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The enantioselective synthesis of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one

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ABSTRACT

A number of approaches to the enantioselective synthesis of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one were studied. A novel one-pot asymmetric reduction/lactamization provided the desired products in high yield and enantiomeric excess.

1. Introduction

3-Amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-ones have emerged as common building blocks in putative chemotherapeutics and molecules with biological activity.[1a,b] During the course of our studies, we required the enantioselective synthesis of 3-amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one **1** (Fig. 1). Despite a number of racemic syntheses for this moiety in the literature,[1] no enantioselective syntheses have been reported. There is a single report of access to enantiomerically pure material via chiral HPLC resolution,[2] but this method is suboptimal due to the intrinsic yield limitations.[3] We investigated several different approaches to this problem. A novel one-pot asymmetric reduction/lactamization ultimately provided the desired products in high yield and enantiomeric excess. Our results indicate that the methodology is scalable and reproducible. Herein we report a robust method for the preparation of optically active 3-amino-dihydronapthyridinones via a one-pot asymmetric hydrogenation/lactamization sequence.

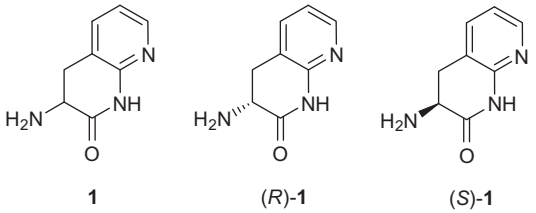

Figure 1. (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one.

2. Results and discussion

Our initial approach to the synthesis of enantiopure **1** employed methodology developed by our co-workers for the synthesis of chiral quinolinones (Scheme 1).[4] We reasoned that asymmetric alkylation of **2** with 3-(bromomethyl)-2-nitropyridine **4** would proceed in an analogous fashion to that with **3**. Repeated attempts gave only a 35% yield of **6** (99% ee),[5] in comparison with a 92% yield of **5** (93% ee). This discrepancy may in part be attributed to the decomposition of **4** under the reaction conditions. The subsequent lactamization afforded a low yield (35%) of (*R*)-**1**. These results, combined with the challenging[6] synthesis of **4**, prompted us to explore suitable replacements.

When 3-(bromomethyl)-2-aminopyridine **9** was used in the place of **4**, none of compound **11** was obtained (Scheme 2). However, when the asymmetric alkylation was attempted with 2-chloro-3-chloromethyl-pyridine **10**, clean conversion to **12** was observed in good yield (75%, 92% ee). With compound **12** in hand, several approaches were investigated to introduce the requisite amino functionality onto the chloropyridine. Attempts at the direct nucleophilic displacement of **12**, with ammonia and 4-methoxybenzylamine to give **13** and **14**, respectively, resulted in rapid decomposition. Buchwald coupling[7] of 4-methoxybenzylamine with **12** was equally unsuccessful, as was sodium azide displacement of **12** to yield **15**.

The asymmetric hydrogenation of olefins with ruthenium and rhodium catalysts is well known.[8] Many of these catalysts are commercially available and can safely be used on a large scale.[9] We sought to apply such a reduction in our system, thus avoiding the aforementioned alkylation chemistry and allowing for a more robust approach to (*R*)-**1** (Scheme 3). Using a high pressure hydrogenation apparatus,[10] we initiated a catalyst screen with enone **18**, which was synthesized in one step (86% yield) from **16** via a Horner–Wadsworth–Emmons olefination.[1d] Upon hydrogenation with a selection of commercially available rhodium and ruthenium cata-

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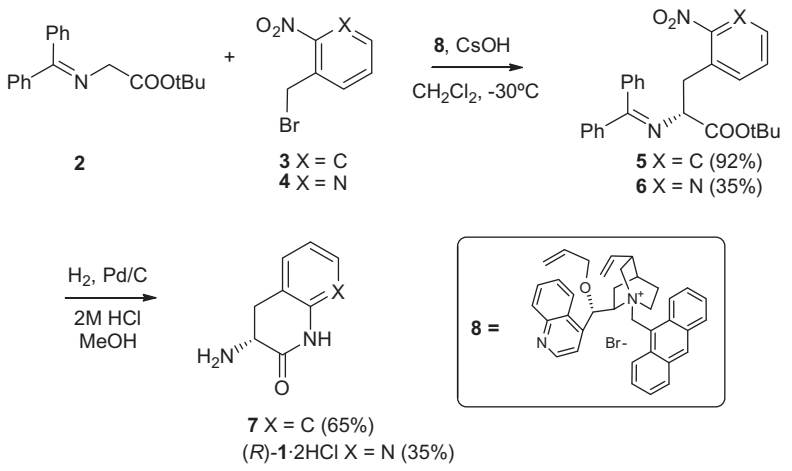
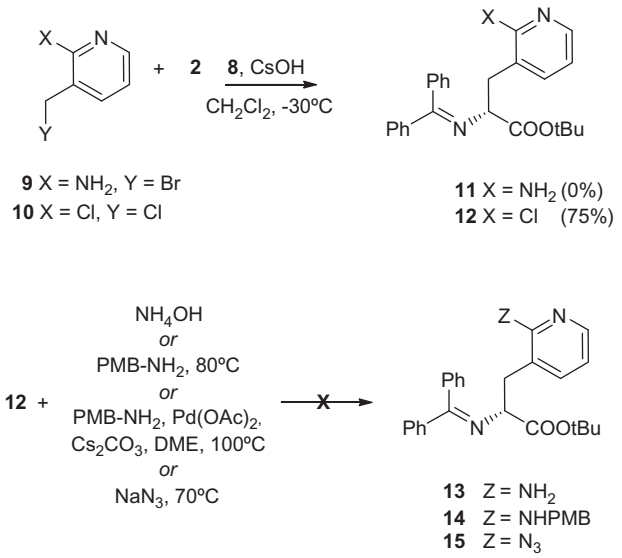


Scheme 1. First approach to (*R*)-**1**.



Scheme 2. Additional approaches to the synthesis of (*R*)-**1**.

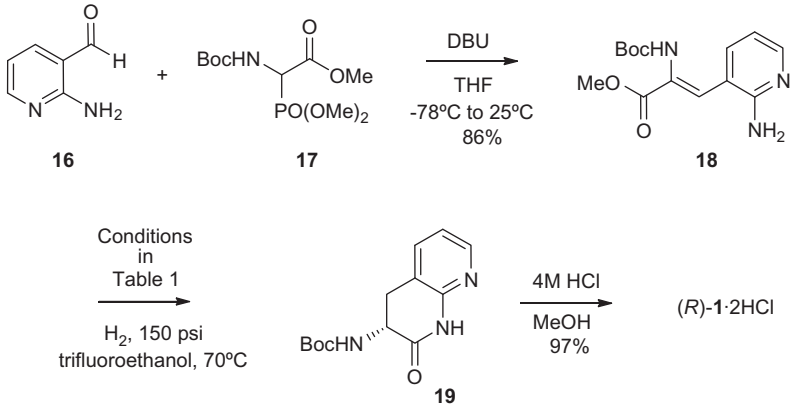
lysts, we were able to obtain **19**, the result of tandem reduction/lactamization sequence. As shown in Table 1, the choice of catalyst appeared to have a significant impact on the observed enantiomeric excess, with results ranging from 76% to 99% ee. The best results in our screen (97% yield, 98% ee) were obtained with 3 mol % Ru((*R*)-BINAP)OAc_2,[11] at 70 °C and 150 psi of hydrogen for 36 h. When these conditions were applied in a gram-scale reactor, as described in Section 4, we achieved an identical yield and enantiomeric excess of **19** (97% yield, 98% ee), when compared to the trial run. Upon treatment of **19** with 4 M HCl, (*R*)-**1** was obtained as the dihydrochloride salt in 97% yield and 98% ee.[12]

Table 1
Asymmetric hydrogenation catalyst screen

Entry	Catalyst	%ee[5] **19**	Yield **19** (%)
1	Ru((*R*)-BINAP)OAc_2	98	97
2[a]	Ru((*R*)-BINAP)OAc_2	92	n/d[b]
3	Ru((*R*)-xylyl-BINAP)Cl_2	82	n/d
4	Rh(COD)((*R*,*R*)-EtDuPhos)SO_3CF_3	80	n/d
5	Rh(COD)(TCFP)BF_4	76	n/d

[a] Ethanol used as solvent.
[b] Not determined.

By simply switching the chirality of the ruthenium catalyst to Ru((*S*)-BINAP)OAc_2 under the identical reaction conditions, we were able to obtain (*S*)-**1** in similar yield and enantiomeric excess (97%, 97% ee for the reduction/lactamization and 96%, 97% ee for the deprotection). When the reduction/lactamization procedure was repeated in the presence of catalytic HCl, in order to affect a simultaneous removal of the *N*-Boc-protecting group, the yield and enantiomeric excess of the reaction were significantly reduced.



Scheme 3. Synthesis of (*R*)-1 via asymmetric hydrogenation.

3. Conclusion

In conclusion, we investigated several enantioselective syntheses of 3-amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-ones, resulting in a highly selective, scalable, and robust one-pot asymmetric hydrogenation/lactamization sequence.

4. Experimental

4.1. (*Z*)-Methyl 3-(2-aminopyridin-3-yl)-2-(*tert*-butoxycarbonyl)-acrylate 18

To −78 °C solution of (±)-Boc-alpha-phosphonoglycine trimethyl ester **17** (12.8 g, 43.0 mmol) in THF (100 mL) was added DBU (6.73 mL, 45.0 mmol) dropwise. After stirring for 20 min at −78 °C, a solution of 2-aminonicotinaldehyde **16** (5.00 g, 40.9 mmol) in THF (20 mL) was added. The reaction was warmed to room temperature and stirred for 18 h. The reaction was evacuated to half-volume and poured into ethyl acetate (200 mL). The organics were washed with water (1 × 100 mL), brine (1 × 100 mL), dried (Na_2SO_4), and evacuated. The resulting solids were triturated with 50:50 diethyl ether/ethyl acetate and vacuum filtered to yield **18** (*E*/*Z* determined by NOE) as an analytically pure yellow solid (10.3 g, 86%). Mp: 163 °C; ^{1}H NMR (400 MHz, MeOD-d_4): δ 7.91 (dd, J = 5.1, 1.8 Hz, 1H), 7.69 (s, 1H), 7.14 (dd, J = 7.6, 1.8 Hz, 1H), 6.67 (dd, J = 7.6, 5.1 Hz, 1H), 3.83 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 158.2, 149.5, 137.2, 127.6, 113.1, 112.9, 79.7, 52.7, 39.6, 28.6; IR (cm^{-1}): 3367, 3210, 2978, 1706, 1449, 1261; MS m/z = 294.3 [M+H]$^+$.

4.2. (*R*)-*tert*-Butyl 2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-ylcarbamate 19

Compound **18** (1.50 g, 5.11 mmol) and Ru((*R*)-BINAP)OAc$_2$ (122 mg, 0.03 equiv) were added to the pressure vessel[10] which was then purged with nitrogen (four times). Nitrogen-flushed trifluoroethanol (15 mL) was added and the reactor was purged with additional nitrogen (four times) and then hydrogen gas (four times). The reactor was heated to 70 °C and then pressurized to 150 psi with hydrogen. After 36 h, the reactor was cooled to ambient temperature and purged with nitrogen (four times). The dark brown solution was concentrated to approximately 5 mL/g and stirred overnight, resulting in the precipitation of off-white solids. These were filtered and slurried in ethanol (3 mL/g). After filtration and air-drying, **19** was obtained as a white solid. (1.30 g, 97%, 98% ee). Mp: 191–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$-d): δ 9.33 (br s, 1H), 8.27 (d, J = 5.1 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 6.99 (dd, J = 7.3, 5.1 Hz, 1H), 5.66 (br s, 1H), 4.38 (m, 1H), 3.54 (m, 1H), 2.80–2.85 (t, J = 15.2, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$-d): δ 172.5, 156.9, 144.0 (2), 137.0, 132.4, 119.1, 79.5, 65.8, 30.6, 28.5; IR (cm^{-1}): 1677, 1522, 1390, 1168; MS m/z = 264.0 [M+H]$^+$; $[\alpha]_D^{20} = +27.0$ (c 1.50 mg/mL, CH_3OH).

4.3. (*S*)-*tert*-Butyl 2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-ylcarbamate

Prepared by the same procedure as **19**. White solid (305 mg, 97%, 97% ee). $[\alpha]_D^{20} = -26.2$ (c 1.95 mg/mL, CH_3OH).

4.4. (*R*)-3-Amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one 2HCl (*R*)-1·2HCl

To a solution of **19** (25 mg, 0.10 mmol) in MeOH (3 mL) was added a solution of HCl (4 M in 1,4-dioxane, 500 μL). The reaction mixture was stirred at room temperature for 2 h. The volatiles were evacuated to afford (*R*)-**1** as a white solid (15 mg, 97%, 98% ee). Mp: >250 °C ^{1}H NMR (400 MHz, DMSO-d_6) 11.14 (s, 1H), 10.3 (br s, 1H), 8.75 (br s, 3H), 8.18 (d, J = 5.1 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.05 (dd, J = 7.42, 4.88 Hz, 1H), 4.31 (m, 1H), 3.21–3.34 (m, 1H), 3.01–3.19 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.8, 144.3, 144.1, 137.5, 132.1, 118.1, 63.2, 32.4; IR (cm^{-1}): 2853, 1732, 1628, 1508, 1236; MS m/z = 164.1 [M+H]$^+$; $[\alpha]_D^{20} = +50.1$ (c 1.25 mg/mL, CH_3OH).

4.5. (*S*)-3-Amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one 2HCl (*S*)-1·2HCl

Prepared by the same procedure as (*R*)-**1**. White solid (14.8 mg, 96%, 97% ee). $[\alpha]_D^{20} = -48.7$ (c 1.15 mg/mL, CH_3OH).

4.6. (*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-3-(2-nitropyridin-3-yl)propanoate 6

To a round-bottomed flask at 0 °C were added diphenylmethylene glycine *t*-butyl ester (377 mg, 1.28 mmol), catalyst **8** (61 mg, 0.13 mmol), 3-(bromomethyl)-2-nitropyridine (252 mg, 1.16 mmol), and DCM (10 mL). The mixture was cooled to −30 °C. Next, CsOH (383 mg, 2.56 mmol) was added and the reaction mixture was stirred at −30 °C for 18 h. The reaction was quenched with water (25 mL) and the mixture was diluted with DCM (50 mL). The layers were separated. The aqueous was extracted with DCM (25 mL) one more time. The organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0–35% EtOAc/heptanes) to afford the desired product (174 mg, 35%, 99% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$-d): δ 8.39 (dd, J = 4.6, 1.7 Hz, 1H), 7.88 (s, 1H), 7.56 (d, J = 7.4 Hz, 2H), 7.28–7.44 (m, 7H), 6.67 (m, 2H), 4.31 (m, 1H), 3.50 (m, 1H), 3.34 (br s, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$-d): δ 171.4, 168.3, 156.2, 144.6, 139.8, 139.0, 133.6, 131.1, 129.0, 128.2(2), 81.3, 70.2, 33.6, 28.7; IR (cm^{-1}): 1740, 1680, 1560; MS m/z 432.3 (M+1). $[\alpha]_D^{20} = +182.6$ (c 10.3 mg/mL, CH_3OH).

4.7. (*R*)-*tert*-Butyl 3-(2-chloropyridin-3-yl)-2-(diphenylmethyleneamino)propanoate 12

To a round-bottommed flask were added 2-chloro-3-(chloromethyl)pyridine (1.00 g, 6.17 mmol), catalyst **8** (324 mg, 0.62 mmol), diphenylmethylene glycine *t*-butyl ester (2.19 g, 7.40 mmol), and DCM (50 mL). The mixture was cooled to −30 °C. CsOH (2.09 g, 12.3 mmol) was added and the reaction mixture was stirred at −30 °C for 18 h. The reaction mixture was warmed to room temperature and water (25 mL) was added. The layers were separated. The aqueous was extracted with DCM (25 mL) once more. The organics were dried (Na_2SO_4) and evacuated. The crude was purified by column chromatography (10–30% EtOAc/heptanes) to afford the desired product (1.96 g, 75%, 99% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$-d): δ 8.21 (dd, J = 4.9, 2.0 Hz, 1H), 7.56 (d, J = 7.4 Hz, 3H), 7.26–7.38 (m, 6H), 7.07 (dd, J = 7.5, 4.8 Hz, 1H), 6.66 (m, 2H), 4.33 (m, 1H), 3.41 (m, 1H), 3.17 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$-d): δ 171.3, 169.2, 147.0, 146.3, 139.9, 138.0, 137.2, 131.1, 129.8, 128.7, 121.3, 82.3, 71.6, 33.5, 28.6. IR (cm^{-1}): 1735; 1540; MS m/z 421.2 (M+1). $[\alpha]_D^{20} = +240.9$ (c 12.7 mg/mL, CH_3OH).

4.8. (*R*)-3-Amino-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one 2HCl (*R*)-1·2HCl

4.8.1. Preparation found in Scheme 1

To a Parr shaker bottle were added **6** (821 mg, 1.91 mmol), 3 mL of MeOH, 10 mL of 2 N HCl, and 10% Pd/C (80 mg). The reaction was placed on the Parr shaker for 18 h at room temperature under

35 psi of H_2. After a nitrogen purge, the solution was filtered through Celite and the filtrate was concentrated. The residue was dissolved in MeOH and precipitated by the dropwise addition of diethyl ether. The reaction mixture was allowed to stand for one hour, at which time white solids crystallized from the solution. The solid was vacuum filtered to afford the desired product (134 mg, 35%). Further crystallization attempts failed to yield additional material. For characterization see (*R*)-**1**·2HCl above.

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