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PAPER

Organocatalytic enantioselective formal synthesis of bromopyrrole alkaloids *via* aza-Michael addition†

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An unprecedented organocatalytic enantioselective formal synthesis of bromopyrrole alkaloid natural products is reported. An organocatalytic aza-Michael addition using pyrroles as the *N*-centered nucleophile is utilized as the enantioselective step to construct the nitrogen-substituted stereogenic carbon center in bromopyrrole alkaloids in good yield and excellent enantioselectivity. The aza-Michael product is converted *via* lactamization using a Staudinger-type reductive cyclization to the key intermediate, which was previously used in the total synthesis of bromopyrrole alkaloid natural products.

Introduction

Bromopyrrole alkaloids, an important class of natural products isolated from marine sponges, possess a variety of interesting biological activities.[1] The pyrrolopiperazinone moiety is one of the key skeletons found in a great number of bromopyrrole alkaloids. Examples of bromopyrrole alkaloids with the pyrrolopiperazinone skeleton include hanishin, longamide B, longamide B methyl ester, cyclooroidin and the agesamides (Fig. 1). Hanishin, isolated with low enantiomeric purity from extracts of the highly polymorphic sponge *Acanthella carteri*, displays cytotoxic activity against NSCLC-N6 human non-small-cell-lung carcinoma.[2] Longamide B, isolated as a racemate from the Caribbean sponge *Agelas dispar*, exhibits antibiotic activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphilococcus aureus*.[3] Longamide B methyl ester, isolated as a racemate from *Homaxinella sp.* and then as a (+)-enantiomer from *Agelas ceylonica*, shows cytotoxic activity against P-388 lymphocytic leukemia cells.[4] (–)-Cyclooroidin[5] and the agesamides as an epimeric mixture[6] were isolated from the Mediterranean sponge *Agelas oroides* and the Okinawan sponge *Agelas sp.*, respectively, but only limited biological investigations were reported.

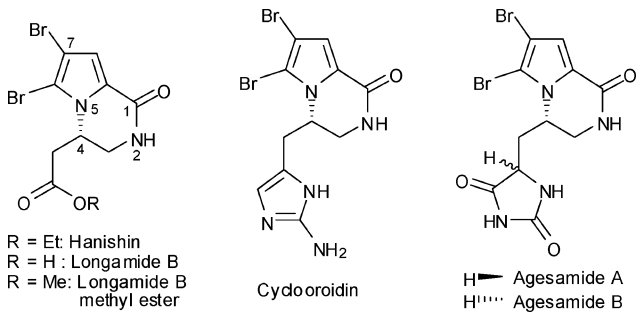
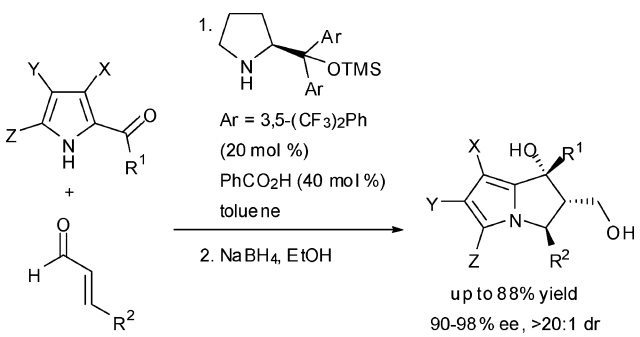


Fig. 1 Bromopyrrole alkaloids with the pyrrolopiperazinone skeleton.

Although their biological activities and chemical structures possessing the relatively rare nitrogen-substituted stereogenic carbon center are interesting, few asymmetric total syntheses of the above bromopyrrole alkaloids have been reported.[7] The known asymmetric syntheses of the bromopyrrole alkaloids have utilized Pd-catalyzed enantioselective annulation[7c,e] and chiral pool strategies[7a,b,d] to construct the chiral pyrrolopiperazinone skeleton. However, it is surprising that the use of organocatalytic synthetic routes remains unexplored in the asymmetric synthesis of the bromopyrrole alkaloids. Recently, we reported the enantio- and diastereoselective organocatalytic cascade aza-Michael addition–aldol reactions of 2-trihaloacetylpyrroles as the *N*-centered heteroaromatic nucleophiles to α,β-unsaturated aldehydes to afford the highly functionalized chiral pyrrolizines (Scheme 1).[8] We deemed the aza-Michael addition process[9,10] in



Scheme 1 Organocatalytic asymmetric cascade aza-Michael addition–aldol reactions of 2-trihaloacetylpyrroles to α,β-unsaturated aldehydes.

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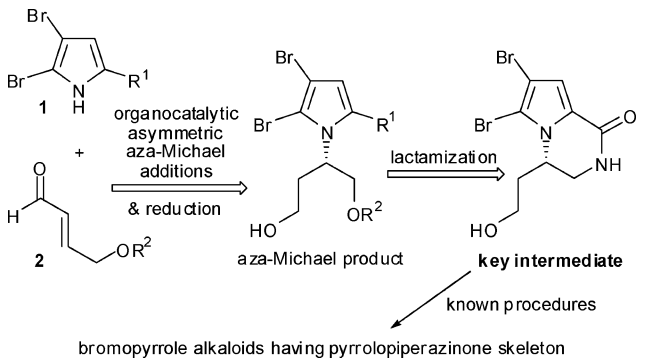
† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **5–22**. Chiral HPLC analysis data for compounds **3**, **5–15**. See DOI: 10.1039/c1ob06078c

this cascade reaction applicable to the asymmetric synthesis of the key intermediate of the bromopyrrole alkaloids.

Therefore, we report an organocatalytic asymmetric formal synthesis of the bromopyrrole alkaloids *via* the enantioselective aza-Michael additions of bromopyrroles as the *N*-centered heteroaromatic nucleophiles to α,β-unsaturated aldehydes bearing protected hydroxymethyl substituents, followed by lactamization using a Staudinger-type reductive cyclization to synthesize the key intermediate previously used in the total synthesis of the bromopyrrole alkaloids (Scheme 2).



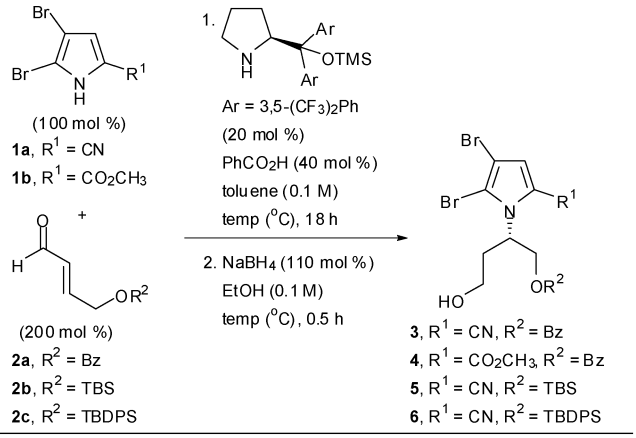
Scheme 2 The synthetic strategy for the formal synthesis of the bromopyrrole alkaloids.

Results and discussion

Our synthetic plan to prepare the common key intermediate in the total syntheses of the bromopyrrole alkaloids focused on efficiently preparing enantiomerically pure aza-Michael product with the defined absolute configuration *via* an organocatalytic enantioselective aza-Michael addition of pyrroles **1** to α,β-unsaturated aldehydes **2**, and constructing the pyrrolopiperazinone skeleton *via* a lactamization of the aza-Michael product. We had previously defined the favorable conditions for the aza-Michael addition step during the stepwise optimization of the cascade reaction of 2,4-dicyanopyrrole with crotonaldehyde.[8] Therefore, we undertook the further optimization of the organocatalytic enantioselective aza-Michael additions of pyrroles **1** with α,β-unsaturated aldehydes **2** (Table 1).

The aza-Michael addition of 4,5-dibromo-1*H*-pyrrole-2-carbonitrile (**1a**) to Bz-protected (*E*)-4-hydroxybut-2-enal **2a** using $PhCO_2H$ (40 mol%) as the acid additive in toluene at –20 °C was performed in the presence of (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether[11] as the organocatalyst, providing the corresponding aza-Michael product **3** in 70% yield and 76% enantiomeric excess (ee) (Table 1, entry 1). All of the products in the addition reactions were obtained after *in situ* reduction of the aza-Michael aldehyde products into the alcohols using $NaBH_4$ in ethanol. However, in the case of methyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (**1b**), the aza-Michael addition did not provide the desired product **4** under the same conditions (Table 1, entry 2). We speculated that the benzoate anion from the acid additive $PhCO_2H$ was not sufficiently basic to deprotonate pyrrole **1b** based on the proposed mechanism of the cascade reaction presented earlier by our group.[8] Through variation of the protecting groups of (*E*)-4-hydroxybut-2-enal in the aza-Michael additions with **1a**, the TBDPS group was identified as the ideal protecting group, affording a 77% yield of **6** in 87% ee (Table 1, entries 3–4). Gratifyingly, by lowering the reaction temperature to –40 °C, the ee of **6** increased to 93%, while sustaining the yield at 76% (Table 1, entries 5–6).

Table 1 Optimization of enantioselective organocatalytic aza-Michael additions of pyrroles **1** with protected (*E*)-4-hydroxybut-2-enals **2**[a]



Entry	R^1	R^2	T/°C	Product	Yield[b] (%)	ee[c] (%)
1	CN	Bz	–20	**3**	70	76
2	CO_2CH_3	Bz	–20	**4**	n.r.[d]	
3	CN	TBS	–20	**5**	78	80
4	CN	TBDPS	–20	**6**	77	87
5	CN	TBDPS	–30	**6**	76	91
6	**CN**	**TBDPS**	**–40**	**6**	**76**	**93**

[a] Procedure: To a mixture of pyrrole **1** (100 mol%), catalyst (20 mol%) and $PhCO_2H$ (40 mol%) in toluene (0.1 M) was added α,β-unsaturated aldehyde **2** (200 mol%) in one portion. The reaction mixture was allowed to stir at –20, –30 or –40 °C for 18 h, at which point the aldehyde was directly reduced to the alcohol with $NaBH_4$ (110 mol%) in EtOH (0.1 M). [b] Isolated yield for two steps. [c] Determined by HPLC analysis on chiral stationary phase (Chiralpak AD-H). [d] No reaction.

Next, we examined the scope of pyrroles as nucleophiles in the enantioselective organocatalytic aza-Michael additions of TBDPS-protected (*E*)-4-hydroxybut-2-enal **2c** under the optimized conditions to explore the feasibility of making a variety of biologically active pyrrolopiperazinone alkaloid derivatives. A series of 2-cyanopyrroles bearing various substituents, such as 4-cyano, 4-nitro and 4,5-dihalo, were examined (Figs 2 and 3). In all cases, chiral aza-Michael products **7–15** were obtained in good yields and excellent enantioselectivities. In particular, chemoselective reductions were developed using the corresponding aza-Michael aldehyde products from 4-halo-5-iodo-1*H*-pyrrole-2-carbonitriles as nucleophiles, depending on the reducing agents (Fig. 3). $NaBH_4$–reduction of the aza-Michael aldehyde products from the pyrroles provided the alcohol products along with the reduction of iodo group on the pyrrole moiety (Fig. 3, **10–12**). In contrast, $BH_3{\cdot}SMe_2$–reduction of the same aza-Michael aldehyde products afforded the alcohol products without any reduction of the iodo group (Fig. 3, **13–15**). The halo groups on the pyrrole moiety in aza-Michael products **7**, **10–15** can be used for carbon–carbon coupling reactions to synthesize various pyrrolopiperazinone alkaloid derivatives.[12]

Elaboration of the aza-Michael product **6** to the key intermediate **22** was achieved in seven steps (Scheme 3).

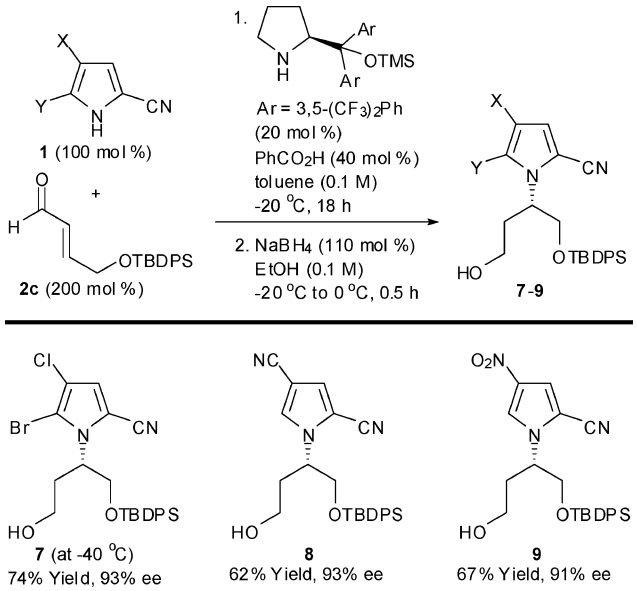


Fig. 2 Enantioselective organocatalytic aza-Michael additions of TBDPS-protected (*E*)-4-hydroxybut-2-enal **2c** with various 2-cyanopyrroles **1**. See the experimental section for detailed procedures. Cited yields are of isolated material for two steps. Enantiomeric excess was determined by HPLC analysis on chiral stationary phase (Chiralpak AD-H).

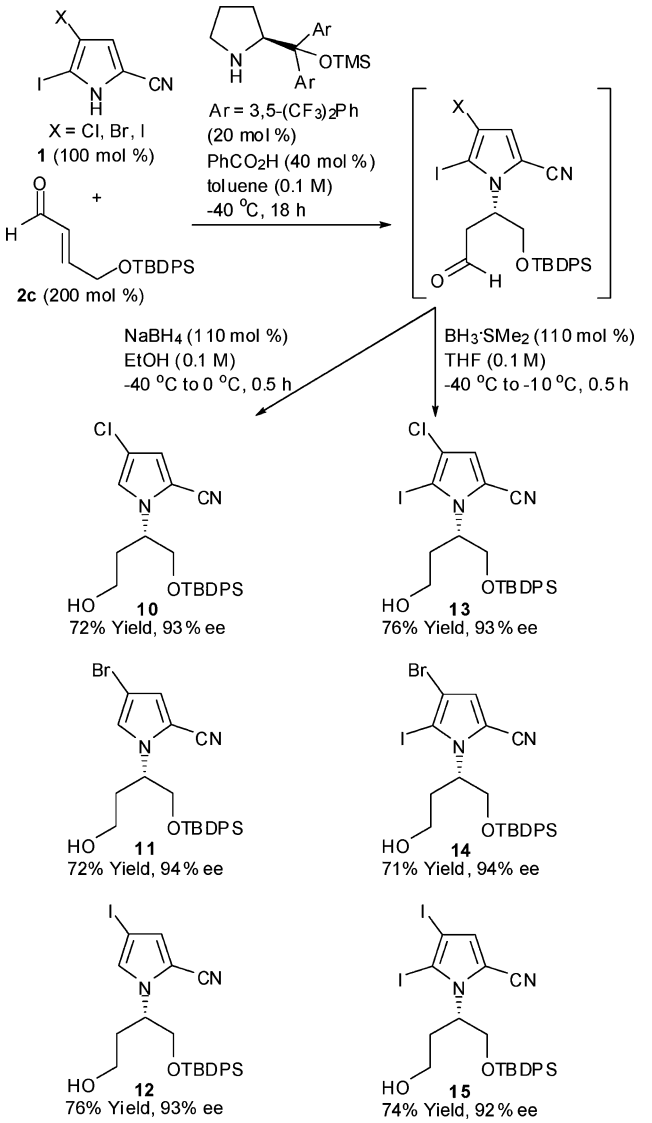
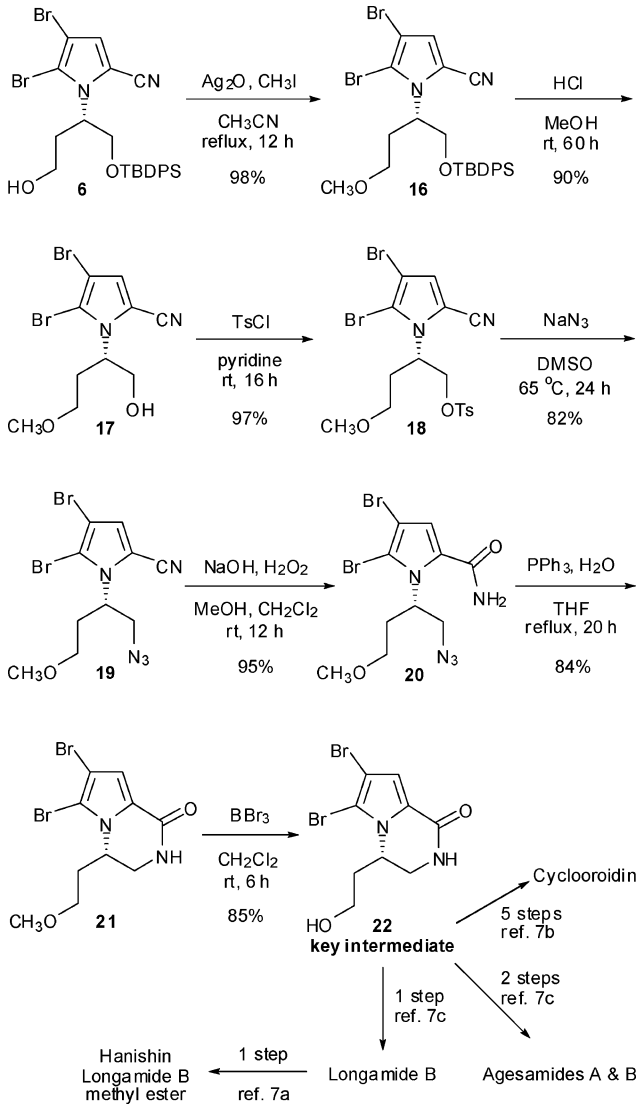


Fig. 3 Enantioselective organocatalytic aza-Michael additions followed by chemoselective reductions of TBDPS-protected (*E*)-4-hydroxybut-2-enal **2c** with 4-halo-5-iodo-1*H*-pyrrole-2-carbonitriles **1**. See the experimental section for detailed procedures. Cited yields are of isolated material for two steps. Enantiomeric excess was determined by HPLC analysis on chiral stationary phase (Chiralpak AD-H).

Methylation of **6** with iodomethane in the presence of silver oxide in acetonitrile at reflux provided the ether **16** in 98% yield.[13] The TBDPS group of **16** was removed by hydrogen chloride in methanol to afford the alcohol **17** in 90% yield. Subsequent tosylation of **17** with *p*-toluenesulfonyl chloride in pyridine gave the tosylate **18** in 97% yield. The introduction of an azide group into **18** using sodium azide in dimethyl sulfoxide provided the azide **19** in 82% yield.[14] The amide formation of **19** was carried out using sodium hydroxide and hydrogen peroxide in methanol–dichloromethane to give the azide–amide **20** in 95% yield.[15]

To complete the formal synthesis of the bromopyrrole alkaloids, a Staudinger reaction of **20** was performed with triphenylphosphine and water in tetrahydrofuran at reflux to provide the corresponding amine product.[16] However, surprisingly, rather than providing the amine product, the reaction gave the pyrrolopiperazinone **21** as the direct conversion product in 84% yield *via* a Staudinger-type reductive cyclization.[17] To the best of our knowledge, there has been no report on the direct lactamization *via* the Staudinger-type reductive cyclization of azides and amides, although the Staudinger ligation of azides and activated carboxy acids, including esters, is well-known.[18] Therefore, it was supposed that the lactamization to construct the pyrrolopiperazinone skeleton would be performed by a nucleophilic attack of the iminophosphorane, generated by the reaction between the azide group and triphenylphosphine, to the amide group followed by hydrolysis, and/or a nucleophilic attack of the amine group generated by the Staudinger reaction to the amide group.[19] Finally, demethylation of **21** using boron tribromide in dichloromethane provided the key intermediate **22** (85% yield)[7a] that had been previously used in the synthesis of the bromopyrrole alkaloids. The spectroscopic and analytical data for **22** were in full agreement with reported values.[7a,c,e] The absolute stereochemistry at C(4) in **22** was assigned by comparing the specific optical rotation of **22** with that reported in the literature.[7a,c,e] The absolute stereochemical assignment of all aza-Michael products is based on the absolute stereochemistry of **6**, which was determined to be the *S* configuration on the basis of the absolute configuration of **22**. Thus our organocatalytic enantioselective formal synthesis of the bromopyrrole alkaloids was accomplished from **1a** in eight linear steps (36% overall yield, 93% ee).[20] The bromopyrrole alkaloids, such as hanishin, longamide B, longamide B methyl ester, cyclooroidin and the agesamides, can be synthesized from the intermediate **22** in a few steps according to known procedures.[7]



Scheme 3 The formal synthesis of the key intermediate **22** from the aza-Michael addition product **6**.

Conclusion

We achieved the concise asymmetric formal synthesis of bromopyrrole alkaloids *via* the organocatalytic enantioselective aza-Michael addition followed by lactamization, from 4,5-dibromo-1*H*-pyrrole-2-carbonitrile (**1a**) to the key intermediate **22** in eight steps. The aza-Michael addition of variously substituted 2-cyanopyrroles, including **1a**, to TBDPS-protected (*E*)-4-hydroxybut-2-enal **2c** using (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether as the organocatalyst and benzoic acid as the acid additive, followed by chemoselective reduction provided the corresponding aza-Michael products **6–15** in good yields and excellent enantioselectivities. In addition, the lactamization of the amide group and the azide group was directly carried out to construct the pyrrolopiperazinone skeleton in good yield *via* a Staudinger-type reductive cyclization. Furthermore, this is the first example of the organocatalytic route for the asymmetric synthesis of the bromopyrrole alkaloids. Future studies will be devoted to the development of new aza-Michael additions and their application to the synthesis of biologically active natural products.

Experimental

General

All reactions were run under an atmosphere of argon, unless otherwise indicated. Toluene was distilled from calcium hydride. Chemical reagents were purchased and used without further purification, unless otherwise noted. Pyrroles **1**[12a,21] and α,β-unsaturated aldehydes **2**[22] were prepared according to the previously reported procedures. TLC analysis was carried out using silica gel plates (Merck 60 F_{254}). Flash column chromatography was carried out on silica gel (230–400 mesh). Melting points were determined on a Barnstead melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded with a Bruker (400 MHz) spectrometer. Chemical shifts are reported in δ units. Coupling constants are reported in Hz. ^{13}C NMR spectra were recorded with a Bruker (100 MHz) spectrometer. Chemical shifts are reported in δ units. ^{13}C NMR spectra were routinely run with broadband decoupling. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. HPLC analysis was performed on an Agilent 1200 Series with UV detector using a chiral separation column (Chiralpak AD-H).

Representative procedure for the organocatalytic enantioselective aza-Michael additions

To a mixture of pyrrole **1** (100 mol%), organocatalyst (20 mol%) and $PhCO_2H$ (40 mol%) in toluene (0.1 M) was added α,β-unsaturated aldehyde **2** (200 mol%) in one portion. The reaction mixture was allowed to stir at –20, –30 or –40 °C for 18 h, at which point the aldehyde was directly reduced with either $NaBH_4$ (110 mol%) in EtOH (0.1 M) or $BH_3{\cdot}SMe_2$ (110 mol%) in THF (0.1 M) to alcohol. After 30 min, the reaction was quenched by saturated aqueous $NaHCO_3$. The mixture was poured into ethyl acetate and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The organic layer was filtered and evaporated. The crude residue was purified by silica gel column chromatography.

(2′*S*)-4,5-dibromo-1-(1′-benzoyloxy-4′-hydroxybutan-2′-yl)-1*H*-pyrrole-2-carbonitrile (3)

Colorless oil (93 mg, 70%); $[\alpha]_D^{22}$ +4.0 (*c* 1, CH_3OH) in the case of 76% ee (Table 1, entry 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 2H), 7.58–7.55 (m, 1H), 7.44–7.40 (m, 2H), 6.99 (s, 1H), 5.33–5.22 (m, 1H), 4.81–4.67 (m, 2H), 3.83–3.77 (m, 1H), 3.50 (dt, J = 10.8, 3.6 Hz, 1H), 2.57–2.45 (m, 1H), 2.34–2.23 (m, 1H), 1.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.3, 129.5, 128.9, 128.4, 124.3, 113.7, 112.7, 102.6, 99.5, 65.2, 57.9, 57.2, 32.6; FTIR (neat) 3487, 3125, 2956, 2221, 1722, 1415, 1314, 1270, 1118, 711 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{14}Br_2N_2O_3$ 439.9371, found 439.9373; HPLC (Chiralpak AD-H, Hexane/IPA = 90/10, 0.9 mL min^{-1}, λ = 254 nm) 24.9 min (minor isomer), 27.2 min (major isomer).

(2′*S*)-4,5-dibromo-1-[1′-(*tert*-butyldimethylsilyloxy)-4′-hydroxybutan-2′-yl]-1*H*-pyrrole-2-carbonitrile (5)

White solid (106 mg, 78%); mp 70–72 °C; $[\alpha]_D^{22}$ −12.0 (*c* 1, CH_3OH) in the case of 80% ee (Table 1, entry 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 4.99–4.88 (m, 1H), 4.09–4.05 (m, 1H), 3.90 (dd, J = 10.8, 5.2 Hz, 1H), 3.75–3.71 (m, 1H), 3.53–3.43 (m, 1H), 2.43–2.32 (m, 1H), 2.18–2.08 (m, 1H), 1.48 (s, 1H), 0.79 (s, 9H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 114.1, 113.0, 102.3, 98.9, 64.4, 60.5, 58.4, 32.4, 25.4, 17.8, −5.6, −5.8; FTIR (neat) 3438, 2928, 2855, 2221, 1413, 1319, 1249, 1109, 835, 777 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{15}H_{25}O_2N_2Br_2Si$ 451.0052, found 451.0049; HPLC (Chiralpak AD-H, Hexane/IPA = 90/10, 0.9 mL min^{-1}, λ = 254 nm) 5.6 min (minor isomer), 6.6 min (major isomer).

(2′*S*)-4,5-dibromo-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-1*H*-pyrrole-2-carbonitrile (6)

White solid (131 mg, 76%); mp 99–101 °C; $[\alpha]_D^{20}$ +18.2 (*c* 1, CH_3OH) in the case of 93% ee (Table 1, entry 6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2H), 7.51–7.34 (m, 8H), 6.91 (s, 1H), 5.07–4.96 (m, 1H), 4.11 (t, J = 10.0 Hz, 1H), 3.93–3.87 (m, 1H), 3.70–3.63 (m, 1H), 3.47–3.38 (m, 1H), 2.36–2.25 (m, 1H), 2.11–2.00 (m, 1H), 1.42 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.6, 132.3, 129.9, 129.8, 127.7, 123.8, 114.2, 112.8, 102.4, 99.0, 65.0, 60.3, 58.2, 32.3, 26.4, 18.9; FTIR (neat) 3391, 2929, 2858, 2223, 2102, 1416, 1311, 1113, 700 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}Br_2N_2O_2Si$ 574.0287, found 574.0286; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 1.0 mL min^{-1}, λ = 254 nm) 7.8 min (minor isomer), 8.7 min (major isomer).

(2′*S*)-5-bromo-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4-chloro-1*H*-pyrrole-2-carbonitrile (7)

Yellow oil (118 mg, 74%); $[\alpha]_D^{21}$ +26.8 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 7.51–7.33 (m, 8H), 6.85 (s, 1H), 5.03–4.93 (m, 1H), 4.12 (t, J = 9.6 Hz, 1H), 3.93–3.86 (m, 1H), 3.68–3.63 (m, 1H), 3.42 (dt, J = 10.0, 3.6 Hz, 1H), 2.36–2.25 (m, 1H), 2.10–1.99 (m, 1H), 1.49 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.6, 132.2, 129.9, 129.8, 127.7, 121.1, 113.4, 112.9, 111.7, 101.4, 64.9, 59.8, 58.2, 32.3, 26.4, 18.9; FTIR (neat) 3368, 3114, 2929, 2858, 2224, 1426, 1329, 1113, 825, 701, 508 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}BrClN_2O_2Si$ 530.0792, found 530.0791; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 1.0 mL min^{-1}, λ = 254 nm) 7.4 min (minor isomer), 8.5 min (major isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-1*H*-pyrrole-2,4-dicarbonitrile (8)

Light yellow solid (83 mg, 62%); mp 93–95 °C; $[\alpha]_D^{22}$ −9.0 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.37 (m, 10H), 7.32 (d, J = 1.2 Hz, 1H), 7.03 (d, J = 1.6 Hz, 1H), 4.71–4.65 (m, 1H), 3.91 (dd, J = 11.2, 3.6 Hz, 1H), 3.83 (dd, J = 11.2, 7.2 Hz, 1H), 3.67–3.62 (m, 1H), 3.44–3.38 (m, 1H), 2.10–1.99 (m, 2H), 1.57 (s, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 135.3, 132.0, 131.9, 130.2, 130.1, 130.0, 127.8, 121.9, 114.2, 111.5, 106.3, 94.5, 65.5, 59.0, 57.8, 33.1, 26.5, 18.9; FTIR (neat) 3447, 3128, 2931, 2858, 2231, 1428, 1114, 702 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{26}H_{29}N_3O_2Si$ 443.2029, found 443.2032; HPLC (Chiralpak AD-H, Hexane/IPA = 90/10, 1.0 mL min^{-1}, λ = 254 nm) 6.0 min (minor isomer), 9.6 min (major isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4-nitro-1*H*-pyrrole-2-carbonitrile (9)

Light yellow solid (93 mg, 67%); mp 88–90 °C; $[\alpha]_D^{21}$ +16.1 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 1.6 Hz, 1H), 7.52–7.34 (m, 11H), 4.70–4.66 (m, 1H), 3.94 (dd, J = 11.2, 3.2 Hz, 1H), 3.86 (dd, J = 11.2, 6.8 Hz, 1H), 3.69–3.64 (m, 1H), 3.48–3.42 (m, 1H), 2.11–2.05 (m, 2H), 1.72 (s, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.4, 135.3, 132.0, 131.9, 130.1, 130.1, 127.8, 123.9, 114.6, 111.2, 105.7, 65.5, 59.3, 57.9, 33.1, 26.6, 18.9; FTIR (neat) 3419, 3127, 2928, 2857, 2230, 1512, 1389, 1308, 1113, 702 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{29}N_3O_4Si$ 463.1927, found 463.1932; HPLC (Chiralpak AD-H, Hexane/IPA = 90/10, 1.0 mL min^{-1}, λ = 254 nm) 11.2 min (minor isomer), 17.8 min (major isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4-chloro-1*H*-pyrrole-2-carbonitrile (10)

Colorless oil (98 mg, 72%); $[\alpha]_D^{24}$ −8.2 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.35 (m, 10H), 6.87 (d, J = 1.6 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 4.61–4.55 (m, 1H), 3.85 (dd, J = 10.8, 3.6 Hz, 1H), 3.76 (dd, J = 10.8, 6.8 Hz, 1H), 3.65–3.59 (m, 1H), 3.46–3.40 (m, 1H), 2.04–1.98 (m, 2H), 1.58 (s, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.4, 132.3, 132.2, 129.9, 129.9, 127.8, 127.8, 121.8, 118.2, 112.9, 112.6, 104.3, 66.1, 58.3, 58.3, 33.5, 26.5, 19.0; FTIR (neat) 3394, 3114, 2930, 2858, 2223, 1427, 1128, 1113, 700 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{29}ClN_2O_2Si$ 452.1687, found 452.1684; HPLC (Chiralpak AD-H, Hexane/IPA = 90/10, 1.0 mL min^{-1}, λ = 254 nm) 7.8 min (minor isomer), 10.1 min (major isomer).

(2′*S*)-4-bromo-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-1*H*-pyrrole-2-carbonitrile (11)

Yellow oil (107 mg, 72%); $[\alpha]_D^{25}$ −9.3 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.36 (m, 10H), 6.92 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 1.6 Hz, 1H), 4.64–4.58 (m, 1H), 3.85 (dd, J = 10.8, 3.6 Hz, 1H), 3.76 (dd, J = 10.8, 6.8 Hz, 1H), 3.67–3.61 (m, 1H), 3.49–3.41 (m, 1H), 2.06–2.00 (m, 2H), 1.47 (s, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 135.4, 132.3, 132.2, 129.9, 129.9, 127.8, 124.3, 120.6, 112.5, 105.2, 96.4, 66.1, 58.3, 58.3, 33.5, 26.5, 19.0; FTIR (neat) 3446, 3071, 2931, 2858, 2221, 1427, 1318, 1113, 758, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{29}BrN_2O_2Si$ 496.1182, found 496.1185; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 0.95 mL min^{-1}, λ = 254 nm) 9.0 min (minor isomer), 11.7 min (major isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4-iodo-1*H*-pyrrole-2-carbonitrile (12)

Light yellow oil (124 mg, 76%); $[\alpha]_D^{21}$ −19.0 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.35 (m, 10H), 6.98 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 1.6 Hz, 1H), 4.64–4.58 (m, 1H), 3.84 (dd, J = 10.8, 3.6 Hz, 1H), 3.77 (dd, J = 10.8, 6.8 Hz, 1H), 3.65–3.60 (m, 1H), 3.47–3.41 (m, 1H), 2.06–2.01 (m, 2H), 1.53 (s, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.4, 132.4, 132.3, 129.9,

129.9, 129.2, 127.8, 127.8, 125.6, 112.3, 106.4, 66.2, 59.9, 58.3, 58.2, 33.6, 26.6, 19.0; FTIR (neat) 3447, 3071, 2930, 2857, 2222, 1589, 1460, 1427, 1310, 1114, 758, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}N_2O_2SiI$ 543.0965, found 543.0968; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 1.0 mL min^{-1}, λ = 254 nm) 9.4 min (major isomer), 10.9 min (minor isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4-chloro-5-iodo-1*H*-pyrrole-2-carbonitrile (13)

Colorless oil (132 mg, 76%); $[\alpha]_D^{21}$ −22.5 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.49–7.34 (m, 8H), 6.99 (s, 1H), 4.99–4.92 (m, 1H), 4.14 (dd, *J* = 10.8, 9.6 Hz, 1H), 3.89 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.70–3.63 (m, 1H), 3.44–3.36 (m, 1H), 2.36–2.27 (m, 1H), 2.09–2.00 (m, 1H), 1.42 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.6, 132.2, 129.9, 129.8, 127.7, 124.3, 112.6, 106.2, 104.4, 89.4, 65.1, 63.4, 58.2, 32.5, 26.5, 18.9; FTIR (neat) 3448, 3071, 2930, 2857, 2219, 1427, 1306, 1113, 741, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}ClN_2O_2SiI$ 578.0653, found 578.0648; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 0.9 mL min^{-1}, λ = 254 nm) 8.0 min (minor isomer), 10.2 min (major isomer).

(2′*S*)-4-bromo-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-5-iodo-1*H*-pyrrole-2-carbonitrile (14)

Yellow oil (133 mg, 71%); $[\alpha]_D^{21}$ −44.8 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.49–7.34 (m, 8H), 6.99 (s, 1H), 4.98–4.92 (m, 1H), 4.14 (dd, *J* = 10.8, 9.6 Hz, 1H), 3.89 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.68–3.63 (m, 1H), 3.40 (dt, *J* = 9.6, 4.0 Hz, 1H), 2.35–2.27 (m, 1H), 2.08–2.00 (m, 1H), 1.47 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 132.6, 132.3, 129.9, 129.8, 127.8, 124.4, 112.6, 106.3, 104.5, 89.3, 65.2, 63.4, 58.3, 32.6, 26.5, 19.0; FTIR (neat) 3456, 3071, 2930, 2219, 1427, 1311, 1114, 758, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}BrN_2O_2SiI$ 622.0148, found 622.0153; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 1.0 mL min^{-1}, λ = 254 nm) 7.8 min (minor isomer), 10.1 min (major isomer).

(2′*S*)-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-hydroxybutan-2′-yl]-4,5-diiodo-1*H*-pyrrole-2-carbonitrile (15)

Light yellow oil (149 mg, 74%); $[\alpha]_D^{21}$ −36.0 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2H), 7.48–7.34 (m, 8H), 7.06 (s, 1H), 5.03–4.96 (m, 1H), 4.12 (dd, *J* = 10.8, 9.6 Hz, 1H), 3.88 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.70–3.62 (m, 1H), 3.45–3.37 (m, 1H), 2.35–2.27 (m, 1H), 2.08–1.99 (m, 1H), 1.40 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.6, 132.3, 129.9, 129.8, 129.7, 127.8, 127.7, 112.3, 105.5, 95.5, 77.2, 75.5, 65.2, 64.3, 58.2, 32.7, 26.5, 19.0; FTIR (neat) 3452, 3071, 2930, 2218, 1427, 1362, 1298, 1113, 757, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{25}H_{28}N_2O_2SiI_2$ 670.0010, found 670.0005; HPLC (Chiralpak AD-H, Hexane/IPA = 95/5, 0.9 mL min^{-1}, λ = 254 nm) 16.6 min (major isomer), 17.7 min (minor isomer).

(2′*S*)-4,5-dibromo-1-[1′-(*tert*-butyldiphenylsilyloxy)-4′-methoxybutan-2′-yl]-1*H*-pyrrole-2-carbonitrile (16)

Iodomethane (6.2 mL, 0.2 M) and silver oxide (431 mg, 1.86 mmol) was added to a solution of the conjugate product **6** (715 mg, 1.24 mmol) in acetonitrile (6.2 mL, 0.2 M) at rt. The mixture was allowed to stir at reflux for 12 h. The solids were removed by filtration and the solvents removed. The residue was purified by flash chromatography (SiO_2: 10% EtOAc in hexanes) to provide the ether **16** in 98% yield (717 mg, 1.22 mmol) as a colorless oil. $[\alpha]_D^{20}$ +30.9 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2H), 7.49–7.34 (m, 8H), 6.92 (s, 1H), 5.01–4.96 (m, 1H), 4.11 (t, *J* = 10.0 Hz, 1H), 3.87 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.40–3.35 (m, 1H), 3.25 (s, 3H), 3.04 (dt, *J* = 9.6, 4.0 Hz, 1H), 2.31–2.25 (m, 1H), 2.08–2.02 (m, 1H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.7, 132.4, 129.8, 129.8, 127.7, 123.7, 114.3, 112.8, 102.4, 98.9, 67.8, 64.9, 60.6, 58.6, 30.1, 26.5, 18.9; FTIR (neat) 3071, 2930, 2857, 2221, 1415, 1313, 1114, 798, 702, 504 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{26}H_{30}Br_2N_2O_2Si$ 588.0443, found 588.0442.

(2′*S*)-4,5-dibromo-1-(1′-hydroxy-4′-methoxybutan-2′-yl)-1*H*-pyrrole-2-carbonitrile (17)

1.25 M HCl solution in methanol (6.4 mL, 8.0 mmol) was added to **16** (236 mg, 0.4 mmol). The mixture was stirred at rt for 12 h, at which point 1.25 M HCl solution in methanol (6.4 mL, 8.0 mmol) was added once more and the mixture was stirred at rt for 48 h. The mixture was evaporated to remove methanol and quenched by saturated $NaHCO_3$. The mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$. Filtration, concentration and purification by flash chromatography (SiO_2: 30% EtOAc in hexanes) provided the alcohol **17** in 90% yield (126 mg, 0.358 mmol) as a white solid. mp 63–65 °C; $[\alpha]_D^{21}$ −5.2 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 4.90–4.84 (m, 1H), 4.19–4.13 (m, 1H), 3.99–3.93 (m, 1H), 3.47–3.42 (m, 1H), 3.29 (s, 3H), 3.10 (dt, *J* = 9.6, 4.0 Hz, 1H), 2.34–2.26 (m, 1H), 2.24–2.15 (m, 1H), 2.05 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 113.9, 112.7, 102.3, 99.5, 67.9, 63.5, 61.0, 58.6, 30.4; FTIR (neat) 3449, 3124, 2890, 2226, 1411, 1379, 1313, 1121, 1085, 828 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{10}H_{12}Br_2N_2O_2$ 349.9265, found 349.9263.

(2′*S*)-4,5-dibromo-1-[4′-methoxy-1′-(*p*-toluenesulfonyloxy)butan-2′-yl]-1*H*-pyrrole-2-carbonitrile (18)

p-Toluenesulfonyl chloride (136 mg, 0.713 mmol) was added to a solution of **17** (114 mg, 0.324 mmol) in pyridine (0.32 mL, 1.0 M). The mixture was allowed to stir at rt for 16 h. The mixture was quenched by water and extracted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4. Filtration, concentration and purification by flash chromatography (SiO_2: 25% EtOAc in hexanes) provided the tosylate **18** in 97% yield (159 mg, 0.314 mmol) as a colorless oil. $[\alpha]_D^{20}$ −12.0 (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 5.11–5.01 (m, 1H), 4.53 (t, *J* = 10.2 Hz, 1H), 4.32 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.41–3.36 (m, 1H), 3.23 (s, 3H), 2.96 (dt, *J* = 9.6, 3.6 Hz, 1H), 2.45 (s, 3H), 2.29–2.20 (m, 1H), 2.16–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 132.0, 129.9, 127.6, 124.0, 113.9, 112.3, 102.1, 99.5, 69.4, 67.2, 58.6, 57.4, 30.3, 21.6; FTIR (neat) 3125, 2927, 2877, 2221, 1598, 1367, 1177, 1122, 981, 813, 666, 554 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{18}Br_2N_2O_4S$ 503.9354, found 503.9358.

(2′*S*)-1-(1′-azido-4′-methoxybutan-2′-yl)-4,5-dibromo-1*H*-pyrrole-2-carbonitrile (19)

Sodium azide (122 mg, 1.884 mmol) was added to a solution of **18** (159 mg, 0.314 mmol) in dimethyl sulfoxide (3.14 mL, 0.1 M) at rt. The mixture was allowed to stir at 65 °C for 24 h. The mixture was quenched by water and extracted with ethyl acetate. The organic layers was washed with water and brine, then dried over Na_2SO_4. Filtration, concentration and purification by flash chromatography (SiO_2: 20% EtOAc in hexanes) provided the azide **19** in 82% yield (97 mg, 0.257 mmol) as a white solid. mp 45–47 °C; $[\alpha]_D^{21}$ +4.0 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.97–4.87 (m, 1H), 4.02–3.92 (m, 1H), 3.67 (dd, J = 13.2, 5.2 Hz, 1H), 3.46–3.41 (m, 1H), 3.28 (s, 3H), 3.03 (dt, J = 10.0, 3.6 Hz, 1H), 2.42–2.32 (m, 1H), 2.20–2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.4, 114.0, 112.7, 102.3, 99.7, 67.4, 58.7, 58.2, 53.6, 31.6; FTIR (neat) 3101, 2936, 2217, 2101, 1413, 1312, 1275, 1121, 1086, 965, 914 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{10}H_{11}Br_2N_5O$ 374.9330, found 374.9328.

(2′*S*)-1-(1′-azido-4′-methoxybutan-2′-yl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (20)

1 N aqueous sodium hydroxide (0.48 mL, 0.48 mmol) and hydrogen peroxide (30 wt.% in H_2O, 0.48 mL, 0.144 mmol) were added to a solution of **19** (91 mg, 0.241 mmol) in methanol–dichloromethane (10 : 1 v/v, 4.82 mL, 0.05 M). The mixture was allowed to stir at rt for 12 h. The mixture was quenched by saturated $Na_2S_2O_3$ and saturated NH_4Cl. The mixture was extracted with dichloromethane and water. The organic layer was dried over $MgSO_4$. Filtration, concentration and purification by flash chromatography (SiO_2: 40% EtOAc in hexanes) provided the azide–amide **20** in 95% yield (91 mg, 0.229 mmol) as a colorless oil. $[\alpha]_D^{19}$ −36.0 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two conformers, major : minor = 57 : 43) δ 6.82 (s, 0.57H) and 6.73 (s, 0.43H), 6.01–5.73 (m, 2.43H) and 4.99–4.89 (m, 0.57H), 4.36 (t, J = 11.2 Hz, 0.57H) and 4.10 (t, J = 11.2 Hz, 0.43H), 3.62 (dd, J = 12.8, 5.2 Hz, 1H), 3.39–3.32 (m, 1H), 3.25 (s, 3H), 3.24–3.17 (m, 0.43H) and 3.06–2.98 (m, 0.57H), 2.50–2.42 (m, 1H), 2.19–2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two conformers) major: δ 161.9, 126.6, 117.8, 114.7, 98.9, 68.5, 59.0, 58.5, 54.1, 31.9, minor: δ 161.9, 129.5, 115.8, 107.2, 101.6, 68.8, 58.5, 55.5, 53.1, 31.1; FTIR (neat) 3345, 3188, 2928, 2874, 2102, 1662, 1606, 1420, 1278, 1118, 953, 758 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{10}H_{13}Br_2N_5O_2$ 392.9436, found 392.9439.

(4*S*)-6,7-dibromo-4-(2′-methoxyethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (21)

Triphenylphosphine (195 mg, 0.75 mmol) was added to a solution of **20** (135 mg, 0.34 mmol) in tetrahydrofuran (3.4 mL, 0.1 M). The mixture was stirred at rt for 1 h, at which point water (0.037 mL, 2.04 mmol) was added and the mixture was refluxed for 20 h. The solvent removed and the residue was purified by flash chromatography (SiO_2: 85% EtOAc in hexanes) to give the pyrrolopiperazinone **21** in 84% yield (100 mg, 0.285 mmol) as a white solid. mp 113–115 °C; $[\alpha]_D^{21}$ −27.1 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 6.98 (s, 1H), 4.52–4.47 (m, 1H), 3.85 (dd, J = 13.2, 4.0 Hz, 1H), 3.65 (dd, J = 13.2, 4.8 Hz, 1H), 3.47–3.44 (m, 2H), 3.35 (s, 3H), 2.13–2.04 (m, 1H), 1.96–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 124.7, 115.6, 106.7, 100.5, 68.7, 58.7, 52.0, 42.9, 31.7; FTIR (neat) 3215, 3083, 2923, 1651, 1547, 1466, 1427, 1332, 1120, 963, 760 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{10}H_{12}Br_2N_2O_2$ 349.9265, found 349.9266.

(4*S*)-6,7-dibromo-4-(2′-hydroxyethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (22)

Boron tribromide (1 M solution in dichloromethane, 1.2 mL, 1.2 mmol) was slowly added to a solution of **21** (84 mg, 0.24 mmol) in dichloromethane (2.8 mL, 0.085 M) at −20 °C. The mixture was stirred at rt for 6 h and quenched by water. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$. Filtration, concentration and purification by flash chromatography (SiO_2: 5% MeOH in dichloromethane) provided the key intermediate **22** in 85% yield (69 mg, 0.204 mmol) as a white solid. mp 139–141 °C; $[\alpha]_D^{19}$ −28.9 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.91 (s, 1H), 4.60–4.56 (m, 1H), 3.81 (dd, J = 13.6, 4.0 Hz, 1H), 3.68–3.63 (m, 3H), 2.03–1.94 (m, 1H), 1.87–1.79 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.1, 126.1, 116.3, 108.0, 101.2, 59.2, 53.3, 43.3, 35.5; FTIR (neat) 3431, 3243, 2921, 1647, 1617, 1545, 1426, 1335, 1053, 960, 750 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_9H_{10}Br_2N_2O_2$ 335.9109, found 335.9109.

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