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Synthesis of enantiomerically pure compounds of biological interest

MUKUND K GURJAR

Indian Institute of Chemical Technology, Hyderabad 500 007, India

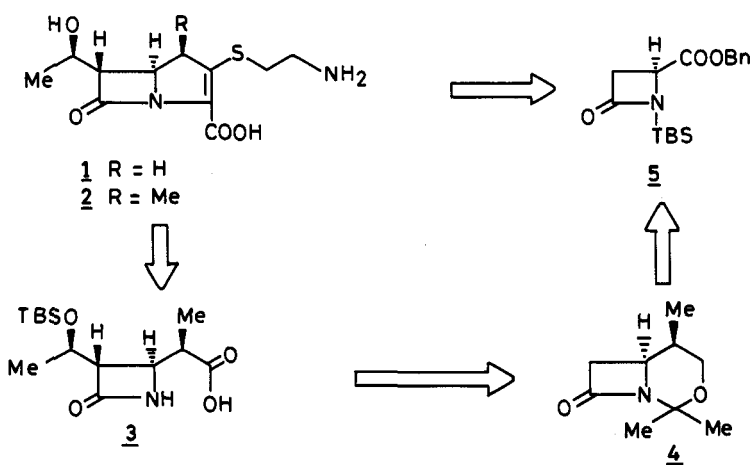
Abstract: Our contributions to the synthesis of enantiomerically pure compounds of biological interest particularly, 1β-methylthienamycin (**2**) and MeBmt (**13**) are reviewed. The salient features of the approaches towards the key intermediate (**3**) of **2** involved a) the stereospecific reduction of **10** and b) the stereoselective hydroboration-oxidation reaction of **7**. A versatile protocol leading to the formation of all the four enantiomerically pure diastereomers of β-hydroxy-α-amino acids, has been forwarded. An application of this protocol for **13** was demonstrated.

The vogue of synthesising biologically active compounds in enantiomerically pure forms owe its origin to the understanding of biological phenomena at the receptor site. It is now well understood that the biological function of an organic molecule and its chirality are inter-related (ref.1). With the advent of several chiral drugs (ref.2) having specific activities (ref.3), it appears that in near future, all the new chiral drugs may be made mandatory for use in enantiomerically pure forms for the consumers market. As a consequence, recourse to new protocols for obtaining chiral molecules, without resorting to the process of resolution, has become the prime objective of several synthetic laboratories. Synthetic chemists have adopted (ref.4) two principal approaches for deriving enantiomerically pure target molecules: (a) asymmetric synthesis and (b) chiron approach. Contributions from our laboratory concerning the use of both these approaches in the synthesis of (a) 1β-methylthienamycin and (b) (4R)-4-[(E)-2-butenyl]-4,N-dimethyl-L-threonine are reviewed.

1β-METHYLTHIENAMYCIN

Since the discovery of penicillin, no class of antibiotics has received such an overwhelming attention and on so many fronts. Over the years (ref.5) several new classes of β-lactam antibiotics have been isolated. However, the most significant discovery of the recent years has been the isolation of thienamycin (**1**), belonging to the class of carbapenems, by the Merck group (ref.6). Thienamycin arose profound interest (ref.6) not only because of its broad spectrum activity particularly against pseudomonas but also due to its unusual structural and functional framework. Thienamycin could not be judged as a potential clinical drug, apparently due to chemical instability and metabolic sensitivity to renal dehydropeptidase-I. As a matter of fact, the low yield of thienamycin from the fermentation broth is attributed to these properties and therefore it is presently produced on a commercial scale by synthesis (ref.7). The quest to enhance the chemical and metabolic stabilities of **1** was intensified and in 1984, the Merck group came out (ref.8) with a simple analogue namely, 1β-methylthienamycin (**2**) possessing the requisite stabilities. The stereocontrolled

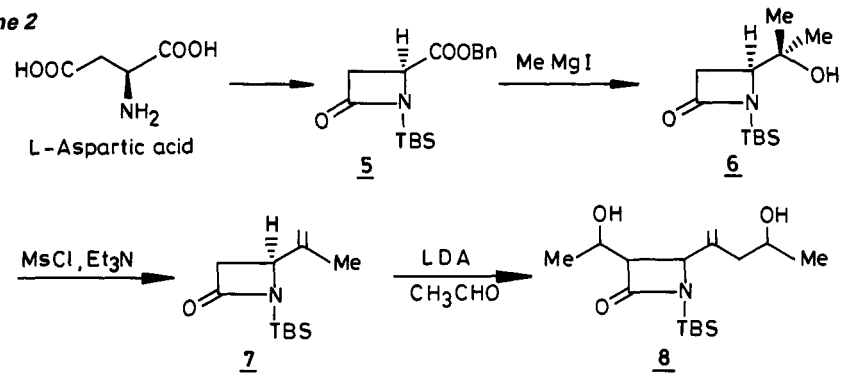
Scheme 1



aldol condensation (ref.9) and the cycloaddition reaction (ref.10) form the basic premise for most of the approaches reported for **2**. However, efforts are on to devise (ref.11) a practical synthetic protocol that would give rise to **2** in an efficient manner.

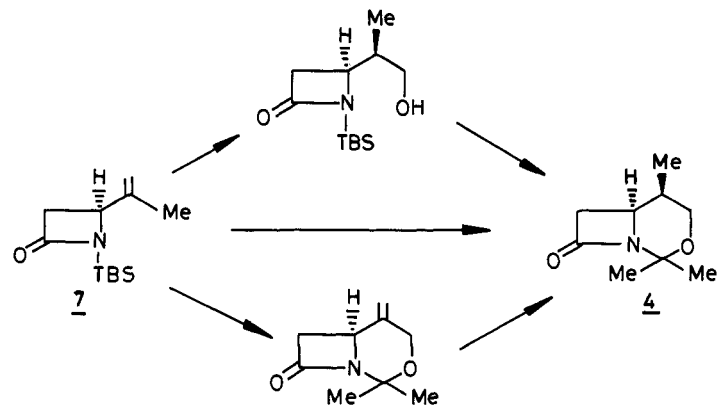
Our retrosynthetic examination of **2** is depicted in scheme 1. The advanced intermediate **3** could be envisaged by extension of the side-chain at carbon α to the carbonyl in compound **4** which in turn could find its origin by chemical manipulation of the easily accessible (S)-4-benzyloxycarbonylazetidin-2-one (**5**).

Scheme 2



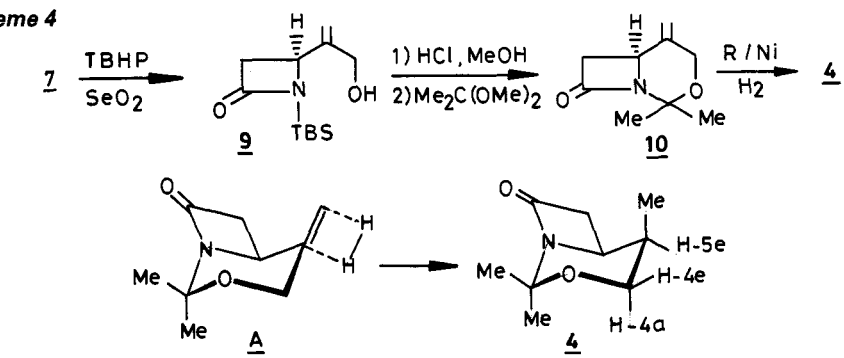
The β-lactam derivative (**5**) was obtained (ref.12) from L-aspartic acid in three high yielding steps. One of the reasons for employing **5** for the present study, could be attributed to the abundant availability of this intermediate as it forms the starting precursor for commercial process of **1** (ref.7). Treatment of **5** with excess of methylmagnesium iodide produced the dimethyl carbinol

Scheme 3



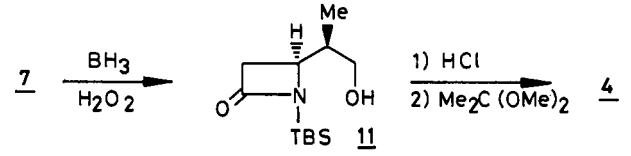
derivative (**6**) in 84% yield (Scheme 2). Subsequent dehydration (ref.13) reaction on **6** was conducted in the presence mesyl chloride-triethylamine to afford the 4-isopropenyl-β-lactam (**7**). At this juncture we examined the introduction of hydroxyethyl side-chain at C-3. Thus, treatment of **7** with LDA at -78°C followed by addition of acetaldehyde gave **8** as a major product. Although the aldol condensation is known (ref.8) to occur α- to the carbonyl function, in this case metallation also took place at the remote γ' position (ref.14). This undersired course of reaction implied that the isopropenyl group in **7** was not suitable, therefore, its stereocontrolled conversion into the 1-methyl-2-hydroxyethyl unit should be our immediate priority. For this objective, we planned two stereoselective approaches (scheme 3) involving hydrogenation and hydroboration-oxidation reaction.

Scheme 4



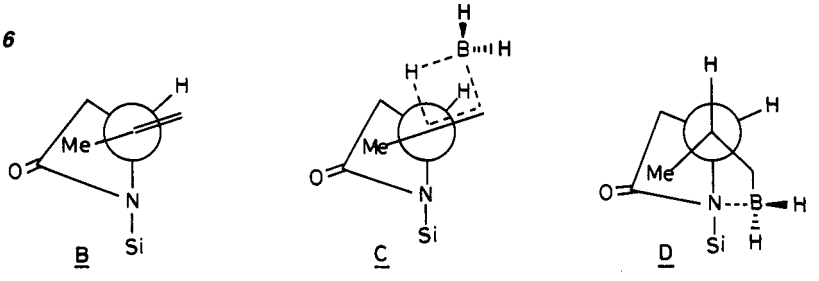
With a view of hydroxylating the allylic carbon in **7**, the Sharpless reaction (ref.15) employing SeO_2 and tert-butylhydrogen peroxide was utilised to give **9** in 55% yield (85% based on recovered **7**) (Scheme 4). Successive deprotection of TBS group with 1N HCl in methanol and treatment of the resulting amido-alcohol with dimethoxypropane-BF_3:OEt_2 gave **10**. Hydrogenation of **10** in the presence of R/Ni (washed with ethylacetate) at normal temperature and pressure gave **4** in 90% yield. The stereospecific hydrogenation was indeed expected to occur in the desired direction as the molecular model A revealed that the delivery of hydrogen should take place from the less hindered α-face. The structure of **4** was unambiguously assigned by ^{1}H NMR spectrum (300 MHz) (ref.16). The coupling constants : $J_{4a,5e}$=2.5, $J_{4e,5e}$=2.2 and $J_{4a,4e}$=12.2 Hz were in agreement with the structure **4**. (scheme 4)

Scheme 5



The stereoselective hydroboration-oxidation reaction of a pro-chiral isopropenyl group adjacent to a chiral center is a topic of current interest (ref.17). The stereochemical outcome of this reaction is profoundly swayed by steric and electronic factors and by the nature of the hydroborating agent. As a consequence, we became interested in performing hydroboration-oxidation reaction on **7** in which the isopropenyl group is flanked with a chiral β-lactam ring system. In case it is successful, the methodology would furnish an alternate approach to the key intermediate **4**. Thus, compound **7** was treated with 2M borane methyl sulfide complex in THF followed by oxidation with H_2O_2-NaOAc to afford **11** in 61% yield. Subsequent removal of TBS group and protection with isopropylidene group afforded **4** which was identical with the sample prepared earlier. (scheme 5)

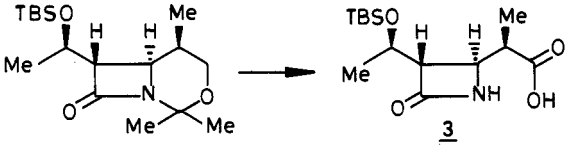
Scheme 6



The highly stereoselective course of hydroboration-oxidation reaction of **7** could be explained by considering the Houk's conformer model **B** (ref.18). The delivery of borane occurred in a directed fashion (transition state C) thus leading to the intermediate D. (scheme 6)

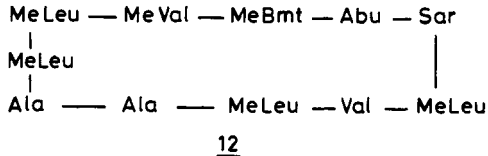
The next concern was to incorporate the chiral side-chain and although several modifications have been suggested, the intrinsic chemistry in all these modifications essentially follow the work of the Merck group (ref.8). This approach was adopted to prepare the key intermediate **3**. (scheme 7)

Scheme 7



(4R)-4[(E)-BUTEN-2-YL]-4,N-DIMETHYL-L-THREONINE

β-Hydroxy-α-amino acids form the partial structure of several polypeptide natural products. For example, the presence (ref.19) of the unusual β-hydroxy-α-amino acid, (4R)-4[(E)-2-butenyl]-4,N-dimethyl-L-threonine (MeBmt) (**13**) in cyclosporin (**12**) constitutes a classical illustration. The utility of cyclosporin as an immunosuppressive agent (ref.20) during organ transplantation such as kidney, lever, heart, bone-marrow etc., is now well recognised. However, the high cost of cyclosporin coupled with the tedious technique of isolation and low-yields, necessitated synthetic efforts towards **12** in various laboratories. The main issue in the synthesis of cyclosporin is the non-availability of MeBmt (**13**) which focussed (ref.21) a great deal of attention in recent years on the development of a practical and efficient approach. As part of a programme, we were interested in establishing a versatile protocol which in principle should provide all the four diastereoisomers of β-hydroxy-α-amino acids. Our attention was drawn towards the readily obtainable optically active cis-oxazolidinone derivative (ref.22) (**B**) which in turn could be realised from the optically active 2,3-epoxy alcohol (**A**) (ref.23). We reasoned that the corresponding oxazolidinone ester (**C**) obtained by the oxidation of the hydroxymethyl group in **B**, on hydrolysis should furnish anti-β-hydroxy-α-amino acid (**D**). Whereas subsequent epimerisation of cis-oxazolidinone (**C**) to a more stable trans-oxazolidinone derivative (**E**) followed by hydrolysis would give rise to syn-β-hydroxy-α-amino acid



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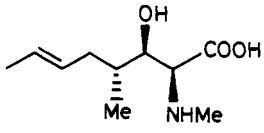

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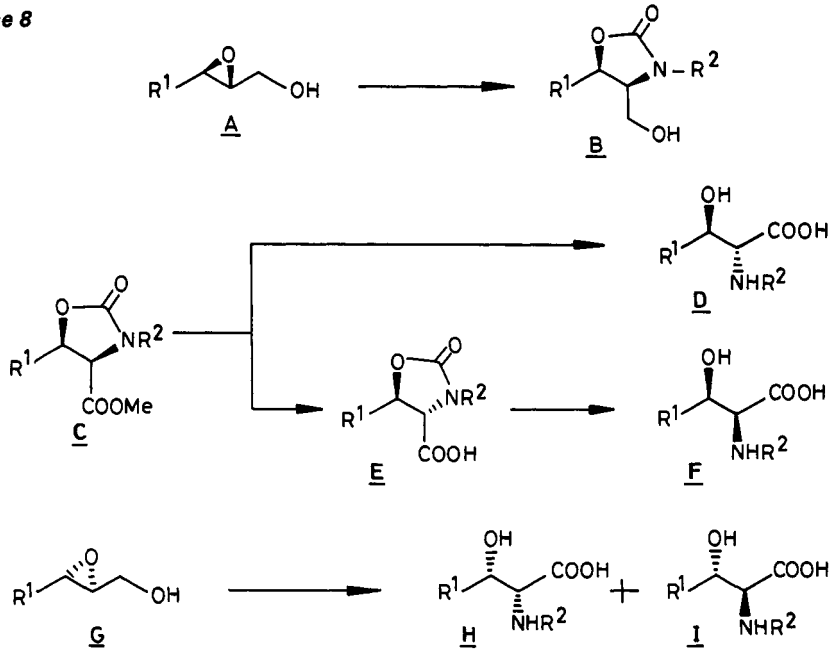
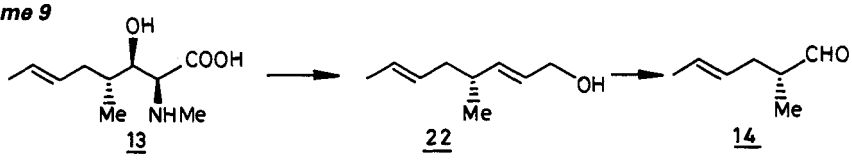
(F). Similarly it becomes apparent that the other two diastereomers namely (H) and (I) could be synthesised from the corresponding optically active 2,3-epoxy alcohol (G) (Scheme 8). Based on

Scheme 8



the above hypothesis, MeBmt (13) was reexamined (Scheme 9).

Scheme 9

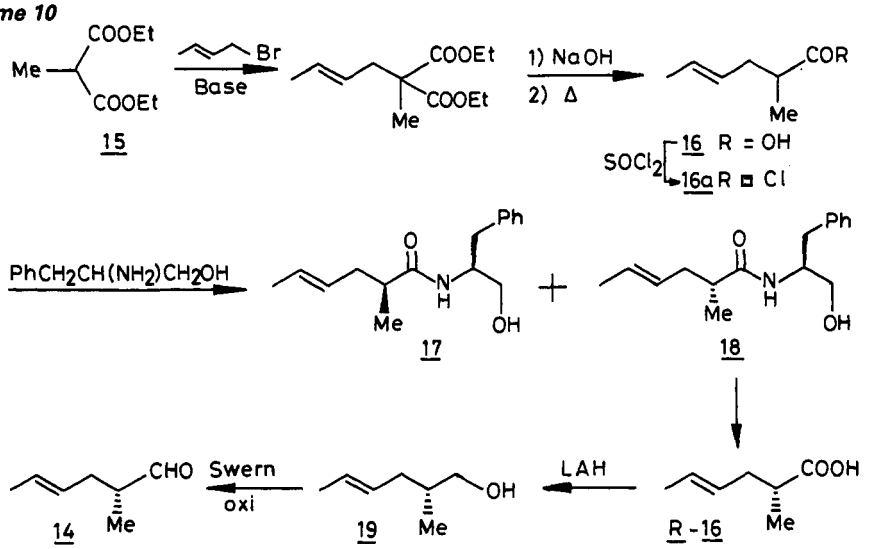


Our first consideration was to obtain the optically pure aldehyde (14). Although 14 was reported (ref.21) earlier, we chose to develop an alternate approach which now enabled us to obtain optically pure 14 in multigram quantities. Thus, diethyl methylmalonate (15) was alkylated (scheme 10) with (E)-crotyl bromide in the presence of a base followed by hydrolysis and decarboxylation by pyrolysis to afford the (±) acid (16). In order to resolve (±) (16), liquid absorption chromatography of the derived diastereomeric mixture of amides (17 and 18) in a directed way was performed (ref.24). The required polar amide (18) was hydrolysed with 3N sulfuric acid and the resulting acid was reduced to the alcohol (19). Subsequent oxidation by adopting Swern procedure gave a rather unstable aldehyde (14).

Wittig reaction of 14 with carboethoxytriphenylmethylenephosphorane at elevated temperature furnished E-product (20), confirmed by ^{1}H NMR spectrum. Reduction of 20 with DIBAL-H at -78°C afforded the optically pure allylic alcohol (21) which on Sharpless asymmetric epoxidation with (-)-diisopropyltartrate as the chiral auxiliary then gave the 2,3-epoxy alcohol (22) in 85% yield. The stereochemical assignments of 22 were based on the predictions reported by Sharpless (ref.23).

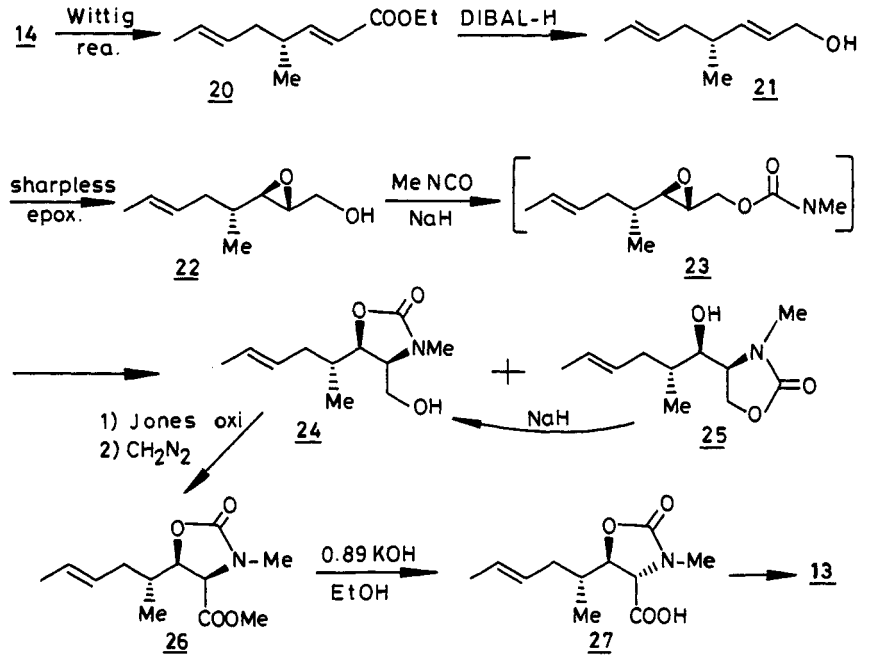
Our next objective (scheme 11) was to realise the optically pure oxazolidinone derivative

Scheme 10



by means of regioselective epoxide opening reaction via the corresponding urethane derivative, a method pioneered by Rousch and coworkers (ref.22). Methylisocyanate was chosen as the suitable reagent for effecting the epoxy-urethane (**23**) formation as it would lead to the oxazolidinone derivative **24** bearing a N-methyl substituent required for the target molecule (**13**). This reaction was conducted in the presence of sodium hydride to afford a mixture of 1,2 and 2,3-oxazolidinone derivatives (**25** and **24**) in a ratio of 3:2. The undesired derivative **25** was further treated with NaH in order to effect the isomerisation which led to a 1:1 mixture of **24** and **25**.

Scheme 11



The combined product (**24**) was oxidised with Jones reagent and then esterified to give **26**.Treatment of **26** with 0.89N KOH solution in refluxing ethanol then gave the isomerised trans-oxazolidinone derivative **27** in 80% yield. The structure of **27** was proved by comparision of its ^{1}H NMR spectra with **26**, a small coupling constant ($J_{4,5}$=4.8 Hz) was indicative of trans geometry between H-4 and H-5 of **27**. In addition, $[\alpha]_D$ +30.5° was in good agreement with the literature (ref.21) value $[\alpha]_D$ +33.5°. Finally **27** was hydrolysed in accordance with literature procedure to afford the optically pure MeBmt (**13**) (ref.21).

Acknowledgements

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