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AN ASYMMETRIC SYNTHESIS OF A KEY INTERMEDIATE TO 1β-METHYLCARBAPENEM ANTIBIOTICS

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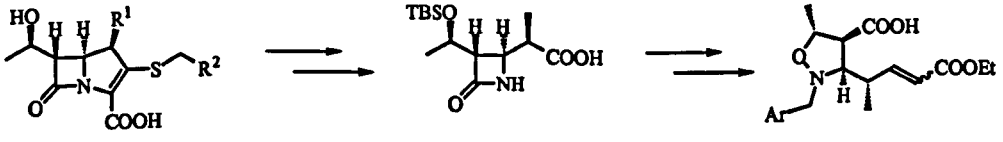
Abstract : 1β-Methylcarbapenem **3** has been enantioselectively synthesized starting from ethoxyethyl ether **8** and methyl (*R*)-3-iodo-2-methylpropionate via the intramolecular 1,3-dipolar cycloaddition of nitrone **6**, in which the requisite chiral centers were settled.

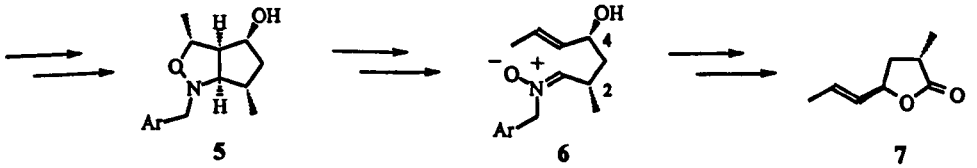
The discovery of (+)-thienamycin **1** from *Streptomyces cattleya* [1] initiated the new generation of carbapenem antibiotics owing to its unusual potency with a broad antibacterial spectrum. In 1984 Shih *et al.* at Merck developed 1β-methylcarbapenem **2** by introducing a β-methyl group at C_1 position on the carbapenem skeleton.[2] It improved the shortcomings of (+)-thienamycin, *i.e.*, chemical instability at high concentration and susceptibility to renal dehydropeptidase-I while preserving its prominent antibacterial activity. Since the synthetic 1β-methylcarbapenem antibiotic possesses a great medicinal value and the unique structure, incessant efforts have been made for its stereoselective synthesis.[3] Herein we also describe an enantioselective synthesis of the key intermediate **3** to 1β-methylcarbapenem **2** via intramolecular nitrone 1,3-dipolar cycloaddition, which was disclosed in the earlier syntheses of carbapenems.[4]

Our retrosynthetic analysis toward **3** proposed isoxazolidine **4** as a crucial intermediate. The four contiguous asymmetric centers would be dictated in the formation of the bicyclic isoxazolidine **5** from nitrone **6** by the steric interactions between C_6-vinylic hydrogen and C_2-methyl group as well as C_4-hydroxyl group.[5]



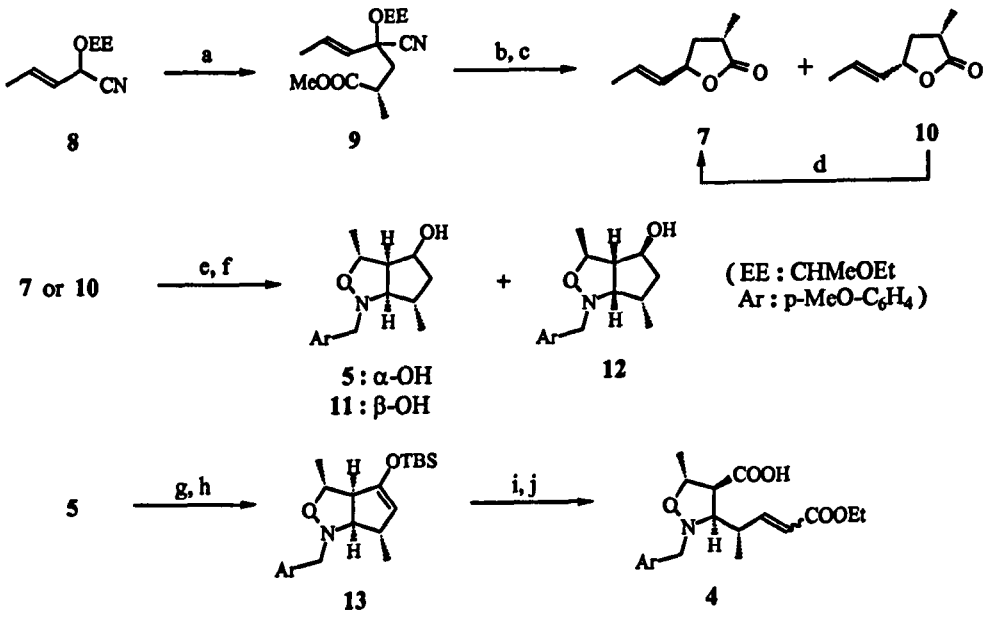
1 : R^1=H, R^2=CH_2NH_2
2 : R^1=Me, R^2=C(=NH)NMe_2

3 **4**



5 **6** **7**

Scheme 1



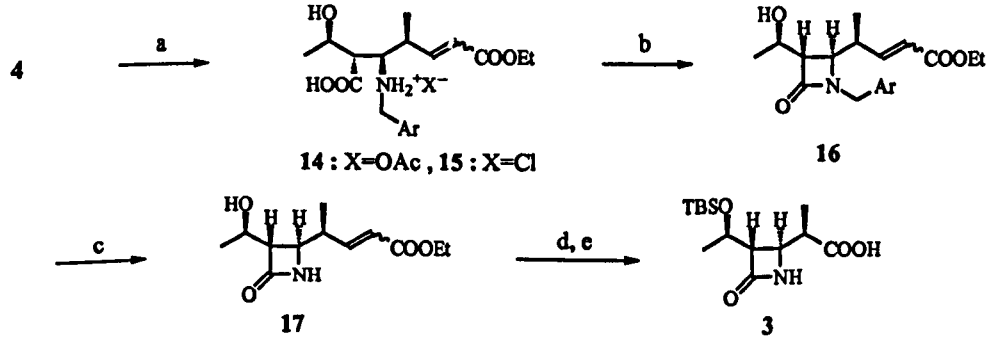
Reagents : a. LiHMDS / THF/ 0°C ; I⁄⁄COOMe / -20°C. b. PPTS/ MeOH/ reflux ; Basic work-up. c. $CeCl_3 \cdot 7H_2O$ (cat.)/ $NaBH_4$/ MeOH/ rt. d. LiOH/ THF-MeOH-H_2O (6:2:3)/ 0°C ; AcOH/ THF ; DEAD/ Ph_3P/ 0°C. e. DIBAL/ CH_2Cl_2/ -78°C ; -78°C ⟶ rt. f. p-MeO-$C_6H_4CH_2NHOH$/ Et_3N/ hydroquinone/ PhH/ Dean-Stark trap/ reflux. g. Swern ox. h. TBSOTf/ Et_3N/ CH_2Cl_2/ rt. i. OsO_4 (cat.)/ $NaIO_4$/ acetone-dioxane-H_2O (1:1:1)/ rt. j. $(EtO)_2POCH_2COOEt$/ n-BuLi/ THF/ 0°C

After deprotonation of ethoxyethyl ether **8** [6] with lithium hexamethyldisilazide (LiHMDS), the generated carbanion reacted with methyl (*R*)-3-iodo-2-methylpropionate [7] to produce a diastereomeric mixture of methyl ester **9** in 94% yield (Scheme 1). The mixture was deprotected with pyridinium p-toluenesulfonate (PPTS) in methanol followed by basic work-up and the resulting ketone, $[\alpha]_D = -17.6°$ ($CHCl_3$, *c* 1.02) was reduced with sodium borohydride in the presence of a catalytic amount of cerium chloride to give a 1:1.3 diastereomeric mixture [8,9] of lactones **7**, $[\alpha]_D = -32.0°$ ($CHCl_3$, *c* 1.00) and **10**, $[\alpha]_D = +4.9°$ ($CHCl_3$, *c* 1.00) in 90% overall yield. [10] After chromatographic separation, each lactone was reduced to the corresponding lactols with diisobutylaluminum hydride (DIBAL). They were subjected to nitrone formation followed by intramolecular 1,3-dipolar cycloaddition. These operations were attained by heating them at reflux with *p*-methoxybenzylhydroxylamine [11] in the presence of triethylamine and hydroquinone in benzene using Dean-Stark trap. While the desired bicyclic isoxazolidine **5**, $[\alpha]_D = -39.7°$ ($CHCl_3$, *c* 0.91) was obtained as a single isomer in 80% overall yield from **7**, a 4:1 mixture of the desired isoxazolidine **11** and its isomer **12** was derived from **10**. [9] Therefore the isomerization of cis-lactone **10** into trans-lactone **7** was intended by hydrolysis with lithium hydroxide and subsequent lactonization under Mitsunobu conditions [12] to furnish a 12:1 mixture of **7** and **10** in 95% yield. Swern oxidation [13] of **5** formed the corresponding ketone, $[\alpha]_D = -133.1°$ ($CHCl_3$, *c* 1.02) in 90% yield and then it was transformed into enol ether **13**, $[\alpha]_D = -13.2°$ ($CHCl_3$, *c* 1.30) in 94% yield using *t*-butyldimethylsilyl triflate (TBSOTf)

in the presence of triethylamine. Oxidative cleavage of **13** was carried out using sodium periodate in the presence of 5 mol % of osmium tetroxide and the cyclic form of the resulting carboxylic acid aldehyde was subjected to Wadsworth-Emmons olefination to provide an isomeric mixture of the conjugated esters **4** in 81% overall yield.

After reductive cleavage of the N-O bond of isoxazolidine **4** with zinc in aqueous acetic acid at 70°C,[14] the generated ammonium acetate **14** was converted into ammonium chloride **15** [15] with methanolic HCl (Scheme 2). Cyclization of **15** was performed using trifluoroacetic anhydride in the presence of 4-dimethylaminopyridine (DMAP).[16] Since the hydroxyl group of **15** was trifluoroacetylated concomitantly, the crude product was readily hydrolyzed with aqueous sodium bicarbonate to give azetidinone **16** in 85% overall yield from **4**. The subsequent removal of *p*-methoxybenzyl group of **16** was attempted using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in wet dichloromethane [17] or ceric ammonium nitrate (CAN) in aqueous acetonitrile. [18] However, the reaction did not proceed or resulted in poor chemical yield. Some experimentation revealed that the difficulties could be overcome by the dropwise addition of water with a syringe pump to the mixture of **16** and CAN in acetonitrile to furnish unmasked azetidinone **17** in 90% yield. The hydroxyl group of **17** was protected with TBSCl in the presence of imidazole and then its conjugated ester group was oxidatively cleaved with potassium permanganate in the presence of tetrabutylammonium bromide in aqueous benzene [19] to provide the desired azetidinone **3** in 97% overall yield. [20]

Scheme 2



Reagents : a. Zn/ AcOH-H_2O (3:2)/ 70°C ; HCl/ MeOH/ 0°C. b. $(CF_3CO)_2O$/ Et_3N/ DMAP/ CH_2Cl_2/ 0°C ; aq. $NaHCO_3$/ THF/ rt. c. CAN/ CH_3CN/ rt ; H_2O ; aq. Na_2SO_3 . d. TBSCl/ imidazole/ DMF/ rt. e. $KMnO_4$/ n-Bu_4NBr/ PhH/ H_2O/ rt ; aq. Na_2SO_3

To sum up, we have established a highly enantioselective synthesis of a key intermediate **3** to 1β-methylcarbapenem antibiotic **2** from methyl (*R*)-3-iodo-2-methylpropionate in 32% overall yield. In addition it seems possible to convert **17** into β-keto ester rather than carboxylic acid **3**.

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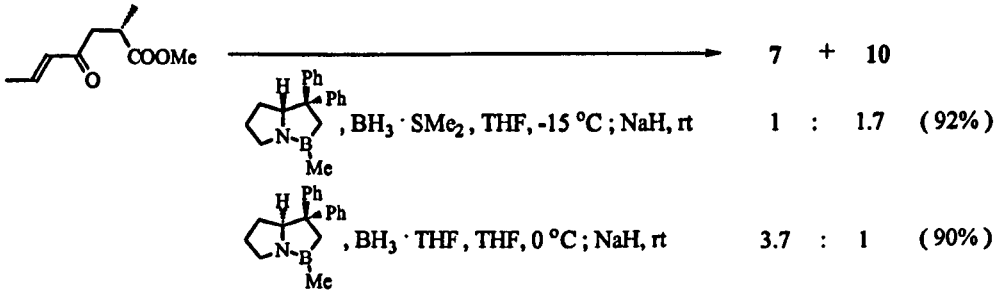
8. In the absence of $CeCl_3$ a 1:2 mixture of **7** and **10** was produced in 81% yield.
9. The relative stereochemistry was unambiguously determined by NOE experiments.
10. Reduction of ketone generated from **9** in the presence of oxazaborolidines proceeded with poor stereoselectivities.



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20. All new compounds showed satisfactory spectral data. The spectral and physical data of **3** were identical with those from Takasago International Corp.

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