Preparation of 5-(2-Methoxy-4-nitrophenyl)oxazole: A Key Intermediate for the **Construction of VX-497**

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Abstract:

A process for the multigram preparation of 5-(2-methoxy-4nitrophenyl)oxazole, a key intermediate for the preparation of the hepatitis C drug candidate VX-497 (merimepodib), has been achieved in good yield from a commercially available dye. Early studies focused on the preparation of the requisite aldehyde by the Beech reaction. A second approach utilized a palladium (0)-catalyzed formylation of an aryl diazonium species, which was followed by condensation of the aldehyde with tosylmethyl isocyanide (TosMIC) to provide the required oxazole. This twostep method has been carried out to provide multigram samples of this key intermediate in 75% overall yield and >95% purity from the commercially available Fast Red B tetrafluoroborate salt.

Introduction

Recently a program was carried out to develop a synthetic route for the multigram scale preparation of the hepatitis C drug candidate VX-497 (3, merimepodib), which is currently in phase II clinical research trials for the selective inhibition of inosine monophosphate dehydrogenase (IMPDH).¹ Our process research efforts were directed toward the preparation of 5-(2-methoxy-4-nitrophenyl)oxazole (1), which was originally reduced and coupled with aniline 2 in a convergent synthesis of **3** (Figure 1).² Our first synthetic approach to **1** involved the copper-catalyzed coupling of an aryl diazonium species with formaldoxime, a variant of the Beech reaction³ that was highlighted as one key step in Woodward's synthesis of reserpine.⁴ Disappointing yields and purities on scale-up led to a second-generation tactic in which the requisite aldehyde was directly prepared by a palladium (0)-catalyzed

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formylation of the aryl diazonium species using Kikuwawa's method.⁵ Condensation of the resulting aldehyde with TosMIC completed the assembly of 3 in 75% yield and >95% purity (by HPLC analysis) for the two-step procedure.

Results and Discussion

The Beech Reaction and Related Work. The initial research efforts centered around the synthesis of the oxazole 1 via aromatic oxime 6, obtained by a modification of the Beech reaction (Scheme 1).³ In this method, aryl diazonium intermediate 5, generated from commercially available 2-methoxy-4-nitroaniline (4),⁶ was decomposed with a copper sulfate/sodium sulfite catalyst in the presence of formaldoxime to produce the aryl oxime 6. Since aryl diazonium species of many salt forms can be prepared from anilines by a variety of literature methods,⁷ it was decided that aniline 4 would serve as a suitable starting material for the exploration of this synthetic route. It was even more fortuitous to find that a few appropriately substituted, commercially available diazonium compounds 5 were offered as technical-grade Fast Red B salts.⁸ Oxime 6 was anticipated to be easily hydrolyzed to aromatic aldehyde 8, a precursor in the Vertex synthesis of the corresponding oxazole 1, as has been reported in the patent literature.²

An existing procedure for the synthesis of an isomeric aldehyde, published by Woodward,⁴ describes the diazotization and oxime formation from the corresponding aniline. The resulting oxime was then hydrolyzed with acid and steam-distilled to obtain the corresponding aldehyde in 63% yield.⁹ It was found that our aniline **4** was indeed converted to the desired intermediate oxime 6, albeit in 24% yield and in 88.5% purity (by HPLC analysis) for the 200-g scale transformation. Additionally, it was found that the commercially available diazonium salts 5, marketed as dyes under

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⁽⁸⁾ At the present time, Fast Red B salts are also offered in 1,5-naphthalenedisulfonate and diacetate salt forms that were not available at the time this research was performed.

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Figure 1. Original synthetic approach to VX-497.

Scheme 1. Beech reaction and hydrolysis strategy



the trade name of Fast Red B salts, would also undergo the transformation to 6 in comparable, best yields of 32% (for the hemi-zinc chloride salt,¹⁰ 150-g scale) and 31% (for the tetrafluoroborate salt,¹¹ 25-g scale). In each case, an aqueous solution of the aryl diazonium intermediate 5 was adjusted to pH 5-6 with sodium acetate in water and the resulting suspension added slowly to a solution of formaldoxime (preformed from hydroxylamine hydrochloride and paraformaldehyde) and the critical copper sulfate/sodium sulfite catalyst in water. Since this reaction also produced a significant amount (10-40%) of the reduced 3-nitroanisole byproduct, the workup conditions were modified. The reaction mixture was extracted into aqueous sodium hydroxide solution (oxime 6 was soluble in aqueous base), clarified with decolorizing charcoal and acidified with concentrated hydrochloric acid to afford oxime 6 as a tan powder in 98.7% purity (by HPLC analysis).

To our surprise intermediate oxime **6** was found to be resistant to hydrolysis by the literature procedures with aqueous sodium metabisulfite,^{4,9} even after a series of cosolvent mixtures and higher-temperature reaction conditions to improve solubility was investigated. Hydrolysis of aromatic oxime **6** to the corresponding aldehyde **8** was finally achieved by formation of the bisulfite adduct **7** of the oxime with sodium bisulfite, followed by acid hydrolysis to **8** using the method of Pines and co-workers (Scheme 1).¹² Thus, a mixture of oxime **6** and sodium bisulfite in ethanol/water

bisulfite adduct 7. The ethanol was removed under reduced pressure, and the resulting orange suspension was acidified with 2 N hydrochloric acid solution. This resulting solution was diluted with methyl tert-butyl ether and the biphasic mixture heated at reflux for 4 h to produce the crude aldehyde 8. Treatment of the aldehyde solution with Panther Creek 200 bentonite clay¹³ followed by filtration was effective in providing relatively clean aldehyde 8 in a 37% isolated (best) yield and in 83.9% purity (by HPLC analysis). It is worth noting that the purification efficiencies of many bentonite clays are affected by pH of both organic and aqueous media,¹⁴ and thus, occasionally it is found that a survey of available bleaching earths in a variety of solvents may provide a convenient initial improvement in crude product purity. We were thus gratified to find that this calcium bentonite support was useful for the slurry purification of 8 in the biphasic aqueous acidic/MTBE solution to an initial 84% purity.¹⁴ Unfortunately, adsorption of product onto the diatomaceous earth was also one likely (but unavoidable) reason for the low product yield. Low mass recovery was also due to the inefficient extraction of the product from the aqueous phase. A few methods to claim further materials from the acidic aqueous layer were examined (e.g., extraction with other organic solvents, and at elevated temperatures), but were not successful at improving product yields.

(1:1) was heated at reflux for 1 h to provide the soluble

⁽¹⁰⁾ This technical-grade reagent is available from Sigma as approximately 20% dye content and was used as received.

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Scheme 2. Palladium-catalyzed formylation route



Formylation and Oxazole Formation. Due to the disappointing yield and purity results of the Beech reaction route, the synthetic efforts were redirected to prepare the aldehyde 8 directly by a modification of the reported palladium-catalyzed carbonylation reaction of aryl diazonium species developed by Kikuwawa (Scheme 2).⁵ Following the literature precedent that this particular insertion reaction is specific to crystalline diazonium salts (particularly for tetrafluoroborate salt forms), the Fast Red B tetrafluoroborate salt 5 was reacted with carbon monoxide (50 psi), triethylsilane, and 2 mol % of palladium (II) acetate in diethyl ether/ acetonitrile (1:1) at room temperature in a Parr Series 4842 stirred autoclave. After chromatographic purification, this procedure afforded the desired aryl aldehyde 8 as an orange solid in 78% isolated yield and >99% purity (by HPLC analysis). The key feature of this process is that the carbonylation reaction proceeded at a much lower carbon monoxide pressure (50 psi versus 80-1200 psi) and a lower molar catalyst loading (2 mol % versus 5-20 mol %) and reaction temperature (ambient versus 80-150 °C) than is reported in the literature for comparable palladium-catalyzed methods.^{15–18} It should be noted at this point that the decision to use the reducing reagent triethylsilane instead of poly-(methylhydrosiloxane)¹⁵ was due to the necessity of HMPA as a cosolvent in the latter case. Similarly, we decided against the use of tributyltin hydride as a reducing agent¹⁶ due to issues of toxic tin byproduct removal.

Initially the crude formylation product was purified by flash column chromatography to remove the 5–10% of 3-nitroanisole byproduct, but it was later found that filtration through a short silica gel plug was useful to quickly provide **8** in >90% purity with no impurities greater than 3% (by HPLC analysis). It was also found that the amount of the reduction byproduct was minimized when the triethylsilane was added in a slow, controlled fashion to the reaction mixture rather than in one portion. This was achieved by metering a solution of the reducing reagent in methyl *tert*butyl ether into the pressurized Parr vessel via a Waters model 510 HPLC pump at a rate of 1.5 mL/min. By control of the rate of addition, the amount of byproduct was reduced to <5%, and the 20 °C exotherm produced by the oxidation/ reduction reaction was minimized.¹⁹ Formation of the aryl oxazole **1** was carried out in the manner described by Vertex Pharmaceuticals,² but with a modification to the purification method. Thus, a mixture of aldehyde **8**, tosylmethyl isocyanide (TosMIC), and potassium carbonate was heated at reflux in methanol for 12 h to produce the crude oxazole. After an aqueous workup, the residue was dissolved in methylene chloride and treated with an acidic activated charcoal/Clarion 550 bentonite clay^{20/} silica gel mixture (1:1:2). After filtration and solvent removal, oxazole **1** was produced as a yellow solid in 96% yield and in 96.8% purity (by HPLC analysis).

To maximize the yield of 1, the two-step process was carried out without purification of intermediate aldehydes 8. The carbonylation reaction was conducted as previously described, except that methyl tert-butyl ether was substituted for diethyl ether. The intermediate aldehyde 8 was isolated by aqueous workup and used directly in the condensation reaction. The crude reaction mixture was treated with the charcoal/diatomaceous earth/silica gel mixture to produce the oxazole 1 as a light orange solid in 85% yield and in >90%purity (by proton NMR analysis) for the two-step operation. Although much effort was expended to find conditions to recrystallize the crude oxazole (to remove 3-nitroanisole byproduct), no conditions were found that afforded 1 of greater purity than was obtained by a simple plug filtration of the material. Thus, this two-step process to provide 8 was achieved from commercially available Fast Red B tetrafluoroborate salt in 75% overall isolated yield and in 97.1% purity (by HPLC analysis).

Conclusions

The development of a synthesis for the key intermediate 5-(2-methoxy-4-nitrophenyl)oxazole (1) amenable to multigram-scale preparation has been achieved in two steps from a commercially available dye substance in 75% overall yield and in >95% purity (by HPLC analysis). This compound is one of two major components for the synthesis of the Vertex Pharmaceuticals compound VX-497 (3, merimepodib).

Experimental Procedures

General. All nonaqueous reactions were performed under a dry atmosphere of nitrogen. Reagents and anhydrous solvents were used as received from vendors, and no attempts were made to purify or dry these components further. Thinlayer chromatography was performed using 1 in. \times 3 in. Analtech GF 350 silica gel plates with fluorescent indicator. Visualization of TLC plates was made by observation in iodine vapors. The proton and carbon magnetic resonance spectra were obtained on a Bruker AC 300 MHz nuclear magnetic resonance spectrometer, using tetramethylsilane as an internal reference. Melting points were obtained using an electrothermal melting point apparatus and are uncor-

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⁽²⁰⁾ Originally purchased from American Colloid Company (Arlington Heights, IL), the comparable bleaching earth is available from Engelhard Corporation (Iselin, NJ) as Engelhard F-105.

rected. Infrared spectra were obtained as KBr pellets and obtained on a Perkin-Elmer Spectrum 1000 FT-infrared spectrophotometer. CI Mass spectroscopic analyses were performed on a Shimadzu QP-5000 GC/mass spectrometer (methane) by direct injection. Combustion analyses were performed by Quantitative Technologies, Inc. of Whitehouse, New Jersey. HPLC analyses were performed on a Waters Symmetry C18 reverse phase column (150 mm × 3.9 mm, 5 μ m particle size), mobile phase 5:95 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column temperature ambient.

Preparation of 2-Methoxy-4-nitrobenzoxime (6) from Fast Red B Hemi(Zinc Chloride) Salt (5). A solution of hydroxylamine hydrochloride (11.0 g, 158 mmol) and paraformaldehyde (4.7 g, 158 mmol) in water (100 mL) in a 3-L, three-neck flask equipped with an overhead stirrer and a reflux condenser was heated at gentle reflux until the solution became clear and colorless (about 15 min). Sodium acetate (13.0 g, 158 mmol) was added, and the solution was heated at reflux for an additional 15 min. The solution was cooled to room temperature, at which point copper (II) sulfate pentahydrate (2.6 g, 10 mmol), sodium sulfite (0.4 g, 3 mmol), and sodium acetate (78.0 g, 840 mmol) in water (100 mL) were added, and the dark green mixture was stirred for 15 min.

In a separate flask, a solution of Fast Red B hemi(zinc chloride) salt (5,10 150.0 g, 105 mmol after correction for assay) and sodium acetate (50.0 g, 610 mmol) in water (200 mL) was prepared. The insoluble zinc salts were removed by filtration, and the filtrate was added via subsurface cannula with positive nitrogen pressure to the formaldoxime solution at a rate that kept the excessive foaming and exotherm (a 10-15 °C rise) to a minimum. The reddish-brown suspension was cooled to room temperature, and stirring was continued for a total of 1 h, after which the mixture was basified with sodium hydroxide pellets (50 g) and treated with decolorizing charcoal (10 g). The mixture was stirred for 15 min and clarified by vacuum filtration through a pad of Celite (200 g), washing the filter cake sequentially with 1 N sodium hydroxide solution (500 mL) and water (500 mL). The filtrate was acidified with concentrated hydrochloric acid (200 mL) to precipitate the oxime, which was collected by vacuum filtration and dried overnight at 40 °C under reduced pressure to produce 2-methoxy-4-nitrobenzoxime (6) as a tan powder (6.7 g, 32%): mp 150–157 °C; ¹H NMR (CDCl₃) δ 8.50 (s, 1H), 7.91 (d, 1H, *J* = 8.6 Hz), 7.85 (d, 1H, *J* = 8.6 Hz), 7.77 (s, 1H), 7.53 (bs, 1H) and 3.97 (s, 3H) ppm; ¹³C NMR $(CDCl_3)$ δ 163.6, 145.3, 135.3, 131.0, 127.3, 116.3, 106.6 and 56.6 ppm; IR (KBr) 3210, 2362, 1519, 1346 and 1255 cm⁻¹; MS m/z 197 (M + H)⁺ Anal. Calcd for C₈H₈N₂O₄: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.71; H, 3.74; N, 13.93. HPLC analysis (reverse phase Waters Symmetry C18 column, 150 mm \times 3.9 mm, 5 μ m particle size, retention time = 16.6 min, mobile phase 5:95 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column

temperature ambient) showed one peak, with a total purity of 98.7% (area percent).

Preparation of 2-Methoxy-4-nitrobenzoxime (6) from 2-Methoxy-4-nitroaniline (4). In a 22-L, four-neck flask equipped with an overhead stirrer, a thermocouple, a reflux condenser, and a pressure-equalizing addition funnel, a solution of hydroxylamine hydrochloride (124.0 g, 1.78 mol) and paraformaldehyde (54.0 g, 1.78 mol) in water (800 mL) was heated at gentle reflux until the solution became clear and colorless (about 30 min). Sodium acetate (150.0 g, 1.78 mol) was added, and the solution was heated at reflux for an additional 15 min. The solution was cooled to room temperature, at which point copper (II) sulfate pentahydrate (30.0 g, 119 mmol), sodium sulfite (4.5 g, 36 mmol), additional sodium acetate (800.0 g), and additional water (500 mL) were successively added portionwise, and the dark green mixture was vigorously stirred for 1 h.

In a separate 5-L, three-neck flask equipped with an overhead stirrer, a thermocouple, and a pressure equilibrating dropwise addition funnel, concentrated hydrochloric acid (270 mL, 3.2 mol) was added dropwise over 15 min to a solution of 2-methoxy-4-nitroaniline (4, 200.0 g, 1.19 mol) in water (250 mL) at room temperature. The mixture was cooled to 0 °C with an ice water bath, and a solution of sodium nitrite (86.0 g, 1.25 mol) in water (100 mL) was added dropwise over 30 min. The bright yellow mixture was stirred at 0 °C for an additional 30 min and then warmed to room temperature for the portionwise addition of solid sodium acetate (150.0 g, 1.78 mol), at which time vigorous off-gassing was observed. The mixture was then slowly added via subsurface cannula with positive nitrogen pressure to the formaldoxime solution at a rate that kept the excessive foaming and exotherm (a 10-15 °C rise) to a minimum (about 45 min). The reddish-brown suspension was stirred at room temperature for 2 h, after which concentrated hydrochloric acid (1.1 L) was added, and the mixture was heated at reflux for 1 h. The orange solid was collected from the cooled mixture by filtration, diluted in 1 M sodium hydroxide solution (500 mL), and treated with decolorizing charcoal (20 g). The mixture clarified by vacuum filtration through a pad of Celite (200 g), washing the filter cake sequentially with water (1 L). The filtrate was acidified with 6 N hydrochloric acid solution (200 mL) to precipitate the product, which was collected by vacuum filtration and dried overnight at 40 °C under reduced pressure to produce 2-methoxy-4-nitrobenzoxime (6) as an orange solid (56.2 g, 24%). The spectral data were consistent with the material prepared by the previous route. HPLC analysis (reverse phase Waters Symmetry C18 column, 150 mm \times 3.9 mm, 5 μ m particle size, retention time = 16.6 min, mobile phase 5:95 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/ (0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column temperature ambient) showed one peak, with a total purity of 88.5% (area %).

Preparation of 2-Methoxy-4-nitrobenzaldehyde (8) from 2-Methoxy-4-nitrobenzoxime (6). A solution of 2-methoxy-4-nitrobenzoxime (6, 3.5 g, 17.8 mmol) and sodium bisulfite (6.5 g, 62.4 mmol) in ethanol (25 mL) and

water (25 mL) in a 250-mL flask equipped with a reflux condenser was heated at reflux for 75 min. The solution was cooled to room temperature, and the ethanol was removed under reduced pressure. The resulting orange suspension of bisulfite adduct 7 was diluted with 2 N hydrochloric acid solution (100 mL) and methyl tert-butyl ether (50 mL). The resulting biphasic mixture was heated at reflux for 4 h and cooled to room temperature, and the organic phase was collected. The aqueous phase was extracted with methyl tertbutyl ether (2 \times 50 mL), and the combined organic extracts were washed with saturated sodium chloride solution (2 \times 100 mL). The organic solution was treated with Panther Creek 200 bentonite clay¹³ (2 g), and the solids were removed by vacuum filtration. The filtrate solvent was removed under reduced pressure to produce 2-methoxy-4-nitrobenzaldehyde (8) as a yellow powder (1.2 g, 37% yield). HPLC analysis (reverse phase Waters Symmetry C18 column, 150 mm \times 3.9 mm, 5 μ m particle size, retention time = 17.1 min, mobile phase 5:95 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column temperature ambient) showed one peak, with a total purity of 83.9% (area %).

Preparation of 2-Methoxy-4-nitrobenzaldehyde (8) from Fast Red B Tetrafluoroborate Salt (5). A suspension of Fast Red B tetrafluoroborate salt (5, 25.0 g, 93.8 mmol) in acetonitrile (50 mL) and methyl tert-butyl ether (50 mL) in a Parr Series 4842 stir-equipped autoclave was sealed and charged with carbon monoxide to a pressure of 50 psi. The solution was vigorously stirred for 10 min after which the pressure was released. This process was repeated twice after which a suspension of palladium (II) acetate (0.40 g, 1.78 mmol) in acetonitrile (10 mL) was added through the sampling port of the reactor. The reactor was then recharged to 50 psi with carbon monoxide. A solution of triethylsilane (10.6 g, 93.8 mmol) in acetonitrile (40 mL) and methyl tertbutyl ether (50 mL) was added to the stirred reaction mixture over 1.5 h through a Waters model 510 HPLC pump plumbed to an inlet port on the autoclave head with stainless steel connectors at a rate of 1.5 mL/min. During the addition, a temperature increase of 25 °C (19-44 °C) and a pressure increase of 40 psi (50-90 psi) were observed. Once the addition was complete, the reaction was stirred for a further 30 min during which time the contents cooled to 35 °C (monitored by an internal reaction temperature probe). The pressure was released, the autoclave was opened, and the dark solution was poured into saturated aqueous sodium carbonate solution (250 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate $(2 \times 50 \text{ mL})$. The combined organic extracts were dried over MgSO₄, and the solvents were removed under reduced pressure to produce a dark brown solid. This residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to provide 2-methoxy-4-nitrobenzaldehyde (8) as a yellow solid (13.2 g, 78% yield): mp 111–113 °C; ¹H NMR (CDCl₃) δ 10.53 (s, 1H), 7.97 (d, 1H, J = 8.7 Hz), 7.87 (d, 1H, J = 8.7 Hz), 7.85 (s, 1H) and 4.05 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 188.4, 162.0, 152.4, 129.7, 128.8, 115.8, 107.4 and 56.7 ppm; MS m/z 182 (M + H)⁺. HPLC analysis (reverse phase Waters Symmetry C18 column, 150 mm × 3.9 mm, 5 μ m particle size, retention time = 17.1 min, mobile phase 5:95 aceto-nitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column temperature ambient) showed one peak, with a total purity of >99% (area %).

Preparation of 5-(2-Methoxy-4-nitrophenyl)oxazole (1) from 2-Methoxy-4-nitrobenzaldehyde (8). To a solution of 2-methoxy-4-nitrobenzaldehyde (8, 5.00 g, 27.5 mmol) in methanol (50 mL) was added tosylmethyl isocyanide (5.37 g, 27.5 mmol) and potassium carbonate (10.0 g, 72.3 mmol), and the resulting brown suspension was heated at reflux for 18 h, after which the dark brown solution was cooled to room temperature. The mixture was concentrated under reduced pressure, and the resulting black solid was partitioned between methylene chloride (50 mL) and water (50 mL). The organic layer was collected, and the aqueous layer was extracted with methylene chloride (2 \times 20 mL). The combined organic extracts were dried over MgSO₄, and the dark green solution was treated with an activated charcoal/ Clarion 550-activated bentonite clay²⁰/silica gel mixture (1: 1:2, 2 g). Clarification by vacuum filtration was followed by concentration under reduced pressure to provide 5-(2methoxy-4-nitrophenyl)oxazole (1) as a yellow solid (5.82 g, 96% yield): mp 150-152 °C; ¹H NMR (CDCl₃) δ 8.03 (s, 1H), 7.96 (s, 1H), 7.94 (s, 1H), 7.87 (s, 1H), 7.75 (s, 1H) and 4.10 (s, 3H); ¹³C NMR (CDCl₃) δ 156.0, 151.2, 148.2, 146.6, 129.0, 126.4, 123.3, 116.7, 106.5 and 56.6 ppm; MS m/z 221 (M + H)⁺. HPLC analysis (reverse phase Waters Symmetry C18 column, 150 mm \times 3.9 mm, 5 μ m particle size, retention time = 18.0 min, mobile phase 5:95 acetonitrile/(0.05% TFA in water) to 100:0 acetonitrile/(0.05% TFA in water) over 25 min, flow rate = 1.0 mL/min, detector at 254 nm, column temperature ambient) showed one peak, with a total purity of 97.1% (area %).

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