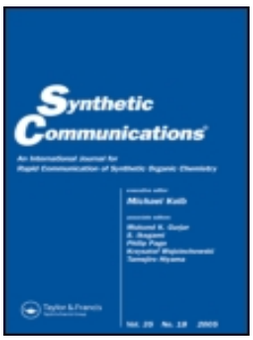

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EFFICIENT SYNTHESIS OF THE NUCLEUS OF ATORVASTATIN CALCIUM

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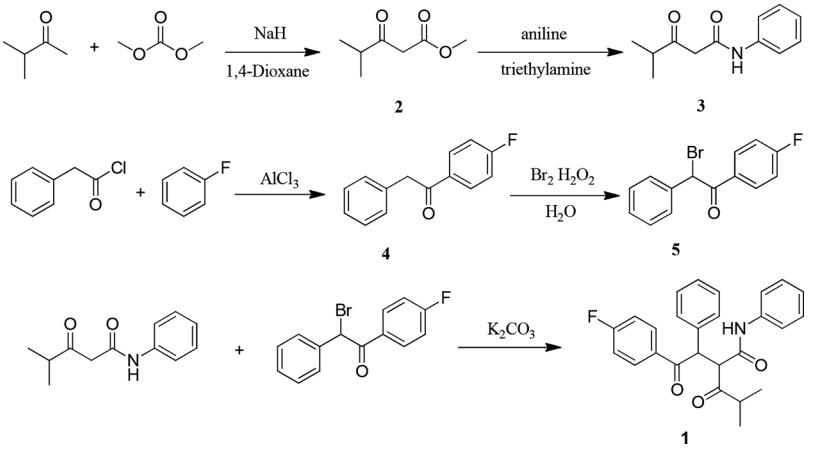
GRAPHICAL ABSTRACT



Abstract *An efficient synthetic route for the parent nucleus of atorvastatin calcium was successfully established through the modification of the related reactions. Under the optimized conditions, compound* ***1*** *was obtained in 61.2% yield (lit. 51.4%) from methyl isopropyl ketone via five steps. Two impurities generated by the aldol condensation of methyl isopropyl ketone were identified by gas chromatography–mass spectrometry and their generation can be inhibited by reducing the mixing time of methyl isopropyl ketone and NaH. One oxybromination protocol with hydrogen peroxide was employed to make the best of bromine. A debromination by-product was isolated and confirmed by* ^{1}H *NMR,* ^{13}C *NMR, and high-resolution mass spectrometry and its generation mechanism was discussed. The impurity can be inhibited by protecting the reaction from light and easily removed by recrystallization.*

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Keywords Atorvastatin calcium; parent nucleus; reaction mechanism; synthesis

INTRODUCTION

Atorvastatin calcium (tradename Lipitor; Fig. 1) is a synthetic HMG-CoA reductase inhibitor, which was discovered and developed by Warner-Lambert (now merged with Pfizer). It lowers plasma cholesterol level by inhibiting endogenous cholesterol synthesis and also reduces low density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglyceride levels.[1] It is an efficient hypolipidemic reducing the rate of mortality in coronary patients. 4-Fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,β-diphenylbenzene butyramide (**1**, Fig. 1) is known as the nucleus of atorvastatin calcium. Hence, the synthesis of compound **1** has been intensively studied.

As reported, compound **1** was normally synthesized from N-phenyl- 4-methyl-3-oxo-pentanamide as a key intermediate, which was conventionally obtained from malonic acid and acetone in four steps.[2] Later, the tedious and inefficient synthetic route mentioned previously was improved[3] through the condensation of aniline and isobutyryl Meldrum's acid in refluxing toluene to yield the key intermediate, but the total yield was still poor. In 2006, an alternative synthetic route was reported[4] (Scheme 1).

Although this route was feasible for large-scale production, the use of unfriendly thiazolidine derivatives and expensive 4-fluorobenzaldehyde made it industrially unattractive. Therefore, it remains a challenge to develop an efficient synthetic methodology for compound **1**.

Based on this work, herein we present a more efficient and higher-yielding synthetic route[5] to compound **1** with an overall yield of 61.2% (Scheme 2).

RESULTS AND DISCUSSION

Initially, the condensation reaction between methyl isopropyl ketone and dimethyl carbonate was examined, and the obtained results are summarized in Table 1.

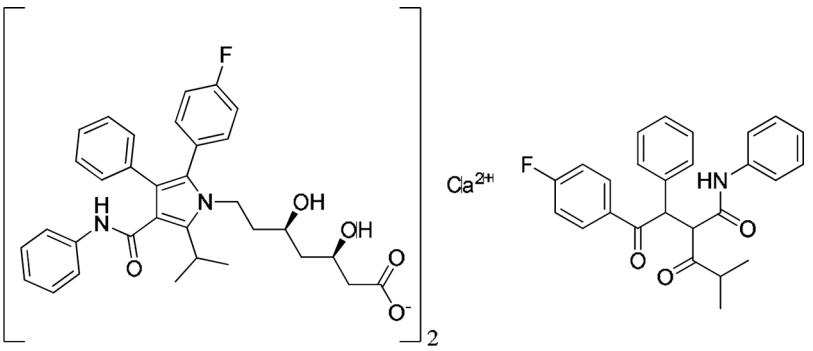
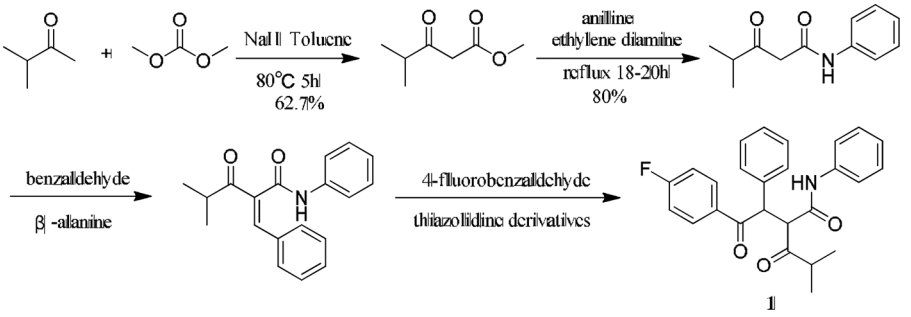
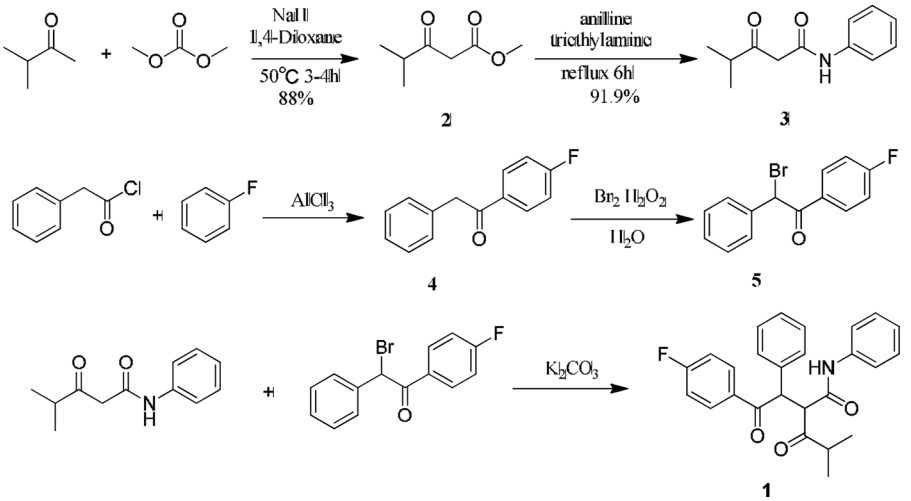


Figure 1. Structures of atorvastatin calcium and compound **1**.



Scheme 1. Synthetic route of compound **1** reported by Lai *et al.*.



Scheme 2. New synthetic route to compound **1**.

Table 1. Optimization of the condensation reaction

Entry	Solvent	Base (equiv)	T (°C)	Time (h)	Yield[a] (%)
1	1,4-Dioxane	CaH_2 (2.0)	30	18	Trace
2	Methanol	CH_3ONa (2.0)	30	18	19
3	1,4-Dioxane	Potassium t-butoxide (2.0)	30	18	38
4	THF	NaH (2.0)	30	6	89
5	Toluene	NaH (2.0)	30	16	41
6	Cyclohexane	NaH (2.0)	30	18	43
7	1,4-Dioxane	NaH (2.0)	30	6	88
8	1,4-Dioxane	NaH (1.5)	30	6	78
9	1,4-Dioxane	NaH (1.1)	30	6	55
10	1,4-Dioxane	NaH (2.2)	30	6	90
11	1,4-Dioxane	NaH (2.0)	10	18	54
12	1,4-Dioxane	NaH (2.0)	50	3.5	92
13	1,4-Dioxane	NaH (2.0)	70	3.5	90

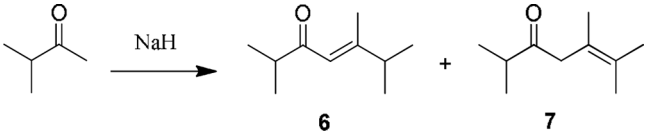
[a]Yields determined by GC.

As shown in Table 1, sodium methoxide, potassium t-butoxide, CaH_2, and NaH were employed in the reaction, only with NaH as a base, compound **2** was obtained in 88% yield (Table 1, entries 1–4). This indicated that NaH is a strong enough base to complete the deprotonation of methyl isopropyl ketone, leading to undergo efficient condensation reaction. Subsequently, several solvents were evaluated for this reaction (Table 1, entries 4–7). Obviously, the solvent polarity is quite important to the reaction, and thus the reaction proceeds smoothly in tetrahydrofuran (THF) or 1,4-dioxane. Because it is hard to isolate and recycle THF from the reaction mixture due to the formation of methanol during the process of reaction, 1,4-dioxane was chosen as the solvent for further optimization. Then, after screening NaH loading and temperature (Table 1, entries 7–13), the optimum conditions of the condensation reaction are 2.0 equiv. of NaH in 1,4-dioxane solvent at 50 °C.

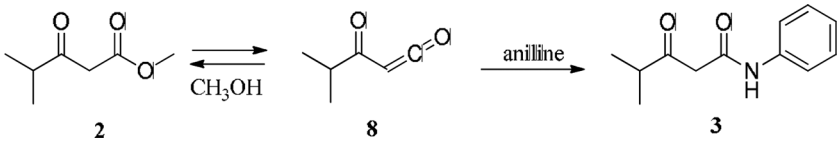
Unexpectedly, two by-products (10% of the total) were detected and confirmed by gas chromatography–mass spectrometry (GC-MS) as compounds **6** and **7**. By-products **6** and **7** were generated via the aldol condensation of methyl isopropyl ketone (Scheme 3). NaH, as a strong base, extracts the proton *alpha* to the carbonyl of methyl isopropyl ketone to form the carbon anion, which, in turn, leads to nucleophilic addition to another methyl isopropyl ketone and then intramolecular dehydration to **6** and **7**. Obviously, it is difficult to prevent the formation of these two by-products in this reaction. Fortunately, the side reaction can be inhibited by reducing the mixing time of methyl isopropyl ketone and NaH. After the examination of the mixing period, it was found that 10 min of stirring is appropriate after addition of methyl isopropyl ketone into a suspension of NaH, and only 2% of by-products were detected.

As described in Scheme 1, compound **3** was prepared by N-acylation of aniline with ester **2** as an acylating agent in the presence of ethylene diamine.[4b] In addition, a solution of ester **2** with 2 equiv. of aniline was stirred at 110 °C in a sealed tube for 20 h, and 4% of compound **2** was still remained by high-performance liquid chromatography (HPLC). As reported,[6,7] acetylketene **8** is a plausible intermediate (Scheme 4) for this reaction, and an equilibrium exists between ester **2** and acetylketene **8**, so removal of the formed methanol during the reaction is a prerequisite for obtaining a good yield of compound **3**. Thus, in this study, in order to avoid the side reaction induced by ethylene diamine, compound **3** was obtained in 91.9% yield (lit.[4b] 80%) in the presence of trimethylamine by removal of methanol in about 6 h.

Compound **4** was synthesized by Friedel–Crafts acylation of fluorobenzene with phenylacetyl chloride in the presence of aluminum chloride.[8] By employing dichloromethane as solvent, the acylation undergoes slowly to present compound **4** with 61% yield in 3 h, while it proceeds effectively to afford compound **4** with 90% yield in 1 h without solvent but with excess of fluorobenzene. Considering that



Scheme 3. Generation of by-products **6** and **7**.



Scheme 4. Proposed mechanism of N-acylation of aniline.

fluorobenzene can be easily recycled by distillation, employment of excess fluorobenzene for this acylation would be the best choice.

2-Bromo-1-(4-fluorophenyl)-2-phenylethanone **5** was obtained by bromination of compound **4** with a suitable brominating agent. Bromine is normally used for bromination reactions by virtue of extensive sources and low favorable *E*-factors.[9] Only 50% of the available bromine was utilized with the formation of HBr as a by-product. Thus, we developed one oxybromination protocol, which was based on the oxidation of HBr to bromine with hydrogen peroxide. This bromination method allows complete utilization of bromine atoms and therefore the atom economy is much greater. Moreover, this method also has the advantage of low cost, high atom efficiency, and environmental friendliness.

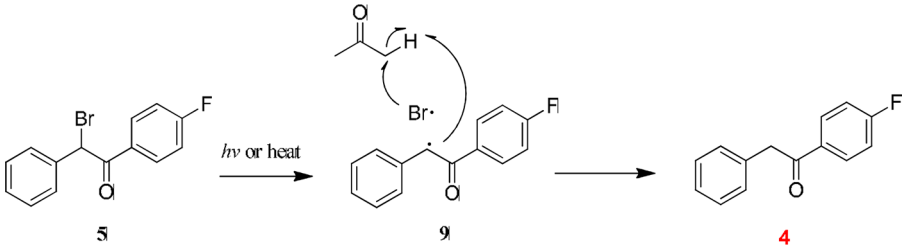
The last step was a nucleophilic substitution of compound **3** with compound **5** in the presence of a base. Initially, the effects of base were examined and summarized in Table 2, and it was found that potassium carbonate, as a base, presented better results than other bases. This indicated that potassium carbonate is the appropriate base to extract the acidic proton *alpha* to the carbonyl of compound **3**, which, in turn, leads to induce the nucleophilic substitution. Weaker or stronger bases would cause undesired side reactions, resulting in poor yield of compound **1**.

During the workup of this nucleophilic substitution to get compound **1**, a by-product (4.5% of the total) was isolated and confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS as compound **4**. When compound **5** and potassium carbonate were mixed in acetone, the compound **4** was not detected by HPLC. With the consideration of the instability of C-Br bond, a plausible debromination mechanism for compound **5** was proposed[12] (Scheme 5). The debromination reaction begins with homolysis of the C-Br bond induced by light or heat to produce radical **9** and bromine radical. Then radical **9** captures a hydrogen from the medium to form the compound **4**. Based on this debromination mechanism, protection of the reaction mixture from light could inhibit this side reaction. Indeed, when the reaction of compounds **3** and **5** proceeded in a sealed flask covered with aluminum foil, the amount of compound **4** in the mixture was reduced to less than 1.0%. Furthermore,

Table 2. Effects of base for the synthesis of compound **1**

Entry	Base	Time (h)	Yield[a] (%)
1	Na_2CO_3	10	50
2	K_2CO_3	5	80
3	NaOH	5	42
4	KOH	5	56
5	Triethylamine	5	60

[a]Isolated yields of products.



Scheme 5. Proposed mechanism for the formation of compound **4**.

compound **4** was easily removed through recrystallization in isopropyl alcohol. Thus, compound **1** with 99.8% purity was efficiently obtained in this way.

CONCLUSION

In conclusion, a cost-effective and high-yielding synthetic method for the nucleus of atorvastatin calcium **1** was established, and the involving reactions were systematically investigated. Two impurities generated by the aldol condensation of methyl isopropyl ketone were detected and confirmed by GC-MS. One oxybromination protocol was employed to make the best use of bromine. A debromination by-product generated in the last step was isolated and confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS, its formation mechanism was proposed, and it could be easily removed by recrystallization in isopropyl alcohol. Finally, compound **1** was obtained in 61.2% total yield and 99.8% purity.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers. The reaction of methyl isopropyl ketone and dimethyl carbonate was monitored by GC with a SE-54 (30 m) capillary column (Chromatographic Technology R&D Center, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences) and flame ionization detector (FID). The composition of the reaction mixture was identified by GC-MS equipped with HP-5 capillary column (30 m × 0.25 mm, 0.2 μm film thickness) and an ion trap MS detector. The other reactions were monitored by thin-layer chromatography (TLC) using commercial silica-gel plates. The purity of products was detected by high-performance liquid chromatography (HPLC) on Agilent 1,100 series instrument. Melting points were observed on YRT-3 melting-point tester. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III 600-MHz instrument. HRMS was measured on a MicrOTOF-Q II instrument.

Preparation of Methyl 4-Methyl-3-oxopentanoate[4b](2)

Methyl isopropyl ketone (10.00 g, 116.10 mmol) was added slowly to a suspension of sodium hydride (60% in mineral oil, 9.29 g, 232.25 mmol) in 1,4-dioxane (70 mL). The mixture was stirred at room temperature for 10 min. Dimethyl carbonate (15.70 g, 174.31 mmol) was added and the mixture was stirred at 50 °C for 3 h.

The mixture was cooled to room temperature, and acetic acid (14 mL) was slowly added. The precipitate was filtered and washed with 1,4-dioxane (20 mL). The filtrate was concentrated under vacuum. Compound **2** was collected at 80–85 °C under vacuum (~10 mbar) as colorless liquid (14.73 g, yield 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.69 (s, 3H), 3.48 (s, 2H), 2.68 (m, 1H), 1.01 (d, $J = 7.2$ Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 205.95, 167.38, 51.44, 46.23, 40.44, 17.26.

Preparation of N-Phenyl-4-methyl-3-oxo-pentanamide[4b] (3)

A mixture of compound **2** (5.00 g, 34.69 mmol), triethylamine (0.88 g, 8.70 mmol), and aniline (3.88 g, 41.62 mmol) in toluene (30 mL) was heated to 70 °C. The reaction mixture was stirred at 70 °C for 1 h and then gradually heated to 110–120 °C. The methanol formed during the reaction was distilled off together with some toluene for 5 h. After cooling to room temperature, the mixture was washed with 5% hydrochloric acid (30 mL) and water (2 × 30 mL). The organic phases were dried over anhydrous magnesium sulfate and then concentrated to give a red oil **3** (6.55 g, 91.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.23 (s, 1H), 7.09–7.55 (m, 5H), 3.59 (s, 2H), 2.73 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 210.4, 164.5, 137.6, 128.8, 124.5, 120.1, 47.7, 41.5, 17.6.

Preparation of 1-(4-Fluorophenyl)-2-phenylethanone[10] (4)

Powdered aluminum chloride (10.36 g, 77.89 mmol) was added to fluorobenzene (40 mL) cooled by an ice bath. Phenyl acetyl chloride (10.00 g, 64.93 mmol) was added dropwise and the mixture was stirred for 1 h at less than 10 °C. The mixture was poured slowly into a mixture of ice (30 g), water (20 mL), and 2 N hydrochloric acid (40 mL), and the obtained aqueous phase was extracted with dichloromethane (2 × 30 mL). The organic phases were combined, washed with 5% $NaHCO_3$ solution (30 mL), and concentrated to give the crude product. Then, the solid was dissolved in petroleum ether (30 mL) and heated to 80–85 °C for a while and then cooled to room temperature. White crystal appeared, and the crystal was filtered and dried to give **4** (12.51 g, 90% yield). Mp 81.8–82.5 °C (lit. mp 80–82 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.06–8.02 (m, 2H), 7.35–7.25 (m, 5H), 7.12 (t, $J = 8.4$ Hz, 2H), 4.26 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 196.05, 167.03, 164.49, 134.51, 133.05, 131.35, 131.26, 129.45, 128.77, 127.02, 115.87, 115.66, 45.49. HRMS (ESI), calcd.: $C_{14}H_{11}FO$ $[M+Na]^+$ m/z: 237.0794; found: 237.0687.

Preparation of 2-Bromo-1-(4-fluorophenyl)-2-phenylethanone[11] (5)

Compound **4** (5.00 g, 23.34 mmol) was suspended in water (15 mL) in a flask covered with aluminum foil. Five drops of 40% aqueous solution of HBr was added. The mixture was stirred at room temperature for 5 min, Br_2 (2.05 g, 12.84 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 5 h, and 30% aqueous solution of H_2O_2 (6.5 mL, 25.70 mmol) was slowly added. After 12 h, dichloromethane (30 mL) was added and the organic layer was washed with 5% aqueous sodium sulfite (10 mL) and 5% aqueous sodium chloride (2 × 20 mL) and then dried over anhydrous magnesium sulfate. The organic mixture was

concentrated to give a light yellow oil **5** (5.82 g, 85% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.01–7.98 (m, 2H), 7.49 (d, $J = 7.2$ Hz, 2H), 7.36–7.30 (m, 3H), 7.07 (t, $J = 8.6$ Hz, 2H), 6.32 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 189.33, 166.29, 164.59, 135.52, 131.69, 131.63, 130.04, 128.89, 128.74, 115.71, 115.57, 51.07.

Preparation of 4-Fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,β-diphenylbenzene Butyramide (1)

To a mixture of compound **3** (3.50 g, 17.06 mmol) and potassium carbonate (3.54 g, 25.61 mmol) in acetone (20 mL), a solution of compound **5** (5.00 g, 17.06 mmol) in acetone (5 mL) was added dropwise, and then the mixture was stirred at room temperature for 5 h. During the whole process, the flask was covered with aluminum foil. The mixture was filtered and the filter cake was washed with acetone (20 mL). The combined filtrate was evaporated to give the crude product. Isopropyl alcohol (30 mL) was added and the mixture was heated to 85–90 °C. After cooling to 0–5 °C, the resulting suspension was filtered, washed with isopropyl alcohol (5 mL), and dried in vacuum oven at 50 °C to afford **1** (5.70 g, 80% yield) as white solid with a purity of 99.8%. Mp 203–205 °C (lit. 206–209 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.20 (s, 1H), 8.13 (t, $J = 7.2$ Hz, 2H), 7.36–7.01 (m, 12H), 5.42 (d, $J = 11.4$ Hz, 1H), 4.87 (d, $J = 11.4$ Hz, 1H), 2.90 (m, 1H), 1.16 (d, $J = 7.2$ Hz, 3H), 0.93 (d, $J = 3.6$ Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 208.08, 196.42, 165.82, 165.01, 164.14, 138.11, 135.09, 132.15, 131.75, 131.69, 128.83, 128.67, 128.61, 127.52, 123.91, 119.63, 115.83, 115.69, 63.02, 51.75, 39.42, 18.80, 17.86. HRMS (ESI), calcd.: $C_{26}H_{24}FNO_3$ $[M\text{-}H]^-$ m/z: 416.1740; found: 416.1716.

SUPPLEMENTAL MATERIAL

Full experimental details, ^{1}H and ^{13}C NMR spectra, and HPLC traces can be accessed on the publisher's website.

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