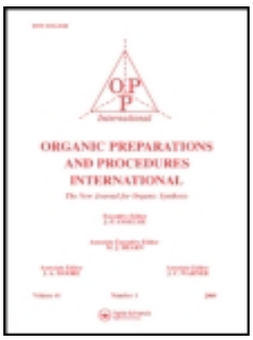

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Improved Large-scale One-pot Synthesis of Pure Doripenem Hydrate (S-4661)

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Carbapenems such as *imipenem*,[1] *biapenem*,[2] *meropenem*,[3] *ertrapenem*[4] and *panipenem*[5] (*Figure 1*) display broad potent anti-bacterial activity. Introduction of a methyl group at the 1β-position in the carbapenem skeleton enhances metabolic stability toward renal dehydropeptidase-1(DHP-1) and leads to higher anti-bacterial potency.[6]

Doripenemhydrate{(4*R*,5*S,6S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-{((3*S*,5*S*)-5-[(sulfamoylamino)methyl}pyrrolidin-3-yl]thio}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxy-lic acid hydrate, S-466, **5**] is highly potent compared to *meropenem* against *Gram*-positive bacteria. It is also superior to *imipenem* against *Gram*-negative bacteria including *pseudomonas aeruginosa. Doripenem hydrate* (**5**) is marketed in the United States as *Doribax*™ and is prescribed as a single agent used for the treatment of complicated urinary tract infections including *pyelonephiritis* caused by *Escherichia coli. Pseudomonas aeruginosa* is one of the most common *Gram*-negative organisms associated with nosocomial infections. The maximum daily dose is 1.5 g in three equal portions.

Some problems were encountered in the preparation of **5** in the first generation process *(Route 1*, *Scheme 1)*[7] involving the reaction of side-chain protected compound **1a** with enolphosphate **3a** as shown in *Scheme 1*. The deprotection of the side-chain of **1a** with strong base led to the formation of less pure **2a** and the generation of high levels of its disulfide; the process also required a chromatographic purification on *Diaion HP-20* and gave a lower yield of **5** at pilot scale-level (49%). Similarly, the preparation of **5** from the reaction of compound **1b**[8] with enol phosphate **3b**[9, 10] *via* the modified Nishino procedure *(Route 2*, *Scheme 1)*[11] gave lower overall yields (64% from **3b**) of less pure products (97% a/a) when compared to the present process (99.68% a/a). Other major problems include *i)* the deprotection of **1b** with H_2SO_4, which led to less pure **5**, *ii)* more numerous isolation steps when compared to the present process, *iii)* use of very large amount of inorganic salts

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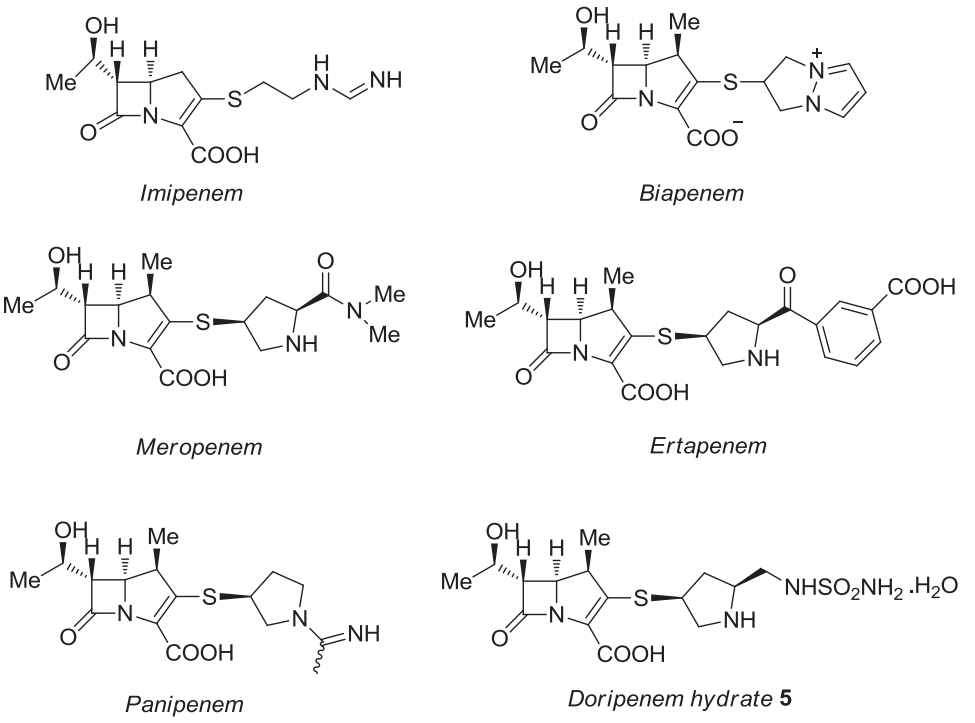
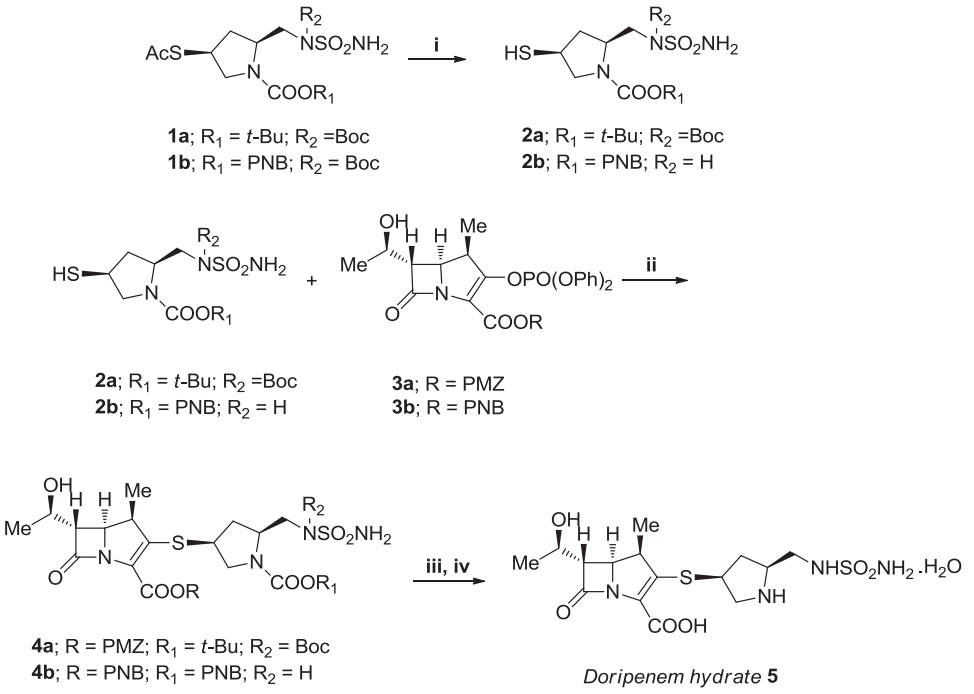


Figure 1

during preparation of **5** and *iv)* utilization of large volumes of solvent (THF) for the removal of *p*-toluidine (by-produt from the reductive deprotection of the ester) and other organic impurities in doripenem. The present article reports improved procedures for the Nishino route based on our patent.[12]

The use of valeryl chloride and methanol for the deprotection of **1b** yielded highly pure compound **2b**, and subsequently compound **4b** did not need to be isolated. The magnesium chloride previously used in the catalytic hydrogenolysis of **4b** evidently crystallized along with **5**, and presence of the salts required separation using column chromatography, a process which is typically not favored on a commercial scale. In our improved procedure, instead of using magnesium chloride, a buffered solution was utilized thereby avoiding the complications involved in the previous processes. The use of Pd/C (1.5 w/w based on **3b**) in the hydrogenolysis of compound **4b** in the Nishino method resulted in a palladium residual level of 430 ppm in **5** as well as 4 ppm in the sterile *Active Pharmaceutical Ingredient* (API) **5**.[11] In our process, the residual palladium was controlled to be less than 0.75 ppm by pre-reduction of Pd (Pd/C). Some of the other processes[13–18] reported in the literature are not viable industrially or economically due to lower yields (48–62% from **3b**) and lesser purity (95–99%) of **5**; in contrast, our improved process gave crude **5** in 71% yield and purity of 99.68% a/a. The present work describes an improved process to increase the yield and purity necessary to meet regulatory requirements. This process does not involve chromatographic purification and reverse osmosis. Tedious work-ups and repeated purifications for the removal of impurities and residual metal content from **5** have been avoided to minimize cost.



PNB = *p*-nitrobenzyl; PMZ = *p*-methoxybenzyl

***Reagents and conditions for first-generation process (Route 1)**: **(i)** NaOMe and MeOH. **(ii)** N,N-dimethyl-formamide **(**DMF) and N-ethyldiisopropyl amine (DIPEA) **(iii)** $AlCl_3$ and anisole **(iv)** Column chromatography.*

***Reagents and conditions for Nishino's process (Route 2): (i)** H_2SO_4, MeOH, reflux **(ii)** DIPEA, DMF, 0-5 °C, EtOAc and toluene **(iii)** Pd/C, THF, $MgCl_2$ and demineralised (DM) water **(iv)** demineralised water, activated carbon and isopropanol.*

Scheme 1

Removal of the *S*-acetyl and *N-t*-Boc groups of **1b** according to the literature procedure[11] led to compound **2b** having 90.42% a/a pure (HPLC) along with impurities of **6, 7** and **8** (*Figure 2*) in the amounts of 0.48% a/a, 0.57% a/a and 1.86% a/a respectively.

In the preparation of **5** from **2b** using the process depicted in *Scheme 2*, impurities derived from *doripenem* such as *tert-butyl doripenem* **9** and compound **10** (*Figure 2*) in the amounts of 0.14% a/a and 0.61% a/a respectively were observed. Removal of these impurities in **5** requires multiple purifications, resulting in a substantial decrease in the yield. Compound **2b** obtained in that process contains1.85% a/a of its disulfide **8**, that is carried through to the next step as the corresponding disulfide **11**, which required ethyl acetate extraction of **5** for its removal.

We found that deprotection of **1b** with excess of methanolic HCl (2 mole ratio) at 48–50°C for 12 h gave an unacceptable level of **7** *(Table, Entry 2*). Subsequently, the deprotection of **1b** was performed using valeryl chloride in methanol varying the conditions of mole ratios, temperature and reaction times, the results are summarized in *Table 1*. Based on these data, the deprotection of the side-chain **1b** with 0.5 mole

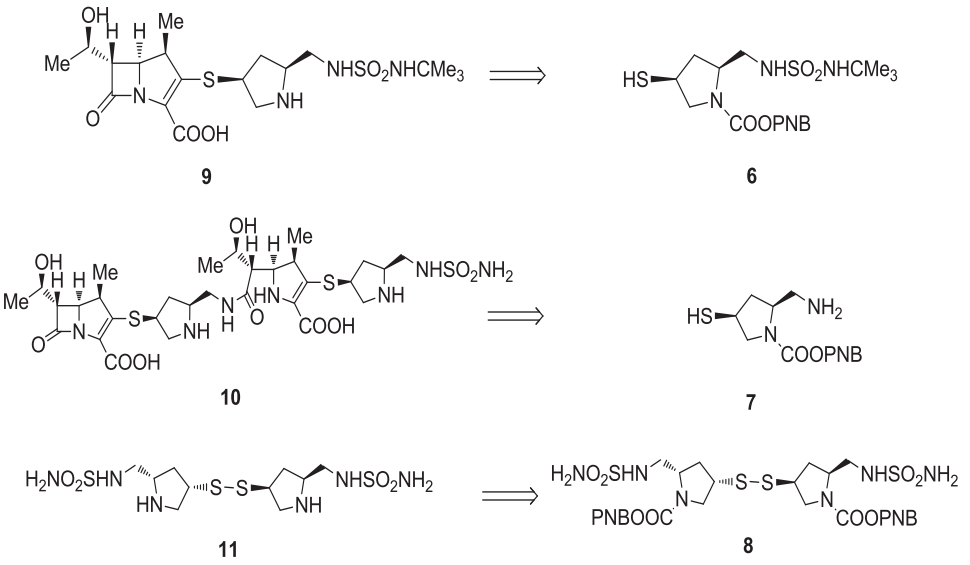
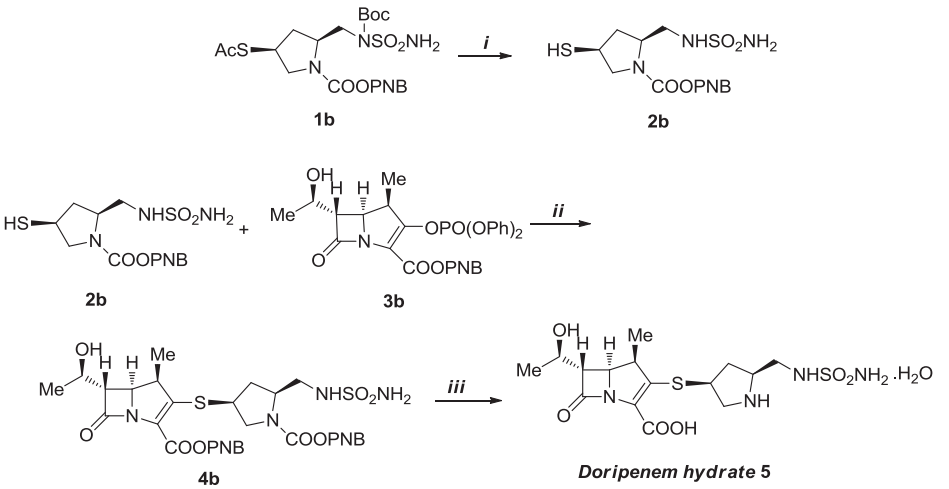


Figure 2

equivalent of valeryl chloride at 48–50°C resulted in compound **2b** having 97.35% a/a HPLC purity, 0.05% a/a of **6** and 0.06% a/a of **7** (*Table 1, Entry 5*). In this process, the formation of **6** and **7** were greatly reduced thus minimizing the presence of **9** and **10** in the final *doripenem hydrate* ***5***.

In addition, we studied the condensation of **2b** with **3b** in the presence of a base such as *N,N*-diisopropylamine (DIPA) or *N*-ethyldiisopropylamine (DIPEA)) to provide **4b** and the results are shown in *Table 2*. The reaction at −40°C with 1.4 equivalent of



Reaction conditions:(i)*Valeryl chloride, methanol, 48 -50 °C and 18 h;****(ii)****DIPEA, DMF,-40 to -20°C and 10h;* ***(iii)*** *Morpholine-acetic acid buffer pH at 7.0-7.3, Pd/C, THF, EtoAc,isopropanol and DM water, 18-20 °C and 2.5h*

Scheme 2

Table 1
Preparation of **2b** by using acid or acid chloride

Entry	Acid/acid chloride	m/r[a]	Time (h)	Temp. (°C)	Compound 2b purity by HPLC[b](% a/a) 2b	6	7	8
1	Sulfuric acid	3	3	60–62	90.42	0.48	0.57	1.86
2	Methanolic HCl	2	9	60–62	97.54	0.09	0.41	1.24
3	Valeryl chloride	1	7	48–50	95.63	0.10	0.12	2.24
4	Valeryl chloride	0.7	8	60–62	97.36	0.10	0.10	1.17
5	Valeryl chloride	0.5	18	48–50	97.6	0.05	0.06	1.57
6	Valeryl chloride	0.5	12	60–62	97.65	0.10	0.08	1.07

(a) Mole ratio and (b) after work-up **2b** purity.

N-ethyl- diisopropylamine results in a product with the highest purity of 95.88% a/a in **10h** (*Table 2, Entry 3*). After completion of the reaction and adjustment of the pH to 2.8–3.0 with 1N HCl, **4b** was extracted into ethyl acetate and the organic extract was concentrated to afford crude **4b**. Although we initially explored the isolation of **4b** by crystallization from toluene, this procedure requires large volumes of toluene to remove the moisture present in the crude **4b** by azeotropic distillation. Furthermore, the purity of the crystallized compound **4b** was not improved. To overcome this problem, the crude **4b** was used directly for the synthesis of **5**.

Initially, the protected doripenem **4b** was hydrogenated according to the reported biphasic process,[16] which resulted in unacceptable yield and quality. Hydrogenation of the protected doripenem in the presence of Pd/C was explored under different conditions (*Table 3)*. When conducted with or without base, less pure **5** was obtained in lower yield (*Table 3, Entries 6 and 7*). However, when the reaction was performed in different buffer solutions such as sodium acetate, 3-morpholinopropanesulfonic acid (MOPS), *N*-methylmorpholine (NMM)-acetic acid or *N*-methylmorpholine-oxalic acid, fruitful results were obtained with the use of *N*-methylmorpholine-acetic acid at pH 7.0–7.3.

The deprotection of compound **4b** using Pd/C (1.5 w/w based on **3b**) in a mixture of tetra-hydrofuran and a buffer solution of *N*-methylmorpholine and acetic acid afforded **5** with a purity and yield of 99.55% a/a and 72% respectively, with $Pd_{residual}$ levels of 430 ppm. Utilization of lesser quantity of Pd/C leads to prolonged reaction time and lesser yields of less pure product. Pre-reduced Pd/C[19,20] (1.5 w/w based on **3b**) gave **5** in excellent purity (99.68% a/a) and good yield (71%) respectively with residual Pd of

Table 2
Preparation of **4b** using different organic bases with various conditions

Entry	Base	Mole ratio	Time (h)	Temp (°C)	Compound 4b purity by HPLC (a/a %) 4b	2b	3b
1	DIPA	1.3	1	−40	93.68	0.92	0.06
2	DIPEA	1.3	12	−40 to −20	92.84	1.88	2.27
3	DIPEA	1.4	10	−40 to −20	95.88	1.14	1.41
4	DIPEA	2	3	−40	86.34	1.24	1.65

Table 3
Preparation of **5** in the presence of various buffer solutions

Entry	Buffer	Purity (% a/a) of 5 by HPLC			Yield (%) of 5 based on 3b
		5	*tert*-Butyl doripenem 9	Compound 10	
1	NMM/MOPS	97.32	0.07	0.05	51.16
2	CH_3COONa	96.13	0.09	ND	46.17
3	NaOH/MOPS	95.32	0.08	ND	52.96
4	NMM/Oxalic acid	98.30	0.06	ND	59.75
5	NMM/Acetic acid	99.57	0.08	ND	71.29
6	2, 6-Lutidine	93.43%	0.20	0.05	50.25
7	—	91.22%	0.16	0.07	43.46

38.44 ppm. The isolated **5** with pre-reduced catalyst yields 90% less $Pd_{residual}$ relatively compared to the use of unreduced Pd/C.

In conclusion, we have developed a new method for one-step synthesis of **5** in 71% yield and purity of 99.68% a/a. This present process is significantly free from palladium, inorganic salts and meets the regulatory norms in terms of quality.

Experimental Section

^{1}H NMR and ^{13}C NMR spectral data were obtained in dimethylsulfoxide (DMSO-d_6) on 500 MHz and 75 MHz spectrometers respectively. The chemical shift values are reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS, $\delta = 0.0$) as an internal standard. IR spectra were recorded in the solid state as KBr dispersions using a Perkin-Elmer spectrum on a Fourier transform (FT)-IR spectrophotometer. The mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with an ESI source used online with an HPLC system after the ultraviolet (UV) detector. HPLC chromatographic purity was determined by using the area normalization method. The HPLC procedure for monitoring the reaction is as follows: Column: Inertsil ODS-3V, 250 mm × 4.6 mm, and 5 μ, Flow rate: 1 mL/min, Detector: UV, 295 nm, Temp: 40°C, Run time: 40 min, Elution: gradient, Buffer: Diammonium hydrogen orthophosphate (2.64 g) was dissolved in 1000 mL of water and pH was adjusted to 7.0 ± 0.05 with a solution of 2% v/v of orthophosphoric acid, Mobile phase A: Buffer and Acetonitrile (98:2 v/v) and Diluent: Mobile phase A and Mobile phase B (98:2 v/v). Mobile phase B: Acetonitrile. HPLC method was used to identify the *doripenem* related substances: Run time 50 min, Buffer pH 6.0 ± 0.05 and remaining parameters same as reaction monitoring conditions. The thermal analysis was carried out on a DSC Q 1000 TA. The thermogram was recorded from 30 to 250°C. The solvents and reagents were used without purification.

*Preparation of (4***R,5S,6S***)-6-[(***R***)-1-Hydroxyethyl)-4-methyl-7-oxo-3-{(3***S,5S***)-5-[(sulfamoylamino)methyl)pyrrolidin-3-yl]thio}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid Hydrate (***Doripenem Hydrate*, *5]***

A mixture of (2S, 4S)-4-(acetylthio)-2-(((tert-butoxycarbonyl)(sulfamoyl)amino) methyl) pyrrolidine-1-carboxylic 4-nitrobenzoic anhydride (**1b**,17.1kg, 32.1mol) and valeryl chloride (1.7 kg, 14.09 mol) in methanol (75 L) was heated to 50°C and stirred at

48–50°C for 18 h. After completion of reaction, the reaction mixture was diluted with dichloromethane (150 L) and water (150 L). The separated organic layer was washed with demineralised water (150 L), followed by 1% w/v aqueous NaCl solution (150 L). After washings the organic layer was concentrated to oil which was dissolved in *N, N*-dimethylformamide (30 L). The solution was added to (*4R,5R,6S*)-4-nitrobenzyl3-((diphenoxyphosphoryl)oxy)-6-((*R*)-1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (**3b**, 15kg, 25.23 mol) in *N,N*-dimethylformamide (45 L) at -40°C. Later *N*-ethyl diisopropylamine (4.53 kg, 35.05 mol) was added to reaction mass and stirred for 4 h at −40°C. The temperature of reaction was then raised to −20°C and stirred for 6 h. The reaction mixture was diluted with ethylacetate (150 L), water (90 L) and acidified to pH 2.8 with 1N aqueous hydrochloric acid (12.45 L) at 5°C. The two layers were separated, and the aqueous layer extracted with ethyl acetate (90 L). The combined organic layers washed with 0.25% w/v aqueous NaCl solution (2 × 150 L) at 15°C and concentrated to a sticky mass which was dissolved in tetrahydrofuran (195 L) at 20°C. A buffer solution (pH 7.1), prepared by mixing *N*-methylmorpoline (2.55 kg, 25.21 mol), acetic acid (1.095 kg, 18.25 mol) and water (82.5 L) at 20°C, which was added to the above reaction mass. The solution was added to pre-reduced Pd/C, obtained by stirring 10% w/w Pd/C (22.5 kg, 50% w/w wet) in DM water (82.5 L) for 1 h under hydrogen atmosphere (0.3 Mpa) at 20°C. The reaction mixture was stirred for 2.5 h under hydrogen atmosphere (0.8 Mpa) at 20°C. The reaction mass was filtered through a Celite bed and the filtrate was washed with a mixture of water (15 L) and tetrahydrofuran (15 L). The aqueous filtrate obtained was extracted with ethyl acetate (210 L) at 20°C. After addition of seed crystals of doripenem (0.03 Kg) at 18°C and slow addition of of isopropanol (507 L) over a period of 5 h, the slurry mass was cooled to 0–5°C and stirred for 8 h. The slurried mass was filtered at 0–5°C to give the wet product which was washed with 20% v/v aqueous isopropanol (30 L, 0–5°C) and dried under vacuum at 45–50°C for 8 h to give *doripenem hydrate* **5** (7.89 kg with 71% yield and 99.68% a/a HPLC purity).

Moisture content by KF: 4.38% w/w.^{1}H NMR (500 MHz, $DMSO_{d6}$): δ 1.23 (d, 3 H, $J = 7.2$ Hz), 1.30 (d, 3H, $J = 6.5$ Hz), 1.77 (ddd, 1H, $J = 6.6$, 9.2 and 14.9 Hz), 2.75 (dt, 1H, $J = 14.3$ and 8.0 Hz), 3.38 (dq, 1H, 1H, $J = 7.2$ and 9.3 Hz), 3.44 (dd, 1 H, $J = 4.2$ and 12.4 Hz), 3.44 (dd, 1H, $J = 8.3$ and 15.0 Hz), 3.48(dd, 1H, $J = 2.5$ and 6.1 Hz), 3.55 (dd, 1H, $J = 4.8$ and 15.0 Hz), 3.72 (dd, 1H, $J = 7.0$ and 12.4 Hz), 3.95 (qd, 1 H, $J = 4.8$ and 8.5 Hz), 4.06 (qd, 1H, $J = 7.4$ and 4.2 Hz), 4.24 (dd, 1H, $J = 2.5$ and 9.3 Hz), 4.26 (m, 1 H).^{13}C NMR (75 MHz, DMSO-d6):16.6, 21.8, 34.6, 39.6, 42.0, 44.4, 52.3, 55.3, 58.1, 59.2, 64.4, 132.6, 137.4, 164.2, 173.4. ESI-MS: 421.1 $[M + H]^{+}$. FT-IR (KBr cm^{-1}): 3534, 3394, 3261, 2978, 2965, 1714, 1631, 1567, 1539, 1455, 1365, 1321, 1162, and 1144. DSC: 144.30°C (10°C/ min).

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