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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 113–117

Regioselective synthesis of 2,4,6-triaminopyridines

Rupa Shetty,[a,*] Duyan Nguyen,[a] Dietmar Flubacher,[b] Franziska Ruggle,[b] Andreas Schumacher,[b] Martha Kelly[a] and Enrique Michelotti[a]

[a]*Department of Chemistry, Locus Pharmaceuticals, Four Valley Square, 512 Townshipline Road, Blue Bell, PA 19422, USA*
[b]*Solvias AG, Klybeckstrasse 191, CH-4002 Basel, Switzerland*

Received 1 December 2005; revised 27 October 2006; accepted 30 October 2006
Available online 21 November 2006

Abstract—A regioselective synthesis of 2,4,6-trisubstituted pyridine is described starting from 2,6-dibromo-4-nitropyridine. All three different regioisomers of the 2,4,6-triamino substituted pyridine have been synthesized in four to five steps. The method described is a general route to unsymmetrical 2,4,6-trisubstituted amino pyridines.

The 2,4,6-triamino substituted pyridines have been of much interest to us as a recurring motif in many structures derived from our computationally driven drug design process.[1] There are numerous examples of triamino substituted pyridines in the literature which are of biological relevance.[2] Of particular interest to us were all possible regioisomers of 2,4,6-trisubstituted pyridines bearing a biphenyl amine, a pyridyl ethylamine and an amino group as depicted in Figure 1.

Our initial effort to synthesize these substituted pyridines was based on the reports by Angiolini et al.[3] The synthesis comprises two sequential nucleophilic substitutions of the fluorine atoms of commercially available pyridine **4**, followed by a hydrogenolytic removal of chlorine atoms (Scheme 1). This methodology is limited however by the amines that could be used, and also the sequence in which they can be used. The first nucleophilc substitution must be done with an arylamine since it is not reactive enough for the second nucleophilic substitution. Also, a high temperature is needed for the reaction with primary amines. The second disadvantage was the difficulty in the removal of the chlorine atoms and finally, only one regioisomer was accessible.

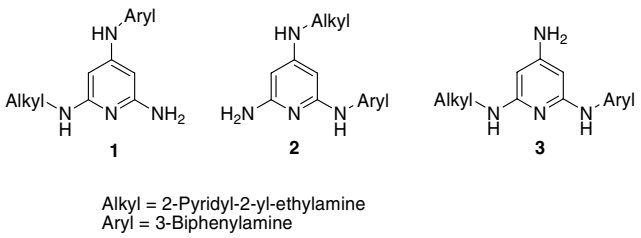

Figure 1.

In order to access all three regioisomers, we focused our synthetic efforts towards utilizing 2,6-dibromo-4-nitropyridine-*N*-oxide **7** as a starting material which can be readily synthesized in large quantities as described in the literature.[3] The 2,6-dibromo-4-nitropyridine-*N*-oxide **7** was converted to 2,4,6-tribromopyridine-*N*-oxide **8** by treatment with acetyl bromide in acetic acid as described by Neumann.[5] However, this procedure gave a very low yield (<5%) of the desired 2,4,6-tribromopyridine-*N*-oxide **8**. In order to improve the yield of this reaction other conditions were explored. We found that when hydrogen bromide was used as the bromide source, the reaction showed a remarkable improvement in yield and proceeded in greater than 90% yield. 2,6-Dibromo-4-nitropyridine *N*-oxide **7** was reduced to 2,6-dibromo-4-nitropyridine **9** by treatment with PBr_3 (Scheme 2).[4]

Two complementary routes starting from either **8** or **9** were developed to access the regioisomers of 2,4,6-trisubstituted pyridines. These routes exploit the differences in the regioselectivity of nucleophilic substitution for the intermediates. In the case of *N*-oxide **8**, the nucleophilic aromatic substitution occurs alternately at the 2- and 6-positions of pyridine without affecting the 4-position, giving a 5:1 ratio of mono-substituted to bis-substituted products. In the case of pyridine **9**, the

* Corresponding author. Tel.: +1 215 358 2037; fax: +1 215 358 2030; e-mail: rshetty@locuspharma.com

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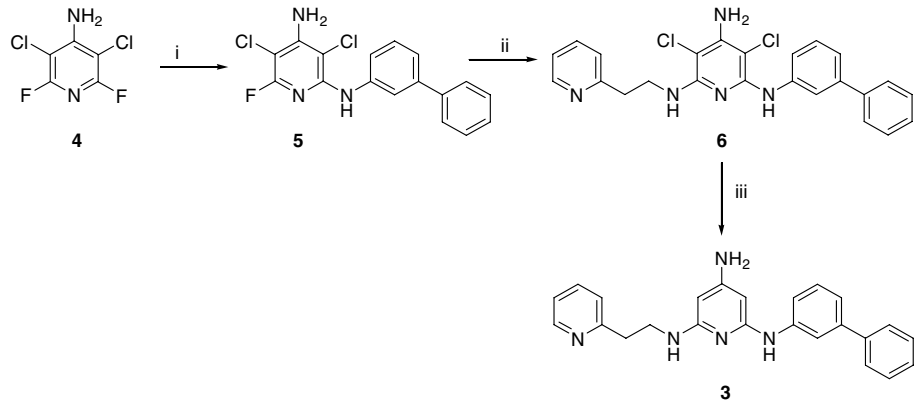
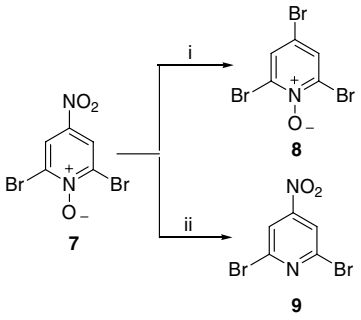
doi:10.1016/j.tetlet.2006.10.159



Scheme 1. Reagents and conditions: (i) 3-biphenyl amine, 150–180 °C, microwave 60 min, 10%; (ii) 2-pyridyl-2-yl-ethylamine, 160 °C, microwave 20 min, 75%; (iii) H_2, Pd/C 10%, 60 psi, MeOH, 18 h, 17%.

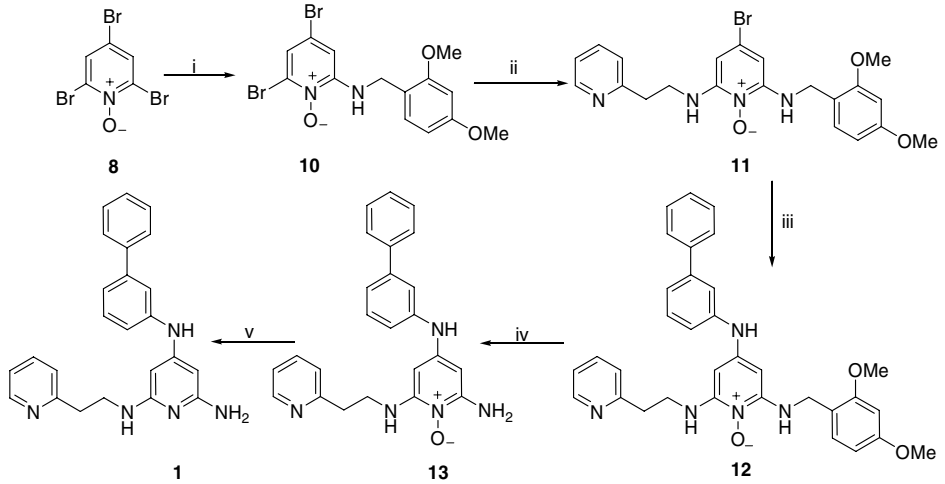


Scheme 2. Reagents and conditions: (i) HBr, AcOH, 60 °C, 2 days, 93%; (ii) PBr_3, $CHCl_3$, reflux, 19 h, 78%.

4-position is more susceptible towards nucleophilic aromatic substitution. The two different synthetic routes developed take advantage of these differences in reactivities and different sequences of addition of various nucleophiles to synthesize the three regioisomers of the 2,4,6-trisubstituted pyridines.

The synthesis of regioisomer **1** is described in Scheme 3. The 2,4,6-tribromo pyridine-*N*-oxide **8** is reacted with 2,4-dimethoxybenzyl amine at a 70 °C in toluene to yield the mono-substituted product **10** in 70% yield.[4] The 2,4-dimethoxybenzyl amine serves as a protected amino group, which can then be deprotected under acidic conditions. The added advantage of using the 2,4-dimethoxybenzyl amine is the control it provides in introducing the amino group, since using ammonia as a nucleophile does not give any selectivity towards mono-substitution.[4,5] The mono-substituted product was then reacted with 2-pyridin-2-yl-ethylamine in 2-methoxyethanol at 130 °C to yield the unsymmetrically di-substituted pyridine **11**. The second substitution requires higher temperature and longer reaction times. The reaction time however could be decreased by subjecting the reaction to microwave conditions. The di-amino substituted pyridine **11** was then reacted with biphenyl amine under standard Buckwald conditions[7] to yield 2,4,6-triamino substituted pyridine-*N*-oxide **12**. 2,4-Dimethoxybenzyl group was cleaved with TFA to give the amine and the *N*-oxide was reduced to yield compound **1**.[4]

Using this sequence of reactions all three of the regioisomers **1**, **2** and **3** can be accessed. However, the nucleo-



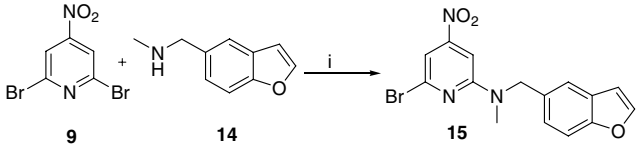
Scheme 3. Reagents and conditions: (i) 2,4-dimethoxybenzylamine, 70 °C, 2 h, 70%; (ii) 2-pyridyl-2-yl-ethylamine, 2-methoxyethanol, 130 °C, 18 h, 94%; (iii) 3-biphenylamine, $Pd_2(dba)_3$, *rac*-BINAP, NaO*t*Bu, toluene, 100 °C, 18 h, 37%; (iv) TFA, DCM, 18 h, 69%; (v) Fe, AcOH, 100 °C, 2 h, 26%.

philic aromatic substitution proceeds in much lower yield when an aryl amine is used. The yield of the reduction of *N*-oxide was also poor. Therefore we explored alternate synthetic routes which did not involve *N*-oxide as the starting material.

This alternate synthetic route utilizes 2,6-dibromo-4-nitropyridine **9** as the starting material. There is a precedence in the literature for nucleophilic displacement of the nitro group by either thiolate or alkoxide salts.[6] The displacement of the nitro group by either primary or secondary amines was reported under thermal displacement conditions using the amine as the solvent.[6] Also reported is the displacement of the nitro group with the Na salt of an arylamine and by aliphatic primary amines using organic bases.[8] In the case of the 2,6-dibromo-4-nitropyridine **9** thermal displacement with secondary amine **14** resulted in the displacement of 2-bromide to give **15** as shown in Scheme 4. This is in contrast to what is observed in the case of 2,6-dichloro-4-nitropyridine where thermal nucleophilic displacement conditions result in the displacement of the nitro group.[8]

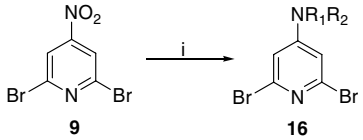
We then explored conditions that would selectively displace the nitro group of pyridine **9** using a variety of amines. We found that using the lithium salt of amines to displace the nitro group is more versatile with respect to the types of amines that could be introduced. As shown in Scheme 5, the substitution of the nitro group of **9** with the lithium salt of amine at −78 °C yielded 4–amino substituted 2,6-dibromopyridine **16** exclusively in a 30–60% yield. The reaction worked with a variety of amines such as anilines, primary amines and secondary amines with yields in the range of 30–60%. This method provides a more convenient route to access various 4-amino-2,6-dibromopyridines. The investigated amines (R_1R_2NH) and overall yield of products **16** are reported in Table 1.

Taking advantage of the reaction conditions developed to introduce the amino group at the 4-position by displacement of the nitro group, all three regioisomers of



9 **14** **15**

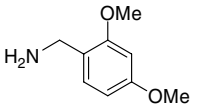
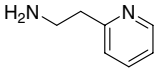
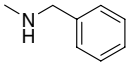
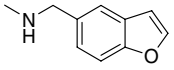
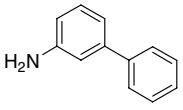
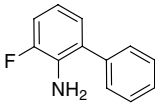
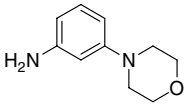
Scheme 4. Reagents and conditions: (i) 2-methoxyethanol, 100 °C, 2 h, 90%.



9 **16**

Scheme 5. Reagents and conditions: (i) NHR_1R_2 2 equiv, *n*-BuLi 2 equiv, −78 °C, 1 h.

Table 1. Investigated amines and overall yields

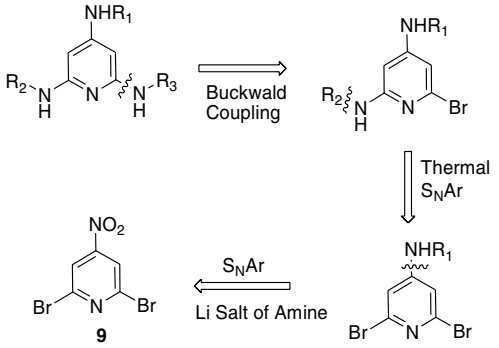
Entry	Amine (R_1R_2NH)	Yield of **16** (%)
1		40
2		40
3		32
4		30
5		57
6		51
7		48

All products were isolated and characterized by NMR and MS spectroscopy; unoptimized yields.

2,4,6-triamino substituted pyridine can be synthesized as shown in Scheme 6.

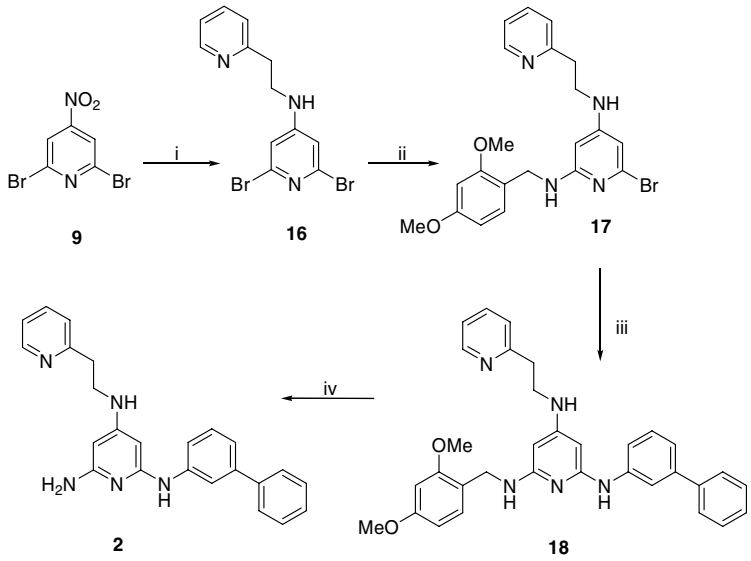
The general synthetic route first involves the displacement of the nitro group at 4-position of the pyridine **9** by the lithium salt of the desired amine. The second amine is then introduced at the 2-position by the reaction of 4-amino-2,6-dibromopyridine with the desired amine in 2-methoxyethanol at 130 °C. Finally the third amine is introduced at the 6-position via a Buckwald reaction.

To illustrate the feasibility of this general synthetic route, the synthesis of regioisomer **2** is shown in Scheme 7. 4-Nitro-2,6-dibromopyridine **9** is reacted with the lithium salt of 2-pyridyl-2-yl-ethylamine at −78 °C to give



9

Scheme 6. Retrosynthetic analysis for 2,4,6-triaminopyridines.



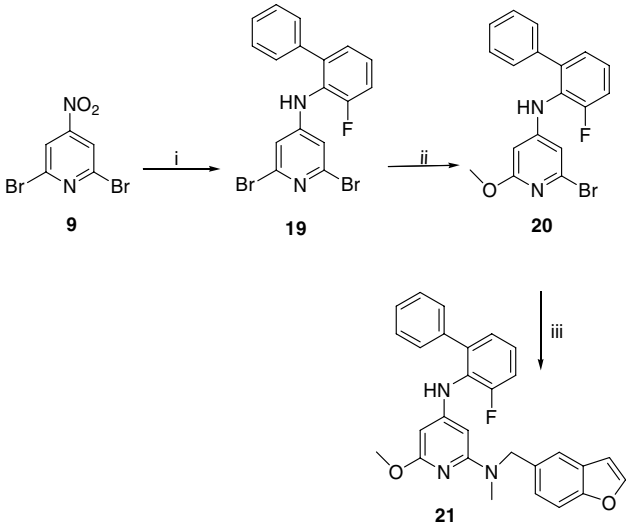
Scheme 7. Reagents and conditions: (i) 2-pyridyl-2-yl-ethylamine, *n*-BuLi, −78 °C, 2 h, 40%; (ii) 2,4-dimethoxybenzyl amine, 2-methoxyethanol, 130 °C, 18 h, 49%; (iii) 3-biphenylamine, $Pd_2(dba)_3$, *rac*-BINAP, NaO*t*Bu, toluene, 100 °C, 18 h, 46%; (iv) TFA, DCM, 6 h, 42%.

4-aminoethyl-2-pyridine **16**.[10] Dibromopyridine **16** is then treated with excess of 2,4-dimethoxybenzyl amine in 2-methoxyethanol at 130 °C to yield the 2,4-diamino substituted pyridine **17**.[11] The 3-biphenylamine was installed via a standard Buckwald coupling to give the triamino substituted intermediate **18**,[12] which was then treated with TFA to provide the final compound **2**.

This synthetic route provides access to all three regioisomers **1**, **2** and **3**. The 4-nitro group of compound **9** can be displaced by the lithium salt of aliphatic primary amines, secondary amines and arylamines, providing a handle to have varied amines at the 4-position. The thermal displacement of 2-bromide is suitable for primary and secondary alkylamines; however, arylamines are poor nucleophilic displacement partners in this reaction. Lastly the Buckwald reaction works well with both alkyl and arylamines.[7]

This synthetic sequence was expanded to make other 2,4,6-trisubstituted pyridines. Since the 4-nitro group of compound **9** can be displaced by thiolates and alkoxides,[6] it is possible to introduce alkoxy or thioalkoxy groups at the 4-position. Once the nitro group is displaced, 2-bromo can also be substituted by other nucleophiles such as alkoxides. Finally 6-bromide, which provide, a handle for the last substitution via a coupling reaction, can be used for other coupling reactions such as a Suzuki coupling.[9] The synthesis of compounds **21** in Scheme 8 is shown to illustrate the diversity of this synthetic approach. The nitro group is initially displaced with a biphenyl amine to give intermediate **19**, which when reacted with NaOMe in dioxane at 100 °C gives 2-methoxy compound **20**. The 6-bromo-2-methoxy pyridine can then undergo a Buckwald reaction to give **21**.

In conclusion two different general regioselective routes were developed for the synthesis of 2,4,6- triaminopyridine in 4–5 synthetic steps from easily accessible intermediates. The second synthetic route has one fewer step and provides a method to synthesize diverse 2,4,6-trisubstituted pyridines.



Scheme 8. Reagents and conditions: (i) 3-fluoro-2-biphenylamine, *n*-BuLi −78 °C, 2 h, 51%; (ii) 2 M MeONa, dioxane, 100 °C, 18 h, 78%; (iii) 3-biphenylamine, $Pd_2(dba)_3$, *rac*-BINAP, NaO*t*Bu, toluene, 100 °C, 18 h, 91%.

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10. *A typical procedure for nucleophilic displacement of 4-nitro with Li salt of amines:* To the 2-pyridyl-2-yl-ethylamine amine (0.3 mL, 2.2 mmol) in 5 mL of anhydrous THF at −78 °C was added *n*-BuLi (0.9 mL, 2.2 mmol) dropwise and stirred for 30 min. The salt formed was added via a canula to a solution of the nitro compound **9** in 5.0 mL of anhydrous THF at −78 °C dropwise. After complete addition, the reaction was stirred for 2 h and then quenched at −78 °C with EtOAc, washed with water followed by brine. The EtOAc layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was chromatographed on Silica gel using 10:1 DCM/MeOH to give 255 mg (40% yield) of **16**. MS (APCI): $m/z = 358.4$ [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.47 (d, $J = 4.7$ Hz, 1H), 7.56 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 2H), 6.50 (s, 2H), 5.59 (s, 1H), 3.44 (q, $J = 5.9$ Hz, 2H), 2.99 (t, $J = 6.2$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 158.9, 156.3, 149.5, 140.9, 137.1, 123.7, 122.2, 110.1, 42.3, 36.3.
11. *A typical procedure for thermal nucleophilic displacement of 2-bromides with amines:* To amine **16** (0.255 g, 0.71 mmol) in 1 mL of 2-methoxyethanol was added 2,4-dimethoxybenzyl amine (1.19 g, 7.1 mmol) and the reaction mixture was sealed and heated at 130 °C for 18 h. The reaction mixture was cooled to room temperature, concentrated, diluted with EtOAc. The organic layer was washed with bicarbonate, followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was chromatographed on Silica gel using 10:1 DCM/MeOH to give 140 mg (49% yield) of **17**. MS (APCI): $m/z = 443.6$ [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.53 (d, $J = 4.7$ Hz, 1H), 7.59 (dt, $J = 7.6$, 1.6 Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.15–7.09 (m, 2H), 6.43 (d, $J = 2.1$ Hz, 1H), 6.40 (dd, $J = 8.1$, 2.3 Hz, 1H), 6.02 (d, $J = 1.6$ Hz, 1H), 5.42 (d, $J = 1.6$ Hz, 1H), 4.85 (t, $J = 5.9$ Hz, 1H), 4.74, (t, $J = 5.3$ Hz, 1H), 4.25 (d, $J = 6.1$ Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.46 (q, $J = 6.2$ Hz, 2H), 3.00 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 160.5, 159.8, 158.6, 156.5, 149.6, 141.1, 136.8, 129.7, 123.6, 121.9, 119.3, 104.1, 102.1, 98.7, 86.0, 55.6, 55.5, 42.4, 41.7, 37.0.
12. *A typical procedure for Buckwald coupling to introduce the third amine*: In a tube (designed for microwave reactions) was added bromopyridine **17** (0.100 g, 0.23 mmol), 3-aminobiphenyl (0.19 g, 1.13 mmol), NaO*t*Bu (0.110 g, 1.1 mmol), *rac*-BINAP (3 mg, 0.004 mmol), $Pd_2(dba)_3$ (4 mg, 0.004 mmol), 1 mL of toluene and bubbled with argon. The tube was sealed and the reaction was heated at 100 °C for 18 h. The reaction was cooled to room temperature and water (2.0 mL) was added, followed by 3.0 mL of 1 N HCl. The resulting aqueous solution was extracted with (3 x 30 mL) CH_2Cl_2. The combined organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated. The crude mixture was chromatographed on Silica gel using 10:1 DCM/MeOH to give 55 mg (46% yield) of **18**. MS (APCI): $m/z = 532.9$ [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.51 (d, $J = 4.1$ Hz, 1H), 7.58–7.53 (m, 3H), 7.48 (t, $J = 1.9$ Hz, 1H), 7.42–7.37 (m, 2H), 7.35–7.29 (m, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.17 (td, $J = 7.5$, 1.3 Hz, 1H), 7.13–7.07 (m, 2H), 6.46–6.39 (m, 2H), 6.18 (s, 1H), 5.60 (d, $J = 1.4$ Hz, 1H), 5.21 (d, $J = 1.4$ Hz, 1H), 4.58 (t, $J = 6.0$ Hz, 1H), 4.39 (t, $J = 5.5$ Hz, 1H), 4.33 (d, $J = 5.9$ Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.48 (q, $J = 6.3$ Hz, 2H), 3.01 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 160.3, 159.6, 159.5, 158.6, 156.9, 155.6, 149.6, 142.4, 142.1, 141.5, 136.8, 129.8, 129.6, 128.9, 127.5, 127.4, 123.6, 121.7, 120.8, 120.3, 119.2, 119.0, 104.1, 98.7, 82.7, 81.8, 55.6, 55.5, 42.8, 41.7, 37.6.