An Unprecedented Ring Transformation of a 4-(Aminomethyl)oxazoline Derivative to a 4-(Hydroxymethyl)imidazoline

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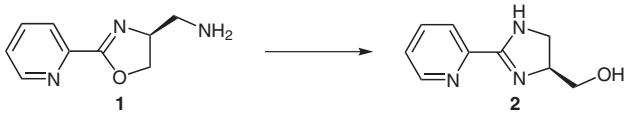
Abstract: An optically active 4-(azidomethyl)-2-(2-pyridyl)oxazoline was prepared starting from L-serine and picolinic acid. Reduction of the azide moiety gave the corresponding 4-(aminomethyl)-2-(2-pyridyl)oxazoline, which is not a stable compound but readily undergoes ring-transformation rearrangement to furnish a 4-(hydroxymethyl)-2-(2-pyridyl)imidazoline. After Boc protection of the amidine function, the material could be further converted into the 4-(aminomethyl)-2-(2-pyridyl)imidazoline via the respective azidomethyl compound.

Key words: heterocycles, oxazolines, imidazolines, pyridines, chiral ligands

Since the first reports by Brunner and co-workers,[1] optically active 2-pyridyloxazolines have become a privileged class of chiral ligands in asymmetric catalysis.[2,3] In continuation of our earlier work on C_1-symmetric, tridentate pyridyloxazolines,[4] we were planning to prepare compound **1** with an aminomethyl group, the latter being perfectly suited for further N-functionalization, for example by amidation reactions. In the event, we were unable to isolate compound **1**, nor its derivatives, as it always underwent ring transformation to furnish the hydroxymethyl-functionalized pyridylimidazoline **2** (Scheme 1). Such a ring transformation has been reported once before for the formation of a cyclic urea from a urethane.[5] It has been at least suspected for [(*N*-arylamino)methyl]oxazolines,[6] but not observed by others, although some researchers claim to have isolated an (aminomethyl)oxazoline as an intermediate product.[7] In one other case, an in situ formed (aminomethyl)oxazoline was protected with CbzCl in the reaction mixture.[8] Since optically active imidazolines are an increasingly important, novel class of chiral ligands,[9] investigations on further conversion of the product **2** seemed promising to us. Therefore, we now report on the preparation of compound **1** and its transformation to imidazoline **2**, as well as some further chemistry starting with the latter compound.



Scheme 1 Facile ring transformation of 4-(aminomethyl)oxazoline **1** to 4-(hydroxymethyl)imidazoline **2**

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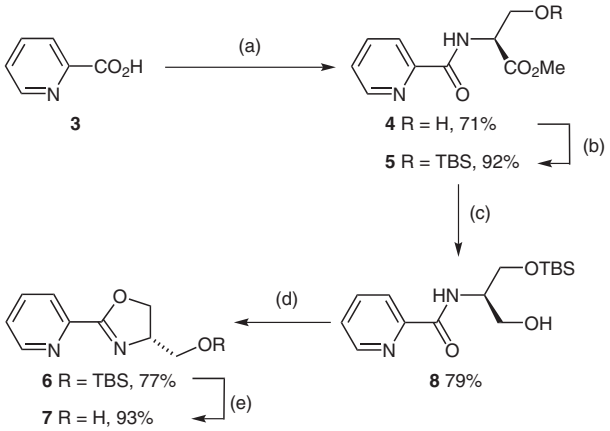
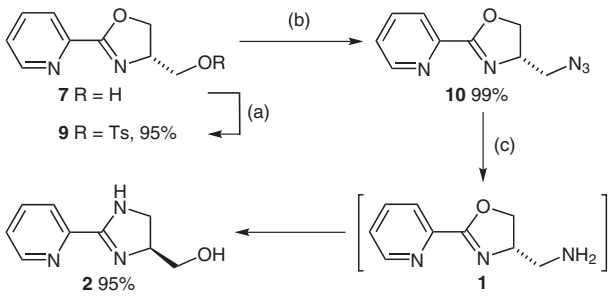
The starting point of our investigation was the hydroxymethyl compound **7**, which was obtained by the five-step sequence outlined in Scheme 2. Picolinic acid (**3**) was first coupled with methyl L-serinate[10] to give amide **4** (71%).[11] The primary alcohol was then TBS protected (92% yield of compound **5**)[12] and the ester moiety reduced to again give a primary alcohol **8** (79%), which was activated with tosyl chloride and cyclized according to a literature protocol.[13] Intermediate product **6** (77%) was finally deprotected with tetrabutylammonium fluoride (93% yield of product **7**).



Scheme 2 Preparation of hydroxymethyl compound **7**. *Reagents and conditions*: (a) NMM (2.3 equiv), $ClCO_2Et$ (1.1 equiv), (*S*)-$MeO_2CCH(CH_2OH)NH_2$·HCl (1.1 equiv), THF, 0 °C to r.t., 2 h; (b) TBSCl (1.3 equiv), imidazole (3 equiv), CH_2Cl_2, r.t., 1 h; (c) $LiBH_4$ (1.3 equiv), THF, 0 °C, 3 h; (d) TsCl (1.2 equiv), DMAP (0.1 equiv), DCE, reflux, 16 h; (e) TBAF·$3H_2O$ (1.2 equiv), THF, r.t., 1 h; TBS = *t*-$BuMe_2Si$, Ts = 4-$MeC_6H_4SO_2$.

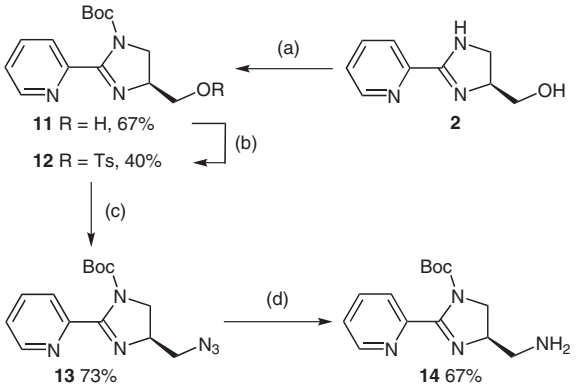
Organoazides are excellent precursors for primary amines; therefore, we activated the primary alcohol function of compound **7** by sulfonyl ester formation (95% of product **9**) and converted it with sodium azide in ethanol following common protocols (Scheme 3).[14] Product **10**, after chromatography, was obtained in almost quantitative yield. Azide **10** was subjected to catalytic hydrogenation to again give a single compound (95% yield) with correct mass (ESI) and ^1H and ^{13}C NMR spectra that seemed to be in agreement with structure **1**; however, all attempts at further derivatization of what we assumed to be an amino function, in particular amide formation, failed. We realized that the ring-transformation reaction of intermediate product **1** with formation of imidazoline **2** would be an explanation for our failure to produce amides of purported

amine **1**. Imidazoline **2** would give similar ^{1}H and ^{13}C NMR spectra, leading us astray. This rearrangement appears obvious, since the amino group as a good nucleophile is at the right distance to form a bicyclo[2.2.1] intermediate structure when adding to the electrophilic imidoester group.



Scheme 3 Preparation and ring transformation of 4-(aminomethyl)oxazoline **1**. *Reagents and conditions*: (a) TsCl (1.5 equiv), KOH, H_2O, CH_2Cl_2, reflux, 3 h; (b) NaN_3 (5 equiv), EtOH, reflux, 16 h; (c) H_2 (1 atm), Pd/C (cat.), MeOH, 23 °C, 16 h.

Definite proof of the structure of compound **2** came from its subsequent chemistry, which was initially difficult as the very basic amidine function caused several problems with chemoselectivity. These problems could, however, be solved by reducing the electron density of **2** by installing a carbamate function (product **11**, 67% yield of crude material; Scheme 4). Interestingly, we obtained a single compound, although one would expect a regioselectivity problem due to the presence of two nucleophilic nitrogen atoms at the amidine function. The depicted regiochemistry was proven by 2D-NMR spectroscopy, after the assignment of all resonances. Firstly, C-4 and 4-H were identified by DEPT135 and HMQC experiments [$\delta(^{13}C)$ = 66.8, $\delta(^{1}H)$ = 4.28 ppm]. Furthermore, the pyridine signals were identified by H,H-COSY and HMQC experiments, as follows [$\delta(^{1}H)$, $\delta(^{13}C)$, in ppm]: 7.5 (3′-H), 123.4 (C-3′); 7.7 (4′-H), 136.3 (C-4′); 7.29 (5′-H), 124.3 (C-5′); 8.58 (6′-H), 148.8 (C-6′). The quaternary pyridine C-2′ was then identified at 151.4 ppm (HMBC cross peaks with 6′-H and 4′-H). Of the two remaining sp^2-carbon resonances, the amidine C-2 was assigned at δ = 159.4 ppm by the HMBC cross peak with 3′-H. Therefore, the carbamate C=O must be the remaining sp^2 signal at δ = 150.4 ppm. The two methylene protons 5-H were then identified at δ = 3.84 and 3.99 ppm by the HMBC cross peak with the amidine C-2; the respective C-5 was identified at δ = 49.3 ppm (HMQC experiment). The remaining 4-CH_2OH was identified at $\delta(^{1}H)$ = 3.64 and 3.74 ppm, and $\delta(^{13}C)$ = 64.3 ppm (HMQC experiment). With this assignment of all proton and carbon resonances in hand, the structure of compound **11** was finally proven by ^{15}N,^{1}H-HMBC spectroscopy; three ^{15}N signals were observed, and were assigned according to the literature data for a similar 1-acetyl-2-aryl-4,5-dihydroimidazole:[15] $\delta(^{15}N)$ = –74.1 (N-1′), –122.8 (N-3), –244.5 (N-1) ppm, with $MeNO_2$ (δ = 0) as external standard. Naturally, within the pyridine ring, N-1′ showed cross peaks to 3′-H, 5′-H and 6′-H. The carbamate N-1 showed three strong cross peaks, to 4-H and both 5-H protons, whereas the imine N-3 showed two strong cross peaks, to both 4-CH_2OH protons, and one weak cross peak, to one 5-H proton.



Scheme 4 Preparation and reduction of azide **13**. *Reagents and conditions*: (a) Boc_2O (2.5 equiv), K_2CO_3 (2 equiv), H_2O, THF, reflux, 24 h; (b) TsCl (6.3 equiv), KOH, H_2O, CH_2Cl_2, reflux, 3 h; (c) NaN_3 (5 equiv), EtOH, reflux, 16 h; (d) H_2 (1 atm), Pd/C (cat.), MeOH, 23 °C, 16 h.

The alcohol function of **11** could then be activated by tosylate formation (40% yield of product **12**) and subsequently be displaced with azide to furnish compound **13** (73% yield). Finally, the aminomethyl compound **14** was obtained by hydrogenation of azide **13** (67% yield), and actually represents the *N*-Boc-imidazoline congener of our initial target compound **1**. This material **14** will now be the cornerstone in future efforts for the synthesis of new libraries of chiral polydentate ligands.

In summary, during our studies towards new, optically active tridentate ligands, we considered aminomethyl-substituted pyridyloxazoline **1** as a core structure which would be ready for further derivatization at the primary amino function. However, attempts to prepare target compound **1** by reduction of the respective azidomethyl precursor **10** directly led to the rearranged product **2** with a hydroxymethyl-substituted imidazoline ring. This very basic amidine moiety hindered subsequent chemistry and was therefore protected with a *tert*-butoxycarbonyl group. It was then possible to access the (aminomethyl)(pyridyl)imidazoline **14** which is now ready for further diversifying derivatization at the primary amino function.

Preparative column chromatography was carried out using Merck silica gel (35–70 μm, type 60 A) with hexane, EtOAc and MeOH as eluents. The column dimensions are given as follows: diameter × height. TLC was performed on Merck aluminum plates coated with silica gel F_{254}. ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on a Bruker Avance DRX 500 instrument. Multiplicities of carbon signals were determined with DEPT experiments. MS and HRMS spectra were obtained with a Waters Q-Tof Premier (ESI) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a Golden Gate diamond ATR unit. Elemental analyses were determined with a Euro EA-CHNS instrument from HEKAtech. Optical rotations were measured with a Polartronic M polarimeter from Schmidt and Haensch. Methyl L-serinate hydro-

chloride was prepared according to a literature procedure.[10] All other starting materials were commercially available.

Methyl (*S*)-*N*-(2-Pyridylcarbonyl)serinate (4)

N-Methylmorpholine (10.3 mL, 9.46 g, 93.5 mmol) and ethyl chloroformate (4.20 mL, 4.85 g, 44.7 mmol) were added to an ice-cooled suspension of picolinic acid (**3**) (5.00 g, 40.6 mmol) in anhydrous THF (50 mL) and the mixture was stirred for 0.5 h at this temperature. Methyl L-serinate hydrochloride (7.00 g, 44.7 mmol) was added and, after further stirring for 2 h at r.t., the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 7 cm × 11 cm; EtOAc–hexane, 2:1, R_f = 0.25) to yield compound **4** (6.46 g, 28.8 mmol, 71%) as a colorless liquid. All spectroscopic data were in accordance with the literature.[11]

$[\alpha]_D^{20}$ +38.9 (*c* 1.03, CH_2Cl_2) [Lit.[11] $[\alpha]_D^{21}$ +39.4 (*c* 2.5, $CHCl_3$)].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (t, *J* = 5.7 Hz, 1 H, OH), 3.82 (s, 3 H), 4.03–4.14 (m, 2 H), 4.87 (dt, *J* = 7.7, 3.9 Hz, 1 H), 7.44 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1 H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1 H), 8.16 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.58 (ddd, *J* = 4.8, 1.5, 0.9 Hz, 1 H), 8.80–8.85 (m, 1 H, NH).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 52.8 (CH), 54.9 (CH_3), 63.5 (CH_2), 122.4 (CH), 126.5 (CH), 137.3 (CH), 148.3 (CH), 149.1 (C), 164.7 (C), 170.7 (C).

Methyl (*S*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(2-pyridylcarbonyl)serinate (5)

TBSCl (4.81 g, 31.9 mmol) and imidazole (5.00 g, 73.5 mmol) were added to a solution of compound **4** (5.49 g, 24.5 mmol) in CH_2Cl_2 (70 mL), and the mixture was stirred for 1 h at r.t. and then filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 7 cm × 11 cm; EtOAc–hexane, 1:2, R_f = 0.40) to yield compound **5** (7.66 g, 22.6 mmol, 92%) as a colorless liquid.

$[\alpha]_D^{20}$ +35.3 (*c* 1.13, CH_2Cl_2).

IR (ATR): 3396 (w), 2953 (w), 2930 (w), 2885 (w), 2857 (w), 1749 (m), 1680 (m), 1592 (w), 1571 (w), 1512 (s), 1465 (m), 1435 (m), 1380 (w), 1352 (m), 1292 (w), 1253 (m), 1207 (m), 1168 (m), 1107 (s), 1043 (m), 998 (m), 965 (w), 939 (w) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.009 (s, 3 H), 0.011 (s, 3 H), 0.89 (s, 9 H), 3.75 (s, 3 H), 3.95 (dd, *J* = 10.1, 3.5 Hz, 1 H), 4.19 (dd, *J* = 10.1, 3.0 Hz, 1 H), 4.86 (dt, *J* = 8.6, 3.2 Hz, 1 H), 7.43 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1 H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1 H), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1 H), 8.60 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1 H), 8.74–8.78 (m, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = –5.6 (CH_3), –5.5 (CH_3), 18.3 (C), 25.8 (3 CH_3), 52.5 (CH), 54.6 (CH_3), 63.8 (CH_2), 122.4 (CH), 126.4 (CH), 137.3 (CH), 148.5 (CH), 149.7 (C), 164.3 (C), 170.9 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{16}H_{26}N_2NaO_4Si$: 361.1560; found: 361.1552.

Anal. Calcd for $C_{16}H_{26}N_2O_4Si$ (338.48): C, 56.78; H, 7.74; N, 8.28. Found: C, 56.77; H, 7.82; N, 8.40.

***N*-[(*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(hydroxymethyl)ethyl]picolinamide (8)**

Compound **5** (9.48 g, 28.0 mmol) was added dropwise to an ice-cooled solution of $LiBH_4$ (18.3 mL of a 2 M solution in THF, 36.6 mmol; diluted with 18.3 mL anhydrous THF) and the mixture was stirred for 3 h at this temperature. Subsequently, H_2O (10 mL) and 10% HCl (ca. 20 mL) were added with caution. After gas evolution had stopped, sat. aq $NaHCO_3$ solution (ca. 40 mL) was added and the mixture was extracted with EtOAc (4 × 40 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 7 cm × 12 cm; EtOAc–hexane, 1:1, R_f = 0.20) to yield compound **8** (6.88 g, 22.2 mmol, 79%) as a colorless liquid.

$[\alpha]_D^{20}$ +3.33 (*c* 1.00, CH_2Cl_2).

IR (ATR): 3384 (m), 2955 (m), 2931 (m), 2885 (w), 2859 (m), 1666 (s), 1593 (w), 1572 (w), 1521 (s), 1466 (m), 1436 (m), 1391 (w), 1363 (w), 1293 (w), 1255 (m), 1091 (s), 1046 (m), 1022 (m), 1000 (m), 940 (w), 835 (s), 779 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.92 (s, 9 H), 3.01 (dd, *J* = 7.8, 4.0 Hz, 1 H), 3.80–3.85 (m, 1 H), 3.86–3.98 (m, 3 H), 4.13–4.20 (m, 1 H), 7.42 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1 H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1 H), 8.19 (dt, *J* = 7.8, 1.0 Hz, 1 H), 8.56 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1 H), 8.63–8.67 (m, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = –5.6 (CH_3), –5.4 (CH_3), 18.3 (C), 26.0 (3 CH_3), 52.5 (CH), 63.8 (CH_2), 64.2 (CH_2), 122.3 (CH), 126.3 (CH), 137.4 (CH), 148.4 (CH), 150.0 (C), 164.9 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{15}H_{26}N_2NaO_3Si$: 333.1610; found: 333.1612.

Anal. Calcd for $C_{15}H_{26}N_2O_3Si$ (310.47): C, 58.03; H, 8.44; N, 9.02. Found: C, 58.01; H, 8.44; N, 9.02.

(*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-2-(2-pyridyl)-4,5-dihydrooxazole (6)

TsCl (1.47 g, 7.73 mmol), DMAP (78 mg, 0.64 mmol) and Et_3N (4.48 mL, 3.26 g, 32.2 mmol) were added to a solution of compound **8** (2.00 g, 6.44 mmol) in DCE (40 mL) and the resulting mixture was heated to reflux for 16 h. The organic layer was washed with H_2O (3 × 30 mL), dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 5 cm × 12 cm; EtOAc–hexane, 1:1, R_f = 0.20) to yield compound **6** (1.45 g, 4.96 mmol, 77%) as a colorless liquid.

$[\alpha]_D^{20}$ –37.5 (*c* 0.99, CH_2Cl_2).

IR (ATR): 2955 (m), 2930 (m), 2899 (w), 2858 (m), 1643 (m), 1585 (w), 1572 (w), 1519 (w), 1473 (m), 1442 (m), 1363 (m), 1253 (m), 1109 (m), 1045 (m), 1009 (m), 967 (m), 940 (w), 897 (w), 835 (s), 803 (m), 777 (s), 746 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 9 H), 3.65–3.70 (m, 1 H), 3.94 (dd, *J* = 10.2, 3.4 Hz, 1 H), 4.42–4.50 (m, 2 H), 4.51–4.57 (m, 1 H), 7.38 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1 H), 7.77 (td, *J* = 7.8, 1.6 Hz, 1 H), 8.03 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.70 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = –5.2 (2 CH_3), 18.4 (C), 26.0 (3 CH_3), 65.2 (CH_2), 68.7 (CH), 71.2 (CH_2), 124.0 (CH), 125.7 (CH), 136.7 (CH), 147.0 (C), 149.9 (CH), 164.1 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{15}H_{24}N_2NaO_2Si$: 315.1505; found: 315.1500.

Anal. Calcd for $C_{15}H_{24}N_2O_2Si$ (292.45): C, 61.60; H, 8.27; N, 9.58. Found: C, 61.59; H, 8.29; N, 9.52.

(*S*)-4-(Hydroxymethyl)-2-(2-pyridyl)-4,5-dihydrooxazole (7)

TBAF·3H_2O (1.94 g, 6.16 mmol) was added to a solution of compound **6** (1.50 g, 5.13 mmol) in THF (50 mL) and the resulting mixture was stirred for 1 h at r.t. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 5 cm × 10 cm; EtOAc–MeOH, 5:1, R_f = 0.24) to yield compound **7** (0.850 g, 4.77 mmol, 93%) as a colorless oil.

$[\alpha]_D^{20}$ –61.6 (*c* 0.69, MeOH).

IR (ATR): 3288 (m), 2982 (w), 2927 (w), 2874 (w), 1664 (m), 1582 (m), 1483 (m), 1432 (m), 1398 (w), 1381 (m), 1360 (s), 1343 (m), 1301 (m), 1285 (m), 1270 (m), 1247 (m), 1222 (m), 1199 (w), 1155 (w), 1125 (s), 1098 (m), 1086 (m), 1070 (s), 1042 (m), 995 (m), 983 (m), 952 (s), 933 (m), 908 (w), 890 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.18 (s, 1 H), 3.70 (dd, *J* = 11.6, 4.0 Hz, 1 H), 4.01 (dd, *J* = 11.6, 3.4 Hz, 1 H), 4.42–4.46 (m, 1 H), 4.47–4.53 (m, 1 H), 4.57 (dd, *J* = 9.5, 7.2 Hz, 1 H), 7.35 (ddd, *J* = 7.6, 4.8, 0.9 Hz, 1 H), 7.73 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.93 (dt, *J* = 7.9, 1.2 Hz, 1 H), 8.64 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 64.0 (CH_2), 68.6 (CH), 70.0 (CH_2), 124.0 (CH), 125.9 (CH), 136.8 (CH), 146.2 (C), 149.9 (CH), 164.5 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_9H_{10}N_2NaO_2$: 201.0640; found: 201.0635.

(*R*)-4-[(4-Methylphenylsulfonyloxy)methyl]-2-(2-pyridyl)-4,5-dihydrooxazole (9)

TsCl (1.07 g, 5.60 mmol) was added to a solution of compound **7** (0.665 g, 3.73 mmol) in 15% aq KOH solution (25 mL) and CH_2Cl_2 (25 mL), and the resulting mixture was heated to reflux for 3 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 5 cm × 8 cm; EtOAc–MeOH, 5:1, R_f = 0.40) to yield compound **9** (1.18 g, 3.56 mmol, 95%) as a colorless solid; mp 113 °C.

$[\alpha]_D^{20}$ –82.9 (*c* 1.15, CH_2Cl_2).

IR (ATR): 3055 (w), 2968 (w), 2902 (w), 2324 (w), 1732 (w), 1645 (m), 1599 (m), 1568 (m), 1494 (w), 1471 (m), 1442 (m), 1348 (m), 1306 (m), 1292 (m), 1280 (m), 1246 (m), 1213 (m), 1175 (s), 1121 (m), 1098 (m), 1080 (m), 1039 (m), 1012 (m), 994 (m), 966 (m), 948 (s), 932 (m), 898 (m), 866 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 4.05 (dd, *J* = 10.0, 6.6 Hz, 1 H), 4.29 (dd, *J* = 10.0, 3.7 Hz, 1 H), 4.36 (dd, *J* = 8.1, 6.7 Hz, 1 H), 4.51–4.62 (m, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.39 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1 H), 7.72–7.79 (m, 3 H), 7.91–7.94 (m, 1 H), 8.68 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 21.7 (CH_3), 65.5 (CH), 70.5 (CH_2), 70.6 (CH_2), 124.2 (CH), 126.1 (CH), 128.1 (2 CH), 130.0 (2 CH), 132.6 (C), 136.8 (CH), 145.2 (C), 146.1 (C), 150.0 (CH), 165.0 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{16}H_{16}N_2NaO_4S$: 355.0728; found: 355.0728.

Anal. Calcd for $C_{16}H_{16}N_2O_4S$ (332.37): C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.91; H, 4.86; N, 8.47; S, 9.65.

(*S*)-4-(Azidomethyl)-2-(2-pyridyl)-4,5-dihydrooxazole (10)

NaN_3 (3.39 g, 52.1 mmol) was added to a solution of compound **9** (3.46 g, 10.4 mmol) in EtOH (150 mL) and the resulting mixture was heated to reflux for 16 h. After the solvent was removed, the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 5 cm × 10 cm; EtOAc–hexane, 9:1, R_f = 0.15) to yield compound **10** (2.12 g, 10.4 mmol, 99%) as a light yellow oil.

$[\alpha]_D^{20}$ –112.5 (*c* 1.01, CH_2Cl_2).

IR (ATR): 3057 (w), 2969 (w), 2902 (w), 2096 (vs), 1639 (m), 1581 (m), 1569 (m), 1516 (w), 1469 (m), 1440 (m), 1366 (m), 1258 (m), 1151 (w), 1102 (s), 1066 (m), 1043 (m), 994 (m), 965 (m), 931 (m), 905 (m), 856 (w), 800 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.53–3.62 (m, 2 H), 4.33–4.41 (m, 1 H), 4.54–4.62 (m, 2 H), 7.42 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1 H), 7.80 (td, *J* = 7.8, 1.7 Hz, 1 H), 8.05 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.72 (ddd, *J* = 4.8, 1.6, 1.0 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 54.2 (CH_2), 66.5 (CH), 70.7 (CH_2), 124.2 (CH), 125.9 (CH), 136.7 (CH), 146.2 (C), 149.9 (CH), 164.5 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_9H_9N_5NaO$: 226.0705; found: 226.0699.

Anal. Calcd for $C_9H_9N_5O$ (203.21): C, 53.20; H, 4.46; N, 34.37. Found: C, 53.16; H, 4.47; N, 34.29.

(*S*)-4-(Hydroxymethyl)-2-(2-pyridyl)-4,5-dihydro-1*H*-imidazole (2)

A suspension of compound **10** (2.21 g, 10.9 mmol) and Pd/C (221 mg, 10% w/w Pd) in MeOH (50 mL) was degassed (three cycles of freeze, pump and thaw) and then stirred under an atmosphere of H_2 (1 atm) for 16 h at 23 °C. The mixture was filtered, then the solvent was removed under reduced pressure to yield compound **2** (1.82 g, 10.3 mmol, 95%) as a yellow oil.

$[\alpha]_D^{20}$ +55.3 (*c* 1.11, MeOH).

IR (ATR): 3279 (br), 2927 (m), 2862 (m), 2453 (w), 1659 (w), 1601 (m), 1566 (m), 1487 (m), 1456 (m), 1421 (m), 1331 (m), 1271 (m), 1189 (m), 1096 (m), 1045 (m), 979 (m), 801 (m) cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 3.61 (dd, *J* = 11.0, 5.6 Hz, 1 H), 3.65 (dd, *J* = 11.1, 5.5 Hz, 1 H), 3.70 (dd, *J* = 12.3, 7.5 Hz, 1 H), 3.92 (dd, *J* = 12.2, 10.9 Hz, 1 H), 4.19 (ddt, *J* = 10.7, 7.5, 5.6 Hz, 1 H), 7.50 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H), 7.90 (td, *J* = 7.8, 1.7 Hz, 1 H), 8.02 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.63 (ddd, *J* = 4.9, 1.5, 1.1 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, CD_3OD): δ = 53.5 (CH_2), 63.6 (CH), 65.5 (CH_2), 123.5 (CH), 126.9 (CH), 138.2 (CH), 148.8 (C), 150.2 (CH), 165.5 (C).

HRMS (ESI, positive mode): *m*/*z* [M + H^+] calcd for $C_9H_{12}N_3O$: 178.0980; found: 178.0975.

Anal. Calcd for $C_9H_{11}N_3O$ (177.21): C, 61.00; H, 6.26; N, 23.71. Found: C, 60.89; H, 6.57; N, 23.73.

(*S*)-1-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)-2-(2-pyridyl)-4,5-dihydro-1*H*-imidazole (11)

K_2CO_3 (2.70 g, 19.5 mmol) and Boc_2O (5.33 g, 24.4 mmol) were added to a solution of compound **2** (1.73 g, 9.76 mmol) in H_2O–THF (30 mL, 1:3) and the resulting mixture was heated to reflux for 24 h. All volatile materials were then removed under reduced pressure, the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL), the aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to yield compound **11** as a mixture with Boc_2O (2.30 g) as crude material (Boc_2O/**11**, 1:3 by ^{1}H NMR spectroscopy; i.e., 1.82 g, 6.57 mmol, 67%), which was used for the next step without further purification. An analytically pure sample was obtained by column chromatography (silica gel, 3 cm × 10 cm; EtOAc–MeOH, 5:1, R_f = 0.22) as a light yellow oil.

$[\alpha]_D^{20}$ +92.5 (*c* 0.46, CH_2Cl_2).

IR (ATR): 3312 (br), 2979 (w), 2932 (w), 2871 (w), 1708 (s), 1631 (m), 1588 (w), 1476 (w), 1365 (vs), 1286 (m), 1138 (vs), 1049 (w), 1025 (w), 917 (w), 729 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (s, 9 H, 3 CH_3), 3.64 (dd, *J* = 11.4, 5.0 Hz, 1 H, 4-C*H*H), 3.74 (dd, *J* = 11.4, 4.5 Hz, 1 H, 4-CH*H*), 3.84 (dd, *J* = 10.5, 8.0 Hz, 1 H, 5-H), 3.99 (t, *J* = 10.4 Hz, 1 H, 5-H), 4.28 (ddt, *J* = 10.3, 8.1, 4.7 Hz, 1 H, 4-H), 7.29 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1 H, 5′-H), 7.47–7.50 (m, 1 H, 3′-H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1 H, 4′-H), 8.58 (ddd, *J* = 4.9, 1.7, 1.1 Hz, 1 H, 6′-H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 27.8 (3 CH_3, C(CH_3)$_3$), 49.3 (CH_2, C-5), 64.3 (CH_2, 4-CH_2), 66.8 (CH, C-4), 81.9 (C, *C*(CH_3)$_3$), 123.4 (CH, C-3′), 124.3 (CH, C-5′), 136.3 (CH, C-4′), 148.8 (CH, C-6′), 150.4 (C, C=O), 151.4 (C, C-2′), 159.4 (C, C-2).

^{15}N NMR (HMBC, 50.7 MHz, $CDCl_3$): δ = –74.1 (N-1′), –122.8 (N-3), –244.5 (N-1).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{14}H_{19}N_3NaO_3$: 300.1324; found: 300.1319.

(*S*)-1-(*tert*-Butoxycarbonyl)-4-[(4-methylphenylsulfonyl-oxy)methyl]-2-(2-pyridyl)-4,5-dihydro-1*H*-imidazole (12)

TsCl (7.23 g, 37.9 mmol) was added to a solution of crude compound **11** (2.10 g, Boc_2O/**11**, 1:3 by ^1H NMR spectroscopy; i.e., 1.66 g, 6.00 mmol) in 15% aq KOH solution (50 mL) and CH_2Cl_2 (50 mL), and the resulting mixture was heated to reflux for 3 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 5 cm × 10 cm; EtOAc–MeOH, 5:1, R_f = 0.23) to yield compound **12** (1.03 g, 2.39 mmol, 40%; 27% over two steps) as a yellow oil.

$[\alpha]_D^{20}$ +65.8 (*c* 0.25, CH_2Cl_2).

IR (ATR): 2978 (w), 2931 (w), 2871 (w), 1708 (s), 1630 (w), 1588 (w), 1474 (w), 1365 (vs), 1288 (m), 1175 (vs), 1096 (m), 1049 (w), 982 (s), 950 (m), 815 (w), 790 (m), 665 (m), 554 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (s, 9 H), 2.43 (s, 3 H), 3.81 (dd, *J* = 11.1, 7.2 Hz, 1 H), 3.99–4.13 (m, 2 H), 4.27 (dd, *J* = 9.9, 4.1 Hz, 1 H), 4.36–4.48 (m, 1 H), 7.29–7.37 (m, 3 H), 7.46 (dt, *J* = 8.0, 0.9 Hz, 1 H), 7.72 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.77–7.81 (m, 2 H), 8.61 (ddd, *J* = 4.9, 1.5, 1.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.8 (CH_3), 27.8 (3 CH_3), 50.0 (CH_2), 63.5 (CH), 70.9 (CH_2), 82.4 (C), 123.4 (CH), 124.5 (CH), 128.2 (2 CH), 130.1 (2 CH), 132.6 (C), 136.4 (CH), 145.1 (C), 149.0 (CH), 150.2 (C), 151.1 (C), 160.5 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{21}H_{25}N_3NaO_5S$: 454.1413; found: 454.1403.

(*S*)-4-(Azidomethyl)-1-(*tert*-butoxycarbonyl)-2-(2-pyridyl)-4,5-dihydro-1*H*-imidazole (13)

A solution of NaN_3 (776 mg, 11.9 mmol) and compound **12** (1.03 g, 2.39 mmol) in EtOH (20 mL) was heated to reflux for 16 h. Then, the solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to yield compound **13** (530 mg, 1.75 mmol, 73%) as a yellow oil.

$[\alpha]_D^{20}$ +95.6 (*c* 0.79, CH_2Cl_2).

IR (ATR): 2979 (w), 2932 (w), 2102 (s), 1711 (s), 1633 (w), 1587 (w), 1520 (w), 1472 (w), 1368 (vs), 1277 (m), 1259 (m), 1168 (m), 1142 (s), 997 (w), 982 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 3.51 (dd, *J* = 12.4, 4.7 Hz, 1 H), 3.59 (dd, *J* = 12.4, 5.4 Hz, 1 H), 3.82 (dd, *J* = 10.9, 7.1 Hz, 1 H), 4.07 (t, *J* = 10.6 Hz, 1 H), 4.36–4.42 (m, 1 H), 7.33 (ddd, *J* = 7.7, 4.8, 1.1 Hz, 1 H), 7.53 (dt, *J* = 7.7, 1.0 Hz, 1 H), 7.74 (td, *J* = 7.7, 1.5 Hz, 1 H), 8.62 (ddd, *J* = 5.4, 1.5, 1.0 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 27.7 (3 CH_3), 50.2 (CH_2), 54.5 (CH_2), 64.6 (CH), 82.1 (C), 123.2 (CH), 124.3 (CH), 136.3 (CH), 148.9 (CH), 150.3 (C), 151.4 (C), 159.9 (C).

HRMS (ESI, positive mode): *m*/*z* [M + Na^+] calcd for $C_{14}H_{18}N_6NaO_2$: 325.1389; found: 325.1380.

(*R*)-4-(Aminomethyl)-1-(*tert*-butoxycarbonyl)-2-(2-pyridyl)-4,5-dihydro-1*H*-imidazole (14)

A suspension of compound **13** (208 mg, 0.69 mmol) and Pd/C (21 mg, 10% w/w Pd) in MeOH (20 mL) was degassed (three cycles of freeze, pump and thaw) and then stirred under an atmosphere of H_2 (1 atm) for 16 h at 23 °C. The mixture was filtered, then the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 3 cm × 5 cm; EtOAc–MeOH, 5:1, R_f = 0.08) to yield compound **14** (126 mg, 0.46 mmol, 67%) as a colorless oil.

$[\alpha]_D^{20}$ –27.8 (*c* 0.85, MeOH).

IR (ATR): 3333 (w), 3055 (w), 2976 (w), 2930 (w), 2867 (w), 1690 (s), 1607 (m), 1567 (m), 1494 (m), 1457 (m), 1421 (m), 1366 (s), 1273 (s), 1249 (s), 1163 (vs), 994 (w), 979 (w), 744 (w) cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 1.33 (s, 9 H), 3.16–3.18 (m, 2 H), 3.57 (dd, *J* = 12.4, 7.2 Hz, 1 H), 3.84 (dd, *J* = 10.7, 7.1 Hz, 1 H), 4.14 (ddt, *J* = 10.9, 7.0, 5.7 Hz, 1 H), 7.42 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1 H), 7.53 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.93 (dt, *J* = 7.9, 1.2 Hz, 1 H), 8.55 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD): δ = 28.7 (3 CH_3), 45.4 (CH_2), 53.9 (CH_2), 62.0 (CH), 80.2 (C), 123.7 (CH), 127.1 (CH), 138.3 (CH), 148.4 (C), 150.3 (CH), 158.7 (C), 165.6 (C).

HRMS (ESI, positive mode): *m*/*z* [M + H^+] calcd for $C_{14}H_{21}N_4O_2$: 277.1665; found: 277.1659.

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