Organic Process Research & Development **2006**, *10*, 28–32

Full Papers

Process Development of (1*S*,2*S*,5*R*,6*S*)-Spiro[bicyclo[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic Acid, (*R*)-α-Methylbenzenemethanamine Salt (LSN344309)

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Abstract:

Process development and a pilot-plant process for the synthesis of 4 and its resolution to obtain (1*S*,2*S*,5*R*,6*S*)-spiro[bicyclo-[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic acid, (*R*)-α-methylbenzenemethanamine salt (5) are described. Starting from the inexpensive raw 2-cyclopenten-1-one and sulfur ylide 1 the racemic bicyclo keto ester 2 was synthesized. Reaction of 2 with potassium cyanide and ammonium carbonate under Bücherer−Berg's reaction conditions affords racemic 3 in 80% yield. Hydrolysis of 3 followed by the resolution with (*R*)-(+)-α-methylbenzylamine gave 4 in excellent yield and purity under optimized conditions. The improvement of the original discovery process to accommodate safety and environmental requirements for scale-up in manufacturing facilities is also discussed.

Introduction

LY544344 hydrochloride **6** is a new chemical entity under investigation by Eli Lilly & Company as a potential treatment of neurological or psychiatric disorders related to the mammalian central nervous system (CNS).[1] Compound **5** is a key intermediate in the synthesis of **6**. The original route involved the synthesis of racemic hydantoin acid **4** followed by resolution using (*R*)-(+)-(α)-methylbenzyylamine in acetone/water (Scheme 1).[2−5] The synthesis of the racemic hydantoin acid comprising four chemical steps with three isolated intermediates is shown in Scheme 1.

Evaluation of the processes before scale up revealed some undesirable features such as: (a) emission of the air pollutants dimethyl sulfide and ethyl bromoacetate during the filtration in step 1 and (b) irreproducibility of the yield and purity of **5** when acetone/water was used as a crystallization medium.

Therefore, our development efforts were focused on addressing these issues and improving processing.

Herein, we describe the results of these efforts.

Results and Discussion

The bicyclic ketone **2** is readily synthesized by the reaction of 2-cyclopentenone with either a diazoester or with a sulfur ylide.[6,7] Although use of a diazoester avoids the odor and emission problems associated with the use of a sulfur ylide and particularly the sulfur ylide generated from **1**, the safety issues associated with handling diazoesters preclude their use in a commercial manufacturing setting. Thus, process development focused on the use of a sulfur ylide. In the initial discovery synthesis, the sulfonium salt **1** resulting from reaction of dimethyl sulfide and ethylbromoacetate was isolated as a crystalline solid. Both the isolation of **1** and its use in step two pose significant odor and volatile emission control problems. One attractive solution to this problem is the use of a nonvolatile polymeric sulfide in the formation of the sulfonium salt and corresponding ylide in steps 1 and 2. However, all our attempts to synthesize **2** using a polymeric sulfide in reaction with ethylbromoacetate to prepare the desired sulfonium salt and corresponding ylide were unsuccessful. Thus, efforts focused on odor and emission minimization by the in situ generation of **1**. Ideally, by combining steps 1 and 2, all processing involving the use or generation of dimethyl sulfide could be conducted in a closed vessel. The dimethyl sulfide would

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Published on Web 12/01/2005

10.1021/op049829e CCC: $33.50

Scheme 1. **Original process for the synthesis of LSN344309**

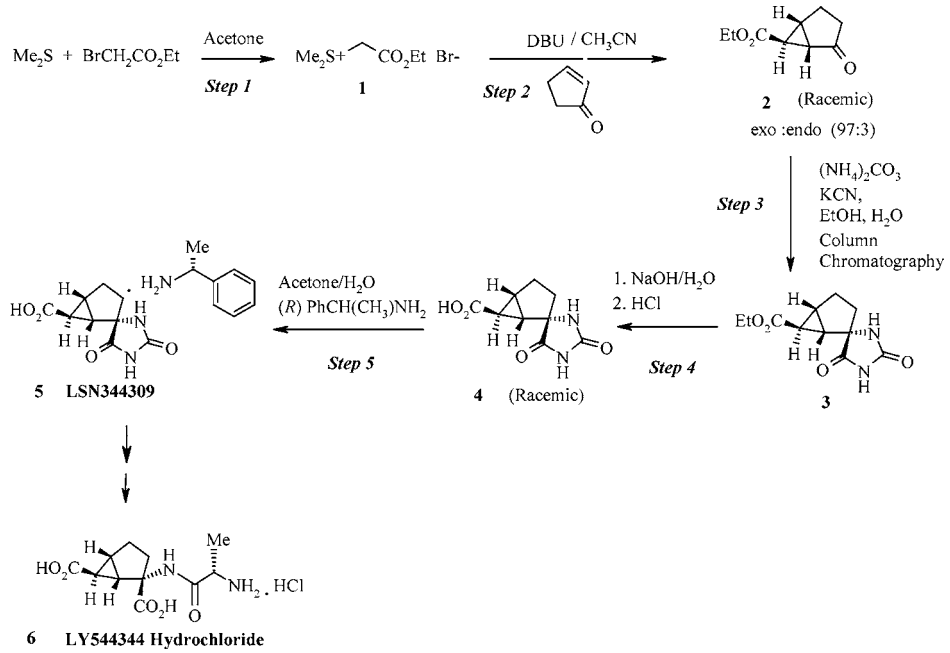


Table 1. **Solvent screening for the synthesis of 1 and 2**

solvent	isolated yield of **1** (%)	in situ yield of **2** (%)	combined steps 1 and 2 isolated yield of **2** (%)
acetone	81.7	61.2	43.5[a]
acetonitrile	60.0	88.7	75.9[a]
dichloromethane	56.3	85.4	35.9[a]
ethyl acetate	51.1	51.6	
tetrahydrofuran	46.9	50.1	
toluene	31.2	78.0	
methyl-*tert*-butyl ether	16.4	62.5	
heptane	13.8	28.9	
N,*N*-dimethylformamide	9.8	85.5	

[a] exo:endo (97:3).

Table 2. **Screening of bases for the formation of 2**

base	yield of **2**[a] (%)
1,8-diazabicyclo[5.4.0]undec-7-ene	77
1,1,3,3-tetramethylguanidine	77
1,5-diazabicyclo[4.3.0]non-5-ene	52
1,4-diazabicyclo[2.2.2]octane	0
N,*N*-diisopropylethylamine	0
triethylamine	0
pyridine	0
potassium carbonate/TBAB	0

[a] exo:endo (97:3).

Table 3. **Impacts of sequential addition times of DBU, and 2-cylopentenone on the yield of 3**

DBU addition time (min)	2-cyclopentenone addition time (min)	yield of **3** (%)
10	15	58.7
42	15	55.9
60	15	53.2
15	10	58.4
15	60	53.2
15	150	49.6

then be removed by distillation and destructive vapor incineration during reaction concentration and product isolation at the end of step 2.

A solvent screen was conducted to find a common solvent for the formation of **1** and its subsequent use in step 2. The results in Table 1 show that, while good yields of the sulfonium salt **1** are obtained in acetone, acetonitrile, and dichloromethane, the best combined step 1/step 2 process yield was obtained with acetonitrile.

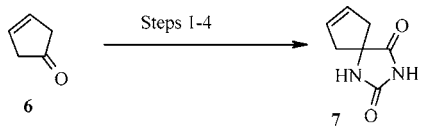
With the choice of acetonitrile made as the common solvent for steps 1 and 2, various bases were screened for their impact on the yield of **2**. The data in Table 2 indicate that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine gave the best yield of **2** with a ratio of exo/endo isomers of 97:3.

Thus, DBU was chosen as the base for the formation of the ylide due to its commercial availability. The crude oil of **2** was then purified by crystallization from heptane to obtain a 66% yield of the pure exo isomer.

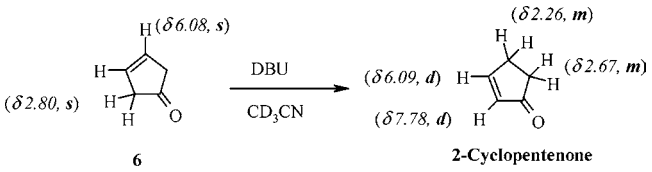
We believed omitting the isolation of intermediate **2** and continuing processing to form **3** by solvent exchange at the end of step 2 would improve process efficiency. However, there was concern that omitting the purification of **2** could affect the quality of **3**, but when this approach was actually tried, it performed adequately, and **3** was obtained in good yield without compromising purity (98−99%).

An important critical process parameter was observed during our process development wherein longer addition times for either DBU or 2-cyclopentenone lowered the yield of **3**. Further investigation confirmed this observation as indicated by the results in Table 3. Hence, the addition times of the DBU and 2-cyclopentanone were held to 15−20 min during the scale-up.

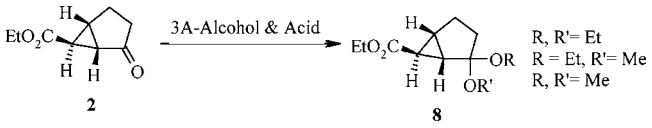
Scheme 2. **Potential formation of 7 from 6 employing chemistry for the synthesis of 4**



Scheme 3. **NMR study for the conversion of 6 to 2-cycopentenone by DBU**



Scheme 4. **Formation of ketals**



Prior to the manufacture of **3**, purchased 2-cylopenten-1-one was found to contain 3% 3-cyclopenten-1-one. This raised a concern for introduction of a new impurity such as **7** during Bücherer−Berg's reaction as shown in Scheme 2.

A literature survey revealed that compounds similar to **6** undergo rearrangement of the double bond in the presence of acid[8] or strong base.[9−13] Therefore, we expected **6** would also rearrange to 2-cyclopentenone in the presence of the base DBU. A study by NMR involving treatment of **6** in CD_3CN with a catalytic amount of DBU showed the conversion of **6** to 2-cyclopentenone. A change in the methylene and olefin proton resonances at δ 2.80 and 6.08 of **6** to the corresponding resonances in 2-cyclopentenone are shown in Scheme 3. Furthermore, subjecting **6** to the same reaction conditions for the conversion of 2-cyclopentenone to **3** gave the expected quality and yield for **3**. Therefore, our concern was alleviated by these results.

Another concern was the formation of ketals of **8** during the solvent exchange from *tert*-butyl methyl ether to 3A-alcohol in preparation for step 3 as shown in Scheme 4. These ketals did not undergo Bücherer−Berg's reaction to give **3**. A solution for this problem was achieved by the treatment of slightly acidic solution of **2** in *tert*-butyl methyl ether with aqueous sodium bicarbonate to remove traces of acid that promote the formation of ketals before the solvent exchange.

The formation of hydantoins **9** and **10** were performed using Bücherer−Berg's reaction conditions[14] as shown in Scheme 5. Thus, treatment of **2** with 1.1 equiv of potassium cyanide and 2 equiv of ammonium carbonate in a mixture

Scheme 5. **Bücherer−Berg's Reaction for the synthesis of 9 and 10**

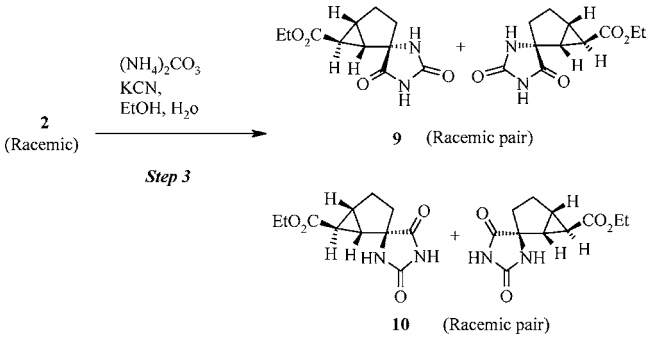


Table 4. **Solvent screening study for Bücherer−Berg's reaction**

solvent system	time for reaction completion (h)	in situ ratio of **9** and **10** %
MeOH	72	92:8
EtOH	58	89:11
EtOH/H_2O (1:1)	40	88:12
DMF/H_2O (1:1)	44	89:11
methanol/H_2O (1:1)	72	90:10
n-propanol/H_2O (1:1)	72	87:13
2-propanol/H_2O (1:1)	72	88:12
ethylene glycol/H_2O (1:1)	72	91:9
DMSO/H_2O (1:1)	72	83:17

of 1:1 ethanol/water at 60 °C for 5 h resulted in the formation of **3** (a mixture of the hydantoin esters **9** and **10**) in 80% yield. The diastereoisomeric ratio of **9** to **10** was 78:22. Recrystallization of this mixture from 2-propanol gave pure **9** in 55% yield.

To enhance the selectivity in Bücherer−Berg's reaction in favor of **9**, a solvent-screening study was conducted to choose the solvent or solvent mixture that favors this selectivity. Table 4 shows the results of the screen.

Slight selectivity was observed employing methanol, methanol/water, and ethylene glycol/water. However a mixture of ethanol/water was chosen because it shortens reaction times. Optimal conditions were then obtained by adjusting the ethanol/water ratio and the temperature as shown by the results in Table 5.

The original resolution procedure for **5** utilized 1.0 equiv of (*R*)-(+)-α-methylbenzylamine in 1.4:1 acetone/water. This procedure initially worked well at laboratory scale; however, the initial scale-up did not achieve the desired resolution, and the product was difficult to filter. NMR and X-ray crystallography analysis of the product indicated the product is a mixture of racemic salts of **5**, and they exist as a unique crystal form in a double salt, rather than a mixture of the two enantiomerically pure forms. It appeared that the racemic double salt was the most thermodynamically stable crystal form, and the desired resolution of **5** could be achieved only under kinetic conditions. To overcome this problem a solvent screen was conducted to find the right solvent combination to provide the desired enantiomer salt of **5.** The results are shown in Table 6.

The data show that tetrahydrofuran/water (2:1) gave the best enantioselectivity. Intermediate **5** was obtained in 42%

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Table 5. **Impact of the ratio of ethanol/water on the ratio of 9:10**[a]

solvent system	reaction temperature (°C)	reaction time (h)	in situ ratio of **9** and **10** (%)
EtOH/H_2O (4:1)	25	24	88:12
EtOH/H_2O (3:2)	25	48	86:14
EtOH/H_2O (2:3)	25	48	81:19
EtOH/H_2O (1:4)	25	72	81:19
EtOH/H_2O (4:1)	35	16	87:13
EtOH/H_2O (4:1)	40	6	87:13
EtOH/H_2O (1:1)	60	5	78:22

[a] This study indicated that a ratio of (4:1) ethanol to water at 40 °C gave the optimum conditions in favor of **9** (**9**/**10**, 87:13) with reaction completion in 6 h. The optimum condition for crystallization and isolation of **9** was achieved by addition of water to adjust the ethanol/water ratio to 1:1. Isolated **3** is a mixture of **9** and **10** in a 98:2 ratio. Hence, the overall yield for the combined three-step process gave **3** in 55−58% yield.

Table 6. **Solvent-screening study for optimization the purity and yield of 5**

solvent system (ratio)	yield of **5** (%)	ee (%)
tetrahydrofuran/water (1:1)	36	99.5
tetrahydrofuran/water (2:1)	42.4	99.9
tetrahydrofuran/water (3:1)	45	93.0
tetrahydrofuran/water (4:1)	46	97.2
acetonitrile/water (1:1)	42.0	98.2
2-propanol/water (1:1)	28.5	96.6

yield and enantomeric enhancement (ee) of 99.5%. The scale-up of step **5** using this condition was robust for yield and ee.

Thus, the original synthesis of **5** using four isolated intermediates was modified to incorporate only one isolated intermediate as shown in Scheme 6. The changes improved overall efficiency and increased the yield from 48% to 55%.

Conclusions

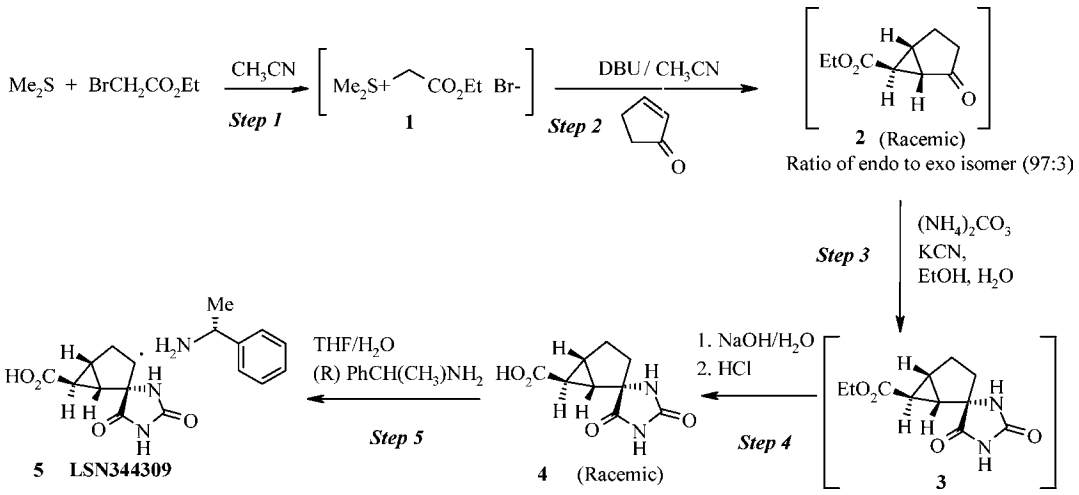
A consolidated process for the synthesis of racemic (1*SR*,2*SR*,5*SR*,6*SR*)-bicyclo[3.1.0]hexane-2-spiro-5′-hydantoin-6-carboxylic acid (**4**) has been developed and demonstrated for the preparation of LY544344·HCl on a manufacturing scale. Also, a robust resolution process for the synthesis of **5** was achieved and demonstrated at manufacturing scale with good yield and excellent purity (>99% ee). These processes addressed manufacturing concerns with respect to safety, throughput, and quality.

Experimental Section

Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR data were obtained at 300 MHZ using a Bruker instrument with TMS as an internal standard. All reagents were commercially available and were used without further purification, unless otherwise stated. 3-Cyclopenten-1-one was obtained from Wacker Chemicals. **1** and **2** were prepared in dry reaction vessels in an atmosphere of dry nitrogen. Reaction completion for **1**, **2**, **3**, and **4** were monitored by HPLC using a Hitachi L-7100 system equipped with a Zorbax SB-Phenyl 25-cm column and the following conditions: eluting solution, 80% 50 mM sodium phosphate monobasic solution adjusted to pH 2.0 with *o*-phosphoric acid and 20% acetonitrile; flow rate equal to 1 mL/min; wavelength equal to 220 nm; and column temperature set at 40 °C. Chiral HPLC to determine chiral purity of **5** was run under the following conditions: column: Daicel Chiralpak AD, 25 cm × 4.6 mm column, 10 μm particle size; column temperature: ambient; flow rate: 0.8 mL/min; detection wavelength equal to 230 nm; injection volume 10 μL; isocratic program with mobile phase of 35/65/0.2 (v/v/v) IPA/hexane/TFA; sample preparation: 20 mg dissolved in 10 mL of mobile phase; retention times: 5.4 min (1*R*,2*R*,5*S*,6*R*), and 9.4 min 1*S*,2*S*,5*R*,6*S* (**5**).

Consolidated Synthesis of Racemic (1*SR*,2*SR*,5*RS*,6*SR*)-Spiro[bicyclo[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic Acid (4). *(i) Synthesis of Carboethoxymethyl Dimethylsulfonium Bromide (**1**).* Acetonitrile (27 mL), ethyl bromoacetate (24.4 g, 0.146 mol), and dimethyl sulfide (10.4 g, 0.17 mol) were added to a dry vessel at 10−15 °C and stirred for 30 min. Carboethoxymethyl dimethylsulfonium bromide **1** (5 mg) was added, and the reaction temperature was adjusted to 20−25 °C to promote crystallization of **1**. The reaction mixture was stirred for 24 h to complete the

Scheme 6. **Modified process for the synthesis of LSN344309**



crystallization of **1**. This slurry was used directly in the synthesis of **2**.

A portion of the slurry was filtered and washed with acetonitrile to isolate **1** for physical data. **1**: mp 42−44 °C [Lit.[3] mp 42−44 °C].

(*ii) Synthesis of Racemic (1SR,5RS,6SR)-2-Oxobicyclo-[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (**2**).* The slurry of **1** (prepared above) was cooled to 0−5 °C, and acetonitrile (52 mL) was added. DBU (22.3 g, 0.146 mol) was then added over 10−15 min, and the temperature was maintained between 0 and 5 °C. The mixture was stirred until all the crystals dissolved (10−15 min), and then 2-cyclopenten-1-one (10 g, 0.122 mol) was added over 10−15 min, maintaining the temperature between 0 and 5 °C. The reaction mixture was warmed gradually to 20−30 °C over 30 min, and then stirred for 8 h. Reaction completion was confirmed by HPLC analysis. Water (50 mL) was added to quench the reaction, and the pH of the media was adjusted to pH 6−8 with concentrated sulfuric acid. Acetonitrile was removed by vacuum distillation at 30−35 °C. The pH of the reaction media was then adjusted to 1−1.5 with sulfuric acid. The product **2** was extracted with 150 mL of *tert*-butyl methyl ether. The resulting organic solution was washed with 20 mL of 5% aqueous sodium bicarbonate. The organic solution was concentrated to an oil by vacuum distillation at 35−40 °C.

*(iii) Synthesis of Racemic (1SR,2SR,5RS,6SR)-Spiro-[bicyclo[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic Acid Ethyl Ester (**3**).* Ethanol (66 mL) was added to **2** (prepared above) and stirred until it dissolved. Water (16 mL), ammonium carbonate (19.9 g, 0.21 mol), and potassium cyanide (7.43 g, 0.11 mol) were added to the solution of **2**, and the slurry was heated to 30−35 °C and stirred until reaction completion was confirmed by HPLC. The reaction slurry was cooled to 20−25 °C, and water (50 mL) was added over 30 min to promote crystallization of **3**. The product slurry was stirred for 30 min, cooled gradually to 0−5 °C, and stirred for 1 h to maximize the crystallization of **3**. The crystals of **3** were filtered, washed with cold water (57 mL), and used as is in the following reaction. A portion of **3** was dried at 40−45 °C under vacuum for determination of the melting point. **3**: mp 218−221 °C [Lit.[3] 219−221 °C].

Synthesis of Racemic (1*S*,2*SR*,5*RS*,6*SR*)-Spiro[bicyclo-[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic Acid (4). Water (120 mL) and sodium hydroxide solution 50% were added to **3** and stirred until hydrolysis completion was confirmed by HPLC (approximately 4 h). The pH of the solution was adjusted to a range between 1.5 and 1 with concentrated hydrochloric acid and was stirred for 30 min at 20−25 °C to promote the crystallization of **4**. The resulting slurry was cooled gradually to 0−5 °C and stirred for 1 h. The product **4** was filtered, washed with cold water (57 mL), and dried at 55−60 °C under vacuum. Overall yield is 57% from 2-cyclopentenone. **4**: mp 278−280 °C [Lit.[3] mp 278−280 °C].

Synthesis of (1*S*,2*S*,5*R*,6*S*)-Spiro[bicyclo[3.1.0]hexane-2′,5′-dioxo-2,4′-imidazolidine]-6-carboxylic Acid, (*R*)-α-Methylbenzenemethanamine Salt (5). Compound **4** (10.0 g, 0.472 mol) was dissolved in THF (100 mL) and water (48 mL) and then heated to 55−60 °C. (*R*)-(+)-α-Methylbenzylamine (4.04 g, 0.333 mol) was added over 20 min, and then the mixture was stirred for 1 h before it was cooled gradually to 0−5 °C. The reaction slurry stirred for 2 h before it was filtered and washed with chilled aqueous THF (40 mL). The product was dried at 55−60 °C under vacuum to give 40−44% yield of **5**: mp 165−168 °C; IR (KBr) 3233, 2937, 1771, 1727, 1619, 1554, 1398, 1384, 1246 cm^{-1}; ^1H NMR (300 mHz, DMSO-d_6) δ 1.32 (2H, m), 1.39 (3H, d, J = 6.7), 1.68 (5H, m), 1.96 (1H, m), 4.19 (1H, q, J = 6.6), 7.26 (1H, t, J = 7.1), 7.33 (2H, t, J = 7.6), 7.43 (2H, d, J = 7.7), 8.06 (1H, br s); $[\alpha]_D = -30.10°$ (c = 1.01, H_2O), Lit.[3] −27.00° (c = 1.01, H_2O).

Acknowledgment

We thank Lilly Analytical Laboratories for providing analytical support for the project. We also thank Dr. D. Kjell for useful suggestions, discussions, and review of the manuscript.

Received for review September 14, 2004.

OP049829E