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Highly Stereoselective Synthesis of α-Hydroxy β-Amino acids through β-Lactams: Application to the Synthesis of the Taxol and Bestatin Side Chains and Related Systems.

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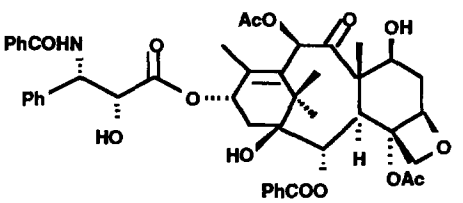
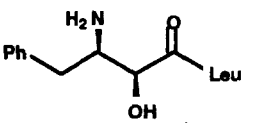
Summary: Formation of α-hydroxy β-lactams, followed by chemical elaboration at C_4 and further β-lactam cleavage afforded functionalised α-hydroxy β-amino acids or their derivatives in a highly stereoselective manner.

The development of highly stereoselective synthesis of α-hydroxy β-amino acids[1] is of considerable interest because the occurrence of these derivatives in many biologically important compounds such as taxol **1**, a highly promising anticancer product[2], and bestatin **2**, a low molecular peptidic enzyme inhibitor with antimicrobial, anticancer and immunomodifier properties[3].

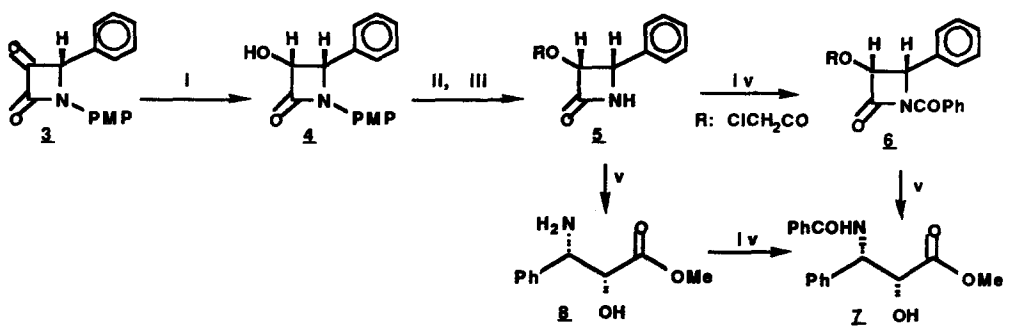


Taxol **1**



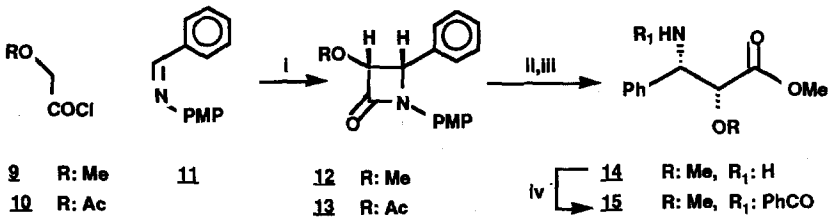
Bestatin **2**

In recent years the β-lactam skeleton has found wide applicability in the synthesis of many natural products including both α- and β-amino acids[4]. The recent work of Terashima and coworkers[5] on the synthesis of some renin inhibitors from β-lactams has prompted us to report our own results in this field. Recently, we have described on the utility of azetidine-2,3-diones as building blocks of α-amino acid derivatives[6]. In this paper, we report the utility of these and related compounds to synthesize α-hydroxy β-amino acids in a highly stereoselective manner. First, the synthesis of the (±)taxol side chain was examined from azetidine-2,3-dione **3** prepared according to our procedure[6]. Thus, borohydride reduction of **3** furnished , as expected by our previous observations[7], the α-hydroxy β-lactam **4** as single *cis* isomer. Protection of the hydroxyl group as chloroacetyl derivative and further N-dearylation[8] affor-



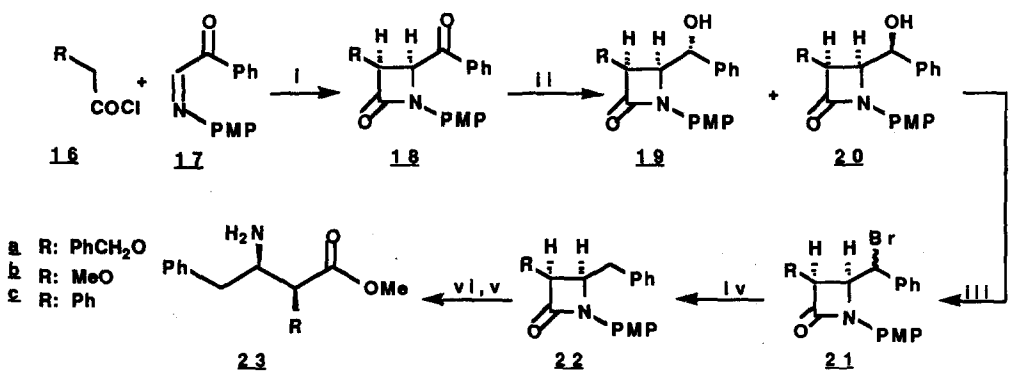
Scheme 1. Reagents and conditions. I, $NaBH_4$, MeOH-THF. II $ClCH_2COCl$, pyridine, CH_2Cl_2, III, (CAN) $(NH_4)_2Ce(NO_3)_6$, MeCN-H_2O, 0-5ºC, 45min. Iv, ClCOPh, CH_2Cl_2, -70—>20ºC, NEt_3, v, $ClSiMe_3$, MeOH.

ded the β-lactam **5** in 70% yield [mp:120-122ºC (Et_2O); δ ppm 5.10(d, 1H, H_3, $J_{3,4}$= 4.7Hz); 5.93(d, 1H, H_4)]. Treatment of β-lactam **5** with trimethylchlorosilane in methanol as solvent produced the β-lactam opening[9] with concomitant deprotection of the hydroxyl group to give the α-hydroxy-β-amino ester **8** in 80% yield, [mp: 87-88ºC (Et_2O)] which was easily transformated into the (±)taxol side chain **7** [mp:165-167ºC (Et_2O), δ ppm: 5.75(d, 1H, C<u>H</u>-Ar, J= 1.7Hz), 4.63(d, 1H, C<u>H</u>-CO_2Me)].



Scheme 2. Reagents and conditions. **i**, NEt_3, CH_2Cl_2, r.t. 24-48h. **ii** CAN, MeCN-H_2O, 0-5ºC, 30min. **iii**, $ClSiMe_3$, MeOH. **iv**, PhCOCl, NEt_3, CH_2Cl_2, r.t., 30min.

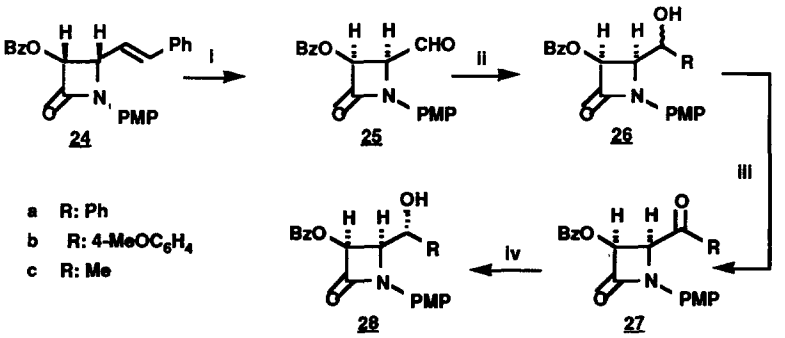
The required alkoxy or acyloxy functionality at C_3 of the β-lactam ring could also be obtained by reaction between the corresponding acetyl chloride **9** or **10** and the imine **11**, under standard conditions[10] (Scheme 2). For example, when methoxyacetyl chloride was allowed to react with the imine **11** in the presence of triethylamine, the β-lactam **12** was isolated in 60% yield as single *cis*-isomer. Similarly, acethoxyacetyl chloride in the presence of triethylamine and the imine **11** afforded the *cis*-β-lactam **13** in 56% yield. The *cis*-β-lactam **12** upon N-dearylation and further treatment with chlorotrimethylsilane-methanol, provided the β-amino ester **14** as an oil which was isolated as benzoyl derivative **15** in 92% yield [mp: 185-187 ºC (Et_2O)]. Following this approach, preparation of the (±)bes-



Scheme 3. Reagents and Conditions. **i**, NEt_3, CH_2Cl_2, r.t., 48h. **ii** $NaBH_4$, MeOH, r.t. **iii** Ph_3PBr_2, CH_2Cl_2,0ºC **iv** nBu_3SnH, benzene, reflux **v** CAN, MeCN-H_2O, 0-5ºC, 45min. **vi** MeOH, $ClSiMe_3$.

tatin side chain was also examined. For instance, reaction between benzyloxyacetyl chloride **16** and the imine **17** under standard conditions[11] furnished the β-lactam **18a** in 70% yield as a mixture of *cis* and *trans* isomers in a ratio 90/10 respectively. The *cis* isomer (m.p: 152-4ºC) was separated by crystallization from ethanol and subjected to treatment with sodium borohydride in methanol, to afford an

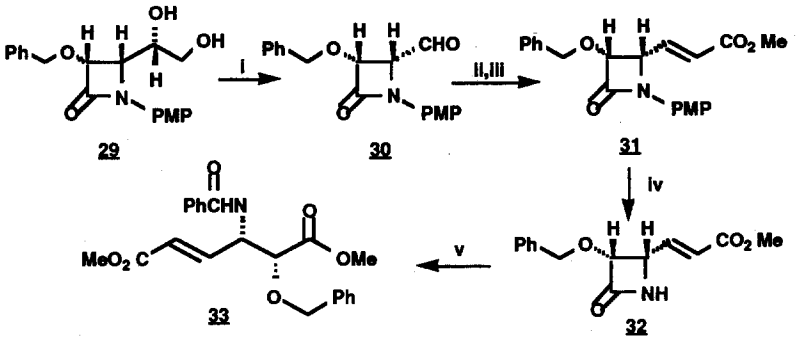
epimeric mixture of alcohols **19a** and **20a** in a ratio 86/14 respectively. Conversion of these alcohols into the bromide **21** and further tributyltin hydride reduction[12], furnished in 75% yield the desired 4-benzyl β-lactam **22a** as intermediate of the (±)bestatin side chain **23a**. In contrast to earlier observations[13], the high stereoselectivity observed in the reduction step, could be attributed to a sterical effect impossed by the bulkyness of the C_3 substituent. For example, while β-lactam **18b** upon borohydride reduction afforded a mixture of **19b** and **20b**, in a ratio 92:8 respectively, the β-lactam **18c** under the same reaction conditions, produced **19c** as single diastereomer[14]. In view of these results, a general route to carbinols of type **19** was next explored. For instance, when racemic β-lactam **25**, prepared by low temperature ozonolysis of **24**, was treated with Grignard reagents, an epimeric mixture of the corresponding carbinols **26** was obtained in nearly quantitative yield. Swern[14] oxidation of these carbinols provided the corresponding keto-β-lactams **27** suitable for further stereoselective reduction. For example, compound **27b** afforded **28b** together with its epimer in a ratio 90:10 which could be separated by column chromatography in 75% overall yield from **25**. Less stereoselectivity was observed for the methyl ketone **27c** which upon borohydride reduction afforded **28c** and its epimer in a ratio 65:35 respectively[16].



Scheme 4. Reagents and Conditions I, O_3, CH_2Cl_2, -78°C, then, Me_2S II, RMgBr, THF, -45°C III, ClCOCOCl, DMSO, CH_2Cl_2, -60°C, then, NEt_3 Iv, $NaBH_4$, MeOH.

The wide scope of the present method is further shown in the asymmetric synthesis of highly functionalyzed β-amino acids, depicted in Scheme 5. Thus the β-lactam **29**, prepared by the method of Bose[17], was converted in the usual way[18] into the formyl derivative **30** in 83% yield [m.p: 154-5°C (Et_2O)] and further transformed into **31** [m.p: 93-95°C(Et_2O)], following our established protocol[7,19]. Compound **31** was N-dearylated to the N-unsubstituted azetidin-2-one **32** in 80% yield, and further converted into the desired β-amino ester **33** in 88% yield[20].

From these results, the most significant feature of our approach is that a wide variety of α-hydroxy β-amino acids can be obtained in a highly stereoselective fashion starting from appropriately substituted azetidin-2-ones[21]. Further studies on the application of this methodology to the synthesis of natural products are now underway in our laboratory.



Scheme 5. Reagents and Conditions I, $NaIO_4$, MeOH, 1h, r.t. II, $BrCH_2COOMe$, Zn, $ClSiMe_3$, THF, r.t. 20min, then, HF-MeOH, CH_2Cl_2, 20min, r.t. III, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 60min, r.t. then, DBU, CH_2Cl_2, 60min., r.t. IV (CAN), CH_3CN-H_2O, 30min, 0ºC. V $ClSiMe_3$-MeOH, 30min, r.t. then, PhCOCl, NEt_3, CH_2Cl_2, 60min, r.t.

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REFERENCES AND NOTES:

1. R.M. Williams in "Synthesis of Optically Active α-Amino Acids". Pergamon. Oxford, 1989.
2. J.-N. Denis, A. Correa, A.E. Greene, **J. Org. Chem.** 1990, 55, 1957. and references therein.
3. R. Herranz, J. Castro-Pichel, S. Vinuesa, M.T. García-López, **J. Org. Chem**,1990, 55, 2232 and references therein.
4. For a recent review, see: M.S. Manhas, D.R. Wagle, J. Chiang, A.K. Bose, **Heterocycles**, 1988, 27, 1755.
5. a) Y. Ito, T. Kamijo, H. Horada, S. Terashima, **Heterocycles**, 1990, 30, 299. b) Y. Kobayashi, Y. Takemoto, Y. Ito, S. Terashima, **Tetrahedron Lett.**, 1990, 31, 3031.
6. F.P. Cossio, C. López, M. Oiarbide, D. Aparicio, G. Rubiales, C. Palomo, **Tetrahedron Lett.**, 1988, 28, 3133.
7. C. Palomo, J.M. Aizpurua, M.C. López, N. Aurrekoetxea, M. Oiarbide, **Tetrahedron Lett.**, preceding paper.
8. D.R. Kronenthal, C.Y. Han, M.K. Taylor, **J. Org. Chem.**, 1982, 47, 2765.
9. Methanolysis could also be performed by means of dry hydrogen chloride, see: F.M. Hauser, S.R. Ellenberger, R.P. Rhee, **J. Org. Chem.**, 1987, 52, 5041. However, we found the use of $ClSiMe_3$ more convenient as source of controlled amounts of HCl.
10. a) A.K. Bose, G. Spiegelman, M.S. Manhas, **Tetrahedron Lett.**, 1971, 3167. b) A.K. Bose, Y.H. Chiang, M.S. Manhas, **Tetrahedron Lett.**, 1972, 4091.
11. B. Alcaide, G. Dominguez, G. Escobar, V. Parreno, J. Plumet, **Heterocycles**, 1986, 24, 1579.
12. For a recent review on tributyltinhydride reduction, see: W. P. Neumann, **Synthesis**, 1987, 665.
13. B. Alcaide, G. Dominguez, J. Plumet, **Heterocycles**, 1989, 29, 217.
14. The starting β-lactam **18b** was produced as a mixture of *cis*/*trans* isomers in a ratio 88/12; [m.p: 145-6ºC(EtOH) for *cis* isomer]. The β-lactam **18c** was formed as single *cis* isomer [mp: 190-2ºC (HCCl3-Hexane)]. The ratio of the epimeric carbinols was determined by 300MHz ^{1}H-NMR analysis.
15. A.J. Mancuso, S.L. Huang, D. Swern, **J. Org. Chem.**, 43, 2480 (1978).
16. Grignard addition to **25** was also stereoselective, except in the formation of **26c** which was produced as nearly equimolar mixture of epimers. **26a** was produced in a 80/20 (R*/S*) ratio and **26b** in a 82/22 (R*/S*) ratio respectively.
17. D.R. Wagle, Ch. Garai, J. Chiang, M.G. Monteleone, B.E. Kurys, T.W. Strohmeyer, V.R. Hegde, M.S. Manhas, A.K. Bose, **J. Org. Chem.**, 1988, 53, 4227.
18. C. Hubschwerlen, G. Schmidt, **Helv. Chim. Acta**, 1983, 66, 2206.
19. C. Palomo, J.M. Aizpurua, M.C. López, N. Aurrekoetxea, **Tetrahedron Lett.**, 1990, 31, 2205.
20. Representative data: **32**, m.p.: 105-107ºC(Et_2O), 250MHz NMR δppm: 3.76(s, 3H, OMe), 4.33-4.35(m, 1H, C_4H), 4.60(d, J= -11.8Hz, 1H, PhCH), 4.71(d, J= -11.8Hz, 1H, PhCH), 4.86(dd, J= 2.5Hz, J'=4.7Hz, 1H, C_3H), 6.02(d, J=15.7Hz, 1H, =CHCO), 6.47(sb, 1H, NH), 6.89(dd, J=7.0Hz, J'=15.7Hz, 1H, =CH), 7.32(sb, 5H, arom.). EI-MS m/e: 170(2.4)(M^+-Bz). **33** (syrup): 3.70(s, 3H, OMe), 3.72(s, 3H, OMe), 4.22(d, J= 2.5Hz, 1H, CHCO), 4.46d, J= -11.7Hz, 1H, PhCH), 4.82(d, J=-11.7Hz, 1H, PhCH), 5.29-5.34(m, 1H, CH), 6.02(dd, J=1.5Hz, J'=15.7Hz, 1H, =CHCO), 6.89(sb, 1H, NH), 6.94(dd, J=5.0Hz, J'=15.7Hz, 1H, =CH), 7.36, 7.77(m, 10H, arom.). EI-MS m/e: 306(1.7)(M+ -Bz). $[\alpha]^{29}_D$ = -30.5 (c= 2.9, CH_2Cl_2).
21. For example, the corresponding enantiomer of **30** could be obtained following the method of Hoffmann-La Roche , see ref. 18. and optically active azetidine-2,3-diones can be obtained by the method of Tufariello and coworkers, see: J.J. Tufariello, D.J.P. Pinto, A.S. Milowsky, D.V. Reinhardt, **Tetrahedron Lett.**, 1987, 28, 5481.

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