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Process Development on (3*S*,4*S*)-[(*R*)-1′-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone: 1-β-Methylcarbapenem Key Intermediate

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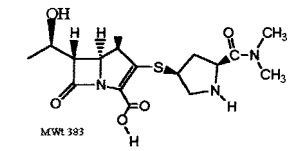
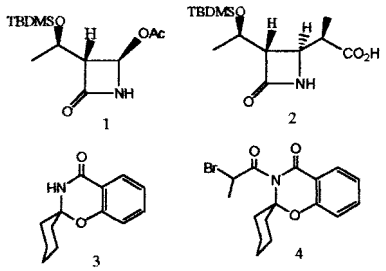
Abstract:

The process for the stereoselective synthesis of the 1-β-methylcarbapenem key intermediate 2 via the Reformatsky-type reaction employing a dihydro-oxazinone derivative has been developed for large-scale production. The most difficult problem involved in the development was the exothermic nature of the reaction. Change of acidification order avoided the heat release in the hydrolysis of 5 to 2.

The carpapenem class of β-lactam antibiotics, in particular those bearing a 1-β-methyl substituent, as exemplified by meropenem[1] and biapenem[2,3] is an important group of drugs and the object of ongoing pharmaceutical research, because of their potent and broad-spectrum antibacterial activities.[4] In all of the synthetic methods for constructing this class of antibiotics, (3*S*,4*S*)-[(*R*)-1′-((*tert*-butyldimethylsilyl)oxy)-ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone **2**, containing the four contiguous stereogenic centers of the 1-β-methyl class of carpabenems,[5] is considered the most important key intermediate. Many elegant synthetic methods[6,7] to **2** have been developed, of which the majority of routes have involved an enolate addition[8] to **1** by a series of pre-made auxiliaries.[9] Recently, the synthesis of the key intermediate **2** and its subsequent conversion to 1-β-methylcarbapenem nucleus via the Reformasky-type[10] reaction with 2-substituted 1,3-dihydro-4H-1,3-benzoxazin-4-ones **3** as the most efficient auxiliary[11] has been reported. The compound **3**, readily made from cheap reagents by a simple single-step synthesis, provided many advantages over the previous auxiliaries. Here we report the process development work and the issues involved in our process development to make **2** via **4** by Reformatsky- type reaction.



Meropenem



Result and Discussion

Zinc-Induced Reformatsky-Type Reaction. Compound **3** can be readily made from condensation of inexpensive salicylamide with cyclohexanone catalyzed by *p*-toluylsulfonic acid in toluene. Compound **4** resulted from bromopropionylation of **3** by the use of pyridine as a base and toluene as a solvent. The reaction was actually run by adding 1.2 equiv of acyl bromide to **3** in 1.2 equiv of pyridine at 40−45 °C and the reaction was complete in 3 h. The development focus was on the Reformatsky-type reaction. As reported, the reaction conditions involved treatment of **1** with 1.5 equiv of **4** and 3 equiv of zinc dust in refluxing THF. The best diasteroselectivity in terms of the β:α ratio of the methyl

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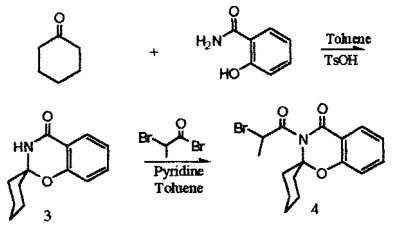
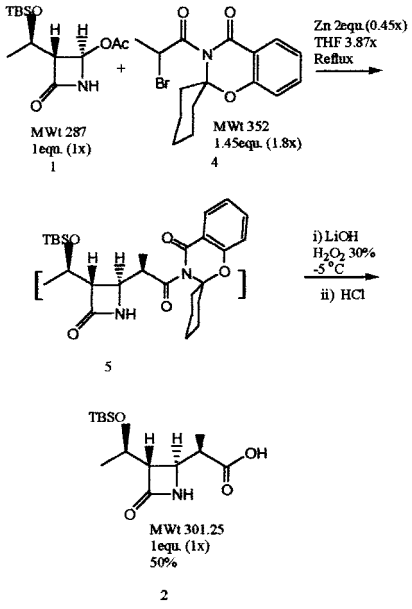
Scheme 1



Scheme 2



group was about 92:8, and the yield was about 65−70% in the laboratory preparation of **2** (Scheme 1).

Issues in the Large-Scale Reformatsky-Type Reaction. According to the literature procedure, **4** was added dropwise to **1** in about 45 min in the lab scale under refluxing condition. The reaction was so exothermic that the rate of addition must be controlled very well to avoid severe overheating. In this case, the large-scale production entailed a long addition time of **4** to make **5** (Scheme 2). Actually for a scale of 1 kg of **1**, the addition time was about 5−6 h. It was found that the yield of **2** would drop tremendously to less than 10% if refluxing extended over 4 h, and **1** would decompose. To overcome the stability problem, the way of addition had to be changed into simultaneous addition of **1** and **4** to the refluxing zinc/THF, instead of adding **4** to the **1** and zinc/THF mixture. This optimization was quite successful with this much easier and more reliable operation, and the yield was also improved. After the Reformatsky-type reaction, THF was evaporated, the reaction mixture was concentrated to its minimum, and toluene was added. The reaction mixture was cooled to 25 °C, filtered through Celite, and then washed with 2 N HCl and brine at 25 °C.

Process Development of Hydrolysis of 5 into 2. The literature process utilized excess lithium hydroperoxide[12] in aqueous THF at very low temperature. When the hydrolysis was over, sodium sulfite aqueous solution was added to quench the extra hydroperoxide, followed by the acidification with HCl to pH = 2 to get **2**. It was very essential to keep the hydrolysis process below 0 °C, and the following quench of extra hydroperoxide and acidification were supposed to be quick and below 0 °C as well. The big problem encountered was the overheating during the quench of the extra hydroperoxide by aqueous Na_2SO_3. The reduction of excess hydroperoxide by aqueous Na_2SO_3 was an enormously heat-releasing process involving a severe exothermic effect. Slowing down the addition of the aqueous Na_2SO_3 to keep the temperature at 0 °C lengthened the reaction to about 16−18 h, and no expected product was obtained under these reaction conditions. Here was the dilemma: the quench of extra hydroperoxide would release a huge amount of heat, and **2** would be degraded into a ring-opened byproduct under basic conditions even at room temperature, and the lower operating temperature at 0 °C would help delay the decomposition but should not take more than 3 h. It was tested that the strong cooling would not help to remove all of the heat produced in a period of 1 h. Theoretically, reducing 1 mol of hydroperoxide by aqueous Na_2SO_3 would release about −370 kJ/mol heat. However, a scale of 1 mol of starting material **1** (287 g) involving 5 mol equiv of hydroperoxide would release corresponding −1850 kJ heat. It was very difficult to control such an exothermic reaction on a large scale in a limited period of 1 h. Finally, we found the solution. We changed the process by doing the acidification first at −5 °C after the hydrolysis to isolate the white solid peracid of **2** whilst avoiding the quench of the extra hydroperoxide that caused the overheating. The subsequent reduction of peracid to release **2** resulted in a very limited amount of heat release (−370 kJ/mol) and was quite easy to control. With this change in the order of acidification implemented, the isolated peracid wet cake, which was quite stable when kept wet and cool, was carried over immediately into **2**. In Table 1 is listed the laboratory and pilot production preparations with the new developed process.

Table 1. **Preparation of 2 by using low-temperature acidification to phase out H_2O_2**

entry	**1** (kg)	**4** (kg)	H_2O_2 30% (kg)	$LiOH·H_2O$ (kg)	Na_2SO_3 (kg)	yield (%)
1[a]	0.516	0.928	1.0	0.218	0.4	55
2	0.516	0.928	1.0	0.218	0.4	56
3[a]	5.16	9.28	9.9	2.18	3.0	46
4	10.32	18.56	19.8	4.36	6.0	50
5	10.32	18.56	19.8	4.36	6.0	50

Experimental Section

General. Melting points are uncorrected. ^1H NMR was recorded on a 200 MHz spectrometer (chemical shifts are given in ppm from internal TMS in $CDCl_3$), IR spectra with Perkin-Elmer 267 spectrometer, and mass spectra with an LKB-9000.

(3*S*, 4*S*)-[(*R*)-1′-((*tert*-Butyldimethylsilyl)oxy) ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone 2. Zn dust (251 g, 3.88 mol) and 540 mL of THF was mixed and heated under reflux for 15 min. Then, **1** (556 g, 1.94 mol) and **4** (1000 g, 2.83

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mol) were mixed and dissolved in 2.16 L of THF and then added dropwise under N_2 to the refluxing Zn dust/THF mixture (*control the addition to avoid overheating*). After this addition, the mixture was concentrated down to half the volume, cooled to 25 °C, filtered, and added to 540 mL of toluene and 1.1 L of water. The mixture was agitated for 15 min and then phase cut. The organic phase was washed with 3 N HCl (540 mL) twice and then with brine (540 mL). To the organic phase was added 1.1 L of THF, and then it was cooled to 0−5 °C. Hydroperoxide (33%) (1065 g, 9.38 mol) was added slowly with the temperature around 0−5 °C. Solid $LiOH \cdot H_2O$ (235 g, 5.59 mol) was added to the reaction mixture. The reaction mixture was then agitated and kept at 0−5 °C for about 1 h. When HPLC monitoring indicated that the reaction had <2% of compound **1** remaining, the aqueous phase was separated from the organic phase. This aqueous phase, with white solid **3** floating on the top layer, was kept at −5 °C and acidified with HCl to pH = 2. The white solid (peracid of **2**) was filtered out and then immediately dissolved into cold 6% NaOH (the pH was kept at 9 by a buffer). The mixture was added to aqueous Na_2SO_3 (431 g, 3.42mol) at 0 °C. The aqueous phase was washed with ethyl acetate twice and was then acidified with aqueous HCl to pH = 2. The white solid was filtered and recrystalized from ethyl acetate/heptane to get **2**, a highly pure white solid 321 g (55%), mp 140−143 °C; IR ($CHCl_3$): 2920 (NH), 3000−4300 (broad COOH), 1742 (β-lactam and acid); NMR (200 MHz): 0.08 (s, CH_3−Si), 0.7 (s, CH_3−C−Si), 1.24 (d, J = 7, CH_3−C−H), 1.3 (d, J = 7.5, CH3−C−H), 2.78 (m, CH_3−CH−C═O), 3.06 (dd, J = 2 and 4.5, H 3), 3.98 (dd, J = 2 and 5, H 4), 4.24 (m, CH_3−CH−O), 6.37 (broad s, NH); ms: *m*/*e* 286 ($M^+ - 15$), 244 ($M^+ - 57$). Anal. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65. Found: C,56,36; H, 9.03; N, 4,48.

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