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AN EXPEDITIOUS SYNTHESIS OF A 1β-METHYLCARBAPENEM KEY INTERMEDIATE

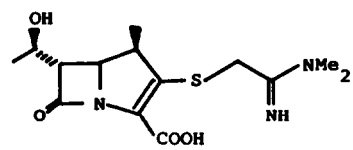
Robert Deziel* and Masaki Endo

Chemical Process Development, Bristol-Myers Pharmaceutical Research and Development Division, Candiac, Quebec, Canada J5R 1J1

Summary: The β-methylcarbapenem key intermediate 4 was prepared *via* a novel aldol-type alkylation of 2 with the divalent tin enolate 6 generated *in situ* from 7 and metallic tin.

A few years ago Merck researchers found that the introduction of a β-methyl at position C-1 on the carbapenem nucleus resulted in a considerable increase of the metabolic and chemical stability; the carbapenem 1 is a good example[1]. Since then, many papers have appeared regarding the stereoselective introduction of the β-methyl substituent[2]. However, most of the reported procedures involve an aldol-type reaction with the azetidinone 2 and enolates of propionic acid derivatives to give the intermediate 3 after removal of the auxiliary[3]. Transformation of 3 into the key intermediate 4, which is the precursor of the requisite bicyclic keto-ester 5, involves several steps, that is chain extension, hydrolysis of the TBDMS protective group and diazotization.

In this communication, we wish to report an expeditious synthesis of the key intermediate 4 involving an aldol-type reaction of the tin (II) enolate 6, generated *in situ* from metallic tin and the α-bromo ketone 7, on the available azetidinone 1[4]. Initially, we attempted the alkylation according to Mukaiyama's original condition for aldol reaction[5] (stepwise process) but the desired alkylation product 8 was obtained in low yield. After several trials, we



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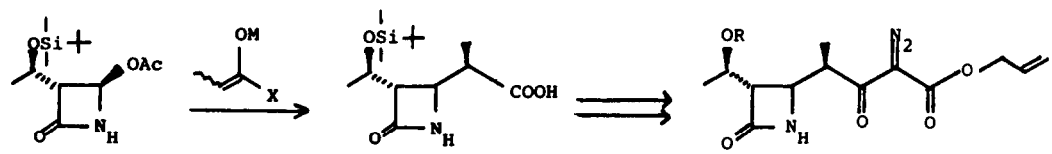
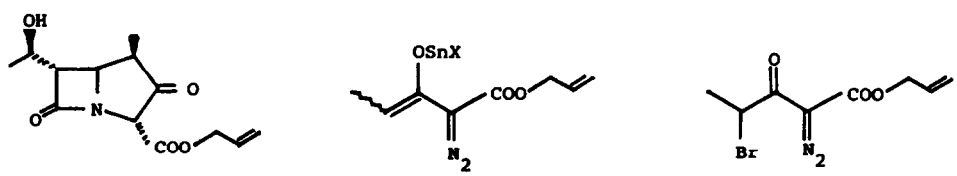
found that a one-pot procedure (i.e. formation of the enolate 6 in the presence of 2 gave much higher yields. It was also found that the choice of the solvent is very important. For example solvents such as THF, diethyl ether and dichloromethane gave very poor results. Polar solvents like DMF are essential and optimum results were obtained in a 2:1 mixture of DMF/CH_2Cl_2. Also the oxidative addition step needs to be initiated, otherwise most of the time no reaction occurs. For this purpose many catalysts were investigated and it was found that addition of $AgBF_4$ (5 mol %) along with a small amount of iodine efficiently promoted the reaction. Thus, under optimum conditions the desired product 8 was obtained in 75-80% yield as a diastereomeric mixture (β:α=3:1). All attempts to separate the diastereomers at this stage by either chromatography or crystallization were fruitless. Nevertheless 8 was hydrolyzed in 1N HCl/CH_3CN to give the desired key intermediate 4 (β:α=3:1) in nearly quantitative yield. Much to our satisfaction we found that at this stage it was possible to isolate the pure β-methyl isomer 4 by a simple crystallization of the crude product in ether. In this way, pure 4 (>98%) was obtained from 1 in 40-45% yield.



2 3 4 (R=H) 8 (R=TBDMS)

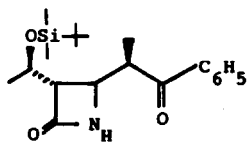


5 6 7

In a similar manner, the β-methyl aryl carbapenem 9 was obtained from 2 and bromopropiophenone in 60% yield[6]. Compound 9 could prove to be a useful intermediate for the synthesis of 2-arylcarbapenems[7].

Finally it is worth mentioning that the 4-chloroazetidinone 10 also undergoes similar reaction at low temperature (-40°C), although good yield was obtained only when an equimolar amount of $AgBF_4$ was present[8].

Thus the methodology described herein constitutes a very short and efficient synthesis of the key intermediate 4 since it involves only two steps and readily available starting materials.



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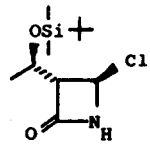

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Procedure: To an ice cooled mixture of metallic tin[9] (71.2 g, 0.60 mol) and 2 (57.5 g, 0.20 mol) in DMF/CH_2Cl_2 (150 mL/75 mL) was added a solution of 7[10] (52.2 g, 0.20 mmol) in DMF/CH_2Cl_2 (50mL/25 mL) followed by the addition of $AgBF_4$ (2.0 g, 0.01 mol) and I_2 (~200 mg). The resulting black suspension was stirred at 0°C for 90 min then a second portion of 7 (26.1 g, 0.1 mol) in DMF/CH_2Cl_2 (25mL/12.5 mL) was added. After 90 min at 0°C the mixture was filtered through Celite, poured into a 1:1 mixture of EtOAc/hexane and washed with 1N HCl (2 x 400 mL), cold 5% NaOH (1.1 L), water (350 mL), 1N HCl (350 mL) and with brine (400 mL). After the organic layer was dried over $MgSO_4$, it was concentrated to give crude 8 (100.5 g). This crude product was hydrolyzed in a mixture of 1N HCl (40 mL) and acetonitrile (400 mL) at room temperature for 18 h, diluted with water (1.16 L) then washed with hexane (3 x 400 mL). The aqueous phase was saturated with NaCl and extracted with EtOAc (500 mL, 2 x 250 mL). The combined organic phases were washed with saturated $NaHCO_3$ (250 mL) and with saturated NH_4Cl solution (500 mL). The organic phase was dried ($MgSO_4$), treated with Norit A and filtered through Celite. The filtrate was concentrated to dryness to give crude 4 which was dissolved in ether (170 mL). The mixture was stirred at room temperature overnight then at 0°C for ~2 h. The solid was filtered and washed with cold ether to give pure 4 as a white powder, 24.2 g, 41%, m.p. 103-105°C[11]. This material contains less than 1% of its α-isomer.

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Notes and references

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6) Analysis of the crude product indicated a β:α ratio of 3:1 and its recrystallization from hexane afford pure 9 (>97%) in 60% yield.

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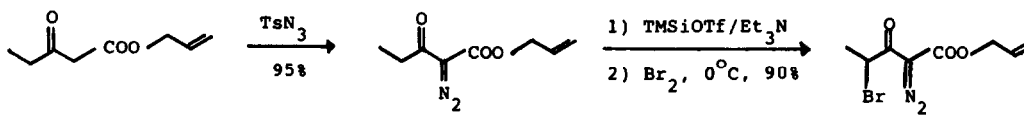
8) Endo, M.; Can. J. Chem., In press.

9) Commercially available tin powder (200 mesh) was activated with 10% NaOH (2 h), washed with water then with methanol and dried *in vacuo* at 130°C.

10) Compound 7 was prepared as follows:



11) Spectral data of 4: IR (CH_2Cl_2) 3500, 2150, 1760, 1720, and 1645 cm^{-1}. NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, J=6.6 Hz, 3H, 1β-CH_3), 1.29 (d, J=6.3 Hz, 3H, CH_3-CH-OH), 2.55 (br s, 1H, OH), 2.88 (dd, J=7.4, 1.3 Hz, 1H, H-3), 3.75 (m, J=6.6 Hz, 1H, CH-CH_3), 3.82 (dd, J=6.5, 2.1 Hz, 1H, H-4), 4.10 (m, 1H, CH-OH), 4.71 (m, 2H, CH_2-CH=CH_2), 5.25 (m, 2H, CH_2=CH), 5.90 (m, 1H, CH=CH_2), 6.03 (s, 1H, N-H).

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