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DIVERGENT SYNTHESIS OF 5,6- AND 3,6-DIHYDROPYRIDIN-2(1*H*)-ONE VIA INTRAMOLECULAR KNOEVENAGEL CONDENSATION

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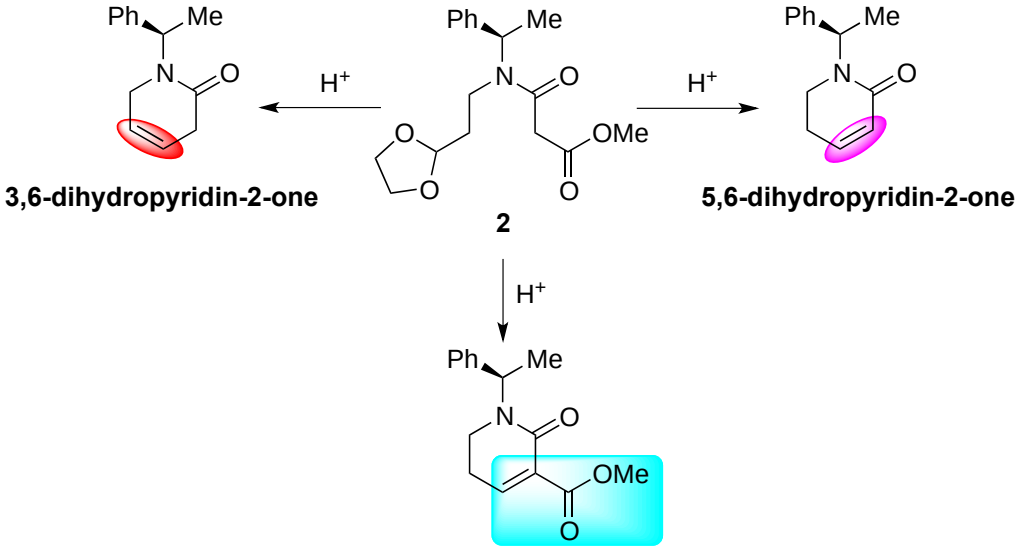
Abstract – A simple and friendly strategy for the regioselective synthesis of 5,6- and 3,6-dihydropyridin-2(1*H*)-one via intramolecular Knoevenagel condensation from a common methyl 3-((2-(1,3-dioxolan-2-yl)ethyl)alkylamino)-3-oxo-propanoate under acidic conditions is reported.

Dihydropyridin-2(1*H*)-ones derivatives have attracted great attention due to these structural features are found in a wide variety of naturally occurring alkaloids.[1] These unsaturated lactams are obtained with the double bond in a specified position, providing great opportunities to functionalized ring, therefore are valuable intermediates for the synthesis of piperidine,[2] quinolone and isoquinoline derivatives[3] and indolizidine and quinolizidine alkaloids.[4]

Specifically, 5,6- and 3,6-dihydropyridin-2(1*H*)-ones are commonly prepared via a ring-closing metathesis reaction.[5] Alternative strategies for the specific synthesis of 5,6-dihydropyridin-2(1*H*)-ones are based on a selenylation/oxidative elimination sequence of the corresponding tetrahydropyridin-2(1*H*)-one,[6] while 3,6-dihydropyridin-2(1*H*)-one has been prepared via Palladium catalyzed decarboxylative carbonylation of 5-vinyloxazolidinones,[7] and also through the gold(I)-catalyzed regioselective cyclization of silyl ketene amides or carbamates with alkynes to construct dehydro-δ-lactams.[8]

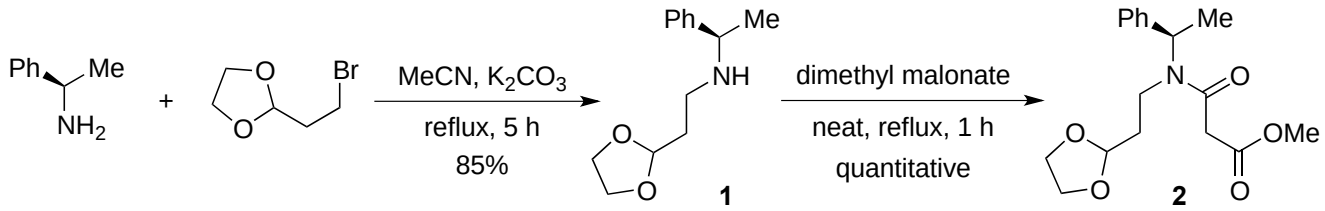
On the other way, Knoevenagel condensation reaction is one of the most important tools for the synthesis of α,β-unsaturated dicarbonyl compounds as a result of a condensation reaction of aldehydes or ketones with active methylene compounds. The resulting α,β-unsaturated dicarbonyl or related functional groups can participate in a range of subsequent transformations with preexisting functional groups.

In consequence and given the importance of 5,6- or 3,6-dihydropyridin-2(1*H*)-ones intermediates, in this letter we wish to report a novel and environmentally friendly strategy for the regioselective synthesis of 5,6- and 3,6-dihydropyridin-2-ones based on an intramolecular Knoevenagel type condensation reaction under acidic conditions starting from a common chiral methyl 3-((2-(1,3-dioxolan-2-yl)ethyl)-alkylamino)-3-oxopropanoate **2**. It is important to mention that polyfunctionalized piperidine precursors bearing a chiral auxiliary bonded to the nitrogen atom, which are defined as molecules having more than one chemically differentiated functional group, have played significant roles in asymmetric synthesis and the synthesis of biologically and pharmacologically active molecules,[9] for that reason (*R*)-(+)-α-methylbenzylamine was selected as chiral auxiliary for the regioselective synthesis of these unsaturated intermediates (Scheme 1).



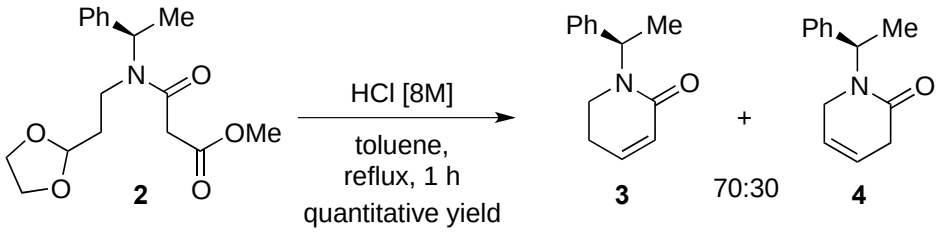
Scheme 1. Divergent synthesis of 3,6- and 5,6-dihydropyridin-2(1*H*)-ones via intramolecular Knoevenagel condensation

The required malonylamide **2** was synthesized in two steps as follow. Firstly, primary chiral amine was allowed to react with 2-(2-bromoethyl)-1,3-dioxolane to access at secondary amine **1**. Subsequently, compound **1** was treated with dimethyl malonate under neat conditions to afford the desired malonylamide **2** in 85% overall yield (Scheme 2).



Scheme 2. Synthesis of chiral malonylamide intermediate **2**

With malonylamide **2**, we explore the intramolecular Knoevenagel condensation by acid-mediated ketal deprotection in HCl(aq). Consequently, compound **2** was treated with aqueous HCl [8M] in reflux toluene during 1 h. Inspection of the ^{1}H NMR spectrum of the crude reaction revealed the presence of two unsaturated lactams **3** and **4** in a 70:30 regioisomeric ratio in favor of 5,6-dihydropyridin-(1*H*)-2-one **3** (Scheme 3).

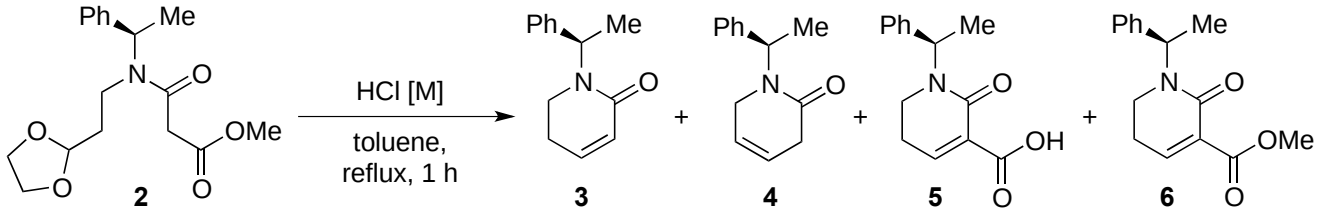


Scheme 3

In this sense, we expected to obtain only compound **3** as a result of an intramolecular Knoevenagel condensation/decarboxylation process, however formation of compound **4** is unexpected, therefore screening experiments were performed in order to control the ring closure reaction favoring one of the two unsaturated lactams.

Initially, we investigate the effect of the HCl(aq) concentration. No significant variation of the ratio of **3**+**4** was observed by the increase of HCl(aq) concentration to [9M] (Entry 2, Table 1). Interestingly, when the reaction was performed using HCl(aq) [6M] (Entry 3, Table 1), a mixture of dihydroyridin-2(1*H*)-ones **3**+**4** and traces of unsaturated carboxylic acid **5** without decarboxylation was detected. This reaction probed to be sensible to concentration of HCl(aq), since the use of HCl(aq) [4M] shown significant increase of unexpected compound **4** (Entry 5, Table 1). Pleasingly, excellent regioselectivity was obtained in favor of compound **4** when the reaction was carried out using HCl(aq) [2M] (Entry 7, Table 1), while the use of HCl(aq) [1M] afforded a mixture of 3,6-dihydropyridin-2(1*H*)-ones **3**+**5** in favor of compound **5** (Entry 8, Table 1). Finally, when the reaction was performed at room temperature and HCl(aq) [2M] exclusively knoevenagel compound **6** was obtained (Entry 9, Table 1).

Table 1. Effect of the HCl(aq) concentration in the regioselective synthesis of dihydropyridin-2(1*H*)-ones

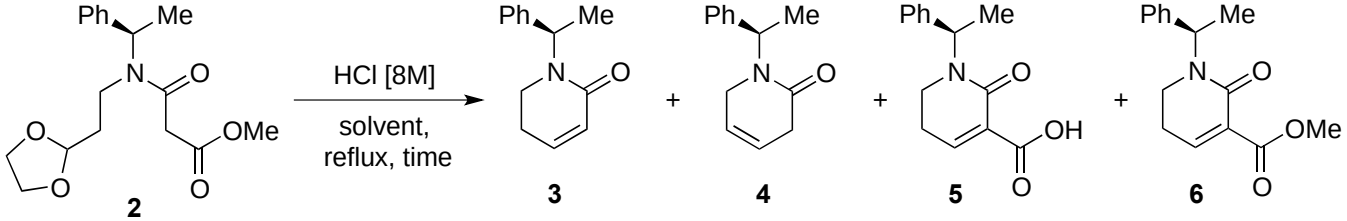


Entry	HCl [M]	time	ratio (**3** : **4** : **5** : **6**)
1	**[8M]**	**1 h**	**70 : 30 : 0 : 0**
2	[9M]	90 min	56 : 44 : 0 : 0
3	[6M]	90 min	46 : 46 : 8 : 0
4	[5M]	1 h	45 : 55 : 0 : 0
5	[4M]	1 h	38 : 62 : 0 : 0
6	[3M]	1 h	25 : 75 : 0 : 0
7	**[2M]**	**1 h**	**4 : 96 : 0 : 0**
8	[1M]	1 h	0 : 28 : 72 : 0
9[a]	**[2M]**	**22 h**	**0 : 0 : 0 : 100**

All reactions were performed using 0.06 g (0.18 mmol) of compound **2** dissolved in 7.5 mL of toluene and 1.5 mL of the corresponding hydrochloric acid solution concentration. Unsaturated lactams were obtained in a quantitative combinatorial yield. All ratios were calculated from the NMR spectrum of the crude reaction. [a]The reaction was performed at room temperature.

Then, the solvent effect was studied. The use of MeOH resulted in a total degradation of the starting material (Entry 1, Table 2), while THF afforded only traces of dihydropyridin-2(1*H*)-ones. CCl_4 provided a mixture of **4**+**5**+**6** and starting material (Entry 3, Table 2). Usage of DCE afforded an inseparable mixture of 5,6-dihydropyridin-2-ones **5**+**6** (Entry 4, Table 2).

Table 2. Solvent effect on the regioselective synthesis of 5,6- and 3,6-dihydropyridin-2(1*H*)-ones



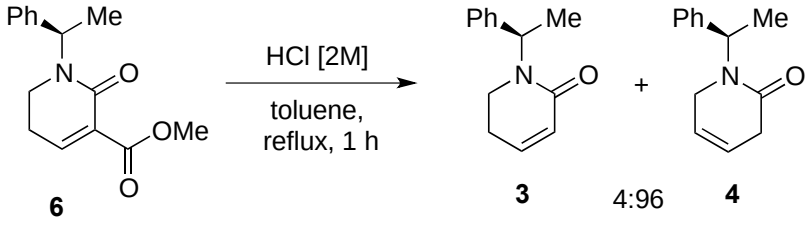
Entry	Solvent	time	ratio (**3** : **4** : **5** : **6**)
1	MeOH	1.5 h	---------

2	THF	2 h	traces
3	CCl_4	2 h	(45 : 32 : 23 : 0)
4	DCE	2 h	(0 : 0 : 81 : 19)

All reactions were performed using 0.06 g (0.18 mmol) of compound **2** dissolved in 7.5 mL of the corresponding solvent and 1.5 mL of HCl(aq) [8M]. All ratios were calculated from the NMR spectrum of the crude reaction.

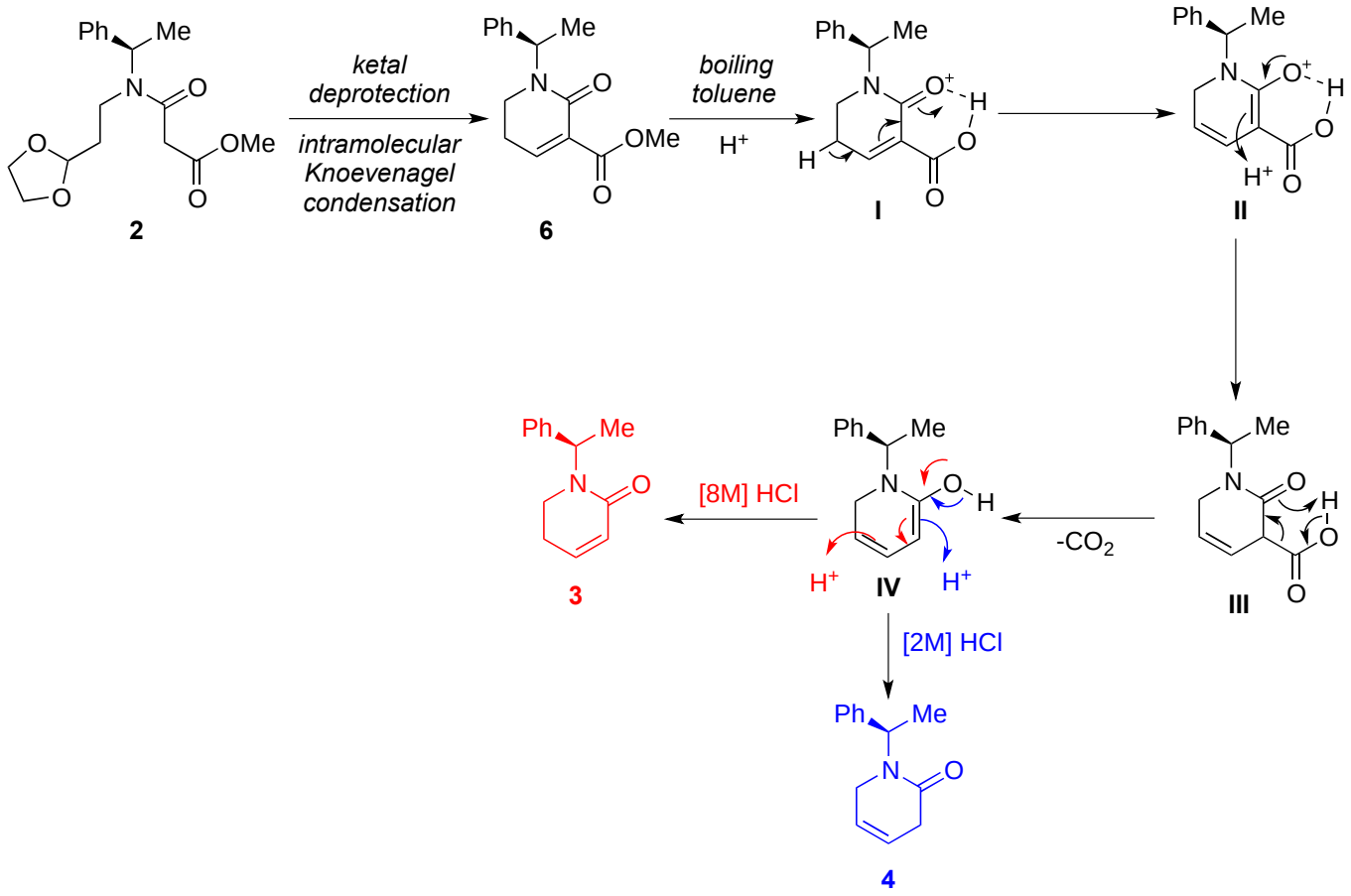
As we described above, the best result was obtained when the intramolecular Knoevenagel condensation reaction was conducted in toluene, and the regioselective formation of dihydropyridin-2(1*H*)-ones **3**, **4** and **6** dependents of the HCl(aq) concentration and temperature.

In order to establish the precursor of unexpected compound **4** we treated separately compound **3** and compound **6** under acidic condition (HCl(aq), [2M]) in boiling toluene. Only compound **6** afforded the unsaturated mixture of compounds **3**+**4** in quantitative yield and 4:96 ratio (Scheme 4), while compound **3** result in a recovery of starting material (not show in Scheme 4).



Scheme 4

Finally, a plausible mechanistic pathway for the formation of unexpected 3,6-dihydropyridin-2(1*H*)-one **4** is outlined in Scheme 5. We assumed that the reaction began with acid-mediated ketal deprotection in aqueous HCl of **2** follows by an intramolecular Knoevenagel condensation to affords the methyl 2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate **6** as a common intermediate. Next, with the compound **6** in medium acid and heating the ester is hydrolysed forming the corresponding carboxylic acid **I**, which the acid hydrogen forms a bridge with the amide carbonyl and then occurs an isomerization process to get the intermediate **II**.[10] Then, intermediate **II** takes a hydrogen from the media forming the intermediate **III**. After, intermediate **III** suffer a descarboxylation process giving intermediate **IV** which depending on the HCl concentration afford majority unsaturated lactam **3** or **4**.



Scheme 5. Plausible mechanism for regioselective formation of compounds **3** and **4**

In conclusion, the present work reports a novel strategy for the regioselective synthesis of chiral 5,6- and 3,6-dihydropyridin-2(1*H*)-ones derivatives in good yields starting from a common intermediate. To the best of our knowledge, there are no reports on the regioselective synthesis of these intermediates via an intramolecular Knoevenagel condensation promoted in acidic conditions. Finally, the presence of a chiral appendage enables further asymmetric transformations of the piperidine skeleton, a reactivity which is under investigation in our laboratory.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in $CDCl_3$ using a Bruker Avance III Spectrometer. Chemical shifts are given in ppm and reported to the residual solvent peak ($CHCl_3$ 7.26 ppm and 77.16 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (*J*, Hz), and integration. Analytical TLC was performed on silica gel 60 F_{254} plates. Column chromatography was carried out on silica gel 60 (63-200 μm). Mass spectra were recorded on JEOL The MStation JMS-700 at a voltage of 70 eV.

Experimental procedure for (*R*)-*N*-(2-(1,3-dioxolan-2-yl)ethyl)-1-phenylethan-1-amine **1**. To a solution of (*R*)-(+)-α-methylbenzylamine (0.5 mL, 3.87 mmol) in MeCN (18 mL), were successively added potassium carbonate (1.0721 g, 7.75 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (0.45 mL, 3.87 mmol), and stirred at reflux for 5 h. The resulting mixture was cooled at room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Petroleum ether/EtOAc 85:15) to afford **1** (0.7295 g, 85%) as a colorless oil. $[\alpha]^{20}_{D}$ +40.7 (*c* 1.00, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 4.88 (t, *J* = 4.7 Hz, 1H), 3.95 (m, 2H), 3.81 (dd, *J* = 5.6, 3.7 Hz, 2H), 3.74 (q, *J* = 6.7 Hz, 1H), 2.60 (m, 3H), 1.84 (td, *J* = 6.8, 4.7 Hz, 2H), 1.35 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 128.4, 126.8, 126.6, 103.9, 64.8, 58.4, 42.9, 34.0, 24.4. HRMS (FAB): Calcd for $C_{13}H_{19}NO_2$: 221.3000. Found: 221.3002.

Methyl (*R*)-3-((2-(1,3-dioxolan-2-yl)ethyl)(1-phenylethyl)amino)-3-oxopropanoate **2**. Compound **1** (0.4277 g, 1.93 mmol) was dissolved in dimethyl malonate (3.6 mL, 31.44 mmol) and refluxed for 1 h. The resulting orange solution was concentrated and the residue was purified by flash chromatography (silica gel, EtOAc/Petroleum ether 80:20) to afford **2** as a yellow oil in quantitative yield. $[\alpha]^{20}_{D}$ +81.9 (*c* 1.00, CH_2Cl_2). This compound shown a dynamic rotameric equilibrium in solution. Only the major rotamer is described: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 5.94 (q, *J* = 7.1 Hz, 1H), 4.61 (t, *J* = 3.9 Hz, 1H), 3.78 (m, 2H), 3.70 (m, 2H), 3.68 (s, 3H), 3.47 (m, 2H), 3.07 (m, 2H), 1.72 (m, 2H), 1.47 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 165.4, 139.3, 127.4, 126.6, 126.5, 100.8, 64.0, 63.9, 51.4, 50.3, 40.0, 37.5, 33.5, 15.5. HRMS (FAB): Calcd for $C_{17}H_{23}NO_5$: 321.1576. Found: 221.1578.

Mixture of (*R*)-1-(1-phenylethyl)-5,6-dihydropyridin-2(1*H*)-one **3** and (*R*)-1-(1-phenylethyl)-3,6-dihydropyridin-2(1*H*)-one **4** in 70:30 ratio. To a solution of **2** (0.06 g, 0.18 mmol) in toluene (7.5 mL), was added a solution of hydrochloric acid ([8N], 1.5 mL). The mixture was heated at reflux for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). After the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a mixture of **3**+**4**. Finally, major regioisomer **3** was separated by flash chromatography (silica gel, Petroleum ether/EtOAc 90:10).

(*R*)-1-(1-Phenylethyl)-5,6-dihydropyridin-2(1*H*)-one **3** is described. $[\alpha]^{20}_{D}$ +68.1 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 6.45 (dt, *J* = 9.8, 4.2 Hz, 1H), 5.98 (q, 1H), 5.95 (d, 1H), 3.15 (ddd, *J* = 12.4, 8.9, 6.4 Hz, 1H), 2.87 (dt, *J* = 12.5, 6.4 Hz, 1H), 2.20 (m, 2H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 138.3, 127.49, 127.41, 126.4, 126.2, 124.5, 48.4, 38.3, 23.3, 14.5. HRMS (FAB) calcd for $C_{13}H_{15}NO$: 201.2631. Found: 201.2632.

Mixture of (*R*)-1-(1-phenylethyl)-5,6-dihydropyridin-2(1*H*)-one **3** and (*R*)-1-(1-phenylethyl)-3,6-dihydropyridin-2(1*H*)-one **4** in 4:96 ratio. To a solution of **2** (0.06 g, 0.18 mmol) in toluene (0.32 mL), was added a solution of aq HCl ([2N], 1 mL). The mixture was heated at reflux for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). After the combined organic extracts were dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure to afford a mixture of regioisomers **3**+**4**. Finally, major regioisomer **4** was separated by flash chromatography (silica gel, Petroleum ether/EtOAc 90:10).

(*R*)-1-(1-Phenylethyl)-3,6-dihydropyridin-2(1*H*)-one **4** is described. $[\alpha]^{20}_D$ +109.6 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.18 (m, 5H), 6.15 (q, *J* = 7.1 Hz, 1H), 5.66 (m, 1H), 5.58 (m, 1H), 3.64 (m, 2H), 2.97 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 138.7, 127.47, 127.4, 126.3, 121.1, 120.0, 48.5, 41.2, 31.6, 14.1. HRMS (FAB) calcd for $C_{13}H_{15}NO$: 201.2631. Found: 201.2633.

Methyl (*R*)-2-oxo-1-(1-phenylethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate, **6**. To a solution of **2** (0.06 g, 0.18 mmol) in toluene (0.32 mL), was added a solution of aq HCl ([2M], 1 mL). The mixture was stirred at room temperature for 22 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). After the combined organic extracts were dried (anhydrous Na_2SO_4), the residue was purified by flash chromatography (EtOAc-Petroleum ether 4:6) to afford **6** (78%) as a colorless oil. $[\alpha]^{20}_D$ +13.4 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.19 (m, 6H), 6.01 (q, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 3.17 (ddd, *J* = 12.7, 9.5, 5.6 Hz, 1H), 2.93 (m, 1H), 2.23 (m, 2H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 160.6, 145.9, 140.5, 129.8, 128.5, 127.4, 127.2, 52.3, 49.6, 38.9, 24.5, 15.6. HRMS (FAB): Calcd for $C_{15}H_{17}NO_3$: 259.1206. Found: 259.1207.

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