RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 17206

Received 9th January 2014
Accepted 31st March 2014

DOI: 10.1039/c4ra00205a

www.rsc.org/advances

Common precursor strategy for the synthesis of bestatin, amprenavir intermediate and *syn*-4-hydroxy-5-phenyl-γ-lactam†

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A common precursor strategy for the synthesis of bestatin hydrochloride, an anticancer agent, 1,3-diaminoalcohol, an amprenavir intermediate, and a *syn*-4-hydroxy-5-phenyl-γ-lactam intermediate of various bioactive molecules using an α,β-unsaturated ester as a common precursor is described. The protocol offers mild reaction conditions, good yields and excellent stereoselectivity.

The vicinal aminoalcohol moiety is not only a widespread structural motif in natural and synthetic biologically active molecules (Fig. 1), but is also used widely as a versatile chiral building block and a chiral catalyst/ligand in a variety of asymmetric syntheses, such as enantioselective dialkylzinc addition to aldehydes,[1] enantioselective conjugated addition[2] and pericyclic reactions.[3] The importance and the need to prepare these compounds, as well as their analogues have dramatically increased the efforts towards the development of newer methods for their synthesis.

In the present work, we have developed a common precursor strategy[4] for the synthesis of three vicinal aminoalcohols *i.e.*, bestatin [(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine] (**1**), 1,3 diaminoalchol (amprenavir intermediate) and *syn*-γ-lactams. Bestatin (**1**) is an effective inhibitor of aminopeptidase N (APN) for the treatment of leukaemia.[5] Besides, it is also a promising drug for the treatment of virus infections and acute pain.[6] Amprenavir is an effective therapeutic agent for the treatment of HIV infection, approved by FDA in 1999. Later, its phosphate ester pro-drug *i.e.* fosamprenavir with improved solubility and bioavailability was approved by the FDA in October 2003. γ-Lactams or 2-oxopyrrolidines are five-membered ring lactams, constituting as an important structural motifs in a variety of biologically active natural products, medicinal leads and approved drugs.[7] Furthermore, the reduced form of γ-lactams provides an access to the pyrrolidine family of alkaloids.[8] The relative and absolute stereochemistry of the ring substituents, as well as their chemical nature play critical roles in the biological properties of γ-lactams and analogues.[9]

The retro-synthetic pathway for the synthesis of bestatin (**1**), di-aminoalcohol (**2**) and *syn*-γ-lactam (**3**) from α,β-unsaturated ester involved stereoselective aminohydroxylation of the double bond as a key reaction step to afford β-amino-α-hydroxy acids (AHPA), whereas the acid/ester itself can be synthesized from phenyl acetaldehyde (Scheme 1). Bestatin and di-aminoalcohol derivatives can be prepared from the same intermediate by condensation with different amines while as γ-butyrolactam is synthesized by installing the aminoalcohol group at the

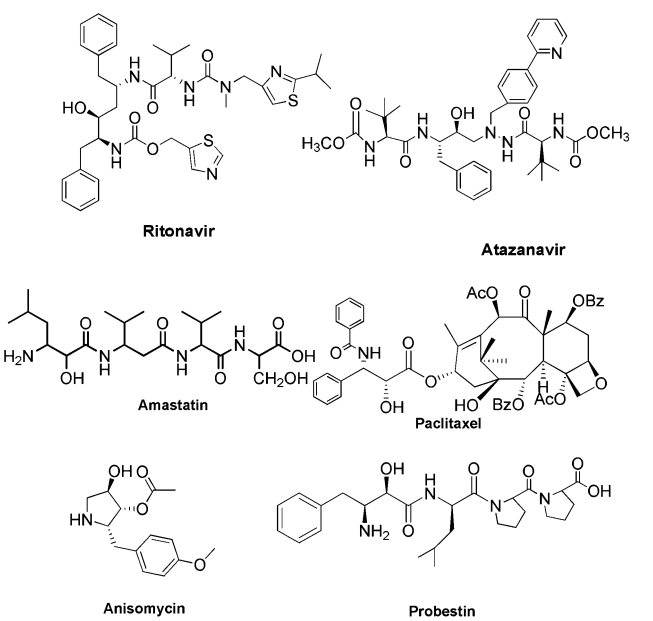

Fig. 1 Some bioactive aminoalcohols.

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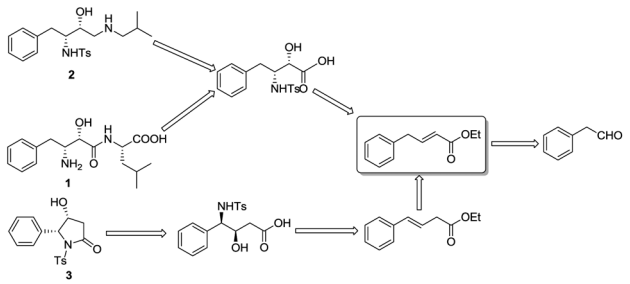
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra00205a



Scheme 1 Consolidated view of retrosynthetic pathways.

β,γ-position of a β,γ-unsaturated ester *via* double bond migration/isomerisation.

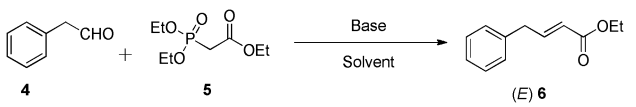
The first step was the preparation of α,β-unsaturated ester (**6**) using Horner–Wadsworth–Emmons reaction (HWE reaction),[10] for the preparation of AHPA. The reaction of phenyl acetaldehyde (**4**) and triethyl phosphonoacetate (**5**) using a base in an inert solvent gave α,β-unsaturated ester (**6**) as a major product. As double bond migration to generate a β,γ-unsaturated ester was also observed during the reaction therefore, it was imperative to study of the effect of the solvents and the bases on the yield, and the reaction time. The reaction was optimized with diethyl ether or THF as the solvent, affording the product in 92% and 88% yield respectively, (Table 1, entries 1 and 2). The use of NaH made this reaction efficient, when performed with 1.2 equivalent NaH in diethyl ether–THF and it proceeded to completion in 2 h at ambient temperature, affording the product in high yield and stereoselectivity. The use of NaOMe and NaOH led to lower stereoselectivity and yields (Table 1, entries 7–9).

The next is the key step to determine the suitable method for the preparation of chiral β-amino-α-hydroxy ester. Our initial attempts employing different methods such as *via* amino halogenations, epoxidation *etc.* met with failure. However, Sharpless aminohydroxylation[11] of **6**, employing chloramine-T trihydrate, $K_2[OsO_2(OH)_4]$ and $(DHQ)_2PHAL$ catalyst in *t*-BuOH : water (1 : 1) at room temperature gave the desired product (**8**) in 50% yield with desired stereoselectivity. Next, the ester (**8**) was hydrolyzed using K_2CO_3 in methanol : water (10 : 1) to obtain the corresponding acid (**9**) in 95% yield. The method was mild enough to preserve stereochemical integrity during the transformation, as established by NMR and optical rotation value.[12] The coupling of acid (**9**) L-leucine benzyl ester was carried out using EDC, *N*,*N*-diisopropylethylamine and HOBt in dimethylformamide at room temperature under nitrogen to afford the corresponding benzyl ester (**10**) in 80% yield. In order to prepare the target product bestatin hydrochloride, it required efficient deprotection of functionalities *i.e.*, debenzylation, followed by detosylation. Thus, debenzylation was carried out *via* hydrogenation in the presence of Pd/C under H_2 atmosphere in methanol. Attempts for detosylation using sodium naphthalenide[13] proved unsuccessful. A milder method using magnesium in dry methanol[14] under refluxing conditions for 12 h, deprotected the *N*-tosyl group successfully. Finally, 6 N HCl in dioxane was used for the preparation of bestatin hydrochloride. The overall yield in the synthesis of **1** is 28% (Scheme 2). The structure of the final product was confirmed by NMR and the comparison with the specific rotation values reported in the literature.[15]

After the successful accomplishment of the bestatin synthesis, the common precursor strategy was extended to the synthesis of the di-aminoalcohol precursor (**2**). The condensation of the acid (**9**) with isobutyl amine in the presence of EDC, followed by the reduction of the amide (**11**) with lithium aluminium hydride gave the desired intermediate **2** in 75% yield (Scheme 3). The structure of **2** was established by NMR.[16]

The preparation of chiral β-hydroxy-γ-lactam moiety, a precursor of several biologically important molecules including substituted cyclic GABA analogues has been the third synthetic target of the present common precursor methodology. The key step was the preparation of β,γ-unsaturated ester (**7**) *via in situ* isomerization of **6** using HWE reaction. Thus, β,γ-unsaturated ester was obtained in one step in 90% yield from phenyl acetaldehyde and triethyl phosphonoacetate, using sodium hydride

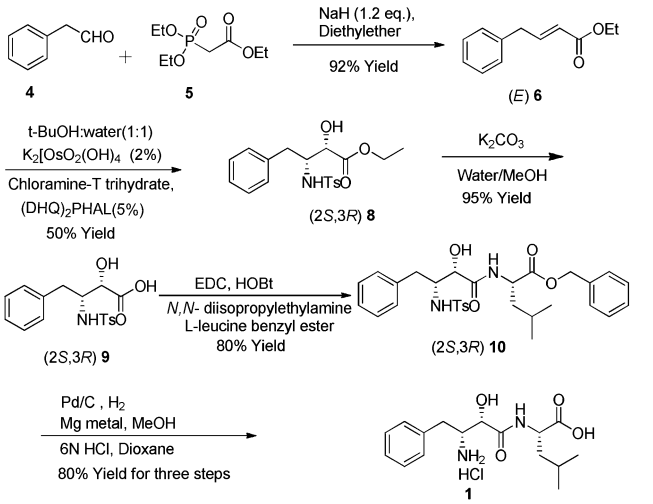
Table 1 Optimization of Horner–Wadsworth–Emmons reaction



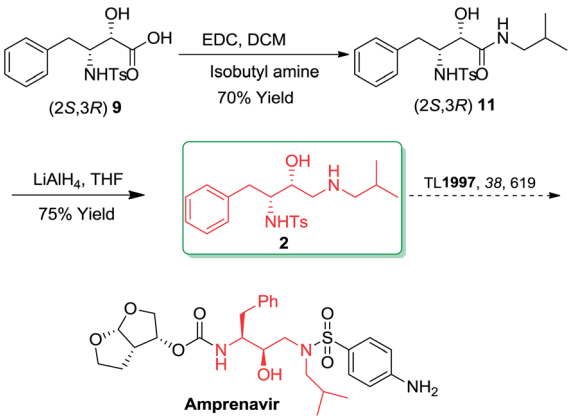
4 5 (*E*) **6**

Entry	Bases (1.2 eq.)	Solvents	Yields[a] (%)
1	NaH	Diethyl ether	92
2	NaH	THF	88
3	NaH	Benzene	85
4	*t*-BuOK	Diethyl ether	94
5	*t*-BuOK	THF	90
6	*t*-BuOK	Benzene	87
7	NaOMe	Diethyl ether	80
8	NaOMe	Benzene	72
9	NaOH	Diethyl ether	60

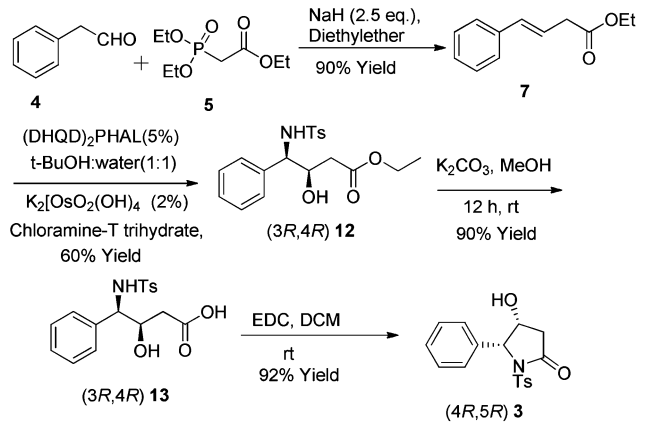
[a] Yields of compound **6** were calculated after purification.



Scheme 2 Synthesis of bestatin hydrochloride.



Scheme 3 Synthesis of di-aminoalcohol precursor **2**.



Scheme 4 Synthesis of 4-hydroxy-5-phenyl-1-tosylpyrrolidin-2-one.

(2.5 eq.) in diethyl ether as a base with the formation *E* isomer only. Notably, in this reaction, the use of higher stoichiometry of the NaH (2.5 eq.) resulted in concurrent isomerisation in high yield.

The next step again was Sharpless asymmetric amino-hydroxylation of β,γ-unsaturated ester (**7**) using chloramine-T trihydrate, $K_2[OsO_2(OH)_4]$ and $(DHQD)_2PHAL$ as asymmetric catalyst in *t*-BuOH : water (1 : 1) at room temperature, providing the desired product γ-amino, β-hydroxy esters (**12**) in 60% yield and excellent selectivity. For the preparation of the acid (**13**), the ester (**12**) was hydrolyzed using K_2CO_3 in methanol and water in 90% yield. In the final step, the intramolecular cyclisation of the γ-amino acid (**13**) was accomplished in 92% yield employing EDC, DMAP in DCM (Scheme 4). The reaction was effected at ambient temperature under neutral conditions and there was no need for the protection of the β-hydroxy group. This flexibility offers an advantage over other known methods for the cyclisation of amino acids to γ-lactams.[17]

Conclusions

In summary, we successfully demonstrated the syntheses of three targeted moieties *i.e.*, bestatin, diaminoalcohol derivative (amprenavir intermediate) and *syn*-disubstituted γ-lactam using a common precursor strategy (α,β-unsaturated ester as a common precursor). Various other bioactive aminoalcohol molecules or intermediate may also be synthesized by using this strategy.

Acknowledgements

The authors (BK, MAA and AR) thank UGC and CSIR, New Delhi for the award of senior research fellowships. The authors are declaring the institutional Publication Number IIIM/1653/2014.

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