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Diastereoselective Synthesis of a Key Intermediate for the Preparation of Tricyclic β-Lactam Antibiotics

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Abstract

Asymmetric synthesis of (*S*)-**5** has been accomplished with an excellent enantiomeric excess by hydrogenation of racemic **5** using ruthenium-BINAP–diamine–KOH system, followed by oxidation. Magnesium enolate of (2*S*)-2-methoxycyclohexanone [(*S*)-**5**] reacts with the 4-acetoxyazetidinone **4** to give the key intermediate **3** with high yield and diastereoselectivity for the synthesis of sanfetrinem **1**.

Keywords; Carbapenems, Asymmetric synthesis, Hydrogenation, Aldol reactions

Since the Glaxo Wellcome group reported that sanfetrinem **1**, the tricyclic β-lactam antibiotic [1] and its orally active ester pro-drug **2** have potent and broad spectrum of antibacterial activity, resistance to β-lactamases, and stability to renal dehydropeptidases, considerable effort has been devoted to the stereoselective synthesis of the optically active key precursor **3**. Among a number of the synthetic methods of **3** so far reported [2,3], stereoselective C_4-alkylation of 4-acetoxyazetidin-2-one derivative **4** with enolates derived from (2*S*)-2-methoxycyclohexanone [(*S*)-**5**] is currently recognized as one of the most promising methods [3]. Glaxo Wellcome researchers have already reported the synthesis of (*S*)-**5** by using enzymatic resolution of racemic 2-methoxycyclohexanol [4] followed by oxidation of (1*S*,2*S*)-2-methoxycyclohexanol (CrO_3 oxidation, >99%ee, 56%yield) [3a]. However, the yield of the desired chiral product does not exceed 50% in this method.

We report herein a highly enantioselective synthesis of (*S*)-**5** and a diastereoselective synthesis of **3** by means of the direct coupling of the acetoxyazetidinone **4** with magnesium enolate prepared by the reaction of (*S*)-**5** with magnesium amide derivatives.

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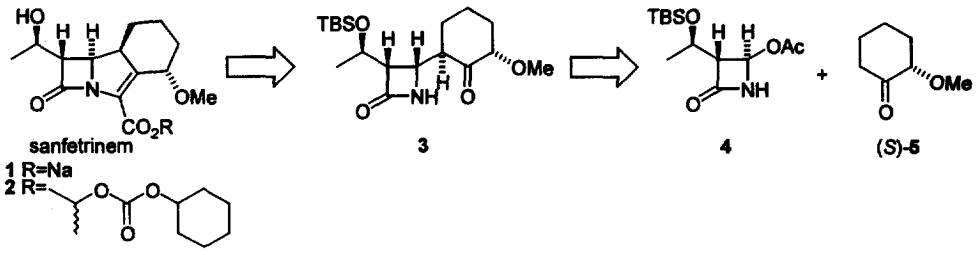
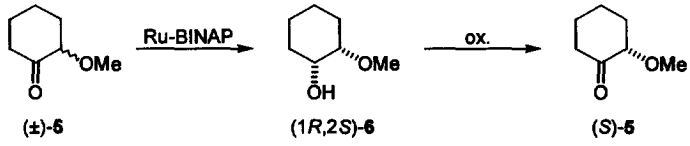


Scheme 1

Firstly, we examined asymmetric hydrogenation of racemic 2-methoxycyclohexanone [(±)-**5**] using $Ru_2Cl_4[(S)\text{-binap}]_2{\bullet}NEt_3$ [5] in 2-propanol at 50°C under H_2 (50kg/cm^2). The hydrogenation proceeded very slowly giving a mixture of four isomers.

In 1996, Noyori et al. reported that asymmetric hydrogenation of 2-isopropylcyclohexanone using $RuCl_2[(S)\text{-binap}](dmf)_n$–(*R*,*R*)-diphenylethylenediamine–KOH ternary system afforded chiral 2-isopropylcyclohexanol with 96% de and 93% ee [6]. As shown in Table 1, the hydrogenation of 2-methoxycyclohexanone (**5**) under the Noyori's conditions proceeded very smoothly to give (1*R*,2*S*)-2-methoxycyclohexanol [(1*R*,2*S*)-**6**] in high yield with 93% de and 87% ee (run 1). The use of $Ru_2Cl_4[(S)\text{-binap}]_2{\bullet}NEt_3$, (*S*,*S*)-diphenylethylenediamine, and KOH ternary system increased the de and ee by 4% and 5%, respectively (run 3). In order to improve the de and the ee many experiments were carried out, and finally we have found that asymmetric hydrogenation of (±)-**5** at 5°C using the ternary system of Ru-(*S*)-3,5-xylyl-BINAP–(*S*,*S*)-diphenylethylenediamine–KOH provided the satisfactory result, giving (1*R*,2*S*)-**6** with 99% de and 99% ee (run 6).



(±)-**5** (1*R*,2*S*)-**6** (*S*)-**5**

Scheme 2

Table 1. Asymmetric hydrogenation of racemic 2-methoxycyclohexanone [(±)-**5**][a]

run	Ru-cat.	H_2(atm)	temp.(°C)	time (h)	conv.(%)[b]	*de*(%)[b]	*ee*(%)[b]
1	$RuCl_2[(S)\text{-binap}](dmf)_n$	50	50	1.0	>99.9	93	87
2[c]	$Ru_2Cl_4[(S)\text{-binap}]_2{\bullet}NEt_3$	50	50	1.0	>99.9	95	90
3	$Ru_2Cl_4[(S)\text{-binap}]_2{\bullet}NEt_3$	50	50	1.0	>99.9	97	92
4	$Ru_2Cl_4[(S)\text{-tol-binap}]_2{\bullet}NEt_3$	50	50	2.5	>99.9	95	88
5	$Ru_2Cl_4[(S)\text{-3,5-xylyl-binap}]_2{\bullet}NEt_3$	50	50	1.0	>99.9	96	96
6	$Ru_2Cl_4[(S)\text{-3,5-xylyl-binap}]_2{\bullet}NEt_3$	50	5	20	>99.9	99	99

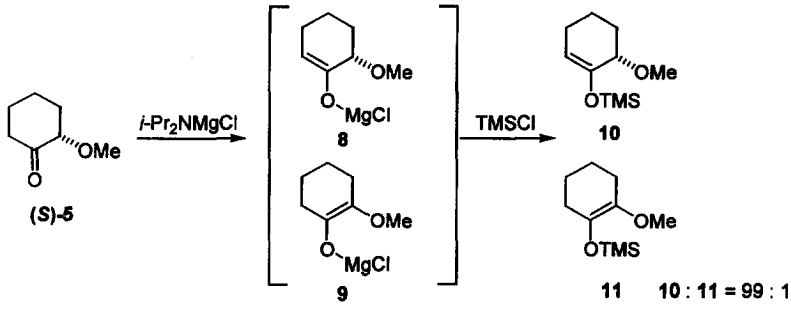
[a] Ru-cat (0.1mol%), (*S*,*S*)-diphenylethylenediamine (0.2 mol%), and KOH (3.0%) were used. All reactions were carried out in 2-propanol. [b] Determind by GC analysis using Chiraldex G-TA. [c](*R*,*R*)-diphenylethylenediamine was used instead of (*S*,*S*)-diphenylethylenediamine.

(1*R*,2*S*)-2-Methoxycyclohexanol [(1*R*,2*S*)-**6**] was oxidized to (*S*)-**5** as reported by the Glaxo Wellcome group [8].

The several methods for the synthesis of **3** from the acetoxyazetidinone **4** have been reported so far. Among them, the most successful method relied on the direct coupling of tin enolate of **5** with **4** [3a]. In this reaction, however, a large amount of $SnCl_4$ was required. High toxicity of $SnCl_4$ is a serious problem in industrial process.

On the other hand, it has been reported that when the azetidinone **4** was reacted with the lithium enolate of **5** (generated with lithium bis(trimethylsilyl)amide in THF at 0°C), several coupling products were obtained [9]. The low selectivity of **3** was due to extensive formation of an undesired enolate of (*S*)-**5** with lithium amide derivatives.

Therefore, we examined other bases which could generate the enolate **8** regioselectively. Among various bases screened, the magnesium amide derivatives were found to be the good bases to generate the enolate **8**. Treatment of **5** with *i*-Pr_2NMgCl (prepared by mixing *i*-Pr_2NH and *t*-BuMgCl in THF at 5°C for 1h), followed by the addition of trimethylchlorosilane gave a high yield of the isomer **10** with a trace of the undesired regioisomer **11** (Scheme 3).



Scheme 3

The reaction of the acetoxyazetidinone **4** with the magnesium enolate **8** generated *in situ* from *i*-Pr_2NMgCl and (*S*)-**5** afforded the desired coupling product **3** in low yield (Table 2, run 1). Removal of free *i*-Pr_2NH by evaporation after the preparation of the enolate **8** from *i*-Pr_2NMgCl and (*S*)-**5**, followed by the addition of **4** remarkably improved the yield of **3** (run 2) [10]. In addition, the use of toluene as a solvent gave **3** in the higher diastereoselectivity and yield. When Et_2NMgCl was used as a base, the yield and diastereoselectivity decreased (run 4).

In conclusion, the key intermediate **3** for the synthesis of sanfetrinem (**1**) has been synthesized with high yield and diastereoselectivity by the direct coupling reaction of the acetoxyazetidinone **4** with magnesium enolate of (2*S*)-2-methoxycyclohexanone [(*S*)-**5**], which has been prepared with excellent enantioselectivity by asymmetric hydrogenation using Ru-(*S*)-3,5-xylyl-BINAP-(*S*,*S*)-dipenylethylenediamine-KOH system, followed by oxidation.

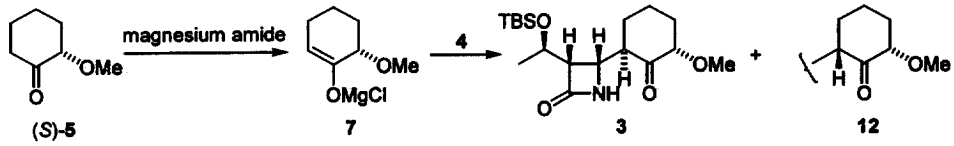


Table 2. Coupling reaction of magnesium enolate **7** with the acetoxyazetidinone **4**.

run	magnesium amide[a]	solvent	temp.(°C)	time (h)	ratio (3/12)[b]	yield of 3 (%)[b]
1[c]	*i*-Pr_2NMgCl	THF	5	0.5	-	20
2	*i*-Pr_2NMgCl	THF	5	0.5	88/12	78
3	*i*-Pr_2NMgCl	toluene	5	0.5	92/8	85
4	Et_2NMgCl	toluene	5	0.5	88/12	56

[a] Magnesium amide was prepared by miximg *t*-BuMgCl and secondary amine in THF at 5°C for 1 h. [b] Determined by HPLC analysis.
[c] No evaporation of amine after preparation of the enolate.

References and notes

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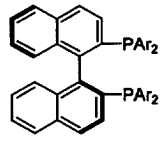
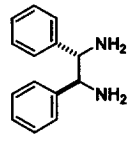
[5] BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.



(*S*)-BINAP: Ar=Ph
(*S*)-3,5-xylyl-BINAP: Ar=3,5-$(CH_3)_2C_6H_3$



(*S,S*)-diphenylethylenediamine

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[8] The oxidation of (1*R*,2*S*)-**6** using CrO_3 gave (*S*)-**5** with 99%ee. The absolute configuration of **5** was determined by sign of optical rotation to be (*S*)-form; see ref [3a]. The enantiomeric excess was determined by GC analysis using Chiraldex G-TA.

[9] Andreotti D, Rossi T, Gaviraghi G, Donati D, Marchioro C, Di Modugno E, Perboni A. Bioorg. Med. Chem. Lett. 1996;6:491.

[10] Experimental procedure for run 1 in Table 2: To a solution of *i*-Pr_2NH (1.96 ml) in THF (10 ml) was added dropwise a solution of *t*-BuMgCl (1.85 mol/l) in THF (6.49 ml) at 0°C and the mixture was stirred for 0.5 h. A solution of (*S*)-**5** (1.41 g) in THF (10 ml) was added dropwise at 0°C over 20 min. The solvent in the reaction mixture was completely evaporated under reduced pressure. The remaining magnesium enolate was dissolved in toluene (15 ml), and cooled to 5°C. A solution of the azetidinone **4** (2.87 g) in toluene (10 ml) was added dropwise at 5°C over 20 min. and the reaction mixture was stirred for 0.5 h. Methanol (10 ml) was added and the mixture was stirred for 10 min, and subsequently, 2NHCl was added. The organic layer was separated and washed with saturated aqueous solution of $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product as an oil (w/w assay by HPLC 85%).