A Straightforward Synthesis of (*S*)-Anabasine via the Catalytic, Enantioselective Vinylogous Mukaiyama–Mannich Reaction

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Abstract: The tobacco alkaloid (*S*)-anabasine was synthesized by a straightforward 4-step sequence with the catalytic enantioselective vinylogous Mannich reaction as a key step. Only 3 mol% of a structurally optimized chiral BINOL-based phosphoric acid was employed to control the absolute configuration of the natural product.

Key words: anabasine, piperidine, alkaloids, vinylogous Mannich reaction, Brønsted acid catalysis

The tobacco alkaloid (–)-anabasine belongs to the large group of piperidine alkaloids[1] containing a 3-pyridyl substituent in the 2-position within the piperidine ring. Along with nicotine it is the minor constituent of *Nicotina tabacum*, the species most commonly used for the production of cigarette tobacco. Although structurally not very complex, only a limited number of stereocontrolled total syntheses of this natural product have been reported, which mainly rely on the use of chiral auxilaries for the establishment of the correct absolute configuration.[2]

Thus, Kunz and co-workers employed a carbohydrate-derived imine for the central ring-forming hetero Diels–Alder reaction with Danishefsky's diene in the first total synthesis of (–)-anabasine.[2a,b] A very similar approach was pursued by Yamamoto and co-workers who mediated the cycloaddition reaction with a chiral boron complex.[2c,d] Later Amat[2i] and Pedrosa[2g] and their respective co-workers employed phenylglycinol as chiral auxiliary in cyclodehydration and reductive ring-opening reactions to arrive at the natural product. Asymmetric Brown allylation reactions were used by Lebreton and co-workers[2e,f] and Breit and co-workers[2k] to establish the correct absolute configuration of the stereogenic center of anabasine. The only catalytic, enantioselective approach thus far which furnished enantiomeric (+)-anabasine was reported by the Kobayashi group. Following the Kunz synthesis very closely they catalyzed the central hetero Diels–Alder reaction with a chiral niobium complex to achieve 92% ee.[2j] However, six additional steps had to be performed to convert the cycloadduct into (+)-anabasine.

We have recently established the first catalytic, enantioselective vinylogous Mukaiyama–Mannich reaction of acyclic silyl dienolates and imines furnishing highly functionalized δ-amino α,β-unsaturated esters and amides, respectively, in high yields and good to very good enantioselectivities (Scheme 1).[3,4] A chiral BINOL-based phosphoric acid was employed to catalyze the reaction and control the enantioselectivity of the carbon–carbon bond-forming step. Such Brønsted acids had been previously introduced by Akiyama[5] and Terada[6] and their respective groups independently into the field of asymmetric organocatalysis in general and imine addition reaction in particular. Subsequent to our report Carretero and co-workers reported a silver-catalyzed vinylogous Mannich reaction with sulfonyl imines, which was also applicable to acyclic silyl dienolates and furnished the products in good enantioselectivities.[7] Other recently reported and highly enantioselective protocols for the execution of the vinylogous Mannich reaction are limited to silyloxyfurans[8] and dicyanoalkenes[9] as the nucleophilic components.

We envisioned a particular vinylogous Mannich product carrying a 3-pyridyl group at the stereogenic center as suitable starting material for a straightforward conversion into (*S*)-anabasine through reduction, cyclization, and deprotection reactions. Accordingly, we investigated phosphoric acid catalyzed vinylogous Mannich reactions of silyl dienolates **2a** and **2b** with 3-pyridylimine **1a** (Table 1). It soon became apparent, however, that our previously optimized conditions for ester-based silyl dienolate **2a** using phosphoric acid **3a** (R = 2,4,6-$Me_3C_6H_2$) as the Brønsted acid catalyst did not give rise to a sufficiently selective reaction and delivered the vinylogous Mannich product **4a** in good yield, but only with 70% ee (entry 1). The enantioselectivity was increased to 79% ee by lowering the reaction temperature to –50 °C (entry 2).

Changing the Brønsted acid catalyst to **3b** (R = $SiPh_3$) significantly enhanced the selectivity to 88% ee with the amide-based silyl dienolate **2b** while maintaining a good yield of product **4b** (entry 3). As previously observed this reaction furnished the opposite enantiomer, however.[3b] In order to further improve the enantioselectivity of the central C–C bond forming event we then screened some additional 3,3′-substituted BINOL-phosphoric acids **3c–e** as catalysts. Indeed, more highly substituted 3,3′-aryl groups or larger substituents in the 3,3′-aryl groups lead to enhanced enantioselectivities as compared to the mesityl-substituted BINOL-phosphoric acid (entries 4–6).

In particular, just 3 mol% of phosphoric acid **3e** carrying the 2,6-Me_2-4-*t*-BuC_6H_2 group as 3,3′-substituents in the BINOL-backbone delivered the vinylogous Mannich

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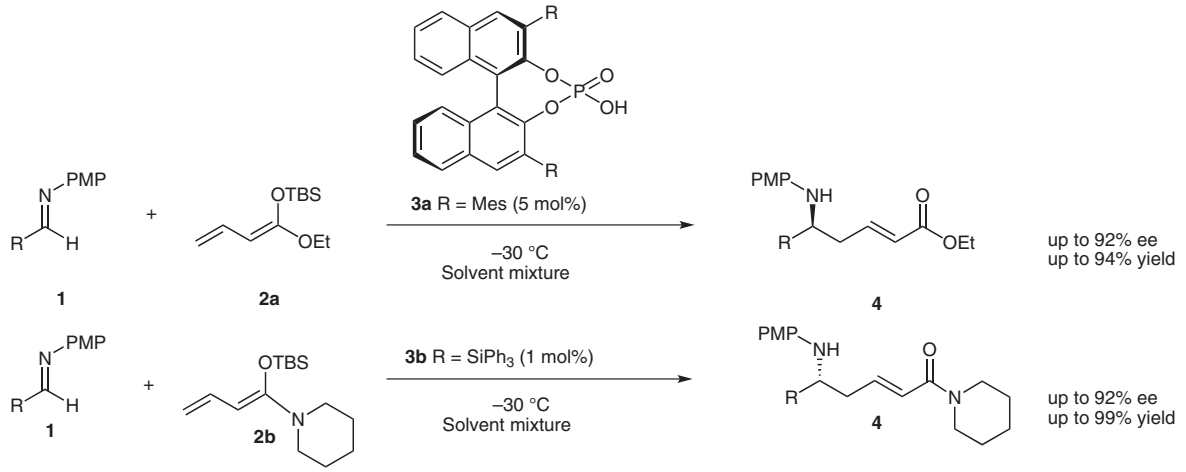
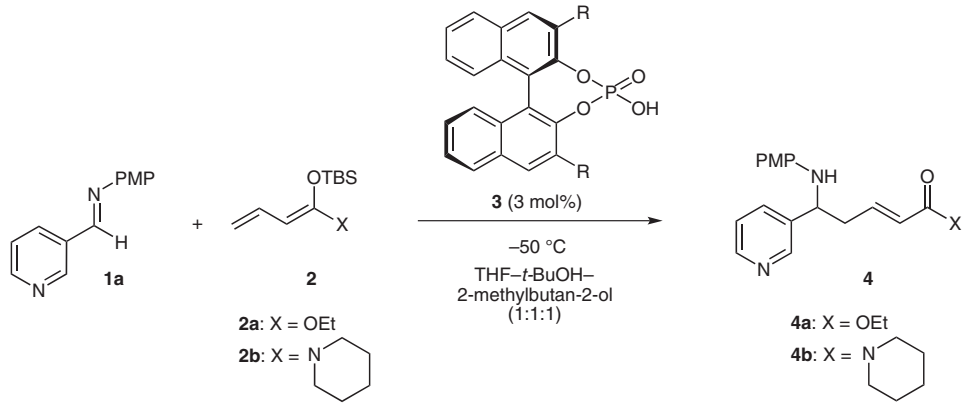


Scheme 1 Brønsted acid catalyzed, enantioselective, vinylogous Mukaiyama–Mannich reaction of acyclic silyl dienes

Table 1 Optimization of the Vinylogous Mukaiyama–Mannich Reaction[a]



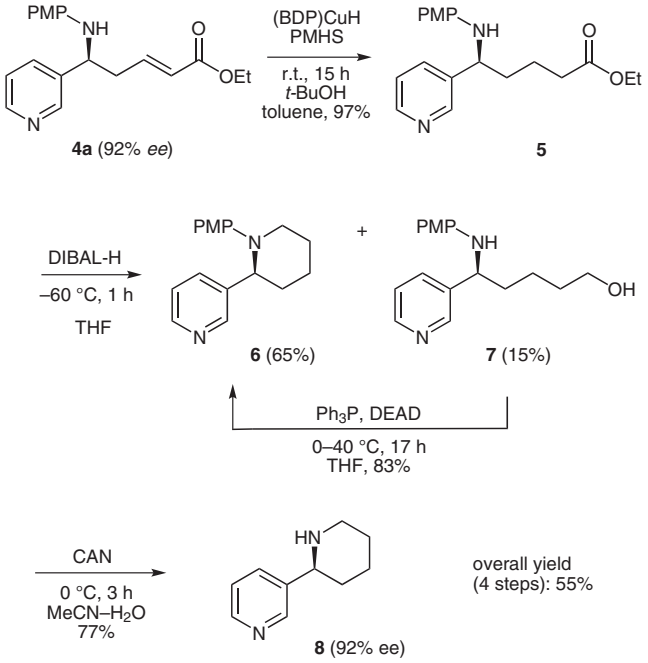
Entry	Silyl dienolate	Catalyst	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	**2a**	**3a** (R = 2,4,6-$Me_3C_6H_2$)	**4a**	24	86	70
2	**2a**	**3a** (R = 2,4,6-$Me_3C_6H_2$)	**4a**	72	94	79
3[d,e]	**2b**	**3b** (R = $SiPh_3$)	**4b**	36	90	–88
4	**2a**	**3c** (R = Me_5C_6)	**4a**	72	91	86
5	**2a**	**3d** (R = 2,4,6-$Et_3C_6H_2$)	**4a**	72	94	89
6	**2a**	**3e** (R = 2,6-Me_2-4-*t*-BuC_6H_2)	**4a**	60	96	92

[a] Reactions were performed with imine **1a** (0.40 mmol) and silyl dienolates **2** (3.0 equiv) at –50 °C in a solvent mixture containing equal amounts of THF, *t*-BuOH, and 2-methylbutan-2-ol with 1.0 equiv H_2O and 3 mol% phosphoric acid **3** at 0.17 M concentration.
[b] Yields refer to chromatographically purified material.
[c] Enantiomeric excesses were determined by HPLC using Chiralcel OD or OD-H columns.
[d] This reaction was conducted at –30 °C.
[e] This reaction was conducted in a 0.2 mmol scale, solvent mixture: equal amounts of i-PrOH, *t*-BuOH, and 2-methylbutan-2-ol with 1.0 equiv H_2O, 1 mol% **3b**, 0.1 M solution.

product **4a** in excellent yield and 92% ee when the reaction was conducted in our previously optimized solvent system at –50 °C (entry 6). Further enhancement of the steric size of the substituents in the 3,3′-aryl groups, however, resulted in a drop of selectivity as we had previously observed in reactions with other imines and the TRIP-phosphoric acid developed by List et al.[10] The vinylogous Mannich reaction with catalyst **3e** could easily be run in a three-component fashion with 3-pyridylaldehyde, *p*-anisidine, and silyl dienolate **2a** as reaction partners giving identical results and obviating the need for a separate synthesis of the imine.

Having established a highly efficient, direct, and enantioselective entry into the synthesis of (*S*)-anabasine we investigated the conversion of vinylogous Mannich product **4a** into the natural product. In related studies we had found $LiBHEt_3$ to be a suitable reducing reagent for the

concomitant 1,4- and 1,2-reduction of α,β-unsaturated carbonyl systems to the fully reduced alcohol.[3b] Presumably due to the presence of the readily reducible pyridine ring in **4a**, however, only low yields of the corresponding saturated alcohol were obtained with this highly reactive reductant. Accordingly, we slightly modified our strategy and first reduced the conjugate double bond of **4a** with the 'hot'-Stryker reagent developed by Lipshutz.[11] This proved to be a remarkably clean and efficient reaction and furnished the saturated ester **5** in almost quantitative yield (Scheme 2).



Scheme 2 Conversion of the vinylogous Mannich product **4a** into (*S*)-anabasine (**8**)

After some experimentation, it was found that DIBAL-H reduction (3 equiv) of ester **5** at –60 °C in THF directly delivered the desired piperidine **6** in 65% yield along with some quantities (15% yield) of the saturated alcohol **7**. Apparently, the secondary amine was intercepted by the in situ formed aldehyde and furnished a cyclic iminium ion, which was further reduced to yield piperidine **6**. When this reduction was attempted at lower temperatures the starting material could be recovered in high yield whereas higher temperatures shifted the ratio of piperidine **6** to alcohol **7** in favor of alcohol **7** in reduced yield. Alcohol **7** could, however, be converted in good yield into piperidine **6** using a Mitsunobu cyclization, which gave a total yield of 77% of piperidine **7** from ester **5**. Finally, CAN-oxidation and removal of the PMP-group deprotected the piperidine and furnished (*S*)-anabasine (**8**) in 77% yield. The analytical and spectroscopic data of the synthetic material was in good agreement with the reported data for (*S*)-anabasine. In addition, the corresponding *p*-nitrobenzoate was prepared and its melting point and optical rotation value matched the reported data.[2a,b]

In conclusion we have reported a straightforward four-step synthesis of the tobacco alkaloid (*S*)-anabasine using our recently developed vinylogous Mannich reaction as the key step. Only 3 mol% of a modified chiral Brønsted acid catalyst was used to establish the absolute configuration with high enantioselectivity. With a total yield of 55% our synthesis ranks among the most efficient syntheses reported to date for this natural product.

All vinylogous Mannich reactions were carried out in oven-dried glassware under air atmosphere. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using a Varian Gemini 2000 spectrometer (200 or 300 MHz) and Bruker Avance DRX 400 (400 MHz). The signals were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C). Chemical shifts are reported in ppm. Melting points were determined on a Boetius heating table and are uncorrected. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). UV spectra were recorded on a UV spectrometer (DU-650 Beckmann). Optical rotations were measured using a Polarotronic polarimeter (Schmidt & Haensch). All ESI mass spectra were recorded on a Bruker APEX II FT-ICR. All EI mass spectra were recorded on a Finnigan MAT 8230. HPLC analyses were carried out on a Jasco MD-2010 plus instrument with chiral stationary phase column (Daicel Chiralcel OD column or Daicel Chiralcel OD-H column).

The solvents were distilled from indicated drying reagents: CH_2Cl_2 (CaH_2), THF (Na, benzophenone), Et_2O (Na, benzophenone), toluene (Na, benzophenone). Et_2O, EtOAc, and petroleum ether (PE, bp 40–70 °C) were technical grade and distilled from KOH. All reactions were monitored by HPLC. Flash column chromatography was performed by using Merck silica gel 60 230–400 mesh (0.040–0.063 mm). Spots were monitored by TLC on precoated silica gel SIL G/UV254 plates (Machery-Nagel & Co.), were visualized by UV and were treated with a solution of phosphomolybdic acid hydrate [5 g in 250 mL MeOH (dried over Mg), Acros, ACS]. The corresponding racemic products were prepared using achiral diphenylphosporic acid (Alfa Aesar) as catalyst. All aldimines were prepared analogous to literature procedures.[12] The nucleophiles 1-(*tert*-butyldimethylsilyloxy)-1-ethoxybuta-1,3-diene (**2a**) and (*Z*)-1-[1-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl]piperidine (**2b**) were prepared according to the literature procedure of Denmark et al.[13] The preparation of chiral phosphoric acid catalysts **3** was done following the procedure described by Akiyama et al.,[14] Yamamoto and co-workers,[15] and MacMillan and co-workers.[16] All other chemicals like *i*-PrOH (HPLC-grade, VWR), *t*-BuOH (99.5%, Acros), and 2-methylbutan-2-ol (>96%, Fluka) were used as received from commercial suppliers.

Ethyl (2*E*,5*S*)-5-(4-Methoxyphenylamino)-5-(pyridin-3-yl)pent-2-enoate (4a)

An oven-dried, 5 mL flask containing a solution of *N*-*p*-methoxyphenylnicotinimine (**1a**; 42.4 mg, 0.20 mmol, 1.0 equiv) and chiral phosphoric acid **3e** (4.00 mg, 0.006 mmol, 0.03 equiv) in a freshly prepared solvent mixture of THF, *t*-BuOH, and 2-methylbutan-2-ol in H_2O (1:1:1 and 1.0 equiv H_2O, 1.2 mL) was cooled to –50 °C. After 1 min, 1-(*tert*-butyldimethylsilyloxy)-1-ethoxybuta-1,3-diene (**2a**; 140 mg, 0.60 mmol, 3.0 equiv, *E*/*Z* = 1:2) was added in one portion. The resulting mixture was stirred rapidly for 60 h at –50 °C whereupon the solvent was removed in vacuo. The residue was purified by silica gel chromatography (EtOAc–PE, 1:2 → 2:1, 10% Et_3N) to afford 125 mg (96%; 92% ee) of **4a** as a colorless oil; R_f = 0.2 (EtOAc–PE, 1:2, 10% Et_3N); $[\alpha]_D^{24}$ +22.9 (*c* = 1.00, $CHCl_3$).

HPLC: Chiralcel OD-H column, solvent: *n*-hexane–*i*-PrOH (4:1), flow rate: 0.5 mL/min, UV detection at 250 nm, major enantiomer t_R = 67.3 min (**4a**), minor enantiomer t_R = 77.0 min (*ent*-**4a**).

IR (film): 3344, 2945, 1715, 1656, 1511, 1427, 1366, 1309, 1239, 1215, 1184, 1162, 1094, 982, 917, 818, 784, 760, 715 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.70 (m, 2 H, H-4), 3.70 (s, 3 H, OCH_3), 3.78 (s, 1 H, NH), 4.19 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 4.49 (t, *J* = 6.5 Hz, 1 H, H-5), 5.93 (dt, *J* = 15.5, 1.5 Hz, 1 H, H-2), 6.45 (m_c, 2 H_{arom}), 6.69 (m_c, 2 H_{arom}), 6.89 (dt, *J* = 15.5, 7.5 Hz, 1 H, H-3), 7.25 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1 H_{arom}), 7.66 (dt, *J* = 8.0, 2.0 Hz, 1 H_{arom}), 8.51 (dd, *J* = 5.0, 2.0 Hz, 1 H_{arom}), 8.63 (d, *J* = 2.0 Hz, 1 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 41.0, 55.6, 55.7, 60.5, 114.8, 115.0, 123.7, 124.9, 133.9, 138.2, 140.3, 143.4, 148.6, 148.9, 152.6, 165.8.

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2O_3$ $[M + H]^+$: 327.17032; found: 327.17011; *m/z* calcd for $C_{19}H_{22}N_2O_3$ + Na $[M + Na]^+$: 349.15226; found: 349.15222; *m/z* calcd for $C_{38}H_{45}N_4O_6$ $[2 M + H]^+$: 653.33336; found: 653.33335; *m/z* calcd for $C_{38}H_{44}N_4O_6$ + Na $[2 M + Na]^+$: 675.31531; found: 675.31519.

(2*E*,5*R*)-5-(4-Methoxyphenylamino)-1-(piperidin-1-yl)-5-(pyridin-3-yl)pent-2-en-1-one (4b)

An oven-dried, 10 mL flask containing a solution of *N*-*p*-methoxyphenylnicotinimine (**1a**; 42.4 mg 0.20 mmol, 1.0 equiv) and chiral phosphoric acid **3b** (1.70 mg, 0.002 mmol, 0.01 equiv) in a freshly prepared solvent mixture of *i*-PrOH, *t*-BuOH, and 2-methylbutan-2-ol in H_2O (1:1:1 and 1.0 equiv H_2O, 2 mL) was cooled to –30 °C. After 1 min, (*Z*)-1-[1-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl]piperidine (**2b**; 160 mg, 0.60 mmol, 3.0 equiv) was added dropwise. The resulting mixture was stirred rapidly for 36 h at –30 °C whereupon the solvent was removed in vacuo. The residue was purified by silica gel chromatography (Et_2O–EtOAc, 3:1) to afford 66 mg (90%; 88% ee) **4b** as a colorless oil; R_f = 0.1 (Et_2O–EtOAc, 3:1); $[\alpha]_D^{24}$ –24.0 (*c* = 1.00, $CHCl_3$).

HPLC: Chiralcel OD column, solvent: *n*-hexane–*i*-PrOH (4:1), flow rate: 1.0 mL/min, UV detection at 250 nm, major enantiomer t_R = 34.3 min (**4b**), minor enantiomer t_R = 53.9 min (*ent*-**4b**).

IR (film): 3329, 2997, 2936, 2855, 1657, 1606, 1512, 1442, 1384, 1238, 1180, 1139, 1125, 1037, 975, 852, 821, 755, 717, 665, 621, 524 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (m, 4 H, CH_2), 1.63 (m, 2 H, CH_2), 2.70 (m, 2 H, H-4), 3.37 (m, 2 H, NCH_2), 3.57 (m, 2 H, NCH_2), 3.69 (s, 3 H, OCH_3), 3.84 (br s, 1 H, NH), 4.48 (t, *J* = 6.5 Hz, 1 H, H-5), 6.29 (dt, *J* = 15.0, 1.5 Hz, 1 H, H-2), 6.44 (m_c, 2 H_{arom}), 6.68 (m_c, 2 H_{arom}), 6.74 (dt, *J* = 15.0, 7.5 Hz, 1 H, H-3), 7.23 (dd, *J* = 8.0, 5.0 Hz, 1 H_{arom}), 7.66 (dt, *J* = 8.0, 2.0 Hz, 1 H_{arom}), 8.49 (dd, *J* = 5.0, 2.0 Hz, 1 H_{arom}), 8.63 (d, *J* = 2.0 Hz, 1 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 25.5, 26.6, 41.3, 43.1, 46.9, 55.7, 55.7, 114.8, 115.0, 123.6, 124.3, 134.1, 138.5, 139.4, 140.5, 148.6, 148.7, 152.5, 164.6.

HRMS (ESI): *m/z* calcd for $C_{22}H_{28}N_3O_2$ $[M + H]^+$: 366.21760; found: 366.21730; *m/z* calcd for $C_{22}H_{27}N_3O_2$ + Na $[M + Na]^+$: 388.19955; found: 388.19934; *m/z* calcd for $C_{44}H_{55}N_6O_4$ $[2 M + H]^+$: 731.42793; found: 731.42740; *m/z* calcd for $C_{44}H_{55}N_6O_4$ + Na $[2 M + Na]^+$: 753.40988; found: 753.40932.

Ethyl (5*S*)-5-(4-Methoxyphenylamino)-5-(pyridin-3-yl)pentanoate (5)[10]

To a flame-dried 20 mL flask, containing a solution of **4a** (200 mg, 0.61 mmol, 1.0 equiv) in degassed anhyd toluene (8 mL) was added *t*-BuOH (175μL, 3.0 equiv). After the addition of (BDP)CuH solution (0.74 mL, 1.0 mM in toluene, prepared following the literature procedure[11]), the resulting red solution was stirred at r.t. for 12 h. The reaction was quenched by addition of sat. aq NH_4Cl (6.0 mL). After dilution with Et_2O (30 mL), the solution was extracted with aq 1 N HCl (5 × 10 mL). The combined aqueous phases were neutralized with K_2CO_3 and then extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in vacuo to afford 194 mg (97%, 0.59 mmol) of **5** as a colorless oil, which did not require further purification; R_f = 0.2 (Et_2O); $[\alpha]_D^{24}$ +5.7 (*c* = 1.06, $CHCl_3$).

IR (film): 3379, 2934, 2832, 1729, 1619, 1578, 1513, 1426, 1384, 1298, 1238, 1181, 1120, 1037, 877, 821, 758, 717, 621, 524 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.67 (m, 1 H, CH*H*), 1.81 (m, 3 H, C*H*H, CH_2), 2.33 (t, *J* = 6.5 Hz, 2 H, H-2), 3.69 (s, 3 H, OCH_3), 3.89 (br s, 1 H, NH), 4.12 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 4.30 (t, *J* = 5.0 Hz, H-5), 6.46 (m_c, 2 H_{arom}), 6.68 (m_c, 2 H_{arom}), 7.23 (dd, *J* = 8.0, 4.5 Hz, 1 H_{arom}), 7.65 (d, *J* = 8.0 Hz, 1 H_{arom}), 8.48 (d, *J* = 4.5 Hz, 1 H_{arom}), 8.60 (s, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.5, 33.7, 37.9, 55.7, 56.6, 60.4, 114.6, 114.8, 123.6, 133.9, 139.3, 140.9, 148.5, 148.7, 152.2, 173.1.

HRMS (ESI): *m/z* calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$: 329.18597; found: 329.18623; *m/z* calcd for $C_{19}H_{24}N_2O_3$ + Na $[M + Na]^+$: 351.16791; found: 351.16809; *m/z* calcd for $C_{38}H_{48}N_4O_6$ + Na $[2 M + Na]^+$: 679.34661; found: 679.34633.

3-[(2*S*)-1-(4-Methoxyphenyl)piperidin-2-yl]pyridine (6) and (5*S*)-5-(4-Methoxyphenylamino)-5-(pyridin-3-yl)pentan-1-ol (7)

A flame-dried 50 mL flask containing a solution of **5** (75.0 mg, 0.23 mmol, 1.0 equiv) in anhyd THF (25 mL) was cooled to –60 °C. DIBAL-H (0.73 mL, 1 M solution in hexane, 0.73 mmol, 3.2 equiv) was added dropwise and the resulting solution was stirred for 1 h at –60 °C. The reaction was quenched by the addition of sat. aq Rochelle salt (15 mL), and the mixture was allowed to warm to r.t. After 30 min, the mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by silica gel chromatography (EtOAc–PE, 1:1 → 1:0) to afford 40.0 mg (65%, 0.15 mmol) of **6** and 10.0 mg (15%, 0.035 mmol) of **7**, both as colorless oils.

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R_f (Et_2O) = 0.3; $[\alpha]_D^{24}$ +39.6 (*c* = 1.52, $CHCl_3$).

IR (film): 2933, 2853, 2720, 1876, 1674, 1578, 1510, 1425, 1385, 1326, 1245, 1182, 1103, 1036, 933, 900, 877, 830, 803, 715, 640, 619, 578, 558, 535 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.57 (m, 1 H, H-4a), 1.64–1.94 (m, 5 H, H-3, H-4b, H-5), 2.82 (ddd, *J* = 12.0, 10.0, 4.0 Hz, 1 H, H-6a), 3.33 (dtd, *J* = 12.0, 3.0, 1.0 Hz, 1 H, H-6b), 3.67 (s, 3 H, OCH_3), 4.01 (dd, *J* = 10.0, 2.5, Hz, 1 H, H-2), 6.64 (m_c, 2 H_{arom}), 6.89 (m_c, 2 H_{arom}), 7.06 (ddd, *J* = 8.0, 4.5, 0.5 Hz, 1 H_{arom}), 7.55 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1 H_{arom}), 8.30 (dd, *J* = 4.5, 2.0 Hz, 1 H_{arom}), 8.46 (d, *J* = 2.0 Hz, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$,): δ = 24.3, 26.4, 36.4, 55.2, 57.1, 62.6, 113.9, 123.2, 124.7, 135.0, 140.1, 145.6, 147.7, 149.3, 155.3.

HRMS (ESI): *m/z* calcd for $C_{17}H_{21}N_2O$ $[M + H]^+$: 269.16484; found: 269.16483; *m/z* calcd for $C_{17}H_{20}N_2O$ + Na $[M + Na]^+$: 291.14678; found: 291.14675; *m/z* calcd for $C_{34}H_{40}N_4O_2$ + Na $[2 M + Na]^+$: 559.30435; found: 559.30449.

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R_f (Et_2O) = 0.1; $[\alpha]_D^{24}$ +8.7 (*c* = 1.60, $CHCl_3$).

IR (film): 3373, 2929, 1592, 1511, 1428, 1385, 1237, 1039, 877, 786, 762, 714 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38–1.63 (m, 4 H, H-2, H-3), 1.72–1.90 (m, 2 H, H-4), 3.63 (t, *J* = 6.0 Hz, 2 H, H-1), 3.68 (s, 3

H, OCH_3), 4.29 (t, J = 6.5 Hz, 1 H, H-5), 6.44 (m_c, 2 H_{arom}), 6.68 (m_c, 2 H_{arom}), 7.23 (dd, J = 8.0, 5.0 Hz, 1 H_{arom}), 7.65 (dt, J = 8.0, 2.0 Hz, 1 H_{arom}), 8.47 (dd, J = 5.0, 2.0 Hz, 1 H_{arom}), 8.59 (d, J = 2.0 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 32.7, 38.5, 55.7, 56.8, 62.4, 114.6, 114.8, 123.7, 134.0, 139.7, 141.0, 148.3, 148.6, 152.2.

HRMS (ESI): *m/z* calcd for $C_{17}H_{23}N_2O_2$ [M + H]$^+$: 287.17540; found: 287.17520; *m/z* calcd for $C_{34}H_{45}N_4O_4$ [2 M + H]$^+$: 573.34353; found: 573.34333.

3-[(2*S*)-1-(4-Methoxyphenyl)piperidin-2-yl]pyridine (6)

A flame-dried 10 mL flask containing a solution of **7** (18.0 mg, 0.063 mmol, 1.0 equiv) and Ph_3P (24.7 mg, 0.094 mmol, 1.5 equiv) in anhyd THF (5 mL) was cooled to 0 °C. Diethyl azodicarboxylate (17 μL 0.094 mmol, 1.5 equiv) was added dropwise and the resulting solution was warmed to 40 °C and stirred for 17 h. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (Et_2O–PE, 1:1) to afford **6** (14.1 mg, 83%, 0.053 mmol) as a colorless oil.

(*S*)-Anabasine (8)[2j]

3-[(2*S*)-1-(4-methoxyphenyl)piperidin-2-yl]pyridine (**6**; 15.0 mg, 0.056 mmol, 1.0 equiv) was dissolved in a solvent mixture of MeCN and H_2O (4:1, 1.5 mL) and the mixture was cooled to 0 °C. After the addition of cerium ammonium nitrate (184.0 mg, 0.336 mmol, 6.0 equiv), the reaction mixture was stirred for 3 h at 0 °C. The mixture was partitioned between H_2O (3 mL) and EtOAc (20 mL), and the aqueous phase was basified with solid K_2CO_3. The mixture was filtered through a pad of Celite and the aqueous phase was extracted with EtOAc (5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (CH_2Cl_2–MeOH, 10:1 → 6:1) to afford 7.0 mg (77%, 0.043 mmol) of (*S*)-anabasine (**8**) as a colorless oil; R_f = 0.2 (CH_2Cl_2–MeOH, 3:1); $[\alpha]_D^{24}$ –78.7 (*c* = 0.13, MeOH).[2f]

IR (film): 3407, 2926, 2854, 1735, 1432, 1385, 1109, 877, 786, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.92 (m, 7 H, H-3, H-4, H-5, NH), 2.81 (td, J = 11.5, 3.0 Hz, 1 H, H-6a), 3.21 (m_c, 1 H, H-6b), 3.64 (m, 1 H, H-2), 7.24 (dd, J = 8.0, 4.5 Hz, 1 H_{arom}), 7.72 (dt, J = 8.0, 2.0 Hz, 1 H_{arom}), 8.49 (d, J = 4.5 Hz, 1 H_{arom}), 8.59 (s, 1 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 23.4, 30.4, 46.2, 59.0, 123.8, 135.2, 143.0, 149.0, 150.0.

HRMS (EI): *m/z* calcd for $C_{10}H_{14}N_2$ [M]$^+$: 162.11570; found: 162.11553.

(2*S*)-*N*-(4-Nitrobenzoyl)-2-(3-pyridyl)piperidine

To a solution of (*S*)-anabasine (**8**; 10.0 mg, 0.062 mmol, 1.0 equiv) in anhyd THF (5 mL) at 0 °C, were added Et_3N (35 μL, 4.0 equiv) and 4-nitrobenzoyl chloride (40.0 mg, 3.5 equiv), and the resulting solution was stirred for 2 h. Additional amounts of Et_3N (35 μL, 4.0 equiv) and 4-nitrobenzoyl chloride (40.0 mg, 3.5 equiv) were added and the solution was stirred for 12 h. The reaction was quenched with H_2O (2 mL), diluted with EtOAc (20 mL) and the organic layer was washed with sat. aq $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography (EtOAc–PE, 1:2 → 2:1) to afford (2*S*)-*N*-(4-nitrobenzoyl)-2-(3-pyridyl)piperidine

(11.6 mg, 60%, 0.037 mmol as a white solid; mp 125–126 °C; R_f = 0.2 (EtOAc–PE, 3:1); $[\alpha]_D^{24}$ –116.5 (*c* = 0.24, MeOH).

HPLC: Chiralcel OD column, solvent: *n*-hexane–*i*-PrOH (4:1), flow rate: 1.0 mL/min, UV-detection at 210 nm, minor enantiomer t_R = 33.5 min (*ent*-**9**), major enantiomer t_R = 57.8 min (**9**).

IR (film): 2943, 2859, 1930, 1715, 1638, 1601, 1526, 1494, 1479, 1429, 1384, 1347, 1277, 1238, 1178, 1125, 1106, 1024, 999, 968, 862, 851, 787, 762, 713, 700, 644, 579 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45–1.71 (m, 5 H, H-3a, H-4, H-5), 1.79 (m, 1 H, H-3b), 2.04 (m, 1 H, H-6a), 2.46 (m_c, 1 H, H-6b), 2.94 (m, 1 H, H-2), 7.36 (dd, J = 8.0, 4.5 Hz, 1 H_{arom}), 7.64 (m, 3 H_{arom}), 8.29 (m_c, 2 H_{arom}), 8.59 (m, 2 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.9, 27.2, 29.7, 47.5, 52.0, 123.8, 124.0, 127.6, 134.1, 134.7, 142.1, 148.2, 148.3, 148.4, 169.1.

HRMS (ESI): *m/z* calcd for $C_{17}H_{18}N_3O_3$ [M + H]$^+$: 312.13427; found: 312.13416; *m/z* calcd for $C_{17}H_{17}N_3O_3$ + Na [M + Na]$^+$: 334.11621; found: 334.11598; *m/z* calcd for $C_{34}H_{34}N_6O_6$ + Na [2 M + Na]$^+$: 645.24321; found: 645.24321.

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