A Stereoselective Synthesis of a Key Intermediate to 1β-Methylcarbapenem via Aziridine Ring-opening Reaction

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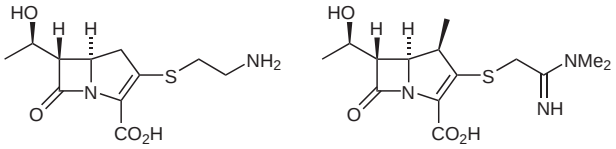
Abstract: A stereocontrolled synthesis of azetidinone **3** as a key intermediate to 1β-methylcarbapenem **2** has been achieved via iodoamidation of trichloroacetimidate prepared from (*Z*)-olefinic allylic alcohol **6**, aziridine ring-opening reaction with cyanide nucleophile and a tandem β-lactam formation.

Key words: stereoselective synthesis, 1β-methylcarbapenem, iodoamidation, aziridine ring-opening, tandem β-lactam formation

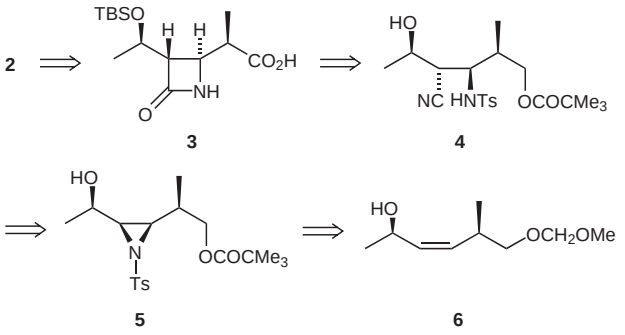
Since the discovery of (+)-thienamycin **1** from *Streptomyces cattleya*,[1] carbapenems have been received considerable attention among the β-lactam antibiotics because of their potent antibacterial activities (Figure 1). While (+)-thienamycin is biologically unstable and metabolized by renal dehydropeptidase I, 1β-methylcarbapenem **2** developed later by the Merck group[2] was found to have the superior stability against enzymatic metabolism as well as the excellent antibiotic potency. Its prospective pharmaceutical utility has led many synthetic organic and medicinal chemists to be engaged in the synthesis of various 1β-methylcarbapenem derivatives, in which azetidinone **3** is evidently one of the most successfully employed key intermediates.[3] Intrigued by its four contiguous asymmetric centers as well as its medicinal value, we herein describe a stereocontrolled synthesis of azetidinone **3**.



1 **2**

Figure 1

Retrosynthetically, aziridine **5** was proposed as our key synthetic intermediate, the regioselective ring-opening reaction of which was planned by cyanide anion to secure all the requisite contiguous chiral centers (Scheme 1). In addition, we envisioned that **5** could be generated via our iodoamidation protocol using (*Z*)-olefinic allylic trichloroacetimidate derived from the corresponding alcohol **6**.[4]



Scheme 1 Retrosynthetic analysis

For the synthesis of **6**, the hydroxyl group of the commercially available alcohol **7** was protected with chloromethyl methyl ether in 91% yield and the resulting bromide was reacted with Ph_3P to render phosphonium salt **8** in 86% yield (Scheme 2). Wittig olefination of **8** with (*R*)-2-*t*-butyldimethylsilyloxypropanal[5] was performed with *n*-butyllithium in HMPA and THF to give a 21:1 unseparable mixture of *cis*- and *trans*-olefins in 90% combined yield. After desilylation using TBAF, the mixture was readily separated to afford the desired *cis*-olefinic allylic alcohol **6** in 94% yield. Iodoamidation of (*Z*)-olefinic allylic trichloroacetimidate has been established to generate *trans*-4,5-disubstituted oxazoline by a preference for 5-*exo* ring closure probably due to the steric interactions in the transition state.[4,6] Accordingly, **6** was reacted with trichloroacetonitrile in the presence of DBU and the resulting crude trichloroacetimidate was intramolecularly cyclized using iodine monobromide at –78 °C to furnish the expected *trans*-oxazoline **9** as a single stereoisomer. The oxazoline **9** was exhaustively deprotected with methanolic HCl, cyclized using sodium bicarbonate in MeOH and tosylated in sequence to give rise to *N*-*p*-toluenesulfonyl aziridine **10** in 95% yield from **9**. In comparison with *N*-*t*-butoxycarbonyl, *N*-benzyloxycarbonyl, *N*-trifluoromethylsulfonyl and *N*-nitrophenylsulfonyl aziridines, the tosyl aziridine was found to be most reactive toward aziridine ring-opening reaction. Also, it was revealed that the protecting group of the primary hydroxyl group of **10** affected the ring-opening reaction significantly. Among silyl, *t*-butoxycarbonyl, triphenymethyl and trimethylacetyl protecting groups, the best experimental results in terms of regioselectivity and chemical yield was attained from trimethylacetate **5**. Treatment of **5** with 5 equivalents of lithium cyanide in HMPA produced a 7:1 separable

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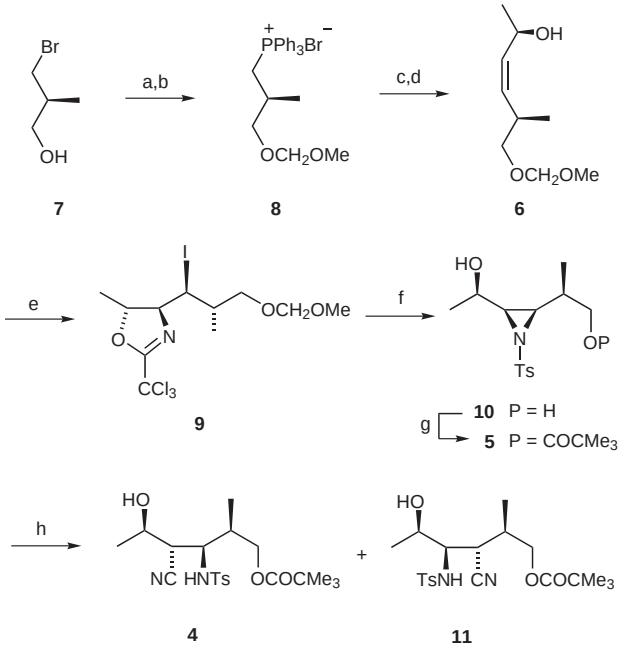
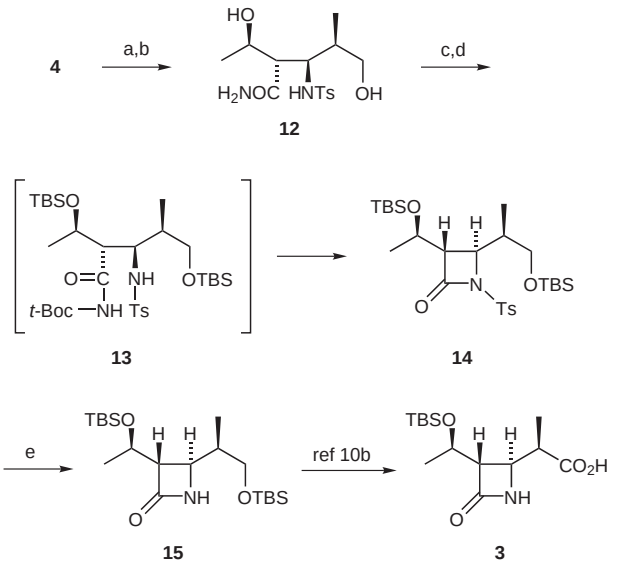


Scheme 2 *Reagents and conditions*: (a) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, r.t., 91%; (b) PPh_3, K_2CO_3, MeCN, 90 °C, 86%; (c) *n*-BuLi, HMPA, THF, –15°C, then (*R*)-2-*t*-butyldimethylsilyloxypropanal, –78 °C to –15 °C, 90%; (d) TBAF, THF, r.t., 94% for *cis*-olefin; (e) Cl_3CCN, DBU, MeCN, 0 °C, then IBr, DBU, CH_2Cl_2, MeCN, –78 °C to –50 °C, 91%; (f) 6 N HCl, MeOH, r.t., then $NaHCO_3$, MeOH, r.t., then TsCl, r.t., 95%; (g) Me_3CCOCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 94%; (h) LiCN, HMPA, r.t., 91%.

mixture of the desired β-amino cyanide **4** and its diastereomer **11** in 91% combined yield.

β-Lactam ring formation was regarded as the crucial step in the next sequence of our synthesis. Our initial effort for the transformation focused on direct or indirect hydrolysis of the cyanide derivatives into carboxylic acids to prove abortive. Alternatively, the intramolecular cyclization was conceived to be attained using amide instead of carboxylic acid. Accordingly, the trimethylacetyl group of **4** was removed with DIBAL and then its cyanide group was hydrolyzed into amide **12** in 81% overall yield using hydrogen peroxide in ethanolic ammonium hydroxide (Scheme 3).[7] After bissilylation of **12** with TBSCl in 87% yield, the resulting amide was subjected to mesyl chloride, tosyl chloride, triflic anhydride, benzyloxycarbonyl chloride, *i*-butoxycarbonyl chloride and di-*t*-butyl dicarbonate. Only di-*t*-butyl dicarbonate turned out to be successfully applied for the cyclization. Treatment of the bissilylated amide with di-*t*-butyl dicarbonate in the presence of DMAP and Et_3N gave the desired azetidinone **14** in 90% yield evidently via *t*-butoxycarbonylamide **13**. Finally, **14** was desulfonylated by sodium naphthalide in DME[8] uneventfully to produce β-lactam **15**[9] ($[\alpha]_D^{15}$ = –8.32, *c* 1.00, $CHCl_3$) in 95% yield, which was converted into a known key intermediate **3** to 1β-methylcarbapenem according to Ohno's procedure.[10]

In summary, we have established a stereoselective synthesis of azetidinone **3** as a key intermediate to **2** via the diastereoselective iodoamidation, the regioselective aziridine ring-opening reaction and the tandem intramolecular cyclization.



Scheme 3 *Reagents and conditions*: (a) DIBAL, CH_2Cl_2, –78 °C, 91%; (b) 30% H_2O_2, EtOH, NH_4OH, r.t., 89%; (c) TBSCl, imidazole, DMF, r.t., 87%; (d) *t*-Boc_2O, DMAP, Et_3N, CH_2Cl_2, r.t., 90%; (e) Na-naphthalide, DME, –78 °C, 95%.

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