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Total synthesis of newbouldine via reductive N–N bond formation

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ABSTRACT

The first total synthesis of newbouldine has been achieved employing a new, reductive N–N bond forming reaction. The asymmetric synthesis confirms that the natural product is a racemate.

1. Introduction

Natural products that contain an N–N bond are relatively scarce.[1] An intriguing representative of this class is keramamine B (**1**, Fig. 1), which contains three contiguous nitrogen atoms as part of a six-membered ring.[2] Elaiomycin (**2**) belongs to a small family of natural products containing the unusual azoxy functionality,[3–5] whereas himastatin (**3**) is a striking example of a natural product featuring the more common piperazic acid moiety.[6] Very recently, dentigerumycin (**4**), a bacterial mediator of ant-fungus symbiosis containing three piperazic acid units, was disclosed by Clardy et al.[7]

Naturally occurring hydrazones are even less common and few examples have to date been described. These include the optically active tricyclic hydrazone cinachyramine (**5**), which was isolated from the Okinawan sponge *Cinachyrella* sp. Its absolute stereochemistry has not yet been defined.[8] The unusual antibiotic NG-067 (**6**) features the hydrazone functionality as part of a quinone imine system.[9]

Another family of alkaloids containing the hydrazone moiety is represented by the molecule newbouldine (**7**), originally isolated from the West African tree *Newbouldia laevis* together with its 4′-hydroxy- and 4′-methoxy derivatives **8** and **9**, as well as withasomnine (**10**), 4′-hydroxywithasomnine (**11**) and 4′-methoxywithasomnine (**12**).[10,11] The root bark of *N. leavis* is used for a wide variety of ethnomedicinal purposes,[12] such as the treatment of enlarged spleen, dysentery, worm infestations, migraine, earache, conjunctivitis, and various forms of orchitis.[13] A crude extract of these alkaloids has been shown to exhibit potent neurological effects.[14]

In terms of their structure, the newbouldines (**7**–**9**) and the withasomnines (**10**–**12**) differ in the extent of saturation of the five-membered heterocyclic ring. The latter contain a pyrazole unit as part of a bicyclic system, whereas the former feature a non-aromatic pyrazoline, thus giving rise to two stereogenic centers.

Remarkably, none of the pyrazoline natural products are optically active, suggesting the racemic nature of their biosynthesis. This is all the more remarkable as the newbouldines (**7**–**9**) are presumably derived from the amino acids proline, phenylalanine, and tyrosine, respectively. It can also be assumed that the N–N bonds in these natural products are formed via oxidative processes, which have been suggested in other biosynthetic pathways.[15–18]

Although a number of chemical syntheses of withasomnine (**10**) have been reported,[19–27] only one of them has exploited an oxidative N–N bond formation methodology.[27] In contrast, no total syntheses of newbouldines (**7**–**9**) have thus far been disclosed. We now report a short and efficient synthesis of **7**, which was fashioned by a reductive hydrazone formation, previously developed in our laboratories.

Our new method was discovered during a total synthesis of amathaspiramide F (**20**), shown in Scheme 1.[28] Its key step was a highly stereoselective alkylation of oxazolidinone **13** with nitroolefin **14** to yield nitroalkane **15**. This was followed by hydrolysis of the aminal function in **15** to yield secondary amine **16** and then by protection to afford trifluoroacetimidate **17**. Subsequent formation

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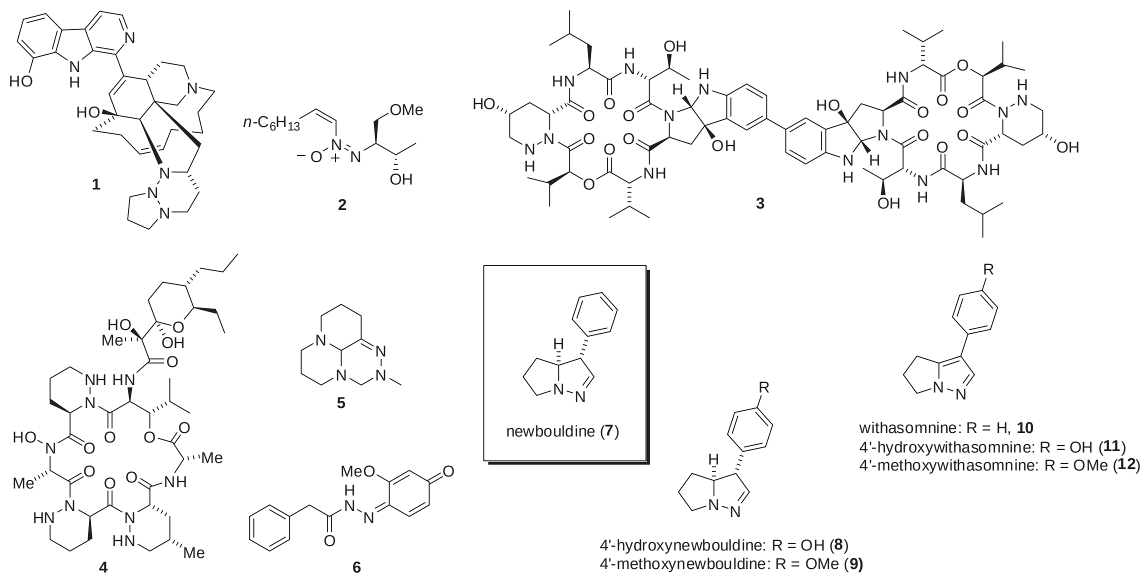
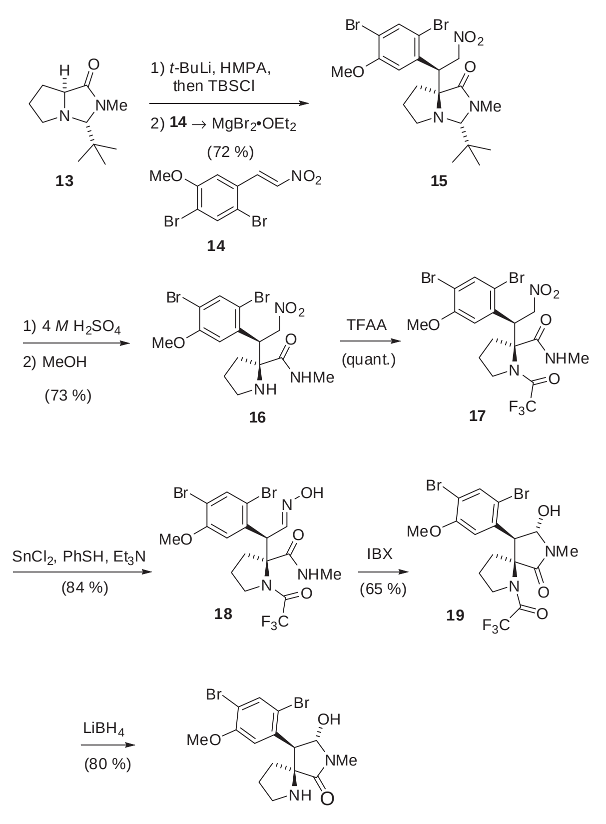


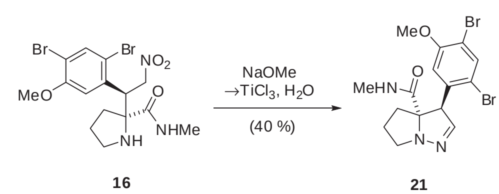
Figure 1. A selection of N–N bond containing natural products.

of oxime **18** under mildly reductive conditions and an unusual hydrolysis in the presence of IBX then gave spiroheterobicyclic intermediate **19**. In the final step, reductive cleavage of the amide provided the natural product **20**. Full details of this total synthesis are reported in the Experimental section.



Scheme 1. Total synthesis of amathaspiramide F (**20**).

As part of this work, we investigated ways to convert nitroalkane intermediate **16** directly to the natural product **29** via Nef reaction. More specifically, it was anticipated that the desired product could be obtained upon treatment with sodium methoxide and titanium(III) chloride. Instead of the desired process, however, an unprecedented reductive N–N bond formation took place, affording bicyclic pyrazoline **21** in modest yield (Scheme 2).[28] The X-ray structure of **21** is shown in Figure 2. It did not escape our notice that compound **21** contained the core 3-phenyl-tetrahydro-3*H*-pyrrolo-pyrazole framework of the newbouldines, albeit with the wrong relative configuration of the aryl ring-bearing stereocenter.



Scheme 2. Discovery of a reductive N–N bond formation method.

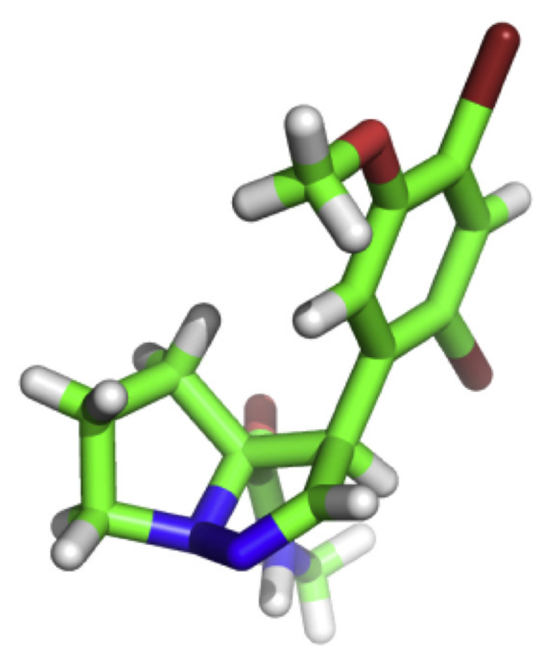
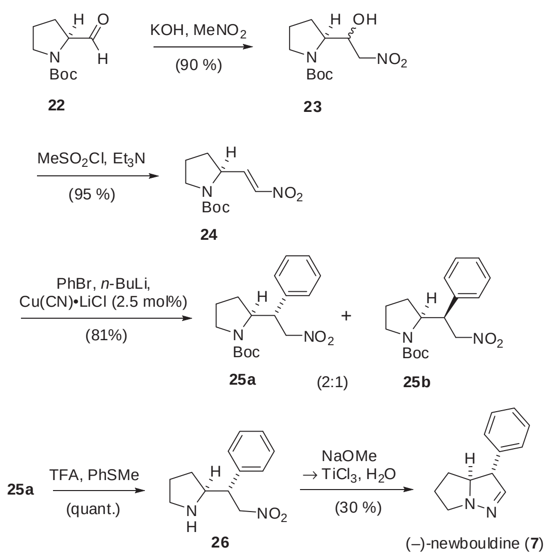


Figure 2. X-ray crystal structure of tetrahydro-3*H*-pyrrolo-pyrazole **21**.

2. Results and discussion

Having made the key discovery that the $TiCl_3$-mediated reductive reaction process can provide quick access to the newbouldine skeleton, we decided to launch a synthesis of the natural product. To confirm the racemic nature of **7**, which had only been indicated by the lack of a detectable optical rotation, we chose to carry out this synthesis in an asymmetric fashion (Scheme 3). It started from known *N*-Boc-(*S*)-prolinal (**22**),[29] which was converted into nitroolefin **24** using an established procedure.[30] Nucleophilic attack of deprotonated nitromethane onto aldehyde **22** gave nitroalcohol **23**, and subsequent elimination provided the desired nitroolefin **24** in high yield. The phenyl ring was installed using a cuprate conjugate addition, which gave the desired 3-amino nitroalkane **25a** together with **25b** as a 2:1 mixture of diastereoisomers. Although careful optimization of the reaction conditions resulted in a good yield (81%), the stereoselectivity of the conjugate addition could not be further improved.

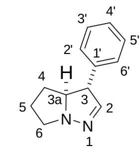


Scheme 3. Total synthesis of newbouldine (**7**).

Deprotection of the secondary amine by treatment with TFA in the presence of thioanisole then provided pyrrolidine **26** in quantitative yield, thus setting the stage for the key N–N bond formation and the completion of the synthesis. We envisaged that the N–N bond would be formed under the same reductive conditions as those discovered in the amathaspiramide F synthesis. Indeed, upon treatment with sodium methoxide and aqueous titanium(III) chloride, this reaction occurred, albeit in very low yield. Further investigations revealed that significant amounts of material were lost during the workup procedure, probably as a result of complexation to titanium salts. Also, we found that crude product mixtures would rapidly decompose on silica, thus making purification difficult. Finally, improved workup conditions allowed access to a single enantiomer of the natural product (**7**) in modest but reproducible yields (30%).

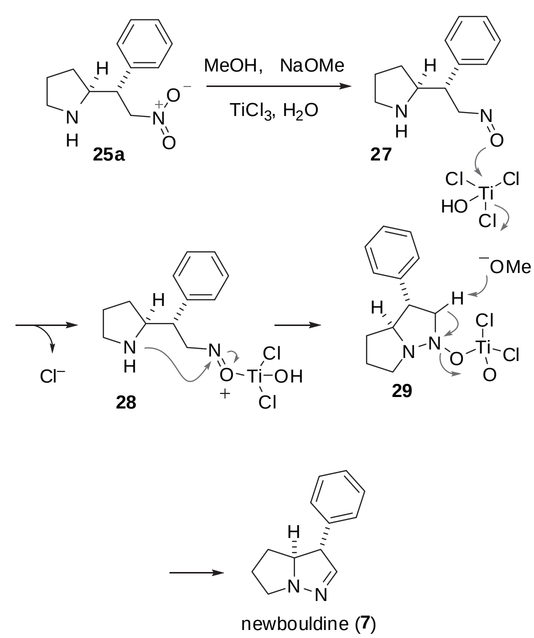
While the NMR data of our synthetic material matched the published data in all respects (Table 1),[10] our enantiomerically pure newbouldine (**7**) showed significant optical activity ($[\alpha]_D^{18}$ −93 (*c* 0.5, MeOH)) in contrast to the natural material ($[\alpha]_D$ 0 (*c* 0.7, $CHCl_3$)), thus confirming that naturally occurring newbouldine (**7**) is indeed a racemate. It would certainly be worthwhile to further investigate the biosynthetic origin of this unusual alkaloid and to establish how the newbouldines relate to their achiral congeners, the withasomnines.

Table 1
NMR data of natural and synthetic **7**



Position	Natural **7**		Synthetic **7**	
	^{1}H	^{13}C	^{1}H	^{13}C
2	6.82 br s	147.0	6.84 br s	147.0
3	4.05 br s	61.1	4.00 br s	61.0
3a	3.68 m	71.4	3.72–3.64 m	71.2
4	α 2.00 m	31.4	α 2.03–1.95 m	31.2
	β 1.56 m		β 1.59–1.55 m	
5	1.70 m	23.9	1.74–1.67 m	23.7
6	3.69 m	53.6	3.72–3.64 m	53.5
	3.17 m		3.23–3.16 m	
1′		140.5		140.3
2′, 6′	}	127.3	}	127.1
3′, 5′	} 7.34–7.26 m	129.0	} 7.36–7.21 m	128.9
4′	}	127.4	}	127.3

It is also interesting to speculate on the mechanism of the key N–N bond formation (Scheme 4). According to McMurry, reduction of the nitro group in **25a** would initially lead to a nitroso compound (**27**).[32] Instead of the usual hydrolysis, however, intermediate **27** coordinates to a Lewis-acidic titanium(IV) species generated in the previous step (→**28**) and thus gets activated toward intramolecular nucleophilic attack of the nearby secondary amine. This would result in N–N bond formation to afford intermediate **29**, which then undergoes elimination of a Ti(IV) oxo species under the strongly basic reaction conditions to yield the final product **7**.



Scheme 4. Suggested mechanism for the formation of newbouldine (**7**).

3. Conclusion

In summary, we have described the first total synthesis of (−)-newbouldine (**7**), which features an unusual key step and proceeds in 14% overall yield. Our asymmetric synthesis confirms that the natural product is a racemate, belying its proposed biosynthetic origin from presumably enantiopure amino acids (i.e., proline and phenylalanine). Our synthetic material is currently being tested for biological activity, the results of which will soon be disclosed.

4. Experimental section

4.1. (*E*)-1,5-Dibromo-2-methoxy-4-(2-nitrovinyl)benzene (14)[28,34]

A solution of 2,4-dibromo-5-methoxybenzaldehyde[33] (5.71 g, 19.4 mmol) and ammonium acetate (6.0 g, 78 mmol) in nitromethane (6.1 mL) and acetic acid (19.4 mL) was heated at reflux for 0.5 h. The mixture was allowed to cool, diluted with water (300 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined extracts were washed with a satd aq $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered. Silica gel (150 mL) was added and the resulting mixture was concentrated to dryness. The product was purified by column chromatography (EtOAc/hex 1:9→1:6) to afford **14** as a yellow solid (4.22 g, 65%): mp 168–172 °C; IR (KBr): 2360, 1629, 1514, 1338; ^{1}H NMR: δ=8.30 (d, *J*=13.6 Hz, 1H), 7.87 (s, 1H), 7.57 (d, *J*=13.6 Hz, 1H), 7.00 (s, 1H), 3.94 (s, 3H); ^{13}C NMR: δ=156.0, 139.2, 137.9, 137.3, 130.3, 117.4, 117.2, 110.5, 56.9; HRMS (EI$^+$): *m*/*z* (M)$^+$ calculated for $C_9H_7{}^{81}Br_2NO_3$: 338.8752; found: 338.8747.

4.2. (3*S*,7a*S*)-3-*tert*-Butyl-7a-((*R*)-1-(2,4-dibromo-5-methoxyphenyl)-3-nitropropyl)-2-methylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (15)

To a solution of (3*R*,7a*S*)-3-*tert*-butyl-2-methylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**13**) (235 mg, 1.19 mmol) in THF (4.0 mL) at −78 °C was added a solution of *t*-BuLi in pentane (0.88 mL, 1.5 M, 1.3 mmol) dropwise using a syringe. After 10 min at −78 °C, HMPA (250 µL, 1.44 mmol) was added and the solution was allowed to warm to room temperature over 1 h. The mixture was then cooled to 0 °C and a solution of *tert*-butyldimethylsilyl chloride (TBSCl, 218 mg, 1.44 mmol) in THF (1.0 mL) was added dropwise using a cannula. Immediately, magnesium bromide diethyl etherate ($MgBr_2 \cdot OEt_2$, 372 mg, 1.44 mmol) was added in one portion. After 2 h at −78 °C, the mixture was allowed to warm to room temperature over 10 h, poured into a satd aq $NaHCO_3$ solution (200 mL) and extracted with CH_2Cl_2 (5×100 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (EtOAc/hex 4:6) to furnish **15** (7:1 mixture of diastereomers) as a white solid (459 mg, 72%). The major isomer could be purified by recrystallisation from CH_2Cl_2/hexanes: $[\alpha]_D^{20}$ −21.7 (*c* 1.00, $CHCl_3$); mp 198–200 °C; IR (KBr): 2966, 1694, 1549, 1476; ^{1}H NMR: δ=7.73 (s, 1H), 6.78 (s, 1H), 4.97 (dd, *J*=13.5, 5.5 Hz, 1H), 4.82 (dd, *J*=13.5, 9.5 Hz, 1H), 4.53 (dd, *J*=9.5, 5.5 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 1H), 3.07 (m, 1H), 2.88 (s, 3H), 2.78 (m, 1H), 2.12–1.99 (m, 2H), 1.84–1.65 (m, 2H), 1.12 (s, 9H); ^{13}C NMR: δ=177.5, 155.6, 136.9, 135.8, 117.7, 112.4, 111.0, 83.6, 76.7, 75.4, 56.7, 49.5, 44.6, 33.4, 30.8, 30.6, 28.7 (br), 25.3; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{20}H_{28}{}^{79}Br^{81}BrN_3O_4$: 534.0426; found: 534.0417.

4.3. (*S*)-2-((*R*)-1-(2,4-Dibromo-5-methoxyphenyl)-3-nitropropyl)-*N*-methylpyrrolidine-2-carboxamide (16)

To a solution of amide **15** (459 mg, 0.861 mmol) in THF (8.8 mL) was added 4 M aq H_2SO_4 (8.8 mL) dropwise via syringe. After 24 h, the solution was cooled to 0 °C and 1 M aq NaOH (35 mL) was added dropwise via cannula. The mixture was diluted with a satd aq $NaHCO_3$ (200 mL) solution and extracted with CH_2Cl_2 (5×100 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (EtOAc/hex 6:4) to yield **16** as a white solid (290 mg, 73%): $[\alpha]_D^{20}$ −36.5 (*c* 1.00, $CHCl_3$); mp 146–147 °C; IR (KBr): 1650, 1549, 1474, 1248; ^{1}H NMR: δ=7.78 (br s, 1H), 7.71 (s, 1H), 6.82 (s, 1H), 5.36 (dd, *J*=14.0, 11.2 Hz, 1H), 5.00 (dd, *J*=14.0, 2.8 Hz, 1H), 4.23 (dd, *J*=11.2, 2.8 Hz, 1H), 3.79 (s, 3H), 3.17–3.08 (m, 1H), 3.01–2.94 (m, 1H), 2.70 (d, *J*=5.2 Hz, 3H), 2.34–2.24 (m, 1H), 2.00–1.85 (m, 2H), 1.81–1.61 (m, 2H); ^{13}C NMR: δ=175.3, 156.0, 136.9, 136.7, 116.7, 112.6, 111.1, 78.6, 71.3, 56.6, 50.3, 46.9, 37.7, 26.0, 25.8; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{15}H_{20}{}^{79}Br^{81}BrN_3O_4$: 465.9800; found: 465.9795.

4.4. (*S*)-2-((*R*)-1-(2,4-Dibromo-5-methoxyphenyl)-3-nitropropyl)-*N*-methyl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (17)

To a solution of amine **16** (400 mg, 0.860 mmol) and pyridine (0.35 mL 4.3 mmol) in CH_2Cl_2 (8.6 mL) at 0 °C was added trifluoroacetic anhydride (0.24 mL, 1.7 mmol) dropwise via syringe. After 1 h at 0 °C, the reaction was quenched with methanol (5 mL). After an additional 2 h at room temperature, the solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (3×80 mL). The combined extracts were washed with water (2×50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (EtOAc/hex 6:4) to give **17** as a white solid (480 mg, quant.): $[\alpha]_D^{20}$ −38.9 (*c* 1.00, $CHCl_3$); mp 72–73 °C; IR (film): 3019, 1695, 1682; ^{1}H NMR: δ=7.77 (s, 1H), 6.66 (s, 1H), 6.25 (s, br, 1H) 5.26 (dd, *J*=10.4, 3.2 Hz, 1H), 5.08 (dd, *J*=14.0, 3.2 Hz, 1H), 4.87 (dd, *J*=14.0, 10.4 Hz, 1H), 3.91–3.81 (m, 1H), 3.82 (s, 3H), 3.36 (m, 1H), 2.83 (d, *J*=4.8 Hz, 3H), 2.53–2.42 (m, 1H), 2.32–2.21 (m, 1H), 1.90–1.76 (m, 1H), 1.62–1.50 (m, 1H); ^{13}C NMR: δ=169.5, 157.6 (q, *J*=37 Hz), 156.1, 137.4, 135.6, 117.9, 116.2 (q, *J*=286 Hz), 113.5, 111.9, 79.1, 75.8, 56.3, 50.0 (q, *J*=4.0 Hz), 46.4, 36.3, 27.3, 23.3; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{17}H_{19}{}^{79}Br_2F_3N_3O_5$: 559.9644; found: 559.9632.

4.5. (*S*)-2-(*R*)-2(*Z*)-1-((2,4-Dibromo-5-methoxyphenyl)-3-(hydroxyimino)propyl)-*N*-methyl-1-(2,2,2-trifluoroacetyl) pyrrolidine-2-carboxamide (18)

To a solution of tin(II) chloride (198 mg, 1.04 mmol) in CH_3CN (10 mL) were added thiophenol (0.32 mL, 3.1 mmol) and Et_3N (0.48 mL, 3.4 mmol) successively via syringe. The mixture turned distinctly yellow. After 0.5 h, a solution of amide **17** in CH_3CN (6.5 mL) was added dropwise via cannula and the flask containing the amide was rinsed with an additional CH_3CN (0.5 mL). After 10 h at room temperature, the mixture was concentrated. The product was purified by column chromatography (EtOAc/hex 6:4) to yield **18** as a white solid (317 mg, 84%): $[\alpha]_D^{20}$ +59.6 (*c* 1.00, $CHCl_3$); mp 72–73 °C; IR (film): 3342, 3017, 1679; ^{1}H NMR: δ=8.05 (br s, 1H), 7.73 (s, 1H), 7.70 (br s, 1H) 7.52 (d, *J*=6.8 Hz, 1H), 6.83 (s, 1H), 5.76 (d, *J*=6.8 Hz, 1H), 3.91 (m, 1H), 3.86 (s, 3H), 3.59 (m, 1H), 2.95 (m, 1H), 2.70 (d, *J*=4.8 Hz, 3H), 2.19 (m, 1H), 1.98–1.73 (m, 2H); ^{13}C NMR: δ=169.4, 158.2 (q, *J*=37 Hz), 155.6, 149.2, 137.0, 135.0, 116.8, 116.4 (q, *J*=287 Hz), 113.6, 112.9, 77.5, 56.6, 50.1 (q, *J*=4.0 Hz), 44.8, 32.4, 26.9, 23.8; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{17}H_{19}{}^{79}Br_2F_3N_3O_4$: 543.9694; found: 543.9657.

4.6. 1-((5*S*,8*S*,9*R*)-9-(2,4-Dibromo-5-methoxyphenyl)-8-hydroxy-7-methyl-1,7-diazaspiro[4.4]nonan-1-yl)-2,2,2-trifluoroethanone (19)

To a solution of oxime **18** (240 mg, 0.440 mmol) in DMSO (1.1 mL) and THF (3.3 mL) was added IBX (148 mg, 0.529 mmol).

After 18 h at room temperature, the reaction was quenched with water. The solution was diluted with additional water (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with water (2×50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and, concentrated. The product was purified by column chromatography (EtOAc/hex 6:4) to give **19** as a white solid (152 mg, 65%): $[\alpha]_D^{20}$ −217.0 (*c* 0.50, THF); mp 226 °C; IR (film): 3385, 3244, 1680; ^{1}H NMR (THF-d_8): δ=7.85 (s, 1H), 6.84 (s, 1H), 5.48 (d, *J*=7.6 Hz, 1H), 5.21 (apparent t, *J*=6.8 Hz, 1H), 3.91 (d, *J*=6.8 Hz, 1H), 3.77 (s, 3H), 3.67–3.59 (m, 1H), 3.32 (m, 1H), 2.87 (s, 3H), 2.58–2.50 (m, 1H), 2.42–2.34 (m, 1H), 2.07–1.97 (m, 1H), 1.86–1.75 (m, 1H); ^{13}C NMR (THF-d_8): δ=171.8, 159.3 (q, *J*=36 Hz), 159.2, 139.9, 120.1, 119.7 (q, *J*=286 Hz), 116.4, 114.8, 91.8, 76.3, 62.1, 58.8, 52.1 (q, *J*=4.0 Hz), 41.4, 33.3, 29.9, 27.4; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{17}H_{18}{}^{79}Br_2F_3N_2O_4$: 528.9585; found: 528.9556.

4.7. (5*S*,8*S*,9*R*)-9-(2,4-Dibromo-5-methoxyphenyl)-7-methyl-1,7-diazaspiro[4.4]nonan-8-ol (amathaspiramide F, 20)

To a solution of acetal **19** (96.2 mg, 0.181 mmol) in THF (1.8 mL) at 0 °C was added a solution of lithium borohydride in THF (0.20 mL, 2.0 M, 0.40 mmol) dropwise via syringe. The solution was allowed to warm to room temperature over 12 h and the reaction was then quenched with a satd aq NH_4Cl solution. The mixture was diluted with a satd aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (EtOAc/acetone 5:1) to afford **20** as a white solid (62.5 mg, 80%). The product was further purified by recrystallisation from $CDCl_3$: $[\alpha]_D^{20}$ −41.0 (*c* 0.50, MeOH); IR, ^{1}H and ^{13}C NMR data are consistent with literature.[31] HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{15}H_{19}{}^{79}Br_2N_2O_3$: 432.9762; found: 432.9757.

4.8. (3*R*,3a*S*)-3-(2,4-Dibromo-5-methoxyphenyl)-*N*-methyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-*b*]pyrazole-3a-carboxamide (21)

To a solution of amine **16** (211 mg, 0.454 mmol) in methanol (4.5 mL) was added sodium methoxide (73.6 mg, 1.36 mmol). After 1 h at room temperature, a solution of titanium(III) chloride (700 mg, 4.54 mmol) in water (2.8 mL) was added dropwise via cannula. After 3 h, the mixture was poured into a 1:1 solution of satd aq $NaHCO_3$ and 10% aq K_2CO_3 (200 mL) and extracted with CH_2Cl_2 (5×50 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (EtOAc→EtOAc/MeOH 19:1) to yield **21** as a white solid (81 mg, 40%): mp 149–151 °C; IR (KBr): 3379, 1683, 1661, 1474; ^{1}H NMR: δ=7.74 (s, 1H), 7.18, (br s, 1H), 6.68 (s, 1H), 6.53 (s, 1H), 4.78 (m, 1H), 3.83 (s, 3H), 3.48–3.39 (m, 1H), 3.32–3.23 (m, 1H), 2.84 (d, *J*=5.2 Hz, 3H), 1.97–1.87 (m, 1H), 1.71–1.60 (m, 2H), 1.58–1.48 (m, 1H); ^{13}C NMR: δ=174.3, 155.3, 145.5, 137.3, 135.5, 115.9, 114.3, 112.3, 81.4, 60.0, 56.6, 54.4, 29.4, 26.4, 25.0; HRMS (FAB$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{15}H_{18}{}^{79}Br_2N_3O_4$: 429.9766; found: 429.9757.

4.9. (*S*)-*tert*-Butyl 2-(1-hydroxy-2-nitroethyl)pyrrolidine-1-carboxylate (23)

To a solution of Boc-L-prolinal **22** (13.1 g, 65.7 mmol, 1.0 equiv) in nitromethane (39.0 mL, 716 mmol, 11.2 equiv) was added 3 M KOH in methanol (1.0 mL, 3.0 mmol). After 4 h at room temperature, acetic acid (0.5 mL, 9.0 mmol) was added and the resulting solution was stirred for 1 h. Subsequently, the reaction mixture was subjected to column chromatography and directly purified ($CHCl_3$/MeOH 100:1). Nitroalcohol **23** was obtained as a 1:1 mixture of diastereomers and crystallized as colorless needles (15.2 g, 90%): R_f: 0.05 ($CHCl_3$); $[\alpha]_D^{18}$ −51 (*c* 1.2, MeOH); IR (film): 3405, 2975, 1663, 1552, 1366, 1254, 1162; ^{1}H NMR (mixture of diastereomers and rotamers): δ=4.90 (br s, 0.55H), 4.75 (br s, 0.45H), 4.53–4.35 (m, 2H), 4.09–3.89 (m, 2H), 3.60–3.13 (m, 2H), 2.44–1.76 (m, 4H), 1.45 (s, 5H), 1.46 (s, 4H); ^{13}C NMR (mixture of diastereomers and rotamers): δ=154.9, 81.1, 81.0, 79.6, 78.4, 78.3, 73.4, 71.6, 71.5, 61.2, 59.9, 59.8, 47.9, 47.5, 28.6, 28.4, 24.3, 24.2, 23.9, 23.8; HRMS (ESI$^+$): *m*/*z* (M+H)$^+$ calculated for $C_{11}H_{21}N_2O_5$: 261.1451; found: 261.1438.

4.10. (*S*)-(*E*)-*tert*-Butyl 2-(2-nitrovinyl)pyrrolidine-1-carboxylate (24)

To a solution of nitroalcohol **23** (14.7 g, 56.5 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added methane sulfonylchloride (6.6 mL, 84.8 mmol, 1.5 equiv) dropwise over 30 min. After 1.5 h at 0 °C, triethylamine (14.1 mL, 102 mmol, 1.8 equiv) was added dropwise over 30 min. After 30 min at 0 °C, the viscous suspension was directly subjected to column chromatography without any previous workup ($CHCl_3$). After removal of solvent, vinylnitrocompound **24** crystallized as yellow crystals (13.1 g, 95%): R_f: 0.17 ($CHCl_3$); $[\alpha]_D^{18}$ −51 (*c* 1.2, MeOH); IR (film): 2976, 2877, 1692, 1521, 1388, 1350, 1160; ^{1}H NMR: δ=7.08 (dd, 1H, *J*=13.3 Hz, 6.3 Hz, 1H), 6.94 (d, 1H, *J*=13.3 Hz, 1H), 4.57–4.45 (m, 1H), 3.44 (br s, 2H), 2.19–2.09 (m, 1H), 1.94–1.85 (m, 3H), 1.41 (s, 9H); ^{13}C NMR: δ=154.0, 142.0, 139.7, 80.2, 54.9, 46.5, 31.5, 28.3, 23.4; HRMS (ESI$^-$): *m*/*z* (M-H)$^-$ calculated for $C_{11}H_{17}N_2O_4$: 241.1188; found: 241.1222.

4.11. (*S*)-*tert*-Butyl 2-((*R*)-2-nitro-1-phenylethyl)pyrrolidine-1-carboxylate (25a)

A solution of CuCN·2LiCl complex in THF was prepared by heating a mixture of LiCl (2.3 g, 54 mmol, 2.0 equiv) and CuCN (2.42 g, 27 mmol, 1.0 equiv) under high vacuum at 100 °C for 24 h. The mixture was then allowed to cool to room temperature under argon atmosphere. THF (20 mL) was added and stirred for 24 h at room temperature until a green colored solution was obtained. To a solution of bromobenzene (1.2 mL, 11.4 mmol, 1.1 equiv) in THF (35 mL) at −110 °C was added *n*-BuLi (2.0 M in cyclohexane, 6.0 mL, 12.0 mmol, 1.15 equiv) dropwise over 10 min. After 45 min at −110 °C, CuCN·2LiCl complex (1.35 M in THF, 0.2 mL, 2.5 mol %) was added in one portion. This reaction mixture was subsequently added to a stirring solution of vinylnitrocompound **24** (2.5 g, 10.4 mmol, 1.0 equiv) in THF (15 mL) at −110 °C over 10 min, using a cannula. After 1 h at −110 °C, the solution was allowed to slowly warm to −78 °C over 3 h. The reaction was quenched with acetic acid (1.0 mL) and allowed to warm to room temperature. The bulk of the solvent was removed and the residue was poured into a satd aq $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined extracts were washed with water (120 mL) and brine (120 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude orange product. Purification by column chromatography (hex/EtOAc 9:1→5:1) yielded **25a** (1.8 g, 55%) as a colorless film, and **25b** (0.91 g, 26%) as a colorless solid.

*4.11.1. Compound **25a**.* R_f: 0.45 ($CHCl_3$); $[\alpha]_D^{21}$ +10.3 (*c* 1.0, MeOH); IR (film): 3349, 2917, 1628, 1536, 1451, 1379, 1059; ^{1}H NMR (mixture of rotamers): δ=7.36–7.10 (m, 5H), 4.90–4.74 (m, 1H), 4.64, (dd, br, *J*=13.2, 9.0 Hz, 1H), 4.26–4.05 (m, 1H), 3.65–3.14 (m, 3H), 2.01–1.35 (m, 13H); ^{13}C NMR (mixture of rotamers): δ=156.2, 155.2, 138.1, 136.6, 129.6, 129.0, 128.2, 127.9, 127.7, 127.6, 81.5, 80.5, 78.7, 78.5, 62.3, 60.3, 49.2, 47.8, 46.8, 46.2, 28.8, 28.5, 28.4, 28.3, 23.2, 22.3;

HRMS (EI^+): m/z $(M)^+$ calculated for $C_{17}H_{24}N_2O_4$: 320.1736; found: 320.1726.

4.11.2. Compound 25b. R_f: 0.42 ($CHCl_3$); $[\alpha]_D^{21}$ −79 (*c* 1.0, MeOH); IR (film): 3350, 2915, 1628, 1550, 1446, 1358, 1059; ^{1}H NMR (mixture of rotamers): δ=7.36–7.15 (m, 5H), 5.03–4.60 (m, 2H), 4.35–3.75 (m, 2H), 3.62–3.17 (m, 1H), 3.17–2.78 (m, 1H), 2.06–1.81 (m, 1H), 1.80–1.68 (m, 1H), 1.50 (s, br, 9H), 1.40–0.82 (m, 2H); ^{13}C NMR (mixture of rotamers): δ=155.7, 136.7, 129.5, 128.6 (br), 127.8, 80.9, 79.9, 78.2, 76.1, 60.4, 59.8, 49.0, 47.8, 46.0, 44.9, 29.4, 29.0, 28.5 (br), 23.5, 23.2; HRMS (ESI^+): m/z $(M+Na)^+$ calculated for $C_{17}H_{24}N_2O_4{}^{23}Na$: 342.1634; found: 343.1628.

4.12. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)pyrrolidine (26)

To a stirred solution of **25a** (1.0 g, 3.1 mmol, 1.0 equiv) and thioanisole (0.4 mL, 3.1 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (6.0 mL, 80 mmol, 25 equiv). After 4 h at room temperature, the mixture was diluted with a satd aq $NaHCO_3$ solution (75 mL) and extracted with CH_2Cl_2 (5×50 mL). The combined extracts were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated to give a crude light yellow product. The product was purified by column chromatography ($CHCl_3$/MeOH/TEA 100:2:1) to yield amine **26** as a colorless solid (0.69 g, quant.): R_f: 0.08 ($CHCl_3$); $[\alpha]_D^{18}$ +36 (*c* 1.2, MeOH); IR (film): 2987, 1658, 1552, 1174; ^{1}H NMR: δ=7.34–7.16 (m, 5H), 4.99 (dd, *J*=12.6, 5.0 Hz, 1H), 4.57 (dd, *J*=12.6, 9.4 Hz, 1H), 3.36 (dt, *J*=9.7, 6.7 Hz, 1H), 3.28 (td, *J*=9.6, 5.0 Hz, 1H) 3.00–2.89 (m, 2H), 2.73 (br s, 1H) 1.83–1.70 (m, 2H), 1.70–1.58 (m, 2H), 1.38–1.29 (m, 1H); ^{13}C NMR: δ=138.9, 128.8, 127.9, 127.6, 79.6, 61.4, 50.6, 47.0, 31.0, 25.9; HRMS (EI^+): m/z $(M+H)^+$ calculated for $C_{12}H_{17}N_2O_2$: 221.1291; found: 221.1278.

4.13. (3*S*)-3-Phenyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-b]pyrazole (newbouldine, 7)

To a solution of amine **26** (50 mg, 0.23 mmol, 1.0 equiv) in MeOH (2.3 mL) was added sodium methoxide (37 mg, 0.69 mmol, 3.0 equiv). After 1 h at room temperature, titanium(III) chloride (420 mg, 2.72 mmol, 12.0 equiv) in degassed water (1.8 mL) was added dropwise over 5 min. After 3.5 h at room temperature, the purple reaction mixture was poured into a 1:1:1:2 mixture of 10% aq K_2CO_3/satd aq Na_2CO_3/satd aq Rochelle salt/CH_2Cl_2 (125 mL) and stirred vigorously for 18 h under argon atmosphere. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give a crude yellow product. The product was purified by column chromatography ($CHCl_3$/MeOH 100:1) to yield **7** as a colorless oil (13 mg, 30%): R_f: 0.11 ($CHCl_3$); $[\alpha]_D^{18}$ −93 (*c* 0.50, MeOH); IR (film): 3854, 3325, 2929, 1684, 1453; ^{1}H NMR: δ=7.36–7.21 (m, 5H), 6.84 (br s, 1H), 4.00 (br s, 1H), 3.72–3.64 (m, 2H), 3.23–3.16 (m, 1H), 2.03–1.95 (m, 1H), 1.74–1.67 (m, 2H), 1.59–1.55 (m, 1H); ^{13}C NMR: δ=147.0, 140.3, 128.9, 127.3, 127.1, 71.2, 61.0, 53.5, 31.2, 23.7; HRMS (ESI^+): m/z $(M+H)^+$ calculated for $C_{12}H_{15}N_2$: 187.1235; found: 187.1230.

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Supplementary data

Crystallographic data for compound **21** have been deposited at the Cambridge Crystallographic Data Center (CCDC 189001). Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.085.

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