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PREPARATION OF CHIRAL β-ENAMINO ESTERS FROM METHYL PROPIOLATE: SYNTHESIS OF CHIRAL METHYL 1-SUBSTITUTED 6-OXO-1,4,5,6-TETRAHYDROPYRIDINE-3-CARBOXYLATES

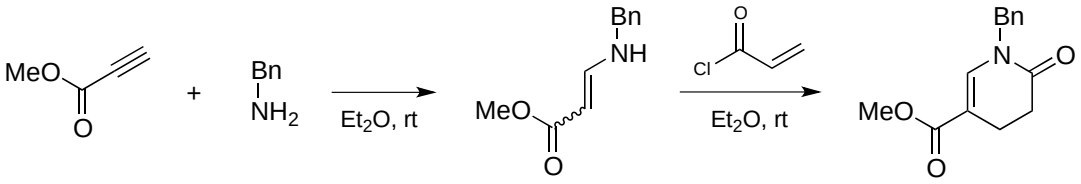
Hugo Pilotzi, Dino Gnecco,* María L. Orea,* Jorge R. Juárez, David M. Aparicio, and Joel L. Terán

Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Edif. IC9, Complejo de Ciencias, C. U. 72570 Puebla, Pue., México. Email: gneccod@yahoo.com.mx

Abstract – An efficient procedure to prepare chiral β-enamino esters by reaction of methyl propiolate with chiral amines is described. Aza-annulation of these chiral β-enamino esters with acryloyl chloride afforded the corresponding chiral methyl 1-substituted 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates in good yield.

β-Enamino ester derivatives of methyl propiolate **1** have long an active topic in organic synthesis. These compounds are key intermediates in the synthesis of natural products and bioactive compounds. In addition, these β-enamino esters are utilized to synthesize methyl 1-substituted 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates, which are widely used as starting materials in organic synthesis. However, this global process generally is reported in low yield.[1-8]

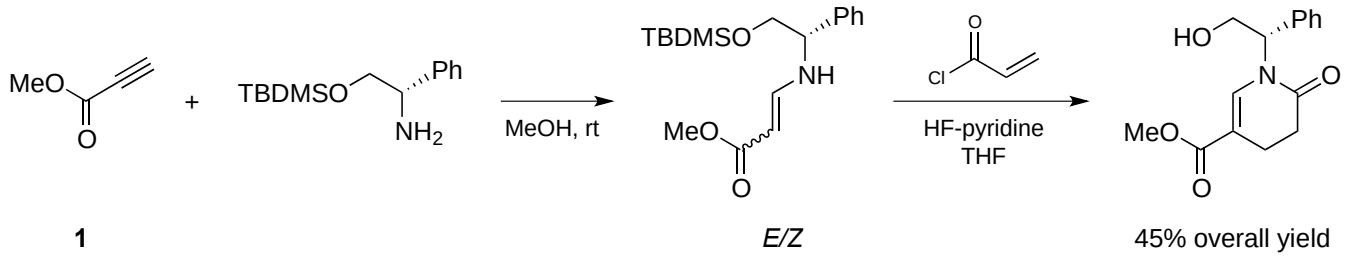
In this sense, Stille et al.[1] specifically reported that the condensation of **1** with benzylamine afforded the β-enamino esters in low yield (neither spectral data nor yields are reported). Then, by the aza-annulation of this compound with acryloyl chloride they obtained the methyl 6-oxo-1-benzyl-1,4,5,6-tetrahydropyridine-3-carboxylate in 53% overall yield (Scheme 1).



1 *E/Z* 53% overall yield

Scheme 1

In the same way, Dechoux et al.[5] published that the condensation of **1** with (*S*)-(-)-2-phenylglycinol protected with TBDMSCl generated the β-enamino ester (neither spectral data nor yields are reported). Finally, its aza-annulation with acryloyl chloride afforded the methyl (*S*)-1-(2-hydroxy-1-pheylethyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate in 45% overall yield, after deprotection and purification by column chromatography. They explained that the low overall yield in this process was due to the poor yield of the condensation between the protected (*S*)-(-)-2-phenylglycinol and the methyl propiolate (Scheme 2).



1 *E/Z* 45% overall yield

Scheme 2

Considering the results reported by Stille et al. and Dechoux et al. we investigate new reaction conditions to improve the yields of these processes. Now we describe an efficient procedure to condense **1** with (*S*)-(-)-1-phenylethan-1-amine **2**, (*R*)-(-)-2-amino-2-phenylacetate **3** and (*R*)-(-)-2-phenylglycinol **4**, to produce the chiral β-enamino esters **5**, **6** and **7** with acryloyl chloride generated the corresponding chiral methyl 1-substituted 6-oxo-1,4,5,6 tetrahydropyridine-3-carboxylates **8**, **9** and **10** in good yields.

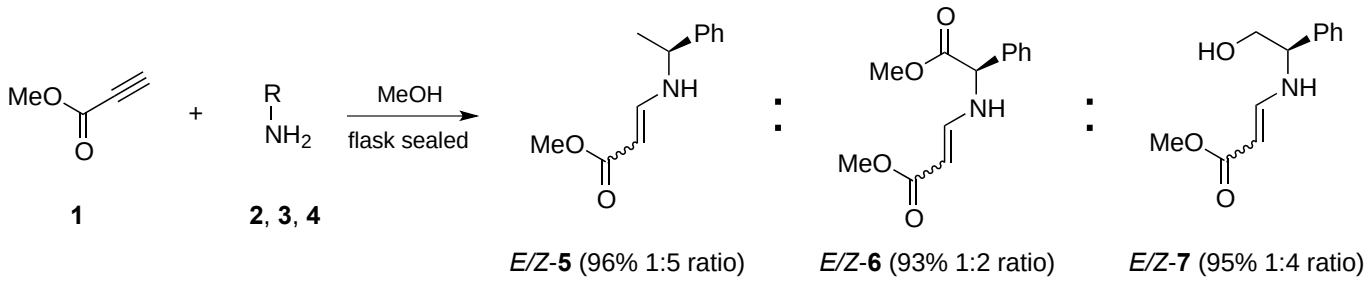
Preparation of chiral β-enamino esters *E*/*Z*-5, *E*/*Z*- 6 and *E*/*Z*-7

Firstly, we carried out the preparation of β-enamino ester **5** derived from (*S*)-(-)-1-phenylethan-1-amine. To a solution of (*S*)-(-)-1-phenylethan-1-amine **2** (1.0 eq.) either in Et_2O, THF or MeOH at 0 °C was added dropwise methyl propiolate **1** (1.2 eq.) and stirred at room temperature for 4 hours.[9] TLC of the reaction mixture showed a proportional amount of amine **2** and β-enamino ester **5** but the methyl propiolate **1** was not observed. The ^{1}H NMR ($CDCl_3$) of the crude reaction product confirmed the observed in TLC. The crude reaction product was purified by column chromatography and the enamino ester **5** was obtained as an amorphous solid in 45% yield (*E*/*Z* mixture 1:4 ratio, determined by ^{1}H NMR) and the amine **2** in 50% yield. The reaction of (*R*)-(-)-2-aminophenylacetate **3** and (*R*)-(-)-2-phenylglycinol **4** with **1** under the same conditions described above afforded after purification by column chromatography the β-enamino ester **6** in 35% yield as an amorphous solid (*E*/*Z* mixture 1:2 ratio), and **7** in 30% yield as a yellow pale oil (*E*/*Z* mixture 1:3 ratio) respectively.

Based on the result described above, we assumed that the volatility of methyl propiolate **1** was the cause

of the low yield of this process. Under this consideration, we carried out the reaction in a sealed system. To a solution of the (*S*)-(-)-1-phenylethan-1-amine **2** (1.0 eq.) in MeOH at 0 °C in a flask sealed with septum rubber was added dropwise methyl propiolate **1** (1.2 eq.). Finally, the reaction was stirred for 4 hours at room temperature and by TLC was confirmed the total consumption of the amine **2**. The solvent was evaporated under reduced pressure and the mixture **5** was obtained in 96% yield as an amorphous solid (*E*/*Z* mixture 1:5 ratio).

The reaction of (*R*)-(-)-2-amino-2-phenylacetate **3** and (*R*)-(-)-2-phenylglycinol **4** with methyl propiolate **1** under the same conditions described above afforded the β-enamino ester **6** in 93% yield as an amorphous solid (*E*/*Z* mixture 1:2 ratio) and the β-enamino ester **7** in 95% yield as a yellow pale oil (*E*/*Z* mixture 1:4 ratio), respectively (Scheme 3).



Scheme 3

The amorphous solid *E*/*Z*-**5** and *E*/*Z*-**6** were crystallized from diethyl ether and the X-ray analysis of each crystalline compound showed only the isomer *E*-**5** and *E*-**6**, respectively (Figure 1).[10]

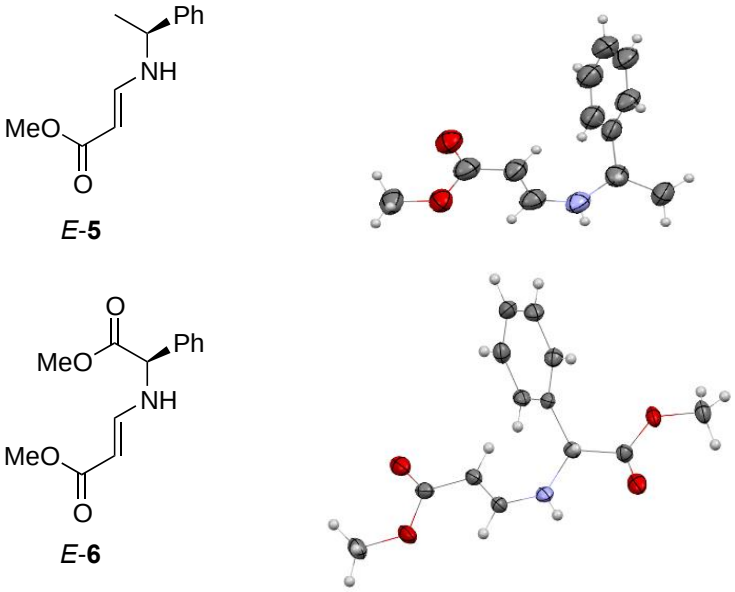


Figure 1. ORTEP drawings of *E*-**5** and *E*-**6**

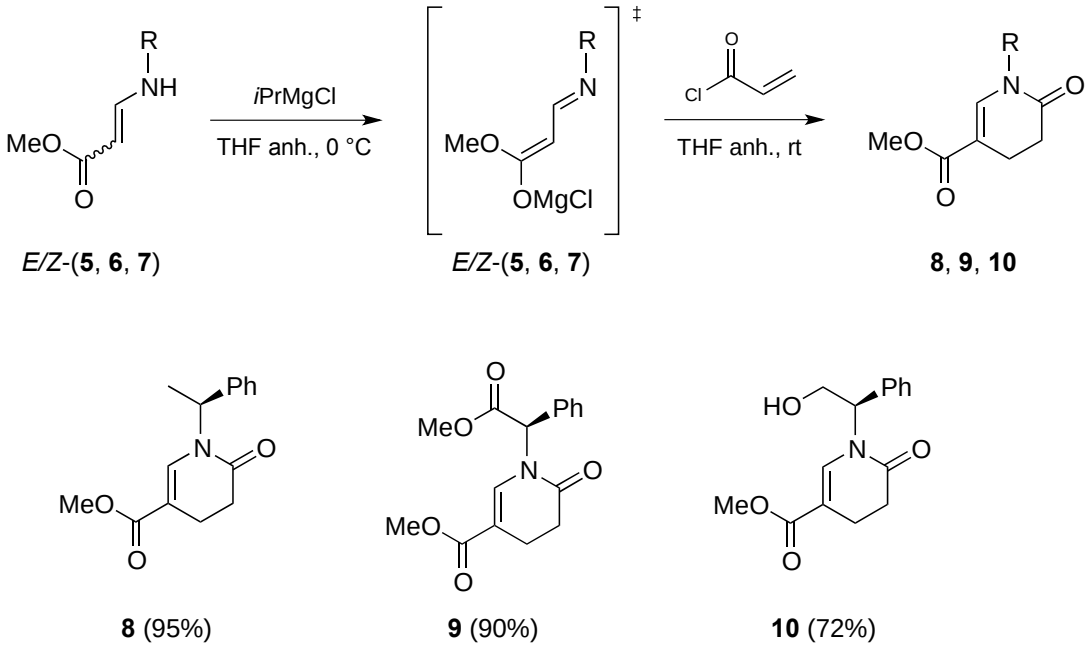
However, ^{1}H NMR ($CDCl_3$) of *E*-**5** and *E*-**6** again revealed the presence of the mixture *E*/*Z*-**5** (1:5 ratio) and *E*/*Z*-**6** (1:2 ratio), respectively. This result is in concordance with dynamic equilibrium that these compounds present in solution. This equilibrium becomes highly important for next reaction.[11,12]

Synthesis of chiral methyl 1-substituted 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates 8, 9 and 10

The first procedure was to react the β-enamino ester *E*/*Z*-**5** in THF at 0 °C with a stoichiometric amount of acryloyl chloride. The reaction was stirred for 4 hours at room temperature and **8** was obtained in 60% yield after purification by column chromatography. Reaction of *E*/*Z*-**6** with acryloyl chloride under the same conditions gave **9** in 50% yield. The mixture *E*/*Z*-**7** afforded a complex mixture as decribed Dechoux et al.[6] Reaction of protected *E*/*Z*-TBDMS-**7**[13] with acryloyl chloride afforded **10** in 48% overall yield after deprotection[14] and purification by column chromatography.

To improve the yield of the reaction described above, the mixture *E*/*Z*-**5**, *E*/*Z*-**6** and *E*/*Z*-TBDMS-**7** were treated with isopropylmagnesium chloride (*i*PrMgCl) to generate the corresponding high energy magnesium intermediate, and then each them was treated with acryloyl chloride.

The first procedure was to react *E*/*Z*-**5** (1.0 eq. in THF anh.) at 0 °C with *i*PrMgCl (1.2 eq.). The reaction was stirred for 30 minutes and the acryloyl chloride (1.1 eq.) was added. The mixture was stirred for 2 hours at room temperature and **8** was obtained in 95% yield after purification by column chromatography. Reaction of *E*/*Z*-**6** in the same conditions afforded **9**[15] in 90%. Reaction of *E*/*Z*-TBDMS-**7** gave **10** in 72% after deprotection and purification by column chromatography (Scheme 4).



Scheme 4

In conclusion, we have described an efficient procedure to prepare the chiral methyl β-enamino esters *E*/*Z*-**5**, *E*/*Z*-**6** and *E*/*Z*-**7** in excellent yield. This is the first work that reports the X-ray of *E*-**5** and *E*-**6**. We have also contributed with an easy method to perform the aza-annulation of these β-enamino esters with acryloyl chloride to obtain the methyl 1-substituted 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **8**, **9** and **10** in good yield. In addition, this is the first time that is reported the synthesis of compound **8** and **9**. We are currently investigating the potential of these compounds as starting material in the asymmetric synthesis of alkaloids.

EXPERIMENTAL

The ^{1}H NMR and ^{13}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. Analysis by HPLC was made in an Agilent 1260. X-Ray diffraction analysis was performed on a diffractometer Agilent Gemini Atlas.

Preparation of methyl β-enamino esters *E*/*Z*-5, *E*/*Z*-6 and *E*/*Z*-7

General Procedure: To a solution of (*S*)-(-)-1-phenylethan-1-amine **2** (500 mg, 4.132 mmol) in MeOH (HPLC, 5 mL) at 0 °C in a flask sealed with septum rubber was added dropwise methyl propiolate **1** (420 mg, 4.957 mmol). The reaction was stirred for 4 h at room temperature and the solvent evaporated under reduced pressure. The mixture *E*/*Z*-**5** (1:5 ratio) was obtained as an amorphous solid in 96% yield. Mp 70-72 °C. MS (FAB): Calcd for $C_{12}H_{15}NO_2$: 205. Found: 205.

Reaction of (*R*)-(-)-2-amino-2-phenylacetate **3** (500 mg, 3.030 mmol) with **1** (300 mg, 3.636 mmol) gave the mixture *E*/*Z*-**6** (1:2 ratio) as an amorphous solid in 93% yield. Mp 92-94 °C. MS (FAB): Calcd for $C_{13}H_{15}NO_4$: 249. Found: 249.

Reaction of (*R*)-(-)-2-phenylglycinol **4** (500 mg, 3.649 mmol) with **1** (368 mg, 4.380 mmol) afforded *E*/*Z*-**7** in 95% yield (1:4 ratio). Yellow pale oil. MS (FAB): Calcd for $C_{12}H_{15}NO_3$: 221. Found: 221.

Methyl (*S*)-3-((1-phenylethyl)amino)acrylate 5*Z*:5*E* 4:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39-*E* (d, *J* = 6.5 Hz, 3H-2'), 1.44-*Z* (d, *J* = 6.5 Hz, 3H-2'), 3.52-*E* (s, 3H-OMe), 3.58-*Z* (s, 3H-OMe), 4.28-*E* (m, 1H-1'), 4.32-*Z* (m, 1H-1'), 4.43-*Z* (d, *J* = 8.0 Hz, 1H-2), 4.54-*E* (d, *J* = 13.5 Hz, 1H-2), 6.50-*Z* (dd, *J* = 8.5, 13.2 Hz, 1H-3), 7.20-7.35, *E* and *Z* (m, 10H), 7.40-*E* (dd, *J* = 8.0, 13.0 Hz, 1H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 23.8, 50.2, 50.6, 57.0, 82.5, 87.3, 125.9-128.9, 143.9, 151.0, 169.8, 171.1.

Methyl (2*R*)-3-((2-methoxy-2-oxo-1-phenylethyl)amino)acrylate 6*Z*:6*E* 2:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59-*E* (s, 3H-OMe), 3.68-*Z* (s, 3H-OMe), 3.72-*E* (s, 3H-OMe), 3.73-*Z* (s,

3H-OMe), 4.57-*E* (d, *J* = 13.5 Hz, 1H-2), 4.61-*Z* (d, *J* = 8.5 Hz, 1H-2), 4.91-*E* (d, *J* = 6.0 Hz, 1H-1'), 4.97-*Z* (d, *J* = 7.0 Hz, 1H-1'), 6.52-*Z* (dd *J* = 8.5, 13.2 Hz, 1H-3), 7.32-7.38, *E* and *Z* (m, 10H), 7.51-*E* (dd, *J* = 8.5, 13.2 Hz, 1H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 50.7, 52.9, 53.1, 63.8, 85.0, 88.7, 127.0-129, 135.5, 137.0, 146.4, 149.4, 169.3, 170.6, 170.8.

Methyl (2*R*)-3-((2-hydroxy-1-phenylethyl)amino)acrylate 7*Z*:7*E* 3:1

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60-*E* (s, 3H-OMe), 3.68-*Z* (s, 3H-OMe), 3.77-*Z,E* (dd, *J* = 8.0, 11.5 Hz, 1H2'), 3.86-*Z* (dd, *J* = 4.5, 11.5 Hz, 1H2'), 3.90-*E* (dd, *J* = 4.5, 11.5 Hz, 1H2'), 4.37-*Z,E* (m, 1H-1'), 4.58-*Z* (d, *J* = 8.0 Hz, 1H-2), 4.60-*E* (d, *J* = 13.5 Hz, 1H-2), 6.68-*Z* (dd, *J* = 8.0, 13.0 Hz, 1H-3), 7.26-7.39, *E* and *Z* (m, 10H), 7.56-*E* (dd, *J* = 8.5, 13.5 Hz, 1H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.4, 50.7, 64.0, 66.4, 67.0, 83.6, 88.2, 126.6-129.0, 138.9, 151.1, 171.3.

Preparation of methyl 1,4,5,6-tetrahydropyridine-3-carboxylates 8, 9 and 10

General Procedure: To a solution of *E*/*Z*-**5** (500 mg, 2.439 mmol) in THF anh. (10 mL) at 0 °C was added dropwise a solution of isopropylmagnesium chloride (0.1825 g, 2.439 mmol) and the reaction was stirred for 30 min. Then, this mixture was treated with a solution of acryloyl chloride (0.245 g, 2.683 mmol) in THF anh. (5 mL). The reaction was stirred at room temperature for 2 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added, stirred for 15 min and extracted with CH_2Cl_2 (3 x 15 mL). The organic phase was separated, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane-AcOEt = 85:15) affording **8** in 95% yield. The mixture *E*/*Z*-**6** in the same conditions gave **9** in 90% yield after flash chromatography on silica gel (hexane-AcOEt = 85:15). Finally, *E*/*Z*-TBDMS-**7** afforded **10** in 72% yield after deprotection and purification by column chromatography on silica gel (hexane-AcOEt = 60:40).

Methyl (*S*)-6-oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 8. Yellow pale oil. $[\alpha]_D^{20}$ -14.1 (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (d, *J* = 7.0 Hz, 3H-2'), 2.58 (m, 4H-4 and 5), 3.60 (s, 3H-OMe), 5.95 (q, *J* = 7.0 Hz, 1H-1'), 7.11 (s, 1H-2), 7.19-7.29 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 19.5, 31.0, 50.6, 109.2, 126.9-128.8, 130.0, 140.0, 166.7, 169.5. HR-MS (EI): Calcd for $C_{15}H_{17}NO_3$ (M): 259.1208. Found: *m/z* 259.1216.

Methyl (*R*)-1-(2-methoxy-2-oxo-1-phenylethyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate 9. Yellow pale oil. $[\alpha]_D^{20}$ -94.9 (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (m, 4H-4 and 5), 3.57 (s, 3H-OMe), 3.72 (s, 3H-OMe), 6.37 (s, 1H-1'), 7.10 (s, 1H-2), 7.17-7.37 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 29.6, 50.6, 51.8, 58.3, 107.9, 127.8-128.3, 132.1, 135.8, 165.6, 169.0, 169.2. HR-MS (EI): Calcd for $C_{16}H_{17}NO_5$ (M): 303.1107. Found: *m/z* 303.1112.

Methyl (*R*)-1-(2-hydroxy-1-phenylethyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate 10. Yellow pale oil. $[\alpha]_D^{20}$ -11.8 (*c* 1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (m, 4H-4 and 5), 3.69 (s,

3H-OMe), 4.20 (AB, *J* = 5.5, 12.0 Hz, 2H-2'), 5.85 (q, *J* = 5.0, 8.0 Hz, 1H-1'), 7.26 (s, 1H-2), 7.28-7.39 (m, 5H).^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 31.0, 51.6, 57.7, 62.5, 109.2, 127.4-129.0, 136.3, 136.6, 166.7, 170.6. MS (FAB): Calcd for $C_{15}H_{17}NO_4$: 275. Found: 275.

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REFERENCES AND NOTES

1. G. R. Cook, L. G. Beholz, and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 3575 and references cited herein.
2. K. Paulvannan and T. Chen, *J. Org. Chem.*, 2000, **65**, 6160 and references cited herein.
3. C. Agami, L. Dechoux, and S. Hebbe, *Tetrahedron Lett.*, 2002, **43**, 2521 and references cited herein.
4. C. Agami, L. Dechoux, C. Ménard, and S. Hebbe, *J. Org. Chem.*, 2002, **67**, 7573.
5. C. Agami, L. Dechoux, and S. Hebbe, *Tetrahedron Lett.*, 2003, **44**, 5311.
6. F. Hendra, M. Nour, I. Baglin, G. Morgant, and C. Cavé, *Tetrahedron: Asymmetry*, 2004, **15**, 1027.
7. C. M. Kascheres, *J. Braz. Chem. Soc.*, 2003, **14**, 945.
8. C. Agami, L. Dechoux, S. Hebbe, and C. Ménard, *Tetrahedron*, 2004, **60**, 5433.
9. The same result was obtained when the reaction time was of 8 hours.
10. CCDC 1419689 (*E*-**5**), and CCDC 1419733 (*E*-**6**). These data can be obtained free charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. T.-L. Shieh, C.-T. Lin, A. T. McKenzie, and S. R. Byrn, *J. Org. Chem.*, 1983, **48**, 3103.
12. D. G. Melillo, R. J. Cvetovich, K. M. Ryan, and M. Sletzinger, *J. Org. Chem.*, 1986, **51**, 1498.
13. Protection of **7** was made as described: T. Isobe, K. Fukuda, K. Yamaguchi, H. Seki, T. Tokunaga, and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7779.
14. Deprotection was made as described: J. Spieler, O. Huttenloch, and H. Waldmann, *Eur. J. Org. Chem.*, 2000, 391.
15. Optical purity of **9** (*R*) was confirmed by HPLC with a chiral column. The analysis of this compound by HPLC was made in an Agilent 1260 with a chiral column ES-OVM 150 x 4.6 mm, 5 μm, mobile phase 50:50 of MeOH:Buffer Na_2HPO_4 4 mM pH 6.0, flow 0.7 mL/min, wavelength 210 nm, time retention of 2.863 min. The compound **9** (*S*) in the same conditions gave a retention time of 2.692 min.