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Synthesis of a Key Intermediate for Thienamycin and Imipenem through Stereoselective Two-direction Elongation of Asymmetrized *Bis*(hydroxymethyl)acetaldehyde (BHYMA*)

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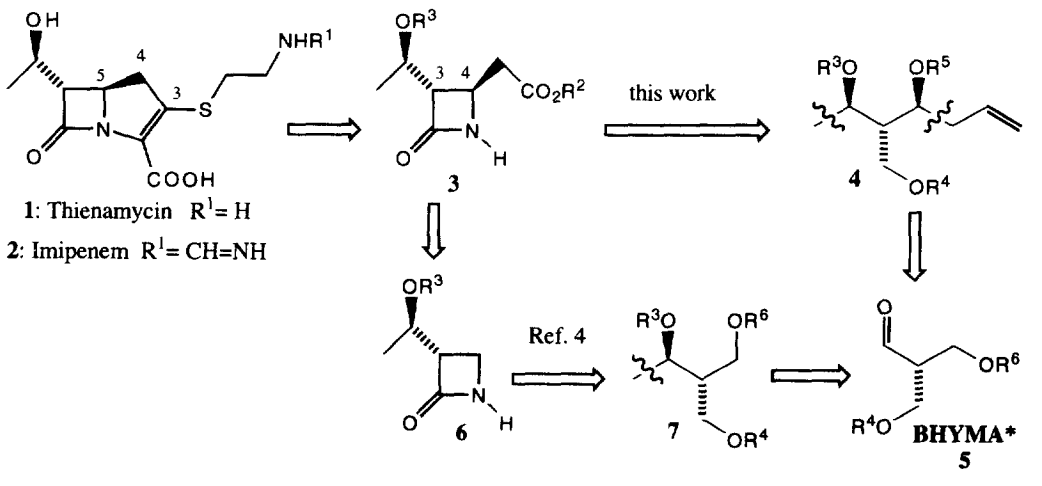
Abstract: The enantioselective formal synthesis of Thienamycin and Imipenem has been realised through two-direction elongation of the chiral building block *bis*(hydroxymethyl)acetaldehyde **5**. The generation of the two additional stereocentres has been carried out with excellent diastereoselectivity thanks to two sequential "protecting group controlled" nucleophilic additions. Another key step was represented by the regioselective oxidation of a primary-secondary 1,3-diol to the corresponding β-hydroxyacid.

The great importance of carbapenems as third generation β-lactam antibiotics endowed with potent broad-spectrum activity, coupled with their unavailability by fermentation methodologies, has stimulated in the last fifteen years many synthetic efforts toward their total synthesis.[1] The most renown representatives of this class are Thienamycin **1** and Imipenem **2** (Scheme 1), which are differentiated only by the side-chain at C-3 (IUPAC numbering). The latter is currently widely used for clinical treatment of various infections. In the previous synthetic approaches, a particular emphasis has been put on the enantio- and diastereoselective preparation of key intermediates characterised by a monocyclic β-lactam containing all the three chiral centres and a substituent at C-4 suitable for further assemblage of the five-membered ring. An example is given by compounds of general formula **3**, which have been often used for the synthesis of **1** or **2**.[2]

We have recently developed an efficient chemoenzymatic methodology for the synthesis of both enantiomers of asymmetrized *bis*(hydroxymethyl)acetaldehydes (BHYMA*) of general formula **5**.[3] Stereoselective one-direction elongation has been later employed by us[4] in the preparation of β-lactam **6**,

Scheme 1

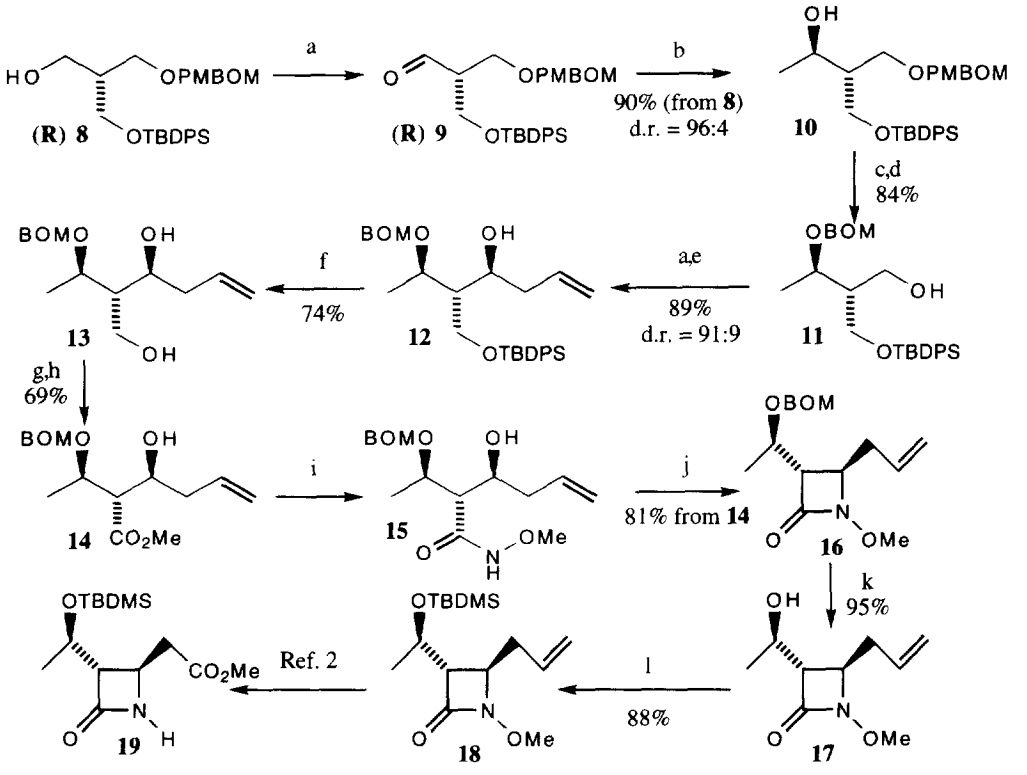


which is also a known intermediate for Thienamycin synthesis. However, since **6** has yet no substituents at C-4, more steps are needed for its transformation into more advanced intermediates, like **3**. Since these latter compounds can be in principle directly prepared by a two-direction elongation of **5**, to give **4**, prior to β-lactam formation, we have now engaged in the development of such strategy.

The general scope of two-direction elongation of **5**, was recently preliminary investigated by us,[5] and we have found at least one efficient way (in term of diastereoselectivity) to convert **5** into each of the 8 possible stereoisomers of protected triols like **4**. This was realised through two consecutive "protecting group controlled"[6] nucleophilic additions or reductions. That is, when the two hydroxymethyl groups are masked with different protecting groups, one of them promoting ("chelating protecting group"), and the other one depressing ("not-chelating protecting group") the co-ordinating aptitude of oxygen, useful levels of diastereoselection could be achieved in additions to **5** (or to the aldehydes obtained after the first stereoselective elongation) under conditions which favour cyclic chelated transition states.

There are in principle 8 ways to synthesise **4** from (*S*) or (*R*) BHYMA* by the "protecting group controlled asymmetric induction" approach.[7] Among them we present therein the one which seemed more attractive for the lower number of step and for the anticipated good diastereoselection (on the basis of our

Scheme 2



a) $(COCl)_2$, DMSO, $Et(iPr)_2N$, CH_2Cl_2, -78°C. **b**) Me_2CuLi, Et_2O, -78°→ -50°C. **c**) BOM-Cl, $Et(iPr)_2N$, CH_2Cl_2. **d**) DDQ, CH_2Cl_2, *t*BuOH, pH 7 buffer. **e**) Allyl-$SnBu_3$, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, -78°→ -50°C. **f**) nBu_4NF, THF. **g**) 1) $CaCO_3$, $TEMPO^+Cl^-$, CH_2Cl_2. 2) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O. **h**) CH_2N_2, Et_2O. **i**) H_2N-OMe•HCl, Me_3Al, THF. **j**) DEAD, Ph_3P, THF. **k**) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2. **l**) Me_2tBuSi-OTf, 2,6-lutidine, CH_2Cl_2.

previous study)(Scheme 2).[5,8]

BHYMA* (*R*) **9** was prepared from alcohol (*R*) **8**[3,9] by modified Swern oxidation,[4,6d] and directly reacted with Me_2CuLi to give, in good yield and with excellent diastereoselection, alcohol **10**. It must be stressed that this elevated induction relies on the different co-ordinating ability of the oxygens of the two protected hydroxymethyl groups, which is in turn suitably modulated by the protecting groups.[6a] Thus, it is only the PMBOM protected alcohol which takes place in chelation, while the bulky silyl ether has the function to shield one of the two carbonyl faces.

At this point, in order to obtain the desired relative configuration in the second nucleophilic addition, we needed to elaborate the PMBOM containing arm, and to block the secondary alcohol with a "chelating" protecting group. For this purpose we took advantage of the orthogonality of the otherwise similar PMBOM and BOM groups. The resulting alcohol **11** was oxidized to the corresponding aldehyde and treated with allyltributyltin in the presence of $MgBr_2$. This condensation turned out to proceed with good stereoselectivity (91:9). This outcome is remarkable, since in this case the stereocentres at the α and β position (relative to the aldehydic group) are expected to exercise opposite stereochemical controls ("mismatched" case) under chelation control.[10] Thus, the diastereoselective formation of **12**[11] indicates once again[5] that, as far as it concerns the allylation reaction, the influence of the β stereocentre is little.

Having solved the stereochemical problem, the completion of the synthesis required the selective oxidation of the branch containing the primary alcoholic function, to give a β-hydroxyacid derivative, well fitted for β-lactam synthesis *via* Miller's biomimetic cyclization.[12] A crucial point was therefore represented by the distinction between the primary alcoholic function and the secondary one at C-4. During the synthesis of **6** we had solved a similar problem through a selective deprotection strategy, which, however, implied two additional steps. In order to find a better way, we thus searched for a method for the selective oxidation of diol **13**, obtained by desilylation of **12**. After various efforts, we finally found that good yields could be achieved by using stoichiometric $TEMPO^+Cl^-$ for the conversion into the β-hydroxyaldehyde, followed by *in situ* treatment with $NaClO_2$.[13-15] The resulting β-hydroxyacid was directly isolated as the methyl ester **14** after reaction with CH_2N_2. This methyl ester was smoothly converted into O-methyl hydroxamate **15**,[16] which underwent Miller's cyclization[12] to afford **16**. Finally, removal of BOM group by "push-pull"[17] reaction with ethanethiol and boron trifluoride, followed by reprotection as the *tert*-butyldimethylsilyl ether, furnished the known[2d] azetidinone **18**,[18] whose two step conversion into **19**, a well known intermediate for the synthesis of Thienamycin and Imipenem,[2] was already reported. The overall yield of **18** from **8** was a remarkable 22.7%.

In conclusion, we have demonstrated that, thanks to the concept of "protecting group controlled" asymmetric induction, the two-direction elongation of BHYMA* can be utilised for the efficient enantio- and diastereoselective preparation of useful intermediates for the synthesis of carbapenem antibiotics. Application of this strategy for the synthesis of other biologically active compounds is in progress in our laboratories.

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7. This fact stems from the high number of variables that can be chosen *en route* from BHYMA* to **4** (or its stereoisomers). For a deeper explanation of all these possibilities, see ref. 5. It is worth noting that in ref. 5 we have already prepared compounds with the same relative configuration of **4**, by employing two routes alternative to the one shown in Scheme 2. Though satisfactory, these two ways were some way less efficient than the one here presented, for a lower overall stereoselectivity, and for the higher number of steps.
8. Another hypothetical route, which would have implied the same number of steps, starts from (*S*) **9** and involves addition of allyl first, and methyl later. However, we discarded this possibility, because of the expected poor diastereoselection during the second nucleophilic addition (of Me_2CuLi) (see ref. 5).
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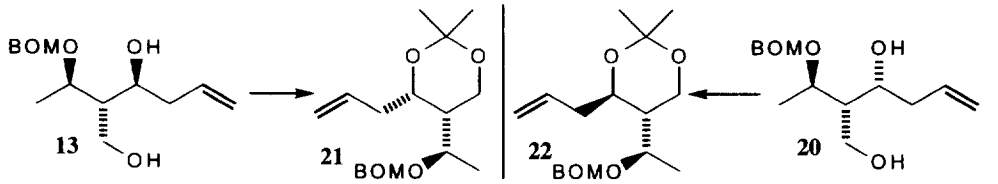
11. The relative configuration of **12** at C-4 and C-5 was demonstrated by transformation (2-methoxypropene, pTSA, CH_2Cl_2) of **13** (91%) or of its epimer **20** (62%), into the corresponding *iso*-propylidene derivatives **21** and **22**. ^1H and ^{13}C n.m.r. analysis clearly showed that **21** was *cis*, while **22** was *trans*.



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13. $TEMPO^+Cl^-$ = 2,2,6,6-tetramethyl-1-oxopiperidinium chloride was prepared from TEMPO radical by oxidation with chlorine. See Rozantsev, E. G.; Sholle, V. D. *Synthesis* **1971**, 401-414.
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15. Our procedure was a modification of that reported in ref. 14. Since the first oxidation tends to stop at ≈ 50% conversion, due to the formation of stable hemiacetals, in order to achieve nearly complete transformation, after addition of $NaClO_2$, two more portions of $TEMPO^+Cl^-$ were added at intervals of 1 h. The presence of $CaCO_3$ slows down hemiacetal formation.
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18. The absence of racemization during the overall synthetic scheme was checked by preparing both Mosher's esters of alcohol **17** and examining them at ^1H n.m.r.

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