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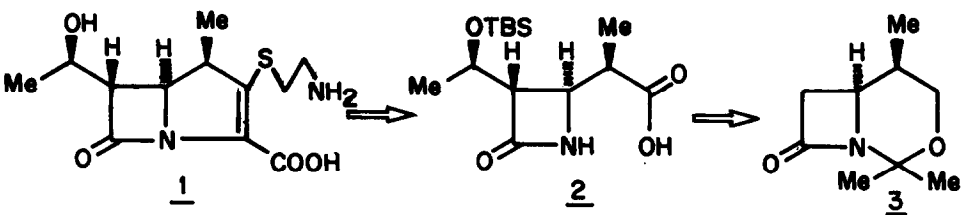
STEREOCONTROLLED APPROACHES TO THE KEY INTERMEDIATE OF 1β-METHYLTHIENAMYCIN

A.V. Rama Rao*, M.K. Gurjar, V.B. Khare, B. Ashok and M.N. Deshmukh
Indian Institute of Chemical Technology, Hyderabad 500 007, India.

Summary: Two stereocontrolled approaches for the advanced intermediate (**2**) of 1β-methylthienamycin have been described.

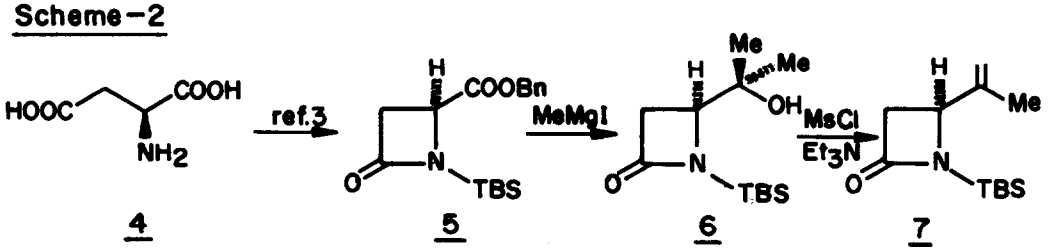
The quest to enhance the chemical and metabolic stabilities of carbapenem antibiotics has been intensified since the introduction of 1β-methylthienamycin (**1**) by the Merck group[1]. Undoubtedly **1** is by far the most promising candidate from clinical and medicinal point of view. The stereocontrolled aldol condensation[2a] and the cycloaddition reaction[2b] form the basic premise for most of the approaches reported for **1**. However efforts[2c] are being continued to devise a practical synthetic protocol that would provide **1** in an efficient manner. In this communication we wish to disclose our own findings towards **2**, an advanced intermediate recognised for **1** (scheme 1). The salient features of our two approaches, reported herein, for introducing the methyl substituent at position 1 of **1** are the stereoselective hydroboration-oxidation reaction of **7** and the stereospecific hydrogenation of **10**.

Scheme-1



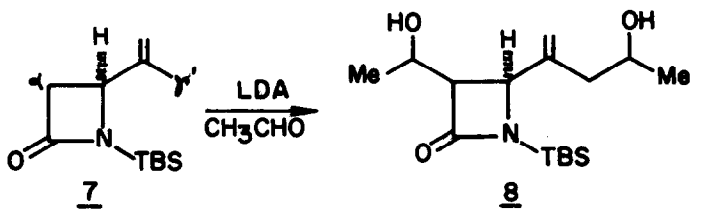
The β-lactam derivative (**5**) was readily obtained from L-aspartic acid in three high yielding steps[3] (scheme 2). Grignard reaction (MeMgI,Et_2O,RT, 16 h) of **5** afforded the dimethylcarbinol derivative (**6**) ($[\alpha]_D$-26.8°(c 1, $CHCl_3$) (84%). Subsequent treatment[4] of **6** with mesyl chloride-triethylamine (CH_2Cl_2,RT, 5h) effected elimination reaction to form **7** ($[\alpha]_D$-16.8° (c 0.8, $CHCl_3$) (82%).

Scheme-2



At this junction we examined the incorporation of hydroxyethyl side-chain at C-3 of **7**. Thus, **7** was reacted (LDA, THF -78°C, 0.5 h) with acetaldehyde, however, the major product isolated from the reaction was found to be **8**. Although condensation of acetaldehyde with lithium enolate of β-lactam was known[5] to occur α to the carbonyl function, in the present case metallation also took place concurrently at the remote γ'-position[6] leading to the formation of **8** (scheme 3). Nevertheless, this finding suggested that the isopropenyl unit at C-4 was not particularly suited, therefore we felt its stereocontrolled conversion into the desired 1-methyl-2-hydroxyethyl unit (**3**) as our immediate priority.

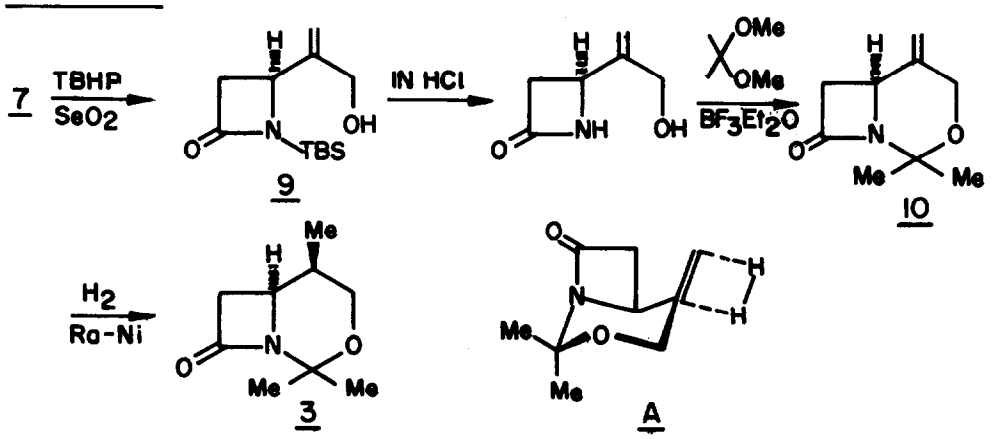
Scheme - 3



7 **8**

With a view of hydroxylating the allylic carbon in **7**, the Sharpless reaction[7] (TBHP, SeO_2, CH_2Cl_2,RT, 48 h) was employed, which afforded **9** ($[\alpha]_D$-88° (c 0.75, $CHCl_3$) (55%, 85% based on recovered **7**) as an exclusive product (scheme 4). The TBS group was cleaved (MeOH, 1N HCl, RT, 1h) and consequently protecting ($Me_2C(OMe)_2$, CH_2Cl_2, BF_3:Et_2O, 45 min) with isopropylidene group afforded **10** ($[\alpha]_D$-112° (c 0.9, $CHCl_3$)(85%). Hydrogenation (Ra/Ni(EtOAc), H_2, MeOH, RT, 4h) of **10** underwent[8] smoothly to afford **3** ($[\alpha]_D$+34.6° (c 0.5, $CHCl_3$) as a sole isolable product (90%). We expected the stereospecific reduction to occur based on the molecular structure A in which the delivery of hydrogen molecule happened from the least hindered α face. The absolute stereochemistry of **3** was established unambiguously by ^1H NMR (300 MHz) spectrum in which the characteristic[9] coupling constants ($J_{4a,5e}$=2.5 Hz, $J_{4e,5e}$=2.2 Hz, $J_{4a,4e}$=12.2 Hz) were observed for H-4 and H-5.

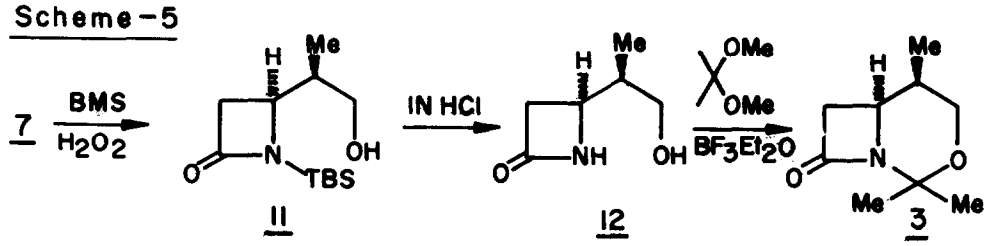
Scheme - 4



9 **10** **3** **A**

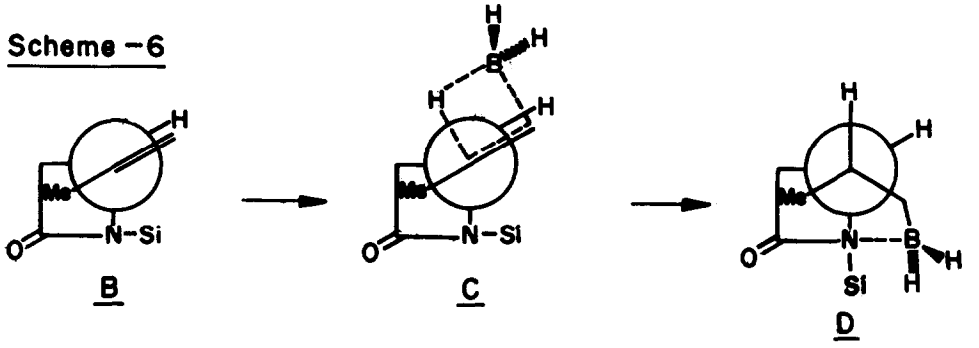
The stereoselective hydroboration-oxidation[10] of pro-chiral isopropenyl substituent containing an adjacent chiral center has been a topic of interesting studies. The stereochemical outcome of this reaction is profoundly swayed by steric and electronic factors and also by the nature of hydroborating reagent. We felt it would be interesting to initiate a study on the stereochemical course of hydroboration reaction of isopropenyl substituent attached directly to the chiral β-lactam ring system such as **7** because if successful, it would also form an efficient alternate strategy for **3** (scheme 5). Thus, compound **7** was treated with 2M solution of borane-methylsulfide complex in THF (0°-RT, 2 h) followed by oxidation (H_2O_2-NaOAc, 2 h) gave a single isomer **11** ($[\alpha]_D$-13° (c 1, $CHCl_3$) (61%). It's subsequent conversion into **3** ($[\alpha]_D$+33.6° (c 0.5, $CHCl_3$) was carried out as described above. Compound **3**, obtained from both the approaches, was identical.

Scheme-5



The highly stereoselective hydroboration-oxidation reaction of **7** with borane could possibly be explained by considering Houk's conformer model B[12]. The delivery of borane to the double bond occurs in a directed way leading to the intermediate D via the transition state C (scheme 6).

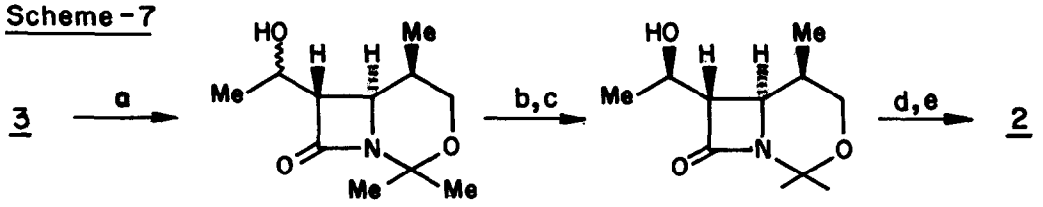
Scheme-6



Having established the strategies to build the intermediate **3** our next concern was to elaborate the hydroxyethyl side chain. Although number of modified procedures[2a] have been developed, by and large the intrinsic chemistry involved in them essentially follow Merck's approach[1,8], which was adopted in the present study to prepare the key intermediate **2** (scheme 7).

It is pertinent to mention in conclusion, that a practical and highly stereocontrolled protocol for the synthesis of **2** has been successfully developed and utilised on multigram scale.

Scheme-7



a LDA, THF, -78 °C, CH_3CHO, 5 min; b TFAA-DMSO, 0 °C, 16 h;

c K-Selectride, Et_2O, 0·5 h; d TBS-Cl, DMF, Imi; e Jones reagent.

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