78 (s, 1H), 8.85 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.81 (dd, $J = 6.8, 2.0$ Hz, 1H), 8.14 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.62 – 7.48 (m, 2H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 3.84 (dd, $J = 7.3, 4.4$ Hz, 1H), 3.57 (s, 3H), 1.94 – 1.76 (m, 2H), 1.72 – 1.58 (m, 5H), 1.56 – 1.46 (m, 2H), 1.28 – 1.11 (m, 6H), 0.91 – 0.79 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.88, 148.67, 139.05, 136.26, 134.17, 128.12, 127.36, 121.91, 121.70, 116.64, 83.72, 58.87, 37.61, 37.38, 33.58, 33.50, 33.45, 26.81, 26.50, 22.53; HRMS (EI) m/z : 340.2151 (M^+); calc. for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$: 340.2151.

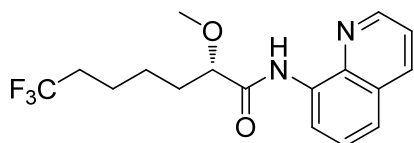
(S)-2-Methoxy-6-phenyl-N-(quinolin-8-yl)hexanamide (3i)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 10:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3i** as a colorless oil (43.3 mg, 62%). $[\alpha]_D^{20} = -65.2$ (CHCl_3 , $c = 1.0$). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.79 (s, 1H), 8.85 (dd, $J = 4.3, 1.5$ Hz, 1H), 8.81 (d, $J = 6.8$ Hz, 1H), 8.14 (d, $J = 8.3$ Hz, 1H), 7.58 – 7.48 (m, 2H), 7.44 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.27 – 7.19 (m, 2H), 7.18 – 7.10 (m, 3H), 3.85 (dd, $J = 6.7, 4.6$ Hz, 1H), 3.56 (s, 3H), 2.61 (t, $J = 7.6$ Hz, 2H), 2.02 – 1.83 (m, 2H), 1.71 – 1.62 (m, 2H), 1.60 – 1.51

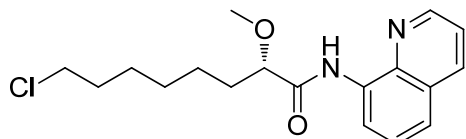
(m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.73, 148.69, 142.62, 139.04, 136.27, 134.12, 128.47, 128.35, 128.12, 127.35, 125.73, 121.96, 121.72, 116.65, 83.54, 58.85, 35.89, 33.03, 31.45, 24.94; HRMS (EI) m/z : 348.1835 (M^+); calc. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$: 348.1838.

(S)-7,7,7-Trifluoro-2-methoxy-N-(quinolin-8-yl)heptanamide (3j)



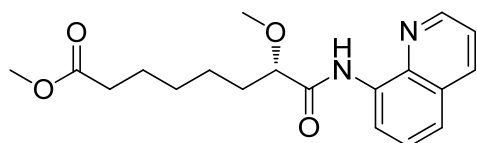
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3j** as a colorless oil (37.9 mg, 56%). $[\alpha]_{\text{D}}^{20} = -88.5$ (CHCl_3 , $c = 0.5$). ^1H NMR (400 MHz, CDCl_3) δ 10.80 (s, 1H), 8.86 (dd, $J = 4.1, 1.5$ Hz, 1H), 8.80 (dd, $J = 6.1, 2.8$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.61 – 7.49 (m, 2H), 7.46 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.86 (dd, $J = 6.8, 4.6$ Hz, 1H), 3.59 (s, 3H), 2.16 – 1.99 (m, 2H), 1.99 – 1.82 (m, 2H), 1.66 – 1.52 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.34, 148.76, 139.04, 136.33, 134.02, 131.38, 128.63, 125.88, 123.14 (q, $J_{\text{C-F}} = 277.4$ Hz), 128.16, 127.36, 122.11, 121.78, 116.70, 83.18, 58.90, 34.17, 33.88, 33.60, 33.32 (q, $J_{\text{C-F}} = 28.6$ Hz), 32.59, 24.32, 21.93, 21.90, 21.87, 21.85 (q, $J_{\text{C-F}} = 2.8$ Hz); HRMS (EI) m/z : 340.1401 (M^+); calc. for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$: 340.1399.

(S)-8-Chloro-2-methoxy-N-(quinolin-8-yl)octanamide (3k)



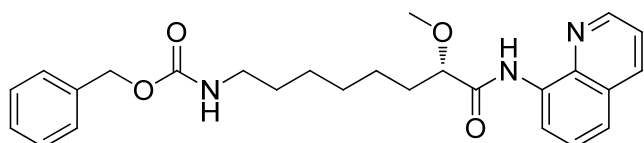
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 12:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3k** as a colorless oil (39.7 mg, 59%). $[\alpha]_{\text{D}}^{20} = -61.1$ (CHCl_3 , $c = 1.08$). ^1H NMR (400 MHz, CDCl_3) δ 10.79 (s, 1H), 8.85 (dd, $J = 4.1, 1.6$ Hz, 1H), 8.80 (dd, $J = 6.5, 2.3$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.64 – 7.47 (m, 2H), 7.44 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.85 (dd, $J = 7.1, 4.5$ Hz, 1H), 3.57 (s, 3H), 3.50 (t, $J = 6.7$ Hz, 2H), 1.98 – 1.80 (m, 2H), 1.79 – 1.70 (m, 2H), 1.56 – 1.47 (m, 2H), 1.46 – 1.32 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.68, 148.70, 139.02, 136.27, 134.09, 128.12, 127.34, 121.98, 121.73, 116.63, 83.50, 58.84, 45.14, 33.01, 32.61, 28.81, 26.82, 24.96; HRMS (EI) m/z : 334.1449 (M^+); calc. for $\text{C}_{18}\text{H}_{23}\text{ClN}_2\text{O}_2$: 334.1448.

(S)-Methyl 7-methoxy-8-oxo-8-(quinolin-8-ylamino)octanoate (3l)



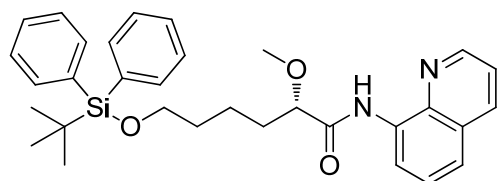
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 6:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3l** as a colorless oil (39.5 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.79 (dd, *J* = 6.5, 2.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.83 (dd, *J* = 7.1, 4.5 Hz, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.97 – 1.78 (m, 2H), 1.62 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.55 – 1.45 (m, 2H), 1.41 – 1.31 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 174.20, 171.63, 148.68, 138.99, 136.25, 134.07, 128.10, 127.31, 121.96, 121.70, 116.61, 83.44, 58.82, 51.51, 34.06, 32.91, 29.03, 24.87, 24.77; HRMS (EI) *m/z*: 344.1740 (M⁺); calc. for C₁₉H₂₄N₂O₄: 344.1736.

(S)-Benzyl (7-methoxy-8-oxo-8-(quinolin-8-ylamino)octyl)carbamate (3m)



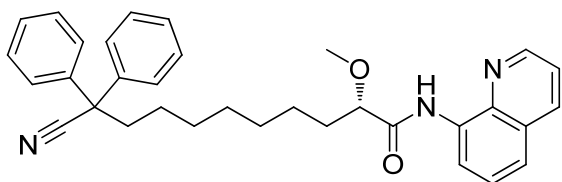
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 5:4:1 petroleum ether: dichloromethane: ethyl acetate, providing **3m** as a white solid (54.1 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 3.9, 1.4 Hz, 1H), 8.80 (dd, *J* = 6.3, 2.4 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.40 – 7.26 (m, 5H), 5.08 (s, 2H), 4.78 (s, 1H), 3.84 (dd, *J* = 6.9, 4.5 Hz, 1H), 3.57 (s, 3H), 3.16 (q, *J* = 6.3 Hz, 2H), 1.96 – 1.80 (m, 2H), 1.56 – 1.43 (m, 4H), 1.39 – 1.28 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 171.73, 156.48, 148.70, 139.02, 136.80, 136.27, 134.09, 128.59, 128.18, 128.13, 127.34, 121.97, 121.72, 116.63, 83.50, 66.63, 58.82, 41.13, 33.00, 29.95, 29.16, 26.64, 25.00; HRMS (ESI) *m/z*: 449.2309 (M⁺); calc. for C₂₆H₃₁N₃O₄: 449.2315.

(S)-6-((tert-Butyldiphenylsilyl)oxy)-2-methoxy-N-(quinolin-8-yl)hexanamide (3n)



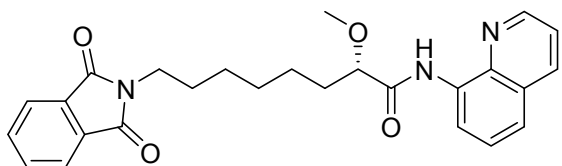
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 15:2:1 petroleum ether: dichloromethane: ethyl acetate, providing **3n** as a colorless oil (67.2 mg, 64%). [α]_D²⁰ = -49.0 (CHCl₃, *c* = 0.9). ¹H NMR (400 MHz, CDCl₃) δ 10.83 (s, 1H), 9.10 – 8.63 (m, 2H), 8.15 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.79 – 7.63 (m, 4H), 7.59 – 7.51 (m, 2H), 7.49 – 7.31 (m, 7H), 3.87 (dd, *J* = 6.2, 4.6 Hz, 1H), 3.69 (t, *J* = 5.8 Hz, 2H), 3.59 (s, 3H), 2.01 – 1.81 (m, 2H), 1.74 – 1.54 (m, 4H), 1.04 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 171.72, 148.66, 139.02, 136.23, 135.66, 134.15, 134.12, 129.58, 128.10, 127.68, 127.34, 121.92, 121.69, 116.64, 83.55, 63.82, 58.82, 32.98, 32.50, 26.95, 21.56, 19.28; HRMS (ESI) *m/z*: 526.2653 (M⁺); calc. for C₃₂H₃₈N₂O₃Si: 526.2652.

(S)-10-Cyano-2-methoxy-10,10-diphenyl-N-(quinolin-8-yl)decanamide (3o)



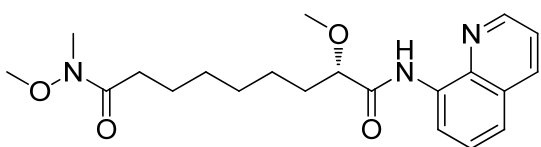
The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 20:3:1 petroleum ether: dichloromethane: acetone, providing **3o** as a colorless oil (35.5 mg, 35%). $[\alpha]_D^{20} = -51.3$ (CHCl₃, c = 1.08). ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 8.85 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.81 (dd, *J* = 6.5, 2.2 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.40 – 7.26 (m, 10H), 3.83 (dd, *J* = 7.0, 4.5 Hz, 1H), 3.57 (s, 3H), 2.41 – 2.27 (m, 2H), 1.95 – 1.76 (m, 2H), 1.50 – 1.38 (m, 4H), 1.36 – 1.27 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 171.79, 148.71, 140.50, 139.04, 136.28, 134.14, 128.93, 128.13, 127.87, 127.36, 126.98, 122.59, 121.96, 121.74, 116.64, 83.58, 58.84, 51.90, 39.74, 33.11, 29.49, 29.43, 29.20, 25.69, 25.04; HRMS (ESI) *m/z*: 505.2734 (M⁺); calc. for C₃₃H₃₅N₃O₂: 505.2729.

(S)-8-(1,3-Dioxoisindolin-2-yl)-2-methoxy-N-(quinolin-8-yl)octanamide (3p)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 5:4:1 petroleum ether: dichloromethane: ethyl acetate, providing **3p** as a white solid (53.6 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 10.76 (s, 1H), 8.83 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.78 (dd, *J* = 6.5, 2.4 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.56 – 7.46 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.82 (dd, *J* = 7.1, 4.5 Hz, 1H), 3.64 (t, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 1.94 – 1.77 (m, 2H), 1.70 – 1.59 (m, 2H), 1.54 – 1.43 (m, 2H), 1.41 – 1.29 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 171.70, 168.48, 148.66, 138.98, 136.21, 134.08, 133.88, 132.23, 128.07, 127.30, 123.20, 121.91, 121.68, 116.60, 83.48, 58.80, 38.04, 33.05, 29.13, 28.61, 26.82, 25.04; HRMS (EI) *m/z*: 445.2004 (M⁺); calc. for C₂₆H₂₇N₃O₄: 445.2002.

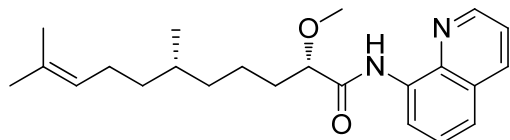
(S)-N⁹,2-Dimethoxy-N⁹-methyl-N¹-(quinolin-8-yl)nonanediamide (3q)



The title compound was prepared according to the **GP**. The crude product was purified by silica gel column chromatography in 3:1 petroleum ether: acetone, providing **3q** as a colorless oil (41.5 mg, 53%). ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H), 8.85 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.79 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.83 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 3.15 (s, 3H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.96 – 1.78 (m, 2H), 1.68 – 1.56 (m, 2H), 1.50 (dt, *J* = 14.6, 7.3 Hz, 2H), 1.40 – 1.29 (m, 4H); ¹³C NMR

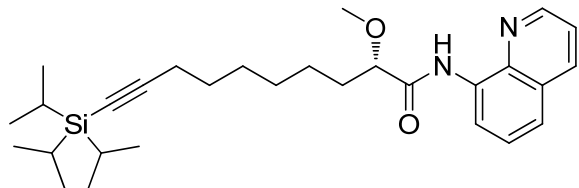
(101 MHz, CDCl₃) δ 174.68, 171.69, 148.59, 138.93, 136.15, 134.03, 128.01, 127.23, 121.83, 121.61, 116.51, 83.47, 61.18, 58.73, 33.03, 32.20, 31.83, 29.26, 29.22, 24.93, 24.56; HRMS (EI) m/z : 387.2158 (M^+); calc. for C₂₁H₂₉N₃O₄: 387.2158.

(2*S*,6*R*)-2-Methoxy-6,10-dimethyl-*N*-(quinolin-8-yl)undec-9-enamide (3r)



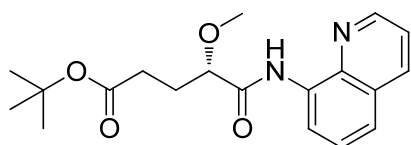
The compound **3r** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 15:2:1. **3r** was obtained as a colorless oil (30.5 mg, 41%). ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 8.85 (dd, J = 4.1, 1.5 Hz, 1H), 8.81 (dd, J = 6.7, 2.0 Hz, 1H), 8.15 (dd, J = 8.2, 1.3 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 5.07 (t, J = 6.3 Hz, 1H), 3.84 (dd, J = 7.2, 4.4 Hz, 1H), 3.58 (s, 3H), 2.06 – 1.74 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.54 – 1.47 (m, 1H), 1.46 – 1.37 (m, 2H), 1.36 – 1.28 (m, 2H), 1.20 – 1.08 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.88, 148.70, 139.06, 136.28, 134.18, 131.10, 128.14, 127.38, 125.11, 121.94, 121.72, 116.67, 83.74, 58.88, 37.17, 36.90, 33.61, 32.45, 25.83, 25.66, 22.76, 19.67, 17.74; HRMS (EI) m/z : 368.2466 (M^+); calc. for C₂₃H₃₂N₂O₂: 368.2464.

(*S*)-2-Methoxy-*N*-(quinolin-8-yl)-10-(triisopropylsilyl)dec-9-ynamide (3s)



The compound **3s** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 15:2:1. **3s** was obtained as a colorless oil (43.0 mg, 45%). [α]_D²⁰ = -39.7(CHCl₃, c = 0.95). ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 8.85 (dd, J = 4.1, 1.5 Hz, 1H), 8.81 (dd, J = 6.7, 2.0 Hz, 1H), 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.62 – 7.49 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 3.84 (dd, J = 7.2, 4.4 Hz, 1H), 3.57 (s, 3H), 2.22 (t, J = 6.7 Hz, 2H), 1.98 – 1.78 (m, 2H), 1.58 – 1.46 (m, 4H), 1.46 – 1.33 (m, 4H), 1.11 – 0.92 (m, 21H); ¹³C NMR (101 MHz, CDCl₃) δ 171.79, 148.68, 139.05, 136.26, 134.16, 128.13, 127.37, 121.93, 121.71, 116.65, 109.32, 83.65, 80.14, 58.84, 33.20, 29.04, 28.88, 28.65, 25.12, 19.90, 18.74, 11.41; HRMS (EI) m/z : 480.3171 (M^+); calc. for C₂₉H₄₄N₂O₂Si: 480.3172.

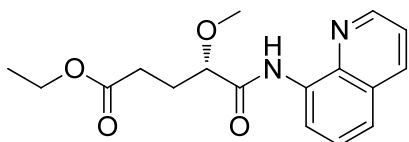
(*S*)-*tert*-Butyl 4-methoxy-5-oxo-5-(quinolin-8-ylamino)pentanoate (3t)



The compound **3t** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 6:3:1. **3t** was obtained as a colorless oil (49.1 mg,

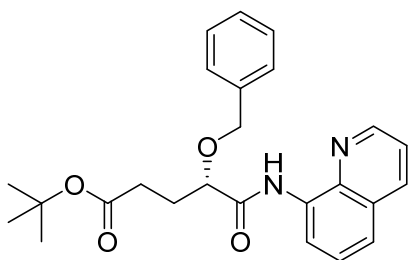
71% using **2ta** as alkylating reagent; 47.2 mg, 68% using **2tb** as alkylating reagent). ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.80 (dd, *J* = 5.9, 2.9 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.61 – 7.47 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.91 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.57 (s, 3H), 2.51 – 2.35 (m, 2H), 2.30 – 2.21 (m, 1H), 2.19 – 2.08 (m, 1H), 1.43 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.38, 170.89, 148.69, 139.00, 136.27, 134.01, 128.10, 127.31, 122.06, 121.73, 116.68, 82.29, 80.40, 58.80, 31.16, 28.17, 28.11; HRMS (EI) *m/z*: 344.1729 (M⁺); calc. for C₁₉H₂₄N₂O₄: 344.1736.

(S)-Ethyl 4-methoxy-5-oxo-5-(quinolin-8-ylamino)pentanoate (3u)



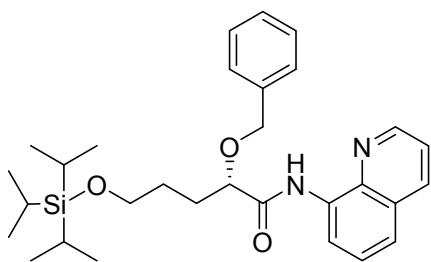
The compound **3u** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 5:4:1. **3u** was obtained as a colorless oil (32.4 mg, 51% using **2za** as alkylating reagent; 16.0 mg, 25% using **2zb** as alkylating reagent). [α]_D²⁰ = -58.5 (CHCl₃, *c* = 1.0). ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.79 (dd, *J* = 5.6, 3.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.12 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.92 (dd, *J* = 6.9, 4.7 Hz, 1H), 3.58 (s, 3H), 2.64 – 2.39 (m, 2H), 2.29 (dtd, *J* = 12.0, 7.5, 4.8 Hz, 1H), 2.19 (ddd, *J* = 14.3, 8.5, 6.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 173.12, 170.77, 148.71, 138.98, 136.29, 133.94, 128.10, 127.31, 122.12, 121.75, 116.70, 82.18, 60.53, 58.85, 29.97, 28.00, 14.29; HRMS (EI) *m/z*: 316.1421 (M⁺); calc. for C₁₇H₂₀N₂O₄: 316.1423.

(S)-tert-Butyl 4-benzyloxy-5-oxo-5-(quinolin-8-ylamino)pentanoate (3v)



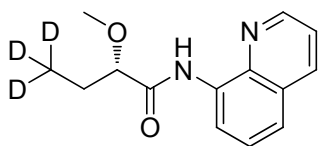
The compound **3v** was prepared according to the **GP** (using **1b** and **2tb** as substrate) and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 6:3:1. **3v** was obtained as a colorless oil (54.0 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 11.06 (s, 1H), 9.02 – 8.62 (m, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.51 (m, 4H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.44 – 7.27 (m, 3H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.15 (dd, *J* = 6.6, 4.8 Hz, 1H), 2.47 (t, *J* = 7.7 Hz, 2H), 2.38 – 2.27 (m, 1H), 2.27 – 2.12 (m, 1H), 1.42 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.32, 170.91, 148.50, 138.95, 137.15, 136.27, 134.03, 128.57, 128.47, 128.21, 128.08, 127.34, 122.05, 121.77, 116.61, 80.43, 79.93, 73.22, 31.23, 28.40, 28.16; HRMS (EI) *m/z*: 420.2049 (M⁺); calc. for C₂₅H₂₈N₂O₄: 420.2046.

(S)-2-(Benzyloxy)-N-(quinolin-8-yl)-5-((triisopropylsilyl)oxy)pentanamide (3w)



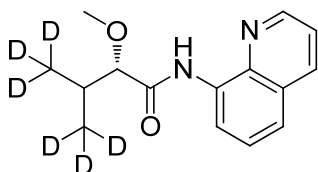
The compound **3w** was prepared according to the **GP** (using **1b** and **2u** as substrate) and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 15:2:1. **3w** was obtained as a colorless oil (46.8 mg, 46%). ¹H NMR (400 MHz, CDCl₃) δ 11.05 (s, 1H), 9.02 – 8.63 (m, 2H), 8.16 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.69 – 7.50 (m, 4H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.44 – 7.27 (m, 3H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.13 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.91 – 3.60 (m, 2H), 2.18 – 2.06 (m, 1H), 1.98 (dt, *J* = 14.0, 7.3 Hz, 1H), 1.86 – 1.75 (m, 2H), 1.22 – 0.97 (m, 21H); ¹³C NMR (101 MHz, CDCl₃) δ 171.66, 148.50, 139.03, 137.43, 136.25, 134.21, 128.55, 128.44, 128.13, 127.39, 121.93, 121.75, 116.62, 81.12, 73.11, 63.17, 29.79, 28.75, 18.15, 12.09; HRMS (EI) *m/z*: 506.2965 (M⁺); calc. for C₃₀H₄₂N₂O₃Si: 506.2966.

(S)-2-Methoxy-N-3-(methyl-*d*₃)-(quinolin-8-yl)propanamide (3x)



The compound **3x** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 12:2:1. **3x** was obtained as a white solid (30.0 mg, 60%) with **3x'** (15.8 mg, 30%) isolated. ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.85 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.81 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.61 – 7.47 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.82 (dd, *J* = 6.6, 4.7 Hz, 1H), 3.58 (s, 3H), 1.96 (dd, *J* = 13.9, 3.6 Hz, 1H), 1.87 (dd, *J* = 14.1, 6.6 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.63, 148.69, 139.04, 136.27, 134.14, 128.13, 127.35, 121.94, 121.71, 116.64, 84.43, 58.72, 25.83; HRMS (EI) *m/z*: 247.1403 (M⁺); calc. for C₁₄H₁₃D₃N₂O₂: 247.1400.

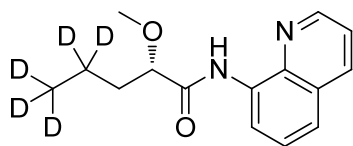
(S)-2-Methoxy-N-3,3-di(methyl-*d*₃)-(quinolin-8-yl)propanamide (3x')



¹H NMR (400 MHz, CDCl₃) δ 10.75 (s, 1H), 8.85 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.82 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.63 (d, *J* = 4.5 Hz, 1H), 3.59 (s, 3H), 2.21 (d, *J* = 4.5 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.40, 148.73, 139.09,

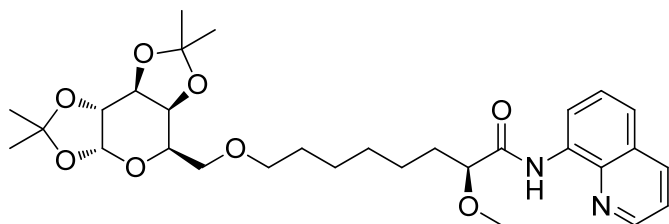
136.27, 134.12, 128.16, 127.39, 121.91, 121.73, 116.63, 88.62, 59.81, 31.66; HRMS (EI) m/z : 264.1746 (M^+); calc. for $C_{15}H_{12}D_6N_2O_2$: 264.1745.

(S)-2-Methoxy-N-3-(ethyl- d_5)-(quinolin-8-yl)propanamide (3y)



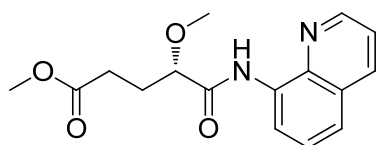
The compound **3y** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 12:2:1. **3y** was obtained as a colorless oil (35.5 mg, 67%). 1H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.81 (dd, J = 6.8, 1.9 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 3.86 (dd, J = 7.2, 4.6 Hz, 1H), 3.58 (s, 3H), 1.85 (qd, J = 14.0, 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.89, 148.68, 139.02, 136.26, 134.15, 128.11, 127.34, 121.92, 121.70, 116.61, 83.46, 58.82, 35.02; HRMS (EI) m/z : 263.1681 (M^+); calc. for $C_{15}H_{13}D_5N_2O_2$: 263.1682.

(S)-2-Methoxy-N-(quinolin-8-yl)-8-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)octanamide (3z)



The compound **3z** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 5:4:1. **3z** was obtained as a white solid (69.5 mg, 62%). 1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.80 (dd, J = 6.5, 2.3 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 5.52 (d, J = 5.0 Hz, 1H), 4.58 (dd, J = 7.9, 2.2 Hz, 1H), 4.28 (dd, J = 5.0, 2.3 Hz, 1H), 4.24 (dd, J = 7.9, 1.7 Hz, 1H), 3.93 (dd, J = 8.5, 3.7 Hz, 1H), 3.83 (dd, J = 7.2, 4.4 Hz, 1H), 3.65 – 3.50 (m, 5H), 3.49 – 3.39 (m, 2H), 1.98 – 1.78 (m, 2H), 1.62 – 1.45 (m, 7H), 1.43 (s, 3H), 1.37 – 1.28 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.83, 148.71, 139.06, 136.28, 134.17, 128.14, 127.38, 121.94, 121.73, 116.65, 109.29, 108.62, 96.50, 83.64, 71.61, 71.32, 70.77, 69.42, 66.83, 58.85, 33.19, 29.65, 29.42, 26.22, 26.11, 26.05, 25.17, 25.06, 24.56; HRMS (EI) m/z : 558.2943 (M^+); calc. for $C_{30}H_{42}N_2O_8$: 558.2941.

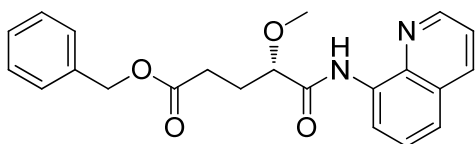
(S)-Methyl 4-methoxy-5-oxo-5-(quinolin-8-ylamino)pentanoate (3aa)



The compound **3aa** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 5:4:1. **3aa** was obtained as a colorless oil (27.0 mg,

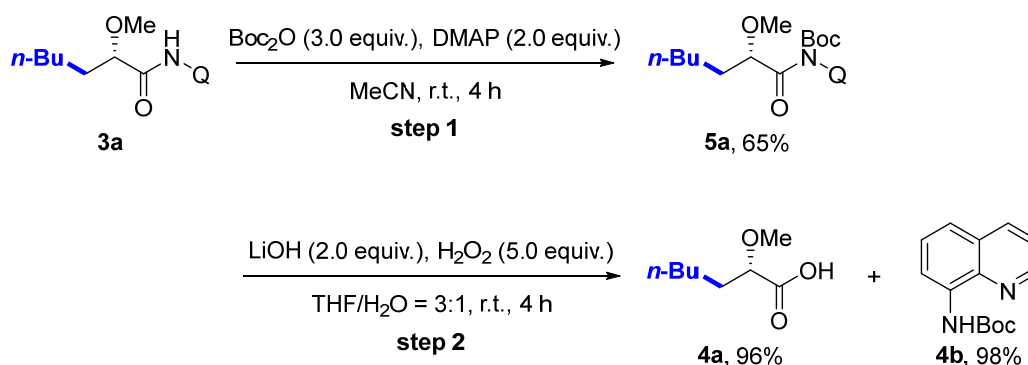
45% using **2ya** as alkylating reagent; 12.2 mg, 20% using **2yb** as alkylating reagent). ^1H NMR (400 MHz, CDCl_3) δ 10.79 (s, 1H), 8.85 (dd, $J = 4.0, 1.4$ Hz, 1H), 8.79 (dd, $J = 5.1, 3.5$ Hz, 1H), 8.16 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.60 – 7.49 (m, 2H), 7.46 (dd, $J = 8.1, 4.1$ Hz, 1H), 3.92 (dd, $J = 6.6, 4.8$ Hz, 1H), 3.67 (s, 3H), 3.58 (s, 3H), 2.62 – 2.44 (m, 2H), 2.36 – 2.14 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.58, 170.73, 148.73, 138.99, 136.30, 133.94, 128.11, 127.32, 122.14, 121.76, 116.72, 82.14, 58.87, 51.76, 29.72, 28.00; HRMS (EI) m/z : 302.1266 (M^+); calc. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$: 302.1267.

(S)-Benzyl 4-methoxy-5-oxo-5-(quinolin-8-ylamino)pentanoate (3ab)

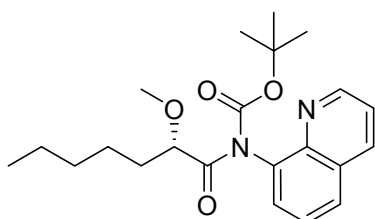


The compound **3ab** was prepared according to the **GP** and purified by column chromatography in petroleum ether: dichloromethane: ethyl acetate = 5:4:1. **3ab** was obtained as a colorless oil (21.4 mg, 28% using **2aaa** as alkylating reagent; 11.5 mg, 15% using **2aab** as alkylating reagent). ^1H NMR (400 MHz, CDCl_3) δ 10.81 (s, 1H), 8.84 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.80 (dd, $J = 5.3, 3.6$ Hz, 1H), 8.16 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.61 – 7.48 (m, 2H), 7.45 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.41 – 7.25 (m, 5H), 5.25 – 4.97 (m, 2H), 3.93 (dd, $J = 6.8, 4.8$ Hz, 1H), 3.55 (s, 3H), 2.71 – 2.44 (m, 2H), 2.33 (dt, $J = 12.0, 7.5$ Hz, 1H), 2.23 (dt, $J = 14.3, 6.8$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.96, 170.72, 148.74, 139.00, 136.31, 136.06, 133.95, 128.64, 128.33, 128.29, 128.12, 127.34, 122.16, 121.77, 116.74, 82.14, 66.43, 58.86, 29.97, 27.94; HRMS (EI) m/z : 378.1584 (M^+); calc. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$: 378.1580.

Removal of 8-AQ Auxiliary

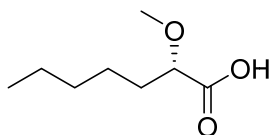


tert-Butyl (*S*)-(2-methoxyheptanoyl)(quinolin-8-yl)carbamate (**5a**)



To a solution of **3a** (114.6 mg, 0.4 mmol) in dry MeCN (4 mL) were added di-*tert*-butyl dicarbonate (Boc₂O, 261.9 mg, 1.2 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP, 97.7 mg, 0.8 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was diluted with dichloromethane (15 mL), washed by water (15 mL), brine (20 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 2:1 gave the product **5a** as a yellow solid (101.1 mg, 65%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.86 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.50 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.05 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.45 (s, 3H), 2.02 (dq, *J* = 10.1, 3.3, 2.9 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.62 – 1.51 (m, 2H), 1.40 – 1.32 (m, 4H), 1.23 (s, 9H), 0.91 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.35, 152.79, 150.29, 144.16, 136.68, 135.91, 128.88, 128.07, 126.04, 121.50, 82.77, 81.52, 77.35, 77.03, 76.71, 57.96, 33.15, 31.73, 27.59, 25.33, 22.56, 14.09.

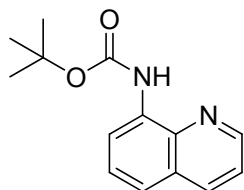
(*S*)-2-Methoxyheptanoic acid (**4a**)



To a solution of **5a** (38.7 mg, 0.1 mmol) in THF/H₂O (3:1, 0.5 mL) were added LiOH (4.8 mg, 0.2 mmol) and H₂O₂ (30%, 50 μL, 0.5 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was acidified by HCl (0.5 M, 12 mL), diluted with ethyl acetate (15 mL), washed by water (15 mL), brine (20 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 1:1 gave the product **4a** as a light yellow oil (15.4 mg, 96%) with **4b** (24.0 mg, 98%) isolated. ¹H NMR (400 MHz, Chloroform-*d*) δ 3.80 (dd, *J* = 6.7, 5.1 Hz, 1H), 3.44 (s, 3H), 1.89 – 1.68 (m, 2H), 1.42 (p, *J* = 7.4 Hz,

2H), 1.35 – 1.27 (m, 4H), 0.89 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.47, 80.23, 77.33, 77.02, 76.70, 58.29, 32.20, 31.46, 24.49, 22.43, 13.96.

***tert*-Butyl quinolin-8-ylcarbamate (4b)**



^1H NMR (400 MHz, CDCl_3) δ 9.02 (s, 1H), 8.79 (dd, $J = 4.1, 1.5$ Hz, 1H), 8.42 (d, $J = 7.4$ Hz, 1H), 8.13 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.46 – 7.35 (m, 2H), 1.58 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.05, 148.09, 138.41, 136.37, 135.35, 128.21, 127.49, 121.63, 120.28, 114.59, 80.54, 28.55; HRMS (EI) m/z : 244.1210 (M^+); calc. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: 244.1212.

References

1. Barrett, A. G. M.; Braddock, D. C.; Christian, P. W. N.; Pilipauskas, D.; White, A. J. P.; Williams, D. J. *Journal of Organic Chemistry*, **1998**, *63*, 5818 – 5823.

