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Concise Synthesis of Key Intermediates of Pyriftalid and Paquinimod via Hydrogenation Method

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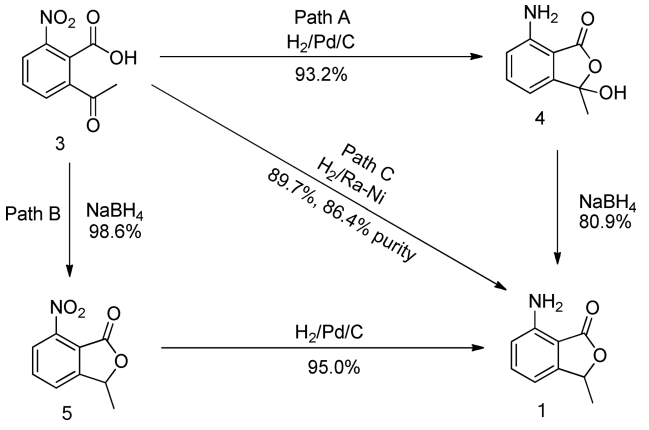
Supporting Information

ABSTRACT: An efficient and scalable synthesis of 7-amino-3-methylisobenzofuran-1(3*H*)-one (**1**) and 2-amino-6-ethylbenzoic acid (**2**) has been developed via a one-step catalytic hydrogenation. The triethylammonium salt of 2-acetyl-6-nitrobenzoic acid was used as the starting material and **1** was prepared in a biphasic solvent system of toluene/H_2O, while **2** was obtained when the solvent was replaced with H_2O. Intermediates **1** and **2** could be used to synthesize Pyriftalid and Paquinimod, respectively.

INTRODUCTION

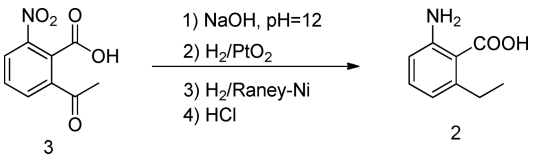
Pyriftalid, an acetolactate synthase (ALS) inhibitor to block the biosynthesis of branched-chain amino acids, can be used to control *Echinochloa*, *Leptochlao*, *Brachiaria*, *Setaria*, and *Ischemeum spp* for the improvement of rice production.[1−3] 7-Amino-3-methylisobenzofuran-1(3*H*)-one **1** is used as a key intermediate in the synthesis of Pyriftalid. Compound **1** can be prepared from 2-acetyl-6-nitrobenzoic acid **3** (Scheme 1), via a two-step reduction with hydrogen and $NaBH_4$ respectively in 75.4% overall yield (Path A) or 93.7% yield when the order of reducing agents is reversed (Path B). However, usage of $NaBH_4$ leads to a relatively high cost, and the two-step methods result in inefficient production. Alternatively, **1** can also be obtained directly by catalytic hydrogenation from **3** in 89.7% yield (Path C), with an unacceptable purity of 86.4%, which restricts its application in industry.[4]

Scheme 1. Reported Synthetic Route of Key Intermediate 1



Paquinimod belongs to the class of 3-quinolinecarboxamide derivatives, whose molecular target has been identified as S100A9 protein. A phase II study of Paquinimod for patients with systemic lupus erythematosus (SLE) has been completed.[5] 2-Amino-6-ethylbenzoic acid **2** is the key intermediate used to prepare paquinimod.[6,7] Compound **3** is also used as the starting material to prepare **2**, via two-step reduction by catalytic hydrogenation, with PtO_2 as catalyst first, and then Raney-Ni, in 90.0% overall yield (Scheme 2).[8] Obviously, the catalyst PtO_2 increases the cost dramatically; also, the continuous usage of two catalysts results in inefficient production and inconvenient catalyst recovery.

Scheme 2. Reported Synthetic Route of Key Intermediate 2



In order to explore an economical and industrial process for the production of **1** (for Pyriftalid) and **2** (for Paquinimod), we intended to develop a novel one-step catalytic hydrogenation method, using **3** as the starting material.

RESULTS AND DISCUSSION

As previously reported,[4] reduction of **3** in a single step afforded **1** in low yield and purity. On this basis, we investigated several types of catalysts and solvents, aiming to improve the yield and purity (Table 1). The reduction process follows the order **3**−**4**−**1**−**6**−**2**.[8,9] The nitro of **3** was reduced to give amino compound **4**, and the benzyl hydroxyl of **4** was then reduced to give lactone compound **1**. Partial hydrolysis of **1** produced **6**, and the benzyl hydroxyl of **6** was subsequently reduced to obtain **2**. Raney-Ni was unable to reduce **4** completely unless HCOOH was added, but 14.69% **2** was generated under these conditions (entries 1, 2). As Pd/C was screened, HCOOH did not work and Pd-ethylene diamine complex also turned out to be ineffective (entries 3, 4). Toluene appeared to be a better solvent (entry 6); when H_2O was added, only 2.60% **4** remained and the purity of **1**

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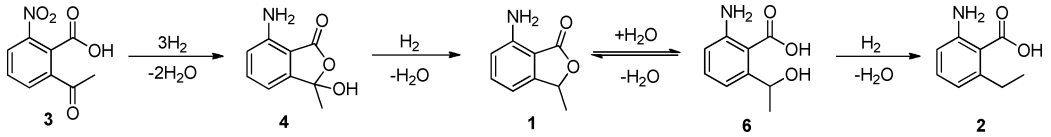
Table 1. Conditions for the Hydrogenation of 3



entry[a]	catalyst	solvent	pressure (atm)	T/t (°C/h)[b]	HPLC (%)[c] 4	1	2
1	R-Ni	ethanol	10	80/20	30.89	46.96	15.30
2	R-Ni	ethanol/HCOOH[d]	10	80/20	ND	72.32	14.69
3	Pd/C	ethanol/HCOOH[d]	5	110/24	74.90	7.20	0.13
4	Pd/C (en)[e]	ethanol	10	110/60	37.02	39.53	1.42
5	Pd/C	dioxane	5	110/24	54.82	37.58	0.78
6	Pd/C	toluene	10	110/18	9.33	72.30	1.95
7	Pd/C	toluene/H_2O[f]	10	110/18	2.60	86.73	1.21
8	R-Co	toluene	10	110/18	72.53	0.39	ND
9	Pt/C	toluene	10	110/18	89.67	4.44	ND

[a]Reaction conditions: **3** (2.00 g), catalyst (0.40 g), solvent (50 mL), autoclave, Model 4760 Pressure Reaction Apparatus, Parr Instrument Company, Moline, IL USA, 300 mL. [b]Bath temperature. [c]Compositions were calculated from HPLC area. [d]2.5 mL of HCOOH was added. [e]Pd-ethylene diamine complex;[10] [f]10 mL of H_2O was added.

Scheme 3. Proposed Reduction Process of Triethylammonium Salt of 3 in Toluene/H_2O

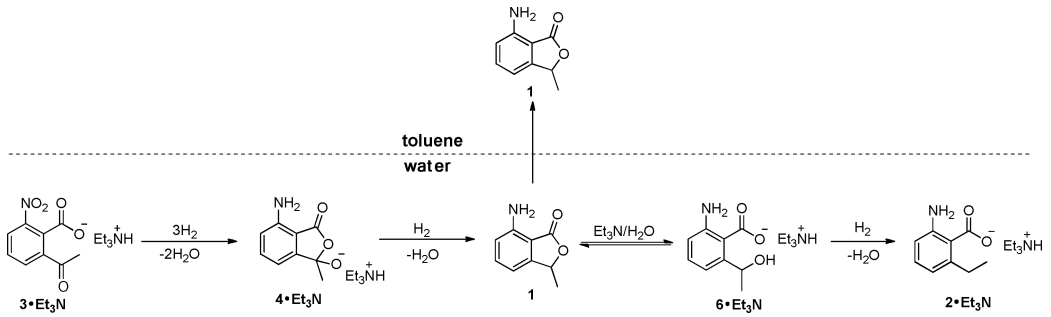
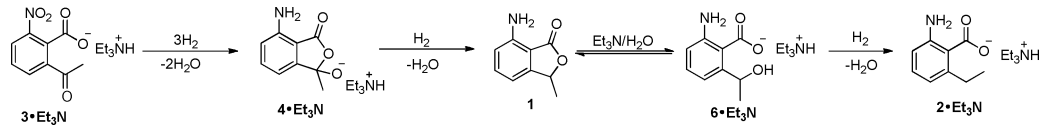


Table 2. Conditions for Reduction of Triethylammonium Salt of 3 To Prepare 1



entry[a]	catalyst	pressure (atm)	T/t (°C/h)[b]	HPLC (%)[c] 4	1	6	2	yield[d] (%)
1	Pd/C	15	120/17	0.71	98.45	0.85	ND	63.9
2	R-Ni	15	120/17	ND	96.68	ND	0.20	76.0
3	R-Ni	15	100/14	ND	99.52	ND	0.14	87.5
4	R-Ni	15	80/6	ND	98.47	0.22	ND	91.3
5	R-Ni	15	80/8	ND	98.70	ND	ND	95.7
6	R-Ni	15	80/14	ND	98.89	0.09	ND	95.1
7	R-Ni	15	60/10	4.08	95.08	ND	ND	27.9
8[e]	R-Ni	15	60/10	64.65	5.28	1.61	0.08	ND
9	R-Ni	4	80/8	0.52	99.17	ND	ND	98.5
10[f]	R-Ni	4	80/8	0.09	99.60	ND	ND	98.3
11[f]	R-Ni	5	80/8	ND	99.68	ND	ND	97.7

[a]Reaction conditions: Triethylammonium salt of **3** (3.00 g), catalyst (0.50 g), toluene (30 mL), H_2O (5 mL), the same autoclave as shown in Table 1. [b]Bath temperature. [c]Compositions of toluene phase were calculated from HPLC area. [d]Isolated yield of **1**. [e]Compositions of aqueous phase of entry 7. [f]Reused Raney-Ni.

dramatically increased to 86.73% (entry 7). Both Raney-Co and Pt/C were ineffective catalysts,[13] as compound **4** was obtained as the main product (entries 8, 9). The best result as shown in entry 7 was still not practical enough for scale-up production.

Based on the results of Table 1, it was clear that stopping the reduction at lactone **1** would be challenging. Separating **1** from the system as the reaction proceeds would be an attractive solution. Fortunately, **1** is the only compound without an acidic

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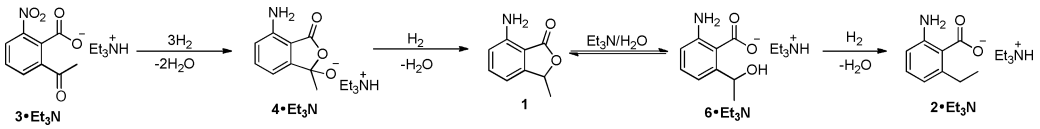
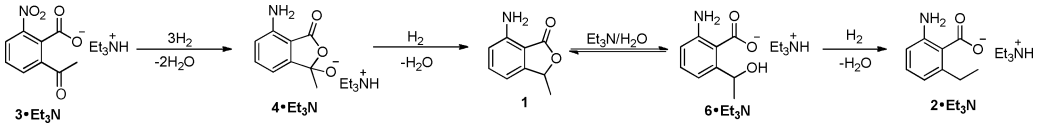
Table 3. Conditions of Raney-Ni for Reduction of Triethylammonium Salt of 3 To Prepare 2



entry[a]	base	pressure (atm)	T (°C)[b]	HPLC (%)[c] 4	1	6	2	yield[d] (%)
1	not added	15	80	0.17	33.12	1.34	64.05	ND
2	not added	14	120	0.33	21.38	0.88	75.09	ND
3	NaOH[e]	20	80	0.68	39.12	3.36	7.42	ND
4	ammonia[f]	20	80	59.50	0.22	ND	ND	ND
5	Et_3N (1.0 equiv)	18	120	ND	9.53	0.63	89.34	ND
6	Et_3N (2.0 equiv)	18	120	ND	1.04	0.48	98.30	93.6
7	Et_3N (2.0 equiv)	20	110	ND	6.61	0.59	92.89	ND
8	Et_3N (2.0 equiv)	20	100	ND	22.92	1.52	74.59	ND
9	Et_3N (2.0 equiv)	14	120	ND	1.57	0.86	97.14	94.2
10	Et_3N (2.0 equiv)	11.5	120	ND	0.56	0.72	98.22	94.5
11	Et_3N (2.0 equiv)	9.5	120	ND	4.77	1.79	93.45	ND

[a]Reaction conditions: triethylammonium salt of **3** (6.20 g), Raney-Ni (1.00 g), H_2O (45 mL), 8 h, the same autoclave as shown in Table 1. [b]Bath temperature. [c]Compositions of reaction mixture were calculated from HPLC area. [d]Isolated yield of **2**. [e]The starting material included **3**, 1.1 equiv of NaOH. [f]The starting material included **3**; adjust the reaction mixture to pH 11.0 with ammonia.

Table 4. Conditions of Pd/C for Reduction of Triethylammonium Salt of 3 To Prepare 2



entry[a]	Pd/C (g)	pressure (atm)	T (°C)[b]	HPLC (%)[c] 4	1	6	2	yield[d] (%)
1	1.00	15	80	10.58	41.10	1.03	47.25	ND
2	1.00	15	90	0.96	5.64	1.38	92.02	ND
3	1.00	11	100	0.30	ND	1.39	98.22	92.7
4	1.00	5	100	23.17	40.17	0.41	36.07	ND
5	0.50	15	100	10.10	20.55	0.80	68.54	ND

[a]Reaction conditions: triethylammonium salt of **3** (6.20 g), H_2O (45 mL), 8 h; the same autoclave as shown in Table 1. [b]Bath temperature. [c]Compositions of reaction mixture were calculated from HPLC area. [d]Isolated yield of **2**.

group in the reduction process. Lactone **1** was further found to be soluble in toluene but insoluble in weak alkaline water (pH = 10). Based on this fact, **3** was prepared as its triethylammonium salt, and toluene/H_2O was selected as the biphasic solvent system. In principle, the reduction would proceed in water; however, as soon as lactone **1** is generated it presumably would partition more favorably into the toluene layer and not be over-reduced (Scheme 3).

Various conditions were investigated in the biphasic solvent system (Table 2). When Pd/C was chosen as the catalyst, the yield of **1** was 63.9% (entry 1). Raney-Ni turned out to be a promising catalyst, as **1** was obtained in higher yield compared to Pd/C in the same conditions (entry 2). The yield of **1** increased significantly to 95.7% at a lower temperature of 80 °C (entry 5); when the temperature was reduced to 60 °C, the yield dropped to 27.9%, and **4** became the main product which existed in aqueous phase in the form of its triethylammonium salt (entries 7, 8). The yield was 95.1% when the reaction time was prolonged to 14 h (entry 6), which indicated **1** was stable at 80 °C. At a lower pressure of 4 atm, **1** was obtained in higher purity and yield (entry 9). Consequently, the reduction was performed as shown in entry 9, and Raney-Ni could be recovered more than three times (entries 10, 11). After the reduction was complete, the toluene layer was separated, followed by evaporation of the solvent, affording **1** in high yield and purity, while compounds **3**, **4**, **6**, **2** stayed in water in the form of their triethylammonium salts.

A further study focused on the synthesis of **2**, which was a key intermediate of Paquinimod. **2** can also be used for the preparation of substituted pyrazolo[1,5-*a*]pyrimidine derivatives as respiratory syncytial virus inhibitors and a nonpeptidic ligand for the molecular imaging of inflammatory processes.[11,12] The triethylammonium salt of **3** could be used to prepare **2** if the reduction was run in water (Table 3). As the reduction progressed, the lactone compound **1** could not be separated from the reaction system. Partial hydrolysis in alkaline solution would produce **6**. The benzyl hydroxyl of **6** would subsequently be reduced to obtain **2**. Various conditions were screened as shown in Table 3, the catalyst was still Raney-Ni. The reduction was initially carried out at 80 and 120 °C; less **1** remained as the temperature increased, but the results were still unsatisfactory (entries 1, 2). However, when the sodium or ammonium salt of **3** was used instead of its triethylammonium salt, only a trace of **2** was generated (entries 3, 4). Addition of an extra equivalent of Et_3N promoted the hydrolysis of **1** (entry 5). When 2.0 equiv of Et_3N was added, only 1.04% **1** remained and **2** was obtained in

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98.30% purity (entry 6). When the temperature was reduced to 110 and 100 °C, **1** could not be completely converted to **2** (entries 7, 8). The pressure could be reduced to 11.5 atm at a temperature of 120 °C to give 98.22% purity of **2** with only 0.56% of **1** remaining (entry 10). Further reduction of the pressure to 9.5 atm left 4.77% of **1** remaining after 8 h (entry 11). After the reduction was complete, the aqueous phase was adjusted to pH 3.0−3.5 with hydrochloric acid, the product was extracted with *n*-butyl acetate, and then the organic solvent was evaporated to obtain **2**. The reaction steps proceeded mostly by sequence; reaction process data could be found in the Supporting Information.

Conditions were investigated when the catalyst was Pd/C (Table 4). The reduction was initially carried out at 80 °C; 41.10% **1** remained (entry 1). When the temperature was increased to 90 °C, the result was still unsatisfactory (entry 2). When the reduction was carried out at 100 °C/11 atm, **1** could be completely converted to **2** (entry 3). At a lower pressure of 5 atm, 40.17% of **1** remained (entry 4). When the amount of Pd/C was reduced to 50%, the reduction could not be completed in 8 h (entry 5).

CONCLUSIONS

An efficient and practical one-step catalytic hydrogenation process for the synthesis of **1** and **2** has been developed. The triethylammonium salt of **3** was used as the starting material. Compound **1** was prepared in a biphasic solvent system of toluene/H_2O, while compound **2** was obtained when the solvent was replaced with water. The reduction was further applied on larger scale; both **1** and **2** were obtained in high, stable yield and purity, which could be used as the key intermediate to synthesize Pyriftalid and Paquinimod, respectively.

EXPERIMENTAL SECTION

General. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker 400 MHz spectrometer. Chemical shift data are reported in δ (ppm) from the internal standard TMS. Mass spectra was recorded on an Agilent 6120B series single quadrupole LC-MS. Melting points were measured on a WRS-1B apparatus. Reaction was monitored by HPLC, and purity was calculated from HPLC area. The HPLC analyses were recorded by a standard method on a Dionex UltiMate 3000 HPLC instrument using an Agilent Extend-C_{18} column (250 mm × 4.6 mm, 5 μm), 30 °C, 1 mL/min, 240 nm, 30 min. Mobile phase: A (0.1% phosphoric acid solution), B (acetonitrile). The initial gradient started with 30% of B, and at 15 min it was up to 70%; the ratio was maintained until 22 min. Then B was decreased to 30% at 23 min and continued to 30 min. Compound **3** was prepared according to the literature procedure in 84% overall yield;[4] mp 199.7−200.1 °C (lit mp 197−198 °C[4]). Pd/C was OURCHEM (China), 10% content, $H_2O \leq 1.0\%$. Raney-Ni was Energy Chemical (China), Ni ≥ 90%, 50 μm (water seal), used directly without additional wash. Pt/C was Energy Chemical, 10% on carbon, 55% water. Raney-Co was Aladdin, 50 μm (water seal). Other materials, solvents, and reagents were of commercial origin and used without additional purification.

*Triethylammonium 2-Acetyl-6-nitrobenzoate (Triethylammonium Salt of **3**).* Compound **3** (321.2 g, 1.54 moL) was added to toluene (1600 mL), and then triethylamine (170.8 g, 1.69 moL) was added. The reaction mixture was heated to 50 °C for 3 h. After cooling to 0 °C, the product was filtered off, washed with toluene (100 mL, 0−5 °C), and then dried under vacuum at 60 °C. The product was obtained as a white solid (465.2 g, 97.6%), with a purity of 99.20%. Mp 122.8−125.1 °C. Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.82; H, 7.18; N, 8.89.

*7-Amino-3-methylisobenzofuran-1(3H)-one (**1**).* The triethylammonium salt of **3** (341.1 g 1.10 moL) was added to water (570 mL) and toluene (1680 mL), and then Raney-Ni (56.7 g) was added to the mixture. After three vacuum/N_2 cycles to remove air, the stirred mixture was hydrogenated at 65 °C, 5 atm, for 8 h. When the reaction was determined to be complete by HPLC (compound **4** in aqueous phase ≤5%), the catalyst was filtered off. The filtrate was separated to give the organic phase, and the aqueous phase was extracted with toluene (1500 mL × 2). Then the organic phases were combined and evaporated under vacuum to give **1** as a white solid (170.4 g, 95.0%), with a purity of 99.42%. Mp 77.3−78.5 °C (lit mp 80−81 °C[4]); ^{1}H NMR (400 MHz, DMSO) δ 7.34 (dd, J = 8.1, 7.3 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 7.3 Hz, 1H), 6.25 (s, 2H), 5.50 (q, J = 6.6 Hz, 1H), 1.48 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 171.47, 152.83, 148.43, 136.06, 113.71, 108.29, 106.74, 77.46, 20.83.

*2-Amino-6-ethylbenzoic Acid (**2**).* The triethylammonium salt of **3** (322.4 g, 1.04 moL) was added to water (2300 mL), and then triethylamine (210.1 g, 2.08 moL) and Raney-Ni (52.0 g) were added to the mixture. After three vacuum/N_2 cycles to remove air, the stirred mixture was hydrogenated at 110 °C, 15 atm, for 8 h. When the reaction was complete as determined by HPLC (compound **1** ≤ 1.5%), the catalyst was filtered off. The pH was adjusted to 3.0−3.5 with hydrochloric acid. The mixture was extracted with *n*-butyl acetate (1800 mL× 3). Then the organic phase was combined and evaporated under vacuum to give **2** as a white loose solid (160.5 g, 93.5%), with a purity of 98.20%. Mp 107.3−108.2 °C (lit mp 107−109 °C[8]); ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 2H), 7.10−6.97 (m, 1H), 6.58 (dd, J = 8.2, 0.8 Hz, 1H), 6.42 (d, J = 7.0 Hz, 1H), 3.35 (s, 1H), 2.70 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 170.70, 149.05, 144.82, 131.45, 117.43, 115.08, 114.29, 28.14, 16.59.

The triethylammonium salt of **3** (6.20 g, 0.02 moL) was added to water (45 mL), and then Pd/C (1.00 g) was added to the mixture. After three vacuum/N_2 cycles to remove air, the stirred mixture was hydrogenated at 100 °C, 11 atm, for 8 h. The catalyst was filtered off. The pH was adjusted to 3.0−3.5 with hydrochloric acid. Then the mixture was extracted with *n*-butyl acetate (45 mL× 3). The organic phases were combined and evaporated under vacuum to give **2** as a white loose solid (3.06 g, 92.7%), with a purity of 98.50%.

*7-Amino-3-hydroxy-3-methylisobenzofuran-1(3H)-one (**4**).* Compound **3** (5.00 g, 23.9 mmoL) was added to ethanol (70 mL), and then Pd/C (3.70 g) was added to the mixture. After three vacuum/N_2 cycles to remove air, the stirred mixture was hydrogenated at 40 °C, 8 atm, for 5 h. After the catalyst was filtered off, the solvent was evaporated under vacuum to give **4** as a yellow solid (4.26 g, 99.5%), with a purity of 97.14%. Mp 158.9−160.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.53 (s, 1H), 7.35 (dd, J = 8.1, 7.4 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 7.2 Hz, 1H), 6.26 (s, 2H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.63, 151.96, 148.07, 136.17, 115.07, 108.66, 107.14, 106.14, 26.79.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00177.

^{1}H NMR, ^{13}C NMR, MS spectra for compounds **1**, **2**, **4**; reaction process data related to Raney-Ni for reduction of triethylammonium salt of **3** to prepare **2** (PDF)

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Notes

The authors declare no competing financial interest.

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