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Total Synthesis and Absolute Configuration of the Natural Amino Acid Tetrahydrolathyrine

Meryem Benohoud,[†] Loic Leman,[†] Silvia H. Cardoso,[‡] Pascal Retailleau,[†] Philippe Dauban,[†] Josiane Thierry,*[,†] and Robert H. Dodd*[,†]

[†]*Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, UPR 2301, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France, and* [‡]*Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Juiz de Fora, 36036-330 Juiz de Fora, MG, Brazil*

robert.dodd@icsn.cnrs-gif.fr

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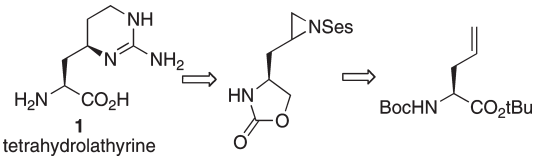

The natural product tetrahydrolathyrine has been synthesized through an iminoiodane-mediated aziridination of a (2*S*)-allylglycinol derivative, which provided a 2:3 mixture of diastereoisomers. One of these diastereoisomers was converted to the natural product and the other to its C-4 epimer. The C-4 configuration was established from NOESY NMR analysis and X-ray structure of compounds derived from the non-natural diastereoisomer. Thus, tetrahydrolathyrine was shown to have the (2*S*,4*R*) absolute configuration.

Introduction

Tetrahydrolathyrine, 3-(2-amino-1,4,5,6-tetrahydropyrimidin-4-yl)-L-alanine (**1**), is a naturally occurring nonproteinogenic amino acid isolated in 1979 from seeds of *Lonchocarpus costaricensis*.[1] Structurally, it has been described as the product of partial reduction of the natural compound lathyrine (β-(2-aminopyrimidin-4-yl)-L-alanine) **2** (Figure 1).[1,2] However, its absolute configuration has not yet been determined. Tetrahydrolathyrine, which can be viewed as a constrained analogue of arginine **3**, belongs to a family of natural amino acids having the terminal guanidine nitrogen atom linked to the methylene backbone (Figure 2).

Most of these amino acids are components of peptide antibiotics isolated from extracts of microorganisms and include enduracididine **4** and alloenduracididine **5** (constituents of enduracidin),[3] β-hydroxyenduracididine **6** and β-hydroxyalloenduracididine **7** (constituents of ($\alpha-\varepsilon$)-mannopeptimycins),[4] capreomycidine **8** (constituent of capreomycins,[5a] tuberactinomycins N and O[6] and chymostatin),[7] epicapreomycidine **9** (constituent of muraymycins),[8] stendomycidine **10** (constituent of stendomycin),[9] tuberactidine **11** (constituent of tuberactinomycin A),[10] and viomycidine **12** (constituent of viomycin).[11] Of these, tetrahydrolathyrine **1**,[1] lathyrine **2**[2] and enduracididine **4**[12] have also been isolated from plants as free amino acids.

Only the total synthesis of capreomycidine has been reported,[5b] while a semisynthesis of tetrahydrolathyrine from lathyrine has been described.[1] Our own laboratory has recently completed the synthesis of a protected form of enduracididine **4**.[13] We report here the first total synthesis of tetrahydrolathyrine, which moreover has allowed the determination of its absolute configuration.

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(10) Nagata, A.; Ando, T.; Izumi, R.; Sakakibara, H.; Take, T.; Hayano, K.; Abe, J. *J. Antibiot*. **1968**, *21*, 681–687.
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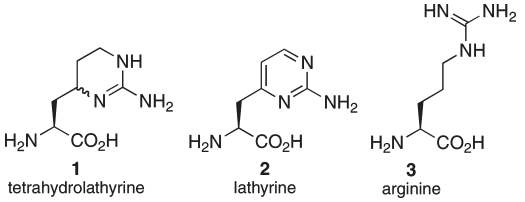


FIGURE 1. Tetrahydrolathyrine, lathyrine, and arginine.

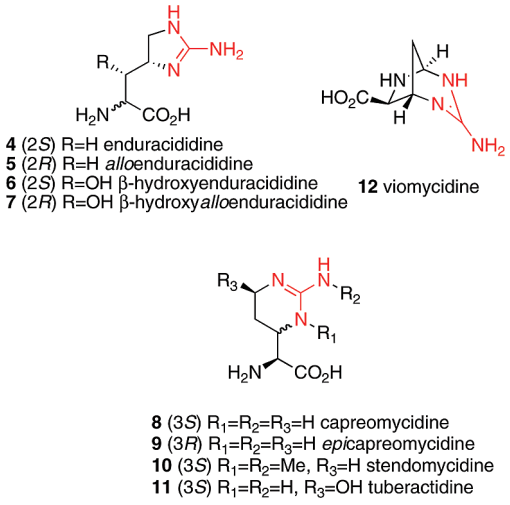


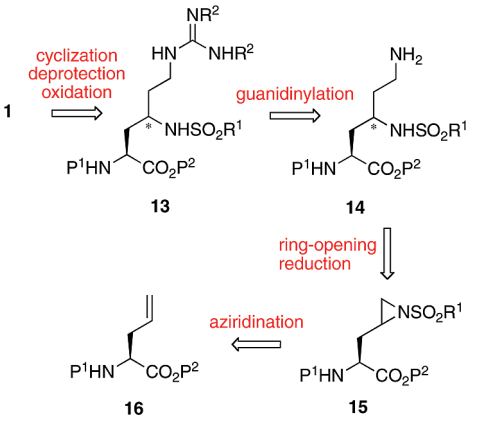
FIGURE 2. Cyclic guanidine amino acid family.

Results and Discussion

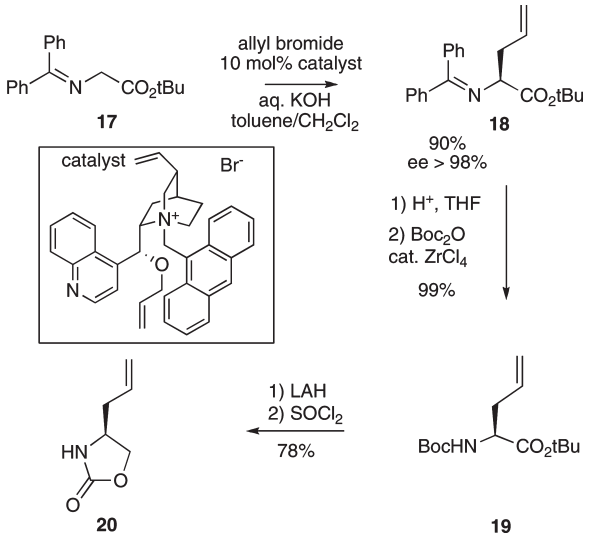
Synthesis. The planned synthetic route, analogous to that previously used by us for the preparation of the lower homologue enduracididine,[13] relied on an iminoiodane-mediated copper-catalyzed aziridination of an allylglycine derivative as the key step. Retrosynthetic analysis suggested that tetrahydrolathyrine **1** could be obtained from the guanidine **13**, which in turn could be constructed from the diamine **14**. The latter could be prepared by cyanide-promoted opening of the aziridine **15** obtained through aziridination of a suitably protected L-allylglycine derivative **16** (Scheme 1).

We first prepared the appropriate L-allylglycine starting material. Very efficient enantioselective methods for the synthesis of α-amino acids have been described independently by Lygo[14] and Corey[15] using *Cinchona*-derived quaternary ammonium salts as chiral catalysts. The allylglycine substrate **18** was thus prepared on a multigram scale by electrophilic alkylation of the Schiff base **17** with allyl bromide using *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide as catalyst (10 mol %). After optimization of the published conditions, product **18** was obtained in good yield (90%) and with an excellent optical purity (>98% as measured by HPLC). Aqueous acid treatment of crude Schiff base **18** gave (*S*)-allylglycine *tert*-butyl ester, the amino function of which was protected by a Boc group using Boc anhydride and $ZrCl_4$ catalysis as described by Sharma et al., giving **19** (Scheme 2).[16]

SCHEME 1. Retrosynthetic Analysis



SCHEME 2



Special attention was given to the choice of carboxylic acid and amine protecting groups since our previous studies concerning the synthesis of enduracididine showed this issue to be crucial.[17] Simultaneous protection of the two functionalities in the form of an oxazolidin-2-one was deemed a good choice, the cyclic carbamate being considered sufficiently electron-withdrawing to minimize copper sequestration during the aziridination step and, moreover, limiting the possibility of intramolecular aziridine ring opening by the nitrogen atom.[18,19] Thus, ester **19** was reduced by $LiAlH_4$, and the resulting *N*-Boc amino alcohol was treated with $SOCl_2$[20] to afford the desired (*S*)-allyloxazolidin-2-one **20** in good yield and without loss of optical purity.

We have previously shown that the iminoiodane-mediated aziridination of a wide range of olefins can be achieved using

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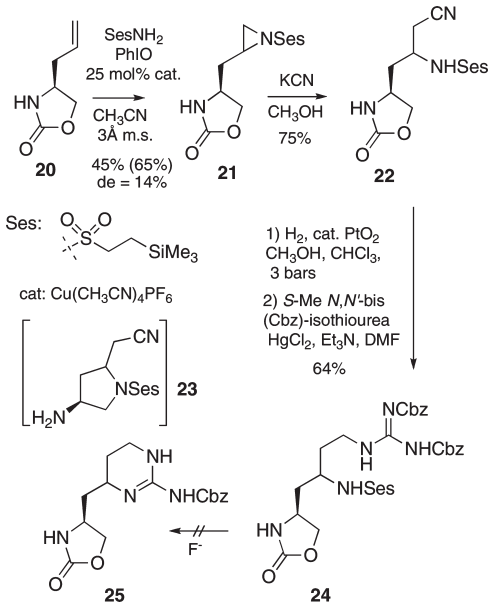
(17) Leman, L.; Sanière, L.; Dauban, P.; Dodd, R. H. *Arkivoc* **2003**, 126–134.
(18) This side reaction was observed when the 2-amino function was protected by a phenylfluorenyl group (PhF); see ref 13.
(19) Simultaneous protection of the two functionalities in the form of a 1,3-oxazoline was also effected. However, iminoiodane-mediated aziridination of the 4-allyl-1,3-oxazoline was not successful.
(20) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275–1294.

SCHEME 3

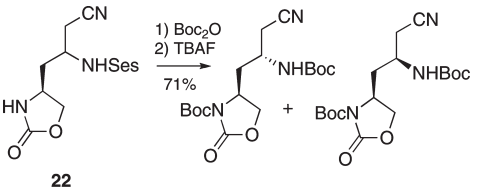


a convenient one-pot procedure.[21] Thus, using our optimized conditions, mixing 1.0 equiv of olefin **20**, 1.2 equiv of iodosylbenzene (PhI=O), and 1.2 equiv of trimethylsilylethanesulfonamide ($SesNH_2$) in the presence of 25 mol % of $Cu(CH_3CN)_4PF_6$ in acetonitrile at room temperature provided the desired *N*-Ses aziridine **21** in 45% yield (65% yield based on recovered starting material) though with only minimal diastereoselectivity (43:57 determined by HPLC) (Scheme 3).[22] At this stage, the two diastereoisomers could not be separated.

Opening of the aziridine ring of **21** (as a mixture of diastereoisomers) using cyanide anion was then investigated.[23] Careful control of the reaction conditions (KCN in MeOH for 16 h at 30 °C) was required in order to minimize the formation of the side product **23** resulting from intramolecular opening of the oxazolidin-2-one **22**. The cyano derivative **22** was thus obtained as the unique product in 75% yield.

The cyano group of **22** was hydrogenated under pressure (3 bar) in $MeOH/CHCl_3$ at room temperature using PtO_2 as catalyst to afford the intermediate amine as the hydrochloride salt in quantitative yield.[24] The latter was reacted directly with *S*-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea using $HgCl_2$[25] as catalyst to give the protected guanidine derivative **24** in 64% yield. Unexpectedly and in contrast to observations made during the synthesis of enduracididine, removal of the Ses group of **24** with cesium fluoride in DMF at 90 °C for 24 h failed to provide the 2-aminotetrahydropyrimidine **25**, which would result from the attack of the free amine on the terminal guanidine. Several attempts were made using different fluoride ion sources (TASF or TBAF), solvents (DMF, THF, MeCN), or temperatures (room temperature, 50 °C, 90 °C), but all resulted in degradation products. On the hypothesis that the guanidino protecting groups did not survive these harsh conditions, it was decided to replace the Ses protecting group by a more easily cleavable Boc group earlier in the synthesis. Thus, treatment of the sulfonamide **22** with Boc_2O in the presence of a catalytic amount of DMAP followed by reaction with fluoride anion cleanly gave the *N*-Boc cyano derivative **26** in 71% yield. At this stage, it was possible to separate the diastereoisomers **26-A** and **26-B** by chromatography on silica gel (Scheme 4).

SCHEME 4



Reduction of the cyano function of **26-A** with PtO_2 using the same conditions as before afforded the intermediate amine that was reacted directly with *S*-methyl *N*,*N*′-bis (benzyloxycarbonyl)isothiourea under conditions described by Izdebski[26] to give the protected guanidine derivative **27-A** in 84% yield (Scheme 5). Treatment of this compound with HCl in methanol for 16 h now allowed the cleavage of both *N*-Boc protecting groups followed by cyclization to provide the 2-aminotetrahydropyrimidine derivative **25-A** in quantitative yield.

Activation of the cyclic carbamate of **25-A** with Boc_2O followed by treatment with a catalytic amount of cesium carbonate[27] in methanol at room temperature afforded the amino alcohol **28-A** in 51% overall yield. Sharpless oxidation[28] of this primary alcohol **28-A** provided the carboxylic acid in 90% yield. In the final step of the synthesis, the amino functionalities were regenerated by refluxing the product in 6 N HCl solution for 1 h, affording amino acid **29-A** in 72% yield for both steps. Treatment of **26-B** in the same manner gave the amino acid **29-B** in comparable overall yield.

At this point, it remained to determine which diastereoisomer, **29-A** or **29-B**, corresponded to the natural amino acid tetrahydrolathyrine. Comparison of the physical and spectral data of compounds **29-A** and **29-B** with the data reported by Fellows et al.[1] for tetrahydrolathyrine and its epimer clearly indicated that **29-B** corresponded to the natural product and **29-A** to its C-4 epimer (see Experimental Section).

Absolute Configuration Determination. The solids obtained by crystallization of **29-A** and **1** were not suitable for X-ray crystallography. Furthermore, because NMR analysis of these flexible compounds did not allow their absolute configuration at C-4 to be determined with certainty, a cyclic derivative, isolated unexpectedly in a parallel

(21) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707–7708.
(22) No efforts were made to improve this step since in our previous study of an allylglycine derivative aziridination, varying the solvents (benzene or dichloromethane) or the reaction temperature resulted in no increase in the yield of aziridine (see ref 17).
(23) Tanner, D.; He, H. M. *Tetrahedron* **1992**, *48*, 6079–6086.
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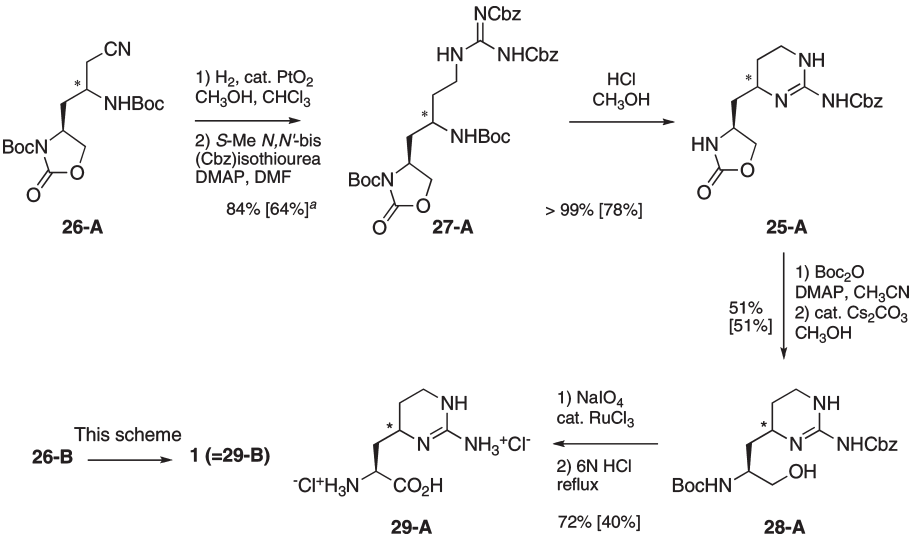
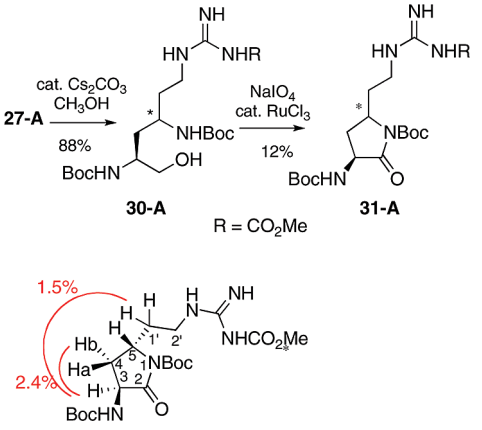
(28) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

SCHEME 5[a]



[a]Yields obtained starting from diastereoisomer **26-B** are indicated in brackets.

SCHEME 6



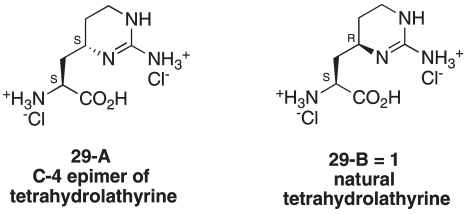


FIGURE 3. Absolute configuration of tetrahydrolathyrine and of its C-4 epimer.

study, proved much more amenable to NMR study. Thus, treatment of **27-A** with catalytic cesium carbonate in methanol afforded the alcohol **30-A** in which one Cbz group was cleaved and the second underwent transesterification. Sharpless oxidation of **30-A** then gave directly lactam **31-A**, though in low yield (Scheme 6). This cyclic compound has both stereocenters incorporated on the ring. Irradiation of CH(3) in a NOE experiment showed enhancements of the signals for $CH_2(1')$, indicating that these protons are in proximity and on the same side of the ring. As the C-3 stereocenter is fixed (i.e., (*S*)), the C-5 stereocenter was assigned the (*S*) configuration.

Final confirmation of the absolute configuration of diastereoisomer A was obtained by X-ray crystallography of **25-A** which was shown to be (2*S*,4*S*) (see Supporting Information). Since compound **25-A** corresponds to the C-4 epimer of **25-B**, the direct precursor of tetrahydrolathyrine **1**, it can be concluded that the latter has the absolute configuration (2*S*,4*R*).

In conclusion, using a one-pot iminoiodane-mediated copper-catalyzed aziridination of an allyloxazolidinone derivative, we have described herein the first total synthesis of the natural nonproteinogenic amino acid tetrahydrolathyrine **1** (= **29-B**) and its diastereoisomer **29-A** (Figure 3). The (2*S* 4*R*) stereochemistry of the natural compound was deduced from NOESY NMR studies of the cyclic derivative **31-A** and confirmed by X-ray crystallography of compound **25-A**.

Experimental Section

(4*S*)-4-[(1-[2-(Trimethylsilyl)ethanesulfonyl]-2-aziridinyl)methyl]-1,3-oxazolidin-2-one (21). To activated 3 Å molecular sieves (16 g) in freshly distilled MeCN (63 mL) were added compound **20** (2.00 g, 15.73 mmol) and $Cu(CH_3CN)_4PF_6$ (0.88 g, 3.93 mmol, 0.25 equiv). A mixture of $SesNH_2$ (3.42 g, 18.88 mmol, 1.2 equiv) and iodosylbenzene (PhIO) (4.15 g, 18.88 mmol, 1.2 equiv) was then introduced in five portions over a 90 min period. The heterogeneous green reaction mixture was stirred overnight at room temperature and then filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/AcOEt 2/1, 1/1, 1/4) to afford the *N*-(Ses)aziridine derivative **21** (2.15 g, 45% yield) as an inseparable mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (2s, 9H), 1.09−1.16 (m, 2H), 1.37−1.56 (m, 1H), 2.10−2.18 (m, 1H), 2.19−2.24 (m, 1H), 2.58 (d, 1H, J = 6.9 Hz), 2.65 (d, 1H, J = 6.9 Hz), 2.75−2.88 (m, 1H), 3.07−3.17 (m, 2H), 3.99−4.08 (m, 1H), 4.08−4.16 (m, 1H), 4.57 (q, 1H, J = 15.6 and 8.1 Hz), 6.06, 6.30 (2s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, 9.6, 9.7, 33.1, 33.4, 34.2, 35.5, 36.6, 36.8, 49.1, 50.8, 51.8, 69.5, 69.9, 158.9, 159.2 ppm. IR (neat) ν 3358, 2952, 1738, 1315, 1248, 1143,

834 cm^{-1}. HRMS calcd for $C_{11}H_{22}N_2O_4SSiNa$ ($M + Na^+$) m/z 329.0967, found 329.0955. Anal. Calcd for $C_{11}H_{22}N_2O_4SSi$: C 43.11, H 7.24, N 9.14. Found: C 42.85, H 7.23, N 8.94. HPLC Hypercarb (150 × 4.6 mm), isocratic MeCN/H_2O 30/70, 1 mL/min, t_{R1} = 15.9 min (43%), t_{R2} = 16.9 min (57%).

Cyano Derivative 22 and Pyrrolidine 23. To a solution of *N*-(Ses)aziridine **21** (300 mg, 0.98 mmol) in dry MeOH (30 mL) at rt under argon was added potassium cyanide (128 mg, 1.96 mmol, 2.0 equiv). The mixture was stirred at 30 °C for 16 h. The solvent was removed under reduced pressure, and the mixture was diluted with water and extracted with ethyl acetate (3 ×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 5% MeOH/DCM) to afford the cyano compound **22** (230 mg, 75% yield) as a mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (2s, 9H), 0.96−1.03 (m, 2H), 1.78−1.84 (m, 1H), 1.93−1.96 (m, 1H), 2.57−2.77 (m, 2H), 2.97−3.08 (m, 2H), 3.65−3.76 (m, 1H), 3.94−4.10 (m, 2H), 4.44−4.51 (m, 1H), 5.56 (bs, 1H), 5.97 (d, 1H, J = 11.4 Hz,) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 10.3, 10.6, 25.5, 25.7, 40.9, 41.4, 48.1, 48.5, 49.3, 50.1, 51.1, 51.3, 70.0, 70.4, 117.2, 117.6, 159.1, 160.5 ppm; IR (neat) ν 3264, 2954, 2250, 1737, 1415, 1312, 1249, 1138, 1021, 835 cm^{-1}; HRMS calcd for $C_{12}H_{23}N_3O_4SSiNa$ m/z 356.1076 ($M + Na^+$), found 356.1081. HPLC Hypercarb (150 × 4.6 mm), isocratic MeCN/H_2O 35/65, 1 mL/min t_{R1} = 8.2 min (42%), t_{R2} = 9.9 min (58%).

Further elution of the column with 20% MeOH/DCM afforded compound **23** as a mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (2s, 9H), 1.00−1.10 (m, 2H), 1.71−2.00 (m, 2H), 2.04−2.10 (m, 1H), 2.68−2.79 (m, 1H), 2.85−3.03 (m, 3H), 3.23−3.54 (m, 1H), 3.57−3.81 (m, 1H), 4.13−4.31 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 10.1, 10.2, 25.0, 25.2, 40.2, 40.6, 47.5, 48.5, 50.5, 51.2, 54.8, 55.0, 56.5, 57.2, 117.5, 117.7 ppm; IR (neat) ν 3368, 2951, 2247, 1323, 1249, 1137, 1020, 832 cm^{-1}; HRMS calcd for $C_{11}H_{24}N_3O_2SSi$ m/z 290.1359 ($M + H^+$), found 290.1349.

Cyano Compounds 26-A and 26-B. To a solution of the mixture of diastereoisomers of the cyano derivative **22** (70 mg, 0.21 mmol) in freshly distilled MeCN (0.50 mL) at rt under argon were added Boc_2O (101 mg, 0.46 mmol, 2.2 equiv) and DMAP (5 mg, 0.04 mmol, 0.2 equiv). The mixture was stirred at rt under argon for 16 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 2% MeOH/DCM) to afford the *N*-(Ses), *N*-(Boc) derivative (94 mg, 84% yield) as an inseparable mixture of diastereoisomers. To this mixture of diastereoisomers (93 mg, 0.17 mmol) was added a solution of 1 M TBAF in THF (0.51 mL, 0.51 mmol, 3 equiv). The mixture was stirred at rt under argon for 16 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, heptane/AcOEt 1/1) to afford compounds **26A** and **26-B** (51 mg, 71% yield) as a mixture of diastereoisomers that could be separated by column chromatography (silica gel, 5% Et_2O/DCM). Diastereoisomer **26-A** eluted first. Diastereoisomer **26-A**: $[\alpha]^{20}_D$ +40.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.55 (s, 9H), 1.82−1.91 (m, 1H), 2.15−2.24 (m, 1H), 2.59−2.78 (m, 2H), 3.83−3.94 (m, 1H), 4.13 (dd, 1H, J = 9.1 and 2.5 Hz), 4.25−4.31 (m, 1H), 4.38 (t, 1H, J = 8.5 Hz), 4.90 (d, 1H, J = 9.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 27.9, 28.2, 37.3, 43.9, 52.1, 66.4, 80.7, 84.4, 116.6, 149.2, 151.5, 155.1 ppm. Diastereoisomer **26-B**: $[\alpha]^{20}_D$ +26.4 (*c* 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.53 (s, 9H), 2.02−2.17 (m, 2H), 2.60−2.71 (m, 2H), 3.89−3.98 (m, 1H), 4.14−4.21 (m, 1H), 4.32−4.40 (m, 2H), 5.41 (d, 1H, J = 9.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 27.9, 28.2, 37.6, 45.7, 53.5, 67.0, 80.5, 84.4, 117.0, 149.2, 151.8, 154.9 ppm; HRMS calcd for $C_{17}H_{27}N_3O_6Na$ m/z 392.1798 ($M + Na^+$), found 392.1805.

Guanidino Compounds 27-A and 27-B. To a solution of the cyano derivative **26-A** (185 mg, 0.50 mmol) in a mixture of dry 10/1 MeOH/$CHCl_3$ (*c* 0.15 M) was added PtO_2 (29 mg, 0.25 mmol, 0.5 equiv). The mixture was stirred under H_2 in a Parr apparatus (3.0 bar) at rt for 6 h then filtered through a pad of Celite and concentrated in vacuo to afford the amine in a quantitative yield as the hydrochloride salt. $[\alpha]^{20}_D$ −14.6 (*c* 0.85, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (s, 9H), 1.47 (s, 9H), 1.62−1.83 (m, 4H), 2.76 (t, 2H, J = 7.5 Hz), 3.47−3.59 (m, 1H), 4.09−4.19 (m, 1H), 4.22−4.26 (m, 1H), 4.32 (t, 1H, J = 9.0 Hz), 6.95 (d, 1H, J = 9.0 Hz), 7.88 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.6, 28.2, 32.7, 36.1, 38.0, 44.3, 52.6, 66.0, 78.0, 82.5, 148.7, 151.6, 155.6 ppm.

To a solution of this amine (554 mg, 1.35 mmol) in dry DMF (2.7 mL) were added *S*-methyl-*N*,*N*′-bis(benzyloxycarbonyl) isothiourea (1.065 g, 2.97 mmol, 2.2 equiv) and DMAP (182 mg, 1.49 mmol, 1.1 equiv). The mixture was stirred for 4 h at rt under argon. The mixture was diluted with ethyl acetate (20 mL) and washed with 10% aqueous citric acid (3×), water (2×), and brine (1×). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 1% MeOH in DCM) to afford the guanidine derivative **27-A** (774 mg, 84% yield). $[\alpha]^{20}_D$ −8.2 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.54 (s, 9H), 1.62−1.68 (m, 1H), 1.69−1.75 (m, 1H), 1.77−1.81 (m, 1H), 1.92−1.97 (m, 1H), 3.30−3.35 (m, 1H), 3.62−3.68 (m, 2H), 4.13−4.16 (m, 1H), 4.24−4.28 (m, 1H), 4.33−4.37 (m, 1H), 4.73 (d, 1H, J = 5.0 Hz), 5.12 (s, 2H), 5.18 (s, 2H), 7.28−7.40 (m, 10H), 8.51 (s, 1H), 11.72 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.3, 35.5, 37.6, 39.1, 45.0, 52.6, 66.7, 67.1, 68.2, 79.8, 83.9, 127.9, 128.1, 128.3, 128.6, 128.7, 128.8, 134.5, 136.7, 149.5, 151.9, 153.7, 156.0, 156.1, 163.6 ppm; HRMS calcd for $C_{34}H_{45}N_5O_{10}Na$ m/z 706.3064 ($M + Na^+$), found 706.3045.

Compound **26-B** was treated under the same conditions as **26-A** to first provide the corresponding amine. $[\alpha]^{20}_D$ +22.9 (*c* 0.40, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 (s, 9H), 1.48 (s, 9H), 1.58−1.69 (m, 2H), 1.76−1.81 (m, 1H), 1.84−1.89 (m, 1H), 2.75 (t, 2H, J = 8.0 Hz), 3.50−3.56 (m, 1H), 4.12−4.14 (m, 1H), 4.18−4.22 (m, 1H), 4.35−4.38 (m, 1H), 6.96 (d, 1H, J = 9.0 Hz), 7.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.6, 28.2, 32.4, 36.1, 38.0, 45.5, 53.2, 66.6, 78.1, 82.6, 148.7, 151.6, 155.6 ppm.

This amine was then transformed into **27-B** (64% yield for both steps). $[\alpha]^{20}_D$ + 31.5 (*c* 0.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.51 (s, 9H), 1.63−1.75 (m, 1H), 1.76−1.87 (m, 2H), 1.95−2.05 (m, 1H), 3.30−3.41 (m, 1H), 3.55−3.66 (m, 2H), 4.16−4.19 (m, 1H), 4.25−4.33 (m, 2H), 5.12 (s, 2H), 5.15 (d, 1H, J = 5.0 Hz), 5.19 (s, 2H), 7.28−7.40 (m, 10H), 8.49 (s, 1H), 11.69 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.3, 34.4, 37.6, 39.4, 46.8, 54.0, 67.0, 67.2, 68.2, 79.8, 83.9, 127.9, 128.0, 128.4, 128.6, 128.7, 128.8, 134.5, 136.6, 149.3, 152.0, 153.6, 156.0, 156.2, 163.5 ppm; HRMS calcd for $C_{34}H_{45}N_5O_{10}Na$ m/z 706.3064 ($M+Na^+$), found 706.3069.

Tetrahydropyrimidines 25-A and 25-B. To a solution of the guanidine compound **27-A** (146 mg, 0.21 mmol) in dry MeOH (3.5 mL) was added HCl (3.5 mL of a 1.25 M solution in MeOH). The mixture was stirred for 16 h at rt under argon, the solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, 5% MeOH in DCM) to furnish the pure product **25-A** in quantitative yield (70 mg). $[\alpha]^{20}_D$ −3.9 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.65 (m, 2H), 1.86−1.96 (m, 1H), 2.01−2.06 (m, 1H), 3.38 (t, 2H, J = 5.7 Hz), 3.67−3.75 (m, 1H), 3.89−3.95 (m, 1H), 3.97−4.04 (m, 1H), 4.44 (t, 1H, J = 8.0 Hz), 4.95 (s, 2H), 5.09 (s, 2H), 7.33−7.35 (m, 5H), 7.50 (s, 1H), 8.78 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 37.0, 40.9, 46.5, 49.6, 66.9, 70.0, 128.0, 128.2, 128.3, 128.5, 128.6, 135.3, 153.6, 156.4,

159.8 ppm; HRMS calcd for $C_{16}H_{21}N_4O_4$ m/z 333.1563 ($M + H^+$), found 333.1557.

The guanidino compound **27-B** was treated in the same way as **27-A** to provide **25-B** in 78% yield. $[\alpha]^{20}_D$ −29.1 (c 0.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 1H), 1.72 (s, 2H), 1.94−2.02 (m, 1H), 3.39 (s, 2H), 3.83−3.93 (m, 2H), 4.15 (s, 1H), 4.44−4.48 (m, 1H), 4.93 (s, 1H), 5.16 (s, 2H), 7.30−7.34 (m, 5H), 7.50 (s, 1H), 8.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 36.9, 40.9, 45.8, 48.9, 66.9, 70.2, 128.0, 128.2, 128.3, 128.5, 128.7, 135.0, 155.4, 156.9, 159.8; HRMS calcd for $C_{16}H_{21}N_4O_4$ m/z 333.1563 ($M + H^+$), found 333.1566.

Tetrahydropyrimidines 28-A and 28-B. To a solution of **25-A** (43 mg, 0.13 mmol) in distilled MeCN (0.65 mL) were added at rt under argon Boc_2O (57 mg, 0.26 mmol, 2.0 equiv) and DMAP (32 mg, 0.26 mmol, 2.0 equiv). The mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 10% MeOH in DCM) to afford the N-Boc carbamate derivative (41 mg, 73% yield). $[\alpha]^{20}_D$ −39.9 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.52−1.57 and 1.63−1.75 (m, 2H), 1.81−1.87 and 2.02−2.07 (m, 2H), 3.17−3.21 (m, 2H), 3.38−3.43 (m, 1H), 3.88−3.90 (m, 1H), 4.23−4.26 (m, 1H), 4.29−4.34 (m, 1H), 5.00 (q, 2H, J = 10.0 Hz), 7.28−7.32 (m, 5H), 9.43 (s, 1H), 11.69 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 27.9, 36.3, 38.7, 44.5, 52.2, 66.2, 66.4, 84.1, 128.0, 128.2, 128.5, 137.2, 148.9, 151.9, 158.7, 163.0 ppm; HRMS calcd for $C_{21}H_{28}N_4O_6Na$ m/z 455.1907 ($M + Na^+$), found 455.1905.

To a solution of this N-Boc-oxazolidinone derivative (40 mg, 0.09 mmol) in dry MeOH (0.5 mL) was added at rt cesium carbonate (6 mg, 0.02 mmol, 0.2 equiv). The mixture was stirred for 4 h, diluted with water, and extracted with ethyl acetate (3 ×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 2% MeOH/DCM) to afford the amino alcohol **28-A** (27 mg, 70% yield). $[\alpha]^{20}_D$ +15.8 (c 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.57−1.63 (m, 1H), 1.69−1.73 (m, 2H), 1.99−2.05 (m, 1H), 3.19−3.31 (m, 2H), 3.46−3.51 (m, 1H), 3.53−3.56 (m, 1H), 3.60−3.63 (m, 1H), 3.67−3.71 (m, 1H), 3.72−3.77 (m, 1H), 5.09 (m, 2H), 7.28−7.38 (m, 5H), 8.83 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 28.4, 37.3, 38.1, 46.3, 49.3, 64.8, 66.0, 79.6, 127.7, 127.9, 128.4, 137.5, 155.9, 158.4, 163.0 ppm; HRMS calcd for $C_{20}H_{30}N_4O_5$-Na m/z 429.2114 ($M + Na^+$), found 429.2120.

The same sequence of reactions as above was applied to **25-B** to first afford the corresponding N-Boc derivative. $[\alpha]^{20}_D$ +2.6 (c 0.82, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 9H), 1.59−1.64 and 1.77−1.83 (m, 2H), 1.87−1.93 and 1.96−2.00 (m, 2H), 3.22−3.24 (m, 2H), 3.51−3.54 (m, 1H), 3.95−3.97 (m, 1H), 4.29−4.39 (m, 2H), 5.09 (s, 2H), 7.28−7.38 (m, 5H), 9.16 (s, 1H), 11.69 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 28.0, 35.9, 40.6, 45.5, 52.5, 66.9, 67.6, 84.6, 128.0, 128.1, 128.2, 128.4, 128.6, 136.3, 150.1, 151.9, 158.5, 163.3 ppm.

This compound was then transformed into compound **28-B** (51% yield for both steps). $[\alpha]^{20}_D$ −21.7 (c 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.62−1.67 (m, 2H), 1.70−1.76 (m, 1H), 1.91−2.05 (m, 1H), 3.26−3.30 (m, 2H), 3.47−3.51 (m, 1H), 3.60−3.63 (m, 1H), 3.67−3.71 (m, 1H), 3.72−3.77 (m, 1H), 5.09 (m, 2H), 7.28−7.38 (m, 5H), 8.82 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 28.4, 36.7, 38.2, 46.1, 49.5, 64.5, 66.2, 79.7, 127.7, 127.9, 128.3, 137.4, 155.9, 158.4, 163.0 ppm; HRMS calcd for $C_{20}H_{31}N_4O_5$ m/z 407.2294 ($M + H^+$), found 407.2295.

(4*S*)-3-[2-Amino-1,4,5,6-tetrahydropyrimidin-4-yl]-L-alanine Hydrochloride (29-A) and Tetrahydrolathyrine (1 = 29B). To a solution of the amino alcohol **28-A** (23 mg, 0.06 mmol) in CCl_4 (1.2 mL), MeCN (1.2 mL), and H_2O (1.8 mL) were added at rt sodium metaperiodate ($NaIO_4$) (39 mg, 0.18 mmol, 3.0 equiv) and ruthenium trichloride hydrate (0.3 mg, 0.001 mmol, 0.022 equiv). The biphasic mixture was stirred vigorously for 3 h at rt. DCM (1 mL) was added, and the phases were separated. The aqueous phase was extracted with DCM (× 3), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 5% MeOH/DCM) to afford the corresponding N-Boc carboxylic acid (21 mg, 90% yield). $[\alpha]^{20}_D$ +58.5 (c 0.11, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.86 (m, 1H), 1.93 (m, 1H), 2.10 (m, 1H), 2.43 (m, 1H), 3.02−3.14 (m, 2H), 3.78 (s, 1H), 4.27 (s, 1H), 5.12 (s, 2H), 6.18 (bs, 1H), 7.36−7.47 (m, 5H), 8.23 (s, 1H), 12.02 (bs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 28.7, 36.1, 36.3, 52.1, 67.9, 79.0, 127.9, 128.5, 128.7, 135.4, 151.9, 155.8, 156.2, 177.7 ppm; HRMS calcd for $C_{20}H_{29}N_4O_6$ m/z 421.2087 ($M + H^+$), found 421.2076.

This product (11.4 mg, 0.027 mmol) was dissolved in 6 N HCl, and the solution was refluxed for 1 h. The solvent was removed by freeze-drying, and the residue was purified by chromatography (C18, H_2O/MeOH, 5% to 50%) affording compound **29-A** in 80% yield (5.6 mg). Mp: 256−258 °C (colorless solid, crystallized from H_2O/MeOH); $[\alpha]^{20}_D$ +39.8 (c 0.20, H_2O); ^1H NMR (500 MHz, D_2O) δ 1.83−1.89 (m, 1H), 2.05−2.12 (m, 1H), 2.17−2.19 (m, 2H), 3.38−3.41 (m, 2H), 3.83−3.88 (m, 1H), 4.12 (t, 1H, J = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, D_2O) δ 24.6, 36.0, 36.3, 45.8, 51.1, 154.4, 173.0 ppm; HRMS calcd for $C_7H_{15}N_4O_2$ m/z 187.1195 ($M + H^+$), found 187.1193.

The same sequence of reactions applied to compound **28-B** first provided the corresponding N-Boc carboxylic acid. $[\alpha]^{20}_D$ −8.2 (c 0.84, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.63−1.67 (m, 2H), 1.70−1.76 (m, 1H), 1.91−1.97 (m, 1H), 3.26−3.30 (m, 2H), 3.47−3.51 (m, 1H), 4.27 (s, 1H), 5.20 (s, 2H), 5.85 (bs, 1H), 7.36−7.47 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.5, 36.3, 36.4, 52.8, 53.4, 67.5, 79.3, 127.7, 128.2, 128.5, 135.4, 151.5, 155.8, 156.3, 177.5 ppm; MS(ESI$^+$) m/z 443.2 ($M + Na^+$), 421.2 ($M + 2H^+$) and 321.2 ([M − Boc] + $2H^+$).

This product was then transformed into tetrahydrolathyrine (**1**) (40% yield for both steps). Mp: 260 °C (colorless solid, crystallized from H_2O/MeOH) (lit.[1] 258−259 °C, crystallized from H_2O/Me_2CO); $[\alpha]^{20}_D$ −20.0 (c 0.20, H_2O) (lit.[1] $[\alpha]^{25}_D$ −18.9 (c 0.175, H_2O)); ^1H NMR (500 MHz, D_2O) δ 1.65−1.71 (m, 1H), 1.90−2.00 (m, 2H), 2.16−2.20 (m, 1H), 3.20−3.27 (m, 2H), 3.65−3.70 (m, 1H), 4.06−4.09 (m, 1H) ppm; ^{13}C NMR (75 MHz, D_2O) δ 23.8, 35.1, 35.4, 44.5, 45.3, 154.5, 176.5 ppm; HRMS calcd for $C_7H_{15}N_4O_2$ m/z 187.1195 ($M + H^+$), found 187.1199.

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Supporting Information Available: General information. Experimental procedures for **18**, **19**, **20**, **24**, **30-A**, **31-A**, and $SesNH_2$. ^1H NMR and ^{13}C NMR spectra of synthetic intermediates of tetrahydrolathyrine **1** and the C-4 epimers. NOE experiments on **31-A**. ORTEP drawing of **25-A** and X-ray data of **25-A** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.