

HETEROCYCLES, Vol. 98, No. 2, 2019, pp. 215 - 223. © 2019 The Japan Institute of Heterocyclic Chemistry  
Received, 16th November, 2018, Accepted, 16th January, 2019, Published online, 22nd January, 2019  
DOI: 10.3987/COM-18-14016

## EFFICIENT SYNTHESIS OF CHIRAL 5-METHOXYCARBONYL-PYRIDIN-2(1*H*)-ONES AND 3-BROMO-5-METHOXYCARBONYL-PYRIDIN-2(1*H*)-ONES

Hugo Pilotzi, Dino Gnecco,\* María L. Orea,\* David M. Aparicio, Sylvain Bernes, Jorge R. Juárez, and Joel L. Terán

Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla. Edif. IC9. Complejo de Ciencias. C.U. 72570 Puebla. Pue. Mexico.

Email: gneccod@yahoo.com.mx.

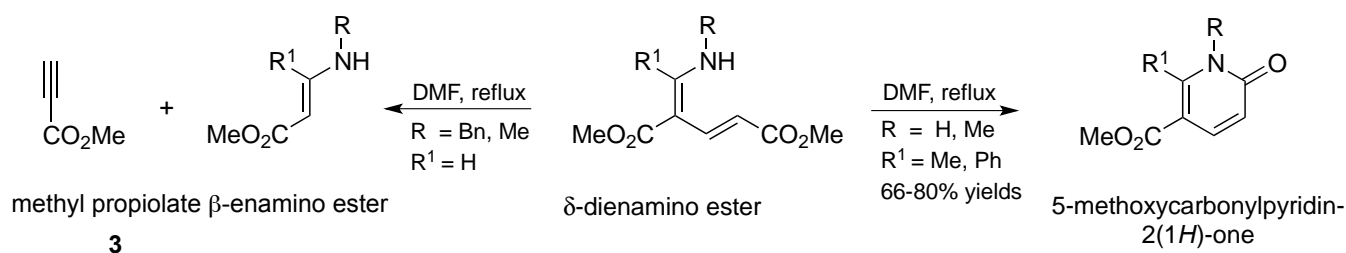
*In memoriam:* Christian Marazano. Institut de Chimie des Substances Naturelles, C.N.R.S. 91198 Gif-sur-Yvette Cedex. France.

**Abstract** – Starting with both the mixture of methyl (*S*)-3-(1-phenylethylamino)acrylate **1**-(*E/Z*) and the mixture of methyl [(*R*)-3-(2-*tert*-butyldimethylsilyloxy)-1-phenylethylamino]acrylate **2**-(*E/Z*), the corresponding chiral 5-methoxycarbonylpyridin-2(1*H*)-ones were synthesized in high yields. By employing these chiral pyridin-2(1*H*)-ones, the corresponding 3-bromo-5-methoxycarbonylpyridin-2(1*H*)-ones were prepared in high yields.

## INTRODUCTION

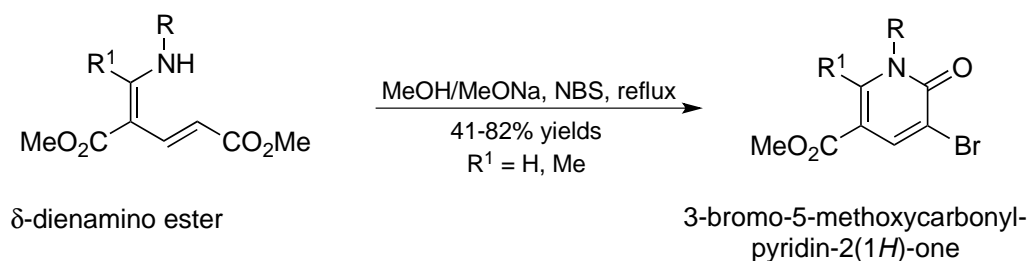
Functionalized pyridin-2(1*H*)-ones are key structural features in numerous natural products. These compounds are generally prepared by oxidation of pyridinium salts diversely substituted and used as starting materials to synthesize different kinds of alkaloids.<sup>1-5</sup> In addition, 5-methoxycarbonylpyridin-2(1*H*)-ones and 3-halo-5-methoxycarbonylpyridin-2(1*H*)-ones are prepared preferentially by aza-annulation of  $\delta$ -dienamino esters derived from  $\beta$ -keto esters and methyl propiolate.<sup>6-15</sup> In this sense, Anghelide and co-workers in 1974 reported the synthesis of 5-methoxycarbonylpyridin-2(1*H*)-ones by heating of  $\delta$ -dienamino ester derivatives ( $R = \text{alkyl or aryl}$ ) derived from the corresponding  $\beta$ -keto esters in refluxing dimethylformamide (DMF) in good yields. However, when they carried out the aza-annulation of  $\delta$ -dienamino esters ( $R^1 = \text{H}$ ) obtained from methyl

propiolate, under the same reaction conditions,  $\beta$ -enamino ester and the methyl propiolate were obtained as a result of retro-Michael reaction<sup>9</sup> (Scheme 1).



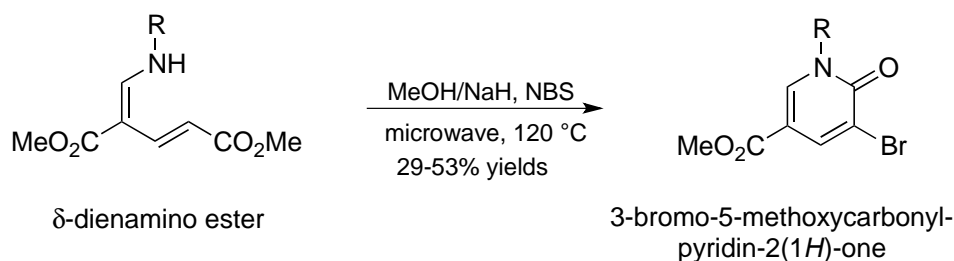
Scheme 1

Additionally, Dechoux and co-workers in 2002 reported the preparation of 3-bromo-5-methoxycarbonylpyridin-2(1H)-ones by refluxing  $N$ -substituted  $\delta$ -dienamino esters with NBS in MeOH in the presence of MeONa<sup>10</sup> (Scheme 2).



Scheme 2

Vounatsos and co-workers in 2006 also reported a variation of the methodology described by Dechoux. They carried out the aza-annulation using MeOH/NaH/NBS and microwave irradiated at 120 °C for 30 minutes. Despite of reducing the reaction time, the desired products were obtained in moderate and low yields<sup>11</sup> (Scheme 3).



Scheme 3

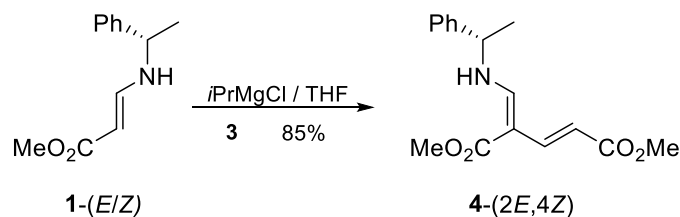
## RESULTS AND DISCUSSION

Considering the antecedents described above and that previously we published the preparation of the  $\beta$ -enamino esters: methyl (*S*)-3-(1-phenylethylamino)acrylate **1-(*E/Z*)** and methyl (*R*)-3-((2-(*tert*-butyldimethylsilyloxy)-1-phenylethylamino)acrylate **2-(*E/Z*)** in high yields,<sup>16</sup> and here, we report the utilization of these  $\beta$ -enamino esters to prepare the corresponding  $\delta$ -dienamino esters **4-(*2E,4Z*)** and **7-(*2E,4Z*)** in high yields. Finally, these compounds were used to synthesize the title compounds of this work.

Firstly, starting with **1-(*E/Z*)** we describe an efficient sequence reactions that allow us to obtain dimethyl (*2E,4Z*)-4-(((*S*)-1-phenylethyl)aminomethylene)pent-2-enedioate **4**, (*S*)-1-(1-phenylethyl)-5-methoxycarbonylpyridin-2(*1H*)-one **5** and (*S*)-3-bromo-5-methoxycarbonyl-1-(1-phenylethyl)pyridin-2(*1H*)-one **6** in high yields.

### Synthesis of dimethyl (*2E,4Z*)-4-(((*S*)-1-phenylethyl)aminomethylene)pent-2-enedioate **4**

To a solution of **1-(*E/Z*)** (1.0 equiv.) in THF at 0 °C was added a solution of *i*PrMgCl<sup>17</sup> (1.1 equiv.), and the reaction mixture was stirred for 30 minutes. Then, methyl propiolate **3** (1.0 equiv.) was added and the resulting mixture was refluxed for 3 hours (completion of the reaction monitored by TLC). The crude product was poured into a saturated aqueous solution of NH<sub>4</sub>Cl and extracted with AcOEt. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified on silica gel column and **4-(*2E,4Z*)** was obtained in 85% yield. The structure including the assigned configuration of this compound was determined by <sup>1</sup>H NMR: d 5.91 ppm (d, *J* = 16 Hz, 1H-2); 7.12 ppm (d, *J* = 16 Hz, 1H-3). These <sup>1</sup>H NMR data are in agreement with the structures (*2E,4Z*) reported by W. Bottomley<sup>18</sup> (Scheme 4). This compound was crystallized from diethyl ether, and the X-ray analysis<sup>19</sup> confirmed unambiguously the proposed structure derived from the analysis of its <sup>1</sup>H NMR spectra (Figure 1).



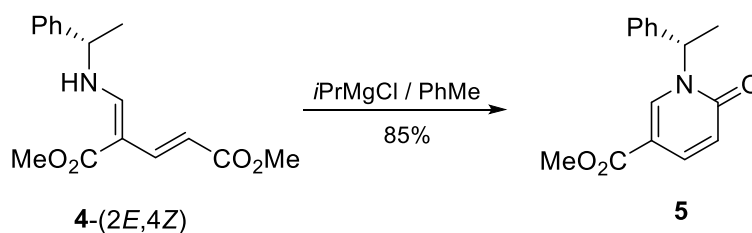
Scheme 4



Figure 1. ORTEP of compound **4-(*2E,4Z*)**

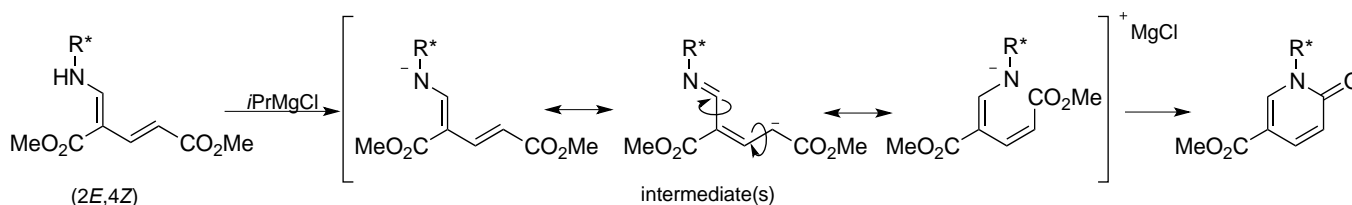
### Synthesis of (*S*)-5-methoxycarbonyl-1-(1-phenylethyl)pyridin-2(1*H*)-one **5**

To a solution of **4**-(2*E*,4*Z*) (1.0 equiv.) in toluene<sup>20</sup> at 0 °C was added *i*PrMgCl (1.1 equiv.) and the mixture was refluxed for 4 hours (completion of the reaction monitored by TLC). The mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl and extracted with AcOEt. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and the compound **5** was obtained in 85% yield. The structure of **5** was assigned by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra (Scheme 5).



Scheme 5

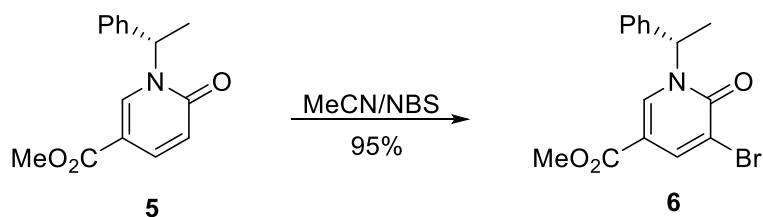
The aza-annulation observed in this process could be explained according to the following mechanism of reaction (Scheme 6).



Scheme 6

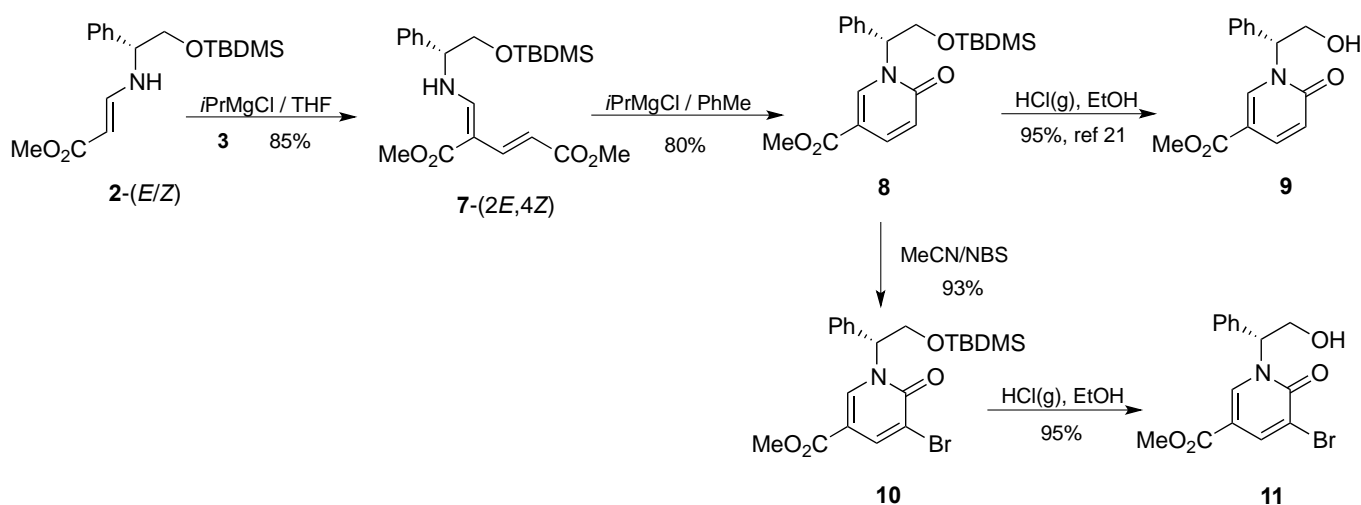
### Synthesis of (*S*)-3-bromo-5-methoxycarbonyl-1-(1-phenylethyl)pyridin-2(1*H*)-one **6**

Finally, to a solution of **5** (1.0 equiv.) in MeCN at room temperature was added a MeCN solution of NBS (1.2 equiv.) and the mixture was stirred for 6 hours (completion of the reaction monitored by TLC). Then, the solvent was removed under vacuum, the crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated aqueous solution of NH<sub>4</sub>Cl. The organic phase was separated, dried, concentrated under reduced pressure, and **6** was obtained in 95% yield. No purification was required. The structure of compound **6** was assigned by <sup>1</sup>H and <sup>13</sup>C NMR spectra (Scheme 7).



Scheme 7

Now, starting with compound **2-(E/Z)** and using the same equivalents, sequence and reaction conditions described above, dimethyl (2*E*,4*E*)-4-(((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-phenylethyl)amino)methylene)pent-2-enedioate **7**, (-)-(*R*)-1-(2-(*tert*-butyldimethylsilyloxy)-1-phenylethyl)-5-methoxycarbonylpyridin-2(*1H*)-one **8**, (*R*)-1-(2-hydroxy-1-phenylethyl)-5-methoxycarbonylpyridin-2(*1H*)-one **9**, (*R*)-3-bromo-1-(2-(*tert*-butyldimethylsilyloxy)-1-phenylethyl)-5-methoxycarbonylpyridin-2(*1H*)-one **10** and (*R*)-3-bromo-1-(2-hydroxy-1-phenylethyl)-5-methoxycarbonylpyridin-2(*1H*)-one **11** were synthesized in high yields (Scheme 8) (see Experimental).



Scheme 8

In summary, we have described an efficient procedure to prepare the chiral  $\delta$ -dienamino esters **4-(2E,4Z)** and **7-(2E,4Z)**. Finally, starting with these structures the title compounds of this work were synthesized in high yields. This is the first time that the synthesis of **5**, **7**, **8**, **9** and **10** is reported and fully characterized. We are currently investigating the use of these compounds in asymmetric synthesis of alkaloids.

## EXPERIMENTAL

The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were determined with a Bruker Avance III Spectrometer operating at 500 and 125 MHz respectively. Optical rotations were determined at room temperature with a

Perkin-Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. Mass spectra were recorded with a JEOL Station JMS-700 instrument at a voltage of 70 eV. IR spectra were obtained with a Nicolet 380 FT-IR instrument in ATR mode.

**(-)-Dimethyl (2*E*,4*Z*)-4-(((*S*)-1-phenylethyl)aminomethylene)pent-2-enedioate (4).** To a solution of  $\beta$ -enamino ester **1**-(*E/Z*), (0.200 g, 0.976 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of *i*PrMgCl (2M/THF, 1.0 mL) (0.088 g, 1.067 mmol). The reaction mixture was stirred at room temperature for 30 min and methyl propiolate **3** (0.089 g, 1.067 mmol) was added. The mixture was refluxed for 3 h, then poured into a saturated aqueous solution of NH<sub>4</sub>Cl (20.0 mL), stirred at room temperature for 15 min and extracted with AcOEt (3x15.0 mL). The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (Hexane: AcOEt = 85:15) and **4**-(2*E*,4*Z*) was obtained in 85%; mp 62-64 °C [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12.5 (c 1, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.52 (d, *J* = 7.0 Hz, 3H-2'), 3.62 (s, 3H-OMe), 3.71 (s, 3H-OMe), 4.43 (m, 1H-1'), 5.91 (d, *J* = 16 Hz, 1H-2), 7.12 (d, *J* = 16 Hz, 1H-3), 7.16-7.31 (m, 5H-Ph, 1H-6), 9.15 (dd, *J* = 5.5 Hz, 12.5 Hz, 1H-NH). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  23.3, 50.9, 51.1, 58.0, 95.1, 107.9, 126.1, 129.0, 142.1, 143.3, 155.8, 169.2, 169.6. IR: 1590, 1659, 2948 cm<sup>-1</sup>. HR-MS (EI): Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub> (M): 289.1314. Found: *m/z* 289.1322.

**(-)-(*S*)-5-Methoxycarbonyl-1-(1-phenylethyl)pyridin-2(1*H*)-one (5).** To a solution of **4**-(2*E*,4*Z*) (0.200 g, 0.692 mmol) in toluene (20.0 mL) at 0 °C was added dropwise a solution of *i*PrMgCl (2M/THF, 0.9 mL) (0.078 g, 0.761 mmol) and then the resulting mixture was refluxed for 4 h. The reaction mixture was poured into a saturated aqueous solution of NH<sub>4</sub>Cl (20.0 mL), stirred at room temperature for 15 min, and extracted with AcOEt (3x15.0 mL), and the organic phase was washed with brine (3x10.0 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (Hexane:AcOEt = 80:20) and the compound **5** was obtained in 85% yield as a yellow pale oil; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -110.1 (c 1, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.68 (d, *J* = 7.0 Hz, 3H-2'), 3.72 (s, 3H-OMe), 6.30 (q, *J* = 7.0, 14.0 Hz, 1H-1'), 6.48 (d, *J* = 9.5 Hz, 1H-5), 7.19-7.29 (m, 5H-Ph), 7.71 (dd, *J* = 2.5, 9.5 Hz, 1H-4), 7.96 (d, *J* = 2.5 Hz, 1H-2). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  19.3, 52.0, 53.4, 110.1, 119.5, 127.3, 129.0, 137.9, 139.4, 162.3, 164.7. IR: 1658, 1716, 2950 cm<sup>-1</sup>. HR-MS (EI): Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub> (M): 257.1052. Found: *m/z* 257.1046.

**(-)-(*S*)-3-Bromo-5-methoxycarbonyl-1-(1-phenylethyl)pyridin-2(1*H*)-one (6).**<sup>10</sup> To a solution of **5** (0.100 g, 0.389 mmol) in MeCN (5.0 mL) at room temperature was added dropwise a solution of NBS (0.0830 g, 0.468 mmol) in MeCN (5.0 mL) and the reaction mixture was stirred for 6 h and the solvent evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL) and the solution washed with water (3x10.0 mL). The organic phase was separated and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated. The

compound **6** was obtained as a pale red oil in 95% yield. No purification was required.  $[\alpha]_{\text{D}}^{20}$  -119.1 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.77 (d,  $J = 7.5$  Hz, 3H-2'), 3.81 (s, 3H-OMe), 6.39 (dd,  $J = 10.0$ , 15.0 Hz, 1H-1'), 7.33-7.39 (m, 5H-Ph), 8.03 (d,  $J = 2.0$  Hz, 1H-4), 8.22 (d,  $J = 2.0$  Hz, 1H-2).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  19.3, 52.3, 55.2, 110.2, 115.5, 127.4, 129.1, 138.7, 139.8, 158.8, 163.7. IR: 1655, 1716, 2951  $\text{cm}^{-1}$ .

**(-)-Dimethyl (2E,4E)-4-(((R)-2-(tert-butyldimethylsilyloxy)-1-phenylethyl)amino)methylene)pent-2-enedioate (7)**. Reaction of **2-(E/Z)** in the same reaction conditions described above gave the compound **7** in 85% yield as a pale yellow oil.  $[\alpha]_{\text{D}}^{20}$  -32.5 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.02 (s, 3H-3'), 0.00 (s, 3H-3'), 0.85 (s, 9H-4'), 3.67 (s, 3H-OMe), 3.71 (dd,  $J = 2.5$  Hz, 8 Hz, 1H-2'), 3.77 (s, 3H-OMe), 3.84 (dd,  $J = 4.0$  Hz, 10.5 Hz, 1H-2'), 4.41 (m, 1H-1'), 5.98 (d,  $J = 15.5$  Hz, 1H-2), 7.21-7.37 (m, 1H-3, 5H-Ph, 1H-6), 9.43 (dd,  $J = 6.5$  Hz, 13.5 Hz, 1H-NH).  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.5, -5.5, 25.7, 51.0, 51.2, 64.5, 67.1, 95.2, 107.6, 127.0, 129.0, 137.5, 143.7, 156.8, 169.4. IR: 1592, 1663. 2949  $\text{cm}^{-1}$ . HR-MS (EI): Calcd for  $\text{C}_{22}\text{H}_{33}\text{NO}_5\text{Si}$  (M): 419.2128. Found:  $m/z$  419.2132.

**(-)-(R)-[1-(2-(tert-Butyldimethylsilyloxy)-1-phenylethyl)]-5-methoxycarbonylpyridin-2(1H)-one (8)**. Reaction of **7-(2E,4Z)** in the same reaction conditions described above gave the compound **8** in 80% yield as a pale yellow oil.  $[\alpha]_{\text{D}}^{20}$  -32.5 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.05 (s, 3H-3'), 0.00 (s, 3H-3'), 0.83 (s, 9H-4'), 3.78 (s, 3H-OMe), 4.15 (dd,  $J = 4.0$  Hz, 11.5 Hz, 1H-2'), 4.33 (dd,  $J = 4.5$  Hz, 13.0 Hz, 1H-2'), 6.24 (t,  $J = 4.0$  Hz, 1H-1'), 6.57 (d,  $J = 10$  Hz, 1H-5), 7.33-7.40 (m, 5H-Ph), 7.85 (dd,  $J = 2.5$  Hz, 9.5 Hz, 1H-4), 8.28 (d,  $J = 2.5$  Hz, 1H-2).  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.51, -5.54, 25.7, 51.0, 51.2, 64.5, 67.1, 95.2, 107.6, 127.0-129.0, 137.5, 143.7, 156.8, 169.4. IR: 1664, 1719, 2950  $\text{cm}^{-1}$ . HR-MS (EI): Calcd for  $\text{C}_{21}\text{H}_{29}\text{NO}_4\text{Si}$  (M): 387.1866 Found:  $m/z$  387.1860.

**(-)-(R)-1-(2-Hydroxy-1-phenylethyl)-5-methoxycarbonylpyridin-2(1H)-one (9)**. To a solution of **8** (0.100 g, 0.388 mmol.) in EtOH (10.0 mL) at room temperature was added HCl(g) and the system sealed.<sup>21</sup> The reaction mixture was stirred at room temperature for 6 h and the solvent evaporated. The compound **9** was obtained in 95% yield as a pale yellow oil. No purification was required.  $[\alpha]_{\text{D}}^{20}$  -42.5 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.40 (w, 1H-OH), 3.73 (s, 3H-OMe), 4.21 (m, 2H-2'), 6.20 (t,  $J = 4.0$  Hz, 1H-1'), 6.45 (d,  $J = 9.5$  Hz, 1H-5), 7.19-7.29 (m, 5H), 7.74 (dd,  $J = 2.5$  Hz, 9.5 Hz, 1H-4), 8.15 (d,  $J = 2.5$  Hz, 1H-2).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  52.2, 60.0, 62.7, 110.2, 119.4, 127.9-129.2, 135.9, 138.5, 140.9, 163.3, 164.7. HR-MS (EI): Calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_4$  (M): 273.1001. Found:  $m/z$  273.1014.

**(-)-(R)-3-Bromo-1-[(2-(tert-butyldimethylsilyloxy)-1-phenylethyl)]-5-methoxycarbonylpyridin-2(1H)-one (10)**. Compound **8** in the same reaction conditions described above gave **10** in 93% yield.  $[\alpha]_{\text{D}}^{20}$  -48.9 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.05 (s, 3H-3'), 0.00 (s, 3H-3'), 0.82 (s, 9H-4'), 3.79

(s, 3H-OMe), 4.13 (dd,  $J = 4.0$  Hz, 11.5 Hz, 1H-2'), 4.33 (dd,  $J = 4.5$  Hz, 11.5 Hz, 1H-2'), 6.22 (t,  $J = 4.5$  Hz, 1H-1'), 7.37–7.38 (m, 5H-Ph), 8.26 (d,  $J = 2.5$  Hz, 1H-4), 8.27 (d,  $J = 2.5$  Hz, 1H-2).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.8, -5.7, 17.9, 25.6, 52.2, 60.7, 62.3, 109.1, 114.9, 128.3, 129.0, 136.3, 140.2, 141.5, 159.0, 163.9. IR: 1660, 1720, 2952  $\text{cm}^{-1}$ . HR-MS (EI): Calcd for  $\text{C}_{21}\text{H}_{28}\text{BrNO}_4\text{Si}$  (M): 465.0971 Found:  $m/z$  456.1931.

**(-)-(R)-3-Bromo-1-(2-hydroxy-1-phenylethyl)-5-methoxycarbonylpyridin-2(1H)-one (11).**<sup>10</sup> To a solution of **10** (0.100 g, 0.284 mmol.) in EtOH (10.0 mL) at room temperature was added HCl(g) and the system sealed. The reaction was stirred at room temperature for 6 h and the solvent evaporated. The compound **11** was obtained in 95% yield as a pale yellow oil. No purification was required.  $[\alpha]_{\text{D}}^{20}$  -50.4 (c 1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.64 (s, 1H-OH), 3.82 (s, 3H-OMe), 4.32(m, 2H-2'), 6.30 (dd,  $J = 5.0$  Hz, 6.5 Hz, 1H-1'), 7.36-7.39 (m, 5H), 8.24 (d,  $J = 2.0$  Hz, 1H-4), 8.26 (d,  $J = 2.0$  Hz, 1H-2).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  52.4, 61.6, 62.7, 110.1, 115.4, 128.0, 128.9, 135.4, 140.0, 140.3, 159.6, 163.8.

## ACKNOWLEDGEMENTS

D. G. and M. L. O. are grateful to CONACyT (Project 256291), and S. B. (Project 268178). H. P. thanks to CONACyT for the scholarship (592119), and Dr. Sylvain Bernes for X-rays analysis.

## REFERENCES AND NOTES

1. J. L. Terán, D. Gnecco, A. Galindo, J. R. Juárez, R. G. Enríquez, M. Soriano, and W. F. Reynolds, *Molecules*, 2000, **5**, 1175, and references cited therein.
2. J. L. Terán, D. Gnecco, A. Galindo, J. R. Juárez, S. Bernès, and R. G. Enríquez, *Tetrahedron: Asymmetry*, 2001, **12**, 357.
3. D. Gnecco, A. M. Lumbreras, J. L. Terán, A. Galindo, J. R. Juárez, M. L. Orea, A. Castro, R. G. Enríquez, and W. F. Reynolds, *Heterocycles*, 2009, **78**, 2589, and references cited therein.
4. L. F. Roa, D. Gnecco, A. Galindo, J. L. Terán, and S. Bernès, *Tetrahedron: Asymmetry*, 2004, **15**, 3393.
5. J.J. Youte, D. Barbier, A. Al-Mourabit, D. Gnecco, and C. Marazano, *J. Org. Chem.*, 2004, **69**, 2737.
6. J. B. Pierce, Z. S. Ariyan, and G. S. Oviden, *J. Med. Chem.*, 1982, **25**, 132.
7. M. Torres, S. Gil, and M. Parra, *Curr. Org. Chem.*, 2005, **9**, 1757, and references cited therein.
8. Q. Li, L. A. Mitscher, and L. L. Shen, *Med. Res. Rev.*, 2000, **20**, 231.
9. N. Anghelide, C. Draghici, and D. R. Eanu, *Tetrahedron*, 1974, **30**, 623, and references cited

therein.

10. C. Agami, L. Dechoux, S. Hebbe, and J. Moulinas, *Synthesis*, 2002, 79, and references cited therein.
11. J. Adams, A. Hardin, and F. Vounatsos, *J. Org. Chem.*, 2006, **71**, 9895.
12. F. Pin, S. Comesse, M. Sanselme, and A. Daich, *J. Org. Chem.*, 2008, **73**, 1975.
13. Y. S. Chun, K. Y. Ryu, Y. O. Ko, J. Y. Hong, J. Hong, H. Shin, and S. Lee, *J. Org. Chem.*, 2009, **74**, 7556.
14. M. C. Bagley and C. Glover, *Molecules*, 2010, **15**, 3211, and references cited therein.
15. M. S. Akhtar, J.-J. Shim, S. H. Kim, and Y. R. Lee, *New J. Chem.*, 2017, **41**, 13027.
16. H. Pilotzi, D. Gnecco, M. L. Orea, J. R. Juárez, D. M. Aparicio, and J. L. Terán, *Heterocycles*, 2018, **96**, 895.
17. When MeMgCl was utilized the compounds **4**-(2*E*,4*Z*) and **5**-(2*E*,4*Z*) were obtained in 60% yield. However, with PhMgCl and NaH in 40% yield.
18. W. Bottomley, *Tetrahedron Lett.*, 1967, **21**, 1997.
19. CCDC-1877449. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
20. When the reaction was carried out in THF, the starting material was recovered.
21. X. Z. Wang, X. Wang, Y. Chen, L. Dai, and X. Li, *J. Zhejiang Univ. SCIENCE A (Applied Physics & Engineering)*, 2016, **17**, 163.