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Development of a Scalable Process for 1-β-Methyl Azetidinone: A Carbapenem Key Intermediate†

Neera Tewari,* Hashim Nizar, Bishwa Prakash Rai, Avinash Mane, and Mohan Prasad

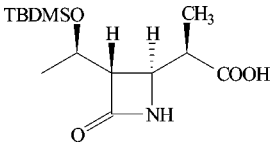
Chemical Research Division, Ranbaxy Research Laboratories, Gurgaon, Haryana - 122 001, India

Abstract:

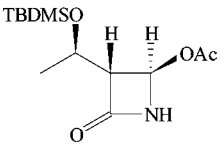
An optimized process for the stereoselective synthesis of 1-β-methyl carbapenem key intermediate (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (1) and (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone has been developed employing commercially available chiral 4-phenyl-2-oxazolidinone. This method provides an efficient and cost-effective process with improved selectivity and higher yield.

Introduction

The β-methyl carbapenem antibiotics exhibit excellent broad spectrum antibacterial activities with increased chemical and metabolic stabilities as exemplified by Meropenem[1], Biapenem,[2] and Ertapenem.[3,4] (3*S*,4*S*)-[(*R*)-1′-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**1**) is a key intermediate for the synthesis of β-methyl carbapenems. Many synthetic methods have been reported for the synthesis of β-methyl azetidinone derivative **1**[5] of which C-4 alkylation of commercially available (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)-ethyl]-2-azetidinone[5] (**2**) with different types of enolates derived from propionic acid derivatives is the most important method for its commercial preparations.[6] Different metal enolates of propionic acid derivatives having chiral and achiral auxiliary have been utilized, including 2-oxazolidinones,[7] 2-picolyl thiols,[8] and 2,3-dihydro-4*H*-1,3-benzoxazin-4-one[9] for improved β-selectivity in the preparation of **1**. Stereoselective introduction of the 1-β-methyl substituent in **2** has been achieved using



1



2

tin enolate of 3-propionyl-2-thiazolidine thiones,[7b,10] boron enolate of 3-propionyl-2-thioazolidinone,[7a] or zirconium enolate of thiol ester of propionic acid.[11] These methods face difficulties in large scale preparation of **1** as they employ more than stoichiometric amounts of the precious chiral sources and/or the expensive or toxic reagents. Different oxazolidinthione derivatives have been used in the preparation of **1** resulting in low yield and varying β:α ratio.[12] In addition the stereoselective synthesis of the key intermediate **1** via a Reformatsky type reaction employing different 3-(2-bromopropyl)-2-oxazolidinones using zinc has been reported.[13] However, these oxazolidinone auxiliaries are difficult to access and expensive. Recently, a commercial method has been reported for the preparation of **1** employing a Reformatsky type reaction using nonchiral dihydrooxazinone derivatives.[14] The best diastereoselectivity reported in terms of the β:α ratio of the methyl group is 92:8. Another diastereoselective synthesis is reported using a titanium enolate of 2′-hydroxy propiophenone[6a] which involves ozonolysis at −78 °C and column chromatography. Herein we report the process development work for the stereoselective synthesis of (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)-ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**1**) utilizing commercially available (*S*)-4-phenyl-2-oxazolidinone (**3**).

Results and Discussion

We explored the possibility of using commercially available chiral (*S*)-4-phenyl-2-oxazolidinone (**3**) as an auxiliary for the synthesis of **1**. The reaction of **3** with propionyl chloride in the presence of triethylamine results in the formation of *N*-propionyl oxazolidinone derivative **4** (Scheme 1). This derivative is treated with titanium tetrachloride in the presence of a tertiary amine base followed by reaction with **2**. After workup the condensed product **5** obtained is

* Author for correspondence. E-mail: neera.tiwari@ranbaxy.com. Telephone: (91-124) 5011832. Fax: (91-124) 5011832.

† A patent application incorporating parts of this report has been filed.

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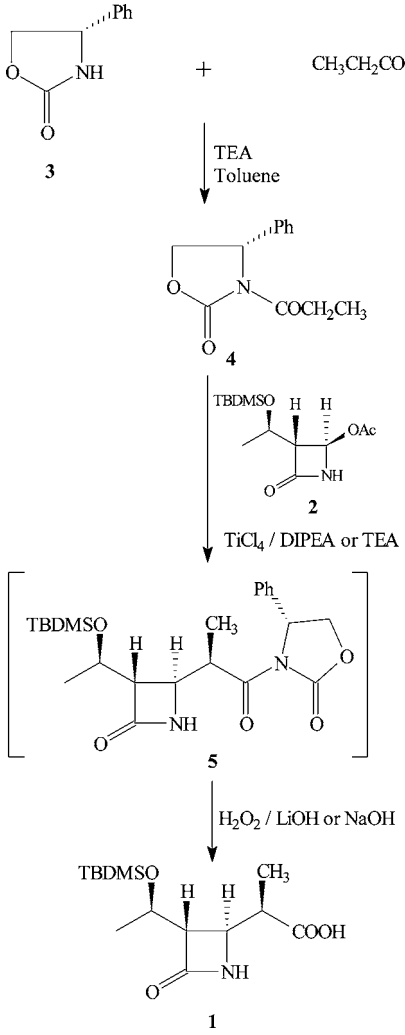
Scheme 1



directly taken for hydrolysis with lithium hydroxide/H_2O_2. The synthesis of **5** is reported in the literature by the condensation of *N*-propyl oxazolidinone **4** with (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone (**2**) in the presence of alkylmagnesium chloride.[15] Adjusting the pH of the reaction mixture to 8.5−9.0, the chiral auxiliary 4-phenyl-2-oxazolidinone (**3**) is precipitated and recovered (∼80% recovery) for reuse. Further adjusting the pH to 2.5 yielded β-methyl azetidinone **1**. From our experiments, we found that the *S*-isomer of **3** selectively gave the β-isomer with overall 65% yield (β:α ratio 99.5:0.5) compared to the earlier best reported method[14] of 55% yield. Similarly the *R*-isomer of **3** gave the α-isomer of **1** selectively (100:0 ratio) in 63% yield.

During the process optimization, we have studied the effect of triethylamine and diisopropyl ethylamine as base during enolate formation. The use of diisopropylethylamine results in 65% yield of **1** (β:α ratio 99.5:0.5) and triethylamine in 52% yield (β:α ratio 99.5:0.5). Similarly the effects of base, lithium hydroxide and sodium hydroxide, during the hydrolysis of **5** have been studied. The yield and quality of the product **1** did not have much effect, but lithium hydroxide requires low temperatures (0−5 °C), whereas with sodium hydroxide the reaction is better optimized at 20−25 °C (Table 1). This optimized process is further scaled up to the 1 kg scale (Experimental Section).

Table 1. . Hydrolysis of 5 with H_2O_2/Base

entry	base	reaction temp (°C)	solvent	yield (%)
1	LiOH	5−8	acetone/water	62
2	LiOH	20−25	acetone/water	55
3	LiOH	0−5	methanol/water	[a]
4	NaOH	5−10	acetone/water	63[b]
5	NaOH	20−25	acetone/water	65
6	NaOH	20−25	methanol/water	[a]

[a] Reaction incomplete. [b] Reaction is slow and requires longer time (4−5 h).

The advantage of this method over the other existing methods are high stereoselectivity, better yield, and use of commercially available and inexpensive (*S*)-4-phenyl-2-oxazolidinone (**3**) auxiliary which is recovered (∼80% recovery) and reused.

In conclusion, a scalable process for the preparation of (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (**1**) using a highly diastereoselective condensation of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone (**2**) with commercially available (*S*)-4-phenyl-2-oxazolidinone (**3**) has been developed. This method is cost-effective and affords the product in better selectivity and yield.

Experimental Section

General. Reagents are used as such without further purification. ^{1}H NMR spectra are recorded using a Bruker 300 MHz spectrometer. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard. Chiral HPLC analysis was performed on a Waters instrument with a UV detector (205 nm) using a Kromasil C_{18}, 3.5 μm (100 mm × 4.6 mm) column (oven temperature 40 °C) and mobile phase phosphate buffer (pH 3.5)/acetonitrile gradient (Buffer/Acetonitrile: 75:25 in 0 min to 60:40 in 20 min; 25 min 60:40 to 25:75 in 30 min; 35 min 25:75 to 75:25 in 40 min) with a flow rate of 1.1 mL/min.

Preparation of (*S*)-4-Phenyl-3-propionyl-2-oxazolidinone (4). To a suspension of (*S*)-4-phenyl-2-oxazolidinone (**3**) (100 g, 0.613 mol) in toluene (500 mL), propionyl chloride (96.4 g, 1.04 mol) was added at 20−25 °C. Triethylamine (111.5 g, 1.10 mol) was then added (*exothermic*) dropwise in 30 min at 25−50 °C and stirred for 1 h at 40−50 °C. After completion of the reaction, the reaction mixture was cooled to 25 °C, treated with 5% aqueous sodium bicarbonate solution (500 mL) and then washed with water (500 mL). The organic layer was concentrated under reduced pressure. To the residue isopropyl alcohol (200 mL) was added, and the precipitate thus obtained was stirred at 0−5 °C for 3 h, filtered, washed with isopropyl alcohol (100 mL), and dried to give **4** (110 g, 82%) as crystalline material. ^{1}H NMR ($CDCl_3$): 1.11 (t, 3H, CH_3), 2.95 (q, 2H, $-CH_2$),

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4.28 (dd, 1H), 4.68 (dd, 1H, H-4), 5.42 (dd, 1H), 7.26−7.39 (m, 5H, Ph-H).

Preparation of (3*S*,4*S*)-[(*R*)-1′-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (1). To a solution of (*S*)-4-phenyl-3-propionyl-2-oxazolidinone (**4**) (92 g, 0.42 mol) in dichloromethane (700 mL) $TiCl_4$ (86 g, 0.45 mol) was added dropwise in ∼30 min at −20 to −25 °C. After stirring of the mixture for 30 min at −20 to −25 °C diisopropyl ethylamine (56 g, 0.434 mol) was added dropwise, and stirring continued for ∼60 min at the same temperature. The reaction mixture was diluted with dichloromethane (300 mL), and (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone (**2**) (100 g, 0.348 mol) added at −15 to −10 °C. The temperature was raised to 20−25 °C in ∼60 min, and then the mixture was stirred at this temperature for ∼3 h. After completion of the reaction, deionized water (1.0 L) was added after cooling to ∼10 °C. The layers were separated, and the organic layer was again washed with deionized water (1.0 L) and concentrated under vacuum to give a residue of intermediate **5**. The residue was dissolved in acetone (700 mL) and added deionized water (350 mL). Cooled aqueous hydrogen peroxide (30% w/w, 118 g, 1.04 mol) solution (*the solution is corrosive and can cause skin burns*) was added followed by dropwise addition of aqueous sodium hydroxide solution (42 g, 1.05 mol) in water (300 mL) at 20−25 °C in 30 min (*slightly exothermic*). After stirring for 1 h the reaction was diluted with deionized water (2.0 L), and the pH was adjusted with 6 N HCl to ∼8.5. The precipitated (*S*)-4-phenyl-2-oxazolidinone (**3**) was collected after filtration (81% recovery, chromatographic purity >98.0%). The filtrate was collected, and its pH was further adjusted to 2.5 with 6 N HCl. The solid thus obtained was filtered (the aqueous stream is peroxide free, checked with starch iodide paper and potassium iodide solution) and washed with water (400 mL) and ethyl acetate (100 mL) which on drying at 40−45 °C yielded 68 g (65%) of **1** as white crystalline material (β:α ratio 99.5:0.5). ^{1}H NMR ($CDCl_3$): 0.05 (s, 6H, CH_3—Si), 0.81 (s, 9H, Si—C—CH_3), 1.13 (d, 3H, CH_3—C—H), 1.18 (d, 3H, CH_3—CH), 2.67 (m, 1H, CH_3—CH—C═O), 2.96 (dd, 1H, H-3), 3.88 (dd, 1H, H-4), 4.14 (m, 1H, CH_3—CH—O), 6.36 (br s, NH).

The above process was scaled up to 1.0 kg input of (3*S*,4*R*)-4-acetoxy-3-[(*R*)-1′-(*tert*-butyldimethylsilyl)oxy)-ethyl]-2-azetidinone (**2**). The condensation reaction was scaled up as in the above procedure. The residue of the condensed product **5** obtained by the above process was dissolved in acetone (7 L), diluted with deionized water (3.5 L), and cooled to 15 °C. Cooled aqueous hydrogen peroxide solution (30% w/w, 1.18 kg, 10.4 mol) was added to the above solution in 10 min at 15−18 °C. Then a cold solution of sodium hydroxide (420 g, 10.5 mol) in deionized water (3 L) was added slowly by keeping the temperature 20−25 °C in 45 min by circulating the jacket of the reactor with brine of temperature −15 to −10 °C. The reaction mixture was stirred for 1 h at 20−25 °C and then diluted with deionized water (20 L), and the pH was adjusted with 6 N HCl to 8.5 at 15−20°C. The precipitate was filtered, washed with water, and dried to give (*S*)-4-phenyl-2-oxazolidinone (**3**) (recovery 79%, chromatographic purity by HPLC 98.9%). The filtrate was collected, and its pH was adjusted to 2.5 with 6 N HCl. The crystalline solid thus obtained was filtered, washed with water (4 L) followed by ethyl acetate (1 L), and dried at 40−45°C to give **1** in 64.5% (675 g) yield (β:α ratio 99.6:0.4).

Preparation of (3*S*,4*S*)-[(*R*)-1′-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(*S*)-1-carboxyethyl]-2-azetidinone. The titled compound was synthesized from (*R*)-4-phenyl-3-propionyl-2-oxazolidinone [prepared from (*R*)-4-phenyl-2-oxazolidinone and propionyl chloride by the above method] and **2** by following the above procedure in 63% yield (β:α ratio 0:100). ^{1}H NMR ($CDCl_3$): 0.06 (s, 6H, CH_3—Si), 0.79 (s, 9H, Si—C—CH_3), 1.18 (dd, 3H, CH_3—CH), 1.20 (dd, 3H, CH_3—CH), 2.48 (m, 1H, CH_3—CH—C═O), 2.72 (dd, 1H, H-3), 3.60 (dd, 1H, H-4), 4.11 (m, 1H, CH_3—CH—O), 6.54 (br s, NH).

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